Neurological Sciences

Founded by Renato Boeri
Official Journal of the Italian Neurological Society

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ISSN 1590-1874 (print version)
ISSN 1590-3478 (electronic version)

Volume 29 (6 issues) will appear in 2008.

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Typesetter

Graphostudio, Milano, Italy

Printer

Grafiche Porpora, Via Buozzi 12/14
I-20090 Segrate, Milano, Italy

Printed on acid free paper

Registrazione del Tribunale di Milano
N. 1 del 3 gennaio 1978

Distribution in Italy occurs according
to the Italian Law 196/2003

Springer
is a part of
Springer Science+Business Media

springer.com

Via Decembrio 28, I-20137 Milano, Italy
Printed in Italy

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COMORBIDITIES AND PHARMACO-RESISTANCE IN HEADACHE: CURRENT AND FUTURE PERSPECTIVES

Taormina, Italy
28-31 May 2008

Proceedings

Neurological Sciences

Volume 29 Supplement 1 2008

ORAL COMMUNICATIONS

Neurol Sci (2008) 29:S1–S6
DOI 10.1007/s10072-008-0875-8

KEY NOTE LECTURE

Cluster headache: from treatment to pathophysiology

Gennaro Bussone

Abstract This key note lecture illustrates the role of clinical developments in stimulating research and discovery in the area of the pathophysiology of cluster headache (CH) and other trigeminal autonomic cephalalgias (TACs), reviewing the physiological, biochemical and neuroimaging data that have suggested involvement of the hypothalamus in CH pathogenesis. These findings suggested the use of deep brain stimulation as a treatment for chronic drug-resistant CH. The typical circadian and circannual periodicity of CH attacks were the fundamental clinical characteristics that shifted focus from peripheral hypotheses to the idea of central origin for this headache form. Functional neuroimaging demonstrated that TACs are associated with activation of the posterior hypothalamus and there is clinical evidence that patients who suffer from CH have altered biological rhythms. Furthermore, the principal seat of biorhythm regulation – the hypothalamus – is known to have a modulatory role on nociceptive and autonomic pathways, specifically trigemino-vascular nociceptive pathways. Future research will elucidate why neuromodulatory approaches are effective in CH and other TACs, determine whether the hypothalamus is itself the generator of CH attacks, or whether it is activated in response to a generator situated elsewhere, and identify pharmacological treatments that directly target the hypothalamus.

Keywords Cluster headache · Central pain · Hypothalamus

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Introduction

Over the last thirty years, notable progress has been made in understanding the pathophysiology of several types of primary headache, particularly cluster headache (CH). Although the absence of suitable animal models for these conditions has constituted a major impediment to progress, the introduction of ever more sophisticated neuroimaging techniques has greatly increased opportunities for investigation. These opportunities have been exploited and as a result not only has our understanding of several primary headaches greatly enlarged, but an effective new therapeutic modality – neurostimulation – has been established.

Clinical aspects

One of the earliest recognisable descriptions of CH was given in 1641 by the German physician Nicolas Tulp [1]. Later, in 1745, van Swieten [2] described patients with a clinical syndrome that we would have no difficulty in recognising as CH. The 20th century was characterised by several descriptions of strictly unilateral headaches with various proposed names for them, as summarised in Table 1. Sometimes these descriptions emphasised peculiar clinical features; sometimes they reveal how the describing specialists (mainly otorhinolaryngologists) were struck by the violence of the pain. The pain was considered "neuralgic" and its location was noted as in the facial area innervated by the branches of the trigeminal nerve. The pain could be accompanied by parasympathetic and sympathetic manifestations.

In 1952 Kunkle et al. [3] proposed that all these strictly unilateral headache conditions were in fact one, and that they should be subsumed under the term CH. In doing so they emphasised characteristics that had been poorly recognised or overlooked by other investigators, i.e., the

circadian recurrence of the attacks and the circannual recurrence of the attack bouts. This periodicity was the fourth cardinal characteristic, which, in combination with violent pain, strict unilaterality and concomitant autonomic manifestations, established CH as a distinctive clinical entity. And although CH is a condition of distinctive and stereotyped clinical expression, it is this fourth characteristic that the clinical researcher must bear in mind when seeking to understand the pathophysiology of CH.

By emphasising the periodicity of CH, Kunkle began turning attention away from the pathogenetic theories of headache that were in vogue at the time. These theories had invoked vascular and peripheral nervous mechanisms, but it was unclear how a vascular or peripheral mechanism could explain the punctual recurrence of attacks at fixed times of day or the re-appearance of bouts of attacks at specific seasons.

In fact a new research direction was required: one that concentrated on changes within the central nervous system, and in particular the mechanisms regulating homeostasis and biological rhythms.

Peripheral pathogenetic theories

One notable theory of CH was that proposed by Horton in 1952. Horton coined the term "histamine headache" for what he called a "new vascular headache syndrome" (in fact CH) and suggested histamine as an abortive agent [4]. He proposed allergic and hyperergic mechanisms for the condition and considered that histamine treatment would work by a desensitising mechanism. Several clinical observations in fact pointed to histamine being involved in CH [5]: during CH pain attacks, histamine levels are increased in blood [6] but not in urine [7]. Furthermore, morphological studies had shown increased numbers of mast cells in the scalp skin of patients with CH, prompting the suggestion that local histamine release was involved in the mechanism of the condition [8]. Whether or not these phenomena are pathogenetically primary or simply epiphenomena accompanying an attack, remains impossible to determine even today. It was certainly reasonable for Horton, with the means available to him in the middle of the last century, to suggest a cause–effect relationship between the observed changes in blood histamine and the headache. The error was to rely on just one blood variable, but this was not the first time a similar mistake had been made in the history of headache research.

The histaminic desensitisation proposed as a treatment by Horton proved ineffective and was soon abandoned. Antihistamine drugs, in particular H_1 and H_2 receptor blockers, also proved ineffective in subsequent controlled trials.

Horton notwithstanding, mainstream thought back in the 1950s and 1960s considered CH to be a variant of migraine, and the principal pathogenetic theory of these "vascular headaches" invoked changes in extra and intracranial blood vessels. Vasoconstrictor ergot derivatives were used to treat both conditions. If used promptly ergot alkaloids are able to abort most CH attacks within a few minutes of administration [9]. Ergotamine blocks the alpha adrenoceptors present in the smooth muscle of extracranial blood vessels and hence exerts a potent vasoconstrictive action [10]. This vasoconstrictive action was considered to explain the efficacy of rapidly acting (parenterally administered) ergot preparations to treat short-lasting headaches [11]. It is not clear, however, that the vasoconstrictor action of ergot alkaloids is responsible for the therapeutic effect. One suggestion was that these substances are effective against so-called vascular headaches because they block neurogenically mediated plasma extravasation (giving rise to sterile inflammation) at the level of the dura mater [12]. They would do this by the peripheral (presynaptic) blocking of small-calibre un-myelinated C fibres.

The sterile inflammation theory was invoked to explain both migraine and CH. However, even though some headache forms have characteristics of both migraine and CH (for example so-called "neuralgic hemicrania" and "cluster migraine"), these two conditions are

Table 1 The various names for cluster headache

Authors	Date	Name	Other names
Romberg	1840	Description only	
Mollendorff	1867		Red Migraine
Eulenburg	1878		Angioparalytic hemicrania
Sluder	1910	Sluder's syndrome	Sphenopalatine neuralgia
			Lower half headache
Bing	1913	Bing's headache	Erythroprosopalgia
		Bing's syndrome	
Harris	1926		Migrainous neuralgia
Harris	1936		Ciliary neuralgia
Vail	1932		Vidian neuralgia
Gardner et al.	1947		Greater superficial petrosal neuralgia
Horton et al.	1939	Horton's headache	Erythromelgia
	1952	Horton's syndrome	Histamine cephalalgia
Kunkle et al.	1952		CH

today considered separate. The International Headache Society (IHS) views CH as clinically and pathogenetically distinct from migraine.

In addition to parenteral ergotamine, oxygen has long been recognised as an effective acute treatment for CH: inhaling 100% oxygen is effective in aborting attacks in most patients [13]. However the mechanism by which oxygen works remains unclear. It had been suggested that oxygen can reduce cerebral blood flow due to cerebrovascular hyper-reactivity in headache patients [14]. More recently it was shown that oxygen has a direct effect on inhibitory projections from the brainstem to the central pain pathway. Oxygen also seems to normalise the activity of hypothalamic neurons whose excitation or inhibition may be responsible for both the pain and autonomic manifestations of a CH attack [15–17].

It was not until the 1990s that attempts to unite migraine and CH within a single pathogenetic umbrella ceased. By that time it had come to be realised that the vascular changes observed in the sinus cavernosus of patients with CH were an aspecific aspect of the pathophysiological process and only apparently of peripheral origin. Any painful stimulation of the ophthalmic branch of the trigeminal results in blood flow changes through the sinus cavernosus as a result of the trigeminoparasympathetic reflex, initially described in experimental animals [18]. The blood flow changes are therefore secondary to the pain and not a cause of it. This realisation was important because earlier, at end of the 1980s, another peripheral hypothesis for the genesis of CH had been proposed, which suggested that the pain of CH was due to inflammation within the sinus cavernosus [19, 20].

Sterile inflammation within the sinus cavernosus is expected to be accompanied by the extravasation of plasma proteins into the surrounding tissue. However a recent SPECT/MRI study [21] found no indication of plasma protein extravasation into the cavernous sinus of CH patients undergoing an attack, providing strong evidence against the sinus cavernosus theory.

Thus the peripheral theories failed to account satisfactorily for the pain and the autonomic phenomena that accompany the pain. They also failed to account for the predominance of CH in men, and above all for the cyclic recurrence of cluster periods and the regular timing of attacks during a cluster period (for example they often develop during the REM phase of sleep, waking the patient). Furthermore the extreme agitation and sometimes aggression often displayed by patients during an attack seem unlikely to be due to pain of purely peripheral origin.

Central pathogenetic theory

One of the key observations that first directed researchers towards the idea of a central origin of CH was the finding that lithium is an effective prophylactic for both episodic and chronic CH attacks. Ekbom and Kudrow first proposed lithium in CH – a cyclic disorder – based on its efficacy in cyclic affective disorders.

In 1974 Ekbom [22] published results on five CH patients (three with chronic CH) treated with lithium for over 18 months. All responded dramatically to the treatment, but after it was discontinued the CH attacks reappeared. Re-starting the treatment brought renewed benefits. However results were better in those with the chronic form of CH. In 1977 Kudrow [23] published a study on the effects of lithium carbonate for around 32 weeks in 32 patients with chronic CH. Treatment was stopped in 4 patients due to side effects, but improvement occurred in 27 of 28 patients. Of the 26 patients who completed the study, 11 (42%) improved by 60%–90%, 14 (54%) by over 90% and only 1 patient did not improve.

These studies indicate that lithium carbonate is an effective prophylactic drug for chronic CH: improvement is generally seen within a week of starting treatment and continues throughout the treatment period. However some patients on lithium experience 3–4-day periods every 3–6 weeks during which mild headaches occur. In some cases also, patients on lithium experience recurrence of moderate or severe CH attacks without any change in the lithium maintenance dose (which is determined by clinical response, side effects and lithium plasma levels). Kudrow noted that lithium did not prevent alcohol-induced attacks, suggesting that lithium blocks the central mechanisms responsible for spontaneous attacks, but does not interfere with peripheral mechanisms [24]. Other studies have confirmed that lithium carbonate is effective in a high proportion of patients with both episodic and chronic CH [25].

How does lithium exert its effect in CH? It is known that lithium accumulates in the hypothalamus, particularly in the area concerned with the regulation of body temperature [26]. There is also evidence that lithium modulates the metabolism of cortical, hippocampal and hypothalamic serotonin [27, 28], the encephalin system, and the structure of sleep and sleep–wake rhythms [29]. These data point to lithium having an effect in CH and bipolar syndrome via a direct central effect [30, 31] on the hypothalamus, a centre that modulates the nervous, endocrine and immune systems [32].

It has also been shown that verapamil is highly effective in CH prophylaxis. According to Solomon [33] the major therapeutic advances in CH therapy over the last 25 years are: subcutaneous sumatriptan for acute attacks, verapamil as the first-choice drug for the prevention of both episodic and chronic CH [34], and more recently hypothalamic stimulation effective in treating intractable chronic CH [35]. It is intriguing that verapamil, a drug pharmacologically so different from lithium, is so effec-

tive in CH prophylaxis. We have noted that lithium interferes with the metabolism of several neurotransmitters, including serotonin. Long-term administration of lithium modifies the pattern of serotonin release in the rat brain with spontaneous serotonin release being reduced in the hippocampus and hypothalamus [28]. Lithium also favours tryptophan uptake in various brain areas but not the cortex [36]. With regard to verapamil, it is noteworthy that it is useful in the treatment of endogenous depression [37] and is also able to reduce anxiety and behavioural disturbances of central origin [38]. Verapamil is a calcium antagonist that interferes with slow calcium channels (voltage-operated channels). Recent observations indicate that verapamil has minimal activity on vascular structures. In patients with CH, verapamil causes minimal changes in cerebral blood flow that are smaller than those induced by other calcium antagonists that are less effective in CH than verapamil, suggesting that verapamil is effective in CH by exerting effects other than those on the vascular bed [39]. Other studies show that verapamil modulates the activity of central neurons via interactions with muscarinic, serotoninergic and dopaminergic receptors [40, 41]. For example, verapamil inhibits presynaptic receptors on hypothalamic noradrenergic neurons, thereby increasing norepinephrine levels in the hypothalamus; it also inhibits the release of cerebral dopamine by antagonising D2 receptors [42]. The opioid system appears particularly sensitive to verapamil. At high doses, verapamil modifies the analgesic effect of morphine, and at low doses it modulates the inhibitory activity of hypothalamic peptides on morphine analgesia [43]. In fact verapamil seems able, after a brief latency, to restore the correct function of the analgesic system in the presence of excess hypothalamic peptides [43].

Verapamil is more rapid in action than lithium, both in CH prophylaxis and in relieving depression, probably because lithium acts mainly to restore serotoninergic tone [44], while verapamil acts mainly on the opioid system [43]. Both serotonin and opioids are concerned with the modulation of pain pathways and act by inhibiting pain perception.

Recently the locus coeruleus and dorsal raphe nucleus of the brainstem have been implicated in the pathogenesis of CH attacks [45, 46]. These nuclei function both to modulate pain input from the trigeminal nucleus and to modulate the vascular activity. In the rat, the hypothalamus receives noradrenergic fibres from the locus coeruleus and serotoninergic fibres from the dorsal raphe nucleus [47]. Dysfunction in these nuclei could therefore give rise to altered monoaminergic regulation of the hypothalamus and hence explain the onset of CH. It is noteworthy that lesions to the dorsal raphe nucleus can reduce serotonin levels in the hypothalamus by 70% – an observation of particular interest given that the suprachiasmatic nucleus is the hypothalamic area most rich in serotonin, and is also implicated in the neuroendocrine alterations that occur in CH [48]. A dysfunction of the monoaminergic pathways that links the hypothalamus to the brainstem could explain this pathology.

The role of hypothalamus

The hypothalamus has a volume of only 4 ml (0.3% of the entire brain) yet is involved in a plethora of functions mainly concerned with maintaining homeostasis. These include hormone synthesis, autonomic nervous system regulation (and hence the cardiovascular system), temperature regulation, and the control of biologic rhythms, behaviour and arousal [49]. The hypothalamus is richly supplied with blood and is sensitive to chemical messengers (including neurotransmitters) in the blood and cerebrospinal fluid, as well as neurotransmitter inputs from neurons. Afferent and efferent nerve fibres connect the hypothalamus to various other CNS structures including the cerebral cortex, thalamus, hippocampus, amygdala, septal area, periaqueductal grey and dorsal horn of the spinal medulla [50]. Connections with the solitary nucleus, medial rostroventral medulla, periaqueductal grey and nucleus raphe magnum integrate with cortico-limbic structures involved in the affective and cognitive aspects of pain [51]. The hypothalamic medial preoptic nucleus has projections to the periaqueductal grey, raphe magnum and rostroventral medulla. The medial preoptic nucleus is known to play a key role in autonomic responses to pain and its stimulation inhibits responses of spinal neurons to painful stimuli [52]. Stimulation of the medial hypothalamus also inhibits responses of spinal medulla neurons to peripheral painful stimuli [53], as does electrical stimulation of the hypothalamic paraventricular nucleus [54].

It is also known that stimulation of the anterior hypothalamus suppresses responses of wide dynamic range neurons in the dorsal horn to painful stimuli [53]. Finally injection of opioids into the posterior, preoptic and arcuate nuclei of the hypothalamus provokes an increase of the pain threshold [55]. These examples serve to emphasise the fundamental role of the hypothalamus in pain perception.

Modern neuroimaging studies have directly implicated the hypothalamus in CH. PET and functional MRI studies have demonstrated that the posterior hypothalamus is activated during both spontaneous and provoked attacks [52] of CH and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). It has also been shown that this brain area has a minimal but permanent structural anomaly in CH patients [56–58].

Based on these neuroimaging findings and on the clinical and pharmacological data reviewed above, electrode stimulation of the posterior hypothalamus was proposed as a treatment of chronic CH in patients unrespon-

sive to medication [59]. This stereotactic neurosurgical technique has proven to be effective in controlling headache attacks in most patients, providing further convincing evidence that the hypothalamus plays a major role in CH pathophysiology [60].

Conclusions

Medical knowledge is acquired piecemeal, in small steps, and for patients it often seems that these steps are excessively small. Progress comes from new findings in basic science, from technological innovation – a good example being the diagnostic revolution brought about by functional neuroimaging – and also from the observations of clinicians skilled in interpreting the vague symptoms reported by their patients and in painstakingly building up an ever more complete picture of an illness. The remarkable progress in understanding CH in recent years is due to close collaboration between clinicians and basic scientists. As Louis Pasteur noted, "Science proceeds by successive answers to questions more and more subtle, coming nearer and nearer to the very essence of phenomena." It seems that we are approaching the true essence of CH. It has been established that the hypothalamus is intimately involved in the pathophysiology of the CH. However a question that future research must seek to answer is whether the hypothalamus is itself the generator of CH attacks, or whether it is activated in response to a generator situated elsewhere. Effort should also be directed to understanding why and how neuromodulatory approaches are effective in CH and other trigeminal autonomic cephalalgia (TACs). We expect that this work will enable us to relieve the suffering of almost all TAC patients, instead of just the majority of patients, as is presently the case.

References

1. Koehler PJ (1993) Prevalence of headache in Tulp's observations medicae (1641) with a description of cluster headache. Cephalalgia 13:318–320
2. Isler H (1993) Episodic headache from a textbook of 1745: van Swieten's classic description. Cephalalgia 13:172–174
3. Kunkle EC, Pfeiffer JR, Wilhoit WM et al (1952) recurrent brief headaches in cluster pattern. Trans Am Neurol Assoc 77:240–243
4. Horton BT (1952) Histaminic cephalalgia. Lancet 2:92–98
5. Horton BT (1956) Histaminic cephalalgia: differential diagnosis and treatment. Mayo Clin Proc 31:325–333
6. Anthony M, Lance JW (1971) Histamine and serotonin in cluster headache. Arch Neurol 25:225–231
7. Sjaastad O, Sjaastad V (1977) Urinary histamine excretion in migraine and cluster headache. J Neurol 216:91–104
8. Appenzeller O, Becker WJ, Ragaz A (1981) Cluster headache. Ultrastructural aspects and pathogenetic mechanisms. Arc Neurol 38:302–306
9. Ekbom K (1975) Same observations on pain in cluster headache. Headache 13:219–225
10. Boes CJ, Capobianco DJ, Matharu MS et al (2000) Wilfred Harris' early description of cluster headache. Neurology 54:1832–1833
11. Mathew NT (1992) Cluster headache. Neurology 42:22–31
12. Saito K, Moskowitz MA (1988) Neurogenically mediated plasma extravasation in dura mater: effect of ergot alkaloids. A possible mechanism of action in vascular headache. Cephalalgia 8:83–91
13. Kudrow L (1981) Response of cluster headache attacks to oxygen inhalation. Headache 21:1–4
14. Sakai F and Meyers JS (1979) Abnormal cerebrovascular reactivity in patients with migraine and cluster headache. Headache 19:257–266
15. Wang L, Bomberg E, Billington C et al (2007) Brain-derived neurotrophic factor in the hypothalamic paraventricular nucleus increases energy expenditure by elevating metabolic rate. Ann J Physiol Regul Integr Comp Physiol 293:R992–1002
16. Ryan JW, Walbrop TG (1995) Hypoxia sensitive neurons in the central hypothalamus project to the periaqueductal gray. Respir Physiol 100:185–194
17. Dillon EH, Waldrop TG (1992) In vitro responses of caudal hypothalamic neurons to hypoxia and hypercapnia. Neuroscience 51:941–950
18. May A, Bahra A, Büche C, Frackowiak RSJ et al (2000) Pet and MRA findings in cluster headache and MRA in experimental pain. Neurology 55:1328–1335
19. Hannerz J (1991) Orbital phlebography and signs of inflammation in episodic and chronic cluster headache. Headache 31:540–542
20. Moskowitz MA (1988) Cluster headache: evidence for a pathophysiologic forms in the superior pericarotid cavernous sinus plexus. Headache 28:584–586
21. Schuh-Hofer S, Richter M, Israel H et al (2006) The use of radiolabelled human serum albumin and SPECT/MRI coregistration to study inflammation in the cavernous sinus of cluster headache patients. Cephalalgia 26:1115–1122
22. Ekbom K (1974) Lithium vid kroniska symptom av cluster headache. Med 19:148–156
23. Kudrow L (1977) Lithium prophylaxis for chronic cluster headache. Headache 17:15–18
24. Kudrow L (1980) Cluster headache: mechanisms and management. Oxford University Press
25. Boiardi A, Bussone G, Merati B et al (1983) Course of chronic cluster headache. Ital J Neurol Sci 4:75–78
26. Mellerup ET, Dam N, Wildschidtz G et al (1978) Lithium effect on various diurnal rhythms in manic melancholic patients. In: Johnson FN, Johnson S (eds) Lithium in medical practice. University Parck Press, Baltimore, pp 267–270
27. Samuel D, Gottesfeld Z (1973) Lithium, mania, depression and the chemistry of the brain. Endeavour 32:122–126
28. Friedmantin E, Wang H (1988) Effect of chronic lithium treatment on 5-hydroxytryptamine and release of 5-(BH) Hydroxytryptamine from/rat brain cortical, hippocampal and hypothalamic slices. J Neurochem 50:195–201
29. Kripke DF, Judd LL, Hubbard B et al (1979) The effect of lithium carbonate on the circadian rhythm of sleep in normal human subjects. Biol Psychol 14:545–548
30. Bussone G, Sinatra MG, Boiardi A et al (1986) Brainstem auditory evoked potentials (BAEPs) in cluster headache (CH). New aspects for a central theory. Headache 26:67–69
31. Peselo ED, Dummer DL, Fieve RR et al (1982) Lithium prophylaxis of depression in unipolar, bipolar and cyclothymic patients. Ann J Psych 139:747–752
32. Cooper PE, Martin JB (1991) Neuroendocrinology. In Rosemberg RN (ed.) Comprehensive neurology. Raven Press Ltd, New York, pp 605–609
33. Solomon S (2007) Major therapeutic advances in the past 25 years. Headache 47:S20–S22

34. Bussone G, Leone M, Peccarisi C et al (1990) Double-blind comparison of lithium and verapamil in cluster headache proyphylaxis. Headache 30:411–417
35. Leone M, Franzini A, D'Amico D et al (2004) Long term follow up hypothalamic stimulation to relieve intractable chronic cluster headache. Neurology 62:A355–A356
36. Swann AC, Heninger GR, Marini JL et al (1980) Lithium effects on high-affinity tryptophan uptake evidence against a stabilization mechanism. Brain Res 194:287–292
37. Giannini AJ, Taraszewki R, Loiselle RH (1987) Verapamil and lithium in maintenance therapy of manic patients. J Clin Pharmacol 27:980–982
38. Dubousky SL, Franks RD, Lifshitz M et al (1982) Effectiveness of verapamil in the treatment of a manic patients. Ann J Psych 139:502–504
39. Jonsdottir M, Meyer SS, Roger LR (1987) Efficacy, side effects and tolerance compared during headache treatment with three different calcium blockers. Headache 27:364–369
40. El-Fakahany E, Richelson E (1983) Effect of some calcium antagonists on muscarinic receptor mediated cyclic GMP formation. J Neurochen 40:705–710
41. Taylor JE, Defeudis EU (1984) Inhibition of (3H) spipirone binding to 5HT2 receptors of rat cerebral cortex by the calcium antagonists verapamil and D600. Eur J Pharmacol 106:215–216
42. Maisel AJ, Motulsky HJ, Insel PA (1985) Hypotension after quinidine plus verapamil: possible additive competition at alpha-adrenergic receptors. N Engl J Med. 312:167–170
43. Kavaliers M (1987) Calcium channel blockers inhibit the antagonist effects of Phe-Met-Arg-Pheamide (FMRF-amide) on morphin and stress induced analgesia in mile. Brain Res 415:380–385
44. Hotta I, Kamawaki S, Segawa T (1986) Long-term lithium treatment causes serotonin receptor down-regulation via serotoninergic presynapses in rat brain. Neuropsychobiology 16:19–26
45. Hodge CJ Jr, Apkarian AV, Stevens R et al (1981) Locus coeruleus modulation of dorsal horn unit responses to cutaneous stimulation. Brain Res 204:415–420
46. Basbaum AI, Moss MS, Glazer EJ (1983) Opiate and stimulation produced analgesia: the contribution of monoamines. Adv Pain Res Ther 5:323–339
47. Malick A, Strassman RM, Burstein R (2000) Trigemino hypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. J Neurophysiol 84:2078–2112
48. Saavedra JM, Palkovits M, Brownstein MJ, Axelrod J (1974) Serotonin distribution in the nuclei of the rat hypothalamus and preoptic region. Brain Res 77:157–165
49. Settle M (2000) The hypothalamus. Neonatal Netw 19:9–14
50. Giesler J, Glenn J (1995) Evidence of direct nociceptive projections from the spinal cord to the hypothalamus and telencephalon. Semin Neurosci 7:253–261
51. Milan MJ (1999) The induction of pain: an integrative review. Prog Neurobiol 58:1–164
52. Lumb BM (1990) Hypothalamic influences on viscero-somatic neurones in the lower thoracic spinal cord of the anaesthetizes rat. J Physiol 424:427–444
53. Carstens E (1986) The induction of pain. An integrative review. Prog Neurobiol 57:1–164
54. Miranda-Cardenas Y, Rojas-Piloni G, Martinez-Lorenzana G et al (2006) Oxytocin and electrical stimulation of the paraventricular hypothalamic nucleus produce antinociceptive effects that are reversed by an oxytocin antagonist. Pain 122:182–189
55. Yaksh TL (1999) Central pharmacology of nociceptive processing. In: Wall PD, Melzack R (eds) Textbook of pain. Churchill Livingstone, Edinburgh, pp 253–308
56. May A, Bahra A, Büchel C et al (2000) PET and MRA findings in cluster headache and MRA in experimental pain. Neurology 55:1328–1335
57. Sprenger T, Boecker H, Tolle TR et al (2004) Specific hypothalamic activation during a spontaneous cluster headache attack. Neurology 62:516–517
58. May A, Ashburner J, Büchel C et al (1999) Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med 5:836–838
59. Leone M, Franzini A, Bussone G (2001) Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. N Engl J Med 345:1428–1429
60. Bussone G, Franzini A, Proietti Cecchini A et al (2007) Deep brain stimulation in craniofacial: seven years' experience. Neurol Sci 28:S146–S149

Neurol Sci (2008) 29:S7–S11
DOI 10.1007/s10072-008-0876-7

Migraine and stroke: from a questioned relationship to a supported comorbidity

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Abstract Migraine and stroke are two common and prevalent diseases. The relationship between them is an ongoing, intriguing matter of debate. About 40 years ago, some different reports on this topic raised the question of the existence of a relationship between the two diseases. To date the existence of a comorbidity between migraine and ischaemic stroke is supported by population and clinical series studies. Literature data on this subject are reviewed in this report.

Keywords Migraine · Ischaemic stroke · Comorbidity

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Introduction

The search for a link between migraine and stroke became particularly active over the last decades of the previous century. Through differently designed and aimed published reports [1–4], an intriguing question arose: is there any "*relationship*" between "migraine and stroke"? The ensuing immense body of research on this topic concluded with a broad international agreement on the existence of a "*comorbidity*" between migraine and stroke [5]. In fact, the term comorbidity appeared as the most appropriate to define the complex and heterogeneous interrelation between these two common and prevalent diseases.

However, is the existence of a "migraine and stroke" comorbidity supported to date? To answer this question, the evolution of scientific evidences on the issue will be briefly reviewed in this report.

Methods

The interrelation between migraine and stroke is multifaceted. The existence of stroke syndromes or isolated stroke that may present themselves with clinical features typical of migraine is well known. They are noteworthy for both diagnostic clinical implications and pathophysiologic mechanism suggestions.

When examining the interrelation between migraine and stroke, a main interest is to define if and how a usually benign disease can evolve into a malignant one. In fact, most of the studies in this issue aim to answer the following main questions:

– Can a stroke occur during the course of a migraine attack?
– Can migraine cause a stroke removed in time from the migraine attack?

– In both of the above hypotheses, does migraine act alone or are other factors needed for stroke to occur?

Concerning this issue, we will firstly separate the literature data for *migraine and haemorrhagic stroke* from that on *migraine and ischaemic stroke.*

Migraine and haemorrhagic stroke

A few studies have evaluated the relationship between migraine and haemorrhagic stroke [4, 6–8]. Henrich et al. [4], in 1986, in a community-based study including patients of all ages, found that a history of any type of migraine was not more common in patients with cerebral infarction than in those with primary intracerebral haemorrhage. Two later studies failed to find any association between migraine and haemorrhagic stroke in women [6, 7]; data are lacking in men [8]. So, to date the existence of a relationship between these two entities is unproven [9].

Migraine and ischaemic stroke

Over the last two decades of the previous century, some isolated reports [10, 11] and the Henrich et al. [4] study prompted researchers to look for the existence of a hypothetical relationship between migraine and IS. In reporting the study results, the literature data will separately be reviewed for:

– migrainous infarction
– migraine as a risk factor for stroke.

Migrainous infarction

After some isolated case reports of "complicated migraine" in migraine patients taking propranolol therapy [10, 11], the first systematic case-control study concerning "migraine stroke" was that of Bogousslavsky et al. [12] in 1988. Twenty-two classic migraine patients who developed an ischaemic stroke (IS) during their typical migraine attacks were compared to two control groups: one control group was formed by classic migraine patients with IS occurring remotely from migraine attacks, and the other one by IS patients without migraine. There were 17 females and 5 males (mean age, 32.7 years) in the study group and 22 patients matched for age and sex in each of control groups. The study and control groups appeared to be comparable with regard to the evaluated vascular risk factors, whereas the evaluated potential causes of IS were significantly prevalent in control groups. On the basis of these results the authors suggested that migraine itself was the most likely cause of IS in their study group. Interestingly, a significantly prevalent involvement of the posterior cerebral artery (PCA) territory was detected in the study group.

In that same year, *migrainous infarction* (MI) was proposed by the International Headache Society [13] as a complication of migraine, namely of migraine with aura (MA).

In 1990 Welch and Levine [14] proposed to rename this clinical entity "migraine-induced stroke", thereby stressing the potential role of migraine itself in inducing the cerebral infarction; the proposal is asserted in a recent textbook on headaches [9].

Actually, many features of MI support a probable causal relationship between migraine and IS in this peculiar disease:

– the occurrence of stroke during the course of a typical migraine attack;
– the prevalent localisation of infarction in the PCA territory, in accordance with spreading cortical depression cerebral involvement;
– the absence of all other causes of stroke.

In spite of some reports of cases of MI occurring in migraine without aura (MO) patients [15–17], the ICHD-II classification [18] confirmed MI as a complication of MA alone.

So, to date *a cause-effect relationship* between MA and IS in this pathologic event is supported.

From the above-mentioned and more recent reports [19], the following picture of MI emerges: onset before 45 years, prevalence in females, possible presence of risk factors for stroke (namely cigarette smoking and oral contraceptive (OC) use) and more frequent involvement of the PCA territory.

Migraine as a risk factor for stroke

As mentioned above, when in 1986 Henrich et al. [4] performed a community-based study concerning stroke and migraine, they found that a history of any migraine was no more common in patients with IS than in patients with haemorrhagic stroke; however, a history of classic migraine was somewhat more common in IS patients.

So, the same authors later addressed a search for the existence of a relationship between migraine and IS [20]. Eighty-nine IS cases were matched to 178 control subjects in a hospital-based study using more selective inclusion patient criteria, such as age between 15 and 65 years and diagnosis of classic or common migraine alone; both sexes were included. The study resulted in a positive significant *association* between classic migraine and IS (OR=2.6), but not between common migraine and IS (OR=1.3); 64% of the patients were men.

These data were not confirmed in 1993 by Tzourio et al. [21] in a sample of 212 IS patients, aged 18–80 years, and 212 controls. In fact, these authors failed to find any association between either MA or MO and IS in the whole

sample, but suggested a significant association between these subtypes of migraine and IS in women aged <45.

To verify this, the same authors two years later performed what can be considered a basic study on this issue [22]. The study, mainly designed to investigate the relationship between migraine and IS in women aged <45, showed a strong association between migraine and IS that persisted after adjustment for the main vascular risk factors (adjusted OR=3.5). MA patients were at higher risk (adjusted OR=6.2) than MO patients (adjusted OR=3.0). Current use of OCs and current heavy smoking significantly increased the risk.

Since then, patients aged under 45 have become the focus of most of the following studies dealing with the association between migraine and stroke [6, 23–25]. Overall, the results of these case-control studies have confirmed the existence of a significant positive association between migraine and IS in *young women*, with a trend in favour of *MA*. In fact, the two studies [23, 25] including both sexes showed no significant association between migraine and IS in young men. Recently Scher et al. [26], in a population-based study, found a positive, but not significant, association between migraine and IS also in young men, but only if affected by MA.

Undoubtedly, *young* people appear to be more suitable subjects in which to evaluate a potential relationship between migraine and stroke; therefore many more studies were performed in this subgroup of patients. However, available data in older subjects [21, 27] failed to find any association between migraine and IS in this subgroup of patients.

In this regard, the findings of two large cohort studies [7, 28] in which the *history of migraine* was analysed separately from the *active migraine* are of interest.

The authors, in their large samples of women aged 45 or older, failed to find any association between the history of migraine and IS, whereas a significant association could be seen in patients affected by active MA, and even more if aged <55. Interestingly, in Scher et al.'s [26] study *current migraineurs*, particularly with aura, showed a higher risk profile for cardiovascular diseases compared with non-migraine individuals; moreover, women with MA were more likely to be current users of OCs than women without migraine.

The prevalence of migraine varies by age, declining sharply after the age of 50 [29]; so, to be "*active migraineurs*" is less probable in the older age groups; accordingly, as suggested, the risk of migraine-related IS decreases with age [8, 17, 30], both in men and in women. However, the recent MRI findings suggesting an increased risk of subclinical brain lesions in migraine patients [31, 32] has raised the possibility of migraine-related consequences also in this age group.

Many more studies including only young *females* have been published. Pooled together, the above data consistently show that migraine, particularly with aura, is a *risk factor for IS* in women under 45 years, mainly if they are smokers and OC users.

Why MA in particular is associated to a higher risk for IS is an intriguing, ongoing matter of debate. On this issue, literature data will be summarised.

Migraine with aura and IS risk

Apart from some possibly distinctive pathophysiologic mechanisms of MA, and Scher et al's data [26] data, in the last decade heterogeneous conditions dealing with increased risk for IS have been associated with this subtype of migraine. Those most discussed are patent foramen ovale (PFO) and coagulation abnormalities.

PFO

A large body of scientific evidence showed a strong and consistent association between PFO and MA [33, 34]. The complex and intriguing data concerning this issue are discussed in other reports in this issue.

Coagulation abnormalities

Studies looking for the presence of *haemostatic abnormalities* and *antiphospholipid antibodies* in migraine patients resulted in conflicting data [35]; when they were present, however, the increased thrombotic risk was detected mainly in MA patients [36].

Elevated values of plasma *homocysteine*, an atherogenic host factor for stroke [37], were reported to be associated with MA in two [38, 39] of the few studies [38–40] on this topic; to date these data lack of consistency.

More interesting are the results of the studies aimed at searching for *genetic* coagulation abnormalities in migraine; among these MTHFR C677T and Factor V Leiden (FVL) G1691A polymorphisms were the most frequently investigated. Several case-control [41–44] and population-based [39] studies agreed in showing a positive association between the *MTHFR 677TT* genotype and MA, suggesting this genetic mutation as a *risk factor for MA*.

To date, data to support this mutation as a risk factor *for IS* are lacking [45]; interestingly, a positive association between the mutation and IS has recently been reported in *younger* subjects [46, 47]. Additionally, both studies underlined the role of environmental factors, such as smoking and OCs, which further increase the risk of stroke. How carriers of MTHFR 677TT are supposed to be at increased risk of IS is only speculative to date.

Elevation of plasma homocysteine could be a rational link [48]; Pezzini et al. [44] suggested migraine as another potential "link", particularly in patients with spontaneous cervical artery dissection (sCAD) IS.

Studies concerning the prevalence of *FVL mutation* in migraine resulted in conflicting data [36]. Interestingly, this genetic variant significantly increased the *risk of IS* at a *young* age *when combined with OC use* [47] or the presence of *PFO* [49].

It was recently suggested that the risk of IS, as of migraine, *increases* when *more* unfavourable *polymorphisms combine* their effects [46, 50, 51].

In migraine patients, Lea et al. [51] showed that the interaction between *ACE I/D* and *MTHFR C677T* gene variants increased migraine susceptibility, mainly to *MA*. The ACE I/D polymorphism is another potential candidate for the pathogenesis of IS [45]. In stroke patients, the ACE D/D genotype alone or in combination with the MTHFR 677T allele was found to be highly specific for small deep infarcts [50]. In migraine patients, the ACE D/D genotype was shown to correlate with an increased MO attack frequency [52].

Finally, in recent years another interesting association has been suggested [53, 54], between sCAD and migraine, but mainly without aura.

Discussion and conclusions

The available literature data failed to support the existence of any association between migraine and haemorrhagic stroke, whereas the existence was consistently shown of a *causal association* between *MA* and *IS at a young age* in the *MI* category and of a *positive significant association* between *migraine*, mainly MA, and *IS at a young age*, mainly in females.

Secondary headaches with clinical features of migraine have not been evaluated in this report.

So, ruling out haemorrhagic strokes, and not considering "secondary migraines", noteworthy associations rise between (primary) *migraine and IS at a young age.*

Therefore, what was once a *questioned relationship* between "*migraine and stroke*" is to date a *supported comorbidity* between "*migraine and IS*".

Many questions remain unresolved:

- Is migraine really an "independent" risk factor for (clinical and subclinical) IS?
- Are migraine and IS two separate phenotypic expressions of shared genetic mutations or not?
- Is migraine an intermediate factor between PFO, sCAD or genetic mutations and IS?
- How do these and the other heterogenous conditions discussed above interact with each other and with the pathophysiologic mechanisms of migraine?

In conclusion, the term comorbidity still appears to be the most appropriate to define the complex association between migraine and stroke, but it is supported only for migraine and IS. Whether this comorbidity should now be further restricted to migraine and *IS at a young age* can be questioned [55, 56].

References

1. Collaborative Group for the Study of Stroke in Young Women (1975) Oral contraceptives and stroke in young women. JAMA 231:718–762
2. Hart RG, Miller VT (1983) Cerebral infarction in young adults: a practical approach. Stroke 14:110–114
3. Spaccavento LJ, Solomon GD (1984) Migraine as an etiology of stroke in young adults. Headache 24:19–22
4. Henrich JB, Sandercock PAG, Warlow CP et al (1986) Stroke and migraine in the Oxfordshire Community Stroke Project. J Neurol 233:257–262
5. Merikangas KR, Rasmussen BK (2000) Migraine comorbidity. In: Olesen J, Tfelt-Hansen P, Welch KMA (eds) The headaches, Vol 29, 2nd Edn. Lippincott Williams & Wilkins, Philadelphia, pp 235–240
6. Chang CL, Donaghy M, Poulter N (1999) Migraine and stroke in young women: case-control study. BMJ 318:13–18
7. Kurth T, Slomke MA, Kase CS (2005) Migraine, headache, and the risk of stroke in women: a prospective study. Neurology 64:1020–1026
8. Buring JE, Herbert P, Romero J (1995) Migraine and subsequent risk of stroke in the Physicians' Health Study. Arch Neurol 52:129–134
9. Welch KMA, Bousser MG, Bogouslavsky J (2006) Migrainous infarction and migraine triggered epilepsy. In: Olesen J, Tfelt-Hansen P, Welch KMA (eds) The headaches, Vol 64, 2nd Edn. Lippincott Williams & Wilkins, Philadelphia, pp 599–612
10. Gilbert GJ (1982) An occurrence of complicated migraine during propranolol therapy. Headache 22:81–83
11. Bardwell A, Trott JA (1987) Stroke in migraine as a consequence of propranolol. Headache 27:381–383
12. Bogousslavsky J, Regli F, Van Melle G et al (1988) Migraine stroke. Neurology 38:223–227
13. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8[Suppl 7]:1–96
14. Welch KMA, Levine SR (1990) Migraine-related stroke in the context of the International Headache Society classification of head pain. Arch Neurol 47:458–462
15. Sacquegna T, Andreoli A, Baldrati A et al (1989) Ischemic stroke in young adults: the relevance of migrainous infarction. Cephalalgia 9:255–258
16. Narbone MC, Leggiadro N, La Spina P et al (1996) Migraine stroke: a possible complication of both migraine with and without aura. Headache 36:481–483
17. Milhaud D, Bogousslavsky J, Van Melle G et al (2001) Ischemic stroke and active migraine. Neurology 1805–1811
18. Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd Edn. Cephalalgia 24:1–160
19. Frigerio R, Santoro P, Ferrarese C, Agostoni E (2004) Migrainous cerebral infarction: case reports. Neurol Sci 25[Suppl 3]:S300–S301
20. Henrich JB, Horwitz RI (1989) A controlled study of ischemic stroke risk in migraine patients. J Clin Epidemiol 42:773–780
21. Tzourio C, Iglesias S, Hubert JB et al (1993) Migraine and risk of IS: a case-control study. BMJ 307:289–292
22. Tzourio C, Tehindrazanarivelo A, Iglesias S et al (1995) Case-control study of migraine and risk of IS in young women. BMJ 310:830–833
23. Carolei A, Marini C, De Matteis G (1996) History of migraine and risk of cerebral ischaemia in young adults. Lancet 347:1503–1506
24. Donaghy M, Chang CL, Poulter N (2002) Duration, frequency, recency and type of migraine and the risk of IS in women of childbearing age. J Neurol Neurosurg Psychiatry 73:747–750
25. Schwaag S, Nabavi DG, Frese A et al (2003) The association between migraine and juvenile stroke: a case-control study. Headache 43:90–95
26. Scher AI, Terwindt GM, Picavet HSJ et al (2005) Cardiovascular risk factors and migraine The GEM population-based study. Neurology 64:614–620
27. Mosek A, Marom R, Korczyn AD, Bornstein N (2001) A histo-

ry of migraine is not a risk factor to develop an ischemic stroke in the elderly. Headache 41:399–401
28. Kurth T, Gaziano JM, Cook NR et al (2006) Migraine and risk of cardiovascular disease in women. JAMA 296:283–291
29. Lipton RB, Scher AI, Kolodner K et al (2002) Migraine in the United States. Neurology 58:885–894
30. Merikangas KR, Fenton BT, Cheng SH (1997) Association between migraine and stroke in a large-scale epidemiological study of the United States. Arch Neurol 54:362–368
31. Kruit MC, Van Buchem MA, Hofman PA (2004) Migraine as a risk factor for subclinical brain lesion. JAMA 291:427–434
32. Swartz R, Kern R (2004) Migraine is associated with MRI white matter abnormalities: a meta-analysis. Arch Neurol 61:1366–1368
33. Schwedt TJ, Dodick W (2006) Patent foramen ovale and migraine – bringing closure to the subject. Headache 46:663–671
34. Schoenen J, Burette PH, Materne P (2006) Foramen Ovale Perméable et Migraines: Association fortuite ou relation causale? Rev Med Liege 61:362–368
35. Crassard I, Conard J, Bousser MG (2001) Migraine and haemostasis. Cephalalgia 21:630–636
36. Moschiano F, D'Amico D, Ciusani E et al (2004) Coagulation abnormalities in migraine and ischaemic stroke cerebrovascular disease: a link between migraine and ischaemic stroke? Neurol Sci 25[Suppl 3]:S126–S128
37. Wolf PA (2004) Epidemiology of stroke. In: Mohr JP, Choi DW, Grotta JC et al (eds) Stroke pathophysiology, diagnosis and management, Vol 2. Churchill Livingstone, Philadelphia, pp 13–34
38. D'Amico D, Moschiano F, Attanasio A et al (2003) Hyperhomocysteinemia in patients with migraine with aura. Cephalalgia 23:742
39. Scher AI, Terwindt GM, Verschuren WMM et al (2006) Migraine and MTHFR C677T genotype in a population-based sample. Ann Neurol 59:372–375
40. Hering-Hanit R, Gadoth N, Yavetz A et al (2001) Is blood homocysteine elevated in migraine? Headache 41:779–781
41. Kowa H, Yasui K, Takeshima T et al (2000) The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. Am J Med Genet 96:762–764
42. Oterino A, Valle N, Bravo Y et al (2004) MTHFR T677 homozygosis influences the presence of aura in migraineurs. Cephalalgia 24:491–494
43. Lea RA, Ovcaric M, Sundholm J et al (2004) The methylenetetrahydrofolate reductase gene variant C677T influences susceptibility to migraine with aura. BMC Med 2:3
44. Pezzini A, Grassi M, Del Zotto E et al (2007) Migraine mediates the influence of C677T MTHFR genotypes on ischemic stroke risk with a stroke-subtype effect. Stroke 38:3145–3151
45. Brey RL, Coull B (2004) Coagulation abnormalities in stroke. In: Mohr JP, Choi DW, Grotta JC (eds) Stroke pathophysiology, diagnosis, and management, Vol 34. Churchill Livingstone, Philadelphia, pp 707–724
46. Pezzini A, Grassi M, Del Zotto E et al (2005) Cumulative effect of predisposing genotypes and their interaction with modifiable factors on the risk of ischemic stroke in young adults. Stroke 36:533–539
47. Slooter AJC, Rosendaal FR, Tanis BC et al (2005) Prothrombotic conditions, oral contraceptives, and the risk of ischemic stroke. J Thromb Haemost 3:1213–1217
48. Casas PJ, Bautista LE, Smeeth L et al (2005) Homocysteine and stroke: evidence on a causal link from mendelian randomization. Lancet 365:224–232
49. Botto N, Spadoni I, Giusti S et al (2007) Prothrombotic mutations as risk factors for cryptogenic ischemic cerebrovascular events in young subjects with patent foramen ovale. Stroke 38:2070–2073
50. Szolnoki Z, Somogyvàri F, Kondacs A et al (2002) Evaluation of the interactions of common genetic mutations in stroke subtypes. J Neurol 249:1391–1397
51. Lea RA, Ovcaric M, Sundholm J et al (2005) Genetic variants of angiotensin converting enzyme and methylenetetrahydrofolate reductase may act in combination to increase migraine susceptibility. Molecular Brain Res 136:112–117
52. Paterna S, Di Pasquale P, D'Angelo A et al (2000) Angiotensin-converting enzyme gene deletion polymorphism determines an increase in frequency of migraine attacks in patients suffering from migraine without aura. Eur Neurol 43:133–136
53. Tzourio C, Benslamia L, Guillon B et al (2002) Migraine and the risk of cervical artery dissection: a case-control study. Neurology 59:435–437
54. Pezzini A, Granella F, Grassi M et al (2005) History of migraine and the risk of spontaneous cervical artery dissection. Cephalalgia 25:575–580
55. Klerman GL (1990) Approaches to the phenomena of comorbidity. In: Maser JD, Cloninger CR (eds) Comorbidity of mood and anxiety disorders. American Psychiatric Press, Washington DC, pp 13–40
56. Burke JD, Wittchen HU, Reiger DA et al (1990) Extracting information from diagnostic interviews on concurrence of symptoms of anxiety and depression. In: Maser JD, Cloninger CR (eds) Comorbidity of mood and anxiety disorders. American Psychiatric Press, Washington DC, pp 649–667

Neurol Sci (2008) 29:S12–S14
DOI 10.1007/s10072-008-0877-6

Migraine and stroke: the role of oral contraceptives

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Abstract The use of oral contraceptives (OCs) confers an increased risk for ischaemic stroke (IS). This risk slightly decreases, but remains significant, if low-dose formulations are used, particularly if other risk factors, such as hypertension or smoking, are associated. Some inherited prothrombotic conditions (e.g., Factor V Leiden, G20210A prothrombin or methylenetetrahydrofolate reductase C677T polymorphism) could also greatly increase the IS risk if present in OC users. Migraine, particularly with aura, is an independent risk factor for IS, and the patient's IS risk is probably affected by other individual risk factors (e.g., age, genetic predisposition to thrombosis, presence of patent foramen ovale or enhanced platelet aggregation) which seem to be over-represented in migraine patients. IS risk among migraineurs is further increased when OCs are currently used and can become very high if associated with smoking. Consequently, in 2004 the WHO stated in its 'Medical Eligibility Criteria for Contraceptive Use' that women suffering from migraine with aura at any age should never use OCs. Moreover, since the exposure to the effects of OCs may greatly increase the IS risk in some migraine subpopulations with specific personal characteristic, testing for these risk factors may allow for more accurate stratification of the population at risk before long-term use of OCs is prescribed.

Keywords Migraine · Oral contraceptives · Stroke

Introduction

The potential thrombotic risk of combined oral contraceptives (OCs) appears to be strictly related to their hormonal dosage. Consequently, the ethinylestradiol (EE) content has been progressively decreased from 100 μg in the earliest formulations to 15 μg in the last ones. Three meta-analyses [1–3] reported an increased summary risk for ischaemic stroke (IS) in current users of all OC formulations, ranging from 2.12 (95% CI 1.56–2.86) to 2.75 (CI 2.24–3.38). The use of low-dose OCs (≤50 μg EE) was associated with a less elevated IS risk, ranging from 1.79 (CI 1.39–2.30) to 2.08 (CI 1.55–2.80).

The progestogen types gestodene and desogestrel have been associated with a less elevated IS risk [1, 3] as compared to levonorgestrel or norethisterone. In any case, stratification by type of OC has revealed a similarly increased OR for both oestrogen dosages (≥50 μg and <50 μg EE), and for both generations of progestins [2].

Acquired risk factors

An increased risk of cardiovascular events is associated with the presence of hypertension, known hyperlipidaemias, or smoking in OC users. Accordingly, these conditions are now considered contraindications to the use of OCs, particularly in women over the age of 35 and obese [4]. The association of hypertension or smoking confers a 2–3 fold increased IS risk in women who use OCs [3].

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Inherited risk factors

Some studies found that FV Leiden (FVL), prothrombin (PT) G20210A and methylenetetrahydrofolate reductase (MTHFR) 677TT polymorphisms may be risk factors for stroke; on the contrary, other Authors did not consider any of these conditions to be associated with an increased risk of IS.

It is probable that common unfavourable genetic factors can greatly increase the susceptibility to IS when associated with clinical risk factors. For example, current smokers carrying FVL show an increased IS risk when compared with non-smoking non-carrier subjects (OR 6.3; CI: 1.3–31.1) [5].

In OC users, compared with non-OC users, the presence of an inherited prothrombotic background (at least one of the polymorphisms FVL, G20210A PT or C677T MTHFR, with a synergistic effect) conferred an IS risk of 22.8 (CI 4.46–116) [6]. In particular, carriers of FVL and carriers of the MTHFR 677TT polymorphism had an IS risk of 11.2 (CI 4.3–29.0) and 5.4 (CI 2.4–12.00) respectively [5].

OCs and IS risk in women with migraine

Migraine is an independent risk factor for IS (Fig. 1) [7–13]; this is particularly true for women suffering from migraine with aura (MA). Moreover, the IS risk in women with migraine is probably affected by other individual risk factors, such as age, genetic predisposition to thrombosis, presence of patent foramen ovale (PFO) or enhanced platelet aggregation.

Three studies [14–16] found a higher prevalence of FVL in MA patients compared to healthy controls; nevertheless, only one [15] found a significant association. The MTHFR 677TT and 1298CC genotypes are over-represented in migraine patients compared to controls [17]. This datum is still being debated: the incidence of the 677TT genotype for migraine in general (12%), for MA (9%) and for migraine without aura (MO) (18%) did not significantly differ from controls (13%). However, the difference was significant when the TT frequency in MA and in MO aura was compared [18]. Moreover, among Caucasians, stratification by migraine subtype indicates that the association between C677T variant and migraine is attributed specifically to MA [19].

Over the last decade, PFO has been identified as an independent risk factor for cerebral infarcts, particularly in young adults with cryptogenic stroke [20]. Recently, migraine was significantly associated to PFO in comparison to controls. At least 50% of MA sufferers presented a PFO, and the shunts were larger in migraineurs than in controls [21]. The association between MA and PFO brings an increased risk of brain infarction (OR 4.72; CI 1.87–11.94)

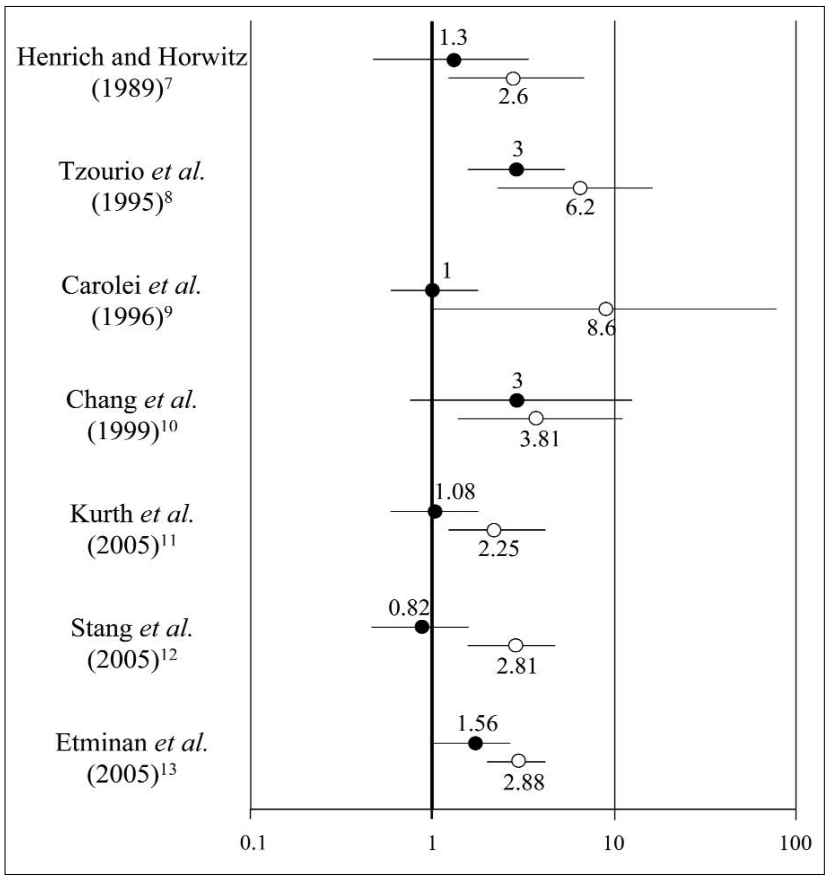

Fig. 1 Risk of IS in women with migraine with aura (*white circle*) and without aura (*black circle*)

[22]. Moreover, the presence of FVL or PT G20210A mutations is an independent risk factor for cryptogenic stroke in adults with PFO compared to healthy controls, with ORs ranging from 4.5 [23] to 14.0 [22].

IS risk among migraineurs is increased even further when OCs are currently used (RR 8.72; CI 5.05–15.05) [13], and can become very high when associated with cigarette smoking [10]. Since MA patients have a higher IS risk than MO patients, and the frequency and recency of auras might further influence their risk when using OCs, in 2004 the WHO stated in its 'Medical Eligibility Criteria for Contraceptive Use' that women suffering from MA at any age should never use OCs [4].

In conclusion, the exposure to the effects of OCs may greatly increase IS risk in migraine subpopulations with specific personal characteristics, e.g., patients showing inherited prothrombotic mutations and right-to-left cardiac shunts. Testing for these risk factors may allow for more accurate stratification of the population at risk before long-term use of OCs is prescribed.

However, IS is fortunately very rare in women of reproductive age: all the ORs should be interpreted in the context of the absolute risk.

References

1. Gillum LA, Mamidipudi SK, Johnston SC (2000) Ischemic stroke risk with oral contraceptives: a meta-analysis. JAMA 284:72–78
2. Chan WS, Ray J, Wai EK et al (2004) Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. Arch Intern Med 164:741–747
3. Baillargeon JP, McClish DK, Essah PA et al (2005) Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. J Clin Endocrinol Metab 90:3863–3870
4. World Health Organization (2004) Improving access to quality care in family planning: medical eligibility criteria for contraceptive use, 3rd Edn. World Health Organization, Geneva
5. Slooter AJ, Rosendaal FR, Tanis BC et al (2005) Prothrombotic conditions, oral contraceptives, and the risk of ischemic stroke. J Thromb Haemost 3:1213–1217
6. Pezzini A, Grassi M, Iacoviello L et al (2007) Inherited thrombophilia and stratification of ischaemic stroke risk among users of oral contraceptives. J Neurol Neurosurg Psychiatry 78:271–276
7. Henrich JB, Horwitz LA (1989) A controlled study of ischemic stroke risk in migraine patient. J Clin Epidemiol 42:733–780
8. Tzourio C, Tehindrazanarivelo A, Iglésias S et al (1995) Case-control study of migraine and risk of ischaemic stroke in young women. BMJ 310:830–833
9. Carolei A, Marini C, De Matteis G (1996) History of migraine and risk of cerebral ischemia in young adults. The Italian National Research Council Study Group on Stroke in the Young. Lancet 347:1503–1506
10. Chang C, Donaghy M, Poulter N et al (1999) Migraine and stroke in young women: case-control study. BMJ 318:13–18
11. Kurth T, Slomke MA, Kase CS et al (2005) Migraine, headache, and the risk of stroke in women: a prospective study. Neurology 64:1020–1026
12. Stang PE, Carson AP, Rose KM et al (2005) Headache, cerebrovascular symptoms and stroke: the Atherosclerosis Risk in Communities Study. Neurology 64:1573–1577
13. Etminan M, Takkouche B, Isorna FC et al (2005) Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. BMJ 330:63–65
14. Corral J, Iniesta JA, González-Conejero R et al (1998) Migraine and prothrombotic genetic risk factors. Cephalalgia 18:257–260
15. D'Amico D, Moschiano F, Leone M et al (1998) Genetic abnormalities of the protein C system: shared risk factors in young adults with migraine with aura and with ischemic stroke? Cephalalgia 18:618–621
16. Intiso D, Crociani P, Fogli D et al (2002) Occurrence of factor V Leiden mutation (Arg506Gln) and anticardiolipin antibodies in migraine patients. Neurol Sci 22:455–458
17. Kara I, Sazci A, Ergul E et al (2003) Association of the C677T and A1298C polymorphisms in the 5,10 methylenetetrahydrofolate reductase gene in patients with migraine risk. Brain Res Mol Brain Res 111:84–90
18. Oterino A, Valle N, Bravo Y et al (2004) MTHFR T677 homozygosis influences the presence of aura in migraineurs. Cephalalgia 24:491–494
19. Lea RA, Ovcaric M, Sundholm J et al (2004) The methylenetetrahydrofolate reductase gene variant C677T influences susceptibility to migraine with aura. BMC Med 2:3
20. Pezzini A, Del Zotto E, Magoni M et al (2003) Inherited thrombophilic disorders in young adults with ischemic stroke and patent foramen ovale. Stroke 34:28–33
21. Anzola GP, Meneghetti G, Zanferrari C et al (2008) Is migraine associated with right-to-left shunt a separate disease? Result of the SAM study. Cephalalgia 28:360–366
22. Karttunen V, Hiltunen L, Rasi V et al (2003) Factor V Leiden and prothrombin gene mutation may predispose to paradoxical embolism in subjects with patent foramen ovale. Blood Coagul Fibrinolysis 14:261–268
23. Botto N, Spadoni I, Giusti S et al (2007) Prothrombotic mutations as risk factors for cryptogenic ischemic cerebrovascular events in young subjects with patent foramen ovale. Stroke 38:2070–2073

Neurol Sci (2008) 29:S15–S18
DOI 10.1007/s10072-008-0878-5

The patent foramen ovale–migraine connection: a new perspective to demonstrate a causal relation

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Abstract In the last ten years a considerable bulk of evidence has accumulated on the relationship between migraine, particularly migraine with aura, and atrial septal defects, particularly patent foramen ovale (PFO). The increased frequency of PFO in migraine with aura, which almost parallels that found in stroke of unknown cause, the fact that in migraine patients PFO tends to be larger than in non-migraine controls and some positive results on migraine severity obtained after PFO closure have spurred speculation on a possible causal relationship. By applying the criteria proposed by Bradford-Hill to establish causality between associated phenomena, we try to demonstrate that PFO is not just a further example of migraine comorbidity but exerts a causal effect at least in the triggering of aura.

Keywords Migraine · Patent foramen ovale · Transcranial Doppler · Causation

Financial Disclosures: G.P. Anzola received honoraria for consultation and lecturing from St Jude Medical and from Cardia. S. Mazzucco: none.

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Foramen ovale is an anatomical structure allowing physiologic right-to-left shunt (RLS) during foetal circulation. In over 70% of the general population, it comes to closure after birth. In the remaining 30% of cases, such communication is left "patent", i.e., "open", and represents a potential substrate for RLS during adult life [1]. Given its high prevalence in the general population, patent foramen ovale (PFO) cannot be considered a pathology itself. Nevertheless, a consistent body of epidemiological evidence has been suggesting a causal relationship between PFO and those strokes where an evident cause cannot be found, particularly in the young population [2]. In this subset of patients, a PFO is found in more than half of cases. Stroke clearly is a pathological condition and secondary prevention has to be pursued by every means, particularly in younger patients. So, there is little doubt that a PFO has to be searched for in young patients with a stroke of unknown origin [2]. But what about the PFO–migraine relation? Indeed, a PFO is as prevalent in migraineurs with aura as in stroke patients of less than 55 years [3, 4]. However, both migraine and PFO are common conditions and it is possible their association is no more than chance. Moreover, migraine is not commonly considered a threat as much as stroke is. Therefore, there is no current indication to screen migraineurs for a PFO. But if a causal link between migraine and PFO was demonstrated, would it change our way of looking at migraine?

In 1965, Sir Austin Bradford-Hill proposed, in a seminal paper [5], his well known criteria on the concept of causation: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy. Such criteria can be advocated to demonstrate that the PFO–migraine connection goes far beyond the simple association by chance of two common conditions.

Strength and consistency

The first two criteria of Bradford-Hill stipulate that to establish a causal relationship between two variables, their association must be strong and consistent across studies. Compared with non-migraineurs or migraineurs without aura, patients with migraine with aura have been invariably shown to have a RLS in about half the cases, with quite narrow confidence limits, the figures ranging from about 40% to about 60% [3, 4, 6–9]. It is perhaps worth noticing that the migraine–PFO association is of the same order of magnitude as that between stroke and hypertension or hypercholesterolaemia and far greater than that between stroke and diabetes [10].

Specificity

What is specifically associated with migraine with aura is not so much the PFO but rather the RLS caused by PFO, as is confirmed by the high prevalence of migraine found in RLS caused by other conditions such as pulmonary arteriovenous malformations (PAMVs). A number of studies demonstrated a significant association between migraine and hereditary haemorrhagic telangiectasia-associated PAMVs [11, 12]. The strongest case for specificity is given by the fact that the association is limited to migraine with aura and does not include migraine without aura or tension headache [4, 7, 9].

Temporality

Little is known on the genetic and biological bases of migraine, and it cannot be excluded that PFO and migraine could be manifestations of a common underlying condition, like endothelial dysfunction [13]. PFO is a physiological condition present well before birth and hence precedes any clinical migraine attack occurring during life.

Biological gradient

The rule of biological gradient implies that an increment in the load of the putative causative agent increases the likelihood of the appearance of the phenomenon under study. Schwerzmann and colleagues [15] have shown by means of transoesophageal echocardiography (TEE) that large shunts are nine times more frequent in migraine patients than in controls. By using transcranial Doppler, which allows a more quantitative measure of the amount of shunted blood delivered to the brain vessels, Anzola and colleagues were able to demonstrate, in a large cohort of more than 400 patients, that the shunt entity follows a gradient of increasing burden from controls to migraine without aura up to migraine with aura and that patients with both migraine and previous stroke have, on average, the largest shunt [16] (Table 1).

Plausibility

It may therefore be plausible to hypothesise that: as PFO is associated with cryptogenic stroke [1, 2], and migraine increases the risk of stroke [16, 17], the underlying mechanism linking stroke and migraine is represented by the increased propensity of migraineurs to develop a paradoxical brain embolism because of a PFO. Wilmshurst and colleagues specifically addressed this issue in a recently published study that assessed the prevalence of clinically relevant atrial shunts in patients with past stroke, in patients with migraine, in patients with both conditions and in healthy controls [19]. The results showed, in line with the findings of Anzola et al., that patients with migraine and stroke had the highest likelihood of exhibiting a clinically relevant shunt, which led the Authors to conclude that "…the increased incidence of stroke in subjects with migraine compared with the general population is because they have a higher prevalence of large atrial shunts and hence an increased risk for paradoxical embolism" [18].

Experimental evidence

The evidence provided by studies reporting the effect of percutaneous PFO and PAVM [19] closure on migraine is quite consistent in suggesting a possible benefit. This applies not only to the oldest, retrospective studies [14, 20–27], but also to the only published prospective case-control study [28] and to the recently published prospec-

Table 1 Age and shunt degree according to cerebrovascular disease (CVD) and migraine condition

	No migraine		Migraine	
	CVD–	CVD+	CVD–	CVD+
n	100	85	139	96
Sex, M/F	40/60	38/47	21/118	18/78
Age, mean±SD	48±17	55±14	36±14	42±11
Mean bubble count (SE)	38 (5)	55 (8)	72 (8)	123 (24)

tive randomised MIST study [29]. The latter failed to demonstrate a significant resolution of migraine in the interventional arm when compared to the sham one. Nevertheless, when the 50% reduction in the number of affected days was considered as a post hoc outcome measure, a significant difference between groups favoured the interventional arm. However, results from both retrospective and prospective studies are in a sense contradictory, given the reported proportion of patients with migraine worsening or occurring *de novo* after PFO percutaneous closure. For these reasons, further studies are clearly needed to confirm and possibly extend these findings and to assess the durability of the effects.

Analogy and coherence

In analogy to the presumed mechanism underlying PFO mediated strokes, it seems reasonable to hypothesise that migraine with aura may be triggered by substances that have escaped the pulmonary clearance, be these platelets or other chemicals. The facilitating effect might occur either through the induction of ischaemia or by direct stimulation of migraine-generating centres. This theory could account even for the mentioned migraine worsening in a proportion of stroke patients who underwent PFO occlusion. The good therapeutical response to clopidogrel in such patients supports the biological plausibility of this hypothesis in that platelet activation could occur on the left atrial disc of an occlusive device [30]. The general theory of the venous to arterial bypass could hold also for patients without PFO when the concentration of migraine-provoking substances in the venous circulation overwhelms the filtering capacity of the lungs [31]. Although admittedly speculative as a general theory, it is nonetheless to be acknowledged that the bubble test with TCD, which replicates the presumed native mechanism, is able to trigger a typical attack of migraine with aura in a small proportion of patients.

Summary

Migraine with aura tends to co-segregate with PFO; PFO in migraine sufferers is larger than in non-migraineurs; the association with PFO could be the main determinant of the increased risk of stroke of female migraineurs; in shunt-associated migraine (SAM), RLS may be a trigger for aura; and closing PFO in SAM may provide a relief (how clinically relevant and how long sustained are presently unknown).

We conclude, based on the Bradford-Hill criteria, that there is a causal relationship between the RLS due to a PFO and migraine, in the "migraine–PFO connection".

Thus, should migraineurs be screened for the presence of a PFO? The answer should be "yes" if we intend to offer migraineurs with a PFO a different treatment compared to non-PFO patients, whether it be by medical means (antiplatelets) or surgical treatment. That would be plausible in two cases: (1) as an extreme attempt to attenuate migraine when refractory to adequate therapy and (2) to reduce the excessive risk of stroke in migraineurs. The validity of both points is to be demonstrated by appropriate studies. We hope that commercial interests will not prevail over scientific and clinical ones, and that research will make its way unhindered to answer both.

References

1. Kizer JR, Devereux RB (2005) Patent foramen ovale in young adults with unexplained stroke. N Engl J Med 353:2361–2372
2. Overell JR, Bone I, Lees KR (2000) Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology 55:1172–1179
3. Del Sette M, Angeli S, Leandri M et al (1998) Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis 8:327–330
4. Anzola GP, Magoni M, Guindani M et al (1999) Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. Neurology 52:1622–1625
5. Bradford-Hill A (1965) The environment and disease: association or causation? Proc R Soc Med 58:295–300
6. Schwerzmann M, Wiher S, Nedeltchev K et al (2004) Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. Neurology 62:1399–1402
7. Domitrz I, Mieszkowski J, Kwiecinski H (2004) The prevalence of patent foramen ovale in patients with migraine. Neurol Neurochir Pol 38:89–92
8. Dalla Volta G, Guindani M, Zavarise P et al (2005) Prevalence of patent foramen ovale in a large series of patients with migraine with aura, migraine without aura and cluster headache, and relationship with clinical phenotype. J Headache Pain 6:328–330
9. Knopf WD (2006) Innovation in intervention summit. J Am Coll Cardiol 47:9–12
11. Schulz UG, Rothwell PM (2003) Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. Stroke 34:2050–2059
12. Post MC, Letteboer TG, Mager JJ et al (2005) A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 128:2485–2489
13. Thenganatt J, Schneiderman J, Hyland RH et al (2006) Migraines linked to intrapulmonary right-to-left shunt. Headache 46:439–443
14. Schwedt TJ, Dodick DW (2006) Patent foramen ovale and migraine- bringing closure to the subject. Headache 46:663–671
15. Schwerzmann M, Nedeltchev K, Lagger F et al (2005) Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. Neurology 62:1399–1401
16. Anzola GP, Morandi E, Casilli F, Onorato E (2006) Different degrees of right-to-left shunting predict migraine and stroke: data from 420 patients. Neurology 66:765–767
17. Etminan M, Takkouche B, Caamaño Isorna F, Samii A (2005) Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. BMJ 330:63
18. Kruit MC, van Buchem MA, Hofman PA et al (2004) Migraine as a risk factor for subclinical brain lesions. JAMA 291:427–434

19. Wilmshurst P, Nightingale S, Pearson M et al (2006) Relation of atrial shunts to migraine in patients with ischemic stroke and peripheral emboli. Am J Cardiol 98:831–833
20. Post MC, Thijs V, Schonewille WJ et al (2006) Embolization of pulmonary arteriovenous malformations and decrease in prevalence of migraine. Neurology 66:202–205
21. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL (2000) Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. Lancet 356:1648–1651
22. Morandi E, Anzola GP, Angeli S et al (2003) Transcatheter closure of patent foramen ovale: a new migraine treatment? J Interv Cardiol 16:39–42
23. Post MC, Thijs V, Herroelen L, Budts WI (2004) Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine. Neurology 62:1439–1440
24. Azarbal B, Tobis J, Suh W et al (2005) Association of interatrial shunts and migraine headaches: impact of transcatheter closure. J Am Coll Cardiol 45:489–492
25. Reisman M, Christofferson RD, Jesurum J et al (2005) Migraine headache relief after transcatheter closure of patent foramen ovale. J Am Coll Cardiol 45:493–495
26. Giardini A, Donti A, Formigari R et al (2006) Transcatheter patent foramen ovale closure mitigates aura migraine headaches abolishing spontaneous right-to-left shunting. Am Heart J 151:922
27. Kimmelstiel C, Gange C, Thaler D (2007) Is patent foramen ovale closure effective in reducing migraine symptoms? A controlled study. Catheter Cardiovasc Interv 69:740–746
28. Anzola GP, Frisoni GB, Morandi E et al (2006) Shunt-associated migraine responds favourably to atrial septal repair: a case-control study. Stroke 37:430–434
29. Dowson A, Mullen MJ, Peatfield R et al (2008) Migraine Intervention With STARFlex Technology (MIST) Trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 117:1397–1404
30. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL (2005) Clopidogrel reduces migraine with aura after transcatheter closure of persistent foramen ovale and atrial septal defects. Heart 91:1173–1175
31. Wilmshurst P, Nightingale S (2006) The role of cardiac and pulmonary pathology in migraine: a hypothesis. Headache 46:429–434

Neurol Sci (2008) 29:S19–S22
DOI 10.1007/s10072-008-0879-4

The diagnostic iter of patent foramen ovale in migraine patients: an update

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Abstract Patent foramen ovale (PFO) is a frequent finding in migraine patients. The standard technique for PFO diagnosis is actually trans-oesophageal echocardiography (TEE). It requires the injection of a contrast agent unable to pass the pulmonary filter; hence, it is possible to detect a right-to-left shunt by observing the presence of the contrast medium in the cardiac left compartment. The transcranial Doppler (TCD) device accurately measures the blood flow velocities in different cerebral arteries. It can record microembolic signals (MES) backscattered by microbubbles travelling in the cerebral circulation, and distinguish cardiac shunts from pulmonary shunts. The number of MES is correlated to the entity of the shunt. The near-infrared spectroscopy (NIRS) technique tracks the changes in the concentration of oxygenated and reduced haemoglobin in the brain tissue. PFO is revealed by an alteration of the normal vasoreactivity pattern of the subject during functional stimuli. Magnetic resonance imaging (MRI) provides, at the same time, detailed anatomical information and functional measurements. MRI dynamic perfusion sequences can be used to reliably detect PFO either by visual assessment or by signal-time curves in the pulmonary artery and in the left atrium. A good correlation between TEE and MRI grading scores has been demonstrated, even though the interindividual variability of performing the Valsalva manoeuvre could greatly reduce the sensitivity of the method. Further prospective studies are needed to confirm the PFO MRI grading and to assess the sensitivity and specificity of the method.

Keywords Magnetic resonance imaging · Migraine · Near-infrared spectroscopy · Patent foramen ovale · Transcranial Doppler

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Introduction

In recent years, there has been growing interest in investigating the association between atrial septal abnormalities and migraine [1]. Patent foramen ovale (PFO) in particular is a frequent finding in subjects affected by severe cerebrovascular diseases [2]. Attention to PFO was initially caused by the increased number of clinical events in scuba divers with an atrial right-to-left shunt (RLS) [3]; then by the high rate of PFO found in young people affected by cryptogenic stroke [4].

Whether PFO constitutes a risk factor for cardiovascular or cerebrovascular pathologies is still an open clinical question, given the wide diffusion of such defects in the normal population.

The standard technique for PFO diagnosis was initially trans-thoracic echocardiography and then trans-oesophageal echocardiography (TEE). Both techniques require the injection of a contrast agent (an agitated mix of saline solution, blood and air) unable to pass the pulmonary filter; hence, it is possible to detect a RLS by observing the presence of the contrast medium in the cardiac left compartment. The severity of the shunt is defined on the basis of two parameters: (i) the number of microbubbles travelling across the RLS and (ii) the presence of a spontaneous shunt vs. a latent shunt, i.e., a shunt that opens only after a Valsalva manoeuvre (VM). If the presence of a spontaneous shunt is an objective datum, often the quantification of the number of bubbles passing through the shunt is not possible. In the literature, there is no agreement about the number of bubbles that are required to deem a shunt "dangerous", even though several studies considered a shunt as "large" if 20 or more microbubbles passed it [5]. Moreover, TEE is not suitable for repeated follow-up of a patient who has undergone percutaneous closure of the PFO due to its intrinsic invasivity. Critical elements of the TEE techniques are the specific positioning of the probe and the difficulty in acquiring a clear and high-resolution image due to motion artefacts and displacements induced by the execution of the VM.

The clinical interest in embolic events involves the neurologist too: embolism may cause not only acute events, but also an ischaemic suffering that could be responsible for the onset of mild cognitive impairment syndrome. This interest, together with the need for minimally invasive diagnostic techniques, led to the development of new methodologies to assess possible PFOs. On one hand, the attention was shifted to the repercussions on the brain, due to the severity of the damages it could suffer as a consequence of embolism. On the other hand, research moved towards techniques that could provide a better anatomical description of the interatrial septum and a more reliable quantification of the shunt entity.

In the following, we report supporting techniques for the assessment of PFO and provide a thorough discussion about their merits and limitations.

Transcranial Doppler

The transcranial Doppler (TCD) device is a low-cost ultrasound instrumentation that accurately measures the blood flow velocities in different cerebral arteries. It can be easily transported, is suitable for bedside monitoring and is highly tolerated by patients.

By injecting in a vein a mixed solution of saline, blood and air, the TCD can record microembolic signals (MES) backscattered by microbubbles travelling in the cerebral circulation. Today, MES originated by microbubbles can be distinguished from artefacts on the basis of an accurate power analysis of the Doppler signals; also, it is possible to distinguish cardiac shunts from pulmonary shunts and from emboli generated by deep venous thrombosis by analysing the time elapsed from the injection of the contrast agent to the arrival of the MES. Modern devices consider a valid indicator of atrial RLS the occurrence of MES within 6 s after the contrast injection. MES can be present immediately after the contrast injection (in this case the shunt is considered permanent) or they can appear only after a VM (in this case the shunt is considered latent and our clinical experience suggests VM should be repeated twice, after another contrast injection). The number of MES is correlated to the entity of the shunt. If the shunt generates few MES it is possible to count them and give an indication of "presence" when the count passes 20 MES. In some conditions, the TCD pattern is characterised by a "curtain" or "shower" appearance that precludes an accurate count of MES, but this pattern is obviously correlated to the presence of a shunt.

Qualifying elements of the TCD are: the possibility of assessing the patient in a quiet and comfortable situation; the need for a preventive instruction of the patient on the manoeuvre he/she should perform; the probe positioning, that is relatively easy and repeatable; the possibility of documenting the blood flow velocity in relation to the phases of the cardiac cycle; the possibility of monitoring MES signals not only by insonating the middle cerebral arteries, but also the vertebrobasilar district [6].

TCD allows a standard indication for what concerns signal intensity and time, but it remains a semi-quantitative technique when used to estimate the shunt entity.

Near-infrared spectroscopy

The near-infrared spectroscopy (NIRS) technique is able to track the changes in the concentration of oxygenated and reduced haemoglobin in the brain tissue. PFO is revealed by an alteration of the normal vasoreactivity pattern of the subject during functional stimuli [7], as reported in Figure 1.

It is a low-cost methodology that is suitable for bedside assessment and does not require the injection of any contrast agent. Its use was stimulated by the work of Karttunen et al. [8] on ear oximetry. In fact, NIRS is the only technique that can track the ratio between O_2 and CO_2 in the cortical tissues with a high temporal resolution, even in response to quick and abrupt transients. NIRS remains a semi-quantitative technique, as it is not possible to measure the absolute concentration of the two kinds of haemoglobin, but only the relative concentration.

We used NIRS with a functional activation given by breath holding. A previous study revealed that NIRS is useful in evidencing the alterations of cerebral vasoreactivity of migraineurs with respect to normal subjects [9]. In

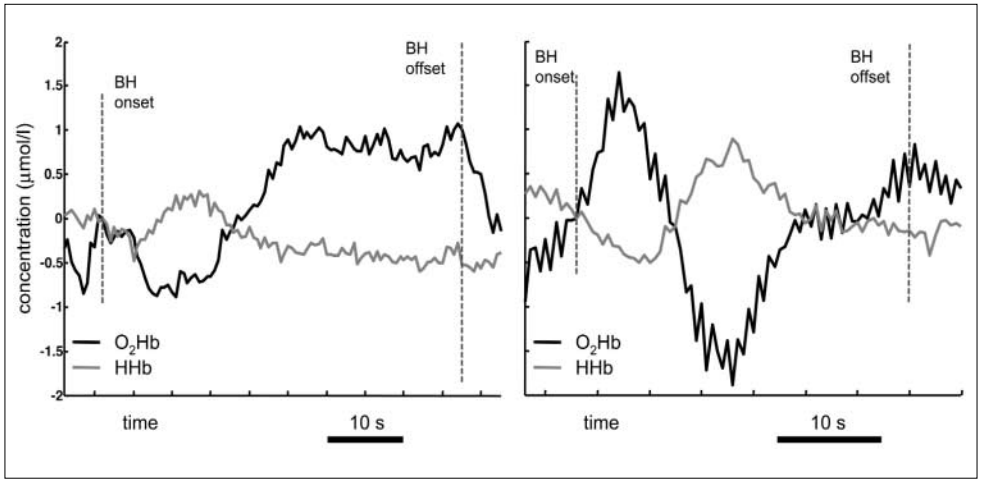

Fig. 1 Time course of the oxygenated (*O_2Hb*) and deoxygenated (*HHb*) haemoglobin during breath holding (*BH*) recorded on migraineurs with aura. *Left panel* is relative to a subject without PFO. *Right panel* is relative to a subject with PFO. O_2Hb is depicted in *black*, HHb in *grey*. Vertical dashed lines represent BH onset and offset. The subject without PFO shows a vasoreactivity characterised by an abrupt increase of the O_2Hb and a constant level of the HHb. The vasoreactivity of the subject with PFO has a precocious O_2Hb increase and a mixture of the haemoglobin types

the presence of a RLS, the behaviour of the NIRS patterns was not easy to detect as the physiological response given by subjects with a permanent shunt was different from that of subjects with a latent shunt. The use of NIRS revealed possible damage in the autoregulation mechanism, as it evidenced the persistence of an increased CO_2 concentration at cortical level during the compensatory vasodilation. This condition could potentially trigger a migraine attack.

Hence, despite all its limitations, NIRS could be useful also for monitoring of patients who have undergone percutaneous closure of the PFO, whose CO_2 level and vasoreactivity patterns could be accurately analysed and correlated to eventual remaining symptoms.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is currently considered one of the most powerful diagnostic techniques in the cardiovascular field. It is capable of providing detailed anatomical information and functional measurements simultaneously. Furthermore, it is a noninvasive technique that avoids the use of potentially harmful ionising radiation. When needed, non-nephrotoxic contrast agents may be administered to increase sensitivity and specificity of the acquired images. MRI has been proposed as an alternative method for the diagnosis of PFO, combining anatomic information with the detection of a RLS [10, 11].

However, when a PFO is suspected, it could be very difficult to detect a measurable shunt, also during the VM. Mohor and coworkers have proposed the use of MRI dynamic perfusion sequences to reliably detect PFO either by visual assessment or by signal-time curves in the pulmonary artery and in the left atrium [12]. They have also demonstrated a good correlation between TEE and MRI grading scores, even though the interindividual variability of performing VM could greatly reduce sensitivity of the method [13]. However, MRI is the best method to noninvasively visualise atrial septal aneurysms [12].

Further prospective studies are needed to support these findings, to confirm the PFO MRI grading and to assess the sensitivity and specificity of the method. Finally, Grebe and coworkers have demonstrated that MRI can accurately depict the anatomy of the interatrial septum after percutaneous closure of the defect, despite the presence of the occluding device [14].

References

1. Diener HC, Kurth T, Dodick D (2007) Patent foramen ovale and migraine. Curr Pain Headache Rep 11:236–240
2. Desai AJ, Fuller CJ, Jesurum JT, Reisman M (2006) Patent foramen ovale and cerebrovascular diseases. Nat Clin Pract Cardiovasc Med 3:446–455
3. Germonpré P (2005) Patent foramen ovale and diving. Cardiol Clin 23:97–104
4. Saver JL (2007) Cryptogenic stroke in patients with patent foramen ovale. Curr Atheroscler Rep 9:319–325
5. Webster MW, Chancellor AM, Smith HJ et al (1988) Patent foramen ovale in young stroke patients. Lancet 2:11–12
6. Del Sette M, Dinia L, Rizzi D et al (2007) Diagnosis of right-to-left shunt with transcranial doppler and vertebrobasilar recording. Stroke 38:2254–2256
7. Liboni W, Molinari F, Allais G et al (2008) Patent foramen ovale detected by near-infrared spectroscopy in patients suffering from migraine with aura. Neurol Sci 29[Suppl 1]:S182–S185
8. Karttunen V, Ventilä M, Ikäheimo M et al (2001) Ear oximetry: a noninvasive method for detection of patent foramen ovale: a study comparing dye dilution method and oximetry with contrast transesophageal echocardiography. Stroke 32:448–453
9. Liboni W, Molinari F, Allais G et al (2007) Why do we need NIRS in migraine? Neurol Sci 28[Suppl 2]:S222–S224
10. Hundley WG, Li HF, Lange RA et al (1995) Assessment of left-to-right intracardiac shunting by velocity encoded, phase-difference magnetic resonance imaging. A comparison with oximetric and indicator dilution techniques. Circulation 91:2955–2960
11. Beerbaum P, Korperich H, Barth P et al (2001) Noninvasive quantification of left-to-right shunts in pediatric patients: phase contrast cine magnetic resonance imaging compared with invasive oximetry. Circulation 103:2476–2482
12. Mohor O, Petersen S, Erkapic D et al (2005) Diagnosis of

patent foramen ovale using contrast-enhanced dynamic MRI: a pilot study. Am J Roentgenol 184:234–240
13. Pfleger S, Konstantin Haase K, Stark S et al (2001) Haemodynamic quantification of different provocation manoeuvres by simultaneous measurement of right and left atrial pressure: implications for the echocardiographic detection of persistent foramen ovale. Eur J Echocardiography 2:88–93
14. Grebe O, Giesler M, Kestler H et al (2004) Magnetic resonance imaging after percutaneous closure of patent foramen ovale. Circulation 104:e117–e118

Neurol Sci (2008) 29:S23–S27
DOI 10.1007/s10072-008-0880-y

Does closure of a patent foramen ovale have a role in the treatment of migraine with aura?

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Abstract Patent foramen ovale (PFO) is associated with ischaemic stroke and migraine with aura (MA), and has been proposed as a cause of both. Numerous studies indicate that percutaneous PFO closure can improve MA, but they all suffer from methodological problems. It is recommended that the advantages and risks of PFO closure be carefully assessed in each individual, bearing in mind that effective prophylactic medications are available for MA patients with high attack frequency.

Keywords Patent foramen ovale (PFO) · Ischaemic stroke · Migraine with aura (MA) · Percutaneous closure

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Introduction

Several retrospective studies [1–7] indicate that a history of migraine, and in particular a history of migraine with aura (MA), may predispose to ischaemic stroke. Pooled data from case-control studies and cohort studies published before 2005 [8] indicate a relative risk for ischaemic stroke of 2.27 [95% CI 1.61–3.19] in MA patients compared to non-migraineurs. An association of MA with ischaemic stroke was also supported by two large prospective cohort studies [9, 10], and a recent population-based follow-up study [11]. In most studies the association was strongest for women under 45 years, although some reports indicate the association holds for both sexes and is independent of age [8–10].

Patent foramen ovale (PFO) has also been proposed as a risk factor for ischaemic stroke, particularly cryptogenic stroke [12–15]. Furthermore, the results of several studies indicate a high prevalence of PFO in MA patients [16–23]. For these reasons, PFO has been proposed as a link between MA and ischaemic stroke. Many studies also indicate that PFO closure can have a beneficial effect on MA itself [24–35].

In this paper we briefly review data on the PFO–MA association and the results of studies suggesting that PFO closure can benefit the migraine condition. We also review data on PFO as a risk factor for ischaemic stroke. The aim is to make recommendations, in the light of the currently available evidence, regarding the efficacy and advisability of PFO closure as a treatment for MA.

Prevalence of PFO in patients with migraine with aura

Increased frequency of PFO in migraineurs was first reported in 1998 by Del Sette et al. in a case-control

study [16] in which transcranial Doppler (TCD) results in 44 MA patients (right-to-left shunt present in 41%) were compared to those in 50 controls and 73 ischaemic stroke patients under age 50 (right-to-left shunt in 16% and 35%, respectively). Similar results were subsequently reported by other studies where presence of PFO was investigated by either TCD [17, 19, 22–24] or by transoesophageal echocardiography with contrast (TEE) [18, 20].

Overall, the frequency of PFO was significantly higher (about two-fold) in migraineurs with aura than non-migraineurs and migraineurs without aura. In most reports, the PFO was generally larger in MA patients than in non-migraineurs, with a higher prevalence of large right-to-left shunts at rest and after Valsalva manoeuvre [18, 20, 34–36]. Data from one of the retrospective studies [19] and from a recent prospective survey [23] failed to show major differences in clinical features between MA patients with or without PFO.

PFO as a risk factor for ischaemic stroke

Two meta-analyses of case-control studies published in 2000 [12] and 2005 [13] concluded that the relative risk of ischaemic stroke in patients younger than 55 years was significantly higher when PFO was present. In a more recent study the association between PFO and cryptogenic ischaemic stroke was also evident in patients older than 55 [14]. In the PICCS study [15] PFO was larger and present in a significantly higher proportion of cryptogenic ischaemic stroke patients than patients with a known cause of ischaemic stroke. On the other hand, two large prospective cohort studies on persons randomly selected from general populations [37, 38] failed to confirm PFO as an independent risk factor for a first cerebrovascular event, over the relatively short observation periods of 4 and 5 years. Retrospective analysis of data from the PICCS study [15] indicated that there was no difference in time to primary end points (recurrent ischaemic stroke or death) between those with and those without PFO, both in the overall population and in the cryptogenic subset.

Similar findings were reported in another cohort study on young adults with cryptogenic ischaemic stroke [39] in which the risk of recurrent stroke after four years was not higher in those with PFO compared to those without PFO. The only group with a substantially higher risk was those with both PFO and atrial septal aneurysm.

Other data suggest that the association of right-to-left shunting at rest with high membrane mobility determined by contrast TEE, and large size PFO assessed by contrast TCD, identify patients at high risk for recurrent cerebral embolism [39, 40].

PFO closure as treatment for migraine with aura

Several retrospective uncontrolled studies published over the last eight years indicate that percutaneous PFO closure may improve MA [24–35]. Changes in MA prevalence or attack frequency, before and after closure, have been assessed in several studies with post-procedure follow-up ranging from 3 to 38 months. A marked reduction in attack frequency was evident in most cases, with complete resolution in around 50% of cases in most studies (range 29% [24] to 92% [31]). In the study of Anzola et al. [31], only 7 of 33 MA patients who underwent closure still experienced attacks, while all 21 patients who were medically treated (control group) still reported attacks one year later. In a retrospective survey [41] the frequency of migraine attacks (the vast majority being with aura) and headache-related disability were significantly lower in patients who underwent PFO closure than a control group of migraineurs without PFO and a group of patients who were not treated.

The only randomised double-blind controlled trial of transcatheter PFO closure in migraineurs performed to date is the MIST trial, whose findings have been published recently [32]. Patients with a history of at least 2 MA attacks, reporting at least 5 days per month with any migraine, who had previously failed ≥2 classes of prophylactic treatments, and with moderate to large PFO by transthoracic contrast echocardiography were randomized to either PFO closure (74 patients) or a sham procedure that included general anaesthesia (73 patients). Complete resolution of attacks 3–6 months after closure was observed in 3 (5%) patients in the treeatment group and in 3 (4%) of the sham group, with no significant difference between them. Reduction in migraine frequency (evaluated as 50% reduction in migraine days) did not differ significantly between the groups. However when an exploratory analysis was performed that excluded 2 patients who were statistical outliers (who between them had over a third of total migraine attacks in the PFO-closure group) a significant reduction in the number of migraine days in the PFO-closure group was found.

Discussion

Published studies have consistently shown that the prevalence of PFO is higher among individuals with MA than control populations. Several studies have reported that percutaneous PFO closure can markedly improve MA. However, crucial data from prospective randomised controlled studies on patients with “pure” MA are not available. In most studies patients underwent PFO closure for disorders other than migraine (cerebrovascular events, decompression illness) and cannot be representative of typical MA patients.

Furthermore, all published studies on PFO closure present methodological problems. The methods used to assess headache frequency were disparate and duration of follow-up was highly variable, rendering comparisons problematic. More importantly, the populations studied were small, control groups were usually lacking and clinical data were collected retrospectively. Thus the presence and frequency of migraine attacks before and after PFO closure were assessed by interviewing patients after PFO closure. In the Anzola et al. [31] study, assessment of headache frequency after PFO closure was prospective, but data on headache occurrence before treatment intervention were collected retrospectively.

These characteristics imply that outcomes could have been influenced by major recall bias as well as by a placebo effect due to the treatment procedure. In two studies [31, 41] the results obtained in MA patients undergoing PFO closure were compared to those reported in other groups: a group of migraineurs with PFO followed medically [31] and migraineurs without PFO or migraineurs with PFO who received no treatment [41]. However, randomisation was not performed in either of these studies, and the medications used in the first study [31] were not specified.

Another possible confounding factor of all published closure studies is that aspirin or clopidogrel (anti-platelet therapy) were administered post-PFO closure and could have had anti-migraine efficacy [42–45].

The clinical implications of the only prospective, randomized, sham procedure-controlled trial are also uncertain [32]. Migraine resolved in only a small percentage of cases who underwent PFO closure and this did not differ from the percentage of resolutions in the sham group. Furthermore, there was no significant difference in post intervention attack frequency between the two groups. It is also important to note that patients with only two aura episodes were eligible for inclusion, and that a separate analysis of changes in MA attack frequency (as opposed to any migraine attack frequency) after intervention is not available.

At present therefore it must be concluded that conclusive evidence for the efficacy PFO closure as a treatment for MA is lacking. It is vital therefore that the decision to perform closure should be carefully weighed, taking into account the following factors:

- Only a minority of MA patients require prophylaxis, because the headache frequency varies irregularly, with spontaneous remissions lasting months or years, and a trend to melioration as the years pass, even without prophylactic treatment, even in patients referred to tertiary care centres [46].
- For the few patients who require prophylaxis, several drugs are available (topiramate, valproate, flunarizine, etc.) whose efficacy and tolerability have been established in randomised, placebo-controlled, double-blind trials in patients with MA and also migraine without aura [47, 48]. The drug lamotrigine has also emerged recently as an effective therapy for MA [49–51]. Acetazolamide may be useful in MA prophylaxis [52], and also aspirin can reduce migraine frequency [42–44] and may be particularly effective in MA (personal unpublished data).

With regard to PFO closure as a primary prevention measure against ischaemic stroke in MA patients, it should be noted that:

- Although there is evidence that MA is an independent risk factor for ischaemic stroke (particularly in young women), the absolute occurrence rate of ischaemic stroke among those with migraine is low: the estimated number of additional stroke cases due to this condition is 18–40 per 100 000 women per year [4, 9].
- The role of PFO as a cause of ischaemic stroke, even in cryptogenic cases, remains controversial. The recently published Italian guidelines on ischaemic stroke management [53] suggest that aspirin should be considered as the first option in cryptogenic ischaemic stroke/TIA patients who have PFO (grade C recommendation), while percutaneous PFO closure (or anticoagulant oral treatment) should be considered only in selected cases, i.e., those with associated atrial septal aneurysm, peripheral venous thrombosis or thrombophilia, and with large shunts and multiple cerebral ischaemic events (grade D recommendations).
- Although generally safe, PFO closure may have adverse events and complications. Complication rates are around 3%–8% [32, 54–57], and include cardiac tamponade requiring surgery, pulmonary embolism, atrial fibrillation, venous access bleeding and retroperitoneal haematoma.

Based on these considerations we propose that before considering PFO closure in MA patients, clinicians should consider the classical risk factors for ischaemic stroke (hypertension, obesity, diabetes, etc.) and the modifiable factors known to markedly increase the risk of ischaemic stroke in MA patients: smoking and oral contraceptive use [4, 6]. MA patients should therefore be discouraged from smoking and from using oral contraceptives. Contraceptive formulations with low doses of oestrogen or progestogen should be prescribed if patients insist on taking them [58]. Patients with MA should be encouraged to have an extensive examination including assessment of prothrombotic abnormalities including genetic abnormalities, hyperhomocysteinaemia and MTHFR polymorphisms, all of which may increase the risk of ischaemic stroke in MA patients [59–63]. This extensive screening is justified also because there is increasing evidence that MA is not only a risk factor for ischaemic stroke but also for myocardial infarction and other ischaemic vascular events [64]. Only in selected cases in which MA and a large PFO are associated with

other disorders (atrial septal aneurysm, peripheral venous thrombosis, thrombophilia) should percutaneous PFO closure be considered. Aspirin may represent a valid alternative [53]. In any event careful assessment of the possible advantages and risks of PFO closure in each individual should be performed by a neurologist and a cardiologist. The patient should be provided with accurate information and involved in the decision as far as possible.

References

1. Henrich JB, Horwitz RI (1989) A controlled study of ischemic stroke risk in migraine patients. J Clin Epidemiol 42:773–780
2. Tzourio C, Iglesias S, Hubert JB et al (1993) Migraine and risk of ischaemic stroke: a case-control study. Br Med J 307:289–292
3. Marini C, Carolei A, Roberts RS et al (1993) Focal cerebral ischemia in young adults: a collaborative case-control study. The National Research Council Study Group. Neuroepidemiology 12:70–81
4. Tzourio C, Tehindrazanarivelo A, Iglesias S et al (1995) Case-control study of migraine and risk of ischaemic stroke in young women. Br Med J 310:830–833
5. Carolei A, Marini C, De Matteis G (1996) History of migraine and risk of cerebral ischaemia in young adults. The Italian National Research Council Study Group on Stroke in the Young. Lancet 347:1503–1506
6. Chang CL, Donaghy M, Poulter N, The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (1999) Migraine and stroke in young women: case-control study. Br Med J 318:13–18
7. Donaghy M, Chang CL, Poulter N (2002) Duration, frequency, recency, and type of migraine and the risk of ischaemic stroke in women of childbearing age. J Neurol Neurosurg Psychiatry 73:747–750
8. Etminan M, Takkouche B, Isorna FC, Samii A (2005) Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. Br Med J 330:63
9. Kurth T, Slomke MA, Kase CS et al (2005) Migraine, headache, and the risk of stroke in women: a prospective study. Neurology 64:1020–1102
10. Stang PE, Carson AP, Rose KM et al (2005) Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. Neurology 64:1573–1577
11. Becker C, Brobert GP, Almqvist PM et al (2007) Migraine and the risk of stroke, TIA, or death in the UK (CME). Headache 47:1374–1384
12. Overell JR, Bone I, Less KR (2000) Interatrial septal abnormalities and stroke. A meta-analysis of case-control studies. Neurology 55:1172–1179
13. Amarenco P (2005) Patent foramen ovale and the risk of stroke: smoking gun guilty by association? Heart 91:441–443
14. Handke M, Harloff A, Olschewski M et al (2007) Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med 357:2262–2268
15. Homma S, Sacco RL, DiTullio MR et al for PICSS Investigators (2202) Effect of medical treatment in stroke patients with patent foramen ovale. Circulation 105:2625–2631
16. Del Sette M, Angeli S, Leandri M et al (1998) Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis 8:327–330
17. Anzola GP, Magoni M, Guindani M et al (1999) Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. Neurology 52:1622–1625
18. Wilmshurst P, Nightingale S. Walsh KP, Morrison WL (2000) Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. Lancet 356:1648–1651
19. Dalla Volta G, Guindani M, Zavarise P et al (2005) Prevalence of patent foramen ovale in a large series of patients with migraine with aura, migraine without aura and cluster headache, and relationship with clinical phenotype. J Headache Pain 6:328–330
20. Schwerzmann M, Nedeltchev K, Lagger F et al (2005) Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 65:1415–1418
21. Carod-Artal FJ, da Silveira Ribeiro L, Braga H et al (2006) Prevalence of patent foramen ovale in migraine patients with and without aura compared with stroke patients. A transcranial Doppler study. Cephalalgia 26:934–939
22. Domitrz I, Mieszkowski J, Kaminska A (2007) Relationship between migraine and patent foramen ovale: a study of 121 patients with migraine. Headache 47:1311–1318
23. Anzola GP, Meneghetti G, Zanferrari C et al; the SaM Study Group (2008) Is migraine associated with right-to-left shunt a separate disease? Results of the SAM study. Cephalalgia 28:360–366
24. Morandi E, Anzola GP, Angeli S et al (2003) Transcatheter closure of patent foramen ovale: a new migraine treatment? J Interv Cardiol 16:39–42
25. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL (2000) Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. Lancet 356:1648–1651
26. Schwerzmann M, Wiher S, Nedeltchev K et al (2004) Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. Neurology 62:1399–1401
27. Post M, Thijs V, Herroelen L, Budts W (2004) Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine. Neurology 62:1439–1440
28. Reisman M, Christofferson RD, Jesurum J et al (2005) Migraine headache relief after transcatheter closure of patent foramen ovale. J Am Coll Cardiol 45:493–495
29. Azarbal B, Tobis J, Suh W et al (2005) Association of interatrial shunts and migraine headaches: impact of transcatheter closure. J Am Coll Cardiol 45:489–492
30. Giardini A, Donti A, Formigari R et al (2006) Long-term efficacy of transcatheter patent foramen ovale closure on migraine headache with aura and recurrent stroke. Catheter Cardiovasc Interv 67:625–629
31. Anzola GP, Frisoni GB, Morandi E et al (2006) Shunt-associated migraine response favorably to atrial septal repair: a case-control study. Stroke 37:430–434
32. Dowson A, Mullen MJ, Peatfield R et al (2008) Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 117:1397–1404
33. Dubiel M, Bruch L, Schmehl I et al (2008) Migraine headache relief after percutaneous transcatheter closure of interatrial communications. J Interv Cardiol 21:32–37
34. Jesurum JT, Fuller CJ, Velez CA et al (2007) Migraineurs with patent foramen ovale have larger right-to-left shunt despite similar atrial septal characteristics. J Headache Pain 8:209–216
35. Giardini A, Donti A, Formigari R et al (2006) Transcatheter patent foramen ovale closure mitigates aura migraine headaches abolishing spontaneous right-to-left shunting. Am Heart J 151:922–925
36. Anzola GP, Morandi E, Casilli F, Onorato E (2006) Different degrees of right-to-left shunting predict migraine and stroke: data from 420 patients. Neurology 66:765–767

37. Meissner I, Khandheira BK, Heit JA et al (2006) Patent foramen ovale; innocent or guilty? J Am Coll Cardiol 47:440–445
38. Di Tullio MR, Sacco RL, Sciacca RR et al (2007) Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. J Am Coll Cardiol 49:797–802
39. Mas JL, Arquizan C, Lamy C et al (2001) Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 345:1740–1746
40. De Castro S, Cartoni D, Fiorelli M et al (2000) Morphological and functional characteristics of patent foramen ovale and their embolic implications. Stroke 31:2407–2413
41. Kimmelstiel C, Gange C, Thaler D (2007) Is patent foramen ovale closure effective in reducing migraine symptoms? A controlled study. Catheter Cardiovasc Interv 69:740–746
42. Buring JE, Peto R, Hennekens CH (1990) Low-dose aspirin for migraine prophylaxis. JAMA 264:1711–1713
43. Diener HC, Hartung E, Chrubasik J et al (2001) A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. Cephalalgia 21:120–128
44. Bensenor IM, Cook NR, Lee IM et al (2001) Low-dose aspirin for migraine prophylaxis in women. Cephalalgia 21:175–183
45. Sharifi M, Burks J (2004) Efficacy of clopidogrel in the treatment of post-ASD closure migraines. Catheter Cardiovasc Interv 63:255
46. Cologno D, Torelli P, Cademartiri C, Manzoni GC (2000) A prospective study of migraine with aura attacks in a headache clinic population. Cephalalgia 20:925–930
47. Silberstein SD for the US Headache Consortium (2000) Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 55:754–762
48. Evers S, Afra J, Frese A, Goadsby PJ et al (2006) EFNS guideline on the drug treatment of migraine-report of an EFNS task force. Eur J Neurol 13:560–572
49. D'Andrea G, Granella F, Cadaldini M, Manzoni GC (1999) Effectiveness of lamotrigine in the prophylaxis of migraine with aura: an open pilot study. Cephalalgia 19:64–66
50. Pascual J, Caminero AB, Mateos V et al (2004) Preventing disturbing migraine aura with lamotrigine: an open study. Headache 44:1024–1028
51. Lampl C, Katsarava Z, Diener HC, Limmroth V (2005) Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. J Neurol Neurosurg Psychiatry 76:1730–1732
52. De Simone R, Marano E, Di Stasio E et al (2005) Acetazolamide efficacy and tolerability in migraine with aura: a pilot study. Headache 45:385–386
53. SPREAD – Stroke Prevention And Educational Awareness Diffusion (2007) Ictus cerebrale: Linee Guida Italiane, V edn. 20 December
54. Khairy P, O'Donnell C, Landzberg MJ (2003) Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli. A systematic review. Ann Intern Med 139:753–760
55. Anzola GP, Morandi E, Casilli F, Onorato E (2004) Does transcatheter closure of patent foramen ovale really "shut the door": a prospective study with transcranial Doppler. Stroke 35:2140–2144
56. Egred M, Andron M, Albouaini K et al (2007) Percutaneous closure of patent foramen ovale and atrial septal defect: procedure outcome and medium-term follow-up. J Interv Cardiol 20:395–401
57. Wahl A, Kunz M, Moscovitis A et al (2008) Long-term results after fluoroscopy guided closure of patent foramen ovale for secondary prevention of paradoxical embolism. Heart 94:336–341
58. Bousser MG (2004) Estrogens, migraine, and stroke. Stroke 35[11 Suppl 1]:2652–2656
59. D'Amico D, Moschiano F, Leone M et al (1998) Genetic abnormalities of the protein C system: shared risk factors in young adults with migraine with aura and with ischemic stroke? Cephalalgia 18:618–621
60. Giardini A, Donti A, Formigari R et al (2007) Spontaneous large right-to-left shunt and migraine headache with aura are risk factors for recurrent stroke in patients with a patent foramen ovale. Int J Cardiol 120:357–362
61. D'Amico D, Moschiano F, Attanasio A et al (2003) Hyperhomocysteinemia in patients with migraine with aura. Cephalalgia 23:742
62. Kowa H, Yasui K, Takeshima T et al (2000) The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. Am J Med Genet 96:762–764
63. Pezzini A, Grassi M, Del Zotto E et al (2007) Migraine mediates the influence of C677T MTHFR genotypes on ischemic stroke risk with a stroke-subtype effect. Stroke 38:3145–3151
64. Diener HC, Kurth T, Dodick D (2007) Patent foramen ovale, stroke, and cardiovascular disease in migraine. Curr Opin Neurol 20:310–319

Neurol Sci (2008) 29:S28–S32
DOI 10.1007/s10072-008-0881-x

Patent foramen ovale closure. Pro and cons

Eustaquio Onorato · Francesco Casilli · Marco Berti · Gian Paolo Anzola

Abstract Because patent foramen ovale (PFO) represents a lesion which may be repaired a number of expert clinicians believe that mechanical closure should be the primary treatment modality for patients with PFO after cryptogenic stroke; interest has grown on percutaneous devices and in the last years there has been great technological advancement of percutaneous techniques for PFO closure. However, we should not close a PFO before establishing the evidence-based indications. At the same time, efforts to develop safer and more effective closure devices are under way. These devices include those with little or no metal component and those with biodegradable discs. Ideally, we should be able to identify at-risk patients before they sustain a stroke and to prevent stroke by closing the PFO with a device that should result in complete closure, be made of material that conforms to both sides of the septum, and have no risk of erosion, infection, arrhythmia, or thrombogenicity. Randomised trials comparing medical and percutaneous closure approaches are underway, but large patient enrollment is necessary because of the low event rate in the younger patients. Meanwhile, as the complication rate from device implantation decreases and simpler devices are developed with reliability further demonstrated, the threshold for percutaneous closure is likely to decline.

Keywords Patent foramen ovale · Atrial septal aneurysm · Paradoxical embolism · Right-to-left shunt · Percutaneous closure

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Introduction

The management of patients with patent foramen ovale (PFO) is controversial. Therapeutic options for secondary stroke prevention in patients with a PFO include two major strategies: (1) conservative long-term medical treatment with antithrombotic therapy (platelet antiaggregating drugs) or oral anticoagulation, and (2) invasive treatment with surgical or interventional closure of the interatrial communication. Until now the available evidence of both pharmacological (antiplatelet or anticoagulant agents) and mechanical approaches has been inadequate for assessment of the relative merits of these options in secondary prevention in cryptogenic stroke in patients with PFO. To date, no study has randomly assigned patients with cryptogenic stroke and PFO to different therapies.

Studies thus far have been observational, with disparate definitions of the qualifying or recurrent cerebrovascular event, non-uniform criteria for interatrial septal abnormalities, absence of blinding during examination of echocardiograms or ascertainment of end points, and incomplete accounting of associated risk factors or the use of adjunctive therapies.

Percutaneous closure

Percutaneous PFO closure is a catheter-based technique using atrial septal occlusion devices. It was initially advocated for prevention of recurrent stroke in 1992 [1]. Since then, safety and feasibility have been addressed in several subsequent studies. Multiple non-randomised trials suggest a potential benefit in PFO closure in patients with cryptogenic stroke who have PFO.

The efficacy of catheter PFO closure in the abolishment of right-to-left shunt (RLS) ranges between 86% and 100%. Recurrent neurological and peripheral embolic events are reported as 0%–3.8% per year.

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A systematic review found that among 1355 patients undergoing percutaneous closure, the rate of recurrent stroke or transient ischaemic attack was 0%–4.9% at one year. Even though cerebrovascular recurrence rate appeared to be higher among 895 patients receiving medical therapy (3.8%–12%), several considerations preclude meaningful comparison: the non-randomised treatment assignment, differences in the clinical characteristics of the patients treated by the various techniques and inconsistent criteria for ascertainment of outcomes. Serious complications of percutaneous closure (major haemorrhage, cardiac tamponade, the need for surgery, pulmonary embolism and death) were reported in 1.5% of the patients, and minor complications (arrhythmia, device fracture or embolisation, air embolism, femoral haematoma and fistula) in 7.9% [2]. Careful analysis of this apparently plain operation reveals that nickel toxicity, thrombus formation, residual shunt, malpositioning and erosions are still active and real problems, whereas the pathophysiology of RLS, the role of coagulation abnormalities, the significance of atrial septal aneurysm and other sources of shunt remain unresolved issues. Aspirin and/or clopidogrel are recommended for a period of three to six months to prevent thrombus formation on the device, until the endothelialisation process is fairly completed. Antibiotic prophylaxis for six months is highly recommended. Krumsdorf et al. [3] reported 1000 consecutive patients undergoing ASD and PFO closure using different transcatheter devices (nine different technologies). The study reported thrombus formation in the left atrium (n=11), right atrium (n=6) or both (n=3) in 1.2% of ASD patients and in 2.5% of PFO patients (p=NS). Thrombus was diagnosed in 14 of 20 patients at four weeks and in 6 of 20 patients later than four weeks. The most frequent thrombus formation occurred on the CardioSEAL device (NMT Medical, Boston, MA) (7.1%), whereas a 5.7% incidence of thrombus formation was observed on the STARFlex device (NMT Medical), 6.6% on the PFO-Star device (Applied Biometrics Inc., Burnsville, MN), 3.6% on the ASDOS device (Osypka Corp., Grenzach-Wyhlen, Germany), 0.8% on the Helex device (WL Gore, Flagstaff, AZ) and no thrombus formation on the Amplatzer device (AGA Medical, Golden Valley, MN). Limitations of this retrospective review include the observation that the effect of heparin was often reversed by protamine immediately after the procedure. It is worth noticing that haematologic screening was not performed before device implant. The authors concluded that thrombus formation on closure devices is low and usually resolves with anticoagulation therapy.

Table 1 New PFO closure devices

New devices	
Bioadsorbable device	BioSTAR, NMT Medical
Self-expanding stent	Coherex FlatStent Closure System
Suturing device	HeartStich Suturing device
"No device" approach	
RF-based thermal energy	PFX TM Closure System, Cierra, Inc.
	Radiofrequency Thermal Coaptation, CoAptus Medical Corporation

Indications for PFO closure

The American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy [4] and the American Heart Association (AHA)/American Stroke Association Council on Stroke Practice Guidelines [5] recommend antiplatelet therapy after cryptogenic stroke in the majority of patients. Warfarin use is suggested in the setting of known deep venous thrombosis or documented hypercoagulable state (Table 2). Scientific societies have commented on the use of closure devices as a therapy for cryptogenic stroke in the presence of a PFO. The American Academy of Neurology (AAN) [6] found "insufficient evidence regarding the effectiveness of either surgical or endovascular closure of PFO" and promotes the enrolment of cryptogenic stroke patients with PFO in randomised controlled studies. The AHA/American Stroke Association concluded that insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO; however PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical therapy (Class IIb, Level of Evidence C).

General agreement exists about the necessity of randomised trials to determine the efficacy of percutaneous occluders in preventing recurrent cryptogenic stroke. Concerning this issue, the Food and Drug Administration (FDA) convened last March 2007 a Meeting of the Circulatory System Devices Panel (CSDP) to discuss the necessity of randomised trials as well as obstacles to trial enrolment and completion [7]. Despite slow enrolment and the requests of sponsors to discard the requirement for randomised trials, the panel firmly asserted that randomised controlled trials are of crucial importance in determining safety and efficacy of PFO percutaneous closure [7]. Among the final recommendations, the CSDP suggested that patients and physicians should be alerted to the lack of evidence of PFO closure benefit and the need for completion of trials (Table 3). As long as we are waiting for the results of randomised trials (results probably not to be expected soon), evidence-based medicine has to be replaced by common sense. Meanwhile, our group, according to actual international evidence, suggest stratification of symptomatic PFO patients with presumed PFO-related stroke in different risk classes to different therapeutic options (medical vs. transcatheter treatment) with a rigorous "decision-making strategy" that must include ce-TCD, which likely represents the new "gold standard" to assess the functional consequences of RLS at least at the

Table 2 Summary of guidelines for PFO closure

Association	Recommendations
American College of Chest Physicians	Antiplatelet therapy after cryptogenic stroke should include 1 of the following: (1) aspirin 50 to 325 mg daily; (2) aspirin 25 mg and extended-release dipyrida-mole 200 mg twice daily; or (3) clopidogrel 75 mg daily. Antiplatelet agents are recommended instead of oral anticoagulati nunless a patient has a well-documented prothrombotic disorder. After cryptogenic ischemic stroke, in the presence of a PFO, antiplatelet therapy is recommended instead of warfarin unless a patient has evidence of deep venous thrombosis.
American Academy of Neurology	After cryptogenic stroke, evidence indicates the risk of recurrent stroke or death does not vary between patients with and without PFOs who are treated medically There is insufficient eviden ce to determine the superiority of antiplatelet agents vs warfarin. There is insufficient evidence regarding the effectiveness of PFO closure.
AHA/American Stroke Association	After noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I, level of evidence A). Aspirin (50 to 325 mg/d), aspirin and extended-release dipyridamole in combination, and clopidogrel are all acceptable options for initial therapy (Class IIa, level of evidence A). After ischemic stroke or TIA in patients with a PFO, antiplatelet therapy is reasonable to prevent a recurrent event (Class IIa, level of evidence B). Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation, such as underlying hyper coagulable state or evidence of venous thrombosis (Class IIa, level of evidence C). Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (Class IIb, level of evidence C).

Table 3 Food and Drug Administration (FDA) Circulatory System Devices Panel (CSDP) Recommendations [7]

1) Randomized controlled trials of PFO closure to prevent recurrent stroke are required.
2) A "proof of principle" trial with pooled data demonstrating that PFO closure does prevent recurrent stroke could allow this question to be answered in a timely fashion, if sponsors are amenable to cooperating and sharing data. "Proof of device" trials demonstrating that an individual device effectively closes a PFO could be done separately.
3) "Off-label" closure should be discouraged. Enrollment in ongoing trials should be encouraged.
4) Patients and physicians should be educated about the lack of evidence of benefit of closure and the need for completion of trials.

brain level. Whereas TEE not only can confirm the cardiac location of the shunt and its volume, but also can look for ASA and study other subtle cardiac abnormalities (presence of Eustachian valve or Chiari network) that can facilitate the passage of venous blood into the systemic circulation, ce-TCD can directly assess the shunt at the level of the brain vessels and quantify more specifically the degree of cerebral RLS. With this combined diagnostic workup it may become easier to stratify patients in different risk classes with different therapeutic options. PFO patients who exhibit small shunts and have no identifiable ASA are probably adequately protected by antiplatelet therapy given the low risk of recurrence. By contrast, in those patients with shower or curtain pattern by ce-TCD in association with ASA, permanent closure of the defect may be advocated given the significant risk of recurrence despite medical treatment, especially in those presenting with multiple cerebrovascular episodes [8]. Randomised controlled trials are needed in other conditions just to ask the question of what the best treatment is.

Future trends

Device-based procedures are associated with complications related to the procedure itself and the implanted occluder devices, including thrombus formation even late after implantation, strut fracture and embolisation [9]. Moreover, device-based therapies may fail due to residual shunting in the mid and long-term follow-up. Current intracardiac closure devices are also prone to cause supraventricular arrhythmia and eventually endocarditis. Further catheter access to the left atrial cavity for electrophysiological procedures may be impeded. Considering the long-term concerns of current PFO closure devices, a variety of new devices for percutaneous PFO closure are either under investigation or under development (Table 1). The most important modifications aimed, on one hand, to decrease the total amount of implant material, particularly on the left atrial side (Premere™ PFO Closure System, St Jude Medical) and, on the other hand, to use bioabsorbable devices (BioSTAR device, NMT Medical) [10] and to implement devices for suture-mediated PFO clo-

sure (HeartStich Suturing device). Vascular stents are perhaps the most widely used therapeutic devices in interventional cardiology. Using the familiar delivery system of a self-expanding vascular stent as a model, the engineering team at Coherex developed the Coherex FlatStent™ PFO Closure System, which redefines the concept of a stent. Instead of using the outward force generated by an expanded stent to open a structure, the FlatStent uses outward force to close a structure. The implantable device is part of a system that is designed to provide three distinct closure mechanisms: lateral force exerted by the deployed FlatStent to close the tunnel from within, a foreign body response to the implant to stimulate endothelialisation and a polymer substrate to promote cellular integration within the tunnel. Coherex FlatStent PFO Closure System has been designed to combine the familiarity and ease of use of a self-expanding vascular stent with a unique fusion of PFO closure technologies.

Finally, a novel PFO closure strategy uses radiofrequency (RF)-based thermal energy to seal the tunnel without an implanted device. (PFX™ Closure System, Cierra Inc.; CoAptus Medical Corporation) [10, 11]. The PFX™ Closure System is the first technology that allows closure of an intracardiac defect without leaving anything behind. It consists of a non-implantable system which employs monopolar RF energy in order to weld the tissues of the septum primum and septum secundum together and it is performed entirely from the right side. PARADIGM I (a single-centre FIM trial) and PARADIGM II (prospective, non-randomised, multicentre trial) demonstrated safety and effectiveness of the PFX™ Closure System for PFO closure (*unpublished data*). Moreover, in the presence of a significant residual RLS, treatment options remain unchanged following RF as a second RF application is eventually feasible and an implant closure is still viable following RF. Further clinical research is underway.

In conclusion, these new strategies seem to be very attractive at least theoretically and may represent device-free alternatives for PFO percutaneous treatment in the near future.

Conclusions

PFO as a cause of cryptogenic stroke is a diagnosis of exclusion and is completely dependent on appropriately ruling out all potential causes. Despite the lack of certainty of causation, the main hypothesis involved for potential stroke in PFO is paradoxical embolism of venous emboli to the arterial circulation. In this regard, deep venous thrombosis and pelvic vein thrombosis have been reported by several authors to be observed more frequently in young patients who suffered from cryptogenic stroke than in those who had stroke from other more defined causes. The association between PFO and paradoxical embolism and the greater frequency of cryptogenic strokes in patients with PFO and prothrombotic states have suggested the potential benefit of antiplatelet therapy with aspirin and possibly clopidogrel, or anticoagulant therapy with warfarin. However, there is neither expert consensus nor sufficient quality evidence to determine which approach, antiplatelet or antithrombotic, is superior. Also, in spite of medical therapy, up to 25% of patients with cryptogenic stroke experience recurrent stroke or transient ischaemic attack within 4 years of the initial event. Because PFO represents a lesion that may be repaired, a number of expert clinicians believe that mechanical closure should be the primary treatment modality for patients with PFO after cryptogenic stroke; interest in percutaneous devices has grown and in the last number of years there has been great technological advancements in percutaneous techniques for PFO closure. We should not close a PFO before establishing the evidence-based indications. Cryptogenic stroke by definition needs thorough investigation in order to rule out all potential causes of stroke. Our goal is to differentiate patients in whom the culprit PFO has to be closed from those who do not need a bystander PFO to be closed. Various factors need to be considered such as atrial anatomic variation (PFO size, ASA, Eustachian valve anatomy), haemodynamic parameters, presence of venous thrombus identified through higher sensitivity tests such as lower extremity/abdominal/pelvic MRI, and the presence of hypercoagulable genetic variables. At the same time, efforts to develop safer and more effective closure devices are underway. These devices include those with little or no metal component and those with biodegradable discs. Ideally, we should be able to identify at-risk patients before they sustain a stroke and to prevent stroke by closing the PFO with a device that should result in complete closure, is made of material that conforms to both sides of the septum and has no risk of erosion, infection, arrhythmia or thrombogenicity. Randomised trials comparing medical and percutaneous closure approaches are underway, but large patient enrolment is necessary because of the low event rate in the younger patients. Meanwhile, as the complication rate from device implantation decreases and simpler devices are developed with reliability further demonstrated, the threshold for percutaneous closure is likely to decline.

References

1. Bridges ND, Hellenbrand W, Latson L et al (1992) Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. Circulation 86:1902–1908
2. Deeik RK, Thomas RM, Sakiyalak P et al (2002) Minimal access closure of patent foramen ovale: is it also recommended for patients with paradoxical emboli? Ann Thorac Surg 74:S1326–S1329
3. Krumsdorf U, Ostermayer S, Billinger K et al (2004) Incidence and clinical course of thrombus formation on atrial septal defect

and patient foramen ovale closure devices in 1.000 consecutive patients. J Am Coll Cardiol 43:302–309
4. Albers GW, Amarenco P, Easton JD et al (2004) Antithrombotic and thrombolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 126:483S–512S
5. Sacco RL, Adams R, Albers G et al (2006) American Heart Association; American Stroke Association Council on Stroke; Council on Cardiovascular Radiology and Intervention; American Academy of Neurology. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 37:577–617
6. Messe SR, Silverman IE, Kizer JR et al (2004) Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 62:1042–1050
7. Slottow TL, Steinberg DH, Waksman R (2007) Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel meeting on patent foramen ovale closure devices. Circulation 116:677–682
8. Onorato E, Melzi G, Casilli F et al (2003) Patent foramen ovale with paradoxical embolism: mid-term results of transcatheter closure in 256 patients. J Interv Cardiol 16:11–18
9. Khairy P, O'Donnell CP, Landzberg MJ (2003) Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. Ann Intern Med 139:753–760
10. Jux C, Bertram H, Wohlsein P et al (2006) Interventional atrial septal defect closure using a totally bioresorbable occluder matrix: development and preclinical evaluation of the BioSTAR device. J Am Coll Cardiol 48:161–169
11. Hara H, Jones TK, Ladich ER et al (2007) Patent foramen ovale closure by radiofrequency thermal coaptation: first experience in the porcine model and healing mechanisms over time. Circulation 116:648–653

Neurol Sci (2008) 29:S33–S36
DOI 10.1007/s10072-008-0882-9

HYPERTENSION AND MIGRAINE

Essential hypertension and the sympathetic nervous system

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Abstract Sympathetic neural factors exert a key role in homeostatic blood pressure control. Evidence is available that abnormalities in sympathetic function may favour the development and progression of the hypertensive state. This paper will review the data collected throughout the years on the role of adrenergic mechanisms in the pathophysiology of the hypertensive state. It will then examine the mechanisms and the consequences of the sympathetic overdrive reported in hypertension, with particular emphasis on its role in the development of target organ damage. Finally the therapeutic implications of hypertension-related neurogenic abnormalities will be highlighted.

Keywords Sympathetic nervous system · Hypertension · Cardiovascular risk · Target organ damage · Antihypertensive drug treatment

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Introduction

Among the various hypotheses advanced throughout the years to explain the pathophysiology of essential hypertension, a major one is the so-called "neurogenic nature of high blood pressure" [1]. This hypothesis claims that a dysfunction in sympathetic modulation of the cardiovascular function is responsible for the hypertensive state, actively participating in its early development and late progression.

This paper will review the evidence collected over the years on this pathogenetic hypothesis. It will also examine the possible mechanisms advanced to explain the neurogenic abnormalities as well as the adverse effects that the adrenergic overdrive exerts on hypertension-related target organ damage as well as on cardiometabolic function. This will allow us to briefly address, in the final part of the manuscript, the issue of the therapeutic implications of the sympathetic abnormalities characterising essential hypertension.

Essential hypertension: a hyperadrenergic state

Based upon the evidence collected in several experimental animal models, the hypothesis that an abnormality in sympathetic control of the cardiovascular system participates in the development and progression of essential hypertension has been repeatedly tested also in humans. Much evidence has been collected over the years on this issue. It has been shown, for example, that a resting tachycardia, associated with a hyperkinetic state, frequently characterises a consistent fraction of juvenile hypertension [2]. These haemodynamic abnormalities are accompanied (and probably triggered) by a state of adrenergic overdrive, given the evidence that the circulating plasma levels of the main adrenergic neurotransmitter, i.e., norepinephrine, are increased in these young patients [2].

A metanalysis of the studies performed by employing plasma norepinephrine as a marker of sympathetic drive has shown that in a consistent number of hypertensive patients the circulating levels of this adrenergic neurotransmitter are increased [3]. This increase is likely to depend on an enhanced central neuroadrenergic drive, given the evidence that direct recording of sympathetic nerve traffic (i.e., the approach allowing an accurate estimation of the neural discharge from the central nervous system) has been shown to be considerably potentiated in essential hypertensive patients [4]. This potentiation has been demonstrated to involve the sympathetic outflow to different cardiovascular districts, as documented by the increased norepinephrine spillover in cerebral, coronary and renal circulation as well [5].

Two other aspects of the adrenergic overdrive characterising hypertensive disease deserve to be mentioned. The first one refers to the evidence that sympathetic overactivity has been detected in different clinical conditions characterised by a blood pressure increase, such as in (a) hypertension of the elderly, (b) pregnancy-induced hypertension and eclampsia, (c) white-coat and masked hypertension and (d) dipping, extreme dipping, non-dipping and reverse dipping hypertension [6]. Thus, the hyperadrenergic state occurring in hypertension is an almost generalised phenomenon occurring independently of any concomitant clinical condition associated with the blood pressure elevation. This conclusion is strengthened by the finding that when hypertension is detected in the obese state, in heart failure syndrome, in metabolic syndrome or in renal failure (i.e., conditions already characterised by a marked increase in adrenergic drive), the degree of the sympathetic activation appears to be markedly enhanced as compared to that seen in the uncomplicated hypertensive state [6–9]. The second aspect that deserves to be mentioned in relation to the neurogenic nature of the essential hypertensive state is that no sympathetic hyperactivity is detectable in secondary forms of hypertension, such as in renovascular hypertension and primary hyperaldosteronism [6]. This is also the case in adrenal pheochromocytoma, in which central sympathetic outflow has been shown to be (1) inhibited by the high levels of plasma norepinephrine and epinephrine secreted by the adrenal mass and (2) restored to normal firing levels when surgical removal of pheochromocytoma has been performed [10]. Taken together these findings support the notion that essential hypertension frequently displays a neurogenic nature, which thus becomes an important therapeutic target.

Mechanisms and consequences of hypertension-related adrenergic activation

Despite years of investigations, the mechanisms responsible for the adrenergic overactivity characterising human hypertension remain undefined. Some hypotheses, however, have been advanced (Fig. 1). It has been, for example, suggested that the increased sympathetic activity is due to a derangement in the sympathoinhibition exerted by reflexogenic areas (such as the arterial baroreceptors, the cardiopulmonary receptors or the chemoreceptors) that tonically restrain adrenergic outflow [6]. It has also been suggested that the metabolic alterations frequently detectable in hypertension, such as the hyperinsulinaemic state and the related insulin resistance, may be the triggering factors. This hypothesis is based on the evidence that insulin may have central sympathoexcitatory effects which may thus be enhanced in hypertensive patients' (which frequently display insulin resistance) adrenergic drive [6]. Finally, it has been

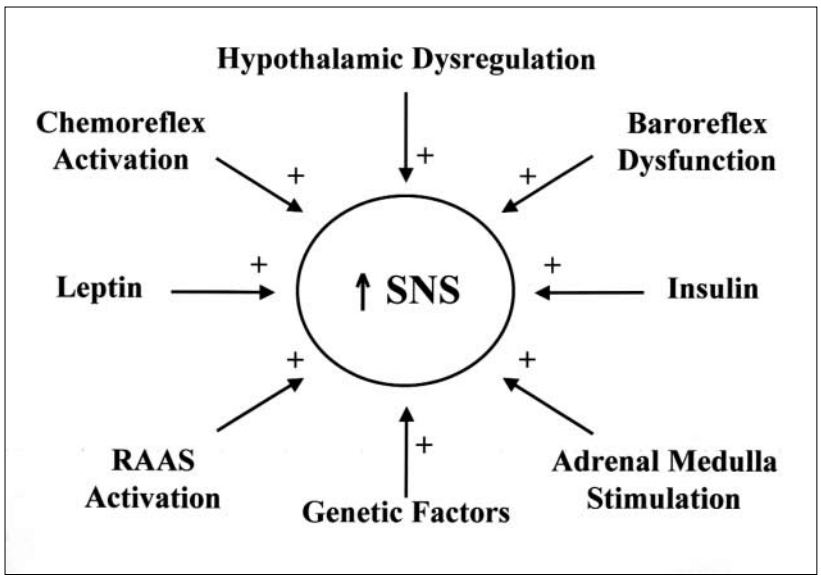

Fig. 1 Schematic drawing illustrating the possible mechanisms responsible for the sympathetic activation of essential hypertension. *SNS*, sympathetic nervous system; *RAAS*, renin-angiotensin-aldosterone system; +, potentiation; ↑, increase

thought that the sympathetic activation of hypertension depends on the renin–angiotensin system, given the evidence that (1) angiotensin II exerts central sympathoexcitatory effects and (2) pharmacologic blockade of the renin–angiotensin system via ACE-inhibitors or angiotensin II receptor blockers exerts sympathomodulatory effects [6, 11, 12].

Among the several adverse consequences of the sympathetic activation occurring in hypertension, the more relevant are those which refer to target organ damage [6]. Indeed norepinephrine has been shown to exert prohypertrophic effects on the myocardial tissue as well as on the peripheral vascular district. This notion, coupled with the evidence that the degree of sympathetic activation detected in hypertension is potentiated when left ventricular hypertrophy is observed at the echocardiographic examination [6], strongly supports the hypothesis that the increase in cardiac wall thickness seen in hypertension depends not only on the haemodynamic overload but also on sympathetic factors. Adrenergic overdrive also unfavourably affects vascular function by reducing arterial distensibility and compliance [6], i.e., two variables whose impairment has been implicated in the genesis of vascular atherogenesis. A number of elegant studies performed in the past few years have shown that sympathetic neural factors may also promote the metabolic abnormalities frequently detected in the clinical history of hypertensive patients [6]. In particular it has been shown that an increase in adrenergic activity may trigger an insulin resistance state via a series of haemodynamic and non-haemodynamic effects causing massive vasoconstriction at the level of the skeletal muscle district, i.e., in the organs involved in the development of insulin resistance [6]. Finally, an increase in sympathetic drive has deleterious renal effects, by favouring a blood pressure elevation via an increase in renal sodium reabsorption [6].

Therapeutic implications

Given the key role exerted by adrenergic factors in the development and progression of hypertension and hypertension-related end organ damage, sympathetic deactivation represents a major goal of the therapeutic approach. Non-pharmacological interventions may indeed exert sympatholytic effects (Table 1) [13, 14]. This is the case for physical training, which lowers both blood pressure and systemic and regional adrenergic drive. This is also the case for interventions capable of reducing body weight. In contrast, a low sodium diet, although capable of exerting some blood pressure lowering effects, has been shown to enhance the already elevated sympathetic drive of hypertensive patients, presumably because it also causes insulin resistance.

Information on the effects of antihypertensive therapeutic interventions on sympathetic function are not limited, however, to non-pharmacologic approaches [13, 14]. Indeed, in the past few years a large number of studies have investigated the impact of the different classes of antihypertensive drugs on adrenergic cardiovascular drive. The information collected so far can be summarised as follows (Table 2). Diuretic agents may trigger some sympathoexcitatory effects, which can also be detected with the use of short-acting calcium channel blockers. In contrast, long-acting calcium antagonists are sympathetically neutral, while β-blockers, ACE-

Table 1 Effects of non-pharmacological interventions on blood pressure (BP) and sympathetic nerve activity in hypertension

Intervention	BP	SNS
Body weight reduction	↓ ↓	↓ ↓
Physical exercise	↓	↓ ↓
Low salt diet		
Marked	↓	↑ ↑
Moderate	↓, =	↑

↑, increase; =, no change; ↓, decrease

Table 2 Effects of different antihypertensive drugs on sympathetic function

Drug class	Heart rate	NE	MSNA	NE spillover (systemic)
Central sympatholytics	↓	↓	↓	↓
Diuretics	=	↑,=	↑,=	↑,=
Calcium antagonist				
Short-acting	↑	↑	↑	↑
Long-acting	=	=	=	=
β-blockers	↓	↓	↓	↓
ACE-inhibitors	=, ↓	=. ↓	=, ↓	=, ↓
Angiotensin II blockers	=, ↓	↓	↓	↓

NE, norepinephrine; *MSNA*, muscle sympathetic nerve traffic; ↑, increase; =, no change; ↓, decrease

inhibitors and angiotensin II receptor blockers exert marked sympathoinhibitory effects, which may explain the ability of these drugs to prevent or slow down hypertension-related target organ damage throughout their so-called "ancillary properties".

Conclusions

The data reviewed in this paper underline the role of sympathetic neural factors as promoters of hypertension. They also indicate that these factors are involved in determining the cardiovascular risk profile of the hypertensive patient. This represents the rationale for considering sympathomodulation as an important goal of the therapeutic approach aimed at lowering elevated blood pressure levels.

References

1. Kuchel O, Genest J (1997) A neurogenic origin of mild high-renin essential hypertension? N Engl J Med 297:222
2. Julius S, Krause L, Schork NJ et al (1991) Hyperkinetic borderline hypertension in Tecumseh, Michigan. J Hypertens 9:77–84
3. Goldstein DS (1983) Plasma catecholamines and essential hypertension. An analytical review. Hypertension 5:86–99
4. Grassi G, Cattaneo BM, Seravalle G (1998) Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. Hypertension 31:68–72
5. Esler M, Lambert G, Jennings G (1989) Regional norepinephrine turnover in human hypertension. Clin Exp Hypertens A 11[Suppl 1]:75–89
6. Grassi G, Mancia G (2007) Hyperadrenergic and labile hypertension. In: Lip GH, Hall J (eds) Comprehensive hypertension. Mosby Elsevier, Philadelphia, pp 719–726
7. Grassi G, Seravalle G, Dell'Oro R et al (2000) Adrenergic and reflex abnormalities in obesity-related hypertension. Hypertension 36:538–542
8. Grassi G, Seravalle G, Quarti-Trevano F et al (2003) Effects of hypertension and obesity on the sympathetic activation of heart failure patients. Hypertension 42:873–877
9. Grassi G, Dell'Oro R, Quarti-Trevano F et al (2005) Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. Diabetologia 48:1359–1365
10. Grassi G, Seravalle G, Turri C, Mancia G (1999) Sympathetic nerve traffic responses to surgical removal of pheochromocytoma. Hypertension 34:461–465
11. Grassi G (2001) Renin-angiotensin-sympathetic crosstalks in hypertension: reappraising the relevance of peripheral interactions. J Hypertens 19:1713–1716
12. Grassi G, Cattaneo BM, Seravalle G et al (1997) Effects of chronic ACE inhibition on sympathetic nerve traffic and baroreflex control of circulation in heart failure. Circulation 96:1173–1179
13. Grassi G (2004) Counteracting the sympathetic nervous system in essential hypertension. Curr Opin Nephrol Hypertens 13:513–519
14. Grassi G, Quarti-Trevano F (2007) Blood pressure control and therapeutic modulation of the adrenergic overdrive. Curr Hypertens Rep 9:167–169

Neurol Sci (2008) 29:S37–S39
DOI 10.1007/s10072-008-0883-8

Migraine and hypertension

Elio Agostoni · Angelo Aliprandi

Abstract Although the possibility of a comorbidity between migraine and hypertension has long been suspected, the epidemiologic evidence is controversial, with studies demonstrating positive, negative or no correlation between the two diseases. A unifying view that takes into account the most recent evidence suggests that there might be a different effect of diastolic and systolic pressure, with the former having a positive and the latter a negative correlation with migraine. In this paper, the methodologic and clinical reasons for the discrepancies in epidemiologic studies are discussed, together with the possible biological mechanisms that might account for the migraine–hypertension correlation. One such mechanisms may be the renin angiotensin system, which is certainly involved in hypertension and has activities in the CNS that may be relevant for migraine pathogenesis. Despite the uncertainty still present in this field, the control of hypertension in migraine patients is an important factor for the success of migraine treatment and to lower cerebrovascular risk.

Keywords Migraine · Hypertension · Comorbidity Cardiovascular risk factors

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Migraine is a chronic neurologic disease characterised by recurrent attacks of headache, associated with nausea and phono- or photophobia. Although the disease is currently thought to originate from neuronal hyperexcitability and to be essentially a process driven by cerebral events, vascular phenomena such as vasoconstriction and platelet hyperactivation are still considered a relevant aspect of the pathogenesis (for a review of migraine physiopathology see Moskowitz [1]). These vascular aspects have focused the interest of researchers on a possible link between migraine and cerebrovascular risk factors, such as hypertension.

However, the data on the relationship between migraine and systemic blood pressure are unclear and controversial. In facts, while some reports showed a positive association [2–6], more recent studies failed to confirm this result [7–9]. Two recent prospective studies even demonstrated a negative correlation between the two disorders [10, 11], with lower systolic pressure levels in migraine patients than in controls. This contradiction might be explained by methodological issues: earlier studies were not based on IHS classification and therefore lack a standardised diagnosis of migraine. The importance of a strict application of IHS guidelines is further stressed by recent research in which elevated blood pressure levels were demonstrated not just in migraine, but also in tension tension-type and in chronic daily headache [12]. However, the results are conflicting also in the more recent studies, so that issues other than misclassification must be involved. A second possible cause of confusion may be that some studies were conducted in a hospital or ambulatory setting, while others were carried out in the general population. Patients referred to headache centres are a selected subpopulation more likely to be affected by hypertension, as high pressure levels may lead to worsening of headache (this effect is sometimes called the Berkson bias). Therefore, the findings in hospital series

may reflect the effect of hypertension on migraine severity, rather than a true comorbidity.

Another possible explanation of the discrepancies in epidemiological studies may be linked to a different effect of systolic and diastolic blood pressure on migraine. As a matter of fact, a very recent population-based study in Iceland demonstrated a negative correlation with systolic and a positive correlation with diastolic pressure levels [13]. As a result of this double correlation, mean blood pressure levels were not correlated with migraine, while increased pulse pressure seemed to have a protective effect. The correlation between migraine and blood pressure may then be a complex one, so that limiting the analysis to mean levels or to a generic diagnosis of hypertension may be an oversimplification. Finally, one last reason for these conflicting results may be patient heterogeneity. In fact, in a recent work which analysed migraine comorbidity with cluster analysis, three different groups were identified: the first showed comorbidity with cardiovascular risk factors, including hypertension, the second with psychiatric conditions, and the third showed no significant correlations [14]. The three groups did not only differ from the point of view of the comorbidity, but also in the characteristics of the headache; the association between migraine and hypertension may then be limited to a distinct subgroups of patients.

The concept that migraine may be associated with cardiovascular risk factors has emerged also in another line of research, which has focused on the relationship with ischaemic stroke. The GEM study demonstrated a higher cardiovascular risk profile in migraineurs, with higher cholesterol and blood pressure levels [15]. However other large, prospective studies, such as the Women's Health Study [16], demonstrated an independent correlation between migraine with aura and risk of stroke or cardiovascular events; it has not been clearly established how this risk combines with that connected with hypertension.

Another, albeit indirect, indication of a link between hypertension and migraine is suggested by the positive results of ACE inhibitors and sartans [17, 18] for migraine prophylaxis. Indeed, the renin angiotensin system, a well known regulator of fluids and electrolyte homeostasis and of systemic pressure, has other interesting peripheral activities which may be relevant for migraine, such as increase of medullary adrenaline release, vasoconstriction and increase of sympathetic discharge. Moreover, angiotensin 2 has central and neuroendocrine effects, as it can modulate calcium and potassium channels of neurons [19], increases dopamine metabolites in animal models [20] and regulates pineal metabolism [21]. Finally, it has been shown to stimulate nitric oxide production through induction of NF-kb nuclear factor [22, 23]. All these mechanisms may be important in the pathogenesis of migraine; a dysregulation of the renin angiotensin pathway may then be the biologic basis of an association between this disease and hypertension. It is interesting to note that the DD mutation of the angiotensin gene, connected with an increased activity of the enzyme, has been shown to be more frequent in migraine patients [24]. A second biologic mechanism involved in migraine/hypertension comorbidity may be related to biochemical variations in neuropeptides and neurotransmitters. Migraine patients have been shown to have higher blood levels of calcitonin gene related peptide (CGRP) [25], but also lower platelet serotonin levels [26], possibly in relation to platelet overactivation with serotonin release. As CGRP and serotonin have opposite vascular effects, as the former is a vasodilator [27] while the latter has vasoconstrictive activity, these biochemical alterations may account for the complexity of the correlation between pressure levels and migraine.

The possibility of a correlation between migraine and hypertension, although still poorly defined on clinical and epidemiological grounds, has biological plausibility and may disclose some relevant aspect of both diseases. Further research is needed, both on the biologic and on the clinical field; the epidemiologic studies should distinguish between systolic and diastolic pressure and should probably be conducted in the general population to avoid selection bias. Despite these limitations, accurate control of hypertension in migraine patients is certainly an important clinical goal, as uncontrolled hypertension may lead to worsening of headache and to therapeutic failure. Correct management of hypertension is also crucial for the control of cerebrovascular risk, which is already increased in patients with migraine with aura.

References

1. Moskowitz MA (2007) Pathophysiology of headache – past and present. Headache 47[Suppl 1]:S58–S63
2. Merikangas KR, Fenton BT (1994) Comorbidity of migraine with somatic disorders in a large-scale epidemiologic study in the United States. In: Olesen J (ed) Headache classification and epidemiology. Raven, New York, pp 301–314
3. Franceschi M, Colombo B, Rossi P, Canal N (1997) Headache in a population-based elderly cohort. An ancillary study to the Italian Longitudinal Study of Aging (ILSA). Headache 37:79–82
4. Cirillo M, Stellato D, Lombardi C et al (1999) Headache and cardiovascular risk factors: positive association with hypertension. Headache 39:409–416
5. Markush RE, Karp HR, Heyman A, O'Fallon WM (1975) Epidemiologic study of migraine symptoms in young women. Neurology 25:430–435
6. Marcoux S, Berube S, Brisson J, Fabia J (1992) History of migraine and risk of pregnancy-induced hypertension. Epidemiology 3:53–56
7. Waters WE (1971) Headache and blood pressure in the community. BMJ 1:142–143

8. Chen TC, Leviton A, Edelstein S, Ellenberg JH (1987) Migraine and other diseases in women of reproductive age. The influence of smoking on observed associations. Arch Neurol 44:1024–1028
9. Rasmussen BK, Olesen J (1992) Symptomatic and nonsymptomatic headaches in a general population. Neurology 42:1225–1231
10. Wiehe M, Fuchs SC, Moreira LB et al (2002) Migraine is more frequent in individuals with optimal and normal blood pressure: a population-based study. J Hypertens 20:1303–1306
11. Tzourio C, Gagniere B, El Amrani M et al (2003) Relationship between migraine, blood pressure and carotid thickness. A population-based study in the elderly. Cephalalgia 23:914–920
12. Pietrini U, De Luca M, De Santis G (2005) Hypertension in headache patients? A clinical study. Acta Neurol Scand 112:259–264
13. Gudmundsson LS, Thorgeirsson G, Sigfusson N et al (2005) Migraine patients have lower systolic but higher diastolic blood pressure compared with controls in a population-based study of 21 537 subjects. The Reykjavik Study. Cephalalgia 26:436–444
14. Gretchen E, Tietjen MD, Nabeel A et al (2007) Migraine comorbidity constellations. Headache 47:857–865
15. Scher AI, Terwindt GM, Picavet HS et al (2005) Cardiovascular risk factors and migraine: the GEM population-based study. Neurology 64:614–620
16. Kurth T, Gaziano JM, Cook NR et al (2006) Migraine and risk of cardiovascular disease in women. JAMA 296:283–291
17. Charles JA, Jotkowitz S, Byrd LH (2006) Prevention of migraine with olmesartan in patients with hypertension/prehypertension. Headache 46:503–507
18. Tronvik E, Stovner LJ, Helde G et al (2003) Prophylactic treatment of migraine with an angiotensin II receptor blocker. JAMA 289:65–69
19. Allen AM, Moeller I, Jenkins TA et al (1998) Angiotensin receptors in the nervous system. Brain Res Bull 47:17–28
20. Mendelsohn FA, Jenkins TA, Berkovic SF (1993) Effects of angiotensin II on dopamine and serotonin turnover in the striatum of conscious rats. Brain Res 613:221–229
21. Baltatu O, Afeche SC, Jose dos Santos SH et al (2002) Locally synthesized angiotensin modulates pineal melatonin generation. J Neurochem 80:328–334
22. Reuter U, Chiarugi A, Bolay H, Moskowitz MA (2002) Nuclear factor-kappa B as a molecular target for migraine therapy. Ann Neurol 51:507–516
23. Lorenzo O, Ruiz-Ortega M, Suzuki Y et al (2002) Angiotensin III activates nuclear transcription factorkappa B in cultured mesangial cells via AT2 receptors. J Am Soc Nephrol 13:1162–1171
24. Paterna S, DiPasquale P, D'Angelo A et al (2000) Angiotensin-converting enzyme gene deletion polymorphism determines an increase in frequency of migraine attacks in patients suffering from migraine without aura. Eur Neurol 43:133–136
25. Juhasz G, Zsombok T, Modos EA et al (2003) NO-induced migraine attack: strong increase in plasma calcitonin gene-related peptide (CGRP) concentration and negative correlation with platelet serotonin release. Pain 106:461–470
26. Franco-Cereceda A, Gennari C, Nami R et al (1987) Cardiovascular effects of calcitonin gene-related peptides I and II in man. Circ Res 60:393–397
27. Juhasz G, Zsombok T, Laszik A et al (2003) Despite the general correlation of the serotonin transporter gene regulatory region polymorphism (5-HTTLPR) and platelet serotonin concentration, lower platelet serotonin concentration in migraine patients is independent of the 5-HTTLPR variants. Neurosci Lett 350:56–60

Neurol Sci (2008) 29:S40–S43
DOI 10.1007/s10072-008-0884-7

HEADACHE CONTROVERSIES

Migraine with and without aura: a single entity?

Gian Camillo Manzoni · Paola Torelli

Abstract A debate has been going on for many years about whether migraine with aura and migraine without aura are part of the same disorder or should instead be considered as two separate disorders. Although no final consensus has yet been reached on this issue, many clinical and pathogenetic elements suggest that the second option is true. Clinically, migraine with aura and migraine without aura are differentiated by epidemiological features, the characteristics of the headache phase, patient behaviour during attacks, natural history, age at onset and age at resolution, the recurrence pattern of attacks, favouring circumstances and trigger factors, correlation to female reproductive events, comorbidity and preventive therapies. Moreover, several literature reports suggest a possible different pathogenetic basis for the two forms of migraine.

Keywords Migraine with aura · Migraine without aura · Migraine

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If by the word "syndrome" we correctly mean the complex of symptoms that characterise a disorder, then migraine with aura (MA) and migraine without aura (MoA) cannot be considered as a single syndrome due to their marked clinical differences.

On the other hand, investigators have been debating for a long time whether these two forms of migraine could be part of the same disorder or are two separate disorders, and the debate heats up periodically. Interest in this topic rose abruptly in the mid-1980s [1–5] in the wake of important studies conducted by Olesen's group [6, 7] on regional cerebral blood flow in MA and MoA.

However, the great progress made in clinical management and pathogenesis of migraine over the last two decades is not enough to provide the final word on the MA/MoA issue and the debate is still open. Many pathogenetic elements seem to differentiate MA from MoA, but perhaps any discussion on this issue should be preceded by a careful clinical evaluation. We here try to compare the different clinical features of the two migraine forms.

Epidemiology

Based on current literature data, about 10%–12% of the general population now appears to suffer from migraine, with a gender (F:M) ratio of 2.5–3 to1 [8]. Most studies on migraine prevalence, however, have not considered the two forms separately. The few studies that specifically evaluated MA prevalence indicate rates of 1%–4% in the male population and 3%–10% in the female population [9].

One of the clinical features that is most often cited to support the theory of a single syndrome is the high probability of MA and MoA attacks coexisting in the same patient. This theory, however, does not appear to be suf-

ficiently corroborated by epidemiological data. If we look at the prevalence study that is so far considered most reliable from the methodological point of view, because it was conducted by directly interviewing all the recruited subjects, only 13% of MA sufferers were found to also have MoA [10], indicating that this could be a mere coincidence. The results of a population-based twin survey on MA and MoA co-occurrence point to the same conclusions [11].

Aura

Of course, aura is the clinical feature that most distinguishes MA from MoA. On this feature, at least, there is no lack of consensus among supporters and opposers of the single-syndrome theory. However, the overwhelming majority of MA patients complain much more about aura than they do about the headache phase; that is to say they experience much more discomfort from the focal neurological symptoms preceding the headache than from the headache itself. In MA, aura *is* the attack and the headache frequently represents nothing more than an often "banal" post-attack phase.

Headache phase

In MoA, the headache is most prominent and clearly disabling, also due to the accompanying symptoms. In MA, the headache may or may not be present, as in so-called migraine aura without headache. When the headache is present, it may be of either a migraine or non-migraine type. In other words, it can have clinical features that have nothing to do with MoA. Indeed, they may be more similar to those of tension-type headache, even though nobody would ever dream of considering these episodes as tension-type headache with aura. However, the fact that some patients may have only this kind of attack should be enough to raise doubts among the advocates of the single-syndrome theory.

Moreover, the average duration of the headache phase in MA is shorter than the duration of an MoA attack.

Patient behaviour during attacks

During MA attacks, patients often behave as if they were experiencing a panic attack and ask for help from other people around them: a patient's anxiety is most acute during aura and decreases considerably in the headache phase. By contrast, during MoA attacks patients tend to isolate themselves and stay still. They feel discomfort and want to be left alone. Instead of seeming restless, they appear to succumb to the pain and be unable to do their normal activities.

Natural history of the disorder

Mean age at MoA onset is about 19 years, with a high probability of onset between childhood and 35 years of age and a very low probability of onset after age 40. In MA, age at onset differs widely, with onset being more frequent in early adulthood but not infrequent in old age [12].

Age at resolution is also very different in the two migraine forms. While MoA tends to resolve spontaneously – or decrease considerably – after age 50, MA usually disappears at an earlier age [13].

Attacks generally recur regularly for years with a frequency of several a month in MoA, while in the overwhelming majority of MA cases the attacks are much less frequent and recur with an irregular, unpredictable and capricious pattern.

Favouring circumstances and trigger factors

MoA attacks are more frequent over weekends and when the patient relaxes after experiencing a stressful event or emotion, such as passing an examination. In women of childbearing age, a specially risky circumstance is the perimenstrual period. Conversely, MA attacks do not have favouring circumstances, though in some cases they can be induced by some strong natural or artificial visual stimulation [14].

Correlation to major female reproductive events

A clear-cut difference between the two migraine forms is represented by the course of the attacks during the main phases of a woman's reproductive life. As has been hinted at before, MoA is greatly influenced by menstruation, but MA is not. Only in about one-fifth of MA cases vs. about three-quarters of MoA cases is there an increased risk of attacks in the perimenstrual period [15].

During pregnancy, MoA disappears in the majority of cases, while MA tends to persist or worsen and in some cases even to occur for the first time [15].

Oral contraceptives do not negatively affect MoA in most cases, while they can worsen MA to the point that some authors consider this form of migraine as a contraindication to the pill.

During menopause, MoA is often attenuated or ceases altogether, while MA appears to be less influenced by it. (Literature data on this subject are very scarce.)

Comorbidity

Among the many possible conditions that are comorbid with migraine, the most widely studied over the last few

years have been psychiatric disorders, stroke and patent foramen ovale (PFO).

In this respect, too, there are marked differences between MA and MoA. MoA is significantly associated with depression [16], while MA is associated with anxiety, particularly panic attacks [17].

Literature reports seem to indicate a six- to eight-fold risk of stroke in 30–40-year-old women with MA vs. controls, while in MoA women this risk does not appear to be increased [18–20].

Recently, a statistically significantly higher frequency of PFO has been reported in adults with MA (about 45%–50% of cases) compared with both non-migraine controls and MoA patients (about 20%–25% of cases) [21].

Preventive therapy

Unfortunately, there are still too few pharmacological studies on migraine dealing separately with MoA and MA cases. In any event, both clinical experience and the few data available from drug trials demonstrate that MoA may benefit from preventive drug therapy with beta-blockers, calcium-channel blockers, partial serotonin agonists, tricyclic agents and antiepileptic agents such as valproate and topiramate. By contrast, MA responds primarily – and often dramatically – to another antiepileptic agent, lamotrigine, which is of no use in MoA.

The clinical features of MA and MoA described in this report appear so distinctive that even international headache classifications – the 1988 International Headache Society classification [22] and the 2004 International Classification of Headache Disorders [23] – have cautiously begun to distance themselves from the single-syndrome theory, trying instead to categorise the two forms separately, albeit within the same chapter.

As to the pathogenetic mechanisms of migraine, which we briefly mentioned at the beginning of this discussion on the MA/MoA issue, we have chosen not to deal at length with the abundant literature data existing on this subject and to limit ourselves to a few conclusive considerations.

Simply put, the main reason we did this is that we should honestly admit that we know nothing about pathogenesis, either of MoA or of MA. We have many working hypotheses – some of them very interesting – but these are, well, just hypotheses. We have many pieces of the migraine puzzle in our hands, but no sure pathogenetic interpretation to complete the picture. Moreover, many of the studies conducted so far did not, unfortunately, consider the two forms of migraine separately. The few studies that did so, not infrequently point to different, if not entirely conflicting, results for MA and MoA.

Examples range from the by-now dated yet still seminal studies of Olesen's group on spreading oligaemia in MA but not in MoA [6, 7], to the more recent studies by Chronicle at al. on cortical hyperexcitability in MA but not in MoA [24].

In conclusion, MA and MoA present two distinct clinical pictures, which – perhaps – have in common only a slightly higher than average chance of coexisting in the same patient. Even if they actually did, the reason could be comorbidity rather than the existence of a single clinical entity. Clarifying the pathogenetic mechanisms of MA and MoA will undoubtedly be of fundamental importance to help define their relationship. Based on present-day knowledge, however, it is not yet possible for investigators to postulate or even consistently hypothesise a common pathophysiological basis for these two migraine forms.

References

1. Ziegler DK (1985) The headache symptom. How many entities? Arch Neurol 42:273–274
2. Dalessio DJ (1985) Is there a difference between classic and common migraine? What is migraine after all? Arch Neurol 42:275–276
3. Hachinski V (1985) Common and classic migraine. One or two entities? Arch Neurol 42:277
4. Wilkinson M, Blau JN (1985) Are classical and common migraine different entities? Headache 25:211–212
5. Olesen J (1985) Are classical and common migraine different entities? Headache 25:213
6. Olesen J, Larsen B, Lauritzen M (1981) Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 9:344–352
7. Olesen J, Tfelt-Hansen P, Henriksen L, Larsen B (1981) The common migraine attack may not be initiated by cerebral ischaemia. Lancet 2:438–440
8. Stovner LJ, Hagen K, Jensen R et al (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia; 27:193–210
9. Manzoni GC, Stovner LJ (2008) Epidemiology of headache. In: Nappi G, Moskowitz MA (eds) Handbook of clinical neurology, 3rd series. Elsevier, Amsterdam (*in press*)
10. Rasmussen BK, Olesen J (1992). Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia 12:221–228
11. Russell MB, Ulrich V, Gervil M, Olesen J (2002) Migraine without aura and migraine with aura are distinct disorders. A population-based twin survey. Headache 42:332–336
12. Fisher CM (1986) Late-life migraine accompaniments – further experience. Stroke 17:1033–1042
13. Nappi G, Manzoni GC (2005) Manuale delle cefalee. Masson, Milan
14. Manzoni GC, Farina S, Lanfranchi M, Solari A (1985) Classic migraine. Clinical findings in 164 patients. Eur Neurol 24:163–169
15. Manzoni GC, Farina S, Granella F et al (1986) Classic and common migraine. Suggestive clinical evidence of two separate entities. Funct Neurol 1:112–122
16. Breslau N, Schultz LR, Stewart WF et al (2000) Headache and major depression: is it the association specific to migraine? Neurology 54:308–313
17. Breslau N (1998) Psychiatric comorbidity in migraine. Cephalalgia 18[Suppl 22]:56–61
18. Tzourio C, Iglesias S, Hubert JB et al (1993) Migraine and risk of ischaemic stroke: a case-control study. BMJ 307:289–292

19. Carolei A, Marini C, De Matteis G (1996) History of migraine and risk of cerebral ischaemia in young adults. Lancet 347:1503–1506
20. Chang CL, Donaghy M, Poulter N (1999) Migraine and stroke in young women: case-control study. BMJ 318:13–18
21. Domitrz I, Mieszkowski J, Kamińska A (2007) Relationship between migraine and patent foramen ovale: a study of 121 patients with migraine. Headache 47:1311–1318
22. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8[Suppl 7]:1–96
23. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders. 2nd Edition. Cephalalgia 24:1–160
24. Chronicle EP, Pearson AJ, Mulleners WM (2006) Objective assessment of cortical excitability in migraine with and without aura. Cephalalgia 26:801–808

Neurol Sci (2008) 29:S44–S46
DOI 10.1007/s10072-008-0885-6

HEADACHE CONTROVERSIES

Migraine with and without aura share the same pathogenic mechanisms

R. Allan Purdy

Abstract Migraine with aura and without aura share the same clinical features with respect to the headache, and differ nosologically in the presence or absence of aura. The mechanisms of aura generation are now becoming clearer, based on imaging studies, and a common migraine pathophysiology for all subtypes of migraine headaches now seems reasonable, as it would seem implausible that all of these neurological events have different pathogenic mechanisms. Both major subtypes of migraine clearly represent a perturbation of normal physiology and employ normal anatomic pathways to generate the aura and headache, similar to aura and a seizure. So what is the mechanism of migraine aura? Do migraine without aura patients have clinically silent aura? Migraine is after all defined as a clinical disorder and is the prototypic primary headache and thus its uniform pathogenesis must underlie all that we know about migraine clinically. This presentation will take the resolve that the migraine with and without aura share the same pathogenic mechanisms.

Keywords Migraine · Aura · Mechanisms · Pathophysiology

Migraine without aura is a common disorder, whereas migraine with aura is less common but more dramatic in that the neurological aura is what "defines" the headache. In migraine without aura it is the headache features that define the disorder [1]. In practice it is the visual aura, usually a fortification spectra or scintillating scotomata [2], which almost makes the diagnosis pathognomonic for migraine with aura. Neurologists have always been interested in neurological symptoms, particularly aura as it relates to migraine or epilepsy [3]. This issue of how the aura is generated is now becoming clearer, based on imaging studies but also the fact that the aura is linked to the headache in some pathophysiological manner. It is inconceivable to this author that migraine without aura, which has identical clinical headache symptoms to

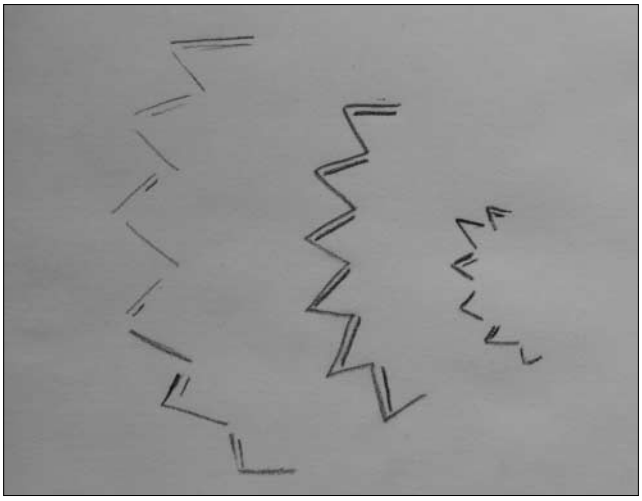

Fig. 1 Author's scintillating zig-zag bright light that moves across visual field over some 20 minutes. On about half of the occasions it is followed by migrainous headache, while the rest of the time, no pain follows at all.

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migraine with aura, can be generated in any other way except by way of the same pathogenic mechanisms. In fact patients can have migraine aura with headache and without headache throughout their lives and particularly later in life, as late life migraine accompaniments, and it would seem implausible that all of these events have different pathogenic mechanisms (Fig. 1). It makes no sense whatsoever clinically to suggest that the aura of migraine should be disconnected from the actual headache any more than the aura of epilepsy should be disconnected from the actual seizure. Both disorders represent perturbations of normal physiology and employ normal anatomic pathways to generate their neurological warnings prior to the generic event that defines the headache or seizure.

What is the mechanism of migraine aura?

Aura is a clinical event in about 20% of migraine patients, using IHS criteria [1]. Aura is typically visual or sensory, and is accompanied by a spreading oligaemia first reported by Olesen et al.'s pioneering studies [4], supported and extended by the work of the Boston Group [5, 6]. The observation of an initial hyperaemic phase [7] secures the validity of comparisons of migraine aura with cortical spreading depression [8], however the headache begins even while the oligaemia is still present [9] and thus these aura studies show that headache is not due to reactive vasodilatation as Wolff had considered [10]. Also it appears that the cortical spreading depression of Leao [11–13] has many similarities with aura, and the human aura is the homologue of that process observed in other species [14]. As only a small percentage of patients report aura, is it absent in most, or present but sub-clinical?

Fundamentally, migraine is an episodic headache with certain associated features, in particular sensitivity to light, sound and smells, as well as a neurological aura in about one third of sufferers. These features give clues to the pathophysiology of acute attacks, and any explanation must account for *all* of these cardinal features.

Do migraine without aura patients have clinically silent aura?

Imaging data overwhelmingly report no change in brain blood flow in migraine without aura [6, 15, 16], so it seems unlikely that aura is unnoticed clinically. A case of bilateral spreading oligaemia observed with positron emission tomography (PET) [17] may support the presence of *silent aura*. This patient did not have typical aura, but blurring, which is not uncommon in all types of migraine. Thus is seems necessary when considering the clinical evolution of migraine to also consider aura as an integral part of the pathogenic mechanisms.

Also, a recent PET study showed that posterior cerebral hypoperfusion accompanying migraine auras could also be present in migraine attacks without aura [18], suggesting a common putative pathogenic mechanism for migraine with aura.

This presentation will take the point of view in the resolution that migraine with aura and migraine without aura do share the same pathogenic mechanisms. Migraine is a clinical disorder and current information supports a common aetiopathogenesis for its various subtypes. Migraine is the prototypic primary headache disorder and thus its uniform pathogenesis must underlie all that we know about migraine clinically.

Acknowledgement Special thanks to Professor Peter Goadsby, Department of Neurology, University of California, San Francisco, CA, for providing some content material for this overview.

References

1. Headache Classification Committee of The International Headache Society (2004) The International Classification of Headache Disorders (second edition). Cephalalgia 24[Suppl 1]:1–160
2. Russell MB, Olesen J (1996) A nosographic analysis of the migraine aura in a general population. Brain 119:355–361
3. Gowers WR (1888) A manual of diseases of the nervous system. P. Blakiston, Son & Co, Philadelphia
4. Olesen J, Larsen B, Lauritzen M (1981) Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 9:344–352
5. Cutrer FM, Sorensen AG, Weisskoff RM et al (1998) Perfusion-weighted imaging defects during spontaneous migrainous aura. Ann Neurol 43:25–31
6. Sanchez del Rio M, Bakker D, Wu O et al (1999) Perfusion weighted imaging during migraine: spontaneous visual aura and headache. Cephalalgia 19:701–707
7. Hadjikhani N, Sanchez del Rio M, Wu O et al (2001) Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci U S A 98:4687–4692
8. Lauritzen M (1994) Pathophysiology of the migraine aura. The spreading depression theory. Brain 117:199–210
9. Olesen J, Friberg L, Skyhoj-Olsen T et al (1990) Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann Neurol 28:791–798
10. Wolff HG (1963) Headache and other head pain, 3rd Edn. Oxford University Press, New York
11. Leao AAP (1944) Spreading depression of activity in cerebral cortex. J Neurophysiol 7:359–390
12. Leao AAP (1947) Further observations on the spreading depression of activity in the cerebral cortex. J Neurophysiol 10:409–414
13. Marshall WH (1959) Spreading cortical depression of Leao. Physiol Rev 39:239–288
14. Lauritzen M (2001) Cortical spreading depression in migraine. Cephalalgia 21:757–760
15. Olesen J (1991) Cerebral and extracranial circulatory disturbances in migraine: pathophysiological implications.

Cerebrovasc Brain Metab Rev 3:1–28
16. Cohen AS, Goadsby PJ (2004) Functional neuroimaging of primary headache disorders. Curr Neurol Neurosci Rep 4:105–110
17. Woods RP, Iacoboni M, Mazziotta JC (1994) Bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. N Engl J Med 331:1689–1692
18. Géraud G, Denuelle M, Fabre N et al (2005) Positron emission studies in migraine. Rev Neurol (Paris) 161:666–670

Neurol Sci (2008) 29:S47–S51
DOI 10.1007/s10072-008-0886-5

HEADACHE CONTROVERSIES

Migraine: a genetic disease?

Pasquale Montagna

Abstract Migraines carry a substantial genetic liability, and in families affected with the typical migraines (migraine with, MA, and without aura, MO) linkage to some chromosomal loci has been reported. As yet however, no genes are known for MA/MO, while the three genes discovered as responsible for familial hemiplegic migraine (FHM) are not involved in the typical migraines. Accordingly, we propose to consider FHM as a syndromic migraine and not as a variety of MA. Moreover, we suggest that epigenetic mechanisms play a role in the determination of the typical migraines, and that the primary headaches represent behavioural responses (sickness behaviour, fight-or-flight responses), having adaptive advantage and having been evolutionary conserved, in which pain represents a signal of homeostatic imbalance. Epigenetic mechanisms and this proposed genetic behavioural model could be usefully incorporated into headache genetic research.

Keywords Migraine · Genetics · Epigenetics · Linkage · Genetic association

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Is migraine a genetic disease?

Any clinician working in the field of headaches is likely to encounter in his/her everyday work a familial aggregation. Migraines are however particularly prevalent among the general population, especially among females in the age range 30–40 years, and therefore any familial aggregation of the disease could be due simply to chance occurrence within the family. In this respect, careful genetic epidemiological studies performed in the last decades have convincingly demonstrated that the recurrence (disease) risk for the so-called typical migraines (by which we mean migraine with, MA, and without aura, MO) in relatives of probands affected with MO and particularly MA is higher than their chance recurrence in the general population. When examining the recurrence rate among first-degree relatives of a MO proband, the resulting risk is about twice that incurred by a random member of the general population; even more remarkably, first-degree relatives of probands with MA carry a recurrence risk for MA that is nearly four times that of any random member of the general population [1].

These findings thus establish that migraine indeed has a familial aggregation. Being familial however is not tantamount to being hereditary, as a familial aggregation could be related to specific environmental factors acting within the family. However, when comparing the relative disease risk for spouses of migraine probands, no increased risk for MA (and only a slightly, 1.4-fold, increased risk for spouses of MO probands) was found, implying a hereditary rather than environmentally determined familial aggregation [1]. Comparisons of mono- vs. di-zygotic twins also indicate that about half of the variation in the concordance rate for the typical migraines is attributable to genetic factors shared by the twins [2]. Thus, overwhelming genetic epidemiological evidence favours a hereditary liability to the typical migraines, probably stronger in the case of MA. Whether

MA and MO represent genetically distinct disorders cannot be ascertained with certainty, however the lack of shared recurrence disease risk for MO among relatives of MA probands suggests that this is indeed the case [1].

Analysis of migraine pedigrees is consequently needed in order to detect the genetic transmission pattern, and many such studies have been performed in the literature [3–6], however with equivocal results. No consistent pattern was detected, and the results of complex segregation analysis were mostly consistent with a multifactorial inheritance pattern, even in those families displaying an apparently autosomal dominant transmission [6].

A multifactorial inheritance pattern is considered for many other medical conditions that are widely prevalent in the general population, and implies that several genes have a role in pathogenesis, each one with a small quantitative effect (each a quantitative trait locus) and interacting with several environmental factors. Multifactorial traits are those that conform to a quantitative, not qualitative, variation, and show a quantitative distribution in the general population. Examples of quantitative traits that vary continuously within a quantitative range are height, body weight, blood pressure, etc. According to the model of multifactorial inheritance, we should expect to detect migraine liability spread over tens or possibly hundreds of genes, each characterised by a small quantitative effect.

It remains unclear however whether migraines represent truly quantitative traits in the general population. A brief consideration of their clinical characteristics suggests that migraines are not phenotypic traits comparable to body weight or blood pressure, but rather disorders with intrinsically consistent clinical features of the attack and specific natural history, and should be rather conceived as behaviours implying more of a qualitative difference (see later). It is therefore likely that migraine genes, probably several, may in fact exist, and that migraines are polygenic (or even oligogenic) rather than multifactorial diseases.

Genes for migraine families?

That the typical migraines are polygenic diseases, conforming to Mendelian patterns of hereditary transmission, is suggested by several linkage and genome-wide scanning studies successfully performed in selected families with recurrence of MA or MO/MA, and in particular by the successful elucidation of the genetics of familial hemiplegic migraine (FHM), a subtype of MA having an autosomal dominant transmission [7].

Genome-wide scans in 50 multi-generational Finnish families with transmission of MA have identified linkage loci to chromosome 4q24 near the marker D4S1647 [8], a linkage locus that was later confirmed (but to 4q21) in Icelandic families having recurrence of MO [9]. Linkage to chromosome 6 was found by Carlsson et al. [10] in a large family from Sweden, with multigenerational recurrence of MA and MO, while in Canadian families with recurrence of MA, linkage was obtained to a locus on chromosome 11q24 with a LOD score of 4.2 [11]. A locus mapping to chromosome 15q11-q13 was detected in Italian families with recurrence of MA in an autosomal dominant pattern, to a genomic region containing three genes encoding for subunits of the GABA-A receptor [12] and to chromosome 14 in a large Italian family with recurrence of MO [13]. Finally, other chromosomal localisations (on chromosomes 1 and 19) have been proposed that shall be discussed later with the FHM genetic contribution to the typical migraines, and to chromosome Xq24-28 in three large Australian pedigrees with recurrence of typical migraine [14, 15].

From the above evidence, and even though specific genes have not yet been identified, it is nonetheless clear that loci for genetic determination exist for the typical migraines, possibly separated for MA *vs*. the more common MO. That indeed migraines can conform to a Mendelian type of genetic transmission is highlighted by the genetics of FHM, even though the relationship of FHM to the genetics and the pathogenesis of the typical migraines remains doubtful.

Familial hemiplegic migraine (FHM): not a good model for the typical migraines

According to the Headache Classification Subcommittee (HCS) [7], FHM is a variety of MA with an autosomal dominant transmission. Three genes have been successively identified in FHM families, the first one, *CACNA1A*, encodes for a subunit of a neuronal calcium channel [16], while the others encode respectively for the A2 subunit of the Na/K ATPase and for the sodium channel *SCN1A* [17, 18]. Accordingly, 3 types of FHM, types 1, 2 and 3, are known; FHM type 1 is moreover allelic with two other neurological conditions, spino-cerebellar ataxia type 6 [19] and episodic ataxia type 2 [16], reflecting the long known fact that some families with FHM display additional signs of cerebellar episodic or progressive involvement.

The discovery of the genetic basis of FHM, at least in some families, since other families do not carry these liability genes and therefore further genetic heterogeneity is implied, has allowed a detailed dissection of the FHM phenotype and the consequent discovery that the FHM mutations are implicated in phenotypes widely different from the prototypical hemiplegic migraines.

Indeed, besides cerebellar ataxia, FHM families may display epileptic seizures of different types [20–23], mental retardation [24–26], paroxysmal psychosis [27],

Table 1 A list of proposed and still provisional syndromic migraines

Syndromic migraines	Genes (chromosome) involved	Migrainous features
Familial hemiplegic migraine, types 1, 2 and 3 (FHM1,2,3)	*CACNA1A* (chromosome 19p13); *ATP1A2* (chromosome 1q23); *SCN1A* (chromosome 2q24)	Attacks with hemiplegic aura
Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes (MELAS)	mtDNA genes *MTTL1, MTTQ, MTTH, MTTK, MTTS1, MTND1, MTND5, MTND6, MTTS2*	Recurrent MA, focal neurological deficits, vomiting and convulsions
Cerebral arteriopathy, autosomal dominant, subcortical infarcts, leukoencephalopathy (CADASIL)	*NOTCH 3* (chromosome 19p13.2-p13.1)	MA/MO in 22 to 38% of those affected
Retinopathy, vascular, cerebral and renal involvement, Raynaud and migraine phenomena (HERNS)	*TREX1* (chromosome 3p21.3-p21.2)	Migraine in 70% of those affected
Familial cerebral cavernous malformations (CCM 1, 2, 3)	CCM 1: *KRYT 1* (chromosome 7q11.2-q21); CCM 2: *CCM2* (chromosome 7p15-p13); CCM 3: *PDCD10* (chromosome 3q25.2-q27)	Convulsions and migraine attacks

movement disorders [28, 29] and even a myasthenic syndrome [30]. Multisystem involvement may be detected even within single families [24, 29] and is found in both FHM types 1 and 2, FHM type 3 probably having been reported too recently for a complete clinical dissection.

The successful discovery of the FHM genes and the consideration that FHM represents a variety of the typical migraines, has brought about the proposal that the typical migraines represent calcium channelopathies [31] and that FHM pathogenesis is a model for the typical migraines [32]. However, lacking from such suggested models are any considerations of the fact that FHM may display symptoms and signs never or very rarely found in the typical migraines, such as cerebellar atrophy, mental retardation or epilepsy, and the fact that FHM mutations may even occur in the absence of the typical hemiplegic migraine features.

Moreover, studies of the possible involvement of the FHM genes in the typical migraines have mostly met with consistently negative results [33–44] and there is no evidence to date that any FHM gene is mutated in migraine pedigrees without members affected by hemiplegic migraine attacks.

A proposal of FHM as a *syndromic* migraine

The lack of any involvement of the FHM genes in the typical migraines and the wide clinical features found in FHM families indicating multisystem pathology argue for a substantially different classification of the FHMs. FHM cannot be construed as a subtype of the typical migraine MA, but rather as an example of *syndromic migraine*, a new nosological category of migraines that we propose as useful for clinical classification and for diagnostic purposes, along with similar categorisations of *syndromic* deafness, epilepsy, mental retardation, etc.

Syndromic migraines, accordingly, are diseases, often genetically determined, in which migraine-like attacks, sometimes indistinguishable from attacks occurring in the typical migraines, recur, compounded by the involvement of other neurological or extra-neurological systems. While the HCS [7] recognises a category of secondary headaches, i.e., attacks of headache/migraine that are secondary to known causes rather than to a primary brain disturbance, it does not recognise the concept of syndromic migraine, which, unlike secondary headaches, refers to clinical syndromes and not simply to a range of headache attacks. While this may be due to the fact that the HCS [7] classifies headache attacks and not headache diseases, introducing the concept of syndromic migraines could be useful not only for clinical but also for scientific reasons.

A number of proposed and still very provisional syndromic migraines, including FHM, are displayed in Table 1 for the sake of providing some examples.

Genetic and epigenetic migraine mechanisms, and a genetic behavioural model

From the above discussion, genes for the typical migraines seem particularly difficult to identify. This may be due to several factors, not the least being the difficulties with diagnosis due to the lack of recognisable laboratory markers for the disease, and the probably wide genetic heterogeneity of such a prevalent disorder. However, several proposals can be made for a fruitful genetic quest.

As envisioned with many other complex and prevalent diseases, epigenetic mechanisms are likely to play a relevant role in the determination of the typical migraines. Attachment styles in the early stages of the nervous development of the infant and child seem to me particularly rel-

evant, given the striking maternal influence on migraine phenotypic variability in offspring. Epigenetic mechanisms are those that result from changes in DNA and in DNA-binding proteins that do not modify the nucleotide sequence of the DNA, and result in the silencing or activation of genes. Several human genes are known to be subjected to epigenetic mechanisms and in particular to imprinting, i.e., their expression depends upon which parent any particular allele is inherited from [45]. Imprinted genes are especially involved in embryonic development and represent susceptibility loci for functional modifications by genetic and epigenetic mechanisms. Moreover, age and even lifestyles (such as dietary influences) have been suggested to play a role in epigenetic mechanisms [46]. Epigenetic factors are thus critically placed at the interface between DNA encoded genetic variability and environmental triggering and modifying factors, especially those acting in the early stages of life. These environmental developmental and triggering factors could be usefully screened and incorporated into the genetic analysis of migraines.

Another consideration stems from a different conceptualisation of the typical migraines (and of the other primary headaches, such as cluster headache) as not simply painful conditions, but rather as behavioural responses to homeostatic perturbations of the brain metabolism that include pain as a clinical feature (in our view migraine pain should thus be conceived as a kind of homeostatic pain, e.g., like the pain of angina pectoris, and surely not as a neuropathic pain [47]).

We therefore consider the behaviour observed during the typical migraine attacks to represent a kind of sickness behaviour, while that during cluster headache a type of fight-or-flight response [48, 49]. Both types of responses are organised by distinct neural networks that include pain as one of various phenotypic elements, have a survival advantage [50] and represent adaptive mechanisms that are present in all mammals under typical conditions of perturbed homeostasis. This novel conception of the primary headaches as evolutionary conserved behavioural responses has been presented in more detail elsewhere [51, 52] as a useful genetic behavioural model to be incorporated into the dissection of the genetics of the migraine diseases.

Acknowledgements I wish to thank Ms. A. Laffi for secretarial help. Supported by the Italian Ministry of University and Research (grant prot. # 2005061313).

References

1. Russell MB, Iselius L, Olesen J (1996) Migraine without aura and migraine with aura are inherited disorders. Cephalalgia 16:305–309
2. Russell MB, Ulrich V, Gervil M, Olesen J (2002) Migraine without aura and migraine with aura are distinct disorders. A population-based twin survey. Headache 42:332–336
3. Devoto M, Lozito A, Staffa G et al (1986) Segregation analysis of migraine in 128 families. Cephalalgia 6:101–105
4. Mochi M, Sangiorgi S, Cortelli P et al (1993) Testing models for genetic determination in migraine. Cephalalgia13:389–394
5. Ulrich V, Gervil M, Kyvik KO et al (1999) The inheritance of migraine with aura estimated by means of structural equation modelling. J Med Genet 36:225–227
6. Ulrich V, Russell MB, Ostergaard S, Olesen J (1997) Analysis of 31 families with an apparently autosomal-dominant transmission of migraine with aura in the nuclear family. Am J Med Genet 74:395–397
7. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders. Cephalalgia 24:1–160
8. Wessman M, Kallela M, Kaunisto MA et al (2002) A susceptibility locus for migraine with aura, on chromosome 4q24. Am J Hum Genet 70:652–662
9. Bjornsson A, Gudmundsson G, Gudfinnsson E et al (2003) Localization of a gene for migraine without aura to chromosome 4q21. Am J Hum Genet 73:986–993
10. Carlsson A, Forsgren L, Nylander PO et al (2002) Identification of a susceptibility locus for migraine with and without aura on 6p12.2-p21.1. Neurology 59:1804–1807
11. Cader ZM, Noble-Topham S, Dyment DA et al (2003) Significant linkage to migraine with aura on chromosome 11q24. Hum Mol Genet 12:2511–2517
12. Russo L, Mariotti P, Sangiorgi E et al (2005) A new susceptibility locus for migraine with aura in the 15q11-q13 genomic region containing three GABA-A receptor genes. Am J Hum Genet 76:327–333
13. Soragna D, Vettori A, Carraro G et al (2003) A locus for migraine without aura maps on chromosome 14q21.2-q22.3. Am J Hum Genet 72:161–167
14. Nyholt DR, Dawkins JL, Brimage PJ et al (1998) Evidence for an X-linked genetic component in familial typical migraine. Hum Mol Genet 7:459–463
15. Nyholt DR, Curtain RP, Griffiths LR (2000) Familial typical migraine: significant linkage and localization of a gene to Xq24-28. Hum Genet 107:18–23
16. Ophoff RA, Terwindt GM, Vergouwe MN et al (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 87:543–552
17. De Fusco M, Marconi R, Silvestri L et al (2003) Haploinsufficiency of ATP1A2 encoding the Na+/K+pump alpha2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 33:192–196
18. Dichgans M, Freilinger T, Eckstein G et al (2005) Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 366:371–377
19. Zhuchenko O, Bailey J, Bonnen P et al (1997) Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel. Nat Genet 15:62–69
20. Jouvenceau A, Eunson LH, Spauschus A et al (2001) Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. Lancet 358:801–807
21. Vanmolkot KR, Kors EE, Hottenga JJ et al (2003) Novel mutations in the Na+,K+-ATPase pump gene ATP1A2 associated with familial hemiplegic migraine and benign familial infantile convulsions. Ann Neurol 54:360–366
22. Kors EE, Melberg A, Vanmolkot KR et al (2004) Childhood epilepsy, familial hemiplegic migraine, cerebellar ataxia, and a new CACNA1A mutation. Neurology 63:1136–1137
23. Beauvais K, Cave-Riant F, De Barace C et al (2004) New CACNA1A gene mutation in a case of familial hemiplegic migraine with status epilepticus. Eur Neurol 52:58–61
24. Cevoli S, Pierangeli G, Monari L et al (2002) Familial hemi-

plegic migraine: clinical features and probable linkage to chromosome 1 in an Italian family. Neurol Sci 23:7–10
25. Jurkat-Rott K, Freilinger T, Dreier JP et al (2004) Variability of familial hemiplegic migraine with novel A1A2 Na+/K+-ATPase variants. Neurology 62:1857–1861
26. Vanmolkot KR, Stroink H, Koenderink JB et al (2006) Severe episodic neurological deficits and permanent mental retardation in a child with a novel FHM2 ATP1A2 mutation. Ann Neurol 59:310–314
27. Spranger M, Spranger S, Schwab S et al (1999) Familial hemiplegic migraine with cerebellar ataxia and paroxysmal psychosis. Eur Neurol 41:150–152
28. Giffin NJ, Benton S, Goadsby PJ (2002) Benign paroxysmal torticollis of infancy: four new cases and linkage to CACNA1A mutation. Dev Med Child Neurol 44:490–493
29. Swoboda KJ, Kanavakis E, Xaidara A et al (2004) Alternating hemiplegia of childhood or familial hemiplegic migraine? A novel ATP1A2 mutation. Ann Neurol 55:884–887
30. Maselli RA, Kong DZ, Bowe CM et al (2000) Presynaptic congenital myasthenic syndrome due to quantal release deficiency. Neurology 57:279–289
31. Terwindt GM, Ophoff RA, Haan J et al (1998) Migraine, ataxia and epilepsy: a challenging spectrum of genetically determined calcium channelopathies. Dutch Migraine Genetics Research Group. Eur J Hum Genet 6:297–307
32. Pietrobon D, Striessnig J (2003) Neurobiology of migraine. Nat Rev Neurosci 4:386–398
33. Hovatta I, Kallela M, Färkkilä M, Peltonen L (1994). Familial migraine: exclusion of the susceptibility gene from the reported locus of familial hemiplegic migraine on 19p. Genomics 23:707–709
34. Monari L, Mochi M, Valentino ML et al (1997) Searching for migraine genes: exclusion of 290 cM out of the whole human genome. Ital J Neurol Sci 18:277–282
35. Noble-Topham SE, Dyment DA, Cader MZ et al (2002) Migraine with aura is not linked to the FHM gene CACNA1A or the chromosomal region, 19p13. Neurology 59:1099–1101
36. Jones KW, Ehm MG, Pericak-Vance MA et al (2001) Migraine with aura susceptibility locus on chromosome 19p13 is distinct from the familial hemiplegic migraine locus. Genomics 78:150–154
37. Brugnoni R, Leone M, Rigamonti A et al (2002) Is the CACNA1A gene involved in familial migraine with aura? Neurol Sci 23:1–5
38. Wieser T, Mueller C, Evers S et al (2003) Absence of known familial hemiplegic migraine (FHM) mutations in the CACNA1A gene in patients with common migraine: implications for genetic testing. Clin Chem Lab Med 41:272–275
39. von Brevern M, Ta N, Shankar A et al (2006) Migrainous vertigo: mutation analysis of the candidate genes CACNA1A, ATP1A2, SCN1A, and CACNB4. Headache 46:1136–1141
40. Netzer C, Todt U, Heinze A et al (2006) Haplotype-based systematic association studies of ATP1A2 in migraine with aura. Am J Med Genet B Neuropsychiatr Genet 141:257–260
41. Kirchmann M, Thomsen LL, Olesen J (2006) The CACNA1A and ATP1A2 genes are not involved in dominantly inherited migraine with aura. Am J Med Genet B Neuropsychiatr Gen 141:250–256
42. Kim JS, Yue Q, Jen JC et al (1998) Familial migraine with vertigo: no mutations found in CACNA1A. Am J Med Genet 79:148–151
43. Jen JC, Kim GW, Dudding KA, Baloh RW (2004) No mutations in CACNA1A and ATP1A2 in probands with common types of migraine. Arch Neurol 61:926–928
44. Curtain RP, Lea RA, Tajouri L et al (2005) Analysis of chromosome 1 microsatellite markers and the FHM2-ATP1A2 gene mutations in migraine pedigrees. Neurol Res 27:647–652
45. Luedi PP, Dietrich FS, Weidman JR et al (2007) Computational and experimental identification of novel human imprinted genes. Genome Res 17: 1723–1730
46. Oommen AM, Griffin JB, Sarath G, Zempleni J (2005) Roles for nutrients in epigenetic events. J Nutr Biochem 16:74–77
47. Craig AD (2003) A new view of pain as a homeostatic emotion. Trends Neurosci 26:303–307
48. Johnson RW (2002) The concept of sickness behavior: a brief chronological account of four key discoveries. Vet Immunol Immunopathol 87:443–450
49. Bracha HS, Ralston TC, Matsukawa JM et al (2004) Does "fight or flight" need updating? Psychosomatics 45:448–449
50. Loder E (2002) What is the evolutionary advantage of migraine? Cephalalgia 22:624–632
51. Montagna P (2008) The primary headaches: genetics, epigenetics and a behavioural genetic model. J Headache Pain 9:57–69
52. Montagna P, Cortelli P (2008) Migraine and the autonomic nervous system. In: Low PA (ed) Clinical autonomic disorders: evaluation and management. Lippincott, Williams and Wilkins (*in press*)

Neurol Sci (2008) 29:S52–S54
DOI 10.1007/s10072-008-0887-4

HEADACHE CONTROVERSIES

Is migraine a genetic illness? The various forms of migraine share a common genetic cause

Michael Bjørn Russell

Abstract Is migraine a genetic illness? This question was previously controversial, but today the answer *yes* is generally accepted. The scientific evidence is the significantly increased familial risk of migraine, and the significantly higher concordance rate of migraine in monozygotic than dizygotic twin pairs. Finally, the three identified ion-channel genes that can cause familial hemiplegic migraine provide very strong evidence of genetics. Mutations in these genes can also cause sporadic hemiplegic migraine. The next question is whether the different types of migraine, i.e. migraine without aura, migraine with aura, sporadic hemiplegic migraine and familial hemiplegic migraine share a common genetic cause. This question is at present controversial. However, the fact that all types of migraine are paroxystic in nature suggest that a common genetic cause could be mutations in ion channels, although a common mutation has not yet been identified in the more common types of migraine: migraine without aura and migraine with aura.

Keywords Migraine without aura · Migraine with aura · Hemiplegic migraine · Genetics

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The diagnosis of migraine relies exclusively on the headache history and exclusion of secondary causes. The lack of an objective marker applicable for usual clinical practice makes case definition a challenge. The International Classification of Headache Disorder provides explicit diagnostic criteria in order to maximise diagnostic precision [1]. Migraine without aura is defined by pain characteristics and accompanying symptoms. The majority of people with migraine without aura have never experienced an aura [2]. Migraine with aura is now subclassified according to headache characteristics and aura symptoms, while the first edition of the International Classification of Headache Disorders subclassified migraine with aura according to the aura symptoms alone [1, 3]. However, both the headache characteristics and aura symptoms usually vary from attack to attack [4]. Hemiplegic migraine includes motor aura and is subclassified into familial hemiplegic migraine and sporadic hemiplegic migraine depending on whether other first- and/or second-degree relatives have experienced motor aura or not. Migraine without aura and migraine with aura are common, affecting more than 10% of the general population, while familial hemiplegic migraine and sporadic hemiplegic migraine are relatively rare [5–8].

Is migraine a genetic illness?

A positive family history of migraine is imprecise, as probands only identify about half of their affected first-degree relatives with migraine [9]. Table 1 shows the familial aggregation in family studies of migraine without aura and migraine with aura. As compared to the general population, first-degree relatives had a significantly increased risk of the probands' disorder in all but the American survey [10–13]. The American survey is biased by family members interviewed only about their most severe type of headache by lay interviewers [13]. The diagnostic precision of lay interviewers is anticipated to be less precise than interviews by a physician, especially with regard to aura symptoms. The Italian and Greek surveys were based on clinic populations which may be subject to selection bias. Thus, the Danish survey conducted by one physician whom was blinded to the diagnosis of the probands is probably the most precise of the genetic epidemiological survey on migraine [11]. An increased familial risk of migraine can be caused by genetic and/or environmental factors. The risk among spouses can be used to evaluate this relation, because probands and spouses in part share a common environment, but differ in genetic constitution. Spouses to probands with migraine without aura had a slightly increased risk of migraine without aura, while spouses to probands with migraine with aura had no increased risk of migraine with aura [11]. Thus, the genetic epidemiological surveys of migraine without aura and migraine with aura support the importance of both genetic and environmental factors.

The literature provides information on several twin studies on migraine. The majority are based on questionnaires and lay interview [14]. The most precise survey was based on a population-based twin registry where the twin pairs were blindly interviewed by physicians [15, 16]. The probandwise concordance rate was significantly higher in monozygotic (MZ) than same gender dizygotic (DZ) twin pairs in both migraine without aura and migraine with aura (Table 2). The concordance rates in MZ twin pairs were less than 100%. The results support importance of both genetic and environmental factors.

A classical segregation analysis analyses for Mendelian inheritance, while a complex segregation analysis also analyses for multifactorial inheritance, as well as transmissible and non transmissible environmental

Table 1 Age and gender standardised risk of migraine without aura (*MO*) and migraine with aura (*MA*)

Disease in proband	Study population	Disease in first-degree relative	No. of affected relatives		Population relative risk (95% CI)
			Observed	Expected	
Migraine without aura					
Italy [10]	Clinic	MO	64	17.7	3.6 (1.1–6.1)
Denmark [11]	General	MO	102	54.8	1.9 (1.6–2.2)
		MA	42	29.2	1.4 (1.0–1.9)
USA [13]	General	MO	30	21.0	1.4 (0.8–2.5)
		MA	10	4.2	2.4 (0.9–6.4)
Migraine with aura					
Italy [10]	Clinic	MA	13	1.9	7.0 (3.2–10.8)
Denmark [11]	General	MA	111	29.3	3.8 (3.2–4.4)
		MO	56	54.9	1.0 (0.8–1.3)
Greece [12]	Clinic	MA	58	4.9	11.9 (7.0–16.7)
USA [13]	General	MA	3	2.4	1.2 (0.3–5.5)
		MO	17	12.1	1.4 (0.7–2.8)

The population relative risk is calculated by available data from the original articles by the Author
CI, confidence interval

Table 2 The probandwise concordance rates in monozygotic (*MZ*) and same gender dizygotic (*DZ*) twin pairs with migraine without aura and migraine with aura

	Men		Women		Total	
	MZ, % (95% CI)	DZ, % (95% CI)	MZ, % (95% CI)	DZ, % (95% CI)	MZ, % (95% CI)	DZ, % (95% CI)
Migraine without aura	29 (3–55)	15 (–19–49)	50 (41–59)	37 (31–43)	43 (37–49)	31 (26–36)
Migraine with aura	53 (35–71)	29 (15–43)	48 (32–64)	15 (4–26)	50 (38–62)	21 (12–30)

CI, confidence interval

factors [17]. A complex segregation analysis of migraine without aura and migraine with aura suggested multifactorial inheritance [18].

Familial hemiplegic migraine is a rare autosomal dominant inherited subtype of migraine with aura [19, 20]. At present three different genes have been identified to cause familial hemiplegic migraine, which is strong evidence of genetics in migraine [21–23].

The question *is migraine a genetic disorder?* was previously controversial, but today the answer *yes* is generally accepted regarding migraine without aura, migraine with aura and familial hemiplegic migraine.

Do the various forms of migraine share a common genetic cause?

The three familial hemiplegic migraine genes identified so far encode three different ion channels. The CACNA1A and SCNA1A genes encode the pore-forming α_1 subunits of the neuronal voltage-gated Ca^{2+} channels $Ca_v2.1$ and Na^+ channels $Na_v1.1$, and the ATP1A2 gene encodes the α_2 subunit of the Na^+,K^+ adenosinetriphosphatase [21–23]. Mutations in CACNA1A, ATP1A2 and SCNA1A genes cause familial hemiplegic migraine types 1, 2 and 3. The phenotypes are quite similar, with the exception that some type 1 families have permanent cerebellar symptoms in addition to familial hemiplegic migraine [20]. Due to the paroxystic nature of migraine it makes good sense that the familial hemiplegic migraine genes encode ion channels. However, are these genes important in other types of migraine? A systematic analysis of 39 patients with sporadic hemiplegic migraine identified one CACNA1A mutation, five ATP1A2 mutations and one SCN1A polymorphism [24]. The CACNA1A and ATP1A2 mutations were also carried by other family members with *non-hemiplegic* migraine with aura. This finding suggests that familial hemiplegic migraine, sporadic hemiplegic migraine and *non-hemiplegic* migraine with aura have a common genetic cause. However at present the three identified ion-channel genes cannot explain all cases of migraine with aura, and it is likely that several other ion-channel genes will be identified in the future. The next question is, what about migraine without aura? It is also a paroxystic disorder with a phenotype quite similar to that of migraine with aura, with the exception that aura is not present. It is likely that migraine without aura is also caused by mutations in ion-channel genes. Whether these possible mutations can cause both migraine without aura and migraine with aura is likely to be elucidated in the future.

References

1. Headache Classification Subcommittee of the International Headache Society (2004) The International classification of headache disorders. Cephalalgia 24[Suppl 1]:1–160
2. Russell MB, Rasmussen BK, Fenger K, Olesen J (1996) Migraine without aura and migraine with aura are distinct clinical entities: a study of 484 male and female migraineurs from the general population. Cephalalgia 16:239–245
3. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8[Suppl 7]:1–96
4. Russell MB, Olesen J (1996) A nosographic analysis of the migraine aura in the general population. Brain 119:355–361
5. Stovner LJ, Hagen K, Jensen R et al (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 27:193–210
6. Thomsen LL, Eriksen MK, Roemer SF et al (2002) A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. Brain 125:1379–1391
7. Thomsen LL, Ostergaard E, Romer SF et al (2003) Sporadic hemiplegic migraine is an aetiologically heterogeneous disorder. Cephalalgia 23:921–928
8. Thomsen LL, Ostergaard E, Olesen J, Russell MB (2003) Evidence for a separate type of migraine with aura: sporadic hemiplegic migraine. Neurology 60:595–601
9. Russell MB, Fenger K, Olesen J (1996) The family history of migraine. Direct versus indirect information. Cephalalgia 16:156–160
10. Mochi M, Sangiorgi S, Cortelli P et al (1993) Testing models for genetic determination in migraine. Cephalalgia 13:389–394
11. Russell MB, Olesen J (1995) Increased familial risk and evidence of genetic factor in migraine. BMJ 311:541–544
12. Kalfakis N, Panas M, Vassilopoulos D, Malliara Loulakaki S (1996) Migraine with aura: segregation analysis and heritability estimation. Headache 36:320–322
13. Stewart WF, Staffa J, Lipton RB, Ottman R (1997) Familial risk of migraine: a population based study. Ann Neurol 41:166–172
14. Russell MB (1997) Genetic epidemiology of migraine and cluster headache. University of Copenhagen. Cephalalgia 17:683–701
15. Ulrich V, Gervil M, Kyvik KO et al (1999) Evidence of a genetic factor in migraine with aura: a population-based Danish twin study. Ann Neurol 45:242–246
16. Gervil M, Ulrich V, Kyvik KO et al (1999) Migraine without aura: a population based twin study. Ann Neurol 46:606–611
17. Lalouel JM, Morton NE (1981) Complex segregation analysis with pointers. Hum Hered 31:312–321
18. Russell MB, Iselius L, Olesen J (1995) Investigation of inheritance of migraine by complex segregation analysis. Hum Genet 96:726–730
19. Joutel A, Bousser MG, Biousse V (1993) A gene for familial hemiplegic migraine maps to chromosome 19. Nat Genet 5:40–45
20. Ducros A, Tournier-Lasserve E, Bousser MG (2002) The genetics of migraine. Lancet Neurol 1:285–293
21. Ophoff RA, Terwindt GM, Vergouwe MN et al (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 87:543–552
22. De Fusco M, Marconi R, Silvestri L et al (2003) Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 33:192–196
23. Dichgans M, Freilinger T, Eckstein G et al (2005) Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 366:371–377
24. de Vries B, Freilinger T, Vanmolkot KR et al (2007) Systematic analysis of three FHM genes in 39 sporadic patients with hemiplegic migraine. Neurology 69:2170–2176

Neurol Sci (2008) 29:S55–S58
DOI 10.1007/s10072-008-0888-3

When should "chronic migraine" patients be considered "refractory" to pharmacological prophylaxis?

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Abstract Patients with chronic headache forms evolving from a previous episodic migraine ('chronic migraine') are often difficult to treat. In this paper we focus attention on aspects we believe important for producing a definition of "refractory" in relation to this headache form. We propose a "chronic migraine" patient should be considered "refractory" to pharmacological prophylaxis when adequate trials of preventive therapies at adequate doses have failed to reduce headache frequency and improve headache-related disability and, in patients with medication overuse, reduce the consumption of symptomatic drugs. However before a definition of "refractory" chronic migraine can become established, generally accepted diagnostic criteria and treatment guidelines for this condition need to be developed.

Keywords Chronic migraine (CM) · Refractory · Prophylaxis

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Introduction

Although much progress has been made in recent years in the management of primary headaches, neither the acute nor the prophylactic therapies currently available for these disorders are effective in all patients. Many patients, particularly those referred to tertiary care centres, have "refractory" headaches. However, universally accepted definitions of "refractory" (or "intractable") are not available. Goadsby et al. examined the issue of the definition of intractable headache for use in clinical practice and trials in a recent letter to *Cephalalgia* [1]. Although mainly concerned with stimulating debate, the letter nevertheless made recommendations regarding the use of "intractable" in relation to headache in general and not to specific headache types, although the authors did provide separate lists of preventive drugs that should be tested in migraine and cluster headache before concluding for intractable forms of these conditions.

We believe that intractability should be established separately for each primary headache, since the aims of therapy, impact of the condition and response to individual drugs varies markedly with headache type – both for the main clinical types of headache (migraine, tension-type headache, cluster headache) and for several subtypes (e.g. migraine without aura vs. migraine with aura vs. chronic migraine; episodic vs. chronic cluster headache). We also believe that intractability should be specified separately in relation to acute and preventive medications, non-pharmacological treatments (e.g. behavioural approaches or physical techniques) and also for each type of modern surgical approach (peripheral nerve stimulation or deep brain stimulation).

What is intractable chronic migraine?

The classification of patients with daily or nearly-daily headaches of long duration and migrainous features (in all

or some attacks) and who usually suffered typical episodic migraine attacks before chronification is still controversial [2–5]. Many patients with "chronic migraine" (CM) overuse acute medications, which may favour evolution to a chronic form and may reduce the efficacy of preventive treatments [6–9]. The situation is further complicated by the finding that CM can not only develop from episodic migraine, but can also revert to an episodic form [8, 9] and these clinical changes can be influenced by various factors including contraceptive pill use, mood changes, hypertension, menopause and other life events.

There are other important areas of uncertainty with regard to CM, particularly when associated to symptomatic medication overuse. Outcome measures used across different studies [10–14] to assess the efficacy of interventions vary (no headache at all, return to an episodic pattern, interruption of overuse, etc.), making it difficult to interpret results and produce standardised guidelines. Most Authors have stressed the importance of treatment plans that promote the withdrawal of overused medications and help patients to overcome their withdrawal symptoms [6, 8, 10–17]. These plans differ across studies, and may include use of NSAIDS, dihydroergotamine infusion, oral or intravenous steroids, anti-emetics, etc. Furthermore, some authors consider patients should be admitted for these treatments, others prefer a day hospital regimen; others again consider that CM patients can be adequately treated as outpatients. Preventive approaches also vary (no prophylaxis, various established anti-migraine prophylactics, antidepressants, etc.) [10, 11, 13, 14, 17, 18]. Few prophylactic drugs have been evaluated for the prevention of "chronic daily headache" and CM in randomised, double-blind, placebo-controlled studies. The clinical relevance of results obtained with tizanidine, fluoxetine, amitriptyline and gabapentin [19–22] is not easy to evaluate because of methodological problems (such as use of composite headache indices or percentage of headache-free days to assess therapeutic efficacy, and small sample sizes). More relevant data on the efficacy of topiramate have been published. One single-centre double-blind trial [23] and two recent multi-centre, randomised, double-blind, placebo-controlled studies [24, 25] showed that topiramate significantly reduces the mean number of headache days in patients with CM.

In an attempt to contribute constructively to clarifying the situation in this area, we will review the factors which in our opinion should be considered in deciding whether a patient with CM is "refractory" to pharmacological prophylaxis. Since the terminology in this area is confused, for the purposes of this paper we define "chronic migraine" (CM) as a headache form characterised by long pain duration (>4 h) and high frequency (≥15 days/month), with at least some attacks displaying typical migraine features. We add that CM as we define is often associated with acute medication overuse.

Reduction in frequency

A satisfactory treatment goal for most CM patients would be return to an episodic pattern, i.e., headache on less than 15 days/month with episodes lasting no longer than 72 h.

However such a goal would be unsatisfactory in patients with lower frequency (15–20 headache days/month), in whom a 50% or more reduction in headache frequency (generally accepted goal in episodic migraine prophylaxis) seems a more reasonable indicator of success.

Note also that CM patients usually experience attacks whose characteristics vary (tension-type-like and migraine-like). The migraine-like attacks are usually of greater severity and are more debilitating. The number of days with migraine headache (and not headache in general) might be a more realistic outcome measure in such patients.

Reduction in headache-related impact

In agreement with Goadsby et al. [1], we feel that "intractable" necessarily implies disability. Improvement in patient functioning and quality of life could be assessed by detailed interview, which investigates the patient's attitudes, and working, family and social context. However, a more objective evaluation requires use of standard validated instruments. The headache-specific MIDAS [26], HIT6 [27] and MSQ [28] instruments seem suitable for assessing functional and health-related quality of life outcomes. MIDAS and HIT6 are brief and easy to score in clinical practice; MIDAS and MSQ have proven sensitive to clinical changes in CM patients [17, 25, 29]. However, there are no data regarding which threshold of score change in these instruments should separate treatment failure from treatment success.

Resolution of medication overuse

We propose that patients should be considered to have failed treatment when medication consumption does not fall below that reported in ICDH II [5] (i.e., use of ergotamine, triptans or combination analgesics ≥10 days/month, or use of simple analgesics or any combination of ergotamine, triptans, analgesics and opioids on ≥15 days/month).

Definition of adequate trial of preventive therapies in CM

Preventive drugs

We propose that the greatest possible number of drugs should be tested and found ineffective (or intolerable) before consid-

ering a CM patient "refractory" to medical prophylaxis. We do not consider it sufficient to try one medication of each pharmacological class (e.g., one beta-blocker, one antiepileptic, etc.) as suggested by Goadsby et al. [1]. The rationale for this is that the members of a given class (e.g., calcium entry blockers or anti-epileptics) may work by various mechanisms. We know from clinical practice for example that a patient unresponsive to one antiepileptic may improve with another, and that tolerability within a class varies too.

We propose that a patient should have adequate courses of all drugs considered as first-line prophylactics for episodic migraine by international guidelines [30, 31], and in addition should receive adequate courses of at least some of the drugs considered second- or third-line prophylactic treatments.

Contraindicated drugs and those likely to cause intolerable side effects should be avoided. Preventive medications used in the past with no efficacy or with intolerable side effects could not be tested again, provided information on duration, dose and adverse events is sufficient and reliable.

Many physicians use polytherapy on CM patients. The use of two or more drugs may be justified by the presence of comorbidities (see below) or by the possibility that the effects of different drugs can "summate" to achieve efficacy. This latter phenomenon is well known in neurological disorders such as epilepsy and Parkinson's disease [32]. However there is insufficient evidence to determine whether polytherapy is superior to monotherapy. Only two double-blind studies [19, 33] and three uncontrolled studies [34–36] have been published in this area. In these studies different combinations of prophylactic drugs were tested against the compounds used in monotherapy in small series of episodic and/or "chronic migraine" patients. A trend for better outcomes with polytherapies was observed in all cases, although only in one retrospective study and in one double-blind study was the difference between the two approaches found to be significant [19, 34].

Trial duration and dosage

Although there is no evidence on the optimal length of prophylactic treatments, 3 months is usually considered sufficient to assess prophylactic efficacy. With regard to dose, clinical experience suggests that some patients benefit from doses above the recommended range.

We propose that a 3-month treatment period is required to assess efficacy but it may be useful to continue for a further 3–6 months if there was some improvement during the first 3 months.

Treatment of medication overuse

It is generally agreed that acute medication overuse should be curtailed before starting prophylaxis in patients with chronic headaches. Various strategies are used in tertiary care centres to achieve this and control withdrawal symptoms, as discussed above. Inpatient treatment with infusion therapies seems to produce satisfactory reduction even in the most difficult cases, although some data suggest that treatment in day hospitals or as outpatients can also be effective [6, 7, 10, 11, 14]. A recent randomised controlled trial indicated that topiramate prophylaxis may be effective in reducing headache frequency in CM patients even when acute medication overuse is not addressed [25], suggesting that withdrawal of overused medications may not be an essential first step. However the issue requires further investigation, particularly because the study in question [25] recruited few patients, no significant reduction in medication consumption in the topiramate group was achieved, and the placebo effect was very small, suggesting the possibility of un-blinding.

Treatment of comorbidities

Migraine patients often report comorbidities [37–39], the presence of which may influence the choice and also the outcome of preventive treatment. Conditions such as depression, sleep disorders, epilepsy, anxiety, hypertension and obesity may increase headache frequency and heighten pain perception. We therefore feel that the identification and appropriate treatment of all clinically significant comorbidities is essential before declaring a treatment failure in CM patients.

Many migraine prophylactics are also useful for controlling comorbidities and may be chosen for a given CM patient with the aim of treating both disorders. As reviewed by Silberstein at al. [39], two alternative strategies could be adopted: treat both headache and comorbidity with a single compound (monotherapy) or treat each condition separately (therapeutic independence). The latter approach may be preferable in most cases, as optimal doses may not be the same for the headache and the other condition, and the anti-migraine drug may not be the first choice treatment for the comorbidity.

Concluding remarks

In this paper we have focused attention on the aspects we believe important for producing a definition of "refractory" in relation to chronic headache forms evolving from episodic migraine, here referred to as "chronic migraine" (CM). We propose that a CM patient should considered "refractory" to pharmacological prophylaxis when adequate trials of preventive therapies at adequate doses have failed to reduce headache frequency and improve headache-related disability. CM patients with medication overuse should also be considered refractory when treatments fail to reduce the consumption of symptomatic drugs. However we recognise that

the term "refractory" in relation to CM can be conclusively established until generally accepted diagnostic criteria, treatment guidelines and treatment outcome measures for this condition have been developed.

References

1. Goadsby PJ, Schoenen J, Ferrari M et al (2006) Towards a definition of intractable headache for use in clinical practice and trials. Cephalalgia 26:1168–1170
2. Silberstein SD, Lipton RB, Sliwinski M (1996) Classification of daily and near-daily headaches. Neurology 47:871–875
3. Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd Edn. Cephalalgia 24[Suppl 1]:9–160
4. Bigal ME, Tepper SJ, Sheftell FD et al (2006) Field testing alternative criteria for chronic migraine. Cephalalgia 26:477–482
5. Headache Classification Committee of the International Headache Society (2006) New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26:742–746
6. Mathew NT, Kurman R, Perez F (1990) Drug induced refractory headache – clinical features and management. Headache 30:634–638
7. Silberstein SD, Lipton RB (2001) Chronic daily headache, including transformed migraine, chronic tension-type headache, and medication overuse. In: Silberstein SD, Lipton RB, Dalessio DJ (eds) Wolff's headache and other head pain, 7th Edn. Oxford University Press
8. Bigal ME, Rapoport AM, Sheftell FD et al (2004) Transformed migraine and medication overuse in a tertiary headache centre-clinical characteristics and treatment outcomes. Cephalalgia 24:483–490
9. Scher AI, Midgette LA, Lipton RB (2008) Risk factors for headache chronification. Headache 48:16–25
10. Diener HC, Limmroth V (2004) Medication overuse headache: a worldwide problem. Lancet Neurol 3:475–483
11. Freitag FG, Lake A 3rd, Lipton R et al (2004) US Headache Guidelines Consortium, Section on Inpatient Treatment Chairpersons. Inpatient treatment of headache: an evidence-based assessment. Headache 44:342–360
12. Katsarava Z, Muessig M, Dzagnidze A et al (2005) Medication overuse headache: rates and predictors for relapse in a 4-year prospective study. Cephalalgia 25:12–15
13. Mathew NT (2006) The prophylactic treatment of chronic daily headache. Headache 46:1552–1564
14. Grazzi L, Andrasik F (2006) Medication-overuse headache: description treatment and relapse prevention. Curr Pain Headache Rep 10:71–77
15. Bonuccelli U, Nuti A, Lucetti C et al (1996) Amitriptyline and dexamethasone combined treatment in drug-induced headache. Cephalalgia 16:197–200
16. Drucker P, Tepper S (1998) Daily sumatriptan for detoxification from rebound. Headache 38:687–690
17. Andrasik F, Grazzi L, Usai S et al (2007) Disability in chronic migraine with medication overuse: treatment effects at 3 years. Headache 47:1277–1281
18. Zeegerg P, Olesen J, Jensen R (2006) Probable medication-overuse headache: the effect of a 2-month drug-free period. Neurology 66:1894–1898
19. Krymchantowski AV, Silva MT, Barbosa JS, Alves LA (2002) Amitriptyline versus amitriptyline combined with fluoxetine in the preventative treatment of transformed migraine: a double-blind study. Headache 42:510–514
20. Saper JR, Lake AE 3rd, Cantrell DT et al (2002) Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. Headache 42:470–482
21. Saper JR, Silberstein SD, Lake AE 3rd, Winters ME (1994) Double-blind trial of fluoxetine: chronic daily headache and migraine. Headache 34:497–502
22. Spira PJ, Beran RG; Australian Gabapentin Chronic Daily Headache Group (2003) Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. Neurology 61:1753–1759
23. Silvestrini M, Bartolini M, Coccia M et al (2003) Topiramate in the treatment of chronic migraine. Cephalalgia 23:820–824
24. Silberstein SD, Lipton RB, Dodick DW et al; Topiramate Chronic Migraine Study Group (2007) Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. Headache 47:170–180
25. Diener HC, Bussone G, Van Oene JC et al; TOPMAT-MIG-201(TOP-CHROME) Study Group (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia 27:814–823
26. Stewart WF, Lipton RB, Whyte J et al (1999) An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology 53:988–994
27. Kosinski M, Bayliss MS, Bjorner JB et al (2003) A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res 12:963–974
28. Cole J, Lin P, Rupnow MF (2007) Validation of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v. 2.1) for patients undergoing prophylactic migraine treatment. Qual Life Res 16:1231–1237
29. Dodick DW, Silberstein S, Saper J et al (2007) The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache 47:1398–1408
30. Silberstein SD, for the US Headache Consortium (2000) Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 55:754–762
31. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sándor PS (2006) EFNS guideline on the drug treatment of migraine-report of an EFNS task force. Eur J Neurol 13:560–572
32. Krymchantowski AV, Bigal ME (2006) Polytherapy in the preventive and acute treatment of migraine: fundamentals for changing the approach. Expert Rev Neurother 6:283–289
33. Bordini CA, Arruda MA, Cicciarelli MC, Speciali JG (1997) Propranolol vs flunarizine vs flunarizine plus propranolol in migraine without aura prophylaxis. A double-blind trial. Arq Neuropsiaqr 55:536–541
34. Pascual J, Leira R, Láinez JM (2003) Combined therapy for migraine prevention? Clinical experience with a beta-blocker plus sodium valproate in 52 resistant migraine patients. Cephalalgia 23:961–962
35. Krymchantowski AV, Hampshire F (2004) Polytherapy in migraine prevention. Clinical experience with the combination of a tricyclic antidepressant plus a calcium channel blocker. Headache 44:499–500
36. Pascual J, Rivas MT, Leira R (2007) Testing the combination beta-blocker plus topiramate in refractory migraine. Acta Neurol Scand 115:81–83
37. Scher AI, Bigal ME, Lipton RB (2005) Comorbidity of migraine. Curr Opin Neurol 18:305–310
38. Scher AI, Stewart WF, Lipton RB (2006) The comorbidity of headache with other pain syndromes. Headache 46:1416–1423
39. Silberstein SD, Dodick D, Freitag F et al (2007) Pharmacological approaches to managing migraine and associated comorbidities – clinical considerations for monotherapy versus polytherapy. Headache 47:585–599

Neurol Sci (2008) 29:S59–S61
DOI 10.1007/s10072-008-0889-2

Therapeutic neurostimulation in chronic headaches: problems of patient selection

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Abstract Chronic daily headache that does not respond or no longer responds to prophylaxis is commonly encountered at specialist headache centres. Animal and brain imaging studies indicate that peripheral neurostimulation affects brain areas involved in pain modulation, providing a rationale for its use in these conditions. We examine problems related to the selection of chronic daily headache patients for peripheral neurostimulation. These conditions are often associated with analgesic (including opioid) overuse, and psychiatric or other comorbidities, and the terms used to describe them (chronic migraine, transformed migraine, chronic daily headache and chronic tension-type headache) are insufficiently informative about these patients when proposed for neurostimulation. Longitudinal studies indicate that pre-existing subclinical depressive and anxious states play a key role in chronicisation and that the probability of responding to treatment is inversely related to headache frequency. These considerations suggest the need for extensive characterisation of patients proposed for neurostimulation. We propose that patients being considered for neurostimulation should be followed for at least a year, and that their headache over this time should consistently be frequent (all or most days) and drug refractory. We also propose that only *completely* drug-resistant (as opposed to *partially* drug-resistant) patients be considered for neurostimulation unless there are other indications.

Keywords Neurostimulation · Selection criteria · Chronic headache · Chronic migraine · Drug-resistant

Introduction

Migraine is common in western countries, with a prevalence of around 10%–15% [1]. It has been estimated to be the most costly neurological disorder in the European Community [2] and one of the most costly neurological disorders in the United States [3]. New therapies in headache are mainly driven by developments in migraine, and this is the case with peripheral neurostimulation, which has been proposed for the treatment of a number of drug-resistant primary headaches [4–8]. Animal studies indicate that peripheral neurostimulation can have an antidolorific effect (for review see Refs. 9 and 10) and may affect brain areas involved in pain modulation, providing a rationale for the use of these techniques in humans [7]. Over the last decade central (hypothalamic) stimulation has emerged as an effective new treatment for drug-resistant chronic cluster headache and other forms of trigeminal autonomic cephalalgia (TAC) (for review see Ref. 11). The introduction of this neurostimulation technique has raised a number of clinical problems regarding patient eligibility for the procedure, including whether the International Headache Society (IHS) definitions of chronic cluster and other TACs are detailed enough to appropriately select patients for neurostimulation [12].

Since neurostimulation is of growing interest as a treatment for drug-resistant primary headaches, we here

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examine some of the problems related to the selection for the technique of patients with chronic long-lasting (≥4 h) primary headache.

Selection for neurostimulation: focus on the headache or on the patient?

The classification published by the IHS [13] proved to be a landmark as it introduced for the first time a common language for headaches and reliable criteria for their diagnosis. Another result was that research into the causes and treatment of headache was greatly stimulated: neuroimaging studies investigated headache attacks, and triptans as treatment for acute neurovascular headaches (migraine and cluster headache) were developed and introduced.

The chronic forms commonly referred to as chronic migraine, transformed migraine, chronic daily headache and chronic tension-type headache remain difficult to classify and diagnose, and a widely used and accepted terminology is still some way off [14]. These forms are also more difficult to treat than episodic headaches, and this is the main reason why patients with severe chronic headaches are increasingly proposed for neurostimulation. The IHS defines these forms when headache is present for at least 15 days per month for the preceding three months [13, 14]. Patients undergoing neurostimulation or other surgery are usually characterised as having "chronic drug-resistant migraine" or "chronic daily drug-resistant headache" [6–8]. These terms encompass headache forms that can be highly heterogeneous in terms of pain localisation, duration and intensity, triggering factors, associated phenomena, association with hormone levels, age of onset, chronicisation pattern, duration of chronic form, etc. Furthermore, these chronic conditions are often associated with analgesic overuse, including opioids, and psychiatric or other comorbidities, including hypertension and cardiovascular disease [15]. Thus the terms chronic migraine, chronic daily headache and chronic tension-type headache are insufficiently informative about the generally complex clinical picture that characterises patients with chronic headache, particularly those proposed for neurostimulation.

Not even the clinical data used to assess the effectiveness of prophylaxis (number of days with headache, pain intensity, number of analgesics consumed, number of working days lost and headache-related disability) provide sufficient information about the patient to assess his or her suitability for neurostimulation.

Although mechanisms underlying the chronicisation of pain and headache are far from being fully understood, longitudinal studies indicate that pre-existing subclinical depressive and anxious states play a key role in chronicisation (for review see Ref. 15). It has also been found that patients with chronic headaches tend to develop complex musculo-skeletal pain syndromes and such patients respond poorly to treatment [16]. Furthermore, the probability of responding to treatment is inversely related to headache frequency [16]. These findings, considered together with heterogeneity and complexity of the clinical pictures of chronic headache patients, suggest that extensive characterisation of those proposed for neurostimulation is necessary. This will allow identification of characteristics that distinguish responders from non-responders, and will in turn suggest hypotheses for prospective studies to identify factors that can guide patient selection.

Definition of chronicity for the purposes of selection for neurostimulation

The problem of the inadequacy of the IHS criteria as a guide to selecting patients for surgical procedures first arose when hypothalamic implant and stimulation was introduced to treat chronic cluster headache [17]. Most chronic cluster headache patients selected for surgery have daily attacks [18], yet the IHS criteria allow a diagnosis of chronic cluster headache when the patient has only 3–4 attacks per month over the preceding year [13] and this diagnosis is insufficient to select patients for surgery. The advantages and limitations of these criteria have been discussed elsewhere [12, 17, 18]. Regarding long-lasting (≥4 h) chronic headaches (chronic migraine, transformed migraine, chronic daily headache, chronic tension-type headache), all the available diagnostic criteria – those included in the IHS classification [13, 14] as well as in other classification systems [19, 20] – require that headaches should be present on 15 days or more per month for at least 3 months. The question arises as to whether headaches present for only 15 days a month and only for the preceding 3 months are sufficient to justify the invasive surgical procedure of neurostimulation. For example, a patient whose migraine has worsened to more than 15 attacks a month in the preceding 3–4 months may simply be experiencing a temporary period of exacerbation and should not therefore be considered for neurostimulation. Migraine is a fluctuating illness in which worsening and spontaneous improvements are not infrequent (for review see Ref. 16). It is also known that factors such as stressful life events, contraceptive pill use, hypertension, mood changes and the use or overuse of certain drugs can favour increase in headache frequency [16]. It seems reasonable therefore that patients fulfilling IHS criteria for chronic migraine (or more generally chronic daily headache) should be thoroughly investigated for the above factors, and where possible treated before considering any kind of surgery [21]. This approach to chronic daily headaches is usually only practised at specialist headache centres. However it is likely that neurostimulation will become available at other centres, and for this reason it is

important that widely accepted detailed criteria for selection for neurostimulation are developed and applied. Based on experience at our headache centre, we consider it reasonable to propose that patients being considered for neurostimulation should be followed for at least a year, and that their headache over this time should consistently be frequent (all or most days) and drug refractory (see below). Of course there may be exceptions, for example patients who are allergic, intolerant or have strong contraindications to several medications. The principle should be that each patient is evaluated individually and exhaustively by a multidisciplinary team (neurologists, psychiatrists, psychologists and neurosurgeons).

Another factor to be considered when evaluating chronic headache patients for neurostimulation is disability. Migraine – and even to a greater extent chronic migraine – may cause severe disability and reduction in quality of life [22]. However our experience is that many patients are able to lead fairly full social and family lives notwithstanding frequent headaches, because they are kept under control by the use of acute medications (analgesics, NSAIDs, triptans, etc.). We therefore propose that, in patients under consideration for neurostimulation, both disability score and number of analgesics/triptans taken should be considered.

Definition of drug-resistance for the purposes of selection for neurostimulation: *partial* and *complete* drug-resistance

Chronic daily headache patients who do not respond or who no longer respond to prophylaxis are commonly encountered in specialist headache centres [23]. The term drug-resistant can be applied to those who do not respond to one or more types of drug [24], as well as to those who do not respond to all known medications. In the former case the patient may well be responsive to one of the untried medications and we propose that *partially* drug-resistant be used for such cases, with *completely* drug-resistant used to specify patients who do not respond to *all* known medications [25]. We consider this distinction useful for assessing patients for neurostimulation and propose that only *completely* drug-resistant patients be considered for neurostimulation. All indicated drugs in the guidelines [25] or wider literature should be tried at adequate dose and for a sufficient period, and shown to be ineffective or associated with intolerable side effects unless contraindicated.

References

1. Rasmussen BK (1995) Epidemiology of headache. Cephalalgia 15:45–68
2. Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J (2005) Cost of disorders of the brain in Europe. Eur J Neurol 12[Suppl 1]:1–27
3. Stewart WF, Ricci JA, Chee E et al (2003) Lost productive time and cost due to common pain conditions in the US workforce. JAMA 290:2443–2454
4. Magis D, Allena M, Bolla M et al (2007) Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. Lancet Neurol 6:314–321
5. Burns B, Watkins L, Goadsby PJ (2007) Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients. Lancet 369:1099–1106
6. Popeney CA, Alo KM (2003) Peripheral neurostimulation for the treatment of chronic, disabling transformed migraine. Headache 43:369–375
7. Matharu MS, Bartsch T, Ward N et al (2004) Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain 127:220–230
8. Schwedt TJ, Dodick DW, Hentz J et al (2007) Occipital nerve stimulation for chronic headache – long-term safety and efficacy. Cephalalgia 27:153–157
9. Goadsby PJ, Bartsch T, Dodick DW (2008) Occipital nerve stimulation for headache: mechanisms and efficacy. Headache 48:313–318
10. Multon S, Schoenen J (2005) Pain control by vagus nerve stimulation: from animal to man… and back. Acta Neurol Belg 105:62–67
11. Leone M, Proietti Cecchini A, Franzini A et al (2008) Lessons from eight years' experience of hypothalamic stimulation in cluster headache. Head Curr (*in press*)
12. Leone M, Franzini A, Proietti Cecchini A et al (2007) Stimulation of occipital nerve for drug-resistant chronic cluster headache. Lancet Neurol 6:289–291
13. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd Edition. Cephalalgia 24[Suppl 1]
14. Olesen J, Bousser MG, Diener HC et al; Headache Classification Committee (2006) New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26:742–746
15. Scher AI, Midgette LA, Lipton RB (2008) Risk factors for headache chronification. Headache 48:16–25
16. Scher AI, Stewart WF, Lipton RB (2006) The comorbidity of headache with other pain syndromes. Headache 46:1416–1423
17. Leone M (2004) Chronic cluster headache: new and emerging treatment options. Curr Pain Headache Rep 8:347–352
18. Leone M, May A, Franzini A et al (2004) Deep brain stimulation for intractable chronic cluster headache: proposals for patient selection. Cephalalgia 24:934–937
19. Silberstein SD, Lipton RB, Sliwinski M (1996) Classification of daily and near-daily headaches. Neurology 47:871–875
20. Bigal ME, Tepper SJ, Sheftell FD et al (2006) Field testing alternative criteria for chronic migraine. Cephalalgia 26:477–482
21. Luconi R, Bartolini M, Taffi R et al (2007) Prognostic significance of personality profiles in patients with chronic migraine. Headache 47:1118–1124
22. D'Amico D, Grazzi L, Usai S (2005) Disability pattern in chronic migraine with medication overuse: a comparison with migraine without aura. Headache 45:553–560
23. Schechter A, Lipton RB, Silberstein SD (2001) Migraine comorbidity. In: Silberstein SD, Lipton RB, Dalessio DJ (eds) Wolff's headache and other head pain. Oxford University Press, New York, pp 108–118
24. Goadsby PJ, Schoenen J, Ferrari MD et al (2006) Towards a definition of intractable headache for use in clinical practice and trials. Cephalalgia 26:1168–1170
25. Evers S, Afra J, Frese A et al (2006) EFNS guidelines in migraine. Eur J Neurol 13:560–572

Neurol Sci (2008) 29:S62–S64
DOI 10.1007/s10072-008-0890-9

Long-term experience of neuromodulation in TACs

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Abstract Improvement in the biomedical and biotechnological research fields have allowed refinement of the neuromodulation approach in the treatment of a subgroup of medical disorders otherwise refractory to pharmacological treatment, such as chronic primary headaches. Chronic pain conditions imply central sensitisations and functional reorganisation that cannot be quickly or easily reversed. It appears evident that conventional treatment can sometimes be unsuccessful or only partially successful, and that relapse is common. Cluster headache (CH) is the most frequent trigeminal autonomic cephalalgia (TAC) and the most representative of this spectrum of disorders characterised by the association of headache and loco-regional signs and symptoms of facial parasympathetic activation. The striking features of circadian rhythmicity of attacks and circannual periodicity of cluster period, together with the neuroendocrine abnormalities, are suggestive of a neurochronobiological disorder with a central-diencephalic pathogenetic involvement, confirmed by direct evidence in functional neuroimaging studies of ipsilateral posterior hypothalamic activation during cluster attack. In 2000 these findings prompted a functional neurosurgery approach, with the first case of deep brain hypothalamic stimulation (DBS) in a severely disabled chronic CH patient. Since then, 18 implants in our centre and many others in different countries have been performed. Although the outcomes are encouraging, the invasive nature of the technique and the occurrence of rare but major adverse events have suggested a safer peripheral approach with occipital nerve stimulation (ONS).

Keywords Cluster headache · SUNCT · TACs · Neurostimulation · DBS · Occipital nerve · ONS

Introduction

Trigemino-autonomic cephalalgias (TACs) are shortlasting unilateral primary headache syndromes grouped together in the second edition of the classification of the International Headache Society (IHS) and comprise cluster headache (CH), paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) [1]. In TACs, pain is accompanied by oculofacial autonomic phenomena [1]. The main differences are to be found in the duration, frequency and rhythmicity of the attacks [2], and in the intensity of pain and autonomic symptoms, as well as treatment options. The concept of TAC is certainly useful for clinicians seeking a pathophysiological understanding of the primary neuro-vascular headaches and allows us to place the various treatments aimed at treating or preventing these headaches into context.

In TACs, pain seems to be driven by activation of trigeminal nerve endings while autonomic phenomena are mainly ascribable to activation of parasympathetic components of facial nerves [3]. Contemporary activation of trigeminal and facial nerves has been named trigeminofacial reflex [4]. Neuroimaging activation studies have shown increased blood flow in the posterior inferior hypothalamic grey in CH, SUNCT and PH [5–8], lending support to the hypothesis that the attack generator in TACs is located at that level. Voxel-based MRI has subsequently shown increased neuronal density in that brain

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area [9] and MR spectroscopy have shown decreased N-acetylaspartate/creatine in patients with CH *vs*. controls [10, 11], reinforcing the hypothesis. These neuroimaging findings suggested a new therapeutic approach to CH. By analogy with the use of deep brain hypothalamic stimulation (DBS) to treat intractable movement disorders, stereotactic stimulation of the hypothalamus appeared attractive as a means of interfering with the supposed *cluster generator* to relieve intractable CH pain [12]. About 15% of cases suffer from chronic CH and a proportion of these do not respond to drugs: such patients are severely debilitated and represent a major clinical problem.

Hypothalamic stimulation

Eighteen hypothalamic implants have since been performed at our centre in 16 CH patients [13, 14]. All had suffered drug-resistant daily attacks for years and were unable to work. After a mean follow-up of over two years, 11 (61%) are completely pain-free and over 70% of postoperative days have been crisis-free [14]. Most patients have resumed work. It took about six weeks (mean value) for the benefits to appear and stimulation parameters required frequent adjustments, mainly amplitude. Typical amplitudes are 1–3.3 V; other stimulation parameters are 180 Hz, 60 μs pulse width and continuous unipolar mode. In all but one of the cases, when the stimulator has been switched off (unknown to the patient) the crises have returned.

Similar results were obtained at other centres [15–18]. After a mean follow-up of 14.5 months, Schoenen et al. [15] concluded the technique was effective for intractable chronic CH. Improvement was not immediate and frequent adjustment of stimulation parameters was necessary. One of the six patients died soon after the operation due to implantation-induced intracerebral haemorrhage, and implantation had to be stopped intraoperatively in another patient because of panic attacks [15].

Both Starr et al. [16] and Bartsch et al. [17] reported that at least 50% of their patients were pain-free after more than 1 year follow-up with no serious side effects. Two other patients with intractable chronic CH have received hypothalamic stimulation at a third centre [18]. Mean follow-up is almost two years. Both became pain-free after about a month. One relapsed, but improved again after the stimulation voltage was increased [18].

Interestingly, continuous long-lasting hypothalamic stimulation did not induce relevant alterations in hypothalamus-controlled functions [19]. However, as the hypothalamus has not previously been chronically stimulated in humans, autonomic function, hormone levels, cardiovascular function [19], behaviour, mood and sleep–waking cycle [20] should be monitored in all patients, particularly while the stimulator is switched on [19, 20].

DBS in SUNCT

Increased blood flow in the ipsilateral posterior inferior hypothalamus, compatible with activation, has been demonstrated during SUNCT attacks [7]. These findings prompted us to propose hypothalamic stimulation in a 66-year-old woman with a two-year history of drug-refractory daily SUNCT attacks. The patient obtained marked benefit from the procedure with no adverse events, reinforcing the hypothesis of crucial hypothalamic involvement in TAC pathophysiology [21].

Greater occipital nerve stimulation

Occipital nerve stimulation (ONS) has also shown a certain efficacy against drug-resistant daily chronic headaches, suggesting a putative therapeutic role also in other primary headaches, namely CH, through a non-specific mechanism [22, 23]. In one, study five of eight operated patients became pain-free or had headache frequency reduced by over 90% [24]. Overall headache attack frequency was in this study much lower than reported in other surgical series, making efficacy comparisons difficult. A matter of discussion is if and in which cases patients with just one to two attacks a week should undergo invasive surgical procedures [25]. Furthermore, only four patients had sufficiently long follow-up (over one year) to provide a useful indication of outcome. In another study on greater occipital nerve (GON) stimulation in chronic CH [26], only three of eight (38%) operated patients improved. Surprisingly, when asked, all patients said they would recommend the operation to others with CH. Factors other than pain relief *per se* might lead patients to express such positive judgements, and the discrepancy between their opinions and established headache severity measures suggest the former might not be the most complete way to report on the efficacy of a surgical procedure in primary headaches [25].

References

1. Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd Edn. Cephalalgia 24[Suppl 1]:1–160
2. Goadsby PJ, Lipton RB (1997) A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. Brain 120:193–209
3. Goadsby PJ, Edvinsson L (1994) Human in vivo evidence for trigeminovascular activation in cluster headache. Brain 117:427–434
4. Goadsby PJ, Edvinsson L, Ekman R (1988) Release of vasoactive

peptides in the extracerebral circulation of man and the cat during activation of the trigeminovascular system. Ann Neurol 23:193–196
5. Sprenger T, Boecker H, Toelle TR et al (2004) Specific hypothalamic activation during a spontaneous cluster headache attack. Neurology 3:516–517
6. May A, Bahra A, Buchel C et al (1998) Hypothalamic activation in cluster headache attacks. Lancet 352:275–278
7. May A, Bahra A, Buchel C et al (1999) Functional MRI in spontaneous attacks of SUNCT: short-lasting neuralgiform headache with conjunctival injection and tearing. Ann Neurol 46:791–793
8. Matharu MS, Cohen AS, Frackowiak RSJ, Goadsby PJ (2006) Posterior hypothalamic activation in paroxysmal hemicrania. Ann Neurol 59:535–545
9. May A, Ashburner J, Buchel C et al (1999) Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med 5:836–838
10. Lodi R, Pierangeli G, Tonon C et al (2006) Study of hypothalamic metabolism in cluster headache by proton MR spectroscopy. Neurology 66:1264–1266
11. Wang SJ, Lirng JF, Fuh JL, Chen JJ (2006) Reduction in hypothalamic 1H-MRS metabolite ratios in patients with cluster headache. J Neurol Neurosurg Psychiatry 77:622–662
12. Leone M, Franzini A, Bussone G (2001) Stereotactic stimulation of posterior hypothalamic gray matter for intractable cluster headache. N Engl J Med 345:1428–1429
13. Leone M, Franzini A, Broggi G et al (2004) Long-term follow up of bilateral hypothalamic stimulation for intractable cluster headache. Brain 127:2259–2264
14. Leone M, Franzini A, Broggi G, Bussone G (2006) Hypothalamic stimulation for intractable cluster headache: long-term experience. Neurology 67:150–152
15. Schoenen J, Di Clemente L, Vandenheede M et al (2005) Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain 128:940–947
16. Starr PA, Barbaro NM, Raskin NH, Ostrem JL (2007) Chronic stimulation of the posterior hypothalamic region for cluster headache: technique and 1-year results in four patients. J Neurosurg 106:999–1005
17. Bartsch T, Pinsker MO, Rasche D et al (2008) Hypothalamic deep brain stimulation for cluster headache – experience from a new multicase series. Cephalalgia 28:285–295
18. D'Andrea G, Nordera GP, Piacentino M (2006) Effectiveness of hypothalamic stimulation in two patients affected by intractable chronic cluster headache. Neurol [Suppl 2]:A 140
19. Cortelli P, Guaraldi P, Leone M et al (2007) Effect of deep brain stimulation of the posterior hypothalamic area on the cardiovascular system in chronic cluster headache patients. Eur J Neurol 14:1008–1015
20. Vetrugno R, Pierangeli G, Leone M et al (2007) Effect on sleep of posterior hypothalamus stimulation in cluster headache. Headache 47:1085–1090
21. Leone M, Franzini A, D'Andrea G et al (2005) Deep brain stimulation to relieve severe drug-resistant SUNCT. Ann Neurol 57:924–927
22. Popeney CA, Alò KM (2003) Peripheral neurostimulation for the treatment of chronic, disabling transformed migraine. Headache 43:369–375
23. Goadsby PJ, Bartsch T, Dodick DW (2008) Occipital nerve stimulation for headache: mechanisms and efficacy. Headache 48:313–318
24. Magis D, Allena M, Bolla M et al (2007) Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. Lancet Neurol 6:314–321
25. Leone M, Franzini A, Proietti Cecchini A et al (2007) Stimulation of occipital nerve for drug-resistant chronic cluster headache. Lancet Neurol 6:289–291
26. Burns B, Watkins L, Goadsby PJ (2007) Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients. Lancet 369:1099–1106

Neurol Sci (2008) 29:S65–S68
DOI 10.1007/s10072-008-0891-8

Neuromodulation in treatment of refractory headaches

Angelo Franzini · Massimo Leone · Giuseppe Messina · Roberto Cordella · Carlo Marras · Gennaro Bussone · Giovanni Broggi

Abstract The field of neuromodulation is emerging as a promising and alternative therapeutical option for many drug-resistant clinical conditions, including painful syndromes such as refractory chronic cluster headache (CCH) and trigeminal neuralgia. We here report a series of patients who have undergone Deep Brain Stimulation (DBS) of Posterior Hypothalamus for chronic cluster headache, trigeminal neuralgia and atypical facial pain, matching their corresponding clinical results and also suggesting a role for Great Occipital Nerve Stimulation (which is a much less invasive procedure) in the treatment of CCH. According to us, the refinement of surgical techniques and of metabolic and functional brain neuroradiological investigations will lead to a refinement of the therapeutical strategies in such patients.

Keywords Trigeminal neuralgia · Cluster headache · Neuromodulation

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Introduction

After the first successful operation on a patient affected by chronic cluster headache (CCH) [1], neuromodulation became an available procedure for patients affected by painful syndromes of the face refractory to conservative treatments. Chronic high-frequency stimulation of the posterior hypothalamus (pHyp) has been the first therapeutic application of functional neuroimaging data [2] to plan a restorative reversible procedure for the treatment of an otherwise refractory neurological condition. Sano et al. [3] were the first to report the correspondent stereotactic pHyp lesional technique. The surgical techniques of deep brain stimulation (DBS) and great occipital nerve (GON) stimulation are reported and discussed.

Material and methods

The technique of DBS in CCH patients has been extensively reported in many published papers [1, 4–10]. DBS of the pHyp has also been performed in three patients affected by atypical facial pain and in five patients affected by multiple sclerosis (MS) and trigeminal neuralgia involving the first trigeminal division (paroxysmal pain within the second and third divisions had been previously treated by repeated selective percutaneous thermorhizotomies). The risks of corneal reflex impairment and cheratitis led us to consider a neuromodulation procedure as an alternative to lesional procedures in MS patients.

In spite of its long-lasting benefits, DBS of the pHyp must be considered a major surgical procedure and so since 2005 we have also used chronic stimulation of the GON [1, 4–8, 11–17] to treat CCH and other painful syndromes of the face before considering DBS. This procedure, in our experience, may provide relief in about 30% of CCH

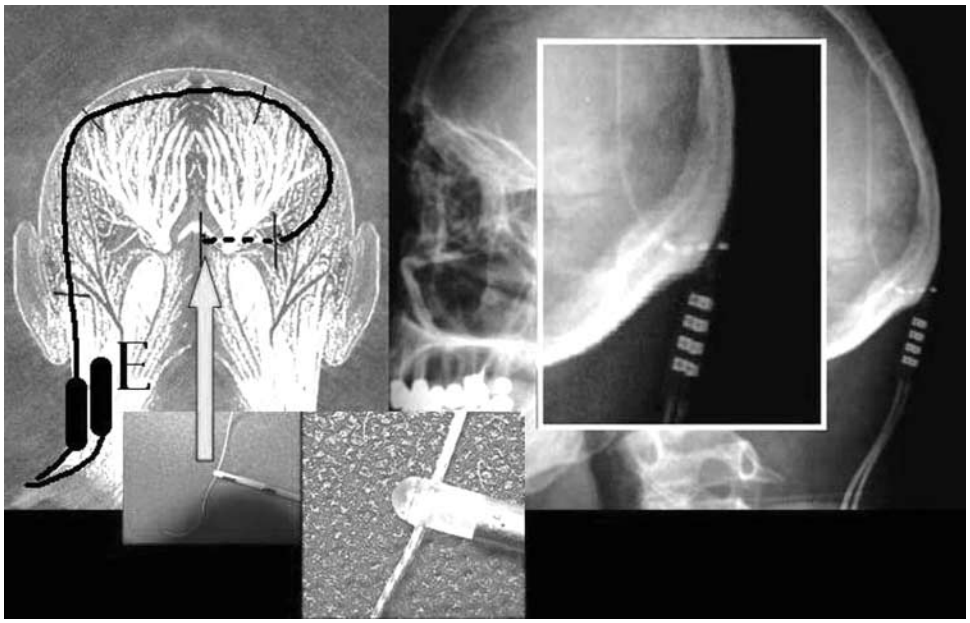

Fig. 1 Stimulation of the GON performed before the pHyp electrode implant. Note the free extension (*E*) of the dual-channel Kinetra (Medtronic inc. Minneapolis) IPG ready for connection to the deep brain electrode

patients, while results in other painful syndromes of the face are promising but still limited to only five patients who are currently under evaluation and whose follow-up is still too short for drawing any conclusion about them.

Surgical technique of GON stimulation

A wired quadripolar electrode lead (PISCES Medtronic, Minneapolis, USA) is placed within the first dividing branches of the GON on the affected side and the tip of the electrode is secured to the fascia of the splenium capitis muscle just laterally to the occipital protuberance. The technique is represented in Figure 1. The lead is then tunnelised subcutaneously to the subclavicular region and connected to the pulse generator (Kinetra, Medtronic, Minneapolis, USA). The stimulation parameters for GON are 50 Hz, 2–4 V and 90 ms PW.

Results of posterior hypothalamus DBS

CCH series

The mean follow-up is 24 months (range 12–62 months). The recently reported detailed results of DBS [6] are summarised in the following remarks:

- In the whole series, 71% of postoperative days were pain free and intensity and duration of pain bouts were significantly reduced.
- Drugs were reduced to less than 20% of the preoperative condition.
- The mean time to stable benefit (pain free or reduction) was 42 days (range 1–86 days).
- The mean stimulation amplitude was 2.4 V (range 0.6–3.3 V).

Twelve of the stimulators (9 patients) were switched off at least once in single-blind fashion. After switching off, pain recurred after an interval of 2 months, which seemed to be unrelated to the duration of previous stimulation; the pain improved or disappeared when the stimulator was turned back on. In patients with bilateral crises, turning the stimulation on and off abolished or improved crises only on the ipsilateral side.

Neuropathic pain and atypical facial pain

After surgery, the 3 operated patients had no reduction in pain. The stimulation parameters were the same as for CCH and SUNCT patients (180 Hz, 60 ms, mean voltage 1.3 V). After four months of continuous stimulation (6, 8 and 10 months, respectively) the continuous pain was the same as preoperatively. Increase of amplitude did not offer any pain relief. Amplitude higher than 3 V induced dizziness and oculomotor activation in all cases. Bipolar stimulation did not offer any improvement. When the internal pulse generator (IPG) was switched off with the patient being unaware of it, the episodes of paroxysmal pain were described by the patient as being slightly more intense than those that occurred during stimulation.

MS trigeminal neuralgia

At 1–3 years of follow-up, two out of five operated patients were pain free and drug free after chronic stimulation, while the remaining three patients had improved

and felt their pain was under control, though they were still taking medication in combination with pHyp stimulation. DBS had beneficial effects on pain limited to the first trigeminal branch for an average of 23 months. After the implant (median 20 months), three patients underwent a further thermorhizotomy lesional procedure to selectively alleviate the pain in the II and III branch, but not in the first, so as to preserve the corneal reflex.

Conclusion and discussion

DBS in CCH patients has achieved a significant reduction of pain bouts. The procedure is also well tolerated. Transient reversible diplopia is the main limitation to increasing amplitude. Before the operation, none of the patients were able to work. As a result of stimulation, most patients' lives have gradually returned to normal; most have resumed work.

Nevertheless, some problems may be seen from our experience. The diagnosis of CCH must be precise and supported by the headache classification criteria [15]. Comorbidity with other painful syndromes of the face and sometimes with personality disorders [18] may result in wrong diagnosis. To avoid this bias in patient selection we suggest strict cooperation with headache specialists, psychiatrists and dedicated headache units. pHyp stimulation benefits only CCH patients and is uneventful in other pain syndromes of the face such as atypical facial pain and neuropathic pain [4].

About 30% of CCH patients may have significant improvement after peripheral neuromodulation procedures (GON), suggesting the existence of different subtypes of patients in the same nosographic class. In other words, in a certain amount of CCH patients the peripheral pathogenetic mechanisms may be more relevant than the central ones. To fix this problem we suggested GON stimulation and sphenopalatine ganglion local anaesthetic blocks prior to DBS surgery. In the future PET studies and brain functional MRI may provide preoperative imaging of hypothalamic involvement in individual patients affected by CCH [13], allowing further refinement of the indication for DBS.

Although an up-to-date worldwide literature analysis limits the percentage of DBS responder patients to about 50%–60% [9, 10], we think that refinement of the targeting procedure and patient selection will further improve the success rate of pHyp stimulation in CCH patients. Nevertheless, DBS has changed the poor therapeutical outcomes in CCH patients we operated on.

Finally, we have to remember that CCH is a dramatic debilitating condition leading to abuse of steroids (two patients of the operated series were unable to walk due to severe leg myopathy induced by chronic steroid abuse). Also, the abuse of triptans may be life-threatening (one patient died before the implant due to myocardial infarct). DBS benefits this condition and the cost of the procedure is largely compensated for within the first year of induced remission, even if the disease cannot be definitively cured by DBS.

Atypical facial pain did not respond at all. Trigeminal paroxysmal pain attacks responded only when limited to the first trigeminal division. These data suggest pathogenetic and anatomic links between the pHyp, the first trigeminal division, the reticular formation and the autonomic system of the face [19]. GON stimulation allows a less invasive way to interact with the descending nucleus of the fifth nerve and brainstem nuclei through an antidromic activation via the C1-C2 roots; the safety of this procedure and the promising preliminary results suggest a future role of GON stimulation in the treatment of refractory headaches.

References

1. Leone M, Franzini A, Bussone G (2001) Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. N Engl J Med 345:1428–1429
2. May A, Bahra A, Buchel C et al (1998) Hypothalamic activation in cluster headache attacks. Lancet 352:275–278
3. Sano K, Mayanagi Y, Sekino H et al (1970) Results of stimulation and destruction of the posterior hypothalamus in man. J Neurosurg 33:689–707
4. Franzini A, Ferroli P, Leone M et al (2004) Hypothalamic deep brain stimulation for the treatment of chronic cluster headaches: a series report. Neuromodulation 7:1–8
5. Franzini A, Ferroli P, Leone M, Broggi G (2003) Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery 52:1095–1099
6. Franzini A, Marras C, Tringali G et al (2007) Chronic high frequency stimulation of the posteromedial hypothalamus in facial pain syndromes and behaviour disorders. Acta Neurochir Suppl 97:399–406
7. Leone M, Franzini A, D'Andrea G et al (2005) Deep brain stimulation to relieve drug-resistant SUNCT. Ann Neurol 57:924–927
8. Leone M, Franzini A, Broggi G, Bussone G (2006) Hypothalamic stimulation for intractable cluster headache: long-term experience. Neurology 67:150–152
9. Schoenen J, Di Clemente L, Vandenheede M et al (2005) Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain 128:940–947
10. Starr PA, Barbaro NM, Raskin NH, Ostrem JL (2007) Chronic stimulation of the posterior hypothalamic region for cluster headache: technique and 1-year results in four patients. J Neurosurg 106:999–1005
11. Burns B, Watkins L, Goadsby PJ (2007) Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients. Lancet 369:1099–1106
12. Cordella R, Carella F, Leone M et al (2007) Spontaneous neuronal activity of the posterior hypothalamus in trigeminal autonomic cephalalgias. Neurol Sci 28:93–95
13. Lodi R, Pierangeli G, Tonon C et al (2006) Study of hypothalamic metabolism in cluster headache by proton MR spectroscopy. Neurology 66:1264–1266
14. Ferroli P, Franzini A, Marras C et al (2004) A simple method to assess accuracy of deep brain stimulation electrode placement:

pre-operative stereotactic CT-postoperative MR image fusion. Stereotact Funct Neurosurg 82:14–19
15. Headache Classification Committee of The International Headache Society (2004) The International Classification of Headache Disorders (2nd Edn). Cephalalgia 24:1–195
16. Jarrar RG, Black DF, Dodick DW, Davis DH (2003) Outcome of trigeminal nerve section in the treatment of chronic cluster headache. Neurology 60:1360–1362
17. Leone M, Franzini A, Cecchini AP et al (2007) Stimulation of occipital nerve for drug-resistant chronic cluster headache. Lancet Neurol 6:289–291
18. Torelli P, Manzoni GC (2003) Pain and behaviour in cluster headache. A prospective study and review of the literature. Funct Neurol 18:205–210
19. Malick A, Strassman AM, Burstein R (2000) Trigemino hypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. J Neurophysiol 84:2078–2112

Neurol Sci (2008) 29:S69–S78
DOI 10.1007/s10072-008-0892-7

Cranial neuralgias: from physiopathology to pharmacological treatment

Roberto De Simone · Angelo Ranieri · Leonilda Bilo · Chiara Fiorillo · Vincenzo Bonavita

Abstract Cranial neuralgias are paroxysmal painful disorders of the head characterised by some shared features such as unilaterality of symptoms, transience and recurrence of attacks, superficial and "shock-like" quality of pain and the presence of triggering factors. Although rare, these disorders must be promptly recognised as they harbour a relatively high risk for underlying compressive or inflammatory disease. Nevertheless, misdiagnosis is frequent. Trigeminal and glossopharyngeal neuralgias are sustained in most cases by a neurovascular conflict in the posterior fossa resulting in a hyperexcitability state of the trigeminal circuitry. If the aetiology of trigeminal neuralgia (TN) and other typical neuralgias must be brought back to the peripheral injury, their pathogenesis could involve central allodynic mechanisms, which, in patients with inter-critical pain, also engage the nociceptive neurons at the thalamic-cortical level. Currently available medical treatments for TN and other cranial neuralgias are reviewed.

Keywords Cranial neuralgias · Trigeminal neuralgia · Glossopharyngeal neuralgia · Physiopathology · Treatment · Review

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Introduction

Cranial neuralgias are paroxysmal painful disorders of the head, rarely seen in clinical practice. They are characterised by some shared features, such as unilaterality of symptoms, transience and recurrence of attacks, superficial and "shock-like" quality of pain, and the presence of triggering factors. Although trigeminal neuralgia (TN) and glossopharyngeal neuralgia are sustained in most cases by a neuro-vascular conflict in the posterior fossa, cranial neuralgias share a relatively high risk for a compressive underlying cause different from the neurovascular conflict.

Classification, epidemiology and clinical aspects

The second edition of the International Classification of Headache Disorders (ICHD-II) [1] codes the cranial neuralgias in Chapter 13 and provides the diagnostic criteria for 18 different subtypes (Table 1) including a number of heterogeneous central causes of facial pain, which will not be discussed here.

Trigeminal neuralgia

Classification and epidemiology

According to the ICHD-II the diagnosis of Classical Trigeminal Neuralgia has to fulfil the criteria listed in Table 2. These criteria must be also present in Symptomatic Trigeminal Neuralgia but in the latter form additional signs and symptoms such as a mild ache between attacks and the presence of sensorial defect in the affected territory are admitted. The boundary between classical and symptomatic forms of TN is therefore rather

Table 1 ICHD-II classification of cranial neuralgias

13. Cranial neuralgias and central causes of facial pain
13.1 Trigeminal neuralgia
13.1.1 Classical trigeminal neuralgia
13.1.2 Symptomatic trigeminal neuralgia
13.2 Glossopharyngeal neuralgia
13.2.1 Classical glossopharyngeal neuralgia
13.2.2 Symptomatic glossopharyngeal neuralgia
13.3 Nervus intermedius neuralgia
13.4 Superior laryngeal neuralgia
13.5 Nasociliary neuralgia
13.6 Supraorbital neuralgia
13.7 Other terminal branch neuralgias
13.8 Occipital neuralgia
13.9 Neck-tongue syndrome
13.10 External compression headache
13.11 Cold-stimulus headache
13.11.1 Headache attributed to external application of a cold stimulus
13.11.2 Headache attributed to ingestion or inhalation of a cold stimulus
13.12 Constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions
13.13 Optic neuritis
13.14 Ocular diabetic neuropathy
13.15 Head or facial pain attributed to herpes zoster
13.15.1 Head or facial pain attributed to acute herpes zoster
13.15.2 Post-herpetic neuralgia
13.16 Tolosa-Hunt syndrome
13.17 Ophthalmoplegic 'migraine'
13.18 Central causes of facial pain
13.18.1 Anaesthesia dolorosa
13.18.2 Central post-stroke pain
13.18.3 Facial pain attributed to multiple sclerosis
13.18.4 Persistent idiopathic facial pain
13.18.5 Burning mouth syndrome
13.19 Other cranial neuralgia or other centrally mediated facial pain

Table 2 ICHD-II criteria for 13.1.1 Classic trigeminal neuralgia

13.1.1 Classic trigeminal neuralgia
A. Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes, affecting one or more divisions of the trigeminal nerve
B. Pain has at least one of the following characteristics:
1. Intense, sharp, superficial or stabbing
2. Precipitated from trigger areas or by trigger factors
C. Attacks are stereotyped in the individual patient
D. There is no clinically evident neurological deficit
E. Not attributed to another disorder

frail and neuroimaging investigations are highly recommended, especially in the cases of recent onset.

Although TN is the most common among the cranial neuralgias, with an incidence of 3–5 new cases for 100,000 subjects per year [2] and a prevalence of 15.5 cases per 100,000 [3], it is still to be considered a rare disease. TN can appear at any age, but the onset is after age 40 in 90% of the cases; women are more likely to be affected than men, with a gender ratio of 2:1. About 2% of the patients with multiple sclerosis (MS) can experience a pain disorder nearly identical to TN [4]; despite the evidence of a substantial clinical overlap [5], neuralgias related to MS are not classified among symptomatic forms, but in a specific subgroup of the same ICHD-II chapter (13.18.3. Facial Pain Attributed Multiple to Sclerosis).

Clinical aspects

The pain in TN usually occurs in brief paroxysmal attacks either isolated or in short clusters. Typically, it is felt superficially and is described as extremely severe and of burning or "shock-like" quality. Attacks tend to be stereotyped and are strictly confined to the territory of distribution of one or more branches of the trigeminal nerve of a single side. The maxillary and mandibular nerves, in combination or alone, are more often affected than the ophthalmic nerve, which is involved alone in less than 5% of cases [6]. The single attack lasts characteristically from less than a second to a few seconds, but it can be present in clusters up to 2 min in length; in many cases it is followed by a brief refractory period during which a new stimulation is not able to evoke the

pain. The location of the pain is typically unilateral, but it can be bilateral in patients with MS, although asynchronously. Interestingly, the right side is more often involved than the left. The disorders seldom affect more members of the same family [7, 8]. The attacks can occur spontaneously or they can be provoked by stimulation of specific trigger areas. These are often localised in the skin around the mouth and at the sides of the nose, due to its higher sensorial innervation, and can also involve the gums. In rare cases the attacks are evoked by extra-trigeminal triggers, such as olfactory or gustatory stimuli [9]. Characteristically, tactile stimuli can trigger an attack while painful stimuli usually do not. Furthermore, the provoking stimuli fall within a physiological range of intensity like those arising from normal daily activities: brushing teeth, shaving, chewing, yawning or swallowing. Quite often patients can experience a muscle spasm involving the mimic muscles occasionally associated with other involuntary movements. The presence of unintentional movements have led to the term "tic douloureux", often used to indicate this condition. Involvement of the autonomic nervous system is not usually present, but when the ophthalmic nerve is affected it is possible to observe a modest tearing discharge without conjunctival injection or any other autonomic sign. These cases create problems of differential diagnosis with the rare primary headache coded in the ICHD-II as sudden onset unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). Differential diagnosis between TN and SUNCT depends on the different intensity and variety of autonomic symptoms involved [10].

Clinical course

The onset of a typical TN is quite often preceded by a painful condition affecting mandibular or maxillary areas. The pain can be variable but it usually resembles the pain of a sinus infection or toothache. This condition is named pretrigeminal neuralgia [11]. It can precede the onset of typical neuralgic symptoms by years and can present with episodes of long-lasting facial pain sometimes triggered by chewing or drinking warm or cold foods. Pretrigeminal neuralgia is responsive to the specific drug treatments for TN and represents a common cause of misdiagnosis in the early phases of disease. The clinical course of the definite disease is very often intermittent; spontaneous remissions of at least 6 months are described in 50% of cases and remissions of at least one year in about 25% of patients [12]. Nevertheless, the usual pattern is for a progressive worsening with increased severity and frequency of pain, prolonged duration of the active phases, lower response to drugs, possible development of constant soreness between attacks (inter-critical pain) and clinically evident defects of trigeminal sensory function.

Diagnosis

A clinical presentation with brief attacks of strict unilateral shock-like pain within trigeminal areas and the presence of typical trigger areas makes this condition easy to recognise. Nevertheless TN is often misdiagnosed in patients affected by cluster headache or sometimes by a side-locked migraine; conversely the correct diagnosis can be delayed until the failure of inappropriate odontostomatological treatments [11].

Like most typical neuralgias, TN is symptomatic in 5%–10% of symptomaticity cases [13]. The recent ICHD-II revision of the International Headache Society (IHS) classification considers the presence of inter-critical pain and sensory deficits as possible predictors of a structural cause; however inter-critical pain and sensory deficits have low specificity [14] and must be cautiously taken into account, especially in cases with a long duration of illness [15]. A possible structural cause must be considered in case of onset before 40 years, bilaterality of the symptoms, presence of neurological signs or atypical pain in terms of quality, affected area, intensity or duration. In these conditions extensive neuroimaging studies are highly recommended. Arterial hypertension is considered a possible risk factor [16]. Included among the possible causes of secondary TN are: MS; Charcot-Marie-Tooth disease [17], meningiomas, neurinomas and other slow-growing tumours of posterior cranial fossa; syringobulbia; arachnoiditis; basilar artery and internal carotids aneurysms; fractures of the cranial base; and herpes zoster.

Recent evidence [18] suggests that trigeminal reflexes studies by blink reflex and laser evoked potentials (LEPs) can differentiate symptomatic TN from classic TN more reliably than any other clinical data, including age of onset. Therefore such techniques could be performed to select those patients who need to be further investigated with neuroimaging.

Glossopharyngeal neuralgia

Neuralgia of glossopharyngeal nerve (GFN) is a rare entity with an estimated incidence of 0.8 cases per 100,000 [2]. As a matter of fact, authors from the Mayo Clinic have reported only 217 cases in 55 years [19]. The prevalence, compared to NT, is of about 1 case of GFN for every 75 of TN [18]. As for other neuralgias, this form is separated into Classical and Symptomatic, which differ mostly by the presence of inter-critical pain and sensory deficit in the territories of distribution of the nerve. The ICHD-II diagnostic criteria for the Classic form of GFN are shown in Table 3. The term Classical, which is also used for TN, has been introduced to make the diagnosis compatible with the presence of neurovascular conflict in posterior fossa. Males and females are

Table 3 ICHD-II criteria for 13.2.1 Classical glossopharyngeal neuralgia

13.2.1 Classical glossopharyngeal neuralgia
A. Paroxysmal attacks of facial pain lasting from a fraction of a second to 2 minutes and fulfilling criteria B and C
B. Pain has all of the following characteristics:
1. Unilateral location
2. Distribution within the posterior part of the tongue, tonsillar fossa, pharynx or beneath the angle of the lower jaw and/or in the ear
3. Sharp, stabbing and severe
4. Precipitated by swallowing, chewing, talking, coughing and/or yawning
C. Attacks are stereotyped in the individual patient
D. There is no clinically evident neurological deficit
E. Not attributed to another disorder

equally affected. Interestingly, the left nerve is more often involved than the right one [20].

From a clinical point of view GFN shares the same basic features of TN with a typical neuralgic pain occurring in a paroxysmal way. Pain is habitually located in the tonsillar region and in the back of the pharynx, with possible transmission to the lower portion of the jaw and to the ear. The painful attacks can be triggered by ordinary activity such as swallowing, chewing, speaking, coughing, sneezing, throat-clearing or by head rotation. The association with NT is not rare, accounting for about 10% of cases [6]. The clinical course is usually episodic, with active phases lasting weeks or months and off-pain periods of different length. Pain attacks are described to worsen in frequency or severity over time, whereas the remission phases tend to shorten.

The pain episodes usually last from less than a second up to 2 min but sometimes they can occur in rapid and continuous sequence (*status neuralgicus*). When the pain is triggered by swallowing, feeding can be impaired for long periods and it is not rare for these patients to undergo a striking weight loss. Unilaterality is a key sign and when the pain is bilateral a possible association with MS must be suspected. In about 2% of cases, patients can experience severe bradycardia with subsequent lost of consciousness [6]. Similarly to TN, the risk of an underlying cause is relatively high and it is always advisable to perform a wide diagnostic work-up in these patients.

Causes of symptomatic GFN are: tumours of the cerebellumpontine angle, nasopharyngeal carcinomas, aneurysms of the carotid, abscesses of tonsils, rare neurinomas of the IX nerve and MS. Worth noting is the syndrome of the stylohyoid apophysis (Eagle's syndrome) [21], in which the neuralgic symptoms are due to irritation of the glossopharyngeal nerve in its esocranial path when stylohyoid process is longer than normal (over 4.5 cm instead of 2.5 cm). Local anaesthesia (lidocaine 10%) of pharyngeal and tonsillar triggers areas has diagnostic value.

Nervus intermedius neuralgia

Also known as *geniculate* or *Hunt's neuralgia*, this form is among the less frequent of the series. Typical clinical features are [22]: paroxysmal unilateral pain lasting from seconds to a few minutes localised deeply in the ear; radiation of pain to the external auditory meatus; occurrence of vegetative symptoms such as abnormal tearing and salivation, taste problems; relapsing course with active phases of disease and symptom-free periods; and higher prevalence in females. Geniculate neuralgia is often correlated with shingles of the external auditory duct.

Occipital neuralgia

Occipital neuralgia is classically characterised by unilateral paroxysmal pain in the areas corresponding to location of lesser and greater occipital nerves. The pain can be associated to inter-critical pain and dysaesthesia [23]. The disease can occur after traumas of the occipital area, even if they are irrelevant, whereas it can be also sustained by numerous medical conditions such as Arnold-Chiari malformation, bone and joint diseases, herpetic neuropathies and masses that can compress the nerve along its path [24].

The pure form (Arnold neuralgia) is very rare compared to the countless syndromes affecting cervical spine, with which it shares some overlapping features. A selective tenderness after pressure on trigger points is also reported.

Superior laryngeal nerve neuralgia

This is an extremely rare form. It is characterised by paroxysmal pain of the lateral part of throat, of the submandibular region, around the ear and along the neck; the paroxysms can be triggered by chewing, and head extension or rotation [25]. The superior laryngeal nerve is a branch of the vagus nerve and it is involved in the sensorial-motor innervation of the larynx and in the glottic reflex. It enters the larynx crossing the lateral aspect of the hyoid membrane. The pain, habitually unilateral, occurs in attacks of a few minutes that re-occur up to 10–30 times in 24 h with clustering of different length and tendency to the remission. The attacks can be associated to an uncontrollable cough and can be triggered by compression of the point of entry through the hyoid

membrane, sideways and immediately above the larynx. Benefits emerging from anaesthesia of these regions are of diagnostic value.

Pathophysiology of the cranial neuralgias

Over the last decades cranial neuralgia pathophysiology has been partly clarified by important research contributions supporting the causative role of a chronic irritation of the affected nerve due to compressive or inflammatory causes. Nevertheless, evidence suggests that central factors can contribute to the development of these forms. The following considerations refer to TN, however it is supposed that also other typical painful diseases of the face, such as glossopharyngeal neuralgia, share similar mechanisms [6].

In 1976 Jannetta [26] published the first extensive case study of subjects with TN in all of which, after investigations of posterior cranial fossa, a causative factor was documented. Besides slow-growing tumours of the cerebellumpontine angle accounting for 6% of the patients, and MS found in another 6% of the cases, in 88% of the subjects a compression of the proximal tract of the root of the V nerve by one or more tortuous or ectasic blood vessels was recognised (Fig. 1). In the site of the neurovascular conflict a demyelination was constantly present. As placing a teflon pad between the two structures – so-called microvascular decompression (MVD) – immediately stopped the attacks, the focal demyelination of the nerve was proposed as the main causative factor. The observations of these Authors have inspired a great deal of research paving the way to important progress on TN mechanisms which led to including this condition, notwithstanding relevant dissimilarities, in the broader chapter of *neuropathic pain.*

Much evidence sustains the causative role of a proximal compression of the trigeminal nerve root including: high frequency of neuroimaging positive report documenting a neurovascular conflict [27]; the prompt resolution of symptoms and nerve conduction defects after MVD [28, 29]; and ultimately the gradual remission of sensory defects of clinical relevance after surgery [30].

Mechanisms of the pain

It is noticeable that the conflict always involves the proximal portion of the trigeminal root, the so-called root entry zones (REZ). Myelin at this level is still of central type and this could impact the resistance of the nerve to mechanical stimuli [31]. The compression probably causes a mechanical twist of the fibres and their secondary demyelination, probably mediated by microvascular ischaemic damages [32]. These changes can significantly lower the excitability threshold and promote an inappropriate ephaptic propagation towards adjacent fibres [33]. Because of the cross-talk, the tactile signals coming from the fast myelinic fibres (A-beta) can directly activate the slow nociceptive fibres (A-delta) and produce repetitive high-frequency discharges responsible for the typical "lightening" pain triggered by tactile stimuli. After a few seconds or minutes the repetitive discharges spontaneously run out and are followed by a brief period of inactivity that explains the "refractory period" clinically evident in many cases [34]. The aetiological role of the focal

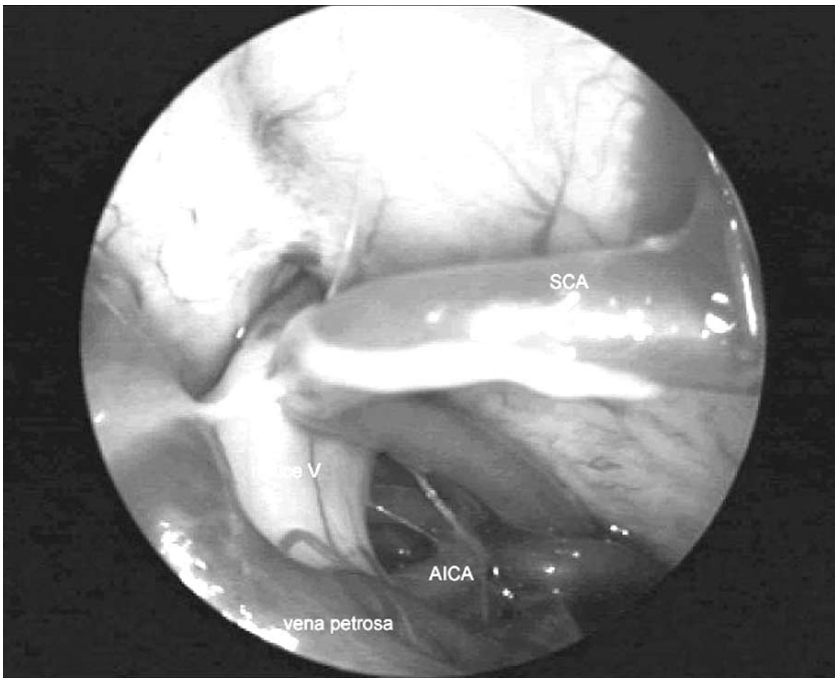

Fig. 1 A triple neurovascular conflict (Courtesy of Prof. P. Cappabianca – Neurosurgery, University of Naples "Federico II", Naples, Italy)

demyelination of the REZ also explains the increased prevalence of NT in subjects with MS, in which demyelinated foci in the mid-pons and the REZ are usually demonstrated [35, 36]. Demyelination and remyelination processes observed in electronic microscopy studies [37] could also explain the typical periodicity of the syndrome.

Although these observations seem to point out that a demyelination of the REZ secondary to tumours, neurovascular conflict or MS is the causal element in all the cases of NT, different observations suggest that the hyperexcitability of the compressed nerve could represent a *necessary* condition, still not *sufficient* to cause the disease. Several autoptic case studies document a high prevalence of neurovascular conflicts at the proximal level in asymptomatic individuals [38–40]; a compression of REZ is not demonstrated in all the patients [41]; at least initially the pain is effectively treated by drugs such as baclofen, which is considered non-active on the peripheral fibres; familiar cases in which a neurovascular conflict is not detectable have been reported [8]. All these observations suggest a possible involvement of relevant central factors.

It has been suggested that a hypersensitivity of the tactile A-beta nerve fibres, initiated by the same nerve injury, leads to a sensitisation of the wide dynamic range neurons (WDRn) [42]. These peculiar nociceptive neurons are placed both in the V lamina of the dorsal horns and in the trigeminal nerve nuclei and are characterised by a progressive facilitation of excitability following repeated stimulation. Since these peculiar nociceptive II order neurons receive convergent information from both tactile A-beta and nociceptive A-delta and C fibres, their sensitisation can ultimately facilitate nociceptive input at the central level while promoting the perception of pain in response to tactile stimuli, a phenomenon called allodynia. The high prevalence of neurovascular conflicts in autoptic studies of asymptomatic subjects suggests that an individual predisposition to allodynic pain could be of great relevance in TN mechanisms. Noteworthy, allodynic sensitisation of thalamic nociceptive neurons has been recently documented in NT patients presenting with a continuous pain between attacks [14], a condition associated with a poor medical and surgical outcome [43]; interestingly, in this study the illness duration was not related to the presence of inter-critical pain, confirming its low specificity as a marker of symptomatic form or of protracted diseases.

Findings from recent studies on animal models point to dorsal root ganglia as a new site possibly involved in neuropathic pain and TN mechanisms [44]. At this level, a chemically mediated cross-talk between somata of both tactile A-type and nociceptive C-type sensory neurons has been recorded in physiologic conditions [45]. The mechanism results in a reciprocal excitability threshold modulation probably aimed to balance pain and tactile excitability in different physiologic conditions. In the presence of an injury-driven nerve sensitisation, the threshold for a cross-excitation between sensitised A and C fibres can be reached at the dorsal root ganglia level [46] and this may lead to pain generation in response to tactile stimuli. A possible involvement of Gasser ganglion in TN pathogenesis is supported by the finding of histological changes at this level both in Classic TN patients [47] and in subjects with TN associated to MS [48].

These observations link the pathophysiology of TN to a hyperexcitability of the trigeminal circuitry sustained by peripheral and central mechanisms. If the aetiology of TN and other typical neuralgias must be brought back to the peripheral injury, their pathogenesis could involve central allodynic mechanisms, which, in patients with inter-critical pain, also engage the nociceptive neurons at the thalamic-cortical level.

Treatment

TN can be treated with drugs or surgical procedures; many patients end up with both treatments, although at different times. As a matter of fact, medical therapy works very well at the beginning and reaches almost complete control of symptoms in more than 80% of patients. As time passes, drugs progressively lose efficacy even if they are in multiple therapy. In these cases possible surgical options must be taken into account. Interestingly most of the drugs that are effective in TN have anti-epileptic activity or, in the case of baclofen, have effect on the central transmission of pain. This fact supports the hypothesis of the hypersensitivity of trigeminal circuitry following a nerve injury in the pathogenesis of TN. Historically phenytoin, used for the first time in 1942 by Berguignon, was the first drug to be reported to be effective in the treatment of TN. Only in 1962 with the introduction of carbamazepine did patients with TN begin to benefit from a truly effective treatment with a satisfying tolerability [6].

Despite the lack of randomised and controlled studies of large samples, due to the rarity of the disease and ethical difficulties in using placebo in such a devastating condition, the spectrum of available drugs has grown in time, adding several other anti-epileptic drugs (AED). Recently, medications that inhibit the transmission of the pain to the central II order neurons such as subcutaneous sumatriptan [49], or treatments with possible action against allodynia like the botulinum toxin [50, 51] have been found effective in pain control. Following is a list of the evidence on the efficacy of the main drugs used in clinical practice for the treatment of these forms.

Anti-epileptic drugs

Carbamazepine (CBZ)

Carbamazepine is considered the mainstay for treating these disorders. It is also the only molecule for which

there is a great deal of evidence (1 systematic review and 4 RCT studies) [52]. Carbamazepine reduces sodium-channel conductivity, stabilising the membrane of pre- and post-synaptic neurons and making trigeminal mechanoceptors less prone to respond to peripheral input. About 80% of patients benefit from this treatment and in 94% of patients there is relief from symptoms in the first 48 h of treatment [53, 54]. As time passes however, the efficacy tends to be lower [55]. The recommended starting dose is 100 mg twice a day; this can be increased by 50–100 mg every 3–4 days up to a final dose of 400–1000 mg to continue until symptoms persist. The most common side effect is drowsiness, however this tends to decrease after a few days of treatment.

Other side effects are cerebellar symptoms, double vision, haematological changes, liver disease, skin rash, nausea and vomiting [56]. Intolerance is seen in 5%–19% of patients.

Oxcarbazepine

Oxcarbazepine is structurally a derivative of carbazepine, therefore it shares carbamazepine's mechanism of action. It can be used if intolerance to carbamazepine is present, or alternatively as the drug of choice [57]. Clinical trials on small groups of patients report that the drug is effective in 24 h and some report a greater efficacy and tolerability compared to carbamazepine [58]. The initial dose is 150 mg, which can be increased every 3 days of by 150–300 mg up to a therapeutic dose of 1200 mg three times a day.

Phenytoin

This is a drug of second or third choice and can added in case of intolerance or low efficacy to carbamazepine. The suggested mechanism of action is stabilisation of the CNS neuron' membrane, modulating sodium channels. Initially the drug is reported to be effective in 60% of patients, but after two years of treatment the efficacy is reduced to about 30%. The recommended starting dose is 200 mg, to be increased to a therapeutic dose of 300–500 mg twice a day. Injectable formulation, with a dose of 250 mg can be used for acute treatment of pain attacks and reaches a pain-free period of 4–72 h [59]. Side effects include double vision, ataxia, liver disease, gum hyperplasia, haematologic disturbance, hirsutism and memory defects.

Gabapentin

Gabapentin is widely used in the treatment of TN although its efficacy has been reported in few non-controlled studies. It has been empirically used because of its proven efficacy in pain control in post-herpetic and diabetic neuropathies [60]. It has been suggested that gabapentin acts by increasing GABA availability in the CNS and modulates the voltage-gated sodium channel, resulting in a reduced discharge of excitatory neurotransmitters. About 50% of patients respond to therapy after 3–4 days of treatment. A full remission from symptoms is achieved after about 2 weeks. The initial recommended dose is 300 mg, which can be doubled every 2–3 days to reach the maximum dose of 900–2400 mg/day. Adverse effects include drowsiness, weakness and abnormalities of kidney function. These effects are lesser and usually better tolerated in old patients compared to those observed with carbamazepine and phenytoin.

Pregabalin

Pregabalin shares the same activity of gabapentin, with better pharmacokinetics. Besides its efficacy in pain control in post-herpetic and diabetic neuropathies, recently pregabalin has been proven to be effective in an open pharmaceutical study showing that 74% of patients improve up to 50% and that efficacy reduction over a year is minor [61]. This study also highlights that patients with a concomitant chronic facial pain are less prone to benefit from treatment. Initially pregabalin can be administered at 75 mg and can be increased up to 600 mg in two separated daily doses. Drowsiness and dizziness are the most common side effects and they tend to recede after a few days of treatment. Higher doses can cause headache, peripheral oedema and dry mouth.

Lamotrigine

Lamotrigine is effective both alone and in combination with carbamazepine or phenytoin [62, 63] especially in elderly patients and in patients with MS with mild symptoms. The drug acts on sodium channels and it stabilises the plasma membrane, preventing neurotransmitter release, especially glutamate. Therapeutic dose is between 100 and 400 mg/day, which needs to be slowly achieved. Side effects are skin rashes, dizziness, constipation, nausea and drowsiness.

Topiramate

Topiramate has been proved effective in isolated clinical trials, in patients with MS and TN [64, 65]. It has a multiple mechanism of action including: blockage of sodium channels; and enhancement of GABA activity in the CNS via interaction with a specific site of action of the GABA A receptors, which is different from the benzodiazepine site of action. Topiramate also inhibits glutamergic excitatory activity through blockage of the AMPA/kainate receptor. Moreover, it inhibits specific carbonic anhydrase isoenzymes. The starting dose is 25 mg/day, which can be increased by 25 mg every week up to a dose of 100–400 mg/day. Side effects include dizziness, double vision, cognitive impairment, weight loss and high endocular pressure.

Baclofen

Baclofen deserves particular attention. It is not an anticonvulsant agent, rather it can be risky for targeting

epilepsy when abruptly stopped. Mechanism of action is at the central level and not on the peripheral nerve. Baclofen mimics GABA and acts on GABA receptors, slowing the influx of calcium ions, therefore decreasing the release of excitatory neurotransmitters. It is slightly less potent than carbamazepine and can be used as first choice or in combination with carbamazepine and phenytoin (synergism) [66].

Starting dose is 5–10 mg/day, which can be slowly increased until a satisfactory clinical response is achieved, which is usually 50–75 mg three times a day. Side effects are usually transient and appear at the beginning of treatment. They include postural hypotension, muscle weakness and gastroenteric discomfort. About 10% of patients show intolerance to the drug. Patients with MS also experience extra benefit from the anti-spastic effect of baclofen.

Other medications

Subcutaneous sumatriptan

Sumatriptan and zolmitriptan showed efficacy in controlling allodynic pain following nerve injury in an animal model for trigeminal neuropathic pain. Both medications have agonistic action on 5-HT1_B, which results in inhibition of neurons of the trigeminal nucleus localised in the medulla. Therefore these drugs are thought to act on the central nervous system [67]. These data were confirmed in another clinical single-blind study of subcutaneous sumatriptan vs. placebo. Results proved efficacy of sumatriptan on pain symptoms in patients with TN after 15 and 30 min compared to placebo. Benefits lasted for 7 h on average and this limits the clinical use of the drug. Potential side effects from subcutaneous injection of sumatriptan include increased blood pressure, nausea and weakness, which are not dangerous [49].

Botulinum toxin

BoNT-A has been used for a long time in the treatment of disorders characterised by pathologically increased muscle tone. Early observations in dystonia also demonstrated an analgesic effect of BoNT-A [68], which led to further investigation on its efficacy for painful conditions including neuropathic pain [50], low back pain [69] and headaches [70]. Evidence shows that BoNT-A reduces the local release of nociceptive neuropeptides such as substance P, glutamate and calcitonin gene-related peptide and inhibits peripheral sensitisation, which would result in decreased central sensitisation [51]. Hence it can be hypothesised that BoNT-A prevents peripheral sensitisation and subsequently central sensitisation. There are reports of isolated cases of NT responding to BoNT-A. In another open study, 13 patients showed significant relief from symptoms after treatment with BoNT-A [71].

References

1. Headache Classification Subcommittee of the International Headache Society (2004). The International Classification of Headache Disorders, 2nd edition. Cephalalgia 24[Suppl 1]:9–160
2. Katusic S, Williams DB, Beard CM et al (1991) Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and differences. Neuroepidemiology 10:276–281
3. MacDonald BK, Cockerel OC, Sander JW (2000) The incidence and lifetime prevalence of neurological disorders in a community based study in UK. Brain 123:665–676
4. Hooge JP, Redekop WK (1995) Trigeminal neuralgia in multiple sclerosis. Neurology 45:1294–1296
5. De Simone R, Marano E, Brescia Morra V et al (2005) A clinical comparison of trigeminal neuralgic pain in patients with and without underlying multiple sclerosis. Neurol Sci 26:S150–S151
6. Rozen TD (2004) Trigeminal Neuralgia and glossopharyngeal neuralgia. Neurol Clin Am 22:185–206
7. Smyth P, Greenough G, Stommel E (2003) Familial trigeminal neuralgia: case reports and review of the literature. Headache 43:910–915
8. Savica R, Laganà A, Siracusano R et al (2007) Idiopathic familial trigeminal neuralgia: a case report. Neurol Sci 28:196–198
9. Scrivani SJ, Keith DA, Kulich R et al (1998) Posttraumatic gustatory neuralgia: a clinical model of trigeminal neuropathic pain. J Orofac Pain 12:287–292
10. Goadsby PJ, Matharu MS, Boes CJ (2001) SUNCT syndrome or trigeminal neuralgia with lacrimation. Cephalalgia 21:82–83
11. Evans WR, Bassiur JP (2005) Pretrigeminal neuralgia. Headache 45:242–244
12. Rushton JG, MacDonald HN (1957) Trigeminal neuralgia. Special considerations of nonsurgical treatment. JAMA 165:437–440
13. Cheng TM, Cascino TL, Onofrio BM (1993) Comprehensive study of diagnosis and treatment of trigeminal neuralgia secondary to tumors. Neurology 43:2298–2302
14. Obermann M, Yoon MS, Ese D et al (2007) Impaired trigeminal nociceptive processing in patients with trigeminal neuralgia. Neurology 69:835–841
15. Burchiel KJ, Slavin KV (2000) On the natural history of trigeminal neuralgia. Neurosurgery 46:152–155
16. Manzoni GC. Torelli P (2005) Epidemiology of typical and atypical craniofacial neuralgias. Neurol Sci 26[Suppl 2]:s65–67
17. Coffey RJ, Fromm GH (1991) Familial trigeminal neuralgia and Charcot-Marie-Tooth neuropathy. Report of two families and review. Surg Neurol 35:49–53
18. Cruccu G, Biasiotta A, Galeotti F et al (2006) Diagnostic accuracy of trigeminal reflex testing in trigeminal neuralgia. Neurology 66:139–141
19. Rushton JG, Stevens JC, Miller RH (1981) Glossopharyngeal (vagoglossopharyngeal) neuralgia. A study of 217 cases. Arch Neurol 38:201–205
20. Bruyn GW (1983) Glossopharyngeal neuralgia. Cephalalgia 3:143–157
21. Montalbetti L, Ferrandi D, Pergami P, Savoldi F (1995) Elongated styloid process and Eagle's syndrome. Cephalalgia 15:80–93
22. Bruyn GW (1984) Nervus intermedius neuralgia (Hunt). Cephalalgia 4:71–78

23. Kuhn WF, Kuhn SC, Gilberstadt H (1997) Occipital neuralgias: clinical recognition of a complicated headache. A case series and literature review. J Orofac Pain 11:158–165
24. Tancredi A, Caputi F (2004) Greater occipital neuralgia and arthrosis of C1-2 lateral joint. Eur J Neurol 11:573–574
25. Bruyn GW (1983) Superior laryngeal neuralgia. Cephalalgia 3:235–240
26. Jannetta PJ (1967) Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. J Neurosurg 26[Suppl]:159–162
27. Boecher-Schwarz HG, Bruehl K, Kessel G (1998) Sensitivity and specificity of MRA in the diagnosis of neurovascular compression in patients with trigeminal neuralgia. A correlation of MRA and surgical findings. Neuroradiology 40:88–95
28. Barker FG, Jannette PJ, Bissonette DJ et al (1996) The long-term outcome of microvascular decompression for trigeminal neuralgia. N Engl J Med 334:1077–1183
29. Leandri M, Eldridge P, Miles J (1998) Recovery of nerve conduction following microvascular decompression for trigeminal neuralgia. Neurology 51:1641–1646
30. Miles JB, Eldridge PR, Haggett CE, Bowsher D (1997) Sensory effects of microvascular decompression in trigeminal neuralgia. J Neurosurg 86:193–196
31. Cruccu G, Leandri M, Feliciani M, Manfredi M (1990) Idiopathic and symptomatic trigeminal pain. J Neurol Neurosurg Psychiatry 53:1034–1042
32. Marinković S, Todorović V, Gibo H et al (2007) The trigeminal vasculature pathology in patients with neuralgia. Headache 47:1334–1339
33. Burchiel KJ (1980) Abnormal impulse generation in focally demyelinated trigeminal roots. J Neurosurg 53:674–683
34. Bennetto L, Patel NK, Fuller G (2007) Trigeminal neuralgia and its management. BMJ 334:201–205
35. Love S, Terry Gradidge T, Coakham HB (2001) Trigeminal neuralgia due to multiple sclerosis: ultrastructural findings in trigeminal rhizotomy specimens. Neuropathol Appl Neurobiol 27:238–244
36. Gass A, Kitchen N, MacManus DG et al (1997) Trigeminal neuralgia in patients with multiple sclerosis: lesion localization with magnetic resonance imaging. Neurology 49:1142–1144
37. Rappaport ZH, Govrin-Lippmann R, Devor M (1997) An electronmicroscopic analysis of biopsy samples of the trigeminal root taken during microvascular decompressive surgery. Stereotact Funct Neurosurg 68:182–186
38. Nurmikko TJ, Eldridge PR (2001) Trigeminal neuralgia pathophysiology, diagnosis and current treatment. Br J Anaesth 87:117–132
39. Adams CBT (1989) Microvascular compression: an alternative view and hypothesis. J Neurosurg 57:1–12
40. Hamlyn PJ, King TJ (1992) Neurovascular compression in trigeminal neuralgia: a clinical and anatomical study. J Neurosurg 76:948–952
41. Sindou M, Leston J, Howeidy T et al (2006) Micro-vascular decompression for primary Trigeminal Neuralgia (typical or atypical). Long-term effectiveness on pain; prospective study with survival analysis in a consecutive series of 362 patients. Acta Neurochir (Wien) 148:1235–1245
42. Fromm GH (1991) Pathophysiology of trigeminal neuralgia. In: Fromm GH, Sessle BJ (eds) Trigeminal Neuralgia: current concepts regarding pathogenesis and treatment. Butterworth-Heinemann, Boston, pp 105–130
43. Szapiro J, Sindou M (1985) Prognostic factors in microvascular decompression for trigeminal neuralgia. Neurosurgery 17:920–929
44. Amir R, Devor M (2000) Functional cross-excitation between afferent A- and C-neurons in dorsal root ganglia. Neuroscience 95:189–195
45. Amir R, Devor M (1996) Chemically mediated cross-excitation in rat dorsal root ganglia. J Neurosci 16:4733–4741
46. Amir R, Michaelis M, Devor M (1999) Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. J Neurosci 19:8589–8596
47. Kerr FWL (1967) Pathology of trigeminal neuralgia: light and electron microscopic observations. J Neurosurg 26:151–156
48. Beaver DL (1967) Electron microscopy of the Gasserian ganglion in trigeminal neuralgia. J Neurosurg 26:138–150
49. Kanai A, Saito M, Hoka S (2006) Subcutaneous sumatriptan for refractory trigeminal neuralgia. Headache 46:577–582.
50. Argoff CE (2002) A focused review on the use of botulinum toxins for neuropathic pain. Clin J Pain 18[Suppl 6]:S177–S181
51. Aoki KR (2005) Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology 26:785–793
52. Wiffen PJ, McQuay HJ, Moore RA (2005) Carbamazepine for acute and chronic pain. Cochrane Database Syst Rev (3):CD005451
53. Rappaport ZH, Devor M (1994) Trigeminal neuralgia: the role of self-sustaining discharge in the trigeminal ganglion. Pain 56:127–138
54. Backonja MM (2002) Use of anticonvulsants for treatment of neuropathic pain. Neurology 59:S14–S17
55. Taylor JC, Brauer S, Espir LE (1981) Long-term treatment of trigeminal neuralgia with carbamazepine. Postgrad Med J 5:16–18
56. Pellock JM (1987) Carbamazepine side effects in children and adults. Epilepsia 28:S64–S70
57. Zakrzewska JM, Lopez BC (2005) Trigeminal neuralgia. Clin Evid :1669–1677
58. Canavero S, Bonicalzi V (2006) Drug therapy of trigeminal neuralgia. Expert Rev Neurother 6:429–440
59. Raskin NH (1988) Facial pain. In: Headache. New York: Churchill Livingstone:333–374.
60. Wiffen PJ, McQuay HJ, Edwards JE, Moore RA (2005) Gabapentin for acute and chronic pain. Cochrane Database Syst Rev (3):CD005452
61. Obermann M, Yoon MS, Sensen K et al (2007) Efficacy of pregabalin in the treatment of trigeminal neuralgia. Cephalalgia 28:174–181
62. Zakrzewska JM, Chaudhry Z, Nurmikko TJ et al (1997) Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind, placebo-controlled, crossover trial. Pain 73:223–230
63. Lunardi G, Leandri M, Albano C et al (1997) Clinical effectiveness of lamotrigine and plasma levels in essential and symptomatic trigeminal neuralgia. Neurology 48:1714–1717
64. Gilron I, Booher SL, Rowan JS, Max MB (2001) Topiramate in trigeminal neuralgia: a randomized, placebo-controlled multiple crossover pilot study. Clin Neuropharmacol 24:109–112
65. Zvartaui-Hind M, Din MU, Gilani A et al (2000) Topiramate relieves refractory trigeminal neuralgia in MS patients. Neurology 55:1587–1588
66. Fromm GH, Terrence CF, Chattha AS (1984) Baclofen in the treatment of trigeminal neuralgia: double blind study and long term follow-up. Ann Neurol 15:240–244
67. Kayser V, Aubel B, Hamon M, Bourgoin S (2002) The antimigraine 5-HT1B/1D receptor agonists, sumatriptan, zolmitriptan and dihydroergotamine, attenuate pain-related behaviour in a rat model of trigeminal neuropathic pain. Br J Pharmacol 137:1287–1297

68. Tsui JK, Eisen A, Stoessl AJ et al (1986) Double-blind study of botulinum toxin in spasmodic torticollis. Lancet 2:245–247
69. Difazio M, Jabbari B (2002) A focused review of the use of botulinum toxins for low back pain. Clin J Pain 18[Suppl 6]:S155–S162
70. Silberstein SD, Stark SR, Lucas SM et al; BoNTA-039 Study Group (2005) Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 80:1126–1137
71. Piovesan EJ, Teive HG, Kowacs PA et al (2005) An open study of botulinum-A toxin treatment of trigeminal neuralgia. Neurology 65:1306–1308

Neurol Sci (2008) 29:S79–S82
DOI 10.1007/s10072-008-0893-6

Treatment strategy for trigeminal neuralgia: a thirty years experience

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Abstract Trigeminal neuralgia is an invalidating disease when become drug-resistant. The only possible treatment is surgery with different modalities, percutaneous, open surgery or radiosurgery. The thirty years experience at the Fondazione Istituto Neurologico C. Besta, Milano, Italy suggests that these surgical strategies are successful in pain control in short and long term period in more than 90% of cases, with a low rate of side effects and high improvement of quality of life. The type of surgery should be tailored on the particular patient considering age, general physical condition, neuroradiological assessment in which MRI with dedicated sequences are mandatory, and also patient's attitude.

Keywords Trigeminal neuralgia · Microvascular decompression · Radiofrequency thermorhyzothomy · Balloon microcompression · Radiosurgery

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Introduction

Trigeminal neuralgia (TN) is characterised by attacks of recurring, paroxysmal, shock-like pain within the distribution of one or more branches of the trigeminal nerve [1]. Even though new drugs have recently been introduced in the treatment of TN, about half of all patients eventually require surgery for pain relief, because of drug resistance or drug intolerance [2, 3]. The neurosurgical armamentarium of the third millennium includes more traditional treatment options, either percutaneous such as radiofrequency thermorhizotomy (TRZ) and balloon microcompression, or open such as microvascular decompression (MVD), along with novel radiosurgical techniques. Since all these treatment options seem to have a good success rate with low risks, the ideal algorithm of treatment is still under debate. In this chapter the authors report on their experience in the treatment of this painful condition and present their own treatment algorithm.

Microvascular decompression

The concept of MVD of the trigeminal nerve was a milestone in the management of medically intractable TN. In the past 30 years thousands of patients have undergone successful MVD and today it represents one of the most widely used surgical options for TN. Our experience with MVD started in 1990 and so far more than 600 patients, including 40 patients affected by multiple sclerosis (MS), have been operated upon. All patients who do not want to experience any sensory disturbance undergo this kind of surgery as a first option. Advanced age *per se* is not considered a contraindication.

Results and prognostic factors

At long-term follow-up (3–10 years) 76% of patients are completely pain-free without medication, 5% are pain-free with a dosage of drugs lower than in the pre-operative period and 15% require repeated surgery or high dosage of drugs. The outcome in the MS group is much worse, with only 39% of patients completely pain-free without medication at long-term follow-up. Several prognostic factors were tested (patient's age and sex; involved side and branch; duration of symptoms; history of previous trigeminal ablative procedures; kind of neurovascular conflict; post-operative numbness; hypertension) and only long duration of clinical history (>84 m) was found to be predictive of a worse outcome.

Surgical technique and side effects

Our experience shows that a learning curve is present in this kind of surgery and that some tricks reduced morbidity almost to zero in the last 400 patients. The invasivity of surgery, its duration and length of hospital stay have all been reduced and now patients are generally discharged home on the third post-operative day after surgery lasting about one hour. Exploration of the cerebello-pontine angle is performed through a small (less than 20 mm in diameter) retromastoid craniectomy, in the supine position with the head rotated to the opposite side of neuralgia. Sitting position and park-bench position were used at the beginning of our experience, but the supine position was soon found to be the easiest and most straightforward. The craniectomy must be exactly placed in the corner between transverse sinus and sigmoid sinus. Image guidance is of great help to avoid any mistakes due to the interindividual variation of the bony surface landmark positions (asterion, mastoid tip and emissary mastoid vein). The margins of the transverse and sigmoid sinuses are minimally exposed and the dura opened along the line bisecting their angle. Mastoid air cavities, if encountered, must be immediately sealed prior to dural opening. Any attempt to reach the nerve through an imperfectly positioned craniectomy must be avoided. The surgical corridor must be the natural supracerebellar corridor created by gravity and CSF suction beneath the tentorium and the superior petrosal sinus. This corridor leads directly to the fifth cranial nerve without any other cranial nerve along the working path. The only anatomical structure that is invariably encountered along this path is the petrosal vein complex that covers the access to the nerve. Delicate arachnoidal dissection depicts the anatomy of these multiple collectors well and greatly increases the working space, making venous sacrifice unnecessary in many cases. When it is necessary to sacrifice some veins, care should be taken to save at least the main collector (especially if it is very big), which, when freed of the arachnoid, can be moved away from the trajectory. Immediately beyond these veins the trigeminal nerve is always found, sometimes in conflict with these veins themselves. Key to this surgery is wide arachnoidal sharp dissection under direct visual control that allows for careful nerve exploration and safe vessel replacement without any traction. Any injury to exposed cerebellar surface, brainstem, arterial vessels and their small perforators is a potentially dangerous mistake. Compressive arteries are fixed away from the nerve by the use of small pieces of fibrillar oxidised cellulose (Fibrillar Surgicel). The aim of surgery is to free the nerve from any unnecessary contact, including that with the material used to fix the compression. An inflammatory tissutal reaction can, in fact, recreate the nerve adhesion and distortion responsible for recurrent pain. Compressive veins are electrocoagulated and divided. A watertight dural closure obtained by reinforcing the suture with dural sealants or muscle fragments and fibrin glue is mandatory to reduce the risk of CSF leakage. Perioperative steroids (desamethazone) are used. Post-op headache and sometimes nausea due to intraoperative CSF suction are common on the first post-operative day but well controlled by drugs and rehydration. Mobilisation is encouraged on the first post-operative day. Home discharge is generally permitted on the third post-operative day. Aseptic or more rarely bacterial meningitis (0.7% in our institution) can delay discharge. Mortality or permanent morbidity have been reported in some early series but their incidence can be greatly minimised when the surgical technique is standardised and accurate [4–9]. Since we were unable to find any age-related difference in the incidence of surgical complications, we perform MVD without any absolute age limit.

Percutaneous methods

Since Hartel [10] introduced his simple and direct percutaneous approach to the foramen ovale and gasserian ganglion in 1914, lots of different methods of creating therapeutic damage to the trigeminal root and ganglion have become available (heating, cooling, chemicals, etc.). Due to an unfavourable recurrence rate and a high incidence of side effects, most of these techniques were progressively abandoned in favour of controlled radiofrequency thermal rhizotomy and mechanical balloon microcompression.

Radiofrequency retrogasserian controlled thermorhizotomy

The efficacy of radiofrequency retrogasserian controlled TRZ has been confirmed by many authors in large series of patients [11–24]. More than 1700 patients have so far

been treated at the Istituto Nazionale Neurologico Carlo Besta since 1974. We followed up 97% of the patients for a time ranging from 2 to 15 years (mean follow-up 72 months): 71% of patients were found to be completely pain-free without medication, 11% were pain-free with low dosage of antineuralgic drugs, while 15% were still experiencing severe pain requiring high dosage of drugs or surgery. Regarding the amount of the inflicted sensory deficit, our data suggest that induced post-operative analgesia prevents the recurrence of pain in most patients. In other words, patients with post-operative hypalgesia have a pain recurrence probability of 41% vs. 7.5% for patients with post-operative analgesia. In all patients the sensory deficit tends to recover with time, nevertheless a high percentage of patients with the more severe sensory post-operative deficit (analgesic patients) complain of dysaesthesias. The total percentage of patients who required drugs for severe dysaesthesia was 5%, with 1.5% with painful anaesthesia that we were never able to definitively alleviate by any of the more advanced surgical antalgic techniques (open or percutaneous trigeminal tractotomy, trigeminal stimulation, cortical stimulation, deep brain stimulation, CSF direct drug infusion). These complications are clearly related to the technique itself and cannot be completely avoided even with a meticulous surgical technique, above all in repeated procedures.

By monitoring the corneal reflex during the procedure, however, major ocular deafferentation complications can be generally avoided and keratitis requiring tarsorrhaphy was observed in only 0.5% of patients, even though the involvement of the first branch was not considered as a contraindication to this kind of surgery. Masseter weakness with minor chewing impairment appeared in 10% of patients, and ocular palsy and diplopia in 0.5%. Major neurological morbidity due to intracranial bleeding was observed in one case. Mortality was null. This method can be proposed to patients who accept the risk of sensory disturbances, when previous less aggressive procedures have failed.

Balloon microcompression of the gasserian ganglion

In 1978 Mullan and Lichtor developed a percutaneous technique for controlled compression of the trigeminal ganglion that could be carried out under short general anaesthetic [25]. The results that we were able to obtain by using balloon microcompression of the gasserian ganglion (PMC) in 235 patients operated upon since 1992 were the following: completely pain free without medication: 136 cases (58 %); requiring low dosage of drugs: 28 (12%); requiring high dosage of drugs or surgery: 71 cases (30%). Side effects were: permanent diplopia 1 patient; dysesthesia requiring medical treatment 10 patients. Painful anesthesia and cheratitis were never observed. The end point for compression was the achievement of a “pear”-shaped balloon in the cavum Meckel. The balloon is then kept inflated for approximately 1 min. A longer compression resulted in a profound hypoaesthesia that often led to complaints of dysaesthesias. This method appears to have the same limitations that characterise trigeminal surgery whatever the lesional procedure used, that is: the more the sensorial deficit, the longer the pain-free interval but the higher the rate of severe dysaesthesia.

However, PMC is easy to perform and the recurrence rate is acceptable, with a low rate of complication even in the case of repeated surgery. Diplopia was sometimes observed but it is generally transient. Since painful anaesthesia and keratitis are, in our opinion, too high a price to be paid for pain relief, this is now the method we prefer when MVD fails or is refused by the patient.

Radiosurgery

Radiosurgery is an old modality of treatment [26] that now can be performed by using very sophisticated and precise methods of targeting such as Cyberknife. In our institution it has been available since March 2004 and 40 patients have undergone this procedure, but the follow-up is too short to allow for a comparison of the efficacy with other radiosurgical and surgical treatment modalities. However, from the analysis of the literature and our initial experience, the following conclusions can be drawn:

Radiosurgery should be considered as a lesional procedure.

A strong correlation between the development of new facial sensory loss and achievement and maintenance of pain relief after this procedure has been described [27].

Quality of data is generally poor: case series have different patient populations, varying doses of radiation and targets, a variety of assessment methods and differing follow-up.

70%–80% of patients are pain-free in the short term, although up to 50% may relapse.

Side effects include facial dysaesthesia (up to 12%), corneal irritation, vascular damage, hearing loss and facial weakness, varying with the dose plan and target area.

Follow-up is short and uncertainty persists about possible late complications of radiation therapy.

Conclusions

MVD is the only surgical option that allows long-term pain relief to be obtained while avoiding any sensory disturbance. In our opinion it remains the treatment of choice for all patients with drug-resistant typical TN. Old age and central demyelination do not constitute absolute contraindications to this kind of surgery. Since sensorial deficits can be far from negligible and well tolerated in

some patients treated with lesional procedures, our policy is to delay destructive surgery as much as possible. When these procedures cannot be avoided, PMC appears to be the easiest to perform with a low complication rate and good long-term results. In cases requiring more aggressive treatment because of recurrent pain, TRZ can be performed. The use of radiosurgery is still under investigation and further studies are required to clarify its role in the treatment of TN. In MS patients, unfortunately neither MVD nor lesional procedures can prevent pain recurrence due to MS-related evolving demyelination. Thus, new treatments aiming to modulate the activity of central trigeminal pathways should be investigated to improve the quality of life of these unfortunate patients.

References

1. Dubner R, Sharav Y, Gracely RH et al (1987) Idiopathic trigeminal neuralgia: sensory features and pain mechanisms. Pain 31:23–33
2. Farago F (1987) Trigeminal neuralgia: its treatment with two new carbamazepine analogues. Eur Neurol 26:73–83
3. Fromm GH, Terrence CF, Maroon JC (1984) Trigeminal neuralgia: current concepts regarding etiology and pathogenesis. Arch Neurol 41:1204–1207
4. Adams CBT (1989) Microvascular decompression: an alternative view and hypothesis. J Neurosurg 57:1–12
5. Apfelbaum RI (1984) Surgery for tic doloreaux. Clin Neurosurg 31:351–368
6. Burchiel KJ, Clarke H, Haglund M, Loeser JD (1988) Long-term efficacy of microvascular decompression in trigeminal neuralgia. J Neurosurg 69:35–38
7. Jannetta PJ (1967) Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. J Neurosurg 26:159–162
8. Jannetta PJ (1993) Vascular compression is the cause of trigeminal neuralgia. AAPS J 2:217–227
9. Taha JM, Tew JM (1996) Comparison of surgical treatments for trigeminal neuralgia: reevaluation of radiofrequency rhizotomy. Neurosurgery 38:865–871
10. Hartel F (1911) Die Leitungsans thesie und injektions behandlung des Ganglion Gasseri und der Trigem inusstmme langenbecks. Arch Klin Chir 100:193
11. Broggi G, Franzini A, Lasio G et al (1990) Long-term results of percutaneous retrogasserian thermorhizotomy for "Essential" trigeminal neuralgia: considerations in 1000 consecutive patients. Neurosurgery 26:783–787
12. Broggi G, Siegfried J (1997) The effect of graded thermocoagulation on trigeminal evoked potentials in the cat. Acta Neurochir (Wien) 24[Suppl]:175–178
13. De la Porte C, Siegfried J (1983) Étude des paramètres de thérmocoagulation à haute fréquence du ganglion de Gasser dans le traitement de la nevralgie du trijumeaux pour l'obtention d'une analgésie sans anésthesie. Neurochirurgie 29:191–195
14. Frank F, Gaist T, Fabrizi A et al (1985) Rèsultats de la thérmocoagulation percutanée sélective du ganglion de Gasser dans la nevralgie faciale essentielle. Synthèse des resultats obtenus chez 939 patients traités. Neurochirurgie 31:179–182
15. Frigyesi T, Siegfried J, Broggi G (1975) The selective vulnerability of evoked potentials in the trigeminal sensory root to graded thermocoagulation. Exp Neurol 49:11–21
16. Mittal B, Thomas DG (1986) Controlled thermocoagulation in trigeminal neuralgia. J Neurol Neurosurg Psychiatry 49:932–936
17. Siegfried J (1984) La nevralgie typique du trijumeau. Considerations cliniques, étiopatogeniques et therapeutiques. Med Hyg 41:1753–1757
18. Siegfried J (1981) Percutaneous controlled thermocoagulation of Gasserian ganglion in trigeminal neuralgia. Experiences with 1,000 cases. In Samii M, Janetta PJ (eds) The cranial nerves. Springer-Verlag, Berlin and Heidelberg, pp 322–330
19. Sweet WH, Wepsic JG (1974) Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. J Neurosurg 40:143–156
20. Tew JM Jr, Keller JT (1977) The treatment of trigeminal neuralgia by percutaneous radiofrequency technique. Clin Neurosurg 24:557–578
21. Broggi G, Ferroli P, Franzini A et al (1999) Role of microvascular decompression in trigeminal neuralgia and multiple sclerosis. Lancet 354:1878–1879
22. Broggi G (2000) Microvascular decompression for trigeminal neuralgia: comments on a series of 250 cases, including 10 patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 68:59–64
23. Broggi G, Ferroli P, Franzini A, Gallosi L (2005) One size does not fit all: choosing a treatment strategy for trigeminal neuralgia. Clin Neurosurg 52:283–291
24. Siegfried J, Vosmansky M (1975) Technique of the controlled thermocoagulation of trigeminal ganglion and spinal roots. In Krayen-Buhl H (ed.) Advances and technical standards in neurosurgery, Vol 2. Springer-Verlag, Wien, Berlin, and New York, pp 199–209
25. Mullan S, Lichtor T (1983) Percutaneous microcompression of the trigeminal ganglion for trigeminal neuralgia. J Neurosurg 59:1007–1012
26. Leksell L (1971) Sterotaxic radiosurgery in trigeminal neuralgia. Acta Chir Scand 137:311–314
27. Pollock BE, Phuong LK, Foote RL et al (2001) High-dose trigeminal neuralgia radiosurgery associated with increased risk of trigeminal nerve dysfunction. Neurosurgery 49:58–62; discussion 62–64

Neurol Sci (2008) 29:S83–S87
DOI 10.1007/s10072-008-0894-5

PSYCHIATRIC STATE AND HEADACHE

Eating disorders and headache: coincidence or consequence?

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Abstract The eating disorders (ED) anorexia nervosa (AN) and bulimia nervosa (BN) are important psychiatric and somatic conditions occurring mainly in young women. The aetiology is unknown, but there are social, biological and psychological factors that play a relevant role in the pathogenesis, along with multiple endocrine abnormalities. Hypothalamic monoamines (especially serotonin), neuropeptides (especially neuropeptide Y and cholecystokinin) and leptin are involved in the regulation of the human appetite. ED share with migraine the same metabolic profile and aspect of psychiatric and psychological conditions. In support of this hypothesis in one study, it has been shown that the incidence of migraine is high in these patients; and it has been shown that the incidence in a female group that suffers from migraine was greater than in the normal population. In order to understand the possible relationship between migraine and ED, we have investigated the incidence of primary headache in a group of AN and BN patients. The result of this study shows that the prevalence of migraine in women affected by AN and BN is very high (75%) in comparison to the general population (12.5% headache incidence in normal population). In most patients the onset of migraine attacks began before or at the same time as the symptoms of AN and BN. We suggest that migraine is a predisposing condition for the occurence of AD in young women.

Keywords Eating disorder · Anorexia · Bulimia · Migraine · Headache · Amines

Introduction

The eating disorders (ED) anorexia nervosa (AN) and bulimia nervosa (BN) are important psychiatric and somatic conditions occurring mainly in young women [1]. Their aetiology is unknown, but there are many social, biological and psychological factors that play a relevant role in their pathogenesis [2]. To understand the causality of ED it is necessary to consider that many factors correlate to this disorder [3]. Our knowledge of correlate and risk factors is increasing daily. Over 30 risk factors for ED have been identified thus far with a reasonable degree of evidence. However it remains very difficult to demonstrate causality. There is a statistically significant chance of their being associated with ED (e.g., depression). Longitudinal studies have underlined that risk factors clearly precede the onset of the illness. In the bio-psycho-social model there are biological, psychological and socio-cultural factors that sustain the onset of ED:

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Biological factors		
Genetic basis	Twin, family and adoption studies Candidate gene studies	ED are not monogenic disorders There is a complex interplay between genetic predisposition and environmental factors
Neurodevelopmental basis	Neuroimaging techniques	It is unclear to what extent hippocampal atrophy might reflect a cause or an effect of the illness
Neuropsychological testing	Perinatal risk factors Retrospective and prospective studies	Mild hypoxia affecting hippocampal and cortical brain development
Puberty	Epidemiological and biological studies	Early-onset menarche Increase in fat mass Oestrogen hormones and serotonin receptors
Psychological factors		
Temperament	Psychometric and clinical studies	Harm avoidance Novelty seeking Persistence Reward dependence Self-directedness
Attachment	Psychometric and clinical studies	Insecure attachment
Self-esteem	Psychometric and clinical studies	Low self-esteem
Traumatic and change events	Psychometric and clinical studies	Abuse, neglect, changes, cultural transitions
Socio-cultural factors		
Obesogenic environment	Studies on abundance of cheap, high-calorie foods Studies on low physical activity	Globesity
Pressure to be thin	Studies on fashion magazines, dolls, commercial images, diet industries, etc.	ED can no longer be thought of as culture-bound syndromes

Among women, the lifetime prevalence of AN is 3–5 in 1000, and the lifetime prevalence of bulimia is 10–15 in 1000 considering the general population. AN is typically found in teenage girls, while for BN the typical age is slightly higher, at 16–35 years. ED are primarily found in females: in AN for 19 females there are 2 males, and in BN for 29 females there is 1 male [4].

Fifty percent of patients with AN go on to develop BN and about a third of patients with BN have had a previous episode of AN.

AN and BN are different pathologies. In the DSM-IV there are diagnostic criteria to distinguish the two pathologies:

- Anorexia nervosa (AN)
  - Body weight <85% of expected weight
  - Intense fear of gaining weight
  - Undue emphasis on body shape or weight
  - Amenorrhoea (in girls and women after menarche) for three consecutive months
- Bulimia nervosa (BN)
  - Recurrent binge eating (at least two times per week for three months)
  - Recurrent, inappropriate, compulsive behaviour to prevent weight gain such as self-induced vomiting, abuse of laxatives, diuretics or other medications, or excessive exercise
  - Persistent overconcern with body shape and/or weight
  - Absence of AN

In the category of ED is possible to identify another pathology called:

- Binge eating disorder (BED)
  - Recurrent episodes of binge eating. An episode is characterised by
    1. Eating a larger amount of food than normal during a short period of time (within any two-hour period).
    2. Lack of control over eating during the binge episode (i.e., the feeling that one cannot stop eating).
  - Binge eating episodes are associated with three or more of the following:
    1. Eating until feeling uncomfortably full.
    2. Eating large amounts of food when not physically hungry.
    3. Eating much more rapidly than normal.
    4. Eating alone because you are embarrassed by how much you are eating.
    5. Feeling disgusted, depressed, or guilty after overeating.
  - Marked distress regarding binge eating is present
  - Binge eating occurs, on average, at least two days a week for six months
  - The binge eating is not associated with the regular use of inappropriate compensatory behaviour (i.e., purging, excessive exercise, etc.) and does not occur exclusively during the course of BN or AN.

In general it is possible to affirm that in AN the Body

Mass Index (BMI) is inferior to 17.5, in the BN the BMI is normal and in the BED the BMI is often elevated.

A lot of physical and psychological inconveniences characterise the "fast syndrome", for example depression, obsession, anxiety, apathy and reduction of cognitive capacity; physiologically there is hypotension, difficulty sleeping, gastrointestinal trouble, reduced libido, etc. In accordance with the data reported from studies in anorexic animals [5], ED seems characterised by the malfunction of neurotransmitters.

A very interesting study of the relationship between migraine and ED relation has shown the incidence of ED in a group of female migraine sufferers to be greater than that in a normal population [6]. In this study a modified version of the Eating Disorder Inventory (EDI) and Diagnostic Survey of Eating Disorders (DSED) was administered to a group of female migraine patients. Eighty-eight percent of these reported dieting behaviour, 59% reported binge eating and 26% reported self-induced vomiting. Moreover, they had an elevated score on four of the eight subscales of EDI (body dissatisfaction, perfectionism, interpersonal distrust and ineffectiveness).

Migraine shares with ED the same metabolic profile [7] and the same psychiatric and psychological conditions. The high level of elusive amines such as tyramine and octopamine in plasma and platelets recently found in migraine patients suggest that a hypothalamic and limbic dysfunction contributes to migraine physiopathology as trace amine associate receptors (TAARs) are mainly localised in such brain areas [8]. Indeed the altered psychological behaviour of ED patients suggests that abnormalities of these brain centres may also play a role in ED pathophysiology.

We have studied the prevalence of migraine in a group of AN and BN patients consecutively treated as inpatients in our ED unit.

Methods

We have examined 109 female inpatients treated in the Unit for ED of the Villa Margherita Neurology and Psychiatric Clinic; 76 were affected by AN and 33 by BN according to the DSM IV criteria [9]. The patients were consecutively treated in our inpatient programme during 2006–2007. Mean age, BMI, duration of illness and other parameters are reported in Table 1. The diagnosis of migraine or other primary headaches was made using a questionnaire that includes questions about the presence of migraine in the patients' first-degree relatives, the diagnostic criteria of the IHS classification [10] (proposed in 1988 by the International Headache Society) and characteristics of headache attacks and their frequency and duration. The questionnaire interviews, administered in the first 20 days of admission, were performed by a neurologist specialised in migraine problems.

Fifty-six percent of patients investigated consumed drugs used in the treatment of mental conditions (antidepressives, antipsychotics, benzodiazepine), while 44% patients were without medication therapy. There is no significant influence of this element on the incidence of headache.

For 22.9% of patients the illness duration was less than four years, for 34.9% illness duration was between four and eight years, and for the majority of patients (42.2%) it was more then eight years

Chi-squared, *t*-test and Mann–Whitney test were used to evaluate the possible statistical significant differences between the control and patient groups or between the patients sub groups.

Results

As shown in Table 2, many patients (in=91, 83.5%) complained of primary headaches. The majority of these suffer from migraine (n=81, 89%). Only 3 (2.8%) women satisfied IHS criteria for the diagnosis of migraine with aura (MwA) but 60 (55%) women satisfied the criteria for migraine without aura (MwwA); 5 (4.6%) women suffered from probable MwwA and 8 (7.3%) from possible MwwA. Only 6 (5.5%) patients were affected by tension headache; 4 (3.7%) subjects showed an unclassifiable headache. Finally, only 18 subjects (16.5%) had no headache symptoms.

Table 1 Characteristics of the female population studied

	ED n=109 100%	AN n=76 69.7%	BN n=33 30.3%	C n=27	*p* *t*-test
Age, years					
Mean±SD	26.6±8.5	26.2±8.1	26.1±8.8	27.7±6.3	
Range	16–58	16–58	17–56	20–53	
BMI±SD	17.4±4.6	15.1±2.1	22.8±4.2		AN vs. BN: <0.001
Patients treated	61 (56.0%)	42 (54.7%)	19 (58.1%)		
Patient without medication	48 (44.0%)	34 (45.3%)	14 (41.9%)	27	

C, control subjects; *ED*, eating disorders; *AN*, anorexia nervosa; *BN*, bulimia nervosa

Table 2 Prevalence of headache patients among ED sufferers

Patients with headache	91 (83.5%)			
	Migraine	81 (89%)	MwA	3 (2.8%)
			MwwA	60 (55%)
			MwwAps	8 (7.3%)
			MwwApr	5 (4.6%)
			CM	5 (4.6%)
	Tension headache	6 (6.6%)	ETH	3 (2.75%)
			CTH	3 (2.75%)
	Other headaches	4 (4.4%)		
Patients without headache	18 (16.5%)			
Total no. patients	109			

MwwAps, possible migraine without aura; *MwwApr*, probable migraine without aura; *CM*, chronic migraine; *ETH*, episodic tension headache; *CTH*, chronic tension headache

Referring to the issue of the beginning of headache (Table 3), in 56.9% of patients the migraine attacks began before the onset of ED symptoms, in 13.8% of subjects the attacks of migraine and the symptoms of ED began in the same period. In the minority of the women studied (12.8%) migraine developed after the onset of the ED. There is no significant difference for this aspect between AN and BN subjects.

There is no significant difference in the incidence of headache disorders between the AN and BN groups that we have studied, as can be seen from Table 4.

Also, frequency and duration of attack do not seem to be meaningfully different between the two diagnostic groups (Tables 5 and 6).

Table 3 The beginning of headache compared to ED

	Total patients	AN	BN	Migraine	Tension headache	Other headache
Before DCA	62 (68.1%)	46 (73.0%)	16 (57.1%)	56 (69.1%)	2 (33.3%)	4 (100%)
Contemporary DCA	15 (16.5%)	10 (15.9%)	5 (17.9%)	14 (17.3%)	1 (16.7%)	
After DCA	14 (15.4%)	7 (11.1%)	7 (25.0%)	11 (13.6%)	3 (50.0%)	

Table 4 Incidence of different headaches types in AN and BN groups

	Migraine	Tension headache	Other headache	Without migraine	Total patients for diagnosis group
AN	55 (72.3%)	4 (5.3%)	4 (5.3%)	13 (17.1%)	76
BN	26 (78.8%)	2 (6.1%)	0 (0.0%)	5 (15.1%)	33
Total patients for headache group	81	6	4	18	109

Table 5 Headache attack duration in AN and BN

	0–4 h	4–8 h	9–24 h	More than 24 h	Constant	Total patients for ED group
AN	20 (31.8%)	15 (23.8%)	17 (27.0%)	9 (14.3%)	2 (3.2%)	63
BN	11 (39.3%)	4 (14.3%)	7 (25.0%)	5 (17.9%)	1 (3.6%)	28
Total patients for attack length	31	19	24	14	3	91

Table 6 Frequency of headache attack in AN and BN groups

	Less than 1 per month	1–4 per month	More than 1 per month	Every day or nearly	Total patients of AN and
AN	13 (20.6%)	22 (34.9%)	17 (27.0%)	11 (17.5%)	63
BN	4 (14.3%)	7 (25.0%)	13 (46.4%)	4 (14.3%)	28
Total patients of AN and BN groups	17	29	30	15	109

Discussion

The prevalence of migraine in women affected by AN and BN is very high (83.5%) in comparison to the general population (12.5% as reported in the normal population). In most (68.1%) of the patients the onset of migraine attacks began before or at the same time as the symptoms of AN and BN. This suggests that migraine could be a pathological condition favourable to the occurrence of these psychiatric diseases. The pathophysiology of AN and BN are not definitively understood. The excessive control of feeding and the low body weight together with reduced sexual desire and disappearance of menstrual cycle suggest that a dysfunction of the hypothalamus [11], limbic [12] and amygdala [13] areas may play an important role in the determination of the disease. The results of our biochemical studies support this hypothesis. The levels of tyramine and dopamine are significantly elevated in the plasma of our patients [14]. It is known the TAARs, possible receptors of elusive amines, are localised in the limbic circuitry, amygdala, hypothalamus, extrapyramidal system and other brain stem nuclei. The high levels of tyramine, octopamine and dopamine suggest an activation of all these CNS centres in this psychiatric syndrome.

Migraine may share pathophysiological aspects and biochemical abnormalities with ED. It has been hypothesised that dysfunctions of the frontal lobe, amygdala, hypothalamus and extrapyramidal system are involved in migraine pathogenesis. The increased amount of neuromodulators and abnormal amount of neurotransmitters in the synaptic clefts cause an anomalous neurotransmission at the different levels of CNS such as the hypothalamus, limbic and connected centres, which may play a role in the pathogenesis of EDs and migraine.

In conclusion, this study shows a comorbidity between ED and migraine; a high percentage of ED patients suffer from migraine. The data suggest that migraine may be considered, on the basis of similar neurotransmitters amines in the two pathological conditions, a predisposing factor for the occurrence of ED.

References

1. Avraham Y, Hao S, Mendelson S, Berry EM (2001) Tyrosine improves appetite, cognition, and exercise tolerance in activity anorexia. Med Sci Sports Exercise 33:2104–2210
2. Management of Eating Disorders (2006) RTI-UNIC Evidence-Based Practice Center, Research Triangle Park, NC. AHRQ Publication N° 06-E010 April
3. Ostuzzi R, Luxardi GL (2003) Figlie in lotta con il cibo. Baldini
4. Ostuzzi R (2007) Un boccone dopo l'altro. Baldini & Castoldi
5. Bravander T, Bryant-Waugh R, Herzog D et al (2007) Classification of child and adolescent eating disturbances. Workgroup for classification of Eating Disorders in Children and Adolescents (WCEDCA). Int J Eat Disord 40[Suppl]:S117–122
6. Brevton TD, George MS (1993) Is migraine related with eating disorders? Int J Eat Disorder 14:75–79
7. D'Andrea G, Perini F, Terrazzino S, Nordera GP (2004) Contributions of biochemistry to the pathogenesis of primary headaches. Neurol Sci 3[Suppl 3]:589–592
8. D'Andrea G, Granella F, Leone M et al (2006) Abnormal platelet trace amine profiles in migraine with and without aura. Cephalalgia 26:968–972
9. – (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th ed. text rev. American Psychiatric Press, Washington DC
10. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd Edition. Cephalalgia 24[Suppl 1]:9–160
11. Stamatakis EA, Hetherington MM (2003) Neuroimaging in eating disorders. Nutr Neurosci 6:325–334
12. Seeger G, Braus DF, Ruf M et al (2002) Body image distortion reveals amygdala activation in patients with anorexia nervosa–a functional magnetic resonance imaging study. Neurosci Lett 326:25–28
13. Uher R, Brammer MJ, Murphy T et al (2003) Recovery and chronicity in anorexia nervosa: brain activity associated with differential Outcomes. Biol Psychiatry 54:934–942
14. D'Andrea G, Terrazzino S, Fortin D et al (2003) Elusive amines and primary headaches: historical background and prospectives. Neurol Sci 24:S65–S67

Neurol Sci (2008) 29:S88–S92
DOI 10.1007/s10072-008-0895-4

PSYCHIATRIC STATE AND HEADACHE

Study of tyrosine metabolism in eating disorders. Possible correlation with migraine

Giovanni D'Andrea · Roberto Ostuzzi · Andrea Bolner · Federica Francesconi · Francesca Musco · Florindo d'Onofrio · Davide Colavito

Abstract In order to understand the possible role of tyrosine metabolism and in particular that of elusive amines in the pathogenesis of eating disorders (ED), we measured the plasma levels of dopamine, noradrenaline, tyramine (Tyr) and octopamine (Oct) in a large group of anorexic and bulimic patients. In comparison to the control group, the levels of nordrenaline were significantly lower and those of dopamine and Tyr higher in the ED patients. The plasma levels of Oct were in the same range in both subject groups. However when comparing the bulimic *vs*. the anorexic group, the Oct levels were significantly lower in the anorexic group, whereas those of Tyr were significantly higher in the bulimic patients, suggesting that different activation in the metabolism of elusive amines may underlie the shift from the anorexic into the bulimic state. These biochemical findings raise the possibility that abnormalities of the limbic and hypothalamic circuitries play a role in the pathogenesis of ED. In addition, the very high prevalence of migraine (>75%) in our group of ED sufferers, and the biochemical profile(s) reported in migraine, which appear similar to that found in ED patients, suggest that migraine constitutes a risk factor for the occurrence of ED in young females.

Keywords Eating disorder · Migraine · Noradrenaline · Dopamine · Trace amines

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Introduction

Eating disorders (ED), such as anorexia and bulimia nervosa, constitute a severe psychiatric and somatic condition occurring mainly in the female population in younger age groups [1]. The aetiology of ED is poorly understood, although biological and psychological factors seem to play a relevant role in the physiopathology of the disorder. Among biological factors, abnormalities of serotonin (5-HT), noradrenaline (NE) and dopamine (DA) metabolism have been reported in anorexic animal models [2] and some human studies [3]. The anomalous eating behaviour, the absence of menses and the sexual appetite that characterise ED suggest that anomalies in these neurotransmitters are localised in the limbic, hypothalamic and dopaminergic circuitries [4].

Intriguingly, migraine presents the same metabolic catecholamine dysfunction as that of ED [5]. In addition, the high level of elusive amines, such as tyramine (Tyr) and octopamine (Oct), in plasma and platelets, recently found in migraine patients, suggests that anomalies of hypothalamic and limbic areas contribute to migraine physiopathology, as trace amine associated receptors (TAARs) are mainly localised in these brain areas [6]. However, whilst these findings suggest that migraine and ED may, to some degree, share similar underlying physiopathological aspects, no information is available with regard to the possible preva-

lence of migraine in ED subjects and it is unknown whether anomalies in the metabolism of trace amines play a role in the pathogenesis of ED. To ascertain this hypothesis we here evaluate plasma levels of NE, DA, Tyr and Oct in a large group of ED sufferers. We also assess the prevalence of migraine in the same patient sample.

Methods

NE, DA Tyr and Oct were measured in plasma of 125 patients affected by anorexia (n=89, 71.2%) or bulimia nervosa (n=36, 28.8%) and 27 healthy control subjects matched for age and sex with the patients. The diagnosis of each type of ED syndrome was, in accordance with the DSM-IV criteria [7], made utilising body mass index (BMI) (below 17.5 for anorexia under 17.5 for bulimia). Forty-eight patients were free from pharmacological treatment (44%); 61 (56%) patients were under antidepressant therapies (Table 1). In the subjects, peripheral venous blood (25 ml) was drawn by the same operator from the antecubital vein, following overnight fasting, at 9 a.m. in supine position and collected in fr/10 volume citric acid/citrate dextrose as anticoagulant for estimation of the biochemical markers. Platelet-poor plasma (PPP) was obtained as described elsewhere [8]. An aliquot of perchloric acid was added to PPP (total volume 4 ml) for the deproteinisation. After brief centrifugation (14000 rpm for 5 min), the supernatant was passed through an ultrafilter membrane. The levels of NE, DA, Tyr and Otc were evaluated using an HPLC coulometric method.

Statistical analysis was conducted by SPSS version 13. Sample distributions were evaluated by a Kolmogorov–Smirnov test. Groups with Gaussian distribution were compared by Welch's *t*-test, while groups displaying non-parametric distribution were compared by the Mann–Whitney test.

Results

Biochemical results

NE was detected in plasma of 103 out of 125 patients and in all controls subjects; DA in 74/107 patients and 13/26 controls; Tyr in 106/107 patients and 25/27 controls; and Oct in 62/107 patients and 19/26 controls. In comparison to the control subjects, the plasma levels of DA and Tyr were significantly higher in ED patients (p=0.05, p<0.001), whereas the plasma levels of NE were lower in the patient group (p<0.04). The levels of Oct were in the same range in both subject groups (Table 2).

Upon comparison of the NE, DA, Tyr and Oct levels of the anorexic with those of bulimic patients and of each group of those of the control subjects, we found that DA and NE plasma levels were in the same range in the two patient groups. In contrast, Tyr plasma levels were signif-

Table 1 Characteristics of the population studied

	ED n=125	AN n=89 (71.2%)	BN n=36 (28.8%)	C n=27
Gender	All females			All females
Age (years)				
Mean±SD	26.56±8.498	26.18±8.128	26.06±8.778	27.73±6.247
Range	16–58	16–58	17–56	20–53
BMI±SD	17.29±4.816	14.93±2.488	22.53±4.130	
Patient treated	61 (55.96%)	42 (54.7%)	19 (58.1%)	
Antidepressivea	54	38	16	
Antipsychoticb	16	9	7	
Benzodiazepinec	37	26	11	
Patient without pharmaceutical therapy	48 (44.04%)	34 (45.3%)	14 (41.9%)	27

ED, eating disorders patient; *AN*, anorexia nervosa; *BN*, bulimia nervosa; *C*, control subjects
[a]antidepressive (SSRI 20 mg/d, valproic acid 400–600 mg/d); [b](benzodiazepine 5–10 mg/d); [c](bromazepan 3–6 mg/d)

Table 2 Plasma levels of Tyr, Oct, noradrenalin and DA in ED patients and control subjects

	ED (n=109) Mean±SD	C (n=27) Mean/SD	*p*
Tyr	0.85±0.61	0.69±0.34	0.05**
Oct	1.18±1.74	1.29±1.35	NS*
NE	104.26±115.51	153.18±73.20	0.039**
DA	14.00±17.02	2.877±4.12	<0.001*

Values are expressed as ng/ml. *M*, mean; *SD*, standard deviation; *ED*, eating disorders patient; *C*, control subjects
*Mann–Whitney 2-tailed unpaired test; ***t*-test

icantly higher in the bulimic patient group when compared to levels found in both the anorexic and control groups (p=0.02, p=0.03 respectively). The Oct plasma levels were more elevated in the anorexic group than in the bulimic group (p=0.03) and the Oct levels of the bulimic group were significantly lower than those of the control subjects (p=0.05) (Table 3).

Prevalence of primary headaches among ED patients

One hundred and nine patients affected by either anorexia (n=76, 70%) and/or bulimia nervosa (n=33, 30%) is referred to the ED Center of Eating Disorders (Casa di Cura Villa Margherita, Arcugnano, Vicenza) were enrolled in the study. All subjects were female and their age ranged between 18 and 32 years (mean age=25). The diagnosis of migraine with and without aura or other primary headaches was made in accordance with IHS criteria [9] utilising a questionnaire that included questions about the presence of migraine in parental first-degree relatives of the patients and characteristics of the headache attacks, i.e., frequency and duration. Ninety-one ED patients complained of primary headaches (84.4%). Eighty-one ED patients satisfied IHS criteria for the diagnosis of migraine (89%), of which 16 (55%) presented migraine without aura (MwwA), 3 (2.8%) presented migraine with aura (MwA), 5 (4.6%) with probable MwwA, 8 (7.3%) with possible MwwA and 5 (4.6%) presented a chronic migraine. Six (6.6%) ED patients were affected by tension-type headache and 4 (4.4%) patients presented non-classifiable headache. Twelve ED patients did not suffer from migraine (11%) but had a first-degree relative affected by MwwA. In 62 patients (68.1%) the migraine attacks had begun prior to the onset of ED symptoms, in 15 patients (16.5%) the attacks began at the same time and in

Table 3 Plasma levels of Tyr, Oct, noradrenalin and DA in anorexic, bulimic patients and control subjects

	AN Mean±SD	BN Mean±SD	C Mean±SD	p
Tyr	0.77±0.56	1.09±0.70	0.69±0.34	AN vs. ctrl: NS** BN vs. ctrl: 0.035* AN vs. BN: 0.026*
Oct	1.34±1.90	0.71±1.02	1.29±1.35	AN vs. ctrl: NS** BN vs. ctrl: 0.05** AN vs. BN: 0.03**
Noradrenalin	105.41±122.76	101.19±95.34	153.18±73.20	AN vs. ctrl:<0.001* BN vs. ctrl: 0.028** AN vs. BN: NS*
DA	12.85±16.54	17.26±2.88	2877±4.12	AN vs. ctrl: 0.006* BN vs. ctrl: <0.001* AN vs. BN: NS*

Values are expressed as ng/ml. *M*, mean; *SD*, standard deviation; *AN*, anorexia nervosa; *BN*, bulimia nervosa; *C*, control subjects
*Mann–Whitney 2-tailed unpaired test; **t-test

Table 4 Prevalence of headache patients among ED sufferers

Total no. patients		109		
Patients with headache		91 (84.4%)		
Migraine		81 (89%)		
MwA		3 (2.8%)		
MwwA		60 (55%)		
MwwAps		8 (7.3%)		
MwwApr		5 (4.6%)		
CM		5 (4.6%)		
Tension headache		6 (6.6%)		
ETH		3 (2.8%)		
CTH		3 (2.8%)		
Other headaches		4 (4.4%)		
Onset of headache		ED	AN	BN
Before ED	62 (68.1%)	46 (73.0%)		16 (57.1%)
Corresponding to ED	15 (16.5%)	10 (15.9%)		5 (17.9%)
After ED	14 (15.4%)	7 (11.1%)		7 (25.0%)
Total patients	91	76		33

MwwAps, migraine without aura possible; *MwwApr*, migraine without aura probably; *CM*, chronic migraine; *ETH*, episodic tension headache; *CTH*, chronic tension headache

the minority (14 patients, 15%) migraine appeared after the onset of ED symptoms (Table 4). The frequency of the attacks in ED patients affected by migraine ranged between 1 and 15 attacks/month and the duration as 8–72 h or more. No statistical differences in the frequency and duration of migraine attacks were found between the anorexic and bulimic patients.

Discussion

The data presented here support the possibility that ED is characterised by an anomalous tyrosine metabolism. In comparison to control subjects, DA plasma levels are several fold higher, whereas NE, derived from its precursor DA via the activation of DA symbol
β-hydroxylase enzyme activity [10], is significantly lower in plasma of ED sufferers. The plasma levels of Tyr, a product of tyrosine decarboxylase enzyme activity, with tyrosine being the substrate [11], are significantly higher in ED *vs*. controls, whereas those of the Oct are apparently similar in both patient groups. However when these data, witch includes both the anorexic and bulimic patient groups, are disaggregated, their profiles change. The anorexic patients show Tyr and Oct plasma levels in the same range as those of controls. The only relevant data in this patient group are that the plasma levels of Oct are inversely correlated with BMI (Pearson test, $p<0.04$), suggesting that the higher levels of Oct are related with the severity of the anorexia. In contrast, in comparison to controls and anorexic subjects, Tyr is significantly higher and Oct is significantly lower in the bulimics. The interpretation of this anomaly of tyrosine levels in ED patients is uncertain; however the large accumulation in plasma of DA and the low levels of noradrenalin strongly suggest that the activity of dopamine β-hydroxylase (DBH) is reduced in both anorexic and bulimic patients. The different profiles of Tyr and Oct plasma levels may indicate that the possible shift from anorexia to a bulimic state may be related with differences in the metabolism of trace amines. It is, in fact, known that Oct regulates the body mass through glucose and lipid metabolism [12, 13]. The low levels of Oct in the bulimic group may favour glucose and lipid synthesis with an increase of body mass in these patients.

The pathophysiology of anorexia and bulimia is not completely understood, however, the obsessive control of the feeding behaviour and the change in body weight, a reduced sexual appetite and disappearance of menstrual cycle suggest that a dysfunction of the hypothalamus [14], limbic centres [15] and amygdala [16] may play an important role in the pathogenesis. BOLD NMR studies show that these CNS structures are activated in ED patients when adequately stimulated with different kinds of foods [17]. Moreover, recovery from ED symptoms seems to be accompanied by activation of the lateral and apical prefrontal cortex, part of the limbic structure [15]. The increase of DA and Tyr along with a decrease of Oct in bulimic patients support this hypothesis, as DA and elusive amine synthesis and their receptors (DA and TAARs) are localised in the limbic, amygdala and hypothalamic circuitries [18]. The activation of dopaminergic pathways, which is also reported in obsessive–compulsive syndromes, may play an important role in the fixation of the repetitive behaviour repertoires that characterise ED patients [19] and in the abnormal feeling of satiety in anorexic sufferers [2].

The biochemical results together with the prevalence of migraine among ED sufferers suggest a strong correlation between ED and migraine. First, in comparison to the general population (12.5%), the prevalence of migraine in the group of ED patients is very high (75%) and, in addition, many of the non-migraine ED sufferers have first-degree relatives affected by migraine. Second, as in ED patients, migraine patients show, in comparison to control subjects, higher DA and lower NE levels in plasma and platelets [20]. In these patients an anomalous activity of DBH has been demonstrated, along with a polymorphism in the gene that controls the function of this enzyme [21]. In addition, metabolism of elusive amines is also deranged in migraine patients [20]. All these findings suggest that migraine and ED share the same anomalies in tyrosine metabolism that may constitute, for the migraine patients, a risk factor for the occurrence of ED. In support of this hypothesis we observed, in this study, that in the majority of ED patients the migraine attacks occurred prior to or in concomitance with the onset of ED symptoms.

In conclusion, the data shown here indicate that ED is characterised by an anomalous tyrosine metabolism, with very high circulating levels of DA and Tyr and low levels of noradrenalin and Oct (the latter amine at least in the bulimic group). These findings support the hypothesis that a metabolic derangement in the limbic, amygdala and hypothalamus centres plays a role in the aetiology of ED. This biochemical profile is similar to that of migraine and prevalence of migraine is overwhelming among ED sufferers. We suggest that migraine may constitute a risk factor for the occurrence of ED.

References

1. Bravander T, Bryant-Waugh R, Herzog D et al (2007) Classification of child and adolescent eating disturbances. Workgroup for classification of Eating Disorders in Children and Adolescents (WCEDCA). Int J Eat Disord 40[Suppl]:S117–S122
2. Avraham Y, Hao S, Mendelson S, Berry EM (2001) Tyrosine improves appetite, cognition, and exercise tolerance in activity anorexia. Med Sci Sports Exerc 33:2104–2110
3. Gross HA, Raymond Lake C, Hebert MH et al (1979)

Catecholamine metabolism in primary anorexia nervosa. J Clin Endocrinol Metab 49:805–809
4. Guido K F, Bailer FU, Shannan H et al (2004) Neuroimaging studies in eating disorders. CNS Spectr 9:539–548
5. D'Andrea G, Perini F, Terrazzino S, Nordera GP (2004) Contributions of biochemistry to the pathogenesis of primary headaches. Neurol Sci 25[Suppl 3]:589–592
6. D'Andrea G, Granella F, Leone M et al (2006) Abnormal platelet trace amine profiles in migraine with and without aura. Cephalalgia 26:968–972
7. – (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th Edn, text rev. American Psychiatric Press, Washington DC
8. D'Andrea G, Terrazzino S, Fortin D et al (2003) HPLC electrochemical detection of trace amines in human plasma and platelets and expression on mRNA transcripts of trace amines receptors in circulating leukocytes. Neurosci Lett 346:89–92
9. – (2004) The International Classification of Headache Disorders, 2nd Edn. Cephalalgia 24[Suppl 1]:1–160
10. D'Andrea G, Terrazzino S, Fortin D et al (2003) Elusive amines and primary headaches: historical background and prospectives. Neurol Sci 24[Suppl]:S65–S67
11. D'Andrea G, Terrazzino S, Leon A et al (2204) Elevated levels of circulating trace amines in primary headaches. Neurology 62:1701–1705
12. Carpéné C, Galitzky J, Fontana E et al (1999) Selective activation of β_3-adrenoceptors by octopamine: comparative studies in mammalian cells. Naunyn-Schmiedeberg's Arch Pharmacol 359:310–321
13. Visintin V, Morin N, Fontana E et al (2001) Dual action of octopamine on glucose transport into adipocytes: inhibition via β_3-adrenoceptor activation and stimulation via oxidation by amine oxidases. J Pharmacol Exp Ther 299:96–104
14. Stamatakis EA, Hetherington MM (2003) Neuroimaging in eating disorders. Nutr Neurosci 6:325–334
15. Uher R, Brammer MJ, Murphy T et al (2003) Recovery and chronicity in anorexia nervosa: brain activity associated with differential outcomes. Biol Psychiatry 54:934–942
16. Seeger G, Braus DF, Ruf M et al (2002) Body image distortion reveals amygdala activation in patients with anorexia nervosa-a functional magnetic resonance imaging study. Neurosci Lett 326:25–28
17. Uher R, Murphy T, Brammer MJ et al (2004) Medial prefrontal cortex activity associated with symptoms provocation in eating disorders. Am J Psychiatry 161:1238–1246
18. Borowsky B, Adham N, Jones KA et al (2001) Trace amines: identification of a family of mammalian G protein-coupled receptors. Proc Natl Acad Sci U S A 98:933–941
19. Jordan J, Joice PR, Carter FA, Horn L et al (2008) Specific and non specific comorbidity in anorexia nervosa. Int J Eat Disord 41:47–56
20. D'Andrea G, Nordera GP, Perini F et al (2007) Biochemistry of neuromodulation in primary headaches: focus on tyrosine metabolism. Neurol Sci 28:S1–S5
21. Fernandez F, Lea RA, Colson NJ et al (2006) Association between a 19bp deletion polymorphism at the dopamine β-hydroxylase (DBH) locus and migraine with aura. J Neurol Sci 251:118–123

Neurol Sci (2008) 29:S93–S95
DOI 10.1007/s10072-008-0896-3

Human psyche and headache: tension-type headache

Paola Torelli · Giorgia Abrignani · Paola Castellini · Giorgio Lambru · Gian Camillo Manzoni

Abstract The role of psychological factors related to headache, particularly tension-type headache (TTH), has long been a focus of investigation. The subject at issue is a complex one, with some aspects that are still being debated by experts. In episodic TTH, it is possible to hypothesise that headache is not only a "primary" headache that causes gratuitous pain to sufferers. In fact, it might represent an improper mode of communicating the sufferers' intimate discomfort, caused by an inadequate relationship between their personality profiles and events in their lives. As in migraine, in TTH, too, evidence has been found of comorbidity between headache and psychiatric disorders, including depression and anxiety disorder. Such evidence will have to be confirmed by further studies on the general population. As regards behaviour and personality traits, subjects with TTH had significantly higher scores than healthy controls on measures of automatic thoughts and alexithymia, and lower scores on assertiveness. Patients with chronic TTH had higher automatic thoughts scores than patients with episodic TTH. These findings suggest that people with TTH may have difficulty in expressing their emotions. Finally, psychological factors and emotional disturbances have been indicated as risk factors for TTH. Indeed, stress and mental tension are the most common factors that cause TTH.

Keywords Tension-type headache · Psychological factors · Stress · Trigger factors · Comorbidity

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Tension-type headache (TTH) has been included in Group 2 of the International Classification of Headache Disorders (ICHD-II, 2004) [1]. Three TTH subtypes are coded at the two-digit level. Infrequent episodic TTH (coded 2.1) and frequent episodic TTH (coded 2.2) are differentiated from each other by frequency of attacks. Chronic TTH (coded 2.3) has a frequency of attacks exceeding 15 a month, the headache may be accompanied by an autonomic symptom, such as photophobia, phonophobia or mild nausea, and pain may persist for a few hours or be continuous. The role of psychological factors related to headache, particularly TTH, has long been a focus of investigation [2, 3]. The subject at issue is a complex one, with some aspects that are still being debated by experts. In summary, this report will discuss the following aspects:

a) the pathogenetic role of psychological factors in episodic TTH;
b) comorbidity between TTH, psychiatric disorders and personality traits; and
c) psychological factors as triggers of TTH.

The pathogenetic role of psychological factors in episodic TTH

Traditionally, TTH has always been considered a form of primary headache, where the pain is gratuitous, useless and purposeless. Where the argument of the supposed gratuitousness of primary headache appears especially questionable is in patients with episodic TTH. Often in these patients it may happen that a careful evaluation of their past medical histories taking into account the different characteristics of their headaches will clearly point to TTH, and that a thorough examination aimed at researching any possible pathological signs will rule out the presence of an organic basis for their disorder. Then, face-to-

face interviews with them, supplemented by the collection of data about the events that occurred to them in close temporal relation to headache onset, may reveal life situations that amply justify the appearance of the disorder.

Frequently, episodic TTH seems to spring from an inadequate relationship between sufferers' personality profiles and events in their lives. Not infrequently, there is a clear-cut cleavage between what we could define – broadly speaking – as patients' personal abilities and the requirements of their surrounding environments. Sometimes, these requirements are too much for patients to cope with or the patients are unable to confront them properly. Thus, episodic TTH may represent a clear signal that something is not right in the lives of those who suffer from it, an indication that their skills and abilities are not adequate to sustain their ways of life. In this respect, headache cannot certainly be considered as gratuitous or useless. On the contrary, it is an important symptom that both patients and their doctors should discuss together to try to understand its meaning. This is an all-important process and one that a correct therapeutic approach certainly cannot do without.

Thus, in many cases, episodic TTH eventually becomes a symptomatic headache, which is secondary not to an organic disease, but to an inappropriate lifestyle. The issue is anything but academic and calls for an adequate therapeutic attitude: a concerted effort will have to be made to try to interpret the signal that the headache is sending, because no treatment will be effective if the origin of the disorder – which is only apparently mysterious – is not revealed in the first place [3].

Comorbidity between TTH, psychiatric disorders and personality traits

Comorbidity between headache and psychiatric disorders is a broad and, in some respects, still unexplored subject. The headache subtype that has been most extensively investigated for psychiatric comorbidity is migraine [4, 5]. Unlike that between migraine psychiatric disorders, comorbidity between TTH and psychiatric disorders has been investigated only in clinical populations. Puca et al. [6] studied a sample of 217 patients with chronic (n=109) and episodic (n=108) TTH, who were followed at 10 Italian headache centres. Psychiatric comorbidity was more frequent in chronic than in episodic TTH patients and depression was the psychiatric disorder most frequently associated with the headache. Holroyd et al. [7] measured psychosocial correlates in 245 chronic TTH sufferers by employing the Primary Care Evaluation for Mental Disorders: 35% of cases were diagnosed with anxiety disorder and 29% with a mood disorder. Based on these data, it can be assumed that the frequency of psychiatric disorders in subjects with TTH is increased three- to 15-fold compared with "healthy" controls (who had fewer than 10 headache days per year). Of the three studies conducted in clinical samples, none reported any significant differences between migraine and TTH in terms of psychiatric comorbidity [8–10]. Recently [11], psychiatric comorbidity was tested in a naturalistic sample of adult patients with pure migraine without aura, and in two control groups of patients, one experiencing pure TTH and the other combined migraine and TTH. The study population included 374 patients (158, 110 and 106) from nine Italian secondary and tertiary centres. Psychiatric comorbidity was recorded through structured interviews and also screened with the Mini International Neuropsychiatry Interview (MINI). Only anxiety and depression were investigated. Psychiatric disorders were reported by 49 patients (14.6%; 10.9% of patients with migraine, 12.8% of patients with TTH and 21.4% of patients with combined migraine and TTH). The MINI interview detected a depressive episode in 59.9% of patients with migraine, 68.3% of patients with TTH and 69.6% of patients with combined migraine and TTH. Depression subtypes were significantly different across groups (p=0.03). Anxiety (mostly generalised) was reported by 18.4% of patients with migraine, 19.3% of patients with TTH and 18.4% of patients with combined migraine and TTH. The values for panic disturbance were 12.7, 5.5 and 14.2, and those for obsessive-compulsive disorders were 2.3, 1.1 and 9.4%, respectively (p=0.009). The authors conclude that psychopathology of primary headache can be a reflection of the burden of the disease rather than a hallmark of a specific headache category.

As regards behaviour and personality traits, Yücel et al. evaluated automatic thoughts, alexithymia and assertiveness in 105 patients with TTH and in 70 healthy controls. Compared with healthy controls, headache patients had significantly higher scores on measures of automatic thoughts and alexithymia, and lower scores on assertiveness. Patients with chronic TTH had higher automatic thoughts scores than those with episodic TTH. These findings suggest that subjects with TTH may have difficulty in expressing their emotions [12].

Psychological factors as triggers of TTH

Careful monitoring of the trigger factors of headache could be an important step in treatment, because their avoidance may lessen the frequency and severity of attacks. In clinical practice, subjects with TTH very frequently report nervous tension, stress, mental fatigue, and prolonged attention and concentration efforts as trigger factors for their headaches. In the medical literature as well, several authors [13, 14] have indicated stress and nervous tension as major trigger factors for TTH attacks. Indeed, these trigger factors are described as such by a proportion of subjects ranging in

the different studies from 56.0% [15] to 70.1% [16]. Zivadinov et al. [17] performed a population-based survey using a "face-to-face door-to-door" interview method in the adult population of Bakar (Croatia) to estimate the prevalence of TTH and to establish the frequency of precipitating factors in subjects with migraine and TTH. They identified 1319 patients affected by TTH and stress was a precipitating factor for TTH attacks in 651 of them (49.4% – odds ratio 1.4; 95% CI 1.17–1.69).

Clinical data and literature reviews confirm the existence of multiple relations between the human psyche and TTH. In a recent review, emotional disturbances have been indicated as risk factors for TTH and the authors conclude that stress and mental tension are the most common factors that cause TTH [18].

References

1. Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd Edition. Cephalalgia 24[Suppl 1]:1–160
2. Holroyd KA (2002) Behavioral and psychologic aspects of the pathophysiology and management of tension-type headache. Curr Pain Headache Rep 6:401–407
3. Nash JM, Thebarge RW (2006) Understanding psychological stress, its biological processes, and impact on primary headache. Headache 46:1377–1386
4. Merikangas KR, Angst J, Isler H (1990) Migraine and psychopathology. Results of the Zurich cohort study of young adults. Arch Gen Psychiatry 47:849–853
5. Breslau N, Davis GC, Andreski P (1991) Migraine, psychiatric disorders, and suicide attempts: an epidemiologic study of young adults. Psychiatry Res 37:11–23
6. Puca F, Genco S, Prudenzano MP et al (1999) Psychiatric comorbidity and psychosocial stress in patients with tension-type headache from headache centers in Italy. The Italian Collaborative Group for the Study of Psychopathological Factors in Primary Headaches. Cephalalgia 19:159–164
7. Holroyd KA, Stensland M, Lipchik GL et al (2000) Psychosocial correlates and impact of chronic tension-type headaches. Headache 40:3–16
8. Mitsikostas DD, Thomas AM (1999) Comorbidity of headache and depressive disorders. Cephalalgia 19:211–217
9. Marazziti D, Toni C, Pedri S et al (1995) Headache, panic disorder and depression: comorbidity or a spectrum? Neuropsychobiology 31:125–129
10. Guidetti V, Galli F, Fabrizi P et al (1998) Headache and psychiatric comorbidity: clinical aspects and outcome in an 8-year follow-up study. Cephalalgia 18:455–462
11. Beghi E, Allais G, Cortelli P et al (2007) Headache and anxiety-depressive disorder comorbidity: the HADAS study. Neurol Sci 28[Suppl 2]:S217–S219
12. Yücel B, Kora K, Ozyalçín S et al (2002) Depression, automatic thoughts, alexithymia, and assertiveness in patients with tension-type headache. Headache 42:194–199
13. Rasmussen BK, Jensen R, Schroll M, Olesen J (1991) Epidemiology of headache in a general population – a prevalence study. J Clin Epidemiol 44:1147–1157
14. Kaynak Key FN, Donmez S, Tuzun U (2004) Epidemiological and clinical characteristics with psychosocial aspects of tension-type headache in Turkish college students. Cephalalgia 24:669–674
15. Ho KH, Ong BK-C (2003) A community-based study of headache diagnosis and prevalence in Singapore. Cephalalgia 23:6–13
16. Wong TW, Wong KS, Yu TS, Kay R (1995) Prevalence of migraine and other headaches in Hong Kong. Neuroepidemiology 14:82–91
17. Zivadinov R, Willheim K, Sepic-Grahovac D et al (2003) Migraine and tension-type headache in Croatia: a population-based survey of precipitating factors. Cephalalgia 23:336–343
18. Fumal A, Schoenen J (2008) Tension-type headache: current research and clinical management. Lancet Neurol 7:70–83

Neurol Sci (2008) 29:S96–S98
DOI 10.1007/s10072-008-0897-2

PSYCHIATRIC STATE AND HEADACHE

Behavioural approach to the "difficult" patient

Licia Grazzi

Abstract The challenges in managing the more complicated headache patients are discussed and reviewed in this article. These patients often have chronic daily headache or high-frequency disabling headache. Some of these patients have problems adhering to treatment regimens, which may reduce treatment efficacy and sometimes lead to medication overuse. Medication overuse itself may induce a transformation of headache to daily by reducing the effectiveness of acute and preventive therapies. Biobehavioural factors are important in the assessment and treatment of headache patients. Also the biobehavioural aspects involved in headache patients will provide a model for integration of behavioural therapies into clinical practice. The purpose of this article is to highlight behavioural/psychological factors important to consider for clinicians managing this particular category of patients.

Keywords Chronic migraine · Medication overuse · Behavioural approach

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Introduction

A biobehavioural approach to headache management has emerged from psychobiological models of headache [1]. This approach is based on the concept that psychological and biological processes are interactive: behaviour, environmental influences and learning are able to modify the biology of organic functions. Psychobiological models suggest that conditions controlling chronic headache are multidimensional, involving cognitive, emotional and behavioural factors as well as neurobiological mechanisms that may change with chronicity.

As a primary headache disorder becomes more severe and chronic, complex processes involving learning and behaviour become important maintenance factors [2]. Risk factors for transformation of migraine from episodic form include obesity, high frequency of attacks, medication overuse, psychiatric comorbidity and stressful life events [3]. Patients with chronic forms are difficult to manage: the challenges include noncompliance to therapy regimens, medication overuse and psychiatric comorbidity. Also, these patients have been refractory to usually effective treatment, and require careful assessment and comprehensive treatment including both pharmacological and non-pharmacological interventions, in particular a behavioural approach [4, 5].

Assessment

Headache patients, in particular patients with a chronic form of headache, present with a history of experiences and expectations with respect to medical and other treatment. For this reason, effective treatment begins with building a therapeutic relationship with patients at the time of the initial consultation. It is important to establish

realistic expectations and the patients have to be actively involved in the management of their headache disorder.

A careful history is necessary for achieving a correct diagnosis and behavioural interviews are important for assessing symptoms. Behaviourally, data are collected with respect to how many days of the month the patient is dysfunctional. It is important to record the impact that severe headache has on the patient's ability to function. The manner in which symptoms are described may provide critical clues as to the underlying psychopathology.

Regarding chronic patients, medication history is a crucial point. It is important to assess what the patient is taking and at what point in the pain process that the patient medicates. The patients' feelings regarding the medication efficacy are important as well as the extent of pain relief.

Headache recurrence should be noted. Medication overuse issues should be evaluated, as this negatively impacts treatment [6]. With respect to past medications, dose levels need to be assessed, whether there was an adequate therapeutic trial previously and whether the medication was taken in the presence of medication overuse headache. The patients' subjective sense of what medication has been the most effective in the past may be revealing.

History of habits, diet and sleep disturbances should be evaluated. A history of psychiatric symptoms and treatment has to be noted. Previous treatment for substance abuse or psychiatric problems, or psychotherapy have to be considered.

Patients are asked how headache affects socialisation, pleasure activities and family life. In particular, absences from the work place and degree of disability should be noted.

Symptom markers begin to emerge that could reflect comorbid aspects that may require pharmacological and also behavioural treatment. Both pharmacological and non-pharmacological treatment have to be considered, as the treatment philosophy is based on the concept of the patient being an active participant in his or her treatment process [7].

Treatment plans

It has to be emphasised that non-pharmacological treatment is not anti-pharmacological. The combination of both pharmacological and non-pharmacological treatment has been shown to be superior to each individually [8] and appears to improve long-term therapeutic effectiveness [9]. Moreover, non-pharmacological treatments help to improve pharmacological therapy compliance, which is crucial with chronic migraine patients [10, 11].

From the clinical point of view, it has been determined that behavioural treatments are effective. There are more than 100 empirical studies that examined the efficacy of biobehavioural strategies for headache management. Relaxation training, thermal and EMG biofeedback, and cognitive behaviour therapy have been shown to be effective for headache and migraine treatment, and this has also been confirmed by metanalytic reviews [8].

A model of behavioural treatment included in a therapeutic strategy for chronic migraine patients has to consider some important steps. Most important is patient education; this is a relevant aspect to consider in the therapeutic programme. Education is a key component at this point regarding not only the clinical diagnosis, but also the proposed treatment options. A detailed education will be helpful for patients, including an emphasis on the complex nature of headache difficulties and explanations of the pathophysiology of headache. This information improves the patients' understanding of the rationale for pharmacological and non-pharmacological choices.

The daily card is a useful instrument to help patients to record headache frequency, intensity, possible relationship between headache attacks and life events, and, most important for chronic migraine overusers, to record the analgesic intake and to note the real efficacy of different compounds.

Education should encourage identification of life habits that can easily induce headache or migraine episodes, and consequently to modification of particular behavioural factors in an effort to decrease headache frequency and severity. Educational intervention includes teaching the correct use of abortive medications, in particular in patients with chronic forms and history of overusing medications, teaching the management of prodromal symptoms, following instructions for preventing rebound induced by overuse of medications and becoming more conscious about the use of medications.

Different clinical programmes have been designed for taking care of these problematic patients. Withdrawal, although with some controversy, is considered the first and principal step so that the migraine can return to a regular pattern and a preventive therapy can be effective; also it is necessary to educate the patients to correctly use the aborting medications, becoming more conscious of their clinical situation.

The model of in-patient withdrawal is generally more comfortable, but other kinds of treatment such as day-hospital withdrawal or, in very motivated patients, out-patient withdrawal are possible. In the latter conditions, the patients are invited to call the doctors regarding any problems or to visit the clinic for regular checks of the daily card and, once more, encouragement, education and support are critical elements in patients reaching their target [12].

The patients also benefit from learning behavioural strategies to help control their headache: improving time management, increasing aerobic exercise and increasing pleasurable activities. It is important to teach the patients coping skills designed to alleviate both the sensory and

reactive component of the pain experience. The former component involves the perception of pain and other physical symptoms, while the latter includes thoughts and feelings accompanying headache and consequently problematic behaviours, such as overuse of analgesic for aborting attacks.

In this sense cognitive-behavioural interventions help to modify the reactive component with specific skills increasing the patient's ability to cope with pain and to decrease headache-related distress [13].

Relaxation therapies and biofeedback include several techniques that aim to enable patients to develop greater body awareness, so as to achieve an overall relaxed state and confidence concerning physiological control and are helpful for patients for learning to bring biological processes normally beyond patients' awareness and control. These therapies enhance the role of thoughts, perceptions, belief systems and self-evaluation. These programmes are step-by-step approaches for teaching patients the skills over a series of sessions.

Also, the patients have to be encouraged to use audiocassettes for practising at home and to become familiar with the relaxation exercises. The patients learn to identify and modify distress-related thoughts and maladaptive styles of thinking that can contribute to headache susceptibility. Also, they can learn to develop alternative cognitive responses to the pain experiences; they try to develop management skills to reduce the anxiety that often increases the symptom itself [4]. Many of these patients with chronic forms need psychotherapeutic support for anxiety and depression, often comorbid aspects with chronic migraine.

The correct and multidisciplinary integration of different therapies such as pharmacological treatment, behavioural techniques and psychotherapeutic approaches can deliver a good outcome of therapeutic strategy, a decrease in symptoms and avoidance of relapses in medication overuse.

Conclusions

Patients with chronic migraine and medication overuse need a comprehensive headache evaluation including screening for behavioural and psychiatric issues. Effective interventions for medication overuse headache and reinforcement of coping skills are necessary to prevent relapse.

These difficult patients need to be seen frequently and for longer time periods to make sure they are getting comprehensive treatment with maximum adherence. Educating patients about headache mechanisms and treatments favours a collaborative relationship between patient and clinician. Education and support to correctly and adequately use the aborting medications is a crucial point in the treatment plan. Behavioural strategies help patients to take an active role in managing their headache disorder and in managing the therapeutic programme.

References

1. Bakal DA (1982) The pathophysiology of chronic headache. Springer, New York
2. Baskin SM, Weeks RE (2003) The biobehavioral treatment of headache. In: Moss D, McGrady A, Davies TC, Wickramasekera I (eds) Handbook of mind-body medicine for primary care. Sage Publications, London, pp 205–222
3. Bigal ME, Lipton RB (2006) Modifiable risk factors for migraine progression. Headache 46:1334–1343
4. Weeks R (2007) Integration of behavioral techniques into clinical practice. Neurol Sci 28[Suppl 2]:S84–S88
5. Baskin S (2007) Managing the "difficult" headache patient. Neurol Sci 28[Suppl 2]:S78–S83
6. Lake AE (2006) Medication overuse headache: biobehavioral issues and solutions. Headache 46[Suppl 3]:S88–S97
7. Weeks R, Weier Z (2006) Psychological assessment of the headache patient. Headache 46:110–118
8. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL (2001) Management of chronic tension-type headache with tricyclic antidepressant medication, stress-management therapy and their combination. A randomized controlled trial. JAMA 285:2208–2215
9. Grazzi L, Andrasik F, D'Amico D et al (2002) Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at three years. Headache 42:483–490
10. Rains JC, Lipchik GL, Penzien DB (2006) Behavioral facilitation of medical treatment for headache. Part I: Review of headache treatment compliance. Headache 46:1387–1394
11. Rains JC, Penzien DB, Lipchik GL (2006) Behavioral facilitation of medical treatment for headache. Part II: Theoretical models and behavioral strategies for improving adherence. Headache 46:1395–1403
12. Grazzi L, Andrasik F (2006). Medication-overuse headache: description, treatment and relapse prevention. Curr Pain Headache Rep 10:71–77
13. Lipchik GL, Smitherman TA, Penzien DB, Holroyd KA (2006) basic principles and techniques of cognitive-behavioral therapies for comorbid psychiatric symptoms among headache patients. Headache 46[Suppl 3]:S119–S132

Neurol Sci (2008) 29:S99–S102
DOI 10.1007/s10072-008-0898-1

KEY NOTE LECTURE

Towards a definition of comorbidity in the light of clinical complexity

Vincenzo Bonavita · Roberto De Simone

Abstract Clinical complexity encompasses multiple levels, including all the disorders and conditions experienced by a person along cross-sectional and longitudinal contexts, the diversity of severity levels and courses of clinical conditions, but also the plurality of values of people experiencing health problems and seeking help for them. The term *comorbidity* refers to the association of two distinct diseases in the same individual at a rate higher than expected by chance. Looking systematically to comorbidity represents the main road to approach patients' clinical complexity. Once epidemiologically established through population or community surveys, the study of the *comorbidity direction* and of the *chronological patterns* of associated clinical entities may offer relevant information from both a clinical and a scientific point of view. Comorbidity profiles of migraine and tension-type headache offer a paradigmatic example to appraise and highlight headache patient clinical complexity, allowing the conversion of diagnosis from a validated cluster of symptoms to a *person-centred clinical diagnosis.*

Keywords Comorbidity · Migraine · Tension-type headache · Person-centred diagnosis · Clinical complexity

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Introduction

A debate on comorbidity is a debate of both clinical and scientific interest. More than 40 years ago Feinstein [1], who is credited with coining the term, defined comorbidity as "any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study". It is quite obvious that the broadness of "additional clinical entities" under the Feinstein concept of comorbidity included even physiological conditions requiring clinical monitoring, such as pregnancy.

The original concept has undergone a historical evolution: comorbidity should be regarded today as a non-casual association of clinical entities [2] or of a clinical entity with a physiological condition requiring clinical monitoring.

Looking systematically to comorbidity represents the main road to converting the diagnosis of a disease into a person-centred clinical diagnosis. This way of looking at the patient underlines clinical complexity as "a pointed indicator of the conceptual and empirical richness of general medicine" and even more so of neurology and psychiatry [3].

The work group on comorbidity of the Word Health Organization has taken into account even the model concept of *hypercomorbidity*, extending comorbidity to the involvement of clinically relevant social conditions. The concept of hypercomorbidity highlights the complexity of clinical medicine, and at the same time the unicity of humanistic, sociological and clinical culture [4].

Let us, however, leave hypercomorbidity on the backstage and, as stated before, highlight comorbidity with a few examples on migraine and tension-type headache (TTH) as appraised from evidence-based data.

The choice of migraine and TTH allows us to describe comorbidity with reference to a disease (migraine) or a syndrome (tension headache).

Comorbidity: a key for approaching clinical complexity

As accepted in modern practice, the term comorbidity refers to the statistical association of two distinct diseases in the same individual at a rate higher than expected by chance [2].

Comorbidity may emerge from population- or community-based studies as well as from clinical series or case control studies. Results from the latter design surveys must be cautiously taken into account due to some methodological biases that can lead to an overestimation of the comorbidity link, such as Berkson's and selection biases.

According to Berkson [5], if an individual is affected by two different diseases at the same time then it is more probable that he will require a medical consultation. This fact impacts on both *clinical* outpatient and inpatient series and can lead to a significant comorbidity overestimation. Probably the most striking example of Berkson's bias comes from the comparison between the rates of psychiatric comorbidity shown by migraine and tension-type patients in clinical vs. population or community comorbidity studies. Epidemiological data from population-based studies demonstrate [6] that, contrary to the common perception, migraineurs have greater *neuroticism* than TTH patients. Although much more prevalent than migraine, due to the mildness of symptomatology only a minority of pure TTH patients require a medical consultation; among those seeking medical help, a severe psychiatric comorbidity is often present.

In a large clinical series, at least one psychosocial stress event or psychiatric disorder was detected in 84.8% of the patients [7]. In such cases the psychiatric comorbidity is responsible for both the emerging need for medical care and the wrong perception by the physician of a high neuroticism in TTH patients.

In association studies the *selection bias* can overestimate comorbidity of diseases presenting a symptomatologic overlap and therefore carrying a partial sharing of diagnostic criteria sets (example: migraine with aura and transient ischaemic attacks).

Once epidemiologically established through population or community studies, a closer evaluation of the comorbidity link characteristics may offer relevant information from both a clinical and a scientific point of view, thus representing indeed the main road to approach clinical complexity.

If properly assessed, a comorbidity link may indicate that a condition is causally involved with the other. The causative effect may be *direct* (atrial fibrillation? stroke) or *indirect* (migraine? medication overuse? medication overuse headache).

Alternatively, it may suggest the existence of a shared physiopathological mechanism independently promoting the development of both diseases in the same individual. The shared mechanism can be *genetically determined* (ionic channel disfunctions can lead to a brain hyperexcitability that can promote both migraine and epilepsy) or *acquired* (a head trauma can lead to both migraine and epilepsy).

The assessment of the *unidirectional* or the *bidirectional* course of the statistical association is the key to interpreting the epidemiological link of associated diseases. Comorbidity may be *unidirectional* (many coeliac individuals suffer from migraine but only a small minority of migraineurs are coeliac) [8, 9], indicating that a condition could promote the other but not vice versa, or *bidirectional*, indicating that a common pathogenetic factor is probably present.

Depending on the study design and the expected course (acute or chronic) of indexed diseases, direction of comorbidity may also be seen as the *ratio* between the probability shown by each condition to onset before the other. In the presence of a *bidirectional* link this ratio approximates unity, indicating that neither disease is involved in the aetiology of the other but that they probably share one or more pathogenetic factors and, therefore, each condition is to be considered as a risk factor for the development of the other. This, again, is the case regarding migraine and epilepsy where observations on wide community samples led to the finding of a statistically significant association in which neither condition has higher probability of onset before the other [10].

A strict chronological association between symptom presentation of conditions with a known comorbidity reduce the probability of a coincidental association and may support a causative link, as in migralepsia, where an epileptic attack occurs during or soon after a migrainous aura.

In the light of exploring clinical complexity, the awareness of the comorbidity profile of a disease can be crucial for prompt identification of the related conditions. Since epilepsy attacks dramatically overwhelm headache, migraine is frequently under-diagnosed and under-treated in epileptic patients [11]. Therapeutically, a known comorbidity may help in preventing inappropriate drug prescription. For example, arterial hypertension and allergic asthma are both considered to be linked to migraine by a comorbidity relation; although beta-blockers are of first choice to prevent migraine in hypertensive migraineurs, in those also affected by asthma they can precipitate bronchoconstriction. Moreover, negative influences of putative clinical relevance between coexistent conditions may result in poor response to treatments if the associated conditions are not diagnosed and treated, as is the case of migraine and depression [12].

Finally, studies on comorbidity are of great scientific interest as they can contribute to the definition of new pathogenetic hypotheses to be tested experimentally.

Comorbidity: lessons from migraine and tension-type headache

Migraine comorbidity has been extensively studied in the last few decades. In Table 1, a list of known migraine comorbidities supported by population and clinical series studies is presented. Based on population or community studies, migraineurs are at a greater risk of stroke, epilepsy and psychiatric disturbances. Evidence from clinical series studies identifies a number of other possible comorbid disease, ranging from arterial hypertension to Marfan syndrome; however, these findings need to be confirmed by population-based observations.

Although much more prevalent, TTH has been less studied than migraine. TTH is characterised by a less detailed clinical picture that reduces specificity of diagnostic criteria and increases the risk of overlooking an underlying disease [13]. The impact on patient's quality of life is very low in episodic forms (ETTH) but can be relevant in chronic forms (CTTH) [14]. TTH comorbidity studies are mainly focused on associated psychiatric conditions. While surveys based on clinical series confirm a high prevalence rate of affective and anxiety disturbances in TTH as well as in migraine outpatients [15], available data on a community sample confirm this finding only in migraineurs, while TTH patients do not differ from controls with respect to affective or anxiety disorder prevalence [6]. According to Berkson's bias, this probably means that a coexistent psychological or psychiatric condition increases the probability of a medical consultation request. Nevertheless, this finding also suggests that, when associated, affective or anxiety disorders and TTH mutually interact, leading to a worsening of both conditions [16]; therefore, that psychiatric comorbidity should always be diagnosed and therapeutically addressed.

Table 1 Migraine: main comorbidity areas

Community-based evidence
Psychiatric disturbances [6, 7]
Stroke [17]
Epilepsy [18]
Clinical series based evidence
Arterial hypertension [19, 20]
PFO [21]
Sydenham's chorea [22]
Tourette syndrome [23]
Essential tremor [24]
Helicobacter pylori [25]
Lupus [26]
Raynaud's phenomenon [27]
Allergy [28]
Coeliac disease [8, 9]
Obesity [29]
Vertigo [30, 31]
Transient global amnesia [32]
Marfan syndrome [33]

Conclusions

Looking at comorbidity is crucial to highlight clinical complexity since comorbidity is reported in 79% of all ill people [3].

The complexity needs to be appraised, understood and formulated to adequately inform the development of crucial clinical tools such as an effective diagnostic model. A broad model relevant to this concern is outlined under the term person-centred integrative diagnosis. Clinical complexity is indeed a protean term encompassing multiple levels and domains; it includes all the disorders and conditions experienced by a person along cross-sectional and longitudinal contexts, the diversity of severity levels and courses of clinical conditions, but also the plurality of values of people experiencing health problems and seeking help for them. No doubt that relevant social and financial-related conditions should also be considered in patient's clinical complexity appraisal [3].

References

1. Feinstein AR (1967) Clinical judgment. Williams and Wilkins, Baltimore
2. Lipton RB, Silberstein SD (1994) Why study the comorbidity of migraine? Neurology 44[10 Suppl 7]:S4–S5
3. Mezzich JE, Salloum IM (2008) Clinical complexity and person-centered integrative diagnosis. World Psychiatry 7:1–2
4. Mezzich JE (2007) Psychiatry for the person: articulating medicine's science and humanism. World Psychiatry 6:65–67
5. Berkson J (1946) Limitation of the application of fourfold table analysis to hospital data. Biometrics Bulletin 2:47–53
6. Merikangas KR, Merikangas JR, Angst J (1993) Headache syndromes and psychiatric disorders: association and familial transmission. J Psychiatr Res 27:197–210
7. Puca F, Genco S, Prudenzano MP et al (1999) Psychiatric comorbidity and psychosocial stress in patients with tension-type headache from headache centers in Italy. The Italian Collaborative Group for the Study of Psychopathological Factors in Primary Headaches. Cephalalgia 19:159–164
8. Gabrielli M, Cremonini F, Fiore G et al (2003) Association between migraine and celiac disease: results from a preliminary case-control and therapeutic study. Am J Gastroenterol 98:625–629
9. Borgna-Pignatti C, Fiumana E, Milani M et al (2004) Celiac disease in children with migraine. Pediatrics 114:1371
10. Lipton RB, Ottman R, Ehrenberg BL, Hauser WA (1994) Comorbidity of migraine: the connection between migraine and epilepsy. Neurology 44[10 Suppl 7]:S28–S32
11. Yamane LE, Montenegro MA, Guerreiro MM (2004) Comorbidity headache and epilepsy in childhood. Neuropediatrics 35:99–102
12. Tietjen GE, Brandes JL, Digre KB et al (2007) High prevalence of somatic symptoms and depression in women with disabling chronic headache. Neurology 68:134–140
13. Schankin CJ, Ferrari U, Reinisch VM et al (2007) Characteristics of brain tumour-associated headache. Cephalalgia 27:904–911
14. Bendtsen L, Jensen R (2006) Tension-type headache: the most common, but also the most neglected, headache disorder. Curr Opin Neurol 19:305–309

15. Mongini F, Rota E, Deregibus A et al (2006) Accompanying symptoms and psychiatric comorbidity in migraine and tension-type headache patients. J Psychosom Res 61:447–451
16. Janke EA, Holroyd KA, Romanek K (2004) Depression increases onset of tension type headache following laboratory stress. Pain 111:230–238
17. Bousser MG, Welch KM (2005) Relation between migraine and stroke. Lancet Neurol 4:533–542
18. De Simone R, Ranieri A, Marano E et al (2007) Migraine and epilepsy: clinical and pathophysiological relations. Neurol Sci 28[Suppl 2]:S150–S155
19. Pietrini U, De Luca M, De Santis G (2005) Hypertension in headache patients? A clinical study. Acta Neurol Scand 112:259–264
20. Prudenzano MP, Monetti C, Merico L et al (2005) The comorbidity of migraine and hypertension. A study in a tertiary care headache centre. J Headache Pain 6:220–222
21. Diener HC, Kurth T, Dodick D (2007) Patent foramen ovale, stroke, and cardiovascular disease in migraine. Curr Opin Neurol 20:310–319
22. Teixeira AL Jr, Meira FC, Maia DP et al (2005) Migraine headache in patients with Sydenham's chorea. Cephalalgia 25:542–544
23. Kwak C, Vuong KD, Jankovic J (2003) Migraine headache in patients with Tourette syndrome. Arch Neurol 60:1595–1598
24. Biary N, Koller W, Langenberg P (1990) Correlation between essential tremor and migraine headache. J Neurol Neurosurg Psychiatry 53:1060–1062
25. Tunca A, Turkay C, Tekin O et al (2004) Is Helicobacter pylori infection a risk factor for migraine? A case-control study. Acta Neurol Belg 104:161–164
26. Weder-Cisneros ND, Tellez-Zenteno JF, Cardiel MH et al (2004) Prevalence and factors associated with headache in patients with systemic lupus erythematosus. Cephalalgia 24:1031–1044
27. Hottenga JJ, Vanmolkot KR, Kors EE et al (2005) The 3p21.1-p21.3 hereditary vascular retinopathy locus increases the risk for Raynaud's phenomenon and migraine. Cephalalgia 25:1168–1172
28. Low NC, Merikangas KR (2003) The comorbidity of migraine. CNS Spectr 8:433–434, 437–444
29. Bigal ME, Lipton RB (2006) Obesity is a risk factor for transformed migraine but not chronic tension-type headache. Neurology 67:252–257
30. Versino M, Sances G, Anghileri E et al (2003) Dizziness and migraine: a causal relationship? Funct Neurol 18:97–101
31. Sen P, Georgalas C, Papesch MJ (2005) Co-morbidity of migraine and Meniere's disease-is allergy the link? Laryngol Otol 119:455–460
32. Schmidtke K, Ehmsen L (1998) Transient global amnesia and migraine A case control study. Eur Neurol 40:9–14
33. Knudsen S, Russell MB (2006) Increased risk of migraine in Marfan's syndrome? Acta Neurol Scand 114:281–286

Neurol Sci (2008) 29:S103–S106
DOI 10.1007/s10072-008-0899-0

Headache in the emergency department. How to handle the problem?

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Abstract Patients presenting to the emergency department (ED) with a chief complaint of headache are common and are frequently clinically challenging. The primary role of ED physicians is to discriminate between the most common primary benign headaches and secondary potentially life-threatening headaches. There are several tools at the physician's disposal to corroborate the diagnosis (anamnesis, examination, neuroimaging, lumbar puncture), but in the busy setting of the ED they are often inadequately used with respect to published standards and recommendations. In 2004 a multidisciplinary workgroup of the Emilia-Romagna region proposed a consensus-based diagnostic algorithm structured in four clinical scenarios aimed at reducing the variability exhibited by ED physicians in management of non-traumatic headache, improving clinical decision-making and optimising the use of limited resources.

Keywords Emergency · Headache · Diagnostic workup · Management

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Background

Headache is one of the commonest neurological symptoms and a complaint for which patients often seek emergency department (ED) care. Studies have shown that of all patients referring yearly to an ED, 0.5% [1] to 4.5% [2–4] report non-traumatic headache as a major medical problem. There is also evidence that most of these subjects will be finally diagnosed with a benign primary headache, while a lower but noteworthy percentage (up to 19%) [1] are diagnosed with a secondary headache, including life-threatening conditions such as subarachnoid haemorrhage (SAH), central nervous system infections and tumours. The primary objective of the ED physician is to determine whether a patient has a secondary headache attributed to an urgent medical condition in order to promptly start the right treatment. However, in the atypical setting of the ED, where time is limited and emergencies are unpredictable and drive the complex organisation of the staff, the management of non-traumatic headache is often challenging. Furthermore, headache clinical presentation may vary from easily recognisable conditions to others that are vague and misleading, making the diagnosis of malignant headache even more difficult.

In particular, when considering a diagnosis of SAH in the ED, which represents a cause of ongoing concern among emergency physicians because of the high risk of related mortality, recent data confirmed it is still significantly missed in about 5% of patients [5].

The need for feasible evidence-based clinical guidelines to improve headache management in the ED has often been emphasised, but these guidelines are still lacking.

Diagnostic tools available in the emergency department

Several tools are at the ED physician's disposal to corroborate the headache diagnosis:

History. A careful anamnesis is essential to make an inventory of salient features of the headache presentation and determine whether there are worrisome features that might point toward a diagnosis of malignant headache [6].

Examination. All patients presenting with headache should have a physical examination including assessment for neck stiffness, rash, a full neurological and ETN examination, and blood pressure measurement. Examination also includes funduscopy, which should be performed when increased intracranial pressure is suspected [6].

Blood chemistry. Raised inflammatory indexes (ESR, C-reactive protein) can strengthen the clinical suspicion of temporal arteritis.

Computed tomography. To determine whether imaging is indicated, the physician should classify the headache presentation to derive a pretest probability of serious intracranial pathology; patients presenting with thunderclap headache are at sufficient risk of SAH and therefore should undergo investigations irrespective of associated clinical features. Patients with migraine with or without typical aura do not usually require neuroimaging [7].

Lumbar puncture. This is used to confirm the suspicion of central nervous system infections and should be mandatory for patients with clinical suspicion of SAH and a negative head CT scan.

Despite these concrete possibilities, previous findings [1] have shown that in the ED setting history and examination were inadequate when compared with published standards, and CT scan and lumbar puncture were underused with respect to published recommendations.

Causes of non-traumatic headache in the emergency department

The clinical heterogeneity of patients attending the ED for headache as the chief complaint is wide, varying from common primary benign headaches (mainly migraine, tension-type headache, cluster headache) to less frequent secondary headaches. Moreover, secondary headaches can be the predominant or the accompanying symptom either of benign medical pathologies (e.g., drug side effects, systemic illness, dental/ENT pathologies) or of serious life-threatening conditions (e.g., SAH, meningitis, tumours, cerebral infarcts).

An exemplification of the "headache spectrum" seen in the ED as it results from a prospective study conducted over a 14-month period by Locker and colleagues [8] is shown in Table 1.

Table 1 Headache diagnosis of patients attending the ED

Diagnosis	%
Primary headaches	54.1
Cluster headache	2.7
Migraine	22
Unspecified primary headache	17.6
Tension-type headache	11.1
Trigeminal neuralgia	0.7
Secondary headaches	42.1
Benign pathologies	28.8
Systemic illness	15.8
Dental/ENT cause	6.3
Cervicogenic headache	3.8
Drug side effect	1.2
Serious pathologies	13.3
Subarachnoid haemorrhage	3.4
Cerebral infarct	2.9
Transient ischaemic attack	2
Meningitis (bacterial and viral)	1.3
Intracerebral haemorrhage	1.3
Neoplasia (primary and secondary)	0.8
Carbon monoxide poisoning	0.4
Temporal arteritis	0.2

Adapted from Locker et al. [8]

The utility of clinical features in patients presenting to the emergency department with non-traumatic headache

According to Edmeads [9], there are three main reasons for patients with headache to attend the ED: (1) they may have experienced a severe headache, unlike any previous one, (2) they may have associated features that are worrisome (altered mental status, fever, focal neurology) or (3) they are experiencing "last straw syndrome", in a history of recurrent headaches that are unresponsive to treatment.

When evaluating patients with headache the anamnesis should be directed at disclosing some crucial information: premonitory symptoms, the onset, character, location and severity of the pain, precipitating factors, associated symptoms and past medical history [10]. This information, together with an appropriate general and neurological examination, can be used to guide the physician in the diagnostic and management processing of headache.

Several authors tried to assess the utility of some clinical features associated to headache as independent factors predictive of malignancy, but with inconclusive results. The prospective observational study conducted by Locker et al. [8] identified 3 features as independent predictors of serious pathology which, in combination, can rule out the presence of such pathology in adults presenting to the ED with non-traumatic headache: age greater than 50, sudden onset and an abnormal neurological examination.

The importance of identifying patients with benign headache who can be easily dismissed from the ED and

managed appropriately in an outpatient setting means avoiding inappropriate admission and focusing on patients suspected of being at risk of serious medical conditions.

The proposal of the multidisciplinary group of Emilia-Romagna

In 2004 a multidisciplinary work-group of the Emilia-Romagna region including neurologists, ED physicians, neurosurgeons, neuroradiologists, infectivologists and epidemiologists proposed a consensus-based diagnostic algorithm structured in four clinical scenarios in which a patient presenting to ED for non-traumatic headache may be included according to history and clinical features [11]. The four scenarios correspond to common situations encountered in clinical practice and each one guides the physician towards the most appropriate diagnostic procedures to be performed in that situation with respect to what is actually recommended in the literature on that topic (Table 2).

In brief, scenario 1 aimed to include sudden stabbing headache attacks associated to SAH or other causes of "thunderclap headache"; scenario 2 aimed to include headaches that may be the expression of central nervous system or systemic infections; scenario 3 aimed to include long-lasting and/or worsening headache possibly associated to brain tumours or temporal arteritis; scenario 4 aimed to include benign headaches that are referred to the ED because attacks fail to respond to usual therapy.

It is important to remember the existence of some malignant causes of headache such as the cerebral venous sinus thrombosis, which can present with a thunderclap headache but which may not be identified by head CT scan or cerebrospinal fluid analysis. In these cases very often only the clinical experience of the physician may suggest other diagnostic investigations like brain MRI [12].

In 2005, the tool was applied for a 30-day period to adult patients referring consecutively to eight EDs of the Emilia Romagna region for non-traumatic headache as major complaint. The distribution of patients recruited in the study (256 over a total of 302 eligible patients; mean prevalence rate: 0.7%) through the four scenarios, plus an undetermined scenario that was chosen when none of the four applied, is illustrated in Fig. 1. The data confirm the majority of patients accessing the ED have potential benign headaches (scenario 4).

Conclusions

An algorithm structured in clinical scenarios could represent a useful tool for improving the physician initial evaluation and management of patients with non-traumatic headache in the busy setting of the ED. The instrument

Table 2 The four clinical scenarios proposed by the Italian multidisciplinary work-group for the management of non-traumatic headache in the ED [11]

Scenario	Clinical features	Recommended diagnostic procedures
1	Adult patients admitted to ED for severe headache ("worst headache") * with acute onset (thunderclap headache), or * with neurological signs (or non-focal as decreased level of consciousness), or * with vomiting or syncope at the onset of headache.	* Head CT must be performed * If the result of TC scan is negative or uncertain or of poor quality, lumbar puncture is indicated. * If lumbar puncture shows no abnormality, the patient should be evaluated by a neurologist within 24 h.
2	Adult patients admitted to ED for severe headache * with fever and/or neck stiffness.	* Head CT and lumbar puncture must be performed
3	Adult patients admitted to ED for * headache of recent onset (days or weeks), or * progressively worsening headache, or persistent headache.	* Head CT and * Routine blood tests, including flogosis indexes (ESR and C-reactive protein) must be performed * Neurological evaluation should be performed within 7 days if tests are negative
4	Adult patients with a previous history of headache * complaining of a headache very similar to previous attacks in term of intensity, duration and associated symptoms.	* Evaluation of vital parameters, neurological examination and routine blood tests are indicated * If tests are negative the patient may be discharged from ED with indication to her/his general practitioner about the management of primary headaches and a prescription for a symptomatic headache treatment * Referring the patient to a neurological service or to a headache centre for long-term follow-up is recommended

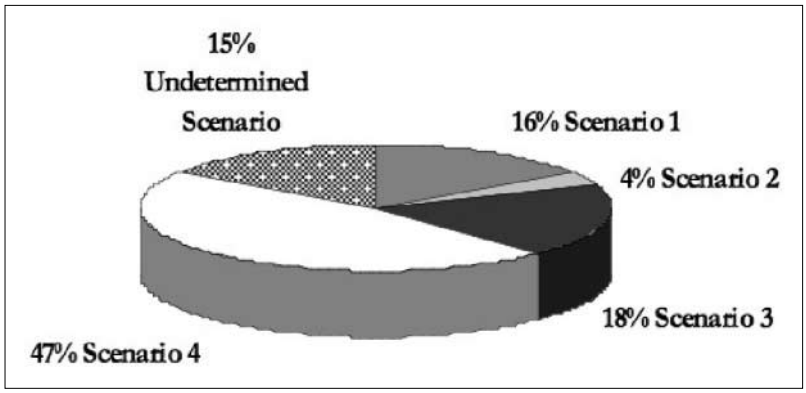

Fig. 1 Patient stratification (n=256) in the different clinical scenarios after the diagnostic algorithm application in eight EDs of Emilia Romagna

could reduce the variability exhibited by physicians in headache management, improve clinical decision-making and optimise the use of limited resources (e.g., head CT scan). The importance of recognising not only malignant headaches that need prompt management but also benign headaches that can be safely dismissed and managed appropriately in an outpatient setting means avoiding inappropriate admission and reducing the number of repeat visits to the ED for headache. Further studies of validation are needed to assess the instrument's utility in practice.

References

1. Locker T, Mason S, Rigby A (2004) Headache management – Are we doing enough? An observational study of patients presenting with headache to the emergency department. Emerg Med J 21:327–332
2. Morgenstern LB, Huber JC, Luna-Gonzales H et al (2001) Headache in the Emergency Department. Headache 41:537–541
3. Stevenson RJ, Dutta D, MacWalter RS (1998) The management of acute headache in adults in an acute admissions unit. Scott Med J 43:173–176
4. Ramirez-Lassepas M, Espinosa CE, Cicero JJ et al (1997) Predictors of intracranial pathologic findings in patients who seek emergency care because of headache. Arch Neurol 54:1506–1509
5. Vermeulen MJ, Schull MJ (2007) Missed diagnosis of subarachnoid haemorrhage in the Emergency Department. Stroke 38:1216–1221
6. Newman LC, Lipton RB (1998) Emergency department evaluation of headache. Neurol Clin 16:285–303
7. Detsky ME, McDonald DR, Baerlocher MD et al (2006) Does this patient with headache have migraine or need neuroimaging? JAMA 296:1274–1283
8. Locker TE, Thompson C, Rylance J, Mason SM (2006) The utility of clinical features in patients presenting with non-traumatic headache: an investigation of adult patients attending an emergency department. Headache 46:954–961
9. Edmeads J (1990) Challenges in the diagnosis of acute headache. Headache 30:537–540
10. Freitag FG, Diamond M (1991) Emergency treatment of headache. Med Clin North Am 75:749–761
11. Cortelli P, Cevoli S, Nonino F et al (2004) Evidence-based diagnosis of nontraumatic headache in the emergency department: a consensus statement on four clinical scenarios. Headache 44:587–595
12. de Bruijn SF, Stam J, Kappelle LJ (1996) Thunderclap headache as first symptom of cerebral venous sinus thrombosis. CVST Study Group. Lancet 348:1623–1625

Neurol Sci (2008) 29:S107–S109
DOI 10.1007/s10072-008-0900-y

EMERGENCY HEADACHES

Dangerous headaches

Elio Agostoni · Andrea Rigamonti

Abstract Headache is a critical problem in the emergency department (ED). The main aim for the ED doctor is to distinguish primary forms of headache from secondary forms. In this paper we will briefly review epidemiological data regarding headache in ED, consider the role of diagnostic alarms and "warning symptoms" in differential diagnosis and describe some "dangerous headaches".

Keywords Headache · Emergency department · Diagnostic alarms · Guidelines and recommendations

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Introduction

In an ED setting it is important to distinguish the primary forms of headache from the secondary forms, which can conceal life-threatening conditions (e.g., tumours, bleeding, CNS infection).

Epidemiology

Headache accounts for 1%–3% of total admissions to the ED [1, 2]. The proportion of primary and secondary headaches differs in various studies. In an ED in Turin, Luda [3] categorised 56% of all headaches as primary. Bigal reported that 77% of ED headache patients in Brazil had a primary headache [4]. Friedman reported 64% primary and 25% secondary headaches in a group of 408 patients attending the ED [5]. In these studies the prevalence for migraine varies from 15% to over 30%. A lot of patients, however, were discharged with a diagnosis of headache "not otherwise specified". An Italian study investigated the agreement between ED doctors and neurologists in evaluating a series of headache patients [6]. Agreement was fair between the ED physician and the headache expert, however lower agreement was found for cases presenting with a first attack.

Critical issues in headache evaluation

Anamnestic data and clinical examination are fundamental for a differential diagnosis between primary and secondary headaches. A list of signs and symptoms requiring prompt referral to the neurologist was originally provided by the NMCA [7]. Some of these items were then grouped under the heading of "headache diagnostic

alarms" and include: (1) age at onset after 50 years, (2) sudden onset, (3) accelerating patterns, (4) new onset in a patient with cancer or HIV, (5) headache with systemic illness, (6) focal neurological signs or symptoms other than typical aura and (7) papilloedema [8]. A further contribution was released by the ACEP in 2002 [9]. This guideline is defined according to the strength of evidence (Class I–III) and classified by level of recommendation (Level A–C). In particular it is recommended that patients with headache and abnormal findings on neurological examination should undergo emergent non-contrast CT scan, the same procedure being recommended for acute sudden-onset headache (Level B). HIV-positive patients with a new type of headache should be considered for an urgent neuroimaging study (Level B). Cases with a thunderclap headache who have negative findings in both CT scan and lumbar puncture (LP) do not need emergent angiography (Level C).

Cortelli identified 4 clinical scenarios of headache patients presenting at the ED [10]. The first scenario includes sudden stabbing headache attacks that could be linked to focal neurological symptoms and to vomiting or syncope at onset. An urgent CT brain scan followed by LP if the CT is negative is indicated in this case. The second scenario includes headache with fever and/or possible signs of meningitis. In this case CT brain and LP are required. The third scenario identifies patients with a long-standing headache lasting weeks or months, which has gradually worsened. These patients should have a CT brain, measurement of inflammatory indices (ESR, C-reactive protein) and a neurological assessment. In the last scenario, patients with a history of headache present at the ED complaining of headache with the usual characteristics, which has failed to respond to therapy. In addition to neurological examination, on discharge these patients are referred to a headache clinic for follow-up.

Dangerous headache

Subarachnoid haemorrhage (SAH)

Bleeding of a cerebral aneurysm is the cause of spontaneous SAH in about 2/3 of cases. Headache is present in about 97% of cases and is usually of sudden onset, excruciating, diffuse and described by patients as "the worst headache of my life" (thunderclap headache) [11]. It may arise during daily rest or in relation to a physical strain. Increased intracranial pressure is the cause of many associated symptoms like photophobia, nausea, vomiting and loss of consciousness. Meningismus and focal neurological signs may be present. Focal neurological deficits occur when an aneurysm compresses a cranial nerve or bleeds into the brain parenchyma, or from focal ischaemia due to acute vasoconstriction after aneurysmal rupture. Neck stiffness is important but not essential for the diagnosis of SAH and appears 24–48 h after the haemorrhagic event. Ocular haemorrhage may be found in 20%–40% of cases, usually in association with aneurysms of the anterior circulation. A CT scan performed within 48 h allows visualisation of recent blood in more than 95% of cases. When SAH is strongly suspected on clinical ground but CT is negative, LP is indicated.

Headache associated with infection

Inflammation of any pain-sensitive structures in the cranial cavity can produce headache. Meningitis and meningoencephalitis both have headache as a major symptom. The characteristic of head pain depends on whether the infection is acute or chronic. Acute meningitis produces a severe headache with neck stiffness, photophobia and irritability. Pain is often retro-orbital and worsened by eye movement. Chronic meningitis can also lead to headache that may be severe and unrelenting.

Intracranial hypertension

An intracranial mass lesion (tumoral, vascular, inflammatory) can cause intracranial hypertension. Headache is a cardinal symptom of this condition and is usually gravative, worse on awakening, aggravated by coughing and straining, and associated with nausea and vomiting. Supratentorial masses generally produce frontal or temporal head pain because of the trigeminal nerve supply to the anterior and middle cranial fossae. Mass lesions of the posterior fossa generally cause occipito-nuchal pain because the meningeal nerve supply is largely through the upper cervical nerves.

Cerebral vein thrombosis (CVT)

Headache is the most frequent (80%–90%) and often the presenting symptom of CVT. Early diagnosis of CVT is essential because the potential for recovery is high if anticoagulant therapy is started early in the course of disease. Headache associated with CVT has no specific features: it can be of any grade of severity and more frequently diffuse (58%) [12]. Its onset is usually subacute over a few days, but it can also be acute or chronic. Pain is mostly persistent, worse on recumbency and is aggravated by a short-term rise in venous pressure as in stooping or coughing [12]. According to IHS classification, headache attributed to CVT is most often diffuse, progressive, severe and associated with other signs of intracranial hypertension [13].

Temporal arteritis

This condition typically affects elderly patients (>50 years), with a prevalence of 133 per 100,000 [14]. Headache is dull, gravative, progressive and located in the temporal region. Skin surrounding the temporal artery is flushed and swollen, pain can be stressed by palpation of the artery and jaw claudication is frequently present. A prompt diagnosis and cortisone treatment are mandatory to avoid the ischaemic degeneration of tissues involved in the arteritic process, especially the retina. Blindness occurs in 50% of untreated cases. An increase of inflammatory indices (ESR, reactive C protein) can be useful in diagnosis but the most important diagnostic procedure is biopsy of an involved artery. Temporal arteritis must always be suspected when a persistent headache occurs in an otherwise asymptomatic adult patient.

Artery dissection

The commonest clinical syndromes associated with carotid dissection include: (1) hemicranial pain plus ipsilateral oculosympathetic palsy, (2) hemicranial pain and delayed focal cerebral ischaemic symptoms, (3) lower cranial nerve palsies, usually with ipsilateral headache or facial pain.

The most common symptom of vertebral dissection is headache and neck pain, followed after a delay by focal CNS ischaemic symptoms.

Pituitary apoplexy

Pituitary apoplexy is due to necrosis and haemorrhage of a pituitary adenoma. Haemorrhage and necrosis of the adenoma induces: (1) a sudden increase of volume inside the sellar region with a consequent straining of walls of cavernous sinuses and of the cranial nerves within it, (2) straining and raising of diaphragma sellae, (3) discharge of necrotic tissue and blood from the sellar region to the subarachnoid space and (4) an acute pituitary insufficiency. Clinically the patient has: (1) deep headache with acute onset, localised to the frontal region or to one or both eyes, (2) sudden appearance of ophthalmoplegia, (3) meningismus, hyperthermia and haematic cerebrospinal fluid, due to effusion of blood into the subarachnoid cisterns, (4) sudden worsening of sight because of acute compression of the optic nerve and (5) severe hypotension and alterations of the level of consciousness, due to pituitary apoplexy and consequent acute hypocorticosurrenalism. The diagnosis is relatively easy when a pituitary adenoma has already been diagnosed; CT scan clearly shows the presence of a mass located in the sellar region.

Conclusions

Management of headache in the ED is an important problem and requires a careful assessment and a well oriented diagnostic algorithm. Current guidelines and recommendations may help in selecting the appropriate series of diagnostic procedures and their timing.

References

1. Barton CV (1994) Evaluation and treatment of headache patients in the emergency department: a survey. Headache 34:91–94
2. Dhopesh V, Anwar R, Herring C (1979) A retrospective assessment of emergency department patients with complaint of headache. Headache 19:37–42
3. Luda E (1995) The symptom of headache in emergency departments: the experience of a neurology emergency department. Ital J Neurol Sci 16:295–301
4. Bigal M (2000) Headache in an emergency room in Brazil. Sao Paulo Med J 118:58–62
5. Friedman B (2007) Applying the international classification of headache disorders to the emergency department: an assessment of reproducibility and the frequency with which a unique diagnosis can be assigned to every acute headache presentation. Ann Emerg Med 49:409–419
6. Agostoni E (2004) Management headache in emergency room. Neurol Sci 25:S187–189
7. NMCA-MPA Workshop "Treatment of Headache Recommendations" (1994–3) The Norvegian Medicines Central Authority, Oslo (ISSN 1101-8127), pp 9–26
8. Silberstein SD (1998) Headache in clinical practice. ISIS Medical Media Ltd, Oxford, pp 11–18
9. American College of Emergency Physician (ACEP) (2002) Clinical policy: critical issues in the evaluation and management of patients presenting to the emergency department with acute headache. Ann Emerg Med 39:108–122
10. Cortelli P on behalf of the Mutidisciplinary Group for Nontraumatic Headache in the Emergency Department (2004) Evidence based diagnosis of non traumatic headache in the emergency department: a consensus statement on four clinical scenarios. Headache 44:587–595
11. Edlow JA, Caplan LR (2000) Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. N Engl J Med 342:29–36
12. Agostoni E (2004) Headache in cerebral venous thrombosis. Neurol Sci 25:S206–S210
13. IHS (2004) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain of the Headache Classification Committee of the IHS. Cephalalgia 24[Suppl 1]
14. Huston KA (1978) Temporal arteritis: a 25-year epidemiologic, clinical and pathologic study. Ann Intern Med 88:162–167

Neurol Sci (2008) 29:S110–S122
DOI 10.1007/s10072-008-0901-x

KEY NOTE LECTURE

Acute and prophylactic treatments for migraine: present and future

Alan M. Rapoport

Abstract Herein I will present general principles of acute-care and preventive therapy of migraine, both in the present and the future. Details of currently used migraine acute-care therapies with their contraindications, drug–drug interactions and adverse events will be presented. Details of migraine preventive therapies with their adverse events and drug–drug interactions will be discussed. Some over-the-counter vitamins, minerals and herbs, used as preventive therapy in migraine, will be discussed. Future treatments in the pipeline will be briefly detailed.

Keywords Migraine · Migraine acute therapy · Migraine preventive therapy · Headache treatment

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Introduction

This paper will address the pharmacological therapy of migraine, both acute care and prevention. Prior to prescribing medication, it is critical for the physician to make an accurate set of diagnoses, to establish a good doctor/patient relationship, review the details of previous treatment regimens, go over the various therapeutic options with the patient (including the nonpharmacologic ones), and reassure the patient that on the basis of the history, examination and appropriate testing, no other significant neurological problems exist. Helping to educate patients as to how to identify and avoid headache triggers and to understand how medications work (including avoidance of adverse reactions and drug–drug interactions) are also essential parts of successful management.

Pharmacotherapy for primary headache disorders is traditionally divided into acute and preventive therapies. Acute treatment (also called abortive treatment) is intended to reverse attacks once they begin, limit disability and to reduce and hopefully stop the pain and associated symptoms, such as nausea, vomiting, photophobia, phonophobia and increased pain with movement. Some patients use only occasional acute treatments and obtain fairly rapid and complete relief when needed. For example, evidence exists that when a migraine attack is treated shortly after the pain has begun and is still of mild intensity, the medication is more effective, often leading to a pain-free state [1]. This treatment approach is also more likely to cause fewer adverse reactions and reduce the chance of a recurrent headache developing within the next 24 h.

Preventive treatment (also called prophylactic treatment) is used in patients with migraine or other headaches who have more than 4–8 significant headaches per month or two or more days of headache-related disability per month; it is also used in those patients who are not rapid-

ly responsive to or cannot take acute-care treatment. Today it may not even be necessary to use preventive medication for patients who have up to 4–8 migraine attacks per month, providing their treatment with acute-care medications (i.e., triptans) is rapidly and completely effective without significant adverse events or recurrence. Prevention is also appropriate for patients who have very frequent headache of any intensity or to treat or avoid medication overuse with resultant rebound headache (now termed medication overuse headache). Patients who have two or more severe migraine attacks per month and a poor response or contraindications to acute treatment, or much disability with their attacks, may also benefit from preventive medication. Even when patients are treated with effective preventive medications, most require acute-care medications for breakthrough headaches. Preventive treatment is commonly used in frequent tension-type headaches, and is almost obligatory when treating both episodic and chronic cluster headache.

Principles of pharmacologic treatment

Once a clinical diagnosis of headache is made, the next task is to develop a successful treatment plan. The goals of such a treatment plan are to:

- reduce headache attack frequency, severity, and duration;
- avoid headache escalation;
- prevent headaches completely, if possible;
- reduce disability;
- rapidly return the patient to normal functioning;
- improve the patient's quality of life;
- avoid medication overuse;
- educate the patient about managing their illness (e.g., trigger avoidance, careful use of acute-care medication to prevent trips to the emergency department and lifestyle changes such as sleeping and eating on time and exercising regularly) [2].

Choosing from the myriad of pharmacotherapies currently available for headache treatment can be difficult. Selecting a first-line treatment is dependent upon a comprehensive evaluation of several clinical factors including: assessment of the severity of illness (e.g., measuring disability or impact of illness), frequency and intensity of attacks and time to peak intensity, pattern of associated features (nausea, vomiting, photophobia, phonophobia, osmophobia and worsening of pain with movement), presence of coexisting conditions (e.g., asthma, allergy, hypertension, depression, anxiety, sleep disorders, pregnancy, etc.) and knowing the efficacy, side-effect profile, drug–drug interactions and contraindications of the medications being considered. Designing the treatment goals with patient input will help to ensure a plan that the patient is willing to follow. Managing patient expectations will help reduce patient frustration early in the course of treatment. To achieve this, it is especially important to understand which features of the attack are most disturbing to the patient (e.g., pain, disability or certain associated symptoms).

In designing the most appropriate treatment plan for each patient, discussion regarding potential adverse events, frequency and timing of dosing as well as patient preference and lifestyle considerations (e.g., alcohol consumption, sleeping and eating patterns, use of OTC products, use of herbal or vitamin supplements, among others) will help ensure the patient receives treatment modalities and medications he or she will take as prescribed. Women of childbearing age should be asked if there is any chance they are pregnant, or if they are planning to become pregnant in the near future, as this will significantly impact treatment choices.

Migraine treatment

Acute-care migraine therapy

Management of patients with migraine requires individualised acute-care therapies that follow several basic principles [2, 3]:

1. Engage the patient in their treatment plan and management of their own illness so there will be a true patient–physician partnership.
2. Tailor treatment to meet individual headache needs based on severity of illness (disability), prior response to specific medications (including efficacy and presence of adverse events) and presence of coexisting medical conditions.
3. Educate headache sufferers about their specific condition and current theories of pathophysiology.
4. Use migraine-specific agents (not analgesics) as first-line treatment when possible.
5. Select a route of administration appropriate for the attack characteristics and patient preferences. Be aware that injections and nasal sprays, by bypassing the gastrointestinal (GI) tract, usually work faster than tablets and are optimal for nauseated and vomiting patients and those whose poorly functioning GI tracts preclude rapid absorption of oral medication.
6. Follow the patient closely and frequently to help improve efficacy and give useful tips about taking medication early and repeating it when needed, manage medication side effects and avoid overuse syndromes.
7. Give the patient a headache calendar (diary) and ask them to fill it in daily and bring it to each office visit for review.

There are over 40 different medications currently prescribed for acute treatment of migraine (of which only

25% have approved indications by regulatory authorities). Some are scientifically proven to be clinically useful in migraine, and others are known to be empirically useful but either lack evidence-based, published supporting data or have it but no indication approved by the FDA or other regulatory authorities. Consequently, choosing a medication for acute therapy is a complex, multi-step process that requires a good understanding of the patient's overall health, the range of appropriate treatment options, patient-specific migraine characteristics and patient preferences.

Simple analgesics

Some patients can successfully treat a migraine attack by taking simple analgesics, especially if treatment is taken early in the course of the attack when the pain is of mild intensity and not associated with severe nausea [1]. Studies suggest that aspirin monotherapy in selected patients, at a dose of 650 mg, may be helpful in alleviating headache. Conflicting evidence in the literature suggests acetaminophen as monotherapy may not be an ideal first-line treatment choice; however, for selected patients with contraindications to other therapies (e.g., pregnancy, easy bruisability or aspirin hypersensitivity), a trial of acetaminophen 1000 mg with a repeat in 2 h may be justified. Sometimes the efficacy of simple analgesics has been supplemented by the co-administration of metoclopramide (5 mg or 10 mg orally, given prior to or concomitantly with oral analgesics); this addition may improve absorption of the aspirin, decrease nausea and improve the therapeutic response. Aspirin can cause GI problems and bleeding, acetaminophen can cause liver toxicity and metoclopramide can cause anxiety and dyskinesia.

Combination analgesics

Caffeine acts as an analgesic adjuvant and vasoconstrictor in the treatment of headache and other pain disorders. Off-the-shelf combination medications that contain caffeine (e.g., 250 mg aspirin, 250 mg acetaminophen and 65 mg caffeine in one preparation, or 325 mg aspirin and 32 mg caffeine in another) are sometimes helpful, but there is an increased risk of overuse in patients who have frequent headaches. At doses of 300–500 mg/day (the equivalent of drinking 3–5 small cups of coffee), several days per week, caffeine can exacerbate the headache syndrome causing caffeine rebound and withdrawal headaches. I usually take my patients off all caffeine gradually at the start of their treatment. Too much caffeine also causes insomnia, tachycardia and jitteriness. Other combination medications contain opiates such as codeine or stronger substances. Often these combinations are tried if migraine-specific medications are ineffective or contraindicated. Care must be taken to avoid overuse with resultant dependency and increase in headache (rebound). I rarely prescribe opiates for migraine, but would limit their use to 2–4 times per month if they were necessary. The main side effects are dependency and sleepiness with decreased ability to function.

Another analgesic, tramadol, is found as a combination of this centrally acting analgesic and acetaminophen (Ultracet), which may help when used sparingly. It should not be used on a regular basis, as it can cause rebound.

Nonsteroidal anti-inflammatory agents

Nonsteroidal anti-inflammatory agents (NSAIDs) have been proven to be clinically effective for acute treatment of migraine [2, 3]. Lack of response to one agent does not preclude response to another. Clinical evidence has shown that diclofenac-K (50–100 mg), flurbiprofen (100–300 mg), ibuprofen (200–800 mg), naproxen sodium (550–1100 mg), piroxicam SL (40 mg) and tolfenamic acid (200–400 mg) are effective in migraine treatment [2]. Ketorolac 15 mg IV or 30 mg IM can be very effective in an office or ER situation. Diclofenac sodium IM also was reported to be clinically useful in migraine [2]. Most of the other NSAIDs have been shown empirically to work on certain patients with migraine.

Indomethacin, which works especially well in several specific headache syndromes (e.g., chronic paroxysmal hemicrania (CPH), episodic paroxysmal hemicrania, exertional headache and hemicrania continua (HC)), can be given by mouth or compounded by a pharmacy into a 50-mg rectal suppository, which can also be very helpful in acute care of migraine.

Rofecoxib, celecoxib and valdecoxib, the COX II inhibiting (COX-1-sparing) NSAIDs, are also options [4]. Despite studies showing that rofecoxib 25 mg is less effective than a triptan, other studies show that a combination of both can be used to reduce recurrence and enhance effectiveness, achieving a better-sustained response [5, 6]. Rofecoxib and valdecoxib have been removed from the market, leaving only celecoxib.

Opiate analgesics

Opiate analgesics have been used for centuries to control pain. Efficacy studies in migraine are limited, but do support a therapeutic role.

Codeine-containing medications and all other opioids and opiates may be used to reduce the pain of migraine. They are not usually as effective at getting rid of headache as triptans. They do not usually reduce the disability from migraine as well as triptans do, and they often cause

drowsiness and decreased cognitive sharpness. However, opiates may be useful as rescue medications when used on an occasional basis, especially when other medications have failed.

Other opiate medications used mostly for rescue and in emergency room settings include: fentanyl by injection, dermal patch or transmucosal "lollypop", hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, pentazocine and propoxyphene. If a patient comes to an emergent care setting and a vasoactive medication has either failed or is contraindicated, then an opiate may be used either alone or in combination with promethazine or another antiemetic. Although meperidine is commonly used, it should be avoided as it may cause a paradoxical reaction and beneficial effect is often inadequate and short in duration. Opiates should not be given to patients who must drive home. Patients should also be advised of the risk of sedation associated with opiate analgesics when working or operating heavy equipment.

A far better choice in an emergent setting is an IV treatment as described below, rather than an opiate. An oral or parenteral steroid would also eventuate in quicker and more complete improvement.

Ergot alkaloids

Ergotamine tartrate

Ergotamine tartrate is recognised as a migraine-specific medication as it has pharmacological actions at the serotonergic receptor, which is involved in the pathophysiology of migraine. Ergotamine was originally discovered and used over 50 years ago, and has been available in oral, sublingual, injectable, inhaled, nasal and rectal preparations. Prior to the availability of the triptans in the early 1990s, it was the only vasoactive medication in widespread use for migraine and cluster headache. Oral ergotamine tartrate is erratically and poorly absorbed, and its bioavailability is less than 5% of the ingested dose. Rectal administration of ergotamine leads to slightly better absorption and better treatment efficacy [7].

Currently the most commonly used ergotamine tartrate preparations are tablets and suppositories. Selected combination tablets contain 1 mg ergotamine tartrate and 100 mg caffeine. The rectal suppositories contain 2 mg ergotamine tartrate and 100 mg caffeine. Because ergotamine is better absorbed rectally, a smaller dose should be given. It is not uncommon to start with only one quarter of a suppository, which can be repeated in 1 h if needed. The maximum dose of ergotamine is 4 mg/day, and it should be used only 1 or 2 days/week to prevent ergotamine-induced rebound headache.

The side effect profile of ergotamine tartrate limits it use as a regular acute-care migraine treatment. The potential adverse events include exacerbation of nausea or vomiting associated with a migraine attack, abdominal pain, distal paraesthesias and muscle cramps. If used more than two times per week, even in low doses, ergotamine tartrate dependency and rebound headaches may develop. Ergotamine is contraindicated in pregnancy, uncontrolled hypertension, coronary artery disease, peripheral vascular disease, sepsis, and liver and kidney disease. It should not be given to a patient on erythromycin or other macrolide antibiotics (which decrease metabolism and raise blood levels). Today in the United States there are few patients who are started on ergotamine tartrate preparations for migraine treatment unless triptans have failed. The triptans work more quickly and completely and also can reduce nausea instead of exacerbating it.

Dihydroergotamine

Dihydroergotamine (DHE) is a hydrogenated ergot preparation that has been available since the early 1940s. Although it is considered a weaker arterial constrictor and a stronger venoconstrictor than ergotamine tartrate, it carries the same contraindications (should not be used in pregnancy, uncontrolled hypertension, coronary artery disease, peripheral vascular disease, sepsis, and liver and kidney disease, or in conjunction with erythromycin or other macrolide antibiotics). DHE has been tested clinically and proven useful when administered IV, IM, subcutaneously and intranasally for acute treatment of migraine. Pretreatment with an antinausea medication such as metoclopramide, promethazine, prochlorperazine or ondansetron is not usually needed unless it is given IV. Because DHE is most effective by parenteral administration, it is less convenient than an oral triptan, but is often quite effective. Although there is no published scientific evidence, it appears clinically to work well into the migraine attack, even if the patient has developed central sensitisation and allodynia. The half-life of DHE is 10 h, which may contribute to its long-lasting effect and low recurrence rate – although vasoconstriction lasts longer also.

The use of DHE for acute treatment of migraine outside the clinic setting is limited to the nasal spray formulation in the USA (Migranal), which is administered as a 0.5 mg dose in each nostril, repeated 15 min later for a total of 4 sprays (2 mg total dose). The nasal spray is well tolerated, with some patients developing nasal stuffiness. DHE given by injection in an emergent care or clinic setting is very effective in reducing migraine pain. The starting dose is often 0.25–0.5 mg given by slow IV push over 5 min through a heparin lock, following administration of an antiemetic. Another 0.5 mg can be given in 60 min if there are no significant side effects. If the patient is hospitalised for repetitive intravenous DHE, the usual dose is between 0.5 and 1 mg given slowly through a heparin lock every 8 h over a period of 3–5 days. An effective way to use DHE is 1 mg IM with or without an antiemetic such as PO or IM promethazine or prochlorperazine. A 4-mg dose of dexamethasone also can be given PO, IM or IV

concomitantly, although there is no good evidence in the literature for its effectiveness. Empirically it has been used effectively for years.

Triptans

Triptans are the most highly selective, migraine-specific, acute-care treatment currently used in the outpatient setting [2, 3, 8]. There are seven triptans available in tablet form. In order of their clinical development and approval by the FDA, the tablets are sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan and eletriptan. Different triptans are available in various strengths and formulations including oral tablets, orally disintegrating tablets, nasal sprays and subcutaneous injection. In Europe, sumatriptan is available as a suppository and some countries do not have all the tablets and melt tablets that are available in the USA. In some countries sumatriptan is available as a generic tablet. Specific differences among the triptans appear to exist as evidenced by different pharmacokinetic profiles including half-life, Tmax, Cmax, AUC, metabolism and drug–drug interaction profiles, among others. How these differences translate to clinical efficacy and tolerability differences is not well understood. Consequently, clinical distinctions among these agents are subtle and require attention to the specific characteristics of the patient as well as individual features of the drug and its tolerability profile. In certain patients, such as those with nausea and vomiting, delivery systems and route of administration may be more critical than which triptan is used.

The delivery system plays an important role in the onset of action of triptans. Subcutaneous delivery of sumatriptan offers the most rapid and complete pain relief of the triptans beginning as early as 10–15 min, with a high percentage of attacks improved by two hours; yet it also is associated with a higher incidence of adverse events and a high recurrence rate. The second most rapid onset of action of the triptans is achieved through nasal spray deliveries of sumatriptan and zolmitriptan nasal spray. Sumatriptan nasal spray has been shown to begin to work in 15 min in 3 of 5 double-blind, placebo-controlled studies, but many patients do not like the taste. Zolmitriptan nasal spray, which has a more neutral taste, has been shown to work in 10 min in one study and 15 min in another. All seven of the triptans are available as conventional tablets, and two (rizatriptan and zolmitriptan) are also available in an orally disintegrating formulation. These formulations are more convenient to use and can be taken when the patient is nauseated, but they do not work faster than tablets in most patients.

Beside delivery options, other clinical distinctions to consider among the triptans are pharmacokinetic differences, the duration of action, the percentage of patient attacks attaining either headache relief or a pain-free state at 2 h, and frequency of recurrence or headache persistence. Sumatriptan has been available for the longest time (since 1993 as an injection in the USA and 1991 in Europe and Canada) and has been given successfully to the most number of patients. Zolmitriptan is the only triptan proven effective when repeated for a persistent headache and the new nasal spray seems to be rapidly effective, with a long-lasting effect and well tolerated. Naratriptan has a slower onset of action but a longer half-life, and possibly a longer duration of action, which may help address the clinical challenges of treating migraine associated with menses or migraine in patients who have a history of long duration attacks. Rizatriptan has the highest 2-h pain-free rates and the fastest response rate for an oral tablet. Almotriptan has a slightly better side-effect profile than sumatriptan with fewer side effects of chest pain. Frovatriptan is a slower acting triptan with the longest half-life (26 h) in the class and may also be useful in menstrual migraine and other long-lasting headaches. One third of patients studied on frovatriptan have an early response and remain early responders in subsequent dosing. Eletriptan is the newest triptan tablet available and works rapidly with a low recurrence rate.

In spite of these differences, the triptans are more similar than different, and one cannot predict which triptan will work best for any given patient [7]. If the first triptan tried is not ideal in all clinical respects, a second or third should be tried. The patient should be questioned carefully to determine if the triptan they are taking is the right one for them in terms of rapid onset of action, complete response, lack of recurrence and minimal side effects. If it is not, but has been given in the maximum dose at an early time point in the attack on at least two occasions, then another triptan should be tried.

Adverse event profiles also may be helpful in determining which triptan is best matched for a particular patient. Sumatriptan, rizatriptan and zolmitriptan should not be used with MAO inhibitor antidepressants. Rizatriptan requires a dose reduction to 5 mg in patients taking propranolol; clearance of naratriptan is reduced with concomitant administration of oral contraceptives, and zolmitriptan may require dose reduction in patients taking cimetidine and oral contraceptives. Eletriptan should not be used with 7 contraindicated CYP3A4 inhibitors.

As a class, triptans are all vasoconstrictive agents causing peripheral and central arterial wall narrowing. Each one stimulates serotonin$_{1B,1D}$ receptors. *In vitro* studies report that the vasoconstriction associated with coronary arteries is minimal with therapeutic doses [9]. However, as a safety precaution, patients with specific vascular risk factors or on other vasoconstrictive medications should not take triptans. Triptan contraindications includes: coronary artery disease and risk factors for coronary artery disease that have not been carefully evaluated (such as smoking, obesity, family history of early or severe coronary disease, diabetes, lack of

exercise, high cholesterol, peripheral vascular or cerebrovascular disease, uncontrolled hypertension and conduction pathway disorders). Triptans should be used cautiously in Raynaud's disease. Triptans should not be used in patients with unusual or prolonged auras, basilar migraine or hemiplegic migraine.

If triptans are given to patients with migraine who have no contraindications or cardiac risk factors, they are very safe drugs. No single triptan has been reported as being any safer than another, even though some (such as almotriptan, frovatriptan and naratriptan) appear to have caused fewer side effects in clinical trials.

Corticosteroids

The mechanism of action of steroids in migraine is not clearly understood but probably relates to their effect on the perivascular neurogenic inflammation in the meninges thought to be one of the neuropathologic mechanisms causing the pain of migraine. Although scientific evidence is limited supporting the use of corticosteroids for acute migraine treatment, several headache specialists and headache centres use it as an oral rescue medication when a triptan is not effective in controlling a migraine attack. Use of oral corticosteroids may decrease the chance of recurrence within 24 h and often for several days. When corticosteroids work, they gradually decrease both the headache and the associated symptoms. The literature contains a few studies suggesting possible efficacy when steroids are given IV as a rescue medication in status migrainosus. Specifically, studies using dexamethasone (with or without an anti-emetic) and hydrocortisone suggest a possible clinical response to treatment [10]. Recent studies show that corticosteroids may work during withdrawal procedures but not acutely in the emergency room to prevent recurrence.

Physicians should always consider the large number of side effects from long-term use of corticosteroids when choosing this option. Although there is no consensus, it appears clinically that two days a month of steroids or a one-week burst given every 2–3 months are safe in persons at no risk of using corticosteroids. Steroids may also be amongst the safest medications to terminate a migraine attack in a pregnant woman after the first trimester, although there is no evidence for this in the literature. There are few adverse events from short-term use of high-dose steroids, the most common being inability to sleep, hyperactivity and unmasking of psychological conditions.

Preventive treatment of migraine

Principles of preventive treatment

The decision to initiate preventive migraine therapy should be based on individual clinical judgement combined with the patient's willingness take daily medication and comply with the treatment regimen. Patients with frequent, prolonged or debilitating headaches often benefit from preventive therapies. However, defining these parameters for a typical patient is not an easy task. Some patients have very infrequent, yet severely debilitating and prolonged migraine attacks and are better managed with preventive therapies. In contrast, other patients have more frequent headaches that respond well to acute-care medications, and they may prefer to avoid daily medication regimens. As a result of these patient preferences and attack differences, clinical decision making regarding use of preventive therapies is often complex and requires individualised consultation with the patient and an in-depth understanding of the impact of the illness on the patient's life [11].

The most frequent indications for daily preventive migraine therapy are high-frequency headaches, great disability associated with individual attacks, contraindications to triptans and other vasoactive medications, and existence of significant triptan side effects. Preventive medications can be chosen based on coexisting medical conditions such as depression, hypertension or asthma. If the correct medication is chosen, the patient may benefit from a daily therapy that treats an underlying medical condition and is also effective in the treatment of migraine. For example, giving a β-blocker, calcium antagonist or angiotensin receptor blocker (ARB) to a severe migraineur with hypertension, or a tricyclic antidepressant to a migraineur who is depressed or having difficulty sleeping, may benefit both medical conditions. The reverse is also true. Certain preventives shoul β-blockers in depression, asthma and hypotension, or carbonic anhydrase inhibitor membrane stabilisers (topiramate and zonisamide) in patients with kidney stones.

Once a decision has been made to initiate preventive pharmacotherapy, several *general principles of management* may prove helpful:

- Begin treating with preventive medications at a low dose and gradually increase over an extended period of time. If you reach a reasonable therapeutic dose without the desired clinical response being achieved, and if no adverse events emerge, then the dose can be escalated further.
- Manage the patient's expectations regarding when they can anticipate clinical benefit. Many preventive medications take 3–6 weeks for a therapeutic response at the appropriate dose (which is often more than two months of therapy), and some take longer. Patients must understand that they have to be on an adequate dose for one to three months before deciding that the medication is ineffective. Most patients will need to remain on a preventive medication for 6–12 months, or longer.
- Establish a comprehensive migraine management plan

that includes long-term goals, tips on when the medication needs to be changed, a schedule of regular office visits, and specific information on adverse reactions and when to contact the office.

Note: Only 5 medications have been approved by the FDA for prevention of migraine:

- methysergide (no longer available in the US)
- propranolol
- timolol
- divalproex sodium
- topiramate

Beta Blockers

Acting at the post-synaptic receptor site, β-blockers are among the most commonly used class of drugs for prevention of migraine. Propranolol, the first β-blocker approved for migraine treatment, was accidentally found to prevent migraine when a patient being treated for angina pectoris noted that his long-standing migraine headaches improved [12]. Both the lipophilic beta blockers that readily pass into the central nervous system (CNS), such as propranolol and metoprolol, and the hydrophilic atenolol and nadolol, which do not appear to enter the CNS, are effective in the prevention of migraine. Cardioselectivity also appears to have no bearing on efficacy. The presence of *intrinsic sympathomimetic* activity may be related to effectiveness. The exact mechanism of action in migraine is unclear.

To date, over 75 controlled clinical studies have been reported in the literature testing the efficacy of β-blockers in the prevention of migraine [11]. Propranolol is the most extensively studied, with additional reports for metoprolol, acebutolol, atenolol, bisoprolol, nadolol, pindolol and timolol [12]. Meta-analyses of these studies report that propranolol provides a moderate reduction in headache frequency or index [9]. Comparative studies among the different β-blockers reported few differences in efficacy between propranolol, metoprolol, timolol, atenolol and nadolol. Long-acting drugs or extended-release formulations also do not appear to confer additional clinical benefits for migraine prevention over regular formulation, but do improve patient compliance. Only propranolol and timolol have been approved for migraine prevention by the FDA in the United States.

For all these agents, lower doses are started during initial treatment and the dose is gradually increased over time. β-blockers as a class may be associated with several adverse events including depression, fatigue, reduced tolerance for physical activity, nausea, dizziness and insomnia. Some patients have reported increased coldness in the extremities, dizziness on standing and abnormal dreaming. These medications are contraindicated in certain disorders such as asthma, chronic lung disease, diabetes, hypoglycaemia, bradycardia, hypotension, Raynaud's disease, peripheral vascular disease and severe depression. Additionally, β-blockers probably should not be used in hemiplegic migraine and cautiously, if at all, in frequent attacks of migraine with aura. When deciding to discontinue therapy, it is essential that the dose be gradually tapered over a period of more than a week or there may be reflex tachycardia. Note that if a patient is taking propranolol for any reason and they are given rizatriptan for acute treatment of migraine, the dose of rizatriptan should be reduced to 5 mg, not the usual 10 mg.

Calcium channel antagonists

Calcium channel antagonists have been used for several years for prevention of migraine, but none have been approved for that condition by the FDA. Over 45 clinical studies report on the efficacy of several different agents including: verapamil, flunarizine (not available in the United States), nimodipine, nifedipine, cyclandelate and nicardipine. Flunarizine (10 mg/day) has been the most extensively studied and has been proven to be clinically effective in multiple controlled trials [13]. Clinical studies of verapamil (240 mg/day) and nimodipine (120 mg/day) report modest clinical benefits; there are conflicting results in the literature with some studies showing significant benefits vs. placebo, and other studies showing little or no improvement in preventing headache [14]. Other agents that are used clinically but have not been tested in clinical trials include diltiazem (Cardizem) (at a starting dose of 30 mg tid, with gradual treatment escalation to 60 mg tid), nisoldipine (Sular®, with a starting dose of 10 mg qd and a maximum of 40 mg qd) and amlodipine (Norvasc®, at a starting does of 2.5 mg qd with gradual increase to a high of 10 mg qd). Newer calcium channel antagonists also may offer therapeutic benefits for migraine prevention including isradipine and nicardipine. Nifedipine may actually worsen headache as it is a strong vasodilator.

The most common side effects reported with calcium channel antagonists are constipation and fluid retention in the ankles. Less frequent but more significant side effects are cardiac dysfunction, hypotension, drowsiness and dizziness. Calcium channel antagonists are contraindicated in congestive heart failure, heart block, bradycardia, sick sinus syndrome and other cardiac problems. Flunarizine is associated with depression, weight gain and secondary Parkinson's syndrome. It should be used with caution in elderly patients. Contrasting with the other calcium channel antagonists, flunarizine produces a synergism when used with propranolol.

Antidepressants

Four major types of antidepressants are available: monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs). All have been used extensively for prevention of migraine. Several of these agents have been specifically tested and proven effective; others are used empirically [15]. None are approved for migraine prevention by the FDA in the USA. One important clinical benefit of these agents is their usefulness in patients with migraine and coexisting depression – a condition previously reported to have a higher prevalence in migraine than in the normal population. Antidepressant use in migraine prevention can also be helpful in patients with coexisting sleep disorders and anxiety. I always warn my migraineurs on SSRIs, however, that their headaches could worsen.

Monoamine oxidase inhibitors

MAOIs appear to work well for frequent or daily headache and depression, as well as transformed migraine with daily milder headache and intermittent migraine. More than 80% of migraine sufferers report an improvement of at least 50%. However, despite their efficacy, MAOIs are not widely used for prevention of migraine because they require significant dietary limitations and extreme caution regarding drug–drug interactions. There are strict rules about giving them with other types of antidepressants, and they can never be given with vasoactive amines such as isometheptene mucate (contained in Midrin®), pseudoephedrine and other vasoconstrictors frequently found in off-the-shelf cold preparations. The consequence of such simultaneous drug use may be serious, including intracerebral haemorrhage and, at the very least, hypertension producing severe headache. Other possible side effects include orthostatic hypotension, weight gain, insomnia, constipation, increased perspiration, peripheral oedema and, less commonly, inhibition of ejaculation or reduced libido. One commonly used MAOI is phenelzine, an MAO-A inhibitor. Given the fact that there are many other effective preventive medications for migraine, MAOIs are often saved for last or ruled out entirely as a treatment.

Tricyclic antidepressants (TCAs)

To date, three agents have been tested in controlled clinical studies: amitriptyline, clomipramine and opipramol (not currently available in the United States). Amitriptyline is the most commonly studied and used TCA treatment for migraine prevention and has been shown to reduce headache severity and frequency [15]. Most of the TCAs including nortriptyline, doxepin, desipramine, imipramine and protriptyline have been successfully used clinically in the United States. There are few good studies showing evidence for therapeutic benefit in migraine prevention [9].

As most of the TCAs are available in a 10-mg dose (as the lowest dose available), a typical regimen for amitriptyline (or nortriptyline and similar medication) begins with 10 mg given at least 60 min before bedtime. The dose may be escalated in 10 mg increments every 5–7 nights as tolerated. The average dose is 50–75 mg, and some patients may require up to 150 mg if they have coexisting conditions including a sleep disorder or depression. Nortriptyline has a narrow therapeutic window and should not be given in too low or too high a dose. Side effects associated with TCAs include weight gain, drowsiness in the morning, dry mouth, constipation, blurred vision, reduced libido, other sexual disturbances and urinary retention. These drugs are contraindicated in the presence of cardiac arrhythmias, glaucoma and urinary retention. Special caution must be taken when using these drugs in elderly patients. The least sedating of these drugs are nortriptyline, desipramine, imipramine and protriptyline.

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs tested for prevention of migraine include fluoxetine and fluvoxamine, with controversial results [15, 16]. Paroxetine, sertraline and citalopram have been shown in some smaller open studies to be helpful but have not been shown to work conclusively in well designed, multicentre studies. Some reports suggest that the SSRIs help in tension-type but not migraine headache. SSRIs can be tried in migraineurs who have a significant coexisting problem with sleep, depression or anxiety.

Serotonin norepinephrine re-uptake inhibitors

Venlafaxine (Effexor) (dose ranges from 37.5 to 225 mg/day, in divided doses or in the long-acting XR form) and mirtazapine (Remeron) (doses range from15 to 45 mg at bedtime) are two selective serotonin and norepinephrine reuptake inhibitors that can be tried in treatment-resistant migraine cases that are complicated by coexisting depression. A newer one, duloxetine (Cymbalta), is approved for both depression and diabetic neuropathy and may prove to be helpful in different types of headache. Its most frequent early adverse event is nausea, which can be made less likely by starting with 20 or 30 mg for a week. The dose for depression is 30 mg for the first week and 60 mg thereafter.

Adverse events often associated with SSRIs are fewer in number, but different in nature from those reported with the TCAs. They include nausea, agitation (which often improves within 1–2 weeks), insomnia, tremor, anorgasmia and other sexual dysfunction. A small percentage of patients have an increase in headaches so patients must be warned about the risk of this adverse event. Although the SSRIs are usually weight neutral, some patients may actually gain weight.

Miscellaneous antidepressants

Some antidepressants fall into the miscellaneous category such as bupropion (Wellbutrin), which stimulates dopamine receptors and is used under a different brand name as a smoking cessation aid; trazodone (Desyrel), which has an active metabolite that may cause headaches, but is very helpful for middle insomnia; and nefazodone (Serzone), which theoretically has an excellent receptor profile for migraine as both a 5-HT_2 antagonist and a serotonin and norepinephrine reuptake inhibitor, and has been shown in clinical studies to be helpful in chronic daily headache. Note that it is one of the 7 CYP-3A4 inhibitors that is contraindicated with the use of eletriptan.

Membrane stabilisers (anticonvulsants)

Membrane stabilisers frequently used in the prevention of migraine include: divalproex sodium (Depakote) [17] (500–1500 mg/day, also available and approved in an extended release form which is given only once per day with a therapeutic serum level of 70–120 mg/l), sodium valproate (800–1500 mg/day with a therapeutic serum level above 50 mg/l), topiramate [18] (50–200 mg/day) and gabapentin (900–2400 mg/day) [19]. Additionally, limited studies with carbamazepine (Tegretol) (600 mg/day) and lamotrigine (Lamictal) have less conclusive clinical evidence regarding their efficacy in prevention of migraine [20, 21]. Lamotrigine has been shown in studies to be useful in the treatment of migraine with aura, but not in migraine without aura. Several other medications in this category such as levetiracetam (Keppra) and zonisamide (Zonegran) have shown promise as migraine preventive medications in open trials [21–23]. Only divalproex sodium in its two available forms and topiramate have been approved by the FDA in this category of drug for migraine prevention.

Dosing regimens for divalproex sodium include starting at a low dose of 250 mg or 500 mg at hour of sleep. A typical dose would be approximately 750 mg/day. If the patient continues to have breakthrough migraine attacks after titration, and there are no significant side effects, the dose can be gradually raised up to 1000–2000 mg; but most patients will not have added improvement over 1000–1500 mg/day. The new long-acting form of divalproex sodium (Depakote® ER) can be given once per day in the evening. The starting dose is usually 500 mg and most patients take 1000 mg hs. There may be fewer side effects from the extended release form. Possible side effects may include weight gain, brittleness of the hair shaft and tremor. Possible endocrine effects in young females may occur [17, 24].

Gabapentin is an anticonvulsant structurally related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Although gabapentin was developed as a structural analogue of GABA that would penetrate the blood–brain barrier (unlike GABA) and mimic the action of GABA at inhibitory neuronal synapses, the drug has no direct GABA-mimetic action, and its precise mechanism of action has not been elucidated. Gabapentin seems to be particularly effective in treating chronic pain syndromes. A recent double-blind trial for migraine prevention that used 1800–2400 mg/day of gabapentin showed it to be superior to placebo in reducing frequency and intensity of migraine pain. Gabapentin was effective as a migraine preventive in 46% of patients vs. 14% of placebo patients [19]. Other than drowsiness at high doses and occasional weight gain, it is usually well tolerated and there are no significant drug–drug interactions.

Pregabilin (Lyrica), which is related to gabapentin, was approved for epilepsy and diabetic neuropathy and has been tried for migraine prevention. The dose usually ranges from 150 to 300 mg daily. It has recently been approved for treatment of fibromyalgia.

Topiramate is a structurally unique anticonvulsant that is rapidly and almost completely absorbed. It differs chemically from other currently available anticonvulsive agents. It has many beneficial properties including inhibiting voltage-gated sodium and T-type calcium channels, glutamate blockade via ampa-kainate receptors, GABA potentiation and carbonic anhydrase inhibition. The spectrum of topiramate's anticonvulsive activity resembles that of carbamazepine and phenytoin, but it is much more efficacious as a migraine preventive. It has been associated with weight loss, making it an almost unique migraine preventive medication. Most of the other anticonvulsants cause weight gain, or, at best, are weight neutral, with the exception of zonisamide, which also causes weight loss. The majority of patients on topiramate (51% in controlled trials) complain about slight peripheral paraesthesias in the hands and feet, which usually become intermittent and often disappear. One much less common side effect, but one that the patient must be warned about, is cognitive dysfunction that is fully reversible when the medication is discontinued. There is a possible interaction between topiramate and oestrogen-based birth control pills at doses of 200 mg or more, with some women developing breakthrough bleeding as their oestrogen levels decrease. Kidney stones have been reported. Rare cases have been reported of reversible, acute, open-angle glaucoma associated with topiramate use. Oligohydrosis, especially in children, is a rare adverse event that patients should be aware of. Most patients develop a clinically insignificant metabolic acidosis, so blood work is usually abnormal. A double-blind study showed that topiramate produced more than 50% decrease in pain in 46.7% of patients vs. 6.7% of placebo [18]. Topiramate must be gradually increased from a 15 or 25 mg/day hs dose and no faster than 25 mg/week in order to avoid side effects. In our experience patients who reach 100 mg over one month and remain at that dose for a sec ond month

without beneficial effect, but who have no significant adverse events, can be raised slowly to 200–400 mg/day, usually without significant adverse events. Some of these patients note better efficacy at these higher doses. The approved target dose is 100 mg/day in divided doses and 200 mg/day is shown to be just as effective.

Zonisamide, an anticonvulsant introduced into the US from Japan, has a unique combination of pharmacological actions: it inhibits voltage-gated Na^+ channels and also blocks T-type calcium channels. Both of these mechanisms may play a role in headache and pain modulation, possibly via neuronal stabilisation. It also acts as a carbonic anhydrase inhibitor. Open-label studies suggested that zonisamide may be an option in the preventive treatment of migraine, particularly in refractory cases. Usual doses range from 100 to 400 mg/day. Due to its long half-life, it can be started as a 100 mg dose every third day and increased slowly to 100–400 mg qd. I typically start dosing at 25 mg hs and increase 25 mg weekly to 100 mg. If that is not effective I continue to increase the dose slowly up to 400 mg as tolerated. Possible side effects include kidney stones, weight loss, coordination problems, paraesthesias, somnolence, dizziness and nausea [12].

Levetiracetam, a pyrrolidine derivative, is an anticonvulsant that is structurally unrelated to other currently available anticonvulsants in the class. The mechanism of anticonvulsant action of levetiracetam is unknown and does not appear to be related to any known mechanisms involved in excitatory or inhibitory neurotransmission. It has recently been shown to bind to the synaptic vesicle protein SV2A. Levetiracetam is not extensively metabolised in humans, with 66% of an administered dose excreted unchanged in the urine. About 24% of an administered dose is metabolised to an inactive metabolite by enzymatic hydrolysis of the acetamide group, which does not depend on hepatic cytochrome P-450 (CYP) isoenzymes. Open-label studies show that levetiracetam, in dosages ranging from 2000 to 4500 mg/day (bid or tid dosing regimens), could be an option in the treatment of refractory headaches [15]. In an open study presented by our group during the 2004 meeting of the AAN, levetiracetam may work to relieve chronic headache. Side effects are uncommon and include somnolence, dizziness, ataxia and anxiety.

Side effects associated with anticonvulsants as a class include weight gain, hair loss, tremor, gastrointestinal upset, sedation, asthenia, dizziness and cognitive changes. Topiramate and zonisamide are unique as they have been associated with weight loss.

If side effects occur, dose reduction or even drug discontinuation is recommended. Most anticonvulsants are contraindicated in pregnancy. Specifically, sodium valproate has been associated with neural tube defects and should be used very cautiously in women of child-bearing potential. The risk of neural tube defects is decreased with administration of supplemental folic acid. The use of sodium valproate in children under age 2 or patients with hepatic disease is not recommended. Sodium valproate interacts with barbiturates and benzodiazepines, so caution is required if these medications are combined because patients may become drowsy. The commonly used butalbutal containing analgesics must be given cautiously if administered with anticonvulsants. Valproate has been associated with pancreatitis and polycystic ovary syndrome [16]. Topiramate is associated with renal stones and rarely narrow angle glaucoma. Zonisamide has been associated with renal stones and ataxia.

Alpha$_2$-agonists

Clinical studies testing the efficacy of centrally acting alpha$_2$-agonists for migraine are limited and report mixed results regarding their therapeutic benefits. Specifically, alpha$_2$-agonists tried for preventive treatment of migraine include clonidine and guanfacine and only report minimal therapeutic benefits. Clonidine has been used successfully in some women with increased headache and vasoactive symptoms associated with perimenopause [14]. Side effects from the alpha$_2$-agonists such as drowsiness, orthostasis and hypotension may limit their use.

Nonsteroidal anti-inflammatory drugs

NSAIDs, often used in acute treatment, also can prevent migraine. A meta-analysis of seven placebo-controlled studies of naproxen (500 mg/day) or naproxen sodium (1100 mg/day) suggest a modest but clinically significant improvement in headache index and reduction in frequency [9].

For migraine associated with menses, NSAIDs may be helpful if started 3–4 days before menses begins (a time of increased risk for headache). One possible treatment regimen includes naproxen sodium 275 mg tid with meals starting three days before menses, and continuing until the third day of the menstrual cycle or until the increased susceptibility to headache is over. Rofecoxib and valdecoxib are COX II inhibitors that were removed from the market as they could cause cardiovascular problems in older patients who took them for extended periods of time. Celecoxib is still available in 100 and 200 mg strengths for bid dosing. When there were 3 COX II inhibitors on the market, all were used empirically for migraine mini-prophylaxis [5, 6, 14].

Serotonergic agents

Methysergide

Methysergide (Sansert) is one of the original medications used for migraine prevention, having become available

over 50 years ago; but its use is limited due to its risk of retroperitoneal and peripleural fibrosis associated with extended use. It has not been available in the US since 2003, but it is in Canada. Several studies report that methysergide is effective as a preventive treatment for migraine. Comparative studies suggest that methysergide confers similar clinical benefit in reducing headache frequency to propranolol [25, 26].

An initial methysergide dose is 2 mg daily, which can be gradually increased to 6 mg/day in 3 divided doses. It is usually well tolerated. Possible side effects include nausea, dizziness, muscle cramps, weight gain, abdominal pain, diarrhoea, psychiatric symptoms, giddiness, drowsiness and paraesthesias. The drug is contraindicated in coronary artery and peripheral vascular disease, hypertension, pregnancy, peptic ulcer, phlebitis, lung disease, liver disease and kidney disease. Manufacturer's labelling suggests that methysergide be discontinued for a 3–4 week washout period following every 6 months of therapy. The risk of developing retroperitoneal or peripleural fibrosis appears to be approximately 1 in 1500 [27]. As it is an ergot, methysergide should not be given concomitantly with triptans or other ergots such as ergotamine tartrate or DHE.

In its absence we use a metabolite methylergonovine (Methergine) at a dose of 0.2 mg qd up to a maximum of 2 tablets tid. We also give drug holidays every 6 months and warm about the same adverse events.

Cyproheptadine

The antihistamine cyproheptadine is a 5-HT_2 antagonist with calcium channel blocking properties. Although its clinical efficacy has not been proven in double-blind, randomised studies, clinical experience suggests that it may confer some benefit in the prevention of migraine, especially in children. Cyproheptadine is contraindicated in closed-angle glaucoma and prostatic hypertrophy [26].

Pizotifen

Pizotifen is a 5-HT_2 antagonist structurally related to cyproheptadine. Although not available in the United States, it is frequently used in several countries. Studies show this drug to be of benefit in 40%–79% of patients when given in doses ranging from 1.5 to 3.0 mg at bedtime [22]. The main side effects are drowsiness and weight gain – similar to cyproheptadine.

Miscellaneous preventive treatments

Lisinopril

Lisinopril (LSN) is a dicarboxyl-containing angiotensin converting enzyme (ACE) inhibitor that has been proven to be effective in the treatment of hypertension and heart failure. LSN has various pharmacological effects that may be relevant in migraine. In addition to blocking the conversion of angiotensin I to angiotensin II, it also alters the sympathetic activity, inhibits free radical activity, increases prostacyclin synthesis and blocks the degradation of bradykinin, encephalin and substance P. Of particular relevance to LSN efficacy in migraine prevention is the recent findings that (1) migraine without aura seems to be more common in people with the ACE DD gene and (2) migraineurs with this gene also have higher ACE activity and a higher frequency of attacks than other migraine sufferers [28].

LSN was studied in a randomised, placebo-controlled, crossover trial for the preventive treatment of migraine, showing moderate efficacy. The main side effects are cough, hypotension and fatigue. The suggested oral doses of LSN for use in hypertension range from 5 to 40 mg daily (in single or divided doses), with 10 mg daily being appropriate for the initiation of therapy.

Candesartan

Candesartan (Atacand) is an angiotensin receptor blocker (ARB) used for treating hypertension. In January of 2003 it was reported in a double-blind, controlled, crossover study to be more effective than placebo in preventing migraine at a dose of 16 mg qd. Clinically it appears to work well in about half the patients who take it and it causes few side effects [29].

Botulinum toxin

Botulinum toxin type-A (Botox) injections often reduce the pain associated with conditions such as cervical dystonia, achalasia, rectal fissures and myofascial pain syndrome. Some open-label, non-controlled studies of botulinum toxin type-A suggested benefits for patients with migraine and several other headache types. A double-blind study, evaluating 25-Unit and 75-Unit doses, showed that, compared with vehicle treatment, subjects in the 25-Unit botulinum toxin type-A treatment group had significantly fewer migraine attacks per month, a reduced maximum severity of migraine, a reduced number of days using acute migraine medications and reduced incidence of migraine-associated vomiting [30]. Other open and controlled trials seem to support this first evidence, but definitive results have not been forthcoming. There is currently a multicentre trial in frequent migraine sufferers who are not on other preventive drugs underway. Many neurologists and headache specialists use the drug off-label and say that it works well in certain patients with few adverse events, in spite of the paucity of evidence.

Hormonal therapy

Hormonal therapy can be tried in both the menstruating females with menstrually related migraine, and the perimenopausal and menopausal female [31]. For women who have either pure menstrual migraine or marked worsening of their migraine perimenstrually (MRM or menstrually related migraine), a burst of oestrogen starting 3–4 days before menses and until the end of menses can be achieved

with an oestradiol gel dermal patch (1.5 mg/day) or pure oestradiol orally or sublingually. Importantly, lower dose studies (50 mcg per day) were not proven effective in reducing migraine frequency or intensity. Giving oestrogen to perimenopausal women with irregular menses and escalating headaches is more likely to worsen the headache syndrome, but can occasionally be very effective.

Herbs, vitamins and supplements

Feverfew

Feverfew (*Tanacetum parthenium*) is a herb that is available as an off-the-shelf remedy, and is used for treatment of mild depression. A few small clinical studies reported feverfew (50–82 mg/day) to decrease the frequency of migraine attacks when used on a daily basis.

Petasites hybridus

Petasites in an extract from the plant *Petasites hybridus* (butterbur) which has been marketed in Germany for the last 25 years. Lipton et al. conducted a double-blind study, showing that petasites 75 mg, given twice a day, was significantly superior to placebo in all parameters in treating migraine [32].

Magnesium

Low levels of magnesium in migraineurs are associated with the cascade of events that trigger migraine attacks. Studies have demonstrated low intracellular magnesium in the migraine brain [33, 34]. Magnesium has been studied in 6 clinical trials for migraine prevention with conflicting but very promising results. The doses tested included 400–600 mg/day and suggest possible therapeutic benefits in some patients.

Riboflavin

A mitochondrial dysfunction resulting in impairment of oxygen metabolism and low cellular energy levels may play a role in migraine pathogenesis [35]. Riboflavin (vitamin B2) is the precursor of flavin mononucleotide and flavin adenine dinucleotide, which are required for the activity of flavoenzymes involved in the electron transport chain in the mitochondria of the cell. Given to patients with mitochondrionopathies, riboflavin improved some clinical and biochemical parameters.

Coenzyme Q 10

Coenzyme Q 10 was shown to be effective in an open study by Rozen at a dose of 150 mg/day. The only controlled study by Sandor showed 300 mg to be the effective dose [36]. There were minimal adverse events.

Melatonin

Melatonin was shown by Peres in an open trial to be effective in migraine prevention at a dose of 3 mg. We have tried up to 15 mg hs empirically and find it may be somewhat more effective for sleep disorders than the headache itself.

Future therapy

We may see Trexemet launched as a tablet in the US in 2008; it is a combination of sumatriptan 85 mg and naproxen sodium 500 mg. MK-0974 is a CGRP antagonist tablet in phase 3 trials, which may be an effective acute-care medication, working as well as a triptan at 2 h, and better at 24 h. It is reported to not constrict blood vessels and to have few of the adverse effects of triptan. When sumatriptan goes generic in the US, there will be a sumatriptan skin patch. There may be an inhaled form of prochlorperazine and also DHE. There may be a nitric oxide synthase inhibitor and an AMPA/kainate antagonist. Many other compounds are in the pipeline at earlier stages. Memantine (Namenda) is available for Alzheimer's disease therapy and has been shown in open-label trails to be helpful in various types of headaches, mainly migraine. The usual dose is 10 mg bid, but higher doses have been tried.

References

1. Cady RK (2001) Treatment strategies for migraine headache. JAMA 285:1014–1015
2. Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine – current understanding and treatment. N Engl J Med 346:257–270
3. Matchar DB, Young WB, Rosenberg JH et al (2000) Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. www.neurology.org. April
4. Mathew NT, Kailasam J, Fischer A (2001) Early intervention using rofecoxib alone, rizatriptan alone and combination of rizatriptan and rofecoxib in acute migraine. Cephalalgia 21:405–432
5. Hawkey CJ (1999) COX-2 inhibitors. Lancet 353:307–314
6. Krymchantowski AV, Barbosa JS (2002) Rizatriptan combined with rofecoxib vs. rizatriptan for the acute treatment of migraine: an open label pilot study. Cephalalgia 22:309–312
7. Klapper J, Stanton J (1991) The emergency treatment of acute migraine headache; a comparison of intravenous dihydroergotamine, dexamethasone, and placebo. Cephalalgia 11[Suppl 11]:159–160
8. Rapoport AM, Tepper SJ (2001) Triptans are all different. Arch Neurol 58:1479–1480
9. Longmore J, Razzaque Z, Shaw D et al (1998) Comparison of the vasoconstrictor effects of rizatriptan and sumatriptan in human isolated cranial arteries: immunohistological demonstration of the involvement of 5-HT1B-receptors. Br J Clin Pharmacol 46:577–582
10. Kuzybski W (1992) Metamizole and hydrocortisone for the interruption of a migraine attack – preliminary study. Headache Q 3:326–328
11. Ramadan NM, Silberstein SD, Freitag FG et al (2000) Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. www.neurology.org. April
12. Weber RB, Reinmuth OM (1971) The treatment of migraine with propranolol. Neurology 21:404–405
13. Reveiz-Herault L, Cardona AF, Ospina EG, Carrillo P (2003)

[Effectiveness of flunarizine in the prophylaxis of migraine: a meta-analytical review of the literature]. Rev Neurol 36:907–912. Review, in Spanish
14. Silberstein SD (2001) Migraine: preventive treatment. Curr Med Res Opin 17[Suppl 1]:s87–s93
15. Tomkins GE, Jackson JL, O'Malley PG et al (2001) Treatment of chronic headache with antidepressants: a meta-analysis. Am J Med 111:54–63
16. Saper JR, Silberstein SD, Lake AE et al (1995) Fluoxetine and migraine: comparison of double-blind trials. Headache 35:233
17. Mathew N, Saper J, Silberstein S et al (1995) Migraine prophylaxis with divalproex. Arch Neurol 52:281–286
18. Edwards KR, Potter DL, Wu SC et al (2003) Topiramate in the preventive treatment of episodic migraine: a combined analysis from pilot, double-blind, placebo-controlled trials. CNS Spectr 8:428–432
19. Mathew NT, Rapoport A, Saper J et al (2001) Efficacy of gabapentin in migraine prophylaxis. Headache 41:119–128
20. Steiner TJ, Findley LJ, Yuen AW (1997) Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia 17:109–112
21. D'Andrea G, Granella F, Cadaldini M, Manzoni GC (1999) Effectiveness of lamotrigine in the prophylaxis of migraine with aura: an open pilot study. Cephalalgia 19:64–66
22. Drake ME, Greathouse NI, Armentbright AD, Renner JB (2001) Preventive treatment of migraine with zonisamide. Cephalalgia 21:374
23. Krusz JC (2001) Levetiracetam as prophylaxis for resistant headaches. Cephalalgia 21:373
24. Sharma S, Jacobs HS (1997) Polycystic ovary syndrome associated with treatment with the anticonvulsant sodium valproate. Curr Opin Obstet Gynecol 9:391–392
25. Muller R, Weller P, Chemaissani A (1991) Pleural fibrosis as a side effect of years-long methysergide therapy. Dtsch Med Wochenschr 116:1433–1436
26. Peatfield R (1986) Drugs acting by modification os serotonin function. Headache 26:129–131
27. Haria M, Balfour JA (1997) Levetiracetam. CNS Drugs 7:159–164
28. Bigal ME, Krymchantowski AV, Rapoport AM (2003) New developments in migraine prophylaxis. Expert Opin Pharmacother 4:433–443. Review
29. Tronvik E, Stovner LJ, Helde G et al (2003) Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA 289:65–69
30. Silberstein S, Mathew N, Saper J, Jenkins S (2000) Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. Headache 40:445–450
31. Wang SJ, Fuh JL, Lu SR et al (2003) Migraine prevalence during menopausal transition. Headache 43:470–478
32. Lipton RB, Gobel H, Wilks K, Mauskop A (2002) Efficacy of petasites (an extract from petasites rhizone) 50 and 75 mg for prophylaxis of migraine: results of a randomized, double-blind, placebo-controlled study. Neurology 58[Suppl 3]:A472
33. Altura BM, Altura BT (1978) Magnesium and vascular tone and reactivity. Blood Vessels 15:5–16
34. Welch KM, Ramadan NM (1995) Mitochondria, magnesium and migraine. J Neurol Sci 134:9–14
35. Schoenen J, Jacquy J, Lenaerts M (1998) Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. Neurology 50:466–470
36. Sandor PS, Clemente LD, Coppola G et al (2005) Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlle trial. Neurology 64:713–715

Neurol Sci (2008) 29:S123–S126
DOI 10.1007/s10072-008-0902-9

Central mechanism of action of antimigraine prophylactic drugs

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Abstract The pathogenesis of migraine is obscure. A hyperexcitable brain state has been postulated. Cortical spreading depression (CSD) is the most suggestive argument for the brain hyperexcitability. It has been showed that valproate, topiramate, amitriptyline and propranolol inhibit CSD in rats, which suggests that most preventative treatments of migraine act by normalising neuronal firing and increasing a genetically lowered and environmentally modified threshold for neuronal discharge. It has also been suggested that some antimigraine prophylactic drugs (i.e., amitriptyline, candesartan and magnesium) may act by restoring central nociceptive dysmodulation.

Keywords Migraine · Cortical spreading depression · Hyperexcitability · Central action · Prophylactic drugs

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Introduction

The exact pathogenesis of migraine remains to be determined. Welch et al. suggested in 1990 that multiple causal factors for migraine converge onto a common hyperexcitable brain state, which constitutes the fundamental susceptibility to migraine attacks [1]. Various causes for hyperexcitability of the migrainous brain have been suggested. These include low concentrations of glutamate, mitochondrial abnormalities, dysfunctions related to nitric oxide or a calcium channelopathy [2, 3]. Cortical spreading depression (CSD) is a spontaneous neuronal depolarisation moving slowly (3 mm/min) on the occipital cortex, which has a clinical counterpart in the scintillating contour (positive scotoma). Neurophysiological and biochemical studies support the hypothesis that neuronal hyperexcitability is the predisposing factor that causes the initial cortical event. CSD (or a similar depolarising event) activates brainstem and gives rise to depolarisation of ascending and descending pathways, perimeningeal vasodilatation and neurogenic inflammation [4, 5]. Therefore, in migraine the excitatory events are believed to be proximal, whereas the neurovascular events that lead to pain production are distal [6]. Repeated episodes of hyperexcitability could parallel, or cause, dysmodulation of nociception pathways, with a resultant chronic state, potential disease progression and the refractoriness to therapy that some patients experience [4]. Central sensitisation, associated with abnormal neuronal excitability in the trigeminal nucleus caudalis, may also play a critical role in migraine pathogenesis, especially in the latter stages of an acute attack, and in the development of chronic forms of the disorder [7, 8]. Nevertheless, progressive damage to the brain's most powerful antinociceptive centre, the periaqueductal grey matter, may also explain some aspects of central sensitisation or change in phenotypic expression of episodic to

chronic headache [9]. Recently, Ayata et al. demonstrated that established preventative drugs, such as valproate, topiramate (TPM), amitriptyline and propranol, inhibit CSD in rats, which argues in favour of the hypothesis that migraine preventive drugs suppress the mechanism of CSD, the main neurobiological marker for the brain hyperexcitability [10]. Therefore, most preventive treatments are thought to act, at least in part, by normalising neuronal firing and increasing a genetically lowered and environmentally modified threshold for neuronal discharge, by blocking excitatory glutamate-mediated or inhibiting gamma-aminobutyric acid (GABA)-mediated central activities [11, 12]. It has also been suggested that some antimigraine prophylactic drugs (amitriptyline, candesartan and magnesium) may act by restoring central nociceptive dysmodulation [13].

Neuromodulators

Numerous neuromodulators (antiepilectic drugs) have demonstrated efficacy in migraine prophylaxis. Neuromodulators exhibit multiple mechanisms that may contribute to reduce the neuronal hyperexcitability in various areas of the brain, both in epilepsy and migraine. TPM and valproic acid (VPA) suppress CSD frequency by 40%–80% and longer treatment durations produce stronger suppression. Direct and indirect effects on inhibition of glutamate release and on blocking NMDA receptors may be relevant for modulating this migraine susceptibility [10].

TPM is used in the treatment of partial-onset and primary generalised tonic–clonic seizures [14]. TPM has emerged recently as a treatment for migraine and is now approved for migraine prevention in several countries. Large, multicentre, randomised, double-blind, placebo-controlled trials have demonstrated the efficacy of TPM in migraine prophylaxis in adults [15–17]. A recent study showed a significant improvement in health-related quality of life in a migraine population [18]. Recent studies showed a significant effect also in paediatric migraine [19, 20]. Adverse central side effects, generally mild, include memory impairment, emotional lability and dysarthria. TPM has multiple mechanisms of action, including: (1) state-dependent blockade of sodium channels, (2) enhancement of GABAa receptor-mediated inhibition, (3) antagonism of glutamate at α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid/kainite (AMPA/kainite) receptors, (4) inhibition of high-voltage-activated (L-type) calcium channels and (5) weak inhibition of some isozymes of carbonic anhydrase [21].

VPA is widely used for the treatment of partial and generalised seizures [22]. The efficacy of VPA in migraine prevention has been shown in several double-blind, randomised, placebo-controlled studies [23–26]. Its more frequent central side effects are tremor, somnolence, dizziness and headache. VPA increases GABA levels in the brain and potentiates GABA-mediated responses. One possibly important action of VPA is the blockade of the degradation of GABA by GABA transaminase, thereby increasing GABA concentrations in both axon and in glial cells. VPA has been found to block voltage-dependent sodium ion channels, thereby modulating release of excitatory amino acids, and to block low threshold T-type calcium ion channels [22].

Various studies suggest that lamotrigine (LTG) constitutes a specific prophylactic treatment of migraine with aura [27–30]. LTG acts by blocking voltage-sensitive sodium channels, leading to an inhibition of the neural release of glutamate [31, 32]. Therefore, if high glutamate levels were responsible for CSD and the clinical symptoms of migraine aura, LTG might suppress this phenomenon and thus prevent aura development. LTG also attenuates calcium influx via its effect on high-voltage-activated calcium channels and prevents calcium overload in neurons. The effective suppression of aura symptoms of LTG may be due to the potent presynaptic and postsynaptic inhibition of glutamate, indicating that LTG would act as a non-competitive NMDA antagonist [33].

Amitriptyline

Serotonin (5-HT) and norepinephrine (NE) signalling has been part of some models of migraine pathophysiology. Amitriptyline is the prototypical tricyclic antidepressant that has well demonstrated efficacy in pain and in migraine [4, 34]. It has mixed serotoninergic and noradrenergic reuptake inhibitor (SNRI) properties, which enhances activity of diffuse noxious inhibitory control. Amitriptyline has other pharmacological mechanisms. These include: adenosine-A1 agonism, which would enhance descending modulation of rostro-ventromedial nucleus (RVM) neurons; increasing GABA-mediated inhibition by positively modulating GABAa receptor and inhibiting the GABA transporter types 1 and 3 (GAT-1 and GAT-3). Recently, it has been shown that amitriptyline inhibits CSD in rats [10].

Propranolol

Evidence has consistently shown the efficacy of propranolol for the prophylaxis of migraine [35]. Its more frequent central side effects are drowsiness, sleep disorders, depression and memory disturbance. Its mechanism of action is not certain. In the rat brainstem, delayed reduction of the locus coeruleus neuron firing rate has been demonstrated after propanolol administration [36]. The central action of propranolol is probably mediated by inhibition of central β-receptors interfering with the vigilance-enhancing adrenergic pathway, interaction with

5-HT receptors and cross-modulation of the serotoninergic system [37]. Propranolol inhibits CSD in rat by blocking glutamate release [38].

Flunarizine

Flunarizine (FZ) has proven efficacy in the prevention of migraine and is commonly used in countries where it is available. A recent review about the pharmacological treatment of migraine headache in children and adolescents by the American Academic of Neurology found that, from 12 anti-migraine preventive drugs evaluated, FZ is probably the only effective agent, but it is not available in the USA [39]. It has also been reported that FZ could be a useful add-on treatment in therapy-resistant forms of epilepsy [40, 41]. It has been suggested that the FZ effect on the central nervous system is due to a stabilising action on the membrane electrical activity of nerve cells close to firing, the so-called burst neurons. The primary pharmacological mechanism of FZ on burst potentials has been attributed to the blockage of calcium/and or sodium ion channels. Studies showed that the FZ reduces the amplitude of the fast phases of vestibular nystagmus in healthy volunteers and hypothesised that FZ acts on the vestibular nystagmus of normal subjects by "suppression of reticular burst neurons or their connections". Because the appearance of abnormal burst activities has been linked to the pathophysiology of migraine and epilepsy, Casucci et al. suggested that the therapeutical effect of FZ on both conditions may be due to a stabilising action on abnormal burst activities of the brainstem [42].

Pizotifen

There is consistent evidence to support pizotifen's efficacy in migraine prevention. Drowsiness is the most frequent central side effect [43, 44]. Its mechanism of action is not certain. It has potent 5-HT2 activity but the selective 5-HT2 receptor antagonist ketanserin (the principal agent used to identify 5-HT2 receptor-mediated actions) seems to be ineffective in migraine. These agents have additional antagonistic effects at histamine H1, muscarinic cholinergic, α-1-adrenergic, α-2-adrenergic and dopamine receptors, but drugs which are selective for these non-5-HT receptors appear to be of no benefit in migraine. An action of pizotifen on 5-HT2 receptors has also been postulated in migraine [45].

Candesartan

Candesartan is an angiotensin II type-1 inhibitor that has demonstrated efficacy in migraine prophylaxis. The mechanism of action in migraine prevention is poorly understood. It presynaptically inhibits GABA release, which theoretically would enhance excitation. However, the co-localisation of AT1, glutamate and GABA receptors on medullary rostral ventromedial neurons suggests a nociceptive modulatory role [46].

Magnesium (Mg)

The possible mechanism of high-dose oral Mg in migraine prevention remains elusive. Open-label and clinical trials have evaluated the role of high-dose oral Mg (up to 600 mg) in migraine prevention, and the results have been conflicting. Mg has a stabilising role on the sodium potassium pump. Dysfunction of the sodium/potassium pump may have relevance in terms of increased glutamate in the synaptic cleft. Low levels of magnesium may also be responsible for release of NMDA receptors, which may lead to spontaneous discharge and CSD [47, 48].

Acetazolamide

Acetazolamide response has been described in familial hemiplegic migraine with associated ataxia and in migraineurs without cerebellar symptoms [49, 50]. It is interesting that TPM shares with acetazolamide the property of carbonic anhydrase inhibition [51]. Also, it was recently reported to suppress susceptibility to CSD in experimental animals [10].

References

1. Welch KM, D'Andrea G, Tepley N et al (1990) The concept of migraine as a state of central neuronal hyperexcitability. Neurol Clin 8:817–828
2. Van der Kamp W, Maassen VanDenBrink A, Ferrari MD, van Dijk JG (1996) Interictal cortical hyperexcitability in migraine patients demonstrated with transcranial magnetic stimulation. J Neurol Sci 139:106–110
3. Aurora SK, Barrodale P, Chronicle EP, Mulleners WM (2005) Cortical inhibition is reduced in chronic and episodic migraine and demonstrates a spectrum of illness. Headache 45:546–552
4. Ramadan NM, Buchanan TM (2006) New and future migraine therapy. Pharmacol Ther 112:199–212
5. Bolay H, Reuter U, Dunn AK et al (2002) Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 8:136–142
6. Haut SR, Bigal ME, Lipton RB (2006) Chronic disorders with episodic manifestations: focus on epilepsy and migraine. Lancet Neurol 5:148–157
7. Piao ZG, Cho IH, Park CK et al (2006) Activation of glia and microglial p38 MAPK in medullary dorsal horn contributes to tactile hypersensitivity following trigeminal sensory nerve injury. Pain 121:219–231
8. Burstein R, Cutrer MF, Yarnitsky D (2000) The development of cutaneous allodynia during a migraine attack clinical evidence

for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain 123:1703–1709
9. Welch KM, Nagesh V, Aurora SK, Gelman N (2001) Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Headache 41:629–637
10. Ayata C, Jin H, Kudo C et al (2006) Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol 59:652–661
11. Goadsby PJ (1997) How do currently used prophylactic agents work in migraine? Cephalalgia 17:85–92
12. Welch KM (2005) Brain hyperexcitability: the basis for antiepilectic drugs in migraine prevention. Headache 45[Suppl 1]:S25–S32
13. Ramadan NM. (2007) Current trends in migraine prophylaxis. Headache 47[Suppl 1]:S52–S57
14. Glauser TA (1999) Topiramate. Epilepsia 40[Suppl 5]:S71–S80
15. Brandes JL, Saper JR, Diamond M et al; MIGR-002 Study Group (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291:965–973
16. Silberstein SD (2004) Topiramate in migraine prevention: evidence-based medicine from clinical trials. Neurol Sci 25[Suppl 3]:S244–S245
17. Bussone G, Diener HC, Pfeil J, Schwalen S (2005) Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomised controlled trials. Int J Clin Pract 59:961–968
18. Diamond M, Dahlöf C, Papadopoulos G et al (2005) Topiramate improves health-related quality of life when used to prevent migraine. Headache 45:1023–1030
19. Winner P, Gendolla A, Stayer C et al (2006) Topiramate for migraine prevention in adolescents: a pooled analysis of efficacy and safety. Headache 46:1503–1510
20. Lakshmi CV, Singhi P, Malhi P, Ray M (2007) Topiramate in the prophylaxis of pediatric migraine: a double-blind placebo-controlled trial. J Child Neurol 22:829–835
21. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE (2000)An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 41[Suppl 1]:S3–S9
22. Löscher W (1999) Valproate: a reappraisal of its pharmacodynamic properties and mechanism of action. Prog Neurobiol 58:31–59
23. Hering R, Kuritzky A (1992) Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia 12:81–84
24. Jensen R, Brinck T, Olesen J (1994) Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. Neurology 44:647–651
25. Klapper J (1997) Divalproex sodium in migraine prophylaxis: a dose-controlled study. Cephalalgia 17:103–108
26. Freitag FG, Collins SD, Carlson HA et al; Depakote ER Migraine Study Group (2002) A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology 58:1652–1659
27. Steiner TJ, Findley LJ, Yuen AW (1997) Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia 17:109–112
28. D'Andrea G, Granella F, Cadaldini M, Manzoni GC (1997) Effectiveness of lamotrigine in the prophylaxis of migraine with aura: an open pilot study. Cephalalgia 19:64–66
29. Lampl C, Katsarava Z, Diener HC, Limmroth V (2005) Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. J Neurol Neurosurg Psychiatry 76:1730–1732
30. Pascual J, Caminero AB, Mateos V et al (2004) Preventing disturbing migraine aura with lamotrigine: an open study. Headache 44:1024–1028
31. Lang DG, Wang CM, Cooper BR (1993) Lamotrigine, phenytoin and carbamazepine interactions on the sodium current present in N4TG1 mouse neuroblastoma cells. J Pharmacol Exp Ther 266:829–835
32. Stefani A, Spadoni F, Siniscalchi A, Bernardi G (1996) Lamotrigine inhibits Ca2+ currents in cortical neurons: functional implications. Eur J Pharmacol 307:113–116
33. Wang SJ, Tsai JJ, Gean PW (1998) Lamotrigine inhibits depolarization-evoked Ca influx in dissociated amygdale neurons. Synapse 29:355–362
34. Buchanan TM, Ramadan NM. (2006) Prophylactic pharmacotherapy for migraine headaches. Semin Neurol 26:188–198
35. Silberstein SD, Goadsby PJ (2002) Migraine preventative treatment. Cephalalgia 22:491–512
36. Ablad B, Dahlöf C (1986) Migraine and beta-blockade: modulation of sympathetic neurotransmission. Cephalalgia 6[Suppl 5]:7–13
37. Koella WP (1985) CNS-related (side-)effects of beta-blockers with special reference to mechanisms of action. Eur J Clin Pharmacol 28[Suppl]:55–63
38. Ricther F, Mikulik O, Ebersberger A, Schaible HG (2005) Noradrenergic agonists and antagonists influence migration of cortical spreading depression in rat – a possible mechanism of migraine prophylaxis and prevention of postischemic neuronal damage. J Cerebr Blood Flow Metab 25:1225–1235
39. Lewis D, Ashwal S, Hershey A et al American Academy of Neurology Quality Standards Subcommittee; Practice Committee of the Child Neurology Society (2004) Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology 63:2215–2224
40. Overweg J, Binnie CD, Meijer JW et al (1984) Double-blind placebo-controlled trial of flunarizine as add-on therapy in epilepsy. Epilepsia 25:217–222
41. Starreveld E, de Beukelaar F, Wilson AF et al (1989) Double-blind cross-over placebo controlled study of flunarizine in patients with therapy resistant epilepsy. Can J Neurol Sci 16:187–190
42. Casucci G, Di Costanzo A, Riva R et al (1994) Central action of Cinnarizine and Flunarizine: a saccadic eye movement study. Clin Neuropharmacol 5:417–422
43. Bellavance AJ, Meliche JP (1990) A comparative study of naproxen sodium, pizotyline and placebo in migraine prophylaxis. Headache 30:710–715
44. Lawrence ER, Hossain M, Littlestone W (1977) Sandomigran for migraine prophylaxis, controlled multicenter trial in general practice. Headache 17:109–112
45. Mylecharane EJ (1991) 5-HT2 receptor antagonists and migraine therapy. J Neurol 238[Suppl 1]:S45–52
46. Tronvik E, Stovner LJ, Helde G et al (2003) Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA 289:65–69
47. Bigal M, Bordini CA, Tepper SJ, Speciali JG (2002) Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura. A randomized, double-blind, placebo-controlled study. Cephalalgia 22:345–353
48. Ramadan NM, Silberstein SD, Freitag FG et al (2000). Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for the prevention of migraine. Available at http://www.aan.com/professionals/practice/pdfs/gl0090.pdf
49. Battistini S, Stenirri S, Piatti M et al (1999) A new CACNA1A gene mutation in acetazolamide-responsive familial hemiplegic migraine and ataxia. Neurology 53:38–43
50. Athwal BS, Lennox GG (1996) Acetazolamide responsiveness in familial hemiplegic migraine. Ann Neurol 40:820–821
51. Shank RP, Doose DR, Streeter AJ, Bialer M (2005) Plasma and whole blood pharmacokinetics of topiramate: the role of carbonic anhydrase. Epilepsy Res 63:103–112

Neurol Sci (2008) 29:S127–S130
DOI 10.1007/s10072-008-0903-8

Peripheral mechanism of action of antimigraine prophylactic drugs

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Migraine is a visceral pain. According to current theories, activation of trigeminocervical nerve endings releases calcitonin gene-related peptide and substance P, inducing vasodilation and plasma protein extravasation, leading to 'neurogenic' inflammation. Activation of the trigeminovascular system is followed by sensitisation of trigeminocervical fibres, maintaining a condition of hypersensitivity to non-noxious stimuli that support persistent pain during migraine attack. Other neurotransmitters (nitric oxide, bradykinins, 5-HT, etc.) play a role in regulating this complex mechanism. In this brief review, we consider the effect of drugs that, acting on the different transmitters involving in pain perception, can stop or inhibit these pathogenetic mechanisms.

Keywords Migraine · Peripheral action · Prophylactic drugs

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Introduction

Migraine has the characteristics of a visceral pain [1]. The dura mater, together with vessels supplying the meninges, receives a dense sensory and autonomic innervation. Noxious stimulation originating from these structures is referred to the forehead, neck or occipital skin areas because nociceptive fibres coming from the intracranial structures converge on the same pool of second-order sensory neurons within the trigeminal nucleus caudalis or upper cervical dorsal horns together with nociceptive inputs from the above-noted cutaneous areas. Ascending fibres from second-order neurons to thalamus send collaterals to autonomic nuclei in the brainstem and to the hypothalamus, which may account for autonomic symptoms and fatigue, appetite disturbances and malaise frequently observed in migraineurs [1, 2].

According to current theories of migraine, initial activation of meningeal nociceptors releases calcitonin gene-related peptide (CGRP) and substance P from trigeminocervical nerve endings and, hence, induces vasodilation and plasma protein extravasation in dura mater, leading to "neurogenic" inflammation with the participation of resident macrophages and mast cells [3, 4]. Supporting this hypothesis, CGRP levels were found to be increased in jugular vein of patients during migraine attacks [5].

It has been proposed that sensitisation of peripheral sensory nerve endings, later followed by sensitisation of central trigeminocervical neurons, may render the nociceptive fibres sensitive to arterial pulse and head movements, which may account for the throbbing nature of migraine pain and its worsening during coughing, bending over and rapid head movement [6]. Basic and clinical pharmacological observations also share several similarities, suggesting involvement of the trigeminovascular system during migraine. The clinically proven potent antimigraine drugs

dihydroergotamine and sumatriptan are effective in blocking neuropeptide release and neurogenic inflammation induced by electrical stimulation of the trigeminal ganglion in rodents [7]. Inhibition of peptide release within trigeminal nucleus caudalis has also been inferred [8].

Stimulation of the trigeminal ganglion causes CGRP release in the plasma obtained from cerebral venous blood in experimental animals and humans. Another trigger of headache (and migraine) in migraineurs is nitric oxide (NO). NO is a potent endogenous vasodilator with an impressive array of biological actions [9]. NO causes headache and migraine in both control volunteers and headache patients, and will also cause a delayed headache that fulfils the International Headache Society criteria for migraine [10] in sufferers several hours after the NO infusion [11–13].

NO-induced migraine can be prevented or alleviated by certain established antimigraine compounds. In non-migraineurs, NO-induced headache is attenuated by sumatriptan when administered prior to the NO infusion [14]. Sumatriptan also inhibits the regional cerebral blood flow increase that was found in the rat in response to NO donor infusion [15], although changes in cerebral blood flow itself are not seen in humans with NO donor infusion [16]. Migraine occurs in afflicted individuals when sensitised nociceptors begin to barrage the spinal cords with stimuli of increasing intensity (peripheral sensitisation), which then leads to central sensitisation and further amplification of the pain. Peripheral sensitisation is due to neuroinflammation of the dural and meningeal trigeminal nociceptors. NO is considered the key molecule in migraine pathogenesis [17, 18], being involved in the activation of the trigeminovascular system and in the regulation of the cerebrovascular tone [19].

Neuromodulators

Numerous novel anti-epileptic drugs (AEDs) have been developed in recent years, and several have demonstrated efficacy in migraine prophylaxis. Neuromodulators or AEDs may contribute to reduced neuronal hyperexcitability in various areas of the brain but recent studies have shown that the AEDs have a peripheral mechanism in migraine prevention. Topiramate (TPM) is a derivate of the naturally occurring monosaccharide D-fructose. It has antiepileptic activity, and established efficacy as a migraine preventive [20, 21].

It is not known by what mechanism TPM acts as a migraine preventive. Storer and Goadsby showed that TPM inhibits neurons of the trigeminocervical complex after superior sagittal sinus stimulation [22]. Akerman and Goadsby demonstrated that this drug was also able to inhibit NO-induced dural blood vessel dilation [23]. It is thought that NO activates trigeminovascular neurons and causes the release of CGRP from the nerve endings, which contributes to the dural blood vessel dilation, as well as the NO acting directly on the dural blood vessels themselves. NO-induced dural and cerebral vasodilation is inhibited by application of a CGRP receptor blocker [24]. Indeed, it is thought that CGRP and NO behave synergistically in promoting trigeminovascular activation, as NO synthase inhibitors are able to inhibit CGRP-induced dilation [25]. Akerman and Goadsby demonstrated that TPM is able to attenuate the NO response, presumably inhibiting the release of CGRP from trigeminal neurons, but there is still the NO–cGMP interaction that produces dilation of blood vessels. It seems unlikely that TPM is acting directly on the dural blood vessels, as it is unable to inhibit CGRP-induced dilation [23].

Amitriptyline

Amitriptyline is the prototypical tricyclic antidepressant that has well demonstrated efficacy in pain and migraine [26]. It has mixed serotoninergic and noradrenergic reuptake inhibitor (SNRI) properties, which enhance activity of diffuse noxious inhibitory control. Amitriptyline has other pharmacological properties. These include: (1) blockade of Na channels thereby inhibiting peripheral sensitisation; (2) reduction of nociceptive discharges starting from myofascial tissues, explaining the control of chronic pain originating in these structures; and (3) 5-HT2 receptor down-regulation [27].

Flunarizine (FZ)

FZ is largely used in migraine prophylaxis because of its effectiveness in limiting frequency of attacks and pain severity [28, 29].

FZ is tested in migraine on the assumption that vasoconstriction initiates the migrainous process, and preventing it could be achieved by maintaining a cerebral vasodilatatory tone. Its antimigraine efficacy has been attributed to inhibition of hypoxia in cerebral neurons, the contraction of vascular smooth muscles, the blockade of the release of 5HT related to neurovascular inflammation anoxia and its ability to block intracranial vasoconstriction [30]. The antimigraine activity of FZ, primarily linked to relief of cerebral vasospasm, possibly depends on its influence on NO generation through a reduction of neuronal NO-synthase activity and of calcium influx in perivascular cranial nerve terminals [31, 32]. It has been suggested that FZ may act as a migraine prophylactic drug by inhibiting Ca2+-dependent enzymes involved in prostaglandin biosynthesis in the modulation of cerebral and extracerebral vasomotion and, possibly, in blocking the release of 5-HT [33]. Besides, FZ, which crosses the blood–brain barrier and modulates several nerve functions [34], may also prevent neuronal hypoxia and neurovascular inflammation [33, 35]. Therefore, the antimigraine activity of FZ might involve its counteraction of the NO production mechanisms and the underlying vascular phenomena taking place in migraine. Making the assumption that

vasoconstriction initiates the migrainous process, preventing it could be achieved by maintaining a cerebral vasodilatatory tone. It is now clear that calcium channel blockers act on many other mechanisms in the migraine cascade. Verapamil inhibits neuronal NOS, blocks hyperalgesia and potentiates analgesia from opioids and acetaminophen [36]. Furthermore, L-type calcium channels are located on neurons containing CGRP in the neurons that innervate the trigeminal vasculature, and are thought to participate in the release of CGRP [37].

Beta-blockers

Beta-blockers have been employed for migraine prevention since the 1980s [38]. The mechanism of action is not certain, but it appears that their antimigraine effect is due to inhibition of the ?-1-mediated mechanism. Beta-blockers result in inhibition of norepinephrine (NE) release by blocking prejunctional beta receptors. In addition, they result in a delayed reduction in tyrosine hydroxylase activity (the rate-limiting step in NE synthesis) in the superior cervical ganglia. In the rat brainstem, delayed reduction of the locus coeruleus neuron firing rate has been demonstrated after propranolol administration [39]. The use of novel beta-blockers, such as carvedilol, for migraine prevention is a new concept because it offers additional ?-1 blocking and antioxidant properties. ?-1 and ?-1 antagonism reduce blood pressure by reducing peripheral vascular resistance with no alteration of heart frequency or cardiac debit [40, 41].

Botulin toxin (BTX)

BTX is a bacterial neurotoxin approved for the treatment of strabismus, blepharospasm, spasticity, tremor, dystonia and other neuromuscular disorders. In the literature, there are conflicting reports on the efficacy of botulin toxin for migraine prevention [42, 43]. Botulin toxin cause muscle relaxation and paralysis by blocking presynaptic acetylcholine release into the neuromuscular junction. The mechanism of action in migraine is highly speculative. It may act via inhibition of peripheral release of proinflammatory and nociceptive mediators such as substance P, glutamate and CGRP [44].

Angiotensin-converting enzyme (ACE) inhibitors

A single, small (60 patients), positive, randomised control trial indicated that lisinopril is modestly effective and well tolerated in migraine as a preventive therapy.

ACE inhibitors, such as lisinopril, modulate vasoreactivity, alter sympathetic tone and promote degradation of proinflammatory factors such as substance P, enkephaline and bradykinin [45].

Simvastatin

Statins, know as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are effective lipid-lowering agents, and are largely used to reduce the risk of initial and recurrent adverse ischaemic cardiovascular and cerebrovascular events. A recent study reported a reduction not only of the frequency of migraine attacks during the preceding 30-day treatment period compared to the baseline phase, but also decreased migraine frequency within each month during the trial. The pleiotropic effects of statins, including anti-inflammatory properties and regulation of endothelial cell function and vasomotor reactivity, provide a plausible mechanism for a potential therapeutic effect in migraine [46].

Acetylsalicylic acid (ASA)

ASA seems to act peripherally upon cyclooxygenase at the vessel site (especially the endothelium), blocking the painful inflammatory process, which is caused by the release of vasoactive neuropeptides from free C-fibre endings [47]. Recent investigations showed that ASA can reduce *de novo* protein synthesis of NO [48]. Various clinical studies confirm efficacy of ASA in migraine prophylaxis [49].

Conclusion

Migraine pathogenesis is a very complex mechanism that shares central and peripheral activation of pain control pathways. The peripheral mechanism is the final common step that leads to head pain. Many drugs act on this final pathway by regulating and/or blocking CGRP, substance P, %-HT, encephalins, bradykinins, and NO release and action. In this way these drugs can decrease cerebral vascular reactivity and inhibit peripheral sensitisation, reducing migraine attack frequency and severity.

References

1. Moskowitz MA (1991) The visceral organ brain: implications for the pathophysiology of vascular head pain. Neurology 41:182–186
2. Malick A, Burstein R (1998) Cells of origin of the trigeminohypothalamic tract in the rat. J Comp Neurol 400:125–144
3. Moskowitz MA (1984) The neurobiology of vascular head pain. Ann Neurol 16:157–168
4. Markovitz S, Saito K, Moskowitz MA (1987) Neurogenically mediated leakage of plasma protein occurs from blood vessels in dura mater but not brain. J Neurosci 7:4129–4136
5. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during

migraine headache. Ann Neurol 28:183–187
6. Burstein R (2001) Deconstructing migraine headache into peripheral and central sensitization. Pain 89:107–110
7. Buzzi MG, Carter WB, Shimizu T et al (1991) Dihydroergotamine and sumatriptan attenuate levels of CGRP in plasma in rat superior sagittal sinus during electrical stimulation of the trigeminal ganglion. Neuropharmacology 30:1193–1200
8. Levy D, Jakubowski M, Burstein R (2004) Disruption of communication between peripheral and central trigeminovascular neurons mediates the antimigraine action of 5HT 1B/1D receptor agonists. Proc Natl Acad Sci U S A 101:4274–4279
9. Moncada S, Palmer RMJ, Higgs EA (1991) Nitric oxide: physiology, pathophysiology and pharmacology. Pharmacol Rev 43:109–142
10. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8:1–96
11. Iversen HK, Olesen J, Tfelt-Hansen P (1989) Intravenous nitroglycerin as an experimental headache model. Basic characteristics. Pain 38:17–24
12. Olesen J, Iversen HK, Thomsen LL (1993) Nitric oxide supersensitivity: a possible molecular mechanism of migraine pain. Neuroreport 4:1027–1030
13. Olesen J, Thomsen LL, Iversen HK (1994) Nitric oxide is a key molecule in migraine and other vascular headaches. Trends Pharmacol Sci 15:149–153
14. Iversen HK, Olesen J (1996) Headache induced by a nitric oxide donor responds to sumatriptan–a human model for development of migraine drugs. Cephalalgia 16:412–418
15. Read SJ, Manning P, McNeil CJ et al. (1999) Effects of sumatriptan on nitric oxide and superoxide balance during glyceryl trinitrate infusion in the rat. Implications for anti-migraine mechanism. Brain Res 847:1–8
16. Withe RP, Deane C, Hindley C et al (2000) The effect of the nitric oxide donor glyceryl trinitrate on global and regional cerebral blood flow in man. J Neurol Sci 178:23–28
17. Olesen J, Jansen-Olesen I (2000) Nitric oxide mechanisms in migraine. Pathol Biol 48:648–657
18. Olesen J, Thomsen LL, Iversen HK (1994) Nitric oxide is a key molecule in migraine and other vascular headaches. Trends Pharmacol Sci 15:149–153
19. Goadsby PJ, Edvinsson L (1993) The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 33:48–56
20. Brandes JL, Saper JR, Diamond M et al (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291:965–973
21. Diener HC, Tfelt-Hansen P, Dahlof C et al (2004) Topiramate in migraine prophylaxis: results from a placebo controlled trial with propranolol as an active control. J Neurol 251:943–950
22. Storer RJ, Goadsby PJ (2004) Topiramate inhibits trigeminovascular neurons in the cat. Cephalalgia 24:1049–1056
23. Akerman S, Goadsby PJ (2005) Topiramate inhibits trigeminovascular activation: an intravital microscopic study. Br J Pharmacol 146:7–14
24. Wei EP, Moskowitz MA, Boccalini P et al (1992) Calcitonin gene-related peptide mediates nitroglycerin and sodium nitroprusside-induced vasodilatation in feline cerebral arterioles. Circ Res 70:1313–1319
25. Akerman S, Williamson DJ, Kaube H et al (2002) Nitric oxide synthase inhibitors can antagonize neurogenic and calcitonin gene-related peptide induced dilation of dural meningeal vessels. Br J Pharmacol 137:62–68
26. Ramadan NM, Silberstein SD, Freitag FG et al (2000) Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for the prevention of migraine. Available at http://www.aan.com/professionals/practice/pdfs/gl0090.pdf
27. Ramadan NM, Buchanan TM (2006) New and future migraine therapy. Pharmacol Ther 112:199–212
28. Montastruc JL, Senard JM (1992) Calcium channel blockers and prevention of migraine. Pathol Biol 40:381–388
29. Louis P (1981) A double-blind, placebo controlled prophylactic study of flunarizine in migraine. Headache 235–239
30. Peroutka SJ (1990) The pharmacology of current antimigraine drugs. Headache 5–11
31. Ayajiki K, Okamura T, Toda N (1997) Flunarizine an antimigraine agent impairs nitroxidergic nerve function in cerebral arteries. Eur J Pharmacol 329:49–53
32. Geer JJ, Dooley DJ, Adams ME (1993) K(+)-stimulated Ca2+ flux into rat neocortical mini-slices is blocked by omega-Aga-IVA and the dual Na+/Ca2+ channel blockers lidoflazide and flunarizine. Neurosci Lett 158:97–100
33. Silberstein SD, Goadsby PJ (2002) Migraine: preventive treatment. Cephalalgia 22:491–512
34. Leão AA (1944) Spreading depression of activity in cerebral cortex. J Neurophysiol 7:359–390
35. Leão AAP (1944) Pial circulation and spreading depression of activity in the cerebral cortex. J Neurophysiol 7:391–396
36. Omote K, Iwasaki H, Kawamata M et al (1995) Effect of verapamil on spinal anesthesia with local anesthetics. Anesth Analg 80:444–448
37. Akerman S, Williamson DJ, Goadsby PJ (2003) Voltage-dependent calcium channels are involved in neurogenic dural vasodilatation via a presynaptic transmitter release mechanism. Br J Pharmacol 140:558–566
38. Diener HC, Brune K, Gerber WD et al (2000) Therapy of migraine attack and migraine prophylaxis. Nervenheilkunde 19:335–345
39. Ablad B, Dahlöf C (1986) Migraine and beta-blockade: modulation of sympathetic neurotransmission. Cephalalgia 6[Suppl 5]:7–13
40. Cleophus TJ, Zwinderman AH (2001) Beta-blockers and heart failure: meta-analysis of mortality trials. Int J Clin F Ther 39:383–387
41. Kaniecki RG (2003) Migraine prevention with carvedilol: a prospective, open-label trial. Headache 43:589
42. Jankovic J (2004) Botulinum toxin in clinical practice. J Neurol Neurosurg Psychiatry 75:951–957
43. Silberstein S et al (2000) Botulinum toxin type A as a migraine preventive treatment: for the Botox Migraine Clinical Research Group. Headache 40:445–450
44. Durham PL, Cady R, Cady R (2004) Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. Headache 44:35–42
45. Schrader H, Stovner LJ, Helde G et al (2001) Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomized, placebo-controlled, cross-over study. BMJ 322:19–22
46. Medeiros FL, Medeiros PL, Valença MM, Dodick D (2007) Simvastatin for migraine prevention. Headache 47:855–856
47. Buzzi MG, Sakas DE, Moskowitz MA (1989) Indomethacin and acetylsalicyclic acid block neurogenic plasma proteins extravasion in rat dura mater. Eur J Pharmacol 165:251–258
48. Olesen J, Thomsen LL, Iversen H (1994) |Nitric oxide is a key molecule in migraine and other vascular headaches. Trends Pharmacol Sci 15:149–153
49. Diener HC, Hartung E, Chrubasik J et al (2001) A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. Cephalalgia 21:120–128

Neurol Sci (2008) 29:S131–S136
DOI 10.1007/s10072-008-0904-7

Headache therapy with neuronal stabilising drugs

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Abstract Migraine is a frequent episodic condition that often requires prophylaxis treatment to reduce the severity, frequency and duration of attacks and to ameliorate disability. Migraine can be interpreted as a disorder of pain modulation, which involves the trigeminovascular system and central nervous system modulation of pain-controlling structures. Antiepileptic drugs (neuronal stabilising drugs, NSD) have been increasingly recommended for migraine prophylaxis because of several well conducted studies confirming their efficacy. Valproate, Topiramate and Gabapentin are indicated as useful drugs for migraine preventive therapy according to the results of randomised double-blind, placebo-controlled trials. Due to these positive results, neuronal stabilisation may be considered as a pivotal approach for headache therapy.

Keywords Antiepileptic drugs · Headache · Therapy · Prophylaxis

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Introduction

Antiepileptic drugs are widely used to treat a great number of non-epileptic pathologies, both in neurological and psychiatric fields. The FDA has approved several antiepileptic drugs for the treatment of neuropathic pain and mania in adults [1]. In the last decade, antiepileptic drugs have found a specific role among first-choice headache prophylaxis, due to a peculiar activity on cortical hyperexcitability.

The hypothesis that cortical hyperexcitability may play a key role in physiopathology of migraine has led to a great number of large, randomised clinical trials to evaluate the efficacy and safety of antiepileptic (neuronal stabilising drugs, NSD) drugs in headache prevention. Actually migraine can be defined as an aberrant physiological state with low threshold for intermittent neuronal excitability [2].

The goals of prophylaxis therapies are to optimise quality of life, decreasing the frequency, severity and duration of attacks and to improve the responsiveness to acute therapy.

Patients with migraine considered for preventive treatment have to show recurrent and frequent headaches interfering with one's daily life (more than three/month), failure or overuse of acute therapy, or concern for conversion to chronic daily headache. Up to now, prophylaxis has not been prescribed to the extent that it should be, considering that only 5% of patients are using preventive drugs to reduce the impact of the disease [3].

Although NSDs are generally able to target the glutamate-mediated and/or the gamma-aminobutyric acid (GABA)-mediated systems in conjunction with a modulation of voltage-gated sodium and calcium channels, decreasing glutamate levels and enhancing GABA activity [4], it is not clear why so few of them have a good efficacy in migraine prophylaxis.

Recent reports have suggested a role of NSD in cluster headache and chronic headache prophylaxis, although controlled studies on larger samples are recommended [5].

The role of neuronal stabilising drugs in headache prophylaxis

Cortical hyperexcitability is due to an imbalance between neuronal excitement, mainly mediated by excitatory aminoacids, and neuronal inhibition mediated by GABA. When glutamate binds to non-NMDA receptors, this causes an influx of sodium ions and an excitatory effect, with displacement of magnesium and influx of calcium and sodium and depolarisation of the postsynaptic membrane. Furthermore, GABA binding causes an influx of chloride ions and efflux of potassium ions, resulting in hyperpolarisation and inhibition of postsynaptic neurons. It can be argued that this imbalance may be selectively expressed in local brain areas specifically involved in pathophysiology of migraine, i.e., cortical regions or brainstem structures. Other processes postulated as pathogenetic steps in migraine are central sensitisation (due to abnormal plastic change inducing a lower threshold for subsequent attacks) and cortical spreading depression (neuroglial depolarisation wave).

NSD may act both by suppression of neuronal hyperexcitability and by modification of the abnormal activities of voltage-dependent ion channels. They inhibit repeated firing (kindling) of pain-processing structures and modulate excitatory pathways mediated by glutamate receptors (Table 1).

Valproic acid was the first NSD studied in migraine prophylaxis, both in open-label and double-blind, randomised, cross-over studies [6, 7] showing efficacy. So far, many other drugs of this class have been increasingly used in prophylaxis of migraine and other headaches as potential new therapies. The doses of NSD for migraine prophylaxis are generally much lower than those suggested for epilepsy.

Sodium valproate (SV)/divalproex (DV)

Significant responder rates (the percentage of patients experiencing 50% or more reduction in attack frequency) derived from published, large, controlled, randomised, double-blind trials with sodium valproate (SV) or divalproex (DV) in migraine prophylaxis (12 weeks of treatment) ranged from 50 to 44% (18–21% with placebo) [8–10]. Only in one study with DV [11] was the responder rate (30%) not significantly greater than that reported in the placebo group (24%). Daily dose ranged from 500 to 1500 mg/day. In long-term treatment (up to 6 years as single or add-on therapy) of patients with chronic headaches, DV was able to reduce (in a retrospective study) the headache frequency by at least 50% in about 2/3 of treated patients [12]. In one multicentre (one week run-in period, 2 weeks treatment, 95 patients enrolled, 50 in active group), double-blind, controlled, parallel-group trial, SV (1000–2000 mg/day) was not able to reduce the attack frequency in cluster headache if compared with placebo (responders rate 62% in placebo group *vs*. 50% in SV group, p=0.23) [13].

Gastrointestinal disturbances (nausea and dyspepsia, with lower incidence after 3 and 6 months of treatment), hair loss, changes in cognitive performances, tremor, weight gain and fatigue are the most common adverse reported event. Ovarian dysfunction, hyperandrogenism and increase of liver enzymes are occasionally described. Discontinuation rates caused by drug intolerance were 8%–13% in controlled trials.

Divalproex sodium has been approved by the US Food and Drug Administration for the prophylaxis of headache in adults.

Table 1 NSD specific activity

NSD	Na chan. block	Ca chan. block	Glu recept. antag.	GABA enhance.	Carb Anhid. inhib.
Levetiracetam		X			
Gabapentin		X		X	
Lamotrigine	X	X			
Topiramate	X	X	X	X	X
Valproate	X	X		X	

Table 2 Prophylaxis: what must be considered for treatment?

Recurring and disabling migraine that interferes with daily routine despite adequate acute therapy (failure or side effects from acute medications)
Frequent headaches (more than three/month)
Specific contraindications to acute therapy
Patient preference
Uncommon and special migraines (hemiplegic migraine, basilar migraine)

Topiramate (TPM)

Topiramate (TPM) was introduced as an anticonvulsant in 1996. The first large, positive, randomised, multicentric, placebo-controlled, double-blind trials with TPM in migraine were published in 2004: 100 mg/day was evaluated as the adequate treatment dose, considering the balance between tolerability and efficacy [14, 15]. Reduction in migraine frequency was significantly greater in the TPM arms (100 and 200 mg/day) if compared with placebo arms. Responder rates were 54% and 49% respectively (23% placebo, $p<0.001$). Pooled data results [16] demonstrated both a significant decrease in mean monthly migraine period ($p<0.001$ vs. placebo) and a higher responder rate ($p<0.001$ vs. placebo).

The 8-month open-label extension study showed a sustained reduction in migraine frequency [17].

TPM (100 or 200 mg/day) was compared to propanolol (160 mg) in a randomised, double-blind, multicentre trial: improvement rates were similar in both groups (37% with TPM, 43% with propanolol, difference significant *vs*. placebo) [18].

In a single-centre, randomised, double-blind, placebo-controlled, phase 4 cross-over trial, low-dose TPM (50 mg) was efficacious in migraine prophylaxis as compared to both placebo (responders rate 63% vs. 30% placebo) and lamotrigine 50 mg (63% vs. 46%) in terms of headache intensity, duration and frequency. The small number of recruited patients (n=60) and short duration of follow-up (one month) were limitations of this study [19].

More recent studies showed that TPM (target dose 100 mg within a range of 50–200 mg/day) is able to reduce headache days in chronic migraine (defined as >15 monthly migraine days): in a randomised, double-blind, placebo-controlled trial TPM significantly reduced the mean number of monthly migraine days if compared with placebo ($p<0.05$), even in the presence of medication overuse [20]. Another study in 559 patients (dose adjusted in the range of 50–200 mg/day, stable for the final 4 weeks) showed that discontinuation of TPM treatment in a double-blind, placebo-controlled study after 6 months of therapy is associated with persistent benefits (26-week phase) in terms of migraine days and quality of life if compared with placebo group [21].

Pooled data from 3 trials in patients with episodic migraine (756 total number) showed that treatment with TPM (100 mg) may reduce the risk of developing chronic forms of headache, with particular efficacy in potentially higher risk patients (greater headache frequency) if compared to the placebo group [22].

Efficacy and safety of TPM was evaluated in a double-blind, parallel-group, dose comparison pilot study in basilar-type migraine in children (14 patients, 6–18 years). Preventive therapy was able to reduce the overall migraine frequency and the specific frequency of basilar-migraine attacks at both 25 and 100 mg doses [23].

Regarding cluster headache, TPM was evaluated in 80 patients (55 episodic and 35 chronic, daily doses ranging from 25 to 200 mg) included in five different open-label studies. In three reports positive results were obtained, whereas in two studies no significant change in mean headache frequency before and after treatment was found [24–28].

A single case report showed efficacy of low-dose TPM in hypnic headache [29].

The cost-effectiveness of TPM depends on utility gains associated with a reduced frequency of migraine attacks: economic savings in cost of acute treatment and work loss offsets 68% of the expected monthly costs of TPM in a pharmacoeconomic model [30].

TPM 100 mg is able to significantly improve daily activities and patient functioning (outcome measures: Migraine Specific Questionnaire and SF-36) in a pooled analysis of three pivotal large randomised, double-blind, placebo-controlled migraine trials [31].

TPM is not licensed for the prophylaxis of headache in children and adolescents. A recent post-hoc analysis of three previously conducted randomised, double-blind, placebo-controlled trials using data collected from the 51 enrolled patients [32] demonstrated a reduction both in monthly migraine frequency and monthly mean number of migraine days, although this was not statistically significant.

Specific treatment-emergent adverse events with TPM 100 mg/day include: paraesthesia (usually transient and self-limiting) in 50.5%, mild to moderate in severity and leading to withdrawal from the trials in 8%, fatigue in 15% leading to withdrawal in 4.7%, anorexia in 14.5%, leading to withdrawal in 4.7%, nausea in 13.2%, leading to withdrawal in 2.3%, weight loss in 9.1%, leading to withdrawal in 2.1%, taste perversion (due to carbonic anhydrase properties causing carbonate drinks to taste different) in 7.8%, leading to withdrawal in 1%, difficulty with memory (dose-related) in 6.7%, leading to withdrawal in 2.6%, language problems such as word-finding difficulties (dose-dependent, generally resolved over time, often after adjustment of dosage) in 6.5%, leading to withdrawal in 1.6%, difficulty with concentration and attention in 6%, leading to withdrawal in 2.1%, and mood disturbances in 6%, leading to withdrawal in 1.3%. A low incidence of kidney stones occurrence (0.8%) is reported: it is important to emphasise the importance of abundant hydration during therapy. Individuals with a positive history of renal stones should not be treated with TPM. Serum bicarbonate may be monitored to evaluate the rare development of metabolic acidosis. Acute myopia and angle closure glaucoma are rarely reported as idiosyncratic reversible reactions. Prompt discontinuation of TPM and ophthalmologic evaluation are suggested. Contraceptive advice is important, as the effect on foetal outcome is currently

unknown. TPM is an enzyme inducer: it accelerates metabolism of oestrogens and progesterones, lowering contraceptive efficacy [16].

In a recent study [33], patients using TPM over a 12-month period were less likely to utilise triptans (both if high or low triptan users) with a 7.5% reduction at 6 months and 19.6% at 12 months and less likely to visit both the emergency room for severe attacks (46% at 6 and 12 months) and to be admitted to hospital (33% at 6 months and 61% at 12 months).

TPM is licensed for prophylaxis of migraine.

Lamotrigine (LTG)

Lamotrigine (LTG) was introduced in 1995 as a broad-spectrum anticonvulsant. Despite the fact that the result of the first trial in migraine prevention (3 months, randomised, placebo-controlled, double-blind parallel group in 74 patients, active group on 200 mg/day) was negative [34], some open-label studies have demonstrated that LTG may be effective in patients affected by migraine with aura. In two small studies [35, 36] the frequency of migraine with aura attacks was significantly reduced by 100 mg/day of LTG, particularly in patients with high frequencies. After cessation of therapy an increase in aura frequency was noticed during a 3-month observation period [36]. A 3-year prospective, open study in 59 patients affected by migraine with aura demonstrated a significant reduction both in mean frequency of aura ($p<0.001$ with a 75% rate of responders) and in frequency of migraine attacks ($p<0.001$).

LTG was effective in the treatment of four cases with SUNCT syndrome [37, 38].

An allergic skin reaction (a simple morbilliform rash) can occur in 10% of patients, usually in the first two months of therapy. The incidence of reported Stevens-Johnson syndrome in clinical trials for diseases other than headache is 1 in 1000, with an increasing incidence when LTG is used as an add-on therapy with VPA (0.3%). LTG should be stopped in patients who develop a rash during treatment, but this side effect can be reduced if the drug is started at very low dosage and slowly increased every week. Other reported side effects were insomnia (more common), nausea, constipation, ataxia and diplopia.

Gabapentin (GBP)

GBP showed Level I evidence (based on at least one well conducted randomised controlled trial) of efficacy in migraine prevention. GBP was particularly studied in two controlled trials [39, 40]. In the first study (single-centre trial on 63 patients) a significant reduction of frequency and intensity of migraine was achieved in 47.6% of patients at 1200 mg/day (no patients withdrew from the trial), whereas in the second study (multicentre, 4-week, single-blind, placebo baseline period followed by a 12-week double-blind treatment period in 143 patients, 98 in active group) responder rate at 2400 mg/day titrated from 300 mg/day (at least 50% reduction in monthly migraine rate) was 46.4% in the GBP group vs. 16.1% in the placebo group. A statistically significant decrease in the average number of migraine monthly days was observed in the active group. The most common adverse events (somnolence in 24.5% of patients and dizziness) were causes for withdrawal (13.3%) in this trial. 3.1% of patients reported an increase in body weight.

In a multicentre, randomised, placebo-controlled, cross-over study [41], GBP at 2400 mg/day showed a significant efficacy both in headache day-free rates ($p=0.0005$, 9.1% difference) and in quality of life in chronic headache patients if compared with placebo (95 patients out of 133 enrolled completed the study). Analgesics overuse was not considered in the results.

An open-label pilot study in a small group of refractory (drug-resistant) cluster headache patients showed remission in all patients with a GBP daily dose of 900 mg after a few days of therapy, with a persistent free period (4 months follow-up) after discontinuation of GBP [42].

Levetiracetam (LTC)

Levetiracetam (LTC) has been evaluated in some open-label trials. In the first study [43] a reduction in migraine frequency and severity was reported (>50%) in 14 out of 30 patients affected by refractory headaches and treated with doses up to 1000 mg twice a day for 3 months. A second study [44] in 50 patients affected by migraine and 12 suffering from chronic daily headache showed encouraging results (at 500–1500 mg/daily). Ten patients discontinued LTC because of adverse events (nausea and drowsiness). In a prospective study (open-label, 36 patients, maximum dose 3000 mg) LTC demonstrated efficacy in transformed migraine with a significant reduction in mean headache frequency per month after one month of therapy, confirmed at two and three months ($p<0.001$) [45]. LTC has been evaluated in paediatric migraine, particularly in an open-label prospective study in 20 patients (mean age 10.65 years, mean duration of migraine headache diagnosis 3.15 years). Dosage was 40 mg/kg/day twice daily after an initial period (one month) at half dose. Results showed a decrease in migraine frequency in 18 out of 20 patients (>50% reduction in monthly headache frequency) and PedMIDAS (a validated questionnaire for disability assessment in paediatric headache) showed significant decrease in disability scores. LTC was generally well tolerated and no patients discontinued drug use due to adverse events. Irritability, aggressiveness and mild memory problems were reported in 3 patients [46].

Conclusions

The specific goals of migraine prophylaxis are to reduce frequency, severity and duration of headache attacks, improve responsiveness to acute treatment, reduce patients' disability and finally reduce the costs of health care (Table 2). The results of clinical trials support the use of NSD for the prophylaxis of migraine, particularly for SV/DV, TPM and GBP. These drugs have shown efficacy in double-blind, controlled trials and have demonstrated a good tolerability and long-term efficacy. For other NSD there is insufficient evidence of efficacy in treating migraine. The choice of a particular NSD should take into account the safety, tolerability and spectrum of efficacy of a particular drug, considering the characteristics of individual patients such as comorbid conditions and concomitant drug interactions.

Homogeneous schemes have to be adopted in order to permit comparisons and to confirm the correct efficacy of therapeutic approach. A general approach with NSD is suggested: start slow and go slow, give an adequate trial of at least six weeks at a correct dosage and consider that a complete therapeutic effect can take as long as 12 weeks to achieve; if a significant improvement is obtained (reduction in migraine frequency of 50% or more), medication should be tapered after 6 months. Dosage should be tailored to individual patient needs and realistic expectations should be set by discussing the treatment benefits in terms of reasonable headache frequency reduction. It is also important to discuss the importance of adherence.

The future of the treatment of migraine may lie in the direction of modulating neuronal excitability to achieve a better neuronal stabilisation. Future targeted clinical trials dealing with the efficacy and tolerability of NSD in migraine prophylaxis, particularly in specific subgroups of patients (chronic headache forms, paediatric migraine, cluster headache) are strongly suggested to confirm the activity of NSD both on patients' overall functional capacity and health perception.

References

1. Colombo B, Annovazzi PO, Comi G. (2006) Medications for neuropathic pain: current trends. Neurol Sci 27[Suppl 2]:S183–S189
2. Welch KM (2003) Contemporary concepts of migraine pathogenesis. Neurology 61[Suppl]:S2–S8
3. Silberstein SD (2006) Preventive treatment of migraine. Trends Pharmacol Sci 27:410–415
4. Pietrobon D (2005) Migraine: new molecular mechanisms. Neuroscientist 11:373–386
5. D'Amico D (2007) Antiepileptic drugs in the prophylaxis of migraine, chronic headache forms and cluster headache: a review of their efficacy and tolerability. Neurol Sci 28[Suppl 2]:S188–S197
6. Sorensen KV (1988) Valproate: a new drug in migraine prophylaxis. Acta Neurol Scand 78:346–348
7. Hering R, Kuritzky A (1992) Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia 12:81–84
8. Jensen R, Brinck T, Olesen J (1994) Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. Neurology 44:647–651
9. Mathew NT, Saper JR, Silberstein SD et al (1995) Migraine prophylaxis with divalproex. Arch Neurol 52:281–286
10. Klapper J (1997) Divalproex sodium in migraine prophylaxis: a dose-controlled study. Cephalalgia 17:103–108
11. Freitag FG, Collins SD, Carlson HA et al (2002) A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology 58:1652–1659
12. Freitag FG, Diamond S, Diamond ML, Urban GJ (2001) Divalproex in the long-term treatment of chronic daily headache. Headache 41:271–278
13. El Amrani M, Massiou H, Bousser MG (2002) A negative trial of sodium valproate in cluster headache: methodological issues. Cephalalgia 22:205–208
14. Silberstein SD, Neto W, Schmitt J, Jacobs D (2004) Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol 61:490–495
15. Brandes JL, Saper JR, Diamond M et al (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291:965–973
16. Bussone G, Diener HC, Pfeil J, Schwalen S (2005) Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomised controlled trials. Int J Clin Pract 59:961–968
17. Rapoport A, Mauskop A, Diener HC et al (2006) Long-term migraine prevention with topiramate: open-label extension of pivotal trials. Headache 46:1151–1160
18. Diener HC, Tfelt-Hansen P, Dahlof C et al (2004) Topiramate in migraine prophylaxis – results from a placebo-controlled trial with propranolol as an active control. J Neurol 251:943–950
19. Gupta P, Singh S, Goyal V et al (2007). Low-dose topiramate versus lamotrigine in migraine prophylaxis (the Lotolamp study). Headache 47:402–412
20. Diener HC, Bussone G, Van Oene JC et al (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia 27:814–823
21. Diener HC, Agosti R, Allais G et al (2007) Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. Lancet Neurol 6:1054–1062
22. Limmroth V, Biondi D, Pfeil J, Schwalen S (2007) Topiramate in patients with episodic migraine: reducing the risk for chronic forms of headache. Headache 47:13–21
23. Lewis D, Paradiso E (2007) A double-blind, dose comparison study of topiramate for prophylaxis of basilar-type migraine in children: a pilot study. Headache 47:1409–1417
24. Mathew NT, Kailasam J, Meadors L (2002) Prophylaxis of migraine, transformed migraine, and cluster headache with topiramate. Headache 42:796–803
25. Wheeler SD, Carrazana EJ (1999) Topiramate-treated cluster headache. Neurology 53:234–236
26. Forderreuther S, Mayer M, Straube A (2002) Treatment of cluster headache with topiramate: effects and side-effects in five patients. Cephalalgia 22:186–189
27. Lainez MJ, Pascual J, Pascual AM et al (2003) Topiramate in the prophylactic treatment of cluster headache. Headache 43:784–789
28. Leone M, Dodick D, Rigamonti A et al (2003) Topiramate in cluster headache prophylaxis: an open trial. Cephalalgia 23:1001–1002

29. Autunno M, Messina C, Blandino A, Rodolico C (2008) Hypnic headache responsive to low-dose topiramate: a case report. Headache 48:292–294
30. Brown JS, Papadopoulos G, Neumann PJ et al (2005) Cost-effectiveness of topiramate in migraine prevention: results from a pharmacoeconomic model of topiramate treatment. Headache 45:1012–1022
31. Dahlof C, Loder E, Diamond M et al (2007) The impact of migraine prevention on daily activities: a longitudinal and responder analysis from three topiramate placebo-controlled clinical trials. Health Qual Life Outcomes 5:56
32. Winner P, Gendolla A, Stayer C et al (2006) Topiramate for migraine prevention in adolescents: a pooled analysis of efficacy and safety. Headache 46:1503–1510
33. Silberstein SD, Feliu AL, Rupnow MF et al (2007) Topiramate in migraine prophylaxis: long-term impact on resource utilization and cost. Headache 47:500–510
34. Steiner TJ, Findley LJ, Yuen AW (1997) Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia 17:109–112
35. D'Andrea G, Granella F, Cadaldini M, Manzoni GC (1999) Effectiveness of lamotrigine in the prophylaxis of migraine with aura: an open pilot study. Cephalalgia 19:64–66
36. Lampl C, Buzath A, Klinger D, Neumann K (1999) Lamotrigine in the prophylactic treatment of migraine aura – a pilot study. Cephalalgia 19:58–63
37. D'Andrea G, Bussone G, Granella F et al (2000) Treatment of SUNCT syndrome with lamotrigine. Cephalalgia 20:377–384
38. D'Andrea G, Granella F, Cadaldini M (1999) Possible usefulness of lamotrigine in the treatment of SUNCT syndrome. Neurology 53:1609–1639
39. Di Trapani G, Mei D, Marra C et al (2000) Gabapentin in the prophylaxis of migraine: a double-blind randomized placebo-controlled study. Clin Ter 151:145–148
40. Mathew NT, Rapoport A, Saper J et al (2001) Efficacy of gabapentin in migraine prophylaxis. Headache 41:119–128
41. Spira PJ, Beran RG (2003) Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. Neurology 61:1753–1759
42. Leandri M, Luzzani M, Cruccu G, Gottlieb A (2001) Drug-resistant cluster headache responding to gabapentin: a pilot study. Cephalalgia 21:744–746
43. Krusz JC (2001) Levetiracetam as prophylaxis for resistant headaches. Cephalalgia 21:373
44. Drake, ME, Greathouse NI, Armentbright AD, Renner JB (2001) Levetiracetam for preventive treatment of migraine. Cephalalgia 21:373
45. Rapoport AM, Sheftell FD, Tepper SJ, Bigal ME (2005) Levetiracetam in the preventive treatment of transformed migraine. Curr Ther Res 66:212–222
46. Pakalnis A, Kring D, Meier L (2007) Levetiracetam prophylaxis in pediatric migraine- an open-label study. Headache 47:427–430

Neurol Sci (2008) 29:S137–S139
DOI 10.1007/s10072-008-0905-6

Treating headaches with botulinum toxin

Marco Aguggia

Abstract Botulinum toxin type A (BT-a) has been shown to effectively treat several types of neurological disorders. For over 15 years it has been used clinically also for the prophylaxis and treatment of various types of primary headache disorders. Although BT-a efficacy has not been proven in tension-type headache, its use in migraine continues to cause controversy. There is adequate data to support the hypothesis, beside its well known effect on acetylcholine release, of an additional antinociceptive effect related to a block in the local release of nociceptive neuropeptides.

Keywords Botulinum toxin type A · Headache · Pain · Prophylaxis

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Introduction

Recent studies demonstrating the effectiveness of botulinum toxin type A (BT-a) in treating several disorders related to muscle spasticity and pain suggest a potential role for this agent in headache treatment [1]. The efficacy of BT-a in headache patients was first noted by William Binder, an otolaryngologist, who noted that patients with migraine headaches recovered from their attacks following BT-a injections for the treatment of facial wrinkles [2]. Exactly why BT-a is effective in relieving headache is not clear, but mechanisms of actions include direct effects at the neuromuscular junction and direct antinociceptive effects on nerves in the face, head and neck [3].

BT-a and mechanisms of action

The ability of BT-a to cause muscle paralysis by blocking acetylcholine release at the neuromuscular junction is well known. The toxin produces this effect by proceeding through a sequence of four steps: (a) binding to receptors on the plasma membrane, (b) penetration of plasma membrane by receptor-mediated endocytosis, (c) penetration of the endosome membrane by pH-induced translocation and (d) intracellular expression of an enzymatic action that culminates in blockade of exocytosis [4]. BT-a not only reduces acetylcholine release from the alpha motor neuron endings, but also decreases the activity of the muscle spindles by inhibiting the signals from gamma motor neurons and subsequently reduces the Ia afferent signals [5]. In addition, an inhibitory effect on the central pain pathways such as trigeminal ganglion or trigeminal cervical complex in the brainstem have been implicated because suppression of the release of substance P from the dorsal root ganglion [6] or calcitonin gene-related peptide (CGRP) from the

trigeminal ganglion [7] has been shown in animal studies. Focussed on an evidence-based method, most of the initial open-labelled reports on BT-a in tension-type headache and migraine were positive. Most recently, these results were, unfortunately, not reproduced as well in controlled trials, suggesting that widespread clinical use of BT-a in headache is not recommended [8].

Methodology

Selection of appropriate candidates for preventive therapy begins with accurate headache diagnosis and classification. According to these rules, BT-a therapy may be appropriate for: patients with disabling primary headaches, patients who have failed to respond adequately to conventional treatments, patients with unacceptable side effects (from existing treatments), patients in whom standard preventive treatments are contraindicated, patients in special populations or situations, patients misusing, abusing or overusing medications, patients with coexisting jaw, head or neck muscle spasm and patients who prefer this treatment [9]. There is no established or standardised methodology for the injection of BT-a for migraine and tension-type headache. BT-a is administered either at fixed injection sites, at sites of pain or tenderness ("follow the pain") or a combination of both [10]. The clinical dose of BT-a commonly used for migraine therapy is between 25–200 units (Botox) and 100–500 units (Dysport); the number of injected sites may vary from 10 to 25. However, the total dosage of toxin administered, the number of units per site of injection, dilution of toxin and sites of injection varied widely between studies. Current data do not appear to indicate a dose response benefit [11, 12]. Therefore, there is a need for further studies in order to identify the minimal effective dosage and optimal individualised dosing regimen. On the other hand, some data report a greater efficacy with repeated dosing [13]. This may be because repeat injections have a step-like therapeutic effect: the consecutive therapeutic effect of each injection builds on the effect previously achieved [14].

Conclusions

Focussed on an evidence-based method, most of the initial open-labelled reports on BT-a in tension-type headache and in migraine were positive. Most recently, these results were, unfortunately, not reproduced as well in controlled trials [15].

The efficacy and safety profile of BT-a suggest that it is an effective, well tolerated prophylactic treatment in migraine patients with chronic daily headache who are not using other prophylactic headache treatments. The data also suggest that assessment of the frequency of headache is a sensitive measure of efficacy in this patient population and that future studies to confirm these findings are needed. The optimal dosing and injection regimens are not yet known. The dosage ranges usually administrated are effective and adverse side effects, which are often mild to moderate, are transient; however they appear to be dose-dependent. A combination of fixed anterior injections with a follow-the-pain approach appears to be optimal, but further studies are necessary to determine the most effective injection regimens. Another aspect is the frequency of treatment, which seems to have a cumulative effect with subsequent injections [15].

The data at this time do not support the efficacy of BT-a for the treatment of episodic migraine or tension-type headache. Two large studies with a total of 1.057 patients investigated the efficacy of BT-a in the treatment of chronic daily headache, but it seems likely that most, if not all, patients enrolled actually had chronic migraine according to the latest iteration of the International Headache Society criteria [16]. In both studies, BT-a failed to increase the frequency of headache-free days (primary endpoint) [17, 18]. Subgroup analysis suggested that headache frequency was reduced in patients who were not taking other preventive medications [19]. Two phase III studies of BT-a in chronic migraine are ongoing and the results are awaited with considerable interest.

Further evidence is needed to determine whether this agent can serve as a first-line therapy for patients with less refractory headaches, and to determine optimal injection sites, doses and frequency of treatment.

References

1. Collins A, Jankovic J (2006) Botulinum toxin injection for congenital muscular torticollis presenting in children and adults. Neurology 76:1083–1085
2. Ewans RW, Blumenfeld A (2003) Botulinum toxin injections for headache. Headache 43:682–685
3. Mathew NT, Kaup AO (2002) The use of botulinum toxin type A in headache treatment. Curr Treat Options Neurol 4:365–373
4. Simpson LL (1981) The origin, structure and pharmacological activity of botulinum toxin. Pharmacol Rev 33:155–188
5. Aoki KR (2001) Pharmacology and immunology of botulinum toxin serotypes. J Neurol 248[Suppl 1]:3–10
6. Purkiss J, Welch MKA, Doward S, Foster K (2000) Capsaicin-stimulated release of substance P from cultured dorsal root ganglion neurons: involvement of two distinct mechanisms. Biochem Pharmacol 59:1403–1406
7. Durham PL, Cady R, Cady R (2004) Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. Headache 44:35–43
8. Schulte-Mattler WJ, Martinez-Castrillo JC (2006) Botulinum toxin therapy of migraine and tension-type headache. Eur J Neurol 13[Suppl 1]:51–54
9. Blumenfeld AM (2003) Botulinum toxin type A as an effective prophylactic treatment in primary headache disorders. Headache 43:853–860

10. Saper JR, Mathew NT, Loder EW et al (2007) A double-blind, randomized, placebo-controlled comparison of botulinum toxin type A injection sites and doses in the prevention of episodic migraine. Pain Med 8:478–485
11. Tepper S, Bigal M, Sheftell F, Rapoport A (2004) Botulinum neurotoxin type A in the preventive treatment of refractory headache. Headache 44:749–800
12. Mathew N, Frishberg BM, Gawel et al (2005) Botulinum toxin type A for the prophylactic treatment of chronic daily headache. Headache 45:293–307
13. Ondo WG, Voung KD, Derman HS (2004) Botulinum toxin A for chronic daily headache. Cephalalgia 24:60–65
14. Schulte-Mattler WJ, Krack P (2004) Treatment of chronic tension-type headache with botulinum toxin A. Pain 109:110–114
15. Goadsby P (2007) Emerging therapies for migraine. Nat Clin Pract Neurol 3:610–619
16. Olesen J, Bousser M-G, Diener H-C et al (2006) New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26:742–746
17. Silberstein SD, Stark SR, Lucas SM et al (2005) Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 80:1126–1137
18. Mathew NT, Frishberg BM, Gawel M et al (2005) Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache 45:293–307
19. Dodick DW, Mauskop A, Elkind AH et al (2005) Botulinum toxin type A for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. Headache 45:315–324

Neurol Sci (2008) 29:S141–S143
DOI 10.1007/s10072-008-0906-5

ORAL COMMUNICATION

A functional MRI study of language disturbances in subjects with migraine headache during treatment with topiramate

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Abstract Topiramate (TPM) is a new antiepileptic drug approved for the prevention of migraine headache. However its use is limited by treatment-emergent adverse events; in particular, therapy can exert profound impact on language function. In this investigation, we used functional magnetic resonance imaging (fMRI) to study the anatomofunctional correlates of language disturbances in TPM patients experiencing subjective cognitive impairment. Ten right-handed individuals receiving therapy (five with and five without language disfluency) and five matched healthy control subjects took part in this study. During fMRI subjects alternately rested and performed a word-generating task. The task comprised the silent generation of words beginning with a different input letter visually presented. The activation paradigm consisted of six activation blocks alternating with six baseline rest blocks. The main fMRI measure was the pattern activation of the prefrontal regions (Brodmann's areas 44, 45, and 46) in both left and right hemispheres. Patients receiving TPM (50–100 mg/day) significantly reduced mean monthly migraine frequency. However several differences in fMRI activation were evident in the subject group comparison. Notably, changes in brain activity were observed during the phonemic task in patients with language disturbances. It is likely that TPM therapy is associated with a "remapping" of the language cerebral network.

Keywords Migraine · Topiramate · Language · Verbal fluency · Functional magnetic resonance imaging

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Introduction

Preventive medications can serve an important role in the treatment of migraine by reducing migraine frequency, severity and disability [1, 2], however the emergence of adverse events is a major issue in the pharmacological treatment. A number of studies suggested that patients treated with topiramate (TPM) show cognitive impairment and, in particular, neuropsychological examination documented a significant negative effect on verbal fluency [3]. So, it has been hypothesised that TPM may affect brain regions related to speech. A means to validate this hypothesis is now available using functional magnetic resonance imaging (fMRI). This technique has enabled the investigation of the neural bases of language in the normal human brain. Therefore the amount of information coming from this approach offers the opportunity to elucidate the mechanisms underlying pharmacologically induced language impairment. Using this paradigm we sought to test the hypothesis that TPM-emergent verbal disfluency is associated with alterations of fMRI activation in language-related brain regions. In this brief paper, we report preliminary data regarding only frontal areas of the language cerebral network.

Methods

Subjects

Ten right-handed patients receiving TPM as monotherapy and five matched healthy control subjects took part in this study. Patients were required to have an established history of migraine with or without aura, as assessed by International Headache Society criteria. All patients were selected during their visits to the outpatient neuroscience department: they started TPM at a dose of 25 mg/day; the daily dose was increased by 25 mg weekly until it reached either the assigned dose of 100 mg/day or the maximum tolerated dose, whichever was less. The frequency, severity and symptoms of all headaches or auras were recorded in a diary including a baseline phase of at least 30 days. All patients underwent neuropsychological testing including language assessment. Five of them experiencing cognitive dysfunction (group A) were included in the fMRI study together with another five patients without cognitive complaint (group B) and five healthy subjects (group C). The three groups did not differ with respect to demographic characteristics (group A: 1M/4F, age mean 37.4, range 26–52 years, education mean 14.6, range 13–18 years; group B: 5F, age mean 41.4, range 21–49 years, education mean 14.4, range 13–18 years; group C: 1M/4F, age mean 31.2, range 25–48 years, education mean 17.6, range 13–19 years). Handedness was assessed by the Edinburgh Inventory. FMRI was performed at least six months after TPM therapy.

Image acquisition parameter

The functional studies were performed on a 1.5-T Philips using a whole-brain single-shot 3D blood oxygen level-dependent echoplanar imaging sequence, with repetition time 3 s, echo time 50 ms, flip angle 90°, voxel size 3.59x3.59x4 mm, matrix 64x64, field of view 230 mm. Head immobilisation was established by head pads and a firm chin strap to immobilise the head in flexion–extension. Thirty-four contiguous slices per volume and 84 volumes per acquisition were obtained.

Cognitive language task

During fMRI subjects alternately rested and performed a word-generating task. The task comprised the silent generation of words beginning with a different input letter visually presented. The activation paradigm consisted of six activation blocks (21 s each) alternating with six baseline rest blocks (21 s each).

Data analysis

The data were analysed with statistical parametric mapping (SPM2) implemented in MATLAB. Specific hypotheses (activation>rest) were tested with a *t*-value [SPM (*t*)] at each voxel. In this preliminary report, an anatomically based region of interest (ROI) analysis method was used to detect pharmacologically induced changes in language-related activation, i.e., the number of activated voxels was determined in predefined brain regions including the bilateral inferior and middle prefrontal cortex (Brodmann's areas 44, 45 and 46).

Results

Clinical evaluation using information from the personal diary of each patient shows that TPM is associated with a very great reduction in mean monthly migraine frequency

Table 1 Number of voxels (*k*) and peak height (*z*=maximum z-values) of activations in Brodmann's areas 44, 45 and 46 evoked by a silent word-generation task

	Controls		TPM-treated patients			
			With language disfluency		Without language disfluency	
	x	Range	*x*	Range	*x*	Range
BA 44 left						
k	167.20	78–297	57.80	3–124	491	148–657
z	6.76	5.93–7.99	5.47	4.03–6.54	9.76	7.55–12.32
BA 44 right						
k	33.80	0–169	18.20	0–29	115.40	0–197
z	1.10	0–5.50	4.04	0–5.79	5.00	0–7.25
BA 44,45,46 left						
k	443	197–770	212.60	103–343	861.80	171–1364
z	8.15	7.59–9.63	6.80	5.64–8.22	10.07	8.70–12.42
BA 44,45,46 right						
k	43	0–135	52.40	0–224	247.60	94–545
z	4.51	0–5.87	4.22	0–5.80	6.43	5.41–7.49

(from 6.5±2.9 at baseline to 2.5±1.6 during the treatment phase). The median daily dose of TPM was 80.7±20.5 mg, without differences between the two subgroups. In our patients therefore the emergence of cognitive side effects seems to be not related to dosage of TPM.

With regard to fMRI, Table 1 reports quantitative analysis of changes in prefrontal activation during the language task. Relative to the control group, the TPM group shows a different pattern of activation. In fact, in patients with language dysfunction, "Broca's area" (BA 44) was significantly underactivated; furthermore peak height of activation was generally localised in areas outside BA 44. On the contrary, patients without language dysfunction showed a more general overactivation in speech areas.

Discussion

The preliminary data derived by our study suggest that language disturbances experienced during TPM treatment are associated with a "remapping" of the language cerebral network. Our findings expand on previous data based on examination of epileptic patients [4]: there is an obvious correspondence between the type and severity of cognitive impairment and the areas observed to have decreased activation. It is noteworthy that changes are observed in patients taking TPM at a low dose level, on a shown titration schedule and with significant clinical effect. An explanation of the high sensitivity of the language-related cerebral regions to TPM remains to be given. In our opinion the different pattern of activation may be linked to different individual ability of cerebral structures to compensate for the abnormalities induced by TPM on the whole brain's functions [5]. Indeed patients with language dysfunction show a marked activation decrease of language network, whereas patients without language dysfunction show a general overactivation, likely linked to a cerebral compensation. Further work is needed to investigate the relationship between individual variables (such as pretreatment level of language performances) and emergence of cognitive side effects. Moreover fMRI may prove a useful tool for screening compounds that are being developed to treat neuropsychiatric disorders.

References

1. Brandes JL, Saper JR, Diamond M et al (2004) Topiramate for migraine prevention. A randomized controlled trial. JAMA 291:965–973
2. Bussone G, Diener HC, Pfeil J, Schwalen S (2005) Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomised controlled trials. Int J Clin Pract 59:961–968
3. Thompson PJ, Baxendale SA, Duncan JS et al (2000) Effects of topiramate on cognitive function. J Neurol Neurosurg Psychiatry 69:636–641
4. Jansen JFA, Aldenkamp AP, Majoie HJM et al (2006) Functional MRI reveals declined prefrontal cortex activation in patients with epilepsy on topiramate therapy. Epilepsy Behav 9:181–185
5. Piccirilli M (2006) Dal cervello alla mente. Morlacchi Ed., Perugia

Neurol Sci (2008) 29:S144–S145
DOI 10.1007/s10072-008-0907-4

ORAL COMMUNICATION

Cerebrovascular risk factors and MRI abnormalities in migraine

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Abstract Case series have demonstrated an increased incidence of white matter lesions (WMLs) in patients with migraine. It is controversial whether the evidence of subclinical brain lesions relates to a higher risk of cerebrovascular disease. The objective of this study was to evaluate the association between magnetic resonance imaging (MRI) subclinical brain lesions and cerebrovascular risk factors (hyperhomocysteinaemia, MTHFR genotype, patent foramen ovale, hypertension, smoking and hypercholesterolaemia). From our database of 1201 patients followed at our Headache Clinic since September 2003 we analysed the MRI findings of 253 individuals. All MRI were blindly analysed by a second neuroradiologist (C.A.) and patients with WMLs (study group) were evaluated. In order to assess the association of WMLs with specific vascular risk factors, patients with WMLs were matched, according to age, sex and ICHD II diagnosis, with an equal number of individuals with normal MRI (control group). Headache was classified by the International Classification of Headache Disorders (ICHD 2004) criteria. We did not find any statistically significant difference between the two groups with regard to the presence of the cerebrovascular disease risk factors considered. Our results confirm that the WMLs are not related to the cerebrovascular disease risk factors.

Keywords Migraine · White matter lesions · Cerebrovascular risk factors

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Introduction

Migraine is a common chronic disease, characterised by the recurrence of disabling attacks and autonomic nervous system dysfunction, and it is associated with transient focal neurological symptoms in up to one out of three patients.

In a subgroup of patients the disease has a malignant evolution and the attacks tend to evolve into a chronic daily headache [1]. Evidence is growing that the recurrence of headache attacks may be associated with permanent changes in the CNS structure [2].

It has been suggested that migraine is an independent risk factor for stroke [3].

White matter lesions (WMLs) on magnetic resonance images (MRI) have been found in patients with migraine, particularly in migraine with aura individuals. They typically occur in the deep or periventricular white matter and are visualised on T2-weighted or fluid-attenuated inversion-recovery (FLAIR) sequences.

The meaning of these abnormalities is still unclear [4–6]. However, a few studies indicate that these abnormalities have been linked to an increased risk of stroke [2, 7].

Methods

From our database of 1201 patients followed at our Headache Clinic since September 2003 we analysed MRI findings in 253 individuals. All MRI were blindly analysed by a second neuroradiologist (C.A.) and patients with WMLs were evaluated. The presence of other MRI abnormalities and a stroke and head trauma history were considered exclusion criteria. In order to evaluate the association of WMLs with specific vascular risk factors, patients with WMLs (study group) were matched by age, sex and ICHD II diagnosis with an equal number of individuals with normal MRI (control group). The presence of cerebrovascular disease risk factors was analysed in all patients. In particular, we evaluated hyperhomocysteinaemia, MTHFR genotype, the presence of hypertension, smoking, hypercholesterolaemia and oral contraceptives. The presence of right-to-left shunt was evaluated by a transcranial Doppler. Headache was classified by the International Classification of Headache Disorders II (ICHD 2004) criteria. A χ^2 test statistical analysis was carried out. Results were evaluated at a $p<0.05$ level of significance within 95% confidence interval.

Results

The age of the 253 patients (60 males and 193 females) ranged from 15 to 71 years (mean 40±12 years, median 40 years), with a duration of disease ranging between 1 and 57 years (mean 19±12 years).

In the 50 patients (10 males and 40 females) with WMLs (study group, SG), age ranged from 16 to 63 years (mean 44±10 years) and the duration of disease ranged from 1 to 44 years (mean 18±11 years). According to the ICHD II, 23 individuals had migraine with aura (MA), 15 migraine without aura (MO) and 12 chronic daily headache (CDH). In the SG, 45 individuals reported more than one monthly attack (90%). WML individuals were matched by sex, age and ICHD diagnosis with 50 control patients without WMLs (control group, CG).

No patient in the two groups reported a history of stroke or transient ischaemic attack or showed relevant abnormalities at standard neurological examination.

In the SG, hyperhomocysteinaemia was present in 11 patients (22%) and MTHFR mutation in 25 (50%). A patent foramen ovale, such as a right-to-left shunt, was found in 22 (44%), and hypertension was reported in 5 (10%), smoking in 8 (16%) and hypercholesterolaemia in 17 (34%). Thirteen (33%) females out of the 40 reported taking an oral contraceptive.

In the CG, hyperhomocysteinaemia was present in 10 patients (20%, $p>0.05$) and MTHFR mutation in 22 (44%, $p>0.05$). A patent foramen ovale was found in 19 patients (38%, $p>0.05$), hypertension was reported in 3 (6%, $p>0.05$), smoking in 13 (26%, $p>0.05$) and hypercholesterolaemia in 11 (22%, $p>0.05$). Seventeen (42%) females out of the 40 reported taking an oral contraceptive ($p>0.05$).

Conclusions

In accordance with the literature, our results confirm a higher frequency of WMLs in both females and patients affected by MA [3]. A frequency of attacks higher than one per month was reported in the majority of our WML group, confirming what has been reported in several studies [2].

The two study groups showed a similar frequency of the cerebrovascular disease risk factors assessed. In particular, the presence of WMLs was independent of a history of hypertension, smoking, hypercholesterolaemia and oral contraceptive use. Moreover, no evidence of a higher frequency of hyperhomocysteinaemia, MTHFR mutation and patent foramen ovale has been found in the study group. These data confirm what is reported in the literature [2].

Similar lesions may have a similar pathogenetic mechanism. The absence of a correlation between these lesions and cerebrovascular risk factors in our and other studies may suggest the existence of a common pathogenetic mechanism, currently unknown.

This also supports the theory that WMLs may be a specific marker of migraine or of its evolution towards stroke. Prospective studies are necessary in order to assess whether migraine patients with WMLs run a higher risk of stroke than migraine patients without WMLs.

References

1. Scher AI, Stewart WF, Liberman J, Lipton RB (1998) Prevalence of frequent headache in a population sample. Headache 38:497–506
2. Wong TY, Klein R, Sharrett AR et al (2002) Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 288:67–74
3. Kruit MC, van Buchem MA, Hofman PA et al (2004) Migraine as a risk factor for subclinical brain lesions. JAMA 291:427–434
4. Cooney BS, Grossman RI, Farber RE et al (1996) Frequency of magnetic resonance imaging abnormalities in patients with migraine. Headache 36:616–621
5. Richard H, Swartz BS, Kern RZ (2004) Migraine is associated with magnetic resonance imaging white matter abnormalities. Arch Neurol 61:1366–1368
6. Narbone MC, Leggiadro N, La Spina T et al (1996) Migraine stroke: a possible complication of both migraine with and without aura. Headache 36:481–483
7. Pezzini A, Del Zotto E, Padovani A (2007) Homocysteine and cerebral ischemia: pathogenic and therapeutical implications. Curr Med Chem 14:249–263

Neurol Sci (2008) 29:S146–S148
DOI 10.1007/s10072-008-0908-3

ORAL COMMUNICATION

Primary headache and multiple sclerosis: preliminary results of a prospective study

Veronica Villani · Luca Prosperini · Alessandro Ciuffoli · Raffaella Pizzolato · Marco Salvetti · Carlo Pozzilli · Giuliano Sette

Abstract The aim of this study was to explore the association between different types of headache (HA) and the clinical features of multiple sclerosis (MS). The relationship between HA and MS-specific therapies was also analysed. A total of 102 MS patients were recruited at the MS Centre of S. Andrea Hospital in Rome. According to International Headache Society criteria, the lifetime prevalence of primary HA was 61.8%. Migraine was observed more often in young relapsing–remitting MS patients, whilst tension-type HA was associated with older age, male gender and a secondary progressive course. Sixty-four patients had a history of ongoing or past interferon beta (IFNb) exposure. Of these, 17 subjects did not have a history of HA, while 24 complained of an increase in frequency of migraine attacks and 7 reported an IFNb-induced HA. Investigating and treating HA in MS patients starting IFNb therapy may improve MS-specific medication compliance.

Keywords Migraine · Headache · Multiple sclerosis · Interferon beta

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Background

The link between multiple sclerosis (MS) and primary headache (HA) is poorly understood and studies investigating their relationship have produced conflicting results. The prevalence of HA in MS patients has been reported to be between 4% and 58% and the frequency of HA as an onset symptom of MS between 1.6% and 26% [1–4]. Several studies suggested that Interferon beta (IFNb) treatment may induce *de novo* HA and exacerbation of pre-existing HA [3, 5, 6].

The primary goal of this study was to investigate the association between MS and HA. The secondary aim of the study was to evaluate the correlation between different types of primary HA and the clinical features of MS. The relationship between HA and MS-specific medication for MS was also evaluated.

Methods

Between October 2006 and January 2007 we prospectively recruited consecutive MS patients, according to the McDonald criteria [7], regularly attending at the MS Centre of S. Andrea Hospital in Rome. We collected demographic and clinical variables for each patients: gender, age at MS onset, previous and ongoing therapy for MS, duration of MS-specific treatment and level of disability assessed by the Expanded Disability Status Scale (EDSS) [8].

All patients underwent: the ID migraine, a semistructured interview guided by a questionnaire based on International Headache Society (IHS) criteria [9] to evaluate and classify HA, the Beck Depression Inventory (BDI) and the Toronto Alexithymia Scale (TAS-20). Patients diagnosed as affected by HA also underwent the Migraine

DIsability Assessment Scale (MIDAS) and the Headache Impact Test-6 (HIT-6) for the assessment of migraine disability.

Data have been analysed using SPSS software. Statistical significance was calculated by the Pearson's Chi-squared test or the Student's independent-samples *t*-test, when appropriate. *p*-values less than 0.05 were considered significant.

Results

A total of 102 MS patients (71 females, 31 males) were recruited. Mean age was 38.7±9.5 years (median 38, range 15–68); mean MS duration was 8.8±7.6 years (median 6, range 1–41). Eighty-three patients had a relapsing–remitting form, while 19 had a secondary progressive (SP) course. Mean EDSS score of whole study population was 2.4±1.6 (median 2.0, range 0–7.0). Twenty patients did not receive any specific MS treatment, while 82 subjects were on therapy with MS-specific drugs: 37 with an IFNβ formulation, 22 with immunosuppressant agents, 18 with natalizumab and 5 with glatiramer acetate.

According to IHS criteria, 63 patients suffered from a primary HA, while 11 patients had a secondary form (7 reported an IFNβ-induced HA as a part of flu-like symptoms, 4 had an atypical neuralgia).

The lifetime prevalence of primary HA in the whole population was 61.8%. HA started at younger age compared with MS onset (21.7±11.9 vs. 29.7±8.8 years; p=0.002). Migraine was observed more often in RR than SP MS patients. Conversely, tension-type HA (TTH) was associated with older age, male gender and progressive course of MS. No relationship between MS duration, age at MS onset, EDSS score and HA was detected (see Table 1).

Sixty-four patients had a history of ongoing or past IFNβ exposure. Among these, 17 (26.5%) did not have a history of HA, 7 (11%) reported an IFNβ-induced HA, 16 (25%) migraineurs reported no changes in frequency of migraine attacks, 24 (37.5%) complained of an increase in frequency (10.5±9.5 vs. 6.5±6.5 days/month; p=0.05) and a slightly higher HIT-6 score (53.6±13.6 vs. 44.0±19.6; p=0.08). We also observed that frequency and intensity of HA was not significantly related with IFNβ dosage, type of molecule (i.e., IFNβ-1a or -1b) and frequency of administration. However, the migrainous subjects taking IFNβ thrice per week or every other day had a higher median number of attacks (2/month vs. 6/month, p=0.05) and higher BDI score (9.6±6.0 vs. 5.3±4.6, p=0.05) than patients treated once weekly.

Table 1 Demographic and clinical characteristics of study population according to subtypes of HA

	Migraine (n=46)	Chronic HA (n=8)	TTH (n=9)	Secondary HA (n=11)	No HA (n=28)	Pooled (n=102)
Gender*						
Female	38	8	3	8	14	71
Male	8	0	6	3	14	31
Current age**						
<30 years	13	0	1	2	4	20
30–40 years	17	5	0	3	13	38
>40 years	16	3	8	6	11	44
Education						
≤8 years	6	0	2	2	3	13
9–13 years	29	6	5	6	19	65
>13 years	11	2	2	3	6	24
MS course**						
RR	40	8	5	9	21	83
SP	6	0	4	2	7	19
MS onset						
<20 years	7	0	0	0	3	10
20–30 years	23	3	3	5	11	45
>30 years	16	5	6	6	14	47
MS duration						
<2 years	6	2	1	3	5	17
2–10 years	23	6	4	5	14	52
>10 years	17	0	4	3	9	33
EDSS score						
≤1.5	21	3	3	3	12	42
2.0–3.5	16	4	2	7	9	38
≥4.0	9	1	4	1	7	22

No HA, patients without headache; *RR*, relapsing–remitting MS; *SP*, secondary progressive MS
*p<0.01 and **p=0.05

Conclusions

Our study shows that HA is common in people with MS: the lifetime prevalence (61.8%) of HA was the highest reported in the literature. We confirmed high prevalence of pre-existing migraine and low prevalence of TTH, which represented the most common type of HA in older males affected by a SP course of MS. Although migraine preceded MS onset by about 8 years, this study cannot rule out the hypothesis that migraine might represent a first symptom of the disease. Further efforts are required to clarify the real link between migraine and MS.

In patients treated with IFNβ we performed an accurate classification of HA aimed to differentiate HA due to flu-like syndrome from primary HA. Treatment with IFNβ triggered *de novo* HA in few subjects, while the majority of patients showed an increased frequency of pre-existing HA. In particular, subjects receiving high-frequency IFNβ treatment had a greater number of migraine attacks and higher BDI score than those on therapy with once weekly administration.

Because of the small number of subjects considered, these finding should be taken with caution, although the head-to-head study comparing every-other-day IFNβ-1b vs. once-weekly IFNβ-1a demonstrated a minor occurrence of HA among patients treated by low-frequency formulation [10].

On the contrary, the association between increased level of depression and high-frequency IFNβ dose recorded in our work conflicts with the results of both the dose-comparison studies showing no differences in prevalence of depression during a follow-up period ranging from 12 to 24 months [11]. However, it has been observed that frequency and duration of migraine attacks is associated with depression or anxiety [12].

We suggest that investigating and treating HA in MS patients starting IFNβ therapy may improve MS-specific medication compliance.

References

1. Freedman MS, Gray TA (1989) Vascular headache: a presenting symptom of multiple sclerosis. Can J Neurol Sci 16:63–66
2. Rolak LA, Brown S (1990) Headaches and multiple sclerosis: a clinical study and review of the literature. J Neurol 237:300–302
3. Pollmann W, Erasmus LP, Feneberg W et al (2002) Interferon beta but not glatiramer acetate therapy aggravates headaches in MS. Neurology 59:636–639
4. D'Amico D, La Mantia L, Rigamonti A et al (2004) Prevalence of primary headaches in people with multiple sclerosis Cephalalgia 24:980–984
5. Brandes JL (2000) Migraine induced by interferon beta therapy for multiple sclerosis. Neurology 54[Suppl 3]:A422
6. La Mantia L, D'Amico D, Rigamonti A et al (2006) Interferon treatment may trigger primary headaches in multiple sclerosis patients. Mult Scler 12:476–480
7. McDonald WI, Compston A, Edan G et al (2001) Recommended diagnostic criteria for multiple sclerosis. Ann Neurol 50:121–127
8. Kurtzke JF (1983) Rating neurological impairment in Multiple Sclerosis. An expanded disability status scale (EDSS). Neurology 33:1444–1452
9. Headache Classification Subcommittee of the International Headache Society (2004) International Classification of Headache Disorders, 2nd Edn Cephalalgia [Suppl 1]:9–160
10. Durelli L, Verdun E, Barbero P et al (2002) Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: a results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet 359:1453–1460
11. Panitch H, Goodin DS, Francis G et al (2002) Randomized, comparative study of interferon beta-1a treatment regimens in MS. The EVIDENCE trial. Neurology 59:1496–1506
12. Mitsikostas DD, Thomas AM (1999) Comorbidity of headache and depressive disorders. Cephalalgia 19:211–217

Neurol Sci (2008) 29:S149–S151
DOI 10.1007/s10072-008-0909-2

ORAL COMMUNICATION

Comorbidity between depressive symptoms and migraine: preliminary data from the Zabút Aging Project

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Abstract We evaluated the association between depressive symptoms and migraine using cross-sectional data from the Zabút Aging Project, a population-based study including subjects aged ≥50 years. A total of 1285 nonmigraineurs and 151 migraineurs were included. Diagnosis of migraine was carried out using the criteria of the International Headache Society. The Center for Epidemiologic Studies Depression scale (CES-D) was used to score depressive symptoms. Depressive symptoms were clustered in four groups: depressed and positive affects, somatic activity and intrapersonal feelings. Migraineurs showed higher total and specific depressive symptoms than controls (p from 0.005 to <0.0001). Mild-to-moderate depressive symptoms (CES-D score of ≥16) were present in 47.2% of migraineurs compared to 15.8% of controls (p<0.0001). After adjustment for demographics, mild-to-moderate depressive symptoms were strongly associated with migraine (OR [95% CI]=4.7 [3.1–7.0]). This association significantly increased in males (OR [95% CI]=6.2 [2.8–14.6]). Depressive features represent highly frequent comorbid symptoms of adult-to-elderly migraineurs.

Keywords Migraine · Epidemiology · Depression · Elderly

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Introduction

Cross-sectional and bi-directional associations between migraine and psychiatric disorders, mainly depression, have been described [1, 2]. Prevalence of major depression in migraineurs has been reported to account for about 25% of subjects [3]. However this field is broad and represents a still unexplored subject. In particular, the association between specific depressive symptoms and migraine has been scarcely investigated. We thus explored the association between migraine and specific clusters of depressive symptoms in a cross-sectional, population-based study.

Methods

Study population and case ascertainment

This study was part of the Zabút Aging Project (ZAP), a comprehensive survey of neuropsychiatric disorders of all subjects aged 50 years or over, living in a village near the city of Palermo, Italy on 31 October 2001. As previously reported [4], the detection of headache sufferers was conducted using a two-phase door-to-door procedure. First, all participants were examined by physicians with a screening questionnaire for the presence/absence of headache. Second, subjects positively screened for migraine were examined by neurologists using a semi-structured questionnaire for headache based on the criteria of the International Headache Society [5]. On the basis of this information, migraine cases were finally ascertained. The Ethics Committee of the Medical Faculty at the University of Palermo approved the baseline data collection and participants gave written informed consent.

Assessment of depressive symptoms

Participants underwent the Center for Epidemiologic Studies Depression scale (CES-D), 20-item version [6], during a physician's interview. Depressive symptoms were then clustered using the original four-factor structure including 16 of the 20 CES-D items [6], as follows: depressed affect (*blues*, *depressed*, *lonely*, *cry*, *sad*), positive affect (*good*, *hopeful*, *happy*, *enjoy*), somatic activity (*bothered*, *appetite*, *effort*, *sleep*, *get going*) and interpersonal feelings (*unfriendly*, *dislike*).

Statistical analyses

Descriptive data between migraineurs and nonmigraineurs were compared with a two-tailed *t*-test or chi-square analysis. Depressive features were treated as continuous and dichotomic variables. For this purpose a cut-off value of ≥16 was used to describe mild-to-moderate depression [6]. The association between migraine and depressive symptoms was evaluated with logistic regression analysis adjusting for age, sex and education. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). For all analyses the level of significance was $p \leq 0.05$.

Results

After excluding subjects with severe psychiatric disorder, dementia, stroke-related aphasia and nonmigraine headache, 1436 individuals collected at baseline were included in this study. The mean age of participants was 73.5 years (10.1 SD) and mean years of education was 5.3 (4.1); females were more represented than males (53.3 vs. 46.7). A total of 151 participants were diagnosed as migraineurs. Subjects with migraine were significantly younger than nonmigraineurs (mean±SD: 68.3±8.6 vs. 74.1±10.1, $p \leq 0.0001$). Furthermore, females were more represented in the migraine group as compared to nonmigraineurs (79.5% vs. 50.2%, $p<0.0001$). Regarding depressive symptoms, migraineurs showed significantly higher total and specific depressive symptoms than controls (p from 0.005 to <0.0001). In particular, mild-to-moderate depressive symptoms were present in 47.2% of migraineurs compared to 15.8% of controls ($p<0.0001$). After adjustment for demographics, mild-to-moderate depressive symptoms were strongly associated with migraine (OR 4.7, [95% CI, 3.1–7.0]). The association between migraine and depressive status significantly increased in males (OR 6.2 [95% CI, 2.8–14.6]).

Discussion

In the ZAP cohort, we found a strong cross-sectional association of migraine with mild-to-moderate depressive symptoms; of interest, the highest association was evidenced in males compared to females. This finding probably accounts for a higher prevalence of vascular comorbidity in males compared to females in our population. Indeed, it is well known that vascular diseases are often associated with depressive symptoms, particularly in males [7]. There is still no clear evidence for the pathogenesis of the comorbidity between migraine and depression. However, based on previous literature reports, a plausible hypothesis suggests that migraine shares some causative, genetic, biochemical or environmental factors with depression [1].

The association between migraine and depression has been previously evaluated in young adults by some population-based, cross-sectional studies [8–10]. According to these data, adjusted ORs range from 2.0 to 3.0. In our study, we found a higher association between migraine and depressive status with respect to previous reports. Differences in study design, diagnostic criteria and demographics (i.e., our study includes subjects with a mean age of 73.5 years) probably account for different results between these data and ours.

Although our study has several strengths, including the large sample size and standardised migraine ascertainment, some shortcomings should be mentioned. First, these represent preliminary data, and control for potential confounders (i.e., vascular disease) should be considered. Second, cross-sectional studies cannot determine whether migraine causes depression or whether other risk factors or a shared susceptibility cause this association. Prospective data of this cohort, however, will provide further information on the causal relationship between migraine and depressive status.

In conclusion, our data suggest that migraineurs, particularly males, had a higher depressive burden than nonmigraineurs. As depression is comorbid with migraine and also is a risk factor for migraine progression [1, 2], subjects with migraine should be carefully screened for depression, with subsequent important clinical and therapeutical implications.

References

1. Breslau N, Lipton RB, Stewart WF, Schultz LR, Welch KM (2003) Comorbidity of migraine and depression: investigating potential etiology and prognosis. Neurology 60:1308–1312
2. Bigal ME, Lipton RB (2006) Modifiable risk factors for migraine progression. Headache 46:1334–1343
3. Patel NV, Bigal ME, Kolodner KB, Leotta C, Lafata JE, Lipton RB (2004) Prevalence and impact of migraine and probable migraine in a health plan. Neurology 63:1432–1438
4. Camarda R, Monastero R (2003) Prevalence of primary headaches in Italian elderly: preliminary data from the Zabút Aging Project. Neurol Sci 24[Suppl 2]:122–124
5. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain.

Cephalalgia 8(Suppl. 7):1–96
6. Radloff LS (1977) The CES-D scale: a self-report depression scale for research in the general population. Applied Psychol Measurement 3:385–401
7. Kales HC, Maixner DF, Mellow AM (2005) Cerebrovascular disease and late-life depression. Am J Geriatr Psychiatry 13:88–98
8. Merikangas KR, Angst J, Isler H (1990) Migraine and psychopathology. Results of the Zurich cohort study of young adults. Arch Gen Psychiatry 47:849–853
9. Swartz KL, Pratt LA, Armenian HK, Lee LC, Eaton WW (2000) Mental disorders and the incidence of migraine headaches in a community sample: results from the Baltimore Epidemiologic Catchment area follow-up study. Arch Gen Psychiatry 57:945–950
10. Zwart JA, Dyb G, Hagen K, Ødegård KJ, Dahl AA, Bovim G et al (2003) Depression and anxiety disorders associated with headache frequency. The Nord-Trøndelag Health Study. Eur J Neurol 10:147–152

Neurol Sci (2008) 29:S152–S154
DOI 10.1007/s10072-008-0910-9

ORAL COMMUNICATION

Personality profile and allodynic migraine

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Abstract Migraine is known to be associated to particular psychological features. Cutaneous allodynia is a painful sensation or discomfort induced by a non-noxious stimulus, and is a frequent complaint during migraine attacks. The aim of this study was to compare the personality profile of allodynic and non-allodynic migraineurs to identify possible relationships between psychological aspects and the presence of allodynia. The Symptom Check List 90-R (SCL90R), a 90-item self-report psychological symptom inventory, was used to investigate the psychological profile of our patients. The presence of allodynia was assessed by a set of semi-structured questions that investigated if the patient experienced abnormal scalp sensitiveness and/or discomfort during headache episodes. Twenty-five non-allodynic patients and 38 allodynic migraineurs were studied. No significant difference was found between the two groups in any area of the personality profile. The psychological profile seems not to affect the presence/absence of cutaneous allodynia in migraine patients. This reinforces the hypothesis that allodynia is a "somatic" symptom, not modified by psychological aspects.

Keywords Allodynia · Psychological profile · Migraine · Symptom Check List 90-R inventory (SCL90R)

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Background

Cutaneous allodynia is described as a painful sensation or discomfort induced by a non-noxious stimulus. It is a frequent complaint during migraine attacks, as approximately two-thirds of patients with migraine may report allodynia during headache attacks [1–3]. Allodynia in migraine is thought to represent a clinical correlate of central sensitisation of the nociceptive neurons that process information from intracranial and extracranial structures. In fact, migraine attacks are accompanied by activation of trigeminal perivascular nociceptive fibres in the meninges. Central sensitisation is an increased central neuronal responsiveness that may cause hyperalgesia and allodynia [4]. Central descending inhibitory systems normally modulate this process. These modulatory systems are thought to be influenced by certain behavioural and cognitive factors [4].

Migraine is known to be associated to particular psychological features, which are related to some extent to age, duration of illness [5] and migraine subtype [6]. Furthermore, comorbidity between headache and psychological disorders may reveal a common central neurogenic mechanism, such as a dysregulation of some neurotransmitter system, which underlies both the headache and the coexistent disorders [7].

Aim of the study

The aim of the present study was to compare the psychological profile of allodynic and non-allodynic migraineurs to identify possible relationships between psychological aspects and the complaint of allodynia.

Methods

Sixty-three consecutive outpatients presenting for the first time at the Headache Center of the L. Sacco Hospital, diagnosed as migraineurs, were included in the study.

The psychological status of patients was assessed by the Symptom Check List 90-R inventory (SCL90R) [8]. The SCL90R is a 90-item self-report psychological symptom questionnaire that assesses the following fields: somatisation, obsessive-compulsive attitude, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. It gives a possible a score for each psychological area, and a total mean score (global gravity index) that defines the global psychological condition. Allodynia was assessed by a set of semi-structured questions, which was used in a previous study [3]. The first question investigated was if the patient experienced abnormal scalp sensitiveness and/or discomfort. Immediately after this screening question, all patients were asked a series of individual questions to assess what daily activities might induce allodynia: touching head skin; touching hair; combing hair; brushing hair; wearing glasses; hairbands, curlers or ponytail; lying with head resting on the side of allodynia. We defined a patient as allodynic when one ore more positive answers were found.

With regard to the specific headache characterisation, patients were diagnosed according to the 2004 International Classification of Headache Disorders (ICHD II) criteria [9].

Both the allodynia questionnaire and the SCL90 test were administered to patients at the first outpatient visit before the diagnostic evaluation.

The *t*-test was applied to compare the scores obtained at each psychological field and the global gravity indexes obtained in allodynic and non-allodynic migraineurs.

Results

We examined 63 consecutive migraineurs presenting for the first time at the Headache Center of the L. Sacco Hospital. A total of 25 non-allodynic (4 males and 21 females) and 38 allodynic (1 male and 37 females) migraineurs were investigated using the SCL90R. In the non-allodynic group 6 (24%) subjects had chronic migraine while 19 (76%) were episodic; the allodynic group included 12 chronic and 26 episodic migraine patients (31.6% and 68.4%, respectively). Six of the 25 non-allodynic patients (24%) had migraine with aura and 19 (76%) had migraine without aura; among the 38 allodynic migraineurs 14 (36.8%) had migraine with aura and 24 (63.2%) without aura.

The mean global gravity index and the mean scores in each single psychological area found both in the allodynic and non-allodynic groups are reported in Table 1.

No significant difference in the global gravity index was found between allodynic and non-allodynic migraineurs. Also, analysing the nine single psychological areas, no differences emerged between the two groups. A borderline result was observed only in the "interpersonal sensitivity" field.

Discussion

The psychological profile seems not to affect the presence/absence of cutaneous allodynia in migraine patients. Our findings may reinforce the hypothesis that allodynia is a "somatic" symptom, not modified by psychological aspects.

On the other hand, the presence of allodynia during migraine attacks, although unpleasant, seems not to be able to modify the mood and the behaviour of the patient.

A small difference between the two groups was observed in only one single psychological field, labelled "Interpersonal sensitivity". This result may partially be attributable to the large number of fields into which the SCL90R test is divided. Increasing the number of parameters in the study, the chance of a significant result increases. The study needs to be repeated on a larger population to verify our results.

The study has several limitations that reduce its power: the size of the sample is still small and both allodynic and non-allodynic groups included patients with different

Table 1 Comparison SCL90R scores (mean values±standard deviation) between allodynic and non-allodynic migraineurs

SCL90R scores	Non-allodynic migraineurs	Allodynic migraineurs	t-test
Global gravity index	0.52±0.25	0.76±0.55	NS
Somatisation	1.07±0.59	1.14±0.61	NS
Obsessive-compulsive attitude	0.64±0.37	0.82±0.72	NS
Interpersonal sensitivity	0.25±0.26	0.76±0.79	0.003
Depression	0.57±0.38	0.91±0.84	NS
Anxiety	0.67±0.35	0.88±0.69	NS
Hostility	0.49±0.44	0.67±0.59	NS
Phobic anxiety	0.17±0.17	0.35±0.40	NS
Paranoid ideation	0.36±0.38	0.62±0.64	NS
Psychoticism	0.18±0.22	0.41±0.50	NS

migraine subforms (migraineurs with and without aura, chronic and episodic), although in balanced proportions. This heterogeneity may cover possible differences that could emerge with a more specific analysis of the different diagnostic groups. Previous studies underlined some differences in the psychological profile between migraineurs with and without aura [5, 6]. On the other hand, the complaint of allodynia may be more frequent among chronic migraine and migraine with aura patients [3].

Notwithstanding these limitations, our study is the first to directly compare the psychological profile of migraineurs with and without allodynia in order to investigate possible endogenous elements facilitating the presence of migraine-related allodynia.

This may have clinical implications. As allodynia is associated with reduced triptan efficacy against acute migraine attacks [10] and it may also interfere with the efficacy of prophylactic medications [11], the possible individuation of environmental or endogenous factors (such as a particular psychological profile) able to facilitate allodynia may be crucial for accurate clinical evaluation and a tailored treatment plan in migraine patients.

References

1. Goadsby PJ (2005) Migraine, allodynia, sensitisation and all of that… Eur Neurol 53[Suppl 1]:10–16
2. Burstein R, Yarnitsky D, Goor-Aryeh I et al (2000) An association between migraine and cutaneous allodynia. Ann Neurol 47:614–624
3. Lovati C, D'Amico D, Bertora P et al (2008) Acute and interictal allodynia in patients with different headache forms: an Italian pilot study. Headache 48:272–277
4. Meeus M, Nijs J (2007) Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clin Rheumatol 26:465–473
5. Puca FM, Antonaci F, Genco S et al (1989) Psychologic factors in chronic headache: assessment by means of the SCL-90-R inventory. Cephalalgia 9:33–51
6. Lovati C, Brambilla A, Bertora P et al (2006) Migraine and personality profile. Neurol Sci 27[Suppl]:S268
7. Puca FM, Prudenzano AM, Savarese M et al (1997) Stress, mood disorders and memory in headache. Int J Clin Pharmacol Res 17:111–114
8. Derogatis LR (1977) SCL-90-R administration, scoring and procedure manual-I for the R(evised) version. LR Derogatis, Baltimore
9. Headache Classification Subcommittee of the International Headache Society (2004) The international classification of headache disorders. Cephalalgia 24[Suppl 1]:24–36
10. Burstein R, Collins B, Jakubowski M (2004) Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. Ann Neurol 55:19–26
11. Weissman-Fogel I, Sprecher E, Granovsky Y, Yarnitsky D (2003) Repeated noxious stimulation of the skin enhances cutaneous pain perception of migraine patients in-between attacks: clinical evidence for continuous sub-threshold increase in membrane excitability of central trigeminovascular neurons. Pain 104:693–700

Neurol Sci (2008) 29:S155–S157
DOI 10.1007/s10072-008-0911-8

ORAL COMMUNICATION

Quality of life, eating and mood disorders in menstrual migraine: a case-control study

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Abstract The aim of this study was to evaluate the prevalence of mood and eating disorders in patients with menstrual migraine. Quality of life and disability were also assessed. The study confirmed the presence of significant disability and poor quality of life due to migraine even in a selected subgroup of patients affected with menstrual migraine. In contrast with the previous literature we did not find any difference in the prevalence of mood and eating disorders.

Keywords Menstrual migraine · Health-related quality of life · Disability

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Introduction

Migraine occurs more frequently in women than in men, affecting about 10%–15% of the general population. Gender differences may be due, in part, to the cyclic changes in female sex hormones. Migraine headache is more likely to occur perimenstrually and to be more severe [1, 2]. Migraine attacks cause significant lost productivity and decreased quality of life [3], mostly if migraine is associated with a psychiatric disorder [4], which is frequently found in comorbidity with migraine [5]. Moreover, Brewerton and George suggested a comorbidity between migraine and eating disorders [6], in line with a probable hypothalamic involvement in migraine pathogenesis [7].

The purpose of our study was to assess the quality of life, using the Migraine Disability Assessment questionnaire (MIDAS) and the Short-Form Health survey (SF-36), concomitant eating disorders, using the Eating Disorders Inventory-II (EDI-II), and psychiatric comorbidity, according to the Beck Depression Inventory-II (BDI-II) and the Mini International Neuropsychiatric Interview (MINI), in menstrual migraine patients.

Methods

Patients

Ninety-one consecutive outpatients with pure menstrual migraine and menstrually related migraine, referred to the Headache Centre of the Neurological Department of the University of Bologna, Italy, were matched by age with 83 healthy women. Pure menstrual migraine and menstrually related migraine were classified according to the ICHD-II criteria [8]; a relation between migraine and menses was documented in diaries filled in for at least three months. The main exclusion criteria were: age <18

years, more than 4–5 migraine attacks per month or chronic headache, patients unable to give useful information and secondary headache.

Data collection

At the time of the visit a headache specialist performed a semi-structured history-taking interview and a neurological examination. Healthy women were interviewed by the same headache specialist to rule out a diagnosis of migraine. Both groups filled in MIDAS, SF-36, BDI and EDI-II questionnaires in their validated Italian versions. The SF-36 questionnaire measures the health-related quality of life across eight dimensions: physical functioning, role limitation due to physical problems, bodily pain, general health, vitality social functioning, role limitation due to emotional problems and mental health.

The MIDAS is a specific questionnaire to assess headache-related disability in three domains of activity over the preceding three months: paid or school work, household work, family, social and leisure activities [9]. The EDI-II is a 91-item inventory that evaluates the symptoms and the psychological characteristics of eating behaviour disorders. It is composed of eight subscales and three provisional subscales: Drive for thinness, Bulimia, Body dissatisfaction, Ineffectiveness, Perfectionism, Interpersonal distrust, Interoceptive awareness, Maturity fears, Ascetism, Impulse regulation, Social insecurity. The BDI is a 21-item multiple-choice test for measuring the severity of depression. The MINI, structured on DSM-IV and ICD-10 criteria, was used by a headache specialist to evaluate the lifetime and current prevalence of mood disorders in migraineurs and controls.

Data analysis

Data were summarised using descriptive statistics (percentages or arithmetic means±SD). Statistical analysis was performed by non-parametric testing. For quantitative data the Mann–Whitney *U*-test was used. Significance level was set at p=0.05.

Results

We enrolled 91 patients (mean age 35.86±7.25) and 83 healthy women (mean age 35.11±8.04). Their demographic data were similar except for marital status (p=0.042) and working status (p=0.009): compared to controls, more women with migraine were married or cohabiting (62.4% vs. 47%) and employed (79.6% vs. 58.8%). In addition, migraine patients had a higher hormonal contraceptive use (p=0.004).

Disability and health-related quality of life

The MIDAS score in migraineurs was 30.98±28.48: 17.6% patients had minimal or infrequent disability, 6.6% had mild or infrequent disability, 18.7% had moderate disability, while 57.1% had severe disability. Migraineurs missed more days from household work and family/leisure activities than from work/school activities (6.51 and 6.38 *vs*. 1.91 days). They reported a reduction by at least half of ability to do household work and performance at work/school activities on 7.63 and 8.56 days respectively.

The patients differed significantly from controls in the following SF-36 subscales: physical functioning (88.95±10.76 vs. 92.59±14.29; p=0.000), role limitation due to physical problems (58.24±37.46 vs. 82.53±31.41; p=0.000), bodily pain (47.9±23.4 vs. 77.97±21.53; p=0.000), general health (61.57±20.4 vs. 73.68±16.98, p=0.000), vitality (50.27±17.94 vs. 58.31±15.44; p=0.002) and social functioning (62.91±22.62 vs. 69.87±22.26; p=0.0032). Physical component summary score was 45.82±7.92 vs. 54.14±7.69 (p=0.000). There was no difference for role limitation due to emotional problems and mental health.

Mood and eating disorders

The scores of all EDI-II subscales were similar in the two groups.

The BDI scores in patients and controls were 4.54±4.51 and 3.57±4.23 respectively (p=0.059).

The MINI interview did not suggest any differences between patients and controls for mood disorders: current major depression (5.4% vs. 4.7%), lifetime major depression (24.7% vs. 28.2%), current panic disorders (1.1% vs. 0%), lifetime panic disorders (11.8% vs. 8.2%), current obsessive-compulsive disorder (2.1% vs. 1.2%), lifetime obsessive-compulsive disorder (6.4% vs. 3.5%), current generalised anxiety disorder (11.8 vs. 5.8%) and lifetime generalised anxiety disorders (20.4% vs. 14.1%).

Discussion

We observed significant disability related to migraine: 57% of women affected with menstrual migraine had severe disability. The patients missed more days from household work and family/leisure activities than from work/school activities, however ability to do household work and performance at work/school activities were reduced by at least half. These results were in line with previous worldwide studies that showed a migraine-related impairment of productivity at work and school

and a reduction of participation in family recreational and social activities among young women [3, 10]. Poor quality of life was described in migraine patients and mood disorders were associated with significant decrements in quality of life [4]. Our patients had lower SF-36 scores across six of the eight domains compared to healthy women. Menstrual migraineurs reported severe limitations due to physical but not emotional problems. In line with these results, but in contrast with the past literature that widely described psychiatric comorbidity in migraine patients [5], the MINI interview did not suggest any differences between the groups for lifetime and current prevalence of mood disorders. This difference may be due to the specific sub-group of migraine patients studied. Finally we did not find significant differences between cases and controls on EDI-II subscales, in contrast with Brewerton and George, who described higher scores on four of the eight subscale of EDI (Body dissatisfaction, Perfectionism, Interpersonal Distrust) in a small sample of migraineur women [6]. Menstrual migraine could be a specific type of migraine, associated with significant disability and reduced quality of life even in the absence of psychiatric comorbidity.

References

1. Stewart WF, Lipton BR, Chee E et al (2000) Menstrual cycle and headache in a population sample of migraineurs. Neurology 55:1517–1523
2. Granella F, Sances G, Allais G et al (2004) Characteristics of menstrual and non menstrual attacks in women with menstrually related migraine referred to headache centres. Cephalalgia 24:707–716
3. MacGregor EA, Brandes J, Eikermann A, Giammarco R (2004) Impact of migraine on patients and their families: the Migraine and Zolmitriptan Evaluation (MAZE) survey-Phase III. Curr Med Res Opin 20:1143–1150
4. Hung C-I, Liu C-Y, Juang Y-Y, Wang S-J (2005) Comorbid migraine is associated with negative impact on quality of life in patients with major depression. Cephalalgia 26:26–32
5. Hamelsky S, Lipton RB (2006) Psychiatric comorbidity of migraine. Headache 46:1327–1333
6. Brewerton T, George M (1993) Is migraine related to eating disorders? Int J Eat Disord 14:75–79
7. Montagna P (2006) Hypothalamus, sleep and headaches. Neurol Sci 27:S138–S143
8. Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edition. Cephalalgia 24[Suppl 1]:9–160
9. D'Amico D, Mosconi P, Genco S et al (2001) The Migraine Disability Assessment (MIDAS) questionnaire: translation and reliability of the Italian version. Cephalalgia 21:947–952
10. Dueland AN, Leira R, Burke T et al (2004) The impact of migraine on work, family, and leisure among young women – a multinational study. Curr Med Res Opin 20:1595–1604

Neurol Sci (2008) 29:S158–S160
DOI 10.1007/s10072-008-0912-7

ORAL COMMUNICATION

Application of revised criteria for Chronic Migraine and Medication Overuse headache in a tertiary Headache Centre

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Abstract Various diagnostic criteria have been proposed for chronic daily headaches. We tested the recently proposed revised criteria of the International Headache Society in a sample of patients with chronic daily headaches, most of whom were overusing acute medications, to assess their applicability in clinical practice compared to alternative classification systems.

Keywords Chronic daily headache · Chronic migraine · Medication overuse headache

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Introduction

Various criteria have been proposed for chronic daily headaches (CDH) – headache forms with long duration of attacks and daily or almost daily occurrence. CDH patients with a history of episodic migraine are the most difficult to classify, particularly when they also overuse acute headache medications. The classification of primary CDH by Silberstein and Lipton [1] included the sub-categories transformed migraine (subsequently chronic migraine (CM), chronic tension-type headache (CTTH), hemicrania continua and new daily persistent headache. Transformed migraine required "some" headache episodes of the migraine type, a history of previous typical episodic migraine (all subforms) or a history of "increasing headache frequency with decreasing severity of migrainous features". In this classification, all CDH forms could be further specified as with or without medication overuse. In the current IHS classification (ICDH-II) published in 2004 [2], CM was defined as the presence of typical migraine without aura attacks on ≥15 days/month. The diagnosis of CM (like that of CTTH) is alternative to the diagnosis of medication overuse headache (MOH). The diagnosis of MOH requires that the overused medication be discontinued for at least 2 months and that the chronic headache improve as a result. For this reason, the terms probable CM (pCM), probable CTTH (pCTTH) and probable MOH (pMOH) were introduced. When patients have migraine ≥15 days/month and they report overuse of acute medications, they should be coded as pCM (preceded by the antecedent migraine subform, usually migraine without aura) plus pMOH. When patients have tension-type headache ≥15 days/month and they report overuse of acute medications, they should be coded as pCTTH plus pMOH. If patients revert to an episodic headache after

discontinuation of overuse, the MOH diagnosis is confirmed; if the CM or CTTH criteria are fulfilled 2 months after medication overuse has ceased, these diagnoses are confirmed.

The ICDH-II criteria for CM and MOH are not easy to apply in clinical practice [3–5]. Alternative criteria were proposed by Bigal et al. [5]. These authors tested different classification proposals on a sample of patients previously diagnosed with transformed migraine, and concluded that the presence of at least 8 days with migraine per month in a patient with CDH was the most suitable threshold for defining transformed migraine. Recently, revised criteria for CM and MOH have been proposed by the IHS [6]. The major changes are as follows. CM should be diagnosed in patients who currently suffer from ≥15 headaches/month, at least eight of which are migraine without aura, and/or who report relief after triptan administration. MOH should be diagnosed in patients who report headache on ≥15 days/month and who use ergotamine, triptans or combination analgesics ≥10 days/month, or simple analgesics or any combination of ergotamine, triptans, analgesics and opioids on ≥15 days/month. Furthermore the MOH diagnosis no longer requires improvement after discontinuation of the overused medications.

The aim of the present study was to evaluate how the revised ICHD-II criteria [6] fit a sample of CDH patients consulting our tertiary Headache Centre, in comparison to the alternative classifications.

Materials and methods

Ninety consecutive patients referred to our Headache Centre with headaches lasting ≥4 h, if not treated, for ≥15 days/month were considered for inclusion. We excluded secondary headaches by clinical examination, biochemical analysis and cerebral MRI, when indicated. A headache specialist performed a semistructured interview in which the characteristics of CDH and pre-CDH headaches, and frequency and type of symptomatic drugs consumed, were elicited. Patients were classified according to the ICHD-II-revised criteria [6], the original ICHD-II criteria [2], the Silberstein and Lipton criteria [1] and the Bigal et al. criteria [5].

Results

Six of the 90 screened patients were excluded as they were unable to give complete information (no headache diary cards available) and a further four were excluded as they were found to have secondary headaches. Thus, 80 patients were studied: 13 men, 67 women; mean age 39.7 years, SD 12.5.

Diagnoses according to the different classification systems are shown in Table 1. By applying the revised ICHD-II criteria, 72/80 of the patients fulfilled the criteria for MOH (column 4 of Table 1).

Discussion

While in the 2004 ICDH-II classification multiple codes are required in most cases, the revised (2006) ICDH-II criteria require a single diagnostic code for each patient, suggesting that the these criteria may be easier to use, as noted by other authors [3, 5, 7, 8]. Easier application may be important in general clinical practice, as it may sensitise clinicians to difficult cases (those with MOH), prompting their referral to specialist centres [6]. However, the revised definition of MOH may result in

Table 1 Diagnoses of 80 patients with chronic daily headaches according to the various diagnostic criteria

Silberstein and Lipton, 1996 [1]		ICDH-II 2004 [2]		Bigal et al., 2006 [5]		ICDH-II revised 2006 [6]		Proposed second code appended to revised ICDH-II diagnosis of MOH	
	n (%)		n (%)		n (%)		n (%)		n (%)
CTTH –	5 (6.25)	CTTH	5 (6.25)	CTTH	5 (6.25)	CTTH	5 (6.25)	N/A	
CTTH +	5 (6.25)	pCTTH +pMOH	5 (6.25)	pCTTH+pMOH	5 (6.25)			CTTH	5 (6.25)
TM +	67 (83.75)	MO+pCM+pMOH	42 (52.5)						
		MO+pCM+pCTTH+ pMOH	10 (12.5)	pCM+pMOH	67 (83.75)	MOH	72 (90)	CM	66 (82.5)
		MO+pCTTH+pMOH	14 (17.5)						
		MA+pCTTH+pMOH	1 (1.25)					MA+CTTH	1 (1.25)
TM –	3 (3.75)	pCM	3 (3.75)	CM	3 (3.75)	CM	3 (3.75)	N/A	
		Total	80	Total	80	Total	80	N/A	

CTTH +, with medication overuse; *CTTH –*, without medication overuse; *N/A*, not applicable; TM, transformed migraine; *TM +*, with medication overuse; *TM –*, without medication overuse; *MO*, migraine without aura; *MA*, migraine with aura; *p*, before any headache form indicates probable

this entity being diagnosed by default in a high proportion of patients attending a tertiary care centre: in our series this was by far the most common diagnosis. Furthermore the MOH diagnosis may not provide sufficient information for patient management. We suggest that a more thorough evaluation of cases with CDH with medication overuse would be encouraged by appending to the diagnostic code for MOH codes indicating the clinical features of the current headache. We therefore propose the modified classification presented in column 5 of Table 1. If we consider the 72 patients fulfilling the criteria for MOH according to the revised ICDH-II classification, 66 would be considered CM according to their clinical characteristics, and of the six remaining patients, five would be CTTH and one would be CTTH plus migraine with aura. Thus, our proposed scheme accepts the revised ICDH-II classification as primary code (suggesting the need to tackle the medication overuse) but also provides a second code indicating the clinical characteristics of the headache and hence suggesting what treatment to apply.

References

1. Silberstein SD, Lipton RB, Sliwinski M (1996) Classification of daily and near-daily headaches. Neurology 47:871–875
2. Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24[Suppl 1]:9–160
3. Bigal ME, Tepper SJ, Sheftell FD et al (2004) Chronic daily headache: correlations between the 2004 and the 1988 International Headache Society diagnostic criteria. Headache 44:684–691
4. Manzoni GC, Torelli P (2004) Headache classification: criticism and suggestion. Neurol Sci 25[Suppl 2]:S67–S69
5. Bigal ME, Tepper SJ, Sheftell FD et al (2006) Field testing alternative criteria for chronic migraine. Cephalalgia 26:477–482
6. Headache Classification Committee of the International Headache Society (2006) New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26:742–746
7. Sancisi E, Cevoli S, Pierangeli G et al (2007) Application of ICHD-II and revised diagnostic criteria to patients with chronic daily headache. Neurol Sci 28:2–8
8. Bigal ME, Rapoport AM, Sheftell FD et al (2007) The International Classification of Headache Disorders revised criteria for chronic migraine: field testing in a headache specialty clinic. Cephalalgia 27:230–234

Neurol Sci (2008) 29:S161–S163
DOI 10.1007/s10072-008-0913-6

ORAL COMMUNICATION

In-patient vs. day-hospital withdrawal treatment for chronic migraine with medication overuse and disability assessment: results at one-year follow-up

Licia Grazzi · Frank Andrasik · Susanna Usai · Gennaro Bussone

Abstract Chronic headaches have increasingly become a focus within the field of head pain. Most patients with frequent headache eventually overuse their medications. The diagnosis of medication-overuse headache is clinically important, because patients rarely respond to preventive medications whilst overusing acute medications. Properly treating medication overuse and preventing relapse require specific therapeutic strategies and the recognition of the different factors that contribute to its development and perpetuation, including some behaviours and psychological elements that are important in sustaining the overuse of medication. Abrupt withdrawal is considered the first step for helping these patients to stop medication overuse. The possibility of withdrawal within a day-hospital setting is considered a therapeutic alternative for these patients and compared to in-patient withdrawal. Long-term results are discussed.

Keywords Chronic headache · Medication overuse headache · In-patient withdrawal · Day-hospital withdrawal · Pharmacological treatment

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Introduction

Patients with chronic migraine and medication overuse are particularly difficult to treat, with no one approach being universally accepted. Among the studies existing on therapeutic approaches for these patients, it is difficult to make comparative statements [1, 2]. In fact different diagnostic criteria have been used, leading to heterogeneous groups of patients, as no clear consensus exists about the proper diagnosis.

Concerning the possibilities for managing these particular patients, there is general consensus on the fact that abrupt drug withdrawal seems to be the most appropriate first step, before introducing any kind of prophylaxis [1, 2].

Medication withdrawal strategies are different. In particular in-patient withdrawal seems the most helpful method and after that it is necessary to follow the patients for an extended time with specific preventive therapy to avoid any relapse to former medication overuse, with results confirmed at long-term follow up [3–5].

In-patient treatment is needed in problematic patients who have problems with other kind of pathologies and in those with barbiturates overuse who need specific management during the withdrawal. Also, most of the patients need to be supported and encouraged by physicians, nurses and family members to follow instructions carefully, to stop the vicious cycle between aborting medication and headache increase in order to be effectively treated by a preventive therapy.

Other models of withdrawal treatment include outpatient treatment or in a day-hospital setting. In these cases the patients have to be highly motivated and self-disciplined to follow the instructions carefully. In the case of a day-hospital setting, the patients need to stay in the hospital for the intravenous therapy for at least 6 h and then they can stay at home for the rest of the day.

The aim of this study was to determine (1) the clinical course of 2 samples of chronic migraine patients with medication overuse 12 months after two different treatment interventions (in-patient or day-hospital withdrawal); and (2) whether functional impairment, assessed by the MIDAS questionnaire, improved upon treatment.

Methods

Two groups of patients were enrolled: for Group A, 146 patients, an in-patient withdrawal was performed; for Group B, 114 patients, an out-patient withdrawal (day-hospital schedule) was performed.

All patients received a diagnosis of chronic migraine with medication overuse according to the Silberstein and Lipton Criteria [6]. The patients took, daily or almost daily, a combination of medications consisting of NSAIDS, barbiturates, ergotamines, triptans and caffeine.

Eighty-four patients from Group A and 65 patients from Group B were seen for the last follow-up, 12 months after withdrawal. Five measures were used to assess outcome. Two of the measures were extracted from the diaries: (1) number of headache days per month and (2) number of analgesic pills consumed per month. All the patients were instructed to use as few analgesic pills as possible, particularly in the first phase of therapy. Also after the withdrawal phase was completed, they were instructed to use triptans only or, in case the triptan was unhelpful, indomethacin.

The remaining measures consisted of the Total Score, headache frequency and headache intensity (A, number of days of headache in the previous 3 months; and B, average pain intensity of the headache attacks) from the Migraine Disability assessment Questionnaire (MIDAS) [7]. The Italian translations of the MIDAS Questionnaire were tested using a standardised methodology [8].

All patients were provided a semi-standardised in-patient or day-hospital withdrawal treatment. The hospitalised patients stayed in the clinical department for a period of 7 days. For the day-hospital group the patients arrived at the hospital at 8.30 a.m., completed their intravenous therapy and then left the hospital at 3 o'clock.

For patients of both groups the treatment consisted of: (1) intravenous hydration for a period of 10 days; (2) intravenous steroids for the first 5 days followed by oral prescription for another 5 days; (3) diazepam per os in 2 prescriptions per day; (4) ev or im metoclopramide or indomethacine when needed for intense rebound headache [9].

On day 6 patients were started on one of the several prophylactic antimigraine compounds recommended by published guidelines [9]: flunarizine, pizotifen, propanolol or amitriptyline, when needed for mood disorder.

All the patients were recommended to stop work or any other activity during the withdrawal in the day-hospital setting, and to stay at home and rest as much as possible after the therapy; the patients of both groups were encouraged to abruptly stop taking analgesics and to use intramuscular indomethacin only for intense headache attacks.

Results

The patients of both groups had improved significantly at 12 months follow up: days of headache per month decreased (Group A: 26.1 vs. 10.7; Group B: 24.3 vs. 9.9), medications/month decreased (Group A: 48.9 vs. 12; Group B: 33.1 vs. 8.1) and a measure of functional impact from the MIDAS questionnaire improved (MIDAS total score: Group A: 70.8 vs. 23.3; Group B: 58.6 vs. 19.1 vs. 8.1).

Conclusions

Medication overuse headache leads to considerable disability prior to treatment. However, notable improvement both in headache parameters and in disability measures can occur after day-hospital withdrawal treatment or after in-patient withdrawal: this emerges from the considerable improvement for both diary-based measures of headache activity, MIDAS-based measures and most importantly the overall measure of disability obtained from MIDAS, in both groups.

These findings confirm previous results in patients followed for 1 and 3 years after a withdrawal treatment performed by an in-patient modality [3, 4], but also after the day-hospital withdrawal in this case and, once again, suggest that successful treatment has wide-ranging positive benefits beyond mere symptom reduction. It also suggests that withdrawal by day-hospital setting is as helpful for these patients as in-patient treatment, the improvement being maintained until 1 year post-treatment after day-hospital treatment also.

This last option, less expensive compared to regular hospitalisation, is effective when the patients are followed and instructed carefully about the treatment and the use of the pharmacological compounds.

The confidence and the compliance, although we did not measure any of these variables, were relevant: the patients came every morning to the clinic, where they were carefully managed and reinforced by daily explanations about what to expect from the therapy.

Although our results are encouraging, with a homogeneous group of patients and reasonably long-term follow up, they cannot be definitive. The major limitation is the absence of a control comparison condition. We felt it was important, as a first step, to test this new option of withdrawal, in order to find alternative approaches to the well known in-patient withdrawal, which is not suitable for all patients, and also to compare these results with those reported from our preceding and different clinical experi-

ences. The patients in this case felt comfortable, as they could spend many hours at home where they learned to manage their rebound headache, when present.

On the basis of these significant findings, we believe it may prove fruitful to compare different treatment approaches for this particular category of patients (in-patient vs. day-hospital treatment vs. out-patient, pharmacological treatment alone or augmented by behavioural and related procedure) in order to find more effective methods for the patients and cost-saving procedures at the same time.

References

1. Diener HC, Limmroth V (2004) Medication overuse headache: a worldwide problem. Lancet Neurol 3:475–483
2. Grazzi L, Andrasik F (2006) Medication overuse headache: description, treatment and relapse prevention. Curr Pain Headache Rep 10:71–77
3. Grazzi L, Andrasik F, D'Amico D et al (2004) Disability in chronic migraine patients with medication overuse: treatment effects at 1 year follow-up. Headache 44:678–683
4. Andrasik F, Grazzi L, Usai S et al (2007) Disability in chronic migraine with medication overuse: treatment effects at 3 years. Headache 47:1277–1281
5. Freitag F, Lake AL III, Lipton R et al (2004) Inpatient treatment of headache: an evidence-based assessment. Headache 44:342–360
6. Silberstein SD, Lipton RB (2000) Chronic daily headache. Curr Opin Neurol 13:277–283
7. Stewart WF, Lipton RB, Whyte J et al (1999) An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology 53:988–994
8. D'Amico D, Mosconi P, Genco S (2001) The Migraine Disability Assessment [MIDAS] questionnaire: translation and reliability of the Italian version. Cephalalgia 21:947–952
9. Grazzi L, Andrasik F, D'Amico D et al (2002) Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at 3 years. Headache 42:483–490

Neurol Sci (2008) 29:S164–S165
DOI 10.1007/s10072-008-0914-5

ORAL COMMUNICATION

Headache attributed to spontaneous intracranial hypotension

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Abstract Recent evidence suggests that spontaneous intracranial hypotension (SIH) is not as rare as previously thought. Orthostatic headache is the prototypical manifestation of SIH, but various headache syndromes have also been reported such as migraine-like headache, tension-type headache and non-specific headaches among the others. The International Headache Society (IHS) has recently proposed diagnostic criteria for headache attributed to SIH. Seventy patients consecutively seen at our institution between 1993 and 2005 and diagnosed with SIH were included in the study. SIH diagnosis was confirmed in all patients by brain-enhanced MRI: 23 were males (33%), 47 females (77%) and mean age was 45 years (range 18–69). Follow-up: median value 35 months (range: 8 months–14 years). Time between symptom onset and diagnosis was 4 months (median) (range 15 days–45 months). The IHS (2004) criteria for "Headache attributed to SIH" were applied. Typical brain imaging findings confirmed the diagnosis of SIH in all patients: criteria B and C were fulfilled in all patients. Criterion A of the IHS classification was not fulfilled in 34 (49%) patients. Sixty-two (89%) patients did not fulfil criterion D of the IHS classification; 28 (40%) did not fulfil both criterion A and D. So far, only 2 (3%) fulfilled all IHS criteria for headache attributed to SIH. The IHS criteria for headache attributed to SIH could not classify the headache in most of our SIH patients. A revision of the IHS criteria for headache attributed to SIH is necessary.

Keywords International Headache Society (IHS) · Spontaneous intracranial hypotension (SIH) · Diagnostic criteria · Headache

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Introduction

Spontaneous intracranial hypotension syndrome (SIH) develops as a result of a marked reduction in the quantity of cerebrospinal fluid (CSF) in the absence of any ascertained cause for loss (for example lumbar puncture or trauma). The condition was first described in 1938 by George Schaltenbrand [1]. SIH affects women more often than men in a ratio of about 2:1 [3], typically in the fourth or fifth decade, with a peak at around 40 years, although the condition has been noted in children and the elderly.

Although the cause of spontaneous loss of CSF is rarely identified, two principal causes appear to be mild trauma and fragile meninges. At least a third of patients report coughing, lifting weights, and sports or other activity prior to the headache, suggesting that mechanical traction can puncture the dural sac [4]. Some authors suggest that a fragile dural sac predisposes to sac defect and hence leakage of CSF into the epidural space [5, 6].

The reduction in CSF volume rather than reduction in pressure has been supposed to be the final common pathway responsible for SIH [7]. The new International

Headache Society (IHS) classification includes headache attributed to spontaneous low CSF pressure (7.2.3) among the secondary headaches [8].

The aim of the study is to apply the IHS diagnostic criteria for headache attributed to SIH to a large SIH population.

Patients and methods

Seventy SIH patients consecutively seen at our institution between 1993 and 2005 were studied. Brain-enhanced MRI confirmed SIH diagnosis in all patients. Twenty-three were males (33%) and 47 females (77%); mean age was 45 years (range 18–69). Follow-up: median value 35 months (range: 8 months–14 years). Time between symptom onset and diagnosis was: 4 months (median) (range 15 days–45 months). Headache and other clinical characteristics were recorded in an ad hoc chart by a semi-structured interview. Patients received epidural blood patch when bed rest, intravenous fluids and conservative treatments including steroids did not improve the condition. The IHS (2004) criteria for "Headache attributed to SIH" were applied.

Results

All patients fulfilled criteria B and C of the IHS classification for Headache attributed to SIH; in all patients typical brain imaging findings confirmed the diagnosis and no previous history of dural puncture or CSF fistula was found (Table 1).

Orthostatic headache was present in 53 patients (76%); in 38 (54%) the headache started within 15 min of the standing position. In 16 patients (23%) headache was not related to standing/sitting position (non-orthostatic headache). Associated phenomena were: nausea 42%, neck stiffness 33%, hypacusia 25%, tinnitus 18% and photophobia 16% in various combinations.

Criterion A of the IHS classification was not fulfilled in 34 (49%) patients (Table 1). This was mainly due to non-orthostatic headache (23%) or orthostatic headache starting after 15 min sitting or standing (21%). Epidural blood patch was performed in 22 (32%) patients: all of these improved but only 8 (11%) did so within 72 h. Sixty-two (89%) patients did not fulfil criterion D of the IHS classification; 28 (40%) did not fulfil both criterion A and D. So far, only 2 (3%) fulfilled all IHS criteria for headache attributed to SIH (Table 1).

Table 1 Application of the IHS diagnostic criteria for headache attributed to SIH in 70 SIH patients

Fulfilled IHS criteria	n	%
Criterion A	36	51
Criterion B	70	100
Criterion C	70	100
Criterion D	8	11
All criteria	2	3

Conclusions

In this study, IHS criteria for headache attributed to SIH did not allow proper classification of the headache in the majority of our SIH patients. A revision of the IHS criteria for headache attributed to SIH is necessary.

References

1. Schaltenbrand G (1938) Neure anschauungen zur pathophyiologie der liquorzirkulation. Zentrabl Neurochir 3:290–300
2. Schievink WI, Maya MM, Moser F et al (2007) Frequency of spontaneous intracranial hypotension in the emergency department. J Headache Pain 8:325–328
3. Schwedt TJ, Dodick DW (2007) Spontaneous intracranial hypotension. Curr Pain Headache Rep 11:56–61
4. Mea E, Savoiardo M, Chiapparini L et al (2007) Headache and spontaneous low cerebrospinal fluid pressure syndrome. Neurol Sci 28[Suppl 2]:S232–S234
5. Schievink WI, Gordon OK, Tourje J (2004) Connective tissue disorders with spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension: a prospective study. Neurosurgery 54:65–70
6. Mokri B, Maher CO, Sencakova D (2002) Spontaneous CSF leaks: underlying disorder of connective tissue. Neurology 58:814–816
7. Mokri B (1999) Spontaneous cerebrospinal fluid leaks: from intracranial hypotension to cerebrospinal fluid hypovolemia – evolution of a concept. Mayo Clin Proc 74:1113–1123
8. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24[Suppl 1]:1–160

Neurol Sci (2008) 29:S166–S168
DOI 10.1007/s10072-008-0915-4

ORAL COMMUNICATION

High prevalence of Dopaminergic Premonitory Symptoms in migraine patients with Restless Legs Syndrome: a pathogenetic link?

Daniela Cologno · Giulio Cicarelli · Vittorio Petretta · Florindo d'Onofrio · Gennaro Bussone

Abstract In order to assess the prevalence of Dopaminergic Premonitory Symptoms (DPS) in migraine patients with Restless Legs Syndrome (RLS), we chose migraine patients from a large Italian clinical headache population previously investigated for an association between primary headaches and RLS. We evaluated a total sample of 164 patients with migraine, in particular 114 with migraine without aura (MO), 10 with migraine with aura (MA) and 40 with MO and MA in various combinations between them or with episodic tension-type headache (ETTH), defined as a "mixed group". About 20% of all migraine patients referred at least one of the following DPS: yawning, nausea, somnolence or food craving, confirming data already indicated in the literature. Among migraine patients with RLS (25.6%), DPS were referred from about half of the patients (47.6%) compared to those without RLS (47.6% vs. 13.1%; $p<0.001$). Based on migraine subtype, patients with MO referred DPS (26.3%) more frequently compared to the MA group and "mixed group" (12.0%, $p<0.05$), particularly in the presence of RLS (63.0% vs. 20.0%, $p<0.01$). No statistical differences were found between clinical and demographic data of the subgroups or related to medical conditions investigated (anxiety, depression, sleep disorders, body mass index). It is interesting that the chances of having RLS in migraine patients were more than 5 times higher in the presence of DPS. These results could support a hypothetical dopaminergic imbalance in RLS and migraine, as the dopamine is involved in the pathogenesis of both disorders and it is responsible for the migraine DPS reported above.

Keywords Migraine · Premonitory symptoms · Dopamine · Restless legs syndrome

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Introduction

Premonitory symptoms (PS) are defined as "symptoms preceding and forewarning of a migraine attack by 2–48 hours, occurring before the aura in migraine with aura and before the onset of pain in migraine without aura" [1]. Prevalence rates of migraine patients reporting one or more PS show wide variability in several clinical studies and rates range between 12% and 80% [2]. Recently, in a Dutch study on almost 500 migraine patients [3], higher rates of PS were reported: at least one PS was reported by 86.9% of

patients and 71.1% reported two or more. The most frequently reported PS were fatigue, phonophobia and yawning. These data were confirmed by Spanish authors that revealed the same rates of migraine PS prevalence (around 80%) [4]. There is some evidence to support the idea that PS could be used as a phenotypical marker to identify subgroups of migraineurs, showing correlations with specific clinical expressions of the disease, genotypes or responses to treatments. The presence of PS is associated with specific migraine clinical aspects, becoming risk factors for migraine with aura (MA) and severe pain [5]. Should these symptoms accurately predict headache, they have considerable implications for the pathophysiology and management of migraine. The neurotransmitters dopamine and serotonin are possibly involved in the development of PS, as demonstrated by experimental models and by the efficacy of migraine abortive and preventive treatments. Among common PS, dopaminergic ones in particular (DPS), such as yawning, nausea, food craving and somnolence, were reported by about 20% of migraineurs, defining a specific subgroup [2]. Based on more recent observations about involvement of dopamine in the pathogenesis of restless legs syndrome (RLS), a movement disorder associated with migraine [6], we evaluated if migraineurs with RLS have a higher prevalence of DPS. If this observation will be demonstrated, DPS in migraine patients with RLS could represent a clinical marker of the association between these disorders, further strengthening the role of dopamine in their pathogenesis.

Methods

In order to assess the prevalence of DPS in migraine patients with RLS, we selected all migraine patients from a wide Italian survey on a clinical headache population previously conducted with the aim of investigating the association between primary headaches and RLS [7]. Patients affected by MA, migraine without aura (MO) or with the two types of migraine combined or associated with episodic tension-type headache (ETTH), defined as a "mixed group", were enrolled. No patients took migraine prophylaxis. Primary headaches were diagnosed according to the International Headache Society (2nd edition) criteria [8] and RLS according to the criteria of the International Restless Legs Syndrome Study Group [9]. The patients were asked to recall the presence of DPS in the time interval ranging between 2 and 48 h before the migraine attack started and without medications. They were also asked to specify which DPS occurred more frequently between yawning, nausea, food craving, somnolence alone or in combination. The clinical and demographic data of migraineurs were registered including lifetime duration of migraine, migraine frequency per month and intensity of migraine attacks. Furthermore, the patients were also asked to fill in a self-assessment questionnaire concerning depression (Beck's Depression Inventory, BDI) [10] and anxiety (Hamilton Rating Scale, HAMA) [11]. Body mass index (BMI) was calculated for each patient. Data are presented as percentage or as arithmetic mean with SD. Statistical analysis was performed by analysis of variance for continuous variables and by non-parametric Chi-square testing for categorical variables. Logistic regression was employed for assessing determinant of RLS in migraine patients. Significance level was set at p=0.05.

Results

We evaluated overall 164 patients with migraine (130 F, 34 M), in particular 114 (90 F, 24 M) with MO, 10 (5 F, 5 M) with MA and 40 (35 F, 5 M) for the "mixed group". At the time of our observation, mean age of the migraine population was 37.1±10.8 years and mean age at onset of migraine was 21.3±7.7 years. The prevalence of RLS in migraine patients was 25.6% (n=42, 35 F, 7 M) with a mean age at RLS onset of 32.5±7.5 years. About 20% (n=37; 32 F, 5 M) of all migraine patients referred more than one DPS with no prevalence either of them. Based on this observation, statistical analysis was performed considering DPS as the single variable. Almost 50% (47.6%) of migraine patients with RLS referred DPS compared to migraine patients without RLS (13.1%), with a statistically significant difference (p<0.001). Based on migraine subtype, more than 80% (n=17) of RLS patients with DPS were affected only by MO, with a significant statistically difference from MA patients and the mixed group patients (p<0.01). No statistical differences were observed between demographic characteristics and clinical features of migraine attacks in the two groups with or without DPS and with or without RLS. Anxiety and depression was diagnosed in 15 (41.7%) migraine patients with DPS and in 38 (29.7%) migraine patients without DPS (p=NS). When only migraine patients with DPS were considered, the prevalence of anxiety and depression was 50.0% (n=10) in patients with RLS and 31.3% (n=5) in patients without RLS (p=NS). Sleep disturbances were diagnosed in 17 (47.2%) migraine patients with DPS and in 40 (31.3%) migraine patients without DPS (p=NS). When only migraine patients with DPS were considered, the prevalence of sleep disturbances was 55.0% (n=11) in patients with RLS and 37.5% (n=6) in patients without RLS (p=NS). In migraine patients with and without DPS, BMI was normal in 77.8% (n=28) and 71.9% (n=92) of cases, respectively (p=NS). When migraine patients with DPS were considered, the prevalence of normal BMI was 75.0% (n=15) in patients with RLS and 81.3% (n=13) in patients without RLS (p=NS). According to multivariate logistic regression analysis the chance of having RLS in migraine patients was more than 5 times higher in the presence of DPS (see Table 1).

Table 1 Odds ratio for determinants of RLS in migraine patients

Variable	Odds ratio	*p*
DPS	5.408	<0.0001
Sleep disturbances	1.947	0.131
Anxiety and depression	1.541	0.336

Discussion

The most important finding of this study is the higher prevalence of DPS in migraineurs affected by RLS. DPS and migraine seem to be independent risk factors for being affected by RLS. Our data confirmed the known association between migraine and RLS [6], suggesting that the most likely important pathogenetical link between the two disorders is dopamine. RLS seems to be based on a dysfunction of the dopaminergic system and the standard therapy for primary RLS is medication with dopamine agonists [12]. On the other hand, clinical evidence and recent genetic findings seem to indicate an involvement of dopamine in the pathophysiology of the migraine attack. Its prodromal symptomatology (mood changes, yawning, drowsiness, food craving), accompanying symptoms (nausea, vomiting, hypotension) and postdromal symptoms (mood changes, drowsiness, tiredness) may be related to dopaminergic activation, which can be detected also in the headache phase, either by taking part in nociception mechanisms or by regulating cerebral blood flow. The literature indicates that migraineurs are hypersensitive to dopamine agonists with respect to some of the PS of migraine such as nausea and yawning. Conversely, dopamine receptor antagonists are effective therapeutic agents in migraine and also a number of polymorphisms of dopaminergic genes related to migraine [13, 14]. Recent studies [15] have suggested that PS of migraine attacks could be explained by involvement of tyrosine metabolism products other than dopamine, defined trace amines (tyramine, octopamine, and synephrine). They are associated with receptors labelled TAARs expressed on the olfactory epithelium, amygdala, hypothalamus, periacqueductal grey, all areas involved in migraine pathophysiology. It has long been hypothesised that the prodromal phase of migraine attacks is initiated by a functional disturbance of the hypothalamus, and that either an episodic disturbance of hypothalamic activity or a labile activation threshold could account for the periodicity of the migraine attack. The latest French data [16] confirmed activation of midbrain and pons nuclei during spontaneous migraine attacks and, for the first time, demonstrated activation of the hypothalamus.

In conclusion, the higher prevalence of DPS in migraineurs with RLS could represent a clinical marker of dopamine impact in both disorders with some indications of the cerebral areas involved. On the other hand, the presence of DPS indicates the likelihood that migraineurs could be affected lifetime by disorders related to dopaminergic imbalance like RLS. We are inclined to consider this chance as plausible, but many other studies are needed to shed light on it.

References

1. Rossi P, Ambrosini A, Buzzi MG (2005) Prodromes and predictors of migraine attack. Funct Neurol 20:185–191
2. Buzzi MG, Cologno D, Formisano R, Rossi P (2005) Prodromes and the early phase of the migraine attack: therapeutic relevance. Funct Neurol 20:179–183
3. Schoonman GG, Evers DJ, Terwindt GM et al (2006) The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. Cephalalgia 26:1209–1213
4. Quintela E, Castillo J, Muñoz P, Pascual J (2006) Premonitory and resolution symptoms in migraine: a prospective study in 100 unselected patients. Cephalalgia 26:1051–1060
5. Kelman L (2004) The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. Headache 44:865–872
6. Rhode AM, Hösing VG, Happe S et al (2007) Comorbidity of migraine and restless legs syndrome – a case-control study. Cephalalgia 27:1255–1260
7. d'Onofrio F, Bussone G, Cologno D et al (2008) Restless legs syndrome and primary headaches: a clinical study. Neurol Sci, *in press*
8. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders. Cephalalgia 24[Suppl 1]:9–160
9. Allen RP, Hening WA, Montplaisir J et al (2003) Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 4:101–119
10. Beck AT, Steer RA, Garbin MG (1988) Psychometric properties of the Beck Depression Inventory. Twenty-five years of evaluation. Clin Psychol Rev 8:77–100
11. Hamilton M (1960) A rating scale for anxiety. J Neurol Neurosurg Psychiatry 23:56–62
12. Allen R (2004) Dopamine and iron in the pathophysiology of restless legs syndrome. Sleep Med 5:385–391
13. Peroutka SJ (1997) Dopamine and migraine. Neurology 49:650–656
14. Akerman S, Goadsby PJ (2007) Dopamine and migraine: biology and clinical implications. Cephalalgia 27:1308–1314
15. D'Andrea G, Nordera GP, Perini F et al (2007) Biochemistry of neuromodulation in primary headaches: focus on anomalies of tyrosine metabolism. Neurol Sci 28[Suppl 2]:S94–96
16. Denuelle M, Fabre N, Payoux P et al (2007) Hypothalamic activation in spontaneous migraine attacks. Headache 47:1418–1426

Neurol Sci (2008) 29:S169–S172
DOI 10.1007/s10072-008-0916-3

ORAL COMMUNICATION

Restless legs syndrome and primary headaches: a clinical study

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Abstract Based on recent data about the association between restless legs syndrome (RLS) and migraine, we performed an observational study on the occurrence of RLS in patients affected by primary headaches. Two hundred headache patients (149 women and 51 men) and 120 (90 women and 30 men) sex- and age-matched control subjects were included. In the headache group, migraine without aura (MO) was the most represented headache type (n=114), followed by the "mixed" group (n=40) with MO, migraine with aura (MA) and frequent episodic tension-type headache (ETTH) in various combinations, and by ETTH alone (n=22). The remaining patients suffered from MA alone (n=10 MA), episodic cluster headache (ECH n=12) and primary stabbing headache (n=2). RLS frequency was significantly higher in headache patients than in control subjects (22.4% vs. 8.3, p=0.002) independently of sex, although with a female preponderance (84%) in both groups. More than 60% (n=27) of RLS patients were affected by MO and 30% (n=13) by a combination of two headache types ($p \geq 0.001$), with a very low frequency of RLS for the other types of headache. No RLS patient had ECH. No statistical differences were observed among clinical characteristics of different types of headache in groups with and without RLS. In both headache and control groups, higher scores for depression and anxiety were more frequent in subjects with RLS compared with those without RLS. Furthermore, headache patients with RLS reported sleep disturbances more frequently compared to those without RLS (50.0% vs. 32.7%; $p<0.0001$) and showed a normal or underweight body mass index. Our data seem to confirm the existence of an association between RLS and primary headaches, particularly with migraine, as already demonstrated. The absence of RLS in ECH patients is very interesting. Many pathogenetic considerations about links between RLS and primary headaches could be given, the most fitting involving dopamine and melatonin.

Keywords Primary headache · Restless legs syndrome · Prevalence · Clinical population · Migraine

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Introduction

Primary headaches have been associated with various movement disorders. In particular, higher prevalence of migraine in essential tremor [1], Tourette's syndrome [2] and Sydenham's chorea [3] and a lower prevalence in Parkinson's disease have been reported [4]. On the other hand, an association between headache and sleep has long been recognised in the medical literature [5]. Very recently, restless legs syndrome (RLS) has been associated with

migraine [6], opening new perspectives for a pathogenetic link other than a comorbidity between the two conditions. RLS, first termed by Ekbom in 1945 [7], is a common neurological condition characterised by unpleasant sensations deep inside the legs, accompanied by an urge to move the limbs and motor restlessness, occurring at rest, especially at bedtime. Its clinical diagnostic criteria were established by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 [8]. The criteria were reviewed and published in 2003 [9]. Idiopathic and symptomatic RLS forms have been recognised, the latter occurring during pregnancy or associated with uraemia, iron depletion, polyneuropathy, spinal disorders and rheumatoid arthritis. The prevalence of RLS varies from 2% to 15% in the general population [10, 11], but it is often not recognised or misdiagnosed. The frequency increases with age and its prevalence is higher in women than in men. The aim of this study was to investigate the prevalence of RLS in an adult clinical population affected by primary headaches, matched by age and sex with a control group of non-headache subjects, in order to confirm the known association between RLS and migraine and to identify any relationship with other primary headaches and their hypothetical pathogenetic links.

Methods

We enrolled 200 consecutive headache patients (149 females, 51 males) aged 18–65 years, referring to three Italian headache centres, during a six-month period. One hundred and twenty healthy headache-free subjects (90 females, 30 males), matched by age and sex, were recruited from among hospital employers and visitors and served as controls. Both headache patients and control subjects underwent a direct interview and neurological examination. The diagnosis of the type of headache was made according to ICHD-II criteria [12] by a headache specialist. All headache patients were not headache prophylaxis medications or antidepressants for at least three months prior to our observation. Episodic cluster headache patients (ECH) were investigated outside the cluster period. Headache clinical features were registered including headache lifetime duration, frequency per month and pain intensity. Diagnosis of RLS (idiopathic or symptomatic) was made by another neurologist blinded for headache diagnosis, following the revised criteria of IRLSSG [9]. All subjects also underwent a semi-structured interview in order to investigate the association with insomnia, body weight and psychiatric disturbances. Insomnia was diagnosed according to international criteria [13]. For all subjects body mass index (BMI) was calculated. We divided subjects into 3 categories based on BMI score: underweight (<18.5 kg/m^2), normal (18.6–24.9 kg/m^2) and overweight (25.0–29.9 kg/m^2). The Hamilton Anxiety Rating Scale (HAMA) [14] and the Beck Depression Inventory (BDI) [15] were used to disclose the presence of anxiety and depression disorders. Diagnoses of anxiety and depression were made with a score of ≥18 respectively. Psychopathological evaluations were conducted by a third specialist who was blind to subject condition. Data are presented as percentage or as arithmetic mean with SD. Statistical analysis was performed by analysis of variance for continuous variables and by non-parametric Chi-square testing for categorical variables. Logistic regression was employed for assessing determinant of RLS in migraine patients. Significance level was set at p=0.05.

Results

Demographic and clinical data of the headache patients and control subjects are presented in Table 1. One hundred and fourteen headache patients (90F, 24M) were affected by migraine without aura (MO), 22 patients (16F, 6M) by frequent episodic tension-type headache (ETTH), 10 patients (5F, 5M) by migraine with aura (MA), 12 patients (1F, 11M) by ECH and 2 patients (2F) by primary stabbing headache (PSH). The remaining 40 patients (35F, 5M) suffered from two primary headaches (MO, MA and ETTH in various combinations). No significant differences were found in the mean age at onset and lifetime duration for any subtype of headache. The prevalence of RLS was 22.4% (n=44) in headache patients and 8.3% (n=10) in control subjects (p=0.002), with a female preponderance in both groups. No statistical differences were observed about demographic characteristics between headache patients and controls affected by RLS and those without RLS. In the RLS-headache group, migraine was the more frequent type of primary headache (MO n=27; MA n=2; "Mixed group" n=13; p<0.001), with a higher frequency of symptomatic cases of RLS compared to controls (38.19% vs. 20.0% of controls; p=NS). In the remaining forms of primary headache, RLS was present in 1 patient with ETTH and 1 patient with PSH. It is worthwhile to observe that no ECH patients were affected by RLS. Among headache clinical features, our results did not show any relationship between RLS and monthly attack frequency, intensity of pain and lifetime duration of headache. Concerning medical conditions investigated in both groups of subjects, higher scores for depression and anxiety were detected in headache patients and controls with RLS compared with those without RLS, with a significant difference only for the headache patients (45.5% vs. 29.5%; p<0.05< 0.05 for headache patients and 50.0% vs. 27.3%; p=NS< 0.05 for controls). Among headache patients, those affected by MO and RLS reported higher scores for anxiety and/or depression with a statistical significant difference compared to those without RLS (p=0.012). Headache patients

Table 1 Demographic and clinical data of the headache patients and control subjects (presented as arithmetic mean and SD or as percentage)

	Headache patients (n=200)	Control subjects (n=120)	*p*-value
Age (years)	37.2±11.1 (18–65)	37.2±8.5 (20–56)	NS
Female age	37.6±11.5 (18–65) (n=149)	36.7±8.1 (20–53) (n=90)	NS
Male age	36.1±10.0 (21–59) (n=51)	38.8±9.6 (20–56) (n=30)	NS
Headache age at onset	22.9±9.4 (8–60)	NA	NA
Headache duration	14.3±10.1 (1–40)	NA	NA
Attack frequency per month	Low (<1/month): 41.0% Medium: (1–3/month): 20.5% High (>3/month): 38.5%	NA	NA
Intensity of pain	Mild: 9.5% Moderate: 50.5% Severe: 40.0%	NA	NA
RLS prevalence	22.4% (n=44)	8.3% (n=10)	0.002
Sex-Female	84.1% (n=37)	80.0% (n=8)	NS
Sex-Male	15.9% (n=7)	20.0% (n=2)	
RLS age at onset (years)	33.23±8,4	29.40±6.,83	0.187
RLS duration (years)	5.6±4.5 (1–20)	4.6±3.1 (1–10)	0.520

NA, not applicable

and controls with RLS report insomnia more frequently compared to those without RLS ($p<0.0001$). This trend was more pronounced in MO patients with no significant statistical difference compared to controls and other headache subtype patients (p=NS).

The BMI calculated for each subject was in the normal range in 68.2% of headache patients and half of controls. In contrast to that previously reported for RLS patients [10], few headache patients with RLS were overweight compared to headache patients without RLS (p=NS). Among all clinical headache features investigated, migraine and MO and BMI in the normal range increase the risk for RLS from five-four to six-fold (migraine: 4.974; normal BMI: 5.840).

Discussion

Since standard diagnostic criteria of RLS were proposed by IRLSSG [8, 9], several epidemiological investigations have reported similar rates of prevalence in the general population for a broad spectrum of adult ages. The widest epidemiological study performed in the USA and in five European countries showed an overall RLS prevalence of 7.2% [16], a rate similar to that found in our control subjects population (8.3%). RLS was found to be associated with several somatic and neuropsychiatric conditions irrespective of a possible causal link. Sleep-related complaints were more frequent among RLS sufferers [17] and also depressed mood [18], reduced libido, hypertension and heart problems [19]. Headache at awakening and daytime headache were reported 3–5 times more frequently among RLS sufferers, although in a male clinical population [19]. Recently, a German case-control study revealed the existence of an association between migraine and RLS [6].

Our study confirmed a higher prevalence of RLS in patients affected by primary headaches (22.4%) compared to headache-free subjects (8.3%). The results revealed that RLS is independent of age and sex both in headache patients and in controls, although it is more frequent in females in both groups.

The evaluation of different headache subtypes showed that MO can increase the risk of RLS, unlike other headache types like ETTH and ECH. In ECH patients, although the size of the sample appears small, it is adequate if we consider the low prevalence in the general population of this kind of headache (0.03%) [20]. So, we could postulate that ECH represents a protective factor from RLS.

Regarding medical conditions investigated, the higher frequency of depression and anxiety found in headache patients with RLS, in particular in those affected by MO, confirmed data already existing in the literature for both disorders. On the contrary, being overweight did not represent a variable that influences the risk of RLS, as previously reported [10], in headache patients. Contrary to expectations, insomnia influences the presence of RLS only in controls but not in headache patients.

The association between RLS and primary headaches, especially for migraine, probably presumes pathogenetic links. Many topics could be implicated: (1) both are central nervous system disorders; (2) RLS pathology likely involves cortical and subcortical areas of the brain, with decreased inhibition of the sensorimotor cortical and an increased cortical silent period [21]; primary headaches, migraine and in particular MA, are related to a status of cortical hyperexcitability or reduced cortical inhibition [22]; (3) the RLS response to dopaminergic therapy suggests a possible role of dopamine in its pathogenesis [23], although functional neuroimaging studies have produced conflicting results [24]; dopaminergic abnormalities have been demonstrated in migraine [25]; (4) a melatonin imbalance could be involved in RLS and cluster headache, both circadian disorders where changes in melatonin secretion have been shown, but with an inverse relation-

ship: nocturnal increase in melatonin secretion correlates with onset and worsening of RLS symptoms mediated by a melatonin inhibition of the central dopamine secretion [26], while a decrease in nocturnal melatonin secretion with lower levels during cluster periods than remissions was demonstrated in CH patients [27, 28].

A link between dopamine and melatonin in RLS has been suggested by RLS animal models where a dysfunction or atrophy of the dopaminergic A11 cell group, the only cells that provide dopaminergic axons to the spinal cord, was reported as the possible pathophysiological correlate of the syndrome. This could explain both the excellent response to dopaminergic drugs and the circadian rhythm of the syndrome, as these cells are in close proximity to the whose hypothalamic circadian pacemaker [29], activation of which is also demonstrated in CH. In this direction we could explain the peculiar absence of RLS in our ECH patients.

Finally, another pathogenetic contact point between RLS and primary headaches is the abnormality of brain iron metabolism. Iron is an important cofactor in dopamine synthesis and this represents a bridge between the two major pathogenetic mechanisms involved in RLS [23]. In migraine, especially in chronic migraine with long duration of illness, brain iron storage has been found in periaqueductal grey matter, indicating an abnormal iron metabolism also in migrainous brain [30]. In conclusion, our data show that migraine could represent a risk factor for RLS, while CH might be an hypothetical protective factor. These findings could shed light on the pathogenesis and treatment of migraine when associated with RLS.

References

1. Biary N, Koller W, Langenberg P (1990) Correlation between essential tremor and migraine headache. J Neurol Neurosurg Psychiatry 53:1060–1062
2. Kwak C, Vuong KD, Jankovic J (2003) Migraine headache in patients with Tourette syndrome. Arch Neurol 60:1595–1598
3. Teixera AL Jr, Meira FC, Maia DP et al (2004) Migraine headache in patients with Sydenham's chorea. Cephalalgia 25:542–544
4. Barbanti P, Fabbrini G (2002) Migraine and the extrapyramidal system. Cephalalgia 22:2–11
5. Rains JC, Poceta JS (2006) Headache and sleep disorders: review and clinical implications for headache management. Headache 46:1344–1363
6. Rhode AM, Hösing VG, Happe S et al (2007) Comorbidity of migraine and restless legs syndrome – a case-control study. Cephalalgia 27:1255–1260
7. Ekbom KA (1945) Restless legs. A clinical study. Acta Med Scand 158[Suppl]:1–123
8. Walters AS, for the International Restless Legs Syndrome Study Group (1995) Toward a better definition of restless legs syndrome. Mov Disord 10:634–642
9. Allen RP, Hening WA, Montplaisir J et al (2003) Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 4:101–119
10. Phillips B, Young T, Finn L et al (2000) Epidemiology of restless legs symptoms in adults. Arch Intern Med 160:2137–2141
11. Zucconi M, Ferini-Strambi L (2004) Epidemiology and clinical findings of restless legs syndrome. Sleep Med 5:293–299
12. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders. Cephalalgia 24[Suppl 1]:9–160
13. American Academy of Sleep Medicine (2005) International Classification of Sleep Disorders: Diagnostic and Coding Manual, 2nd Edn. American Academy of Sleep Medicine, Westchester, IL
14. Hamilton M (1960) A rating scale for anxiety. J Neurol Neurosurg Psychiatry 23:56–62
15. Beck AT, Steer RA, Garbin MG (1988) Psychometric properties of the Beck Depression Inventory. Twenty-five years of evaluation. Clin Psychol Rev 8:77–100
16. Allen RP, Walters AS, Montplaisir J et al (2005) Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 165:1286–1292
17. Bjorvatn B, Leissner L, Ulfberg J et al (2005) Prevalence, severity and risk factors of restless legs syndrome in the general adult population in two Scandinavian countries. Sleep Med 6:307–312
18. Sevim S, Dogu O, Kaleagasi H et al (2004) Correlation of anxiety and depression symptoms in patients with restless legs syndrome: a population based survey. J Neurol Neurosurg Psychiatry 75:226–230
19. Ulfberg J, Nystrom B, Carter N, Edling C (2001) Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. Mov Disord 16:1159–1163
20. Torelli P, Beghi E, Manzoni GC (2005) Cluster headache prevalence in the Italian general population. Neurology 64:469–474
21. Entezari T, Singleton JR, Jones CR et al (1999) Changes in excitability of motor cortical circuitry in primary restless legs syndrome. Neurology 53:1201–1205
22. Brighina F, Piazza A, Daniele O, Fierro B (2002) Modulation of visual cortical excitability in migraine with aura: effects of 1 Hz repetitive transcranial magnetic stimulation. Exp Brain Res 145:177–181
23. Allen R (2004) Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). Sleep Med 5:385–391
24. Wetter TC, Eisensehr I, Trenkwalder C (2004) Functional neuroimaging studies in restless legs syndrome. Sleep Med 5:401–406
25. Fanciullacci M, Alessandri M, Del Rosso A (2000) Dopamine involvement in the migraine attack. Funct Neurol 15[Suppl 3]:171–181
26. Michaud M, Dumont M, Selmaoui B et al (2004) Circadian rhythm of restless legs syndrome: relationship with biological markers. Ann Neurol 55:372–380
27. Waldenlind E, Gustafsson S, Ekbom K, Wetterberg L (1987) Circadian secretion of cortisol and melatonin in cluster headache during active cluster periods and remission. J Neurol Neurosurg Psychiatry 50:207–213
28. Leone M, Lucini V, D'Amico D et al (1995) Twenty-four- hour melatonin and cortisol plasma levels in relation to timing of cluster headache. Cephalalgia 15:224–229
29. Ondo WG, He Y, Rajasekaran S, Le WD (2000) Clinical correlates of 6-hydroxydopamine injections into A11 dopaminergic neurons in rats: a possible model for restless legs syndrome. Mov Disord 15:154–158
30. Welch KM, Nagesh V, Aurora SK, Gelman N (2001) Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Headache 41:629–637

Neurol Sci (2008) 29:S173–S175
DOI 10.1007/s10072-008-0917-2

ORAL COMMUNICATION

Homocysteine plasma levels in patients with migraine with aura

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Abstract We investigated homocysteine plasma levels in 136 MA sufferers and in 117 sex- and age-matched controls. Mean homocysteine plasma levels – as well as the proportion of subjects with hyperhomocysteinaemia – were significantly higher in patients with MA than in healthy controls. Hyperhomocysteinaemia may be a link between MA and ischaemic stroke.

Keywords Migraine with aura (MA) · Homocysteine · Hyperhomocysteinaemia · Stroke

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Introduction

Migraineurs, particularly those with migraine with aura (MA), have an increased risk for clinical and subclinical vascular brain lesions [1, 2], and MA has been established as an independent risk factor for juvenile ischaemic stroke [3, 4]. The reasons explaining the association between MA and cerebrovascular disease are unknown, and classic vascular risk factors do not appear to be involved [2, 5].

Homocysteine is a sulphur-containing amino acid involved in the metabolism of methionine. The presence of high homocysteine plasma levels (hyperhomocysteinaemia) is an independent risk factor for thrombosis, atherosclerosis and various forms of ischaemic vascular disease, such as myocardial infarction – and particularly for ischaemic stroke [6–9].

The aim of this study was to investigate homocysteine plasma levels in a sample of MA patients in view of a possible role of hyperhomocysteinaemia as a putative causal factor for the MA/stroke association.

Materials and methods

A total of 136 consecutive subjects fulfilling the ICHD-II 2004 criteria for MA [10] were enrolled among those presenting to the Headache Centres of the C. Besta Neurological Institute in Milan and of the L. Mandic Hospital in Merate (LC) from April 2004 to December 2006. They were 90 females and 46 males; the age range was 14–61 years (mean 30.1 years, SD 10.1). Neurological and clinical examinations were performed in addition to ophthalmological evaluation in all patients.

The control group consisted of 117 subjects, who were volunteers from among the medical staff and regular blood donors; 66 were females and 51 were males; the

age range was 24–61 years (mean age 36.1 years, SD 8.26).

The presence of several conditions possibly inducing increased homocysteine levels (chronic heart disease, previous stroke, chronic renal failure, immunodeficiency disease, vegetarian diet) were investigated either in MA patients and in controls: all these conditions were absent in the enrolled subjects. Personal history of migraine or of thromboembolic diseases was excluded by clinical interview in controls.

Plasma homocysteine was measured in the morning after a 12-h fast by immunochemical methods (IMX, Abbot Laboratories). Mean homocysteine plasma levels were calculated in the two studied groups and compared using the Student-Newman-Keuls test. The proportions of subjects with hyperhomocysteinaemia (defined as plasma levels higher than 10 μ/l in women and higher than 15 μ/l in men) were evaluated both in MA patients and in controls, and the differences between the two studied groups were assessed by chi square test.

Results

Mean homocysteine plasma levels were higher in MA patients than in controls (Table 1).

The proportions of subjects with hyperhomocysteinaemia were also higher among MA (Table 2).

Statistical analyses showed that these differences were significant as far as total groups for both comparisons. When analyses were made by gender distribution, differences were significant in men and not in women (Tables 1 and 2).

Discussion

We found an increase in homocysteine plasma levels – and a higher proportion of subjects with hyperhomocysteinaemia – in MA patients as compared to healthy controls, particularly among men.

The association between migraine and homocysteine has not been extensively studied. Only two studies have been published, which led to controversial results [11, 12]. Our findings are partially in line with previous studies. Hering-Hanit et al. [11] reported that homocysteine plasma levels were not increased in a sample of migraineurs (56 with migraine without aura, 22 with MA), although analysis by gender showed that homocysteine levels were higher in men. Evers et al. [12] reported higher homocysteine plasma levels in a group of migraine patients, which were significantly increased only in those with MA.

We note that case control studies [13–16] showed that the T/T homozygosis in the MTHFR C677T genotype – a genetic condition which is known to cause hyperhocysteinaemia – was associated with increased risk of MA in selected clinical samples. The same genetic condition was found to induce a two-fold increase in the risk of developing MA according to data from a population study in which MA subjects were compared to migraine without aura subjects and with nonmigraineurs [17]: T/T genotype was associated with increased odds of MA (OR 2.05, 95% confidence interval, 1.2–3.4; $p<0.006$).

There is evidence that elevated homocysteine is a risk factor for ischaemic stroke [6–9]. Thus, hyperhomocysteine may be a possible link between MA and stroke, particularly in young adults. An increase in plasma levels of this amino acid could in fact cause endothelial dysfunction [18–20], which in turn may play a role in the development of cortical spreading depression (a mechanism involved in the pathogenesis of migraine aura) and in the activation of the coagulation cascade (with increased risk for ischaemic cerebrovascular events).

Further studies are needed to confirm our findings, possibly on greater samples. We note that the hypothesis of a putative role of hyperhomocysteinaemia in the MA/stroke association may have relevant implications also in the ther-

Table 1 Mean homocysteine plasma levels (μmol/l) in the studied groups (analysis by Student-Newman-Keuls test)

	MA patients			Controls			*p*
	n	Mean	SD	n	Mean	SD	
All	136	12.31	11.02	117	9.86	3.71	0.023
Women	90	9.79	6.11	66	8.82	2.22	Not significant
Men	46	17.24	15.89	51	11.21	4.71	0.011

Table 2 Proportions of subjects with hyperhomocysteinaemia in the two studied groups (analysis by Chi square test)

	MA patients		Controls		*p*
	n	Hyperhomocysteinaemia	n	Hyperhomocysteinaemia	
All	136	47 (34.5)	117	20 (17.1)	0.002
Women	90	32 (35.5)	66	15 (22.7)	Not significant
Men	46	15 (32.6)	51	5 (9.8)	0.006

apeutic field: dietary supplementation with B vitamins and folic acid may reduce the plasma levels of this amino acid [21–24], and thus studies to assess the possible therapeutic effect on both these conditions as well as in reducing the risk of stroke in MA patients are warranted.

References

1. Swartz RH, Kern RZ (2004) Migraine is associated with magnetic resonance imaging white abnormalities: a meta-analysis. Arch Neurol 61:1366–1368
2. Kruit MC, van Buchem MA, Hofman PA et al (2004) Migraine as a risk factor for subclinical brain lesions. JAMA 291:427–434
3. Schwaag S, Nabavi DG, Frese A et al (2003) The association between migraine and juvenile stroke: a case-control study. Headache 43:90–95
4. Merikangas KR, Fenton BT, Cheng SH et al (1997) Association between migraine and stroke in a large-scale epidemiological study of the United States. Arch Neurol 54:362–368
5. Scher AJ, Terwind GM, Picaves HSJ et al (2005) Cardiovascular risk factors and migraine: the GEM population-based study. Neurology 64:614–620
6. Bautista LE, Arenas IA, Peñuela A, Martínez LX (2002) Total plasma homocysteine level and risk of cardiovascular disease: a meta-analysis of prospective cohort studies. J Clin Epidemiol 55:882–887
7. Casas JP, Bautista LE, Smeeth L et al (2005) Homocysteine and stroke; evidence on causal link from mendelian randomisation. Lancet 365:224–232
8. – (2007) SPREAD – Stroke Prevention And Educational Awareness Diffusion. Ictus cerebrale: Linee Guida Italiane (5 edizione, 20 dicembre)
9. Homocysteine Studies Collaboration (2002) Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 288:2015–2022
10. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24[Suppl 1]:1–160
11. Hering-Hanit R, Gadoth N, Yavetz A et al (2001) Is blood homocysteine elevated in migraine? Headache 41:779–781
12. Evers S, Koch HG, Suhr B, Husstedt IW (1998) Increased homocysteine level in migraine with aura. Eur J Neurol 5[Suppl 3]:S51–S52
13. Kowa H, Yasui K, Takeshima T et al (2000) The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. Am J Med Gener 96:762–764
14. Lea RA, Ovcaric M, Sundholm J et al (2004) The methylenetetrahydrofolate reductase gene variant C677T influences susceptibility to migraine with aura. BMC Med 2:3
15. Kara I, Sazci A Ergul E et al (2003) Association of the C677T and A1298C polymorphisms in the 5,10 methylenetetrahydrofolate reductase gene in patients with migraine risk. Brain Res Mol Brain Res 111:84–90
16. Oterino A, Valle N (2004) MTHFR T677 homozygosis influences the presence of aura in migraineurs. Cephalalgia 24:491–494
17. Scher AI, Terwindt G, Verschuren WM et al (2006) Migraine and MTHFR C677T genotype in a population-based sample. Ann Neurol 59:372–375
18. Dreier JP, Kleeberg J, Petzold G et al (2002) Endothelin-1 potently induces Leao's cortical spreading depression in vivo in the rat: a model for an endothelial trigger of migrainous aura? Brain 125:102–112
19. Splaver A, Lamas GA, Hennekens CH (2004) Homocysteine and cardiovascular disease: biological mechanisms, observational epidemiology, and need for randomized trials. Am Heart J 148: 34–40
20. Hadjikhani N, Sanchez Del Rio M, Wu O et al (2001) Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci U S A 98:4687–4692
21. Goldstein LB, Adams R, Alberts MJ et al (2006) Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council. Stroke 37:1583–1633
22. Toole JF, Malinow MR, Chambless LE et al (2004) Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death; the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 291:565–575
23. Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators (2006) Homocysteine lowering with folic acid and vitamins in vascular disease. N Engl J Med 354:1567–1577
24. Bonaa KH, Njolstad I, Ueland PM et al (2006) NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 354:1578–1588

Neurol Sci (2008) 29:S176–S178
DOI 10.1007/s10072-008-0918-1

ORAL COMMUNICATION

Reduction in the impact of chronic migraine with medication overuse after day-hospital withdrawal therapy

Susanna Usai · Licia Grazzi · Domenico D'Amico · Frank Andrasik · Gennaro Bussone

Abstract The 6-item Headache Impact Test questionnaire (HIT-6) is a simple and reliable tool to measure the impact headaches have on patients' lives. Patients with chronic migraine (CM) and medication overuse are markedly impaired in their functional activity. The aim of this study was to investigate the responsiveness of the HIT-6 tool to clinical changes induced by treatment in patients with CM and medication overuse. A sample of 160 patients underwent a day-hospital withdrawal treatment followed by prophylaxis. Sixty-two of them completed the12-month follow up. Patients improved significantly after treatment intervention, as days of headache per month and medications/month decreased from baseline to follow up. Also HIT-6 scores improved, with mean score decreasing from 65±5.4 (median 65) to 59.4±8.5 (median 62) (Student's *t*-test $p<0.00001$) and with a reduction in the percentage of patients with very severe headache-related impact one year after withdrawal therapy.

Keywords Headache impact test (HIT-6) · Headache-related disability · Chronic migraine · Medication overuse · Day hospital withdrawal

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Introduction

The negative effects of headache on patients' functional ability and health-related quality of life (QoL) are well established [1, 2]. The evaluation of headache-related disability and quality of life may have an important role in clinical practice and in clinical research, in order to guide treatment choices as well as to assess the outcome of treatment interventions [3, 4].

The 6-item Headache Impact Test questionnaire (HIT-6) is a simple and reliable tool to measure the impact of headache using only 6 questions, broadening it to include social-role functioning, pain, emotional distress and well-being, cognitive functioning and vitality [5]. Each of the six questions is responded to using one of a five-point response scale of "never", "rarely", "sometimes", "very often" and "always". For each item, 6, 8, 10, 11 or 13 points, respectively, are assigned to the response provided [6].

HIT-6 quantifies headache impact by an easily understood score which varies from 36 to 78. This score relates to the degree of headache impact: little or no impact from 36 to 49, some impact from 50 to 55, substantial impact from 56 to 59 and very severe impact above 60 [6].

Among the general population, the HIT-6 has good reliability and validity for measuring patients' subjective experience of the impact of headache on health-related quality of life [6, 7].

However, the characteristics of this tool have not been widely established among people with chronic migraine (CM) and medication overuse [8].

The impact of CM and similar headaches has been less extensively evaluated than that of episodic migraine. Some studies have addressed QoL evaluation [9–12]. Less information is available on the functional disability induced by headache in these patients [10, 13, 14]. Overall, the results of these studies suggested that CM is associated with signif-

Table 1 Distribution of scores in patients who completed follow-up

HIT-6 score	Baseline	1-year follow-up
36–49	0 (0%)	12 (19.3%)
50–55	4 (6.4%)	7 (11.3%)
56–59	5 (8.1%)	5 (8.1%)
60–78	53 (85.5%)	38 (61.3%)

icant burden of suffering, which is greater than that caused by episodic migraine [15].

The objective of the present study was to investigate the reduction of the impact of CM with medication overuse 12 months after day-hospital withdrawal therapy, using the HIT-6 tool.

Methods

Patients

All consecutive patients suffering from CM and medication overuse were recruited from outpatients attending our headache centre. All patients received the diagnosis of CM with medication overuse according to the Silberstein and Lipton Criteria [16].

Treatment interventions

They underwent a day-hospital withdrawal treatment consisting in intravenous hydration for a period of 10 days and steroids from day 1 to 5, followed by oral prescription steroids for another 5 days, and then were given preventive therapy with different anti-migraine prophylactic drugs.

Follow-up

Follow-up sessions were planned for 3, 6 and 12 months after day hospital therapy.

Measures

A diary card was given for recording days with headache and the medications taken for aborting headaches. The Italian version of the HIT-6 Questionnaire was filled in by patients at the moment of enrolment (baseline) and at follow-up visits.

Results

A total of 160 consecutive patients were enrolled (135 females and 25 males; mean age was 40.3±10.2). Mean duration of illness was 19.4±9.7 years. The mean number of days of headache per month was from 23.7±5.7; the mean number of medications/month was 28.9±18.1. The mean HIT-6 test score was 65.7±4.8 (median 66) at the baseline.

Of the 160 initial patients, 62 (38.7%) have already achieved the 1-year follow-up. The clinical improvement was significant: the mean number of days of headache per month decreased from 23.1±5.9 to 9±7.8; the mean number of medications/month decreased from 30.5±23.8 to 8.4±6.3. The mean HIT-6 test score was 65±5.4 (median 65) *vs*. 59.4±8.5 (median 62) at the 12-month follow up (Student's *t*-test $p<0.00001$).

The mean score for HIT-6 at baseline in our study population was >60, which suggests a severe headache-related impact. The distribution of scores in those patients who completed the follow-up is shown in Table 1.

Conclusions

Our findings suggest that CM patients with medication overuse are highly disabled in their daily activities, with the vast majority of them scoring in the "very severe impact" level of the HIT-6 tool.

The day-hospital withdrawal therapy, followed by preventive treatment, induced a marked clinical improvement (reduction in headache frequency and in medication consumption), which was mirrored by improvement in headache-related impact. The mean score of HIT-6 decreased at follow up, and the functional improvement was confirmed by a decrease in the percentage of patients with a "very severe" impact, and an increase in percentages of those with "little or no" impact and with only "some" impact.

Thus, HIT-6 seems a useful tool for assessing headache-related disability in CM patients with medication overuse, being easy to use and sensitive to clinical changes induced by treatment intervention.

References

1. Lipton RB, Hamelsky S, Kolodner KB et al (2000) Migraine, quality of life and depression: a population based case-control study. Neurology 55:629–635
2. Terwindt G, Ferrari M, Tihuis M et al (2000) The impact of migraine on quality of life in the general population: the GEM study. Neurology 55:624–629
3. Matchar DB, Young WB, Rosenerg J et al and the US Headache Consortium (2000) Multispecialty consensus on diagnosis and treatment of headache: pharmacological management of acute

attacks. www.aan.com/professionals/practice/pdfs/gl0087.pdf
4. Ramadan NM, Silberstein SD, Freitag FG et al and the US Headache Consortium. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. www.aan.com/professionals/practice/pdfs/gl0090.pdf
5. Kosinski M, Bayliss MS, Bjorner JB et al (2003) A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res 12:963–974
6. Kawata AK, Coeytaux RR, Devellis RF et al (2005) Psychometric properties of the HIT-6 among patients in a headache-specialty practice. Headache 45:638–643
7. De Diego EV, Lanteri-Minet M (2005) Recognition and management of migraine in primary care: influence of functional impact measured by the headache impact test (HIT). Cephalalgia 25:184–190
8. Coeytaux RR, Linville JC (2007) Chronic daily headache in a primary care population: prevalence and headache impact test scores. Headache 47:7–12
9. Monzon MJ, Lainez MJ (1998) Quality of life in migraine and chronic daily headache patients. Cephalalgia 18:638–643
10. Meletiche DM, Lofland JH, Young WB (2001) Quality-of life differences between patients with episodic and transformed migraine. Headache 41:573–578
11. Wang SJ, Fuh JL, Lu SR, Juang KD (2001) Quality of life differs among headache diagnoses: analysis of SF-36 survey in 901 headache patients. Pain 89:285–292
12. Guitera V, Munoz P, Castillo J, Pascual J (2002) Quality of life in chronic daily headache: a study in a general population. Neurology 58:1062–1065
13. Magnusson JE, Becker WJ (2002) A comparison of disability and psychological factors in migraine and transformed migraine. Cephalalgia 22:172–178
14. Bigal ME, Rapoport AM, Lipton RB et al (2003) Assessment of migraine disability using the migraine disability assessment (MIDAS) questionnaire: a comparison of chronic migraine with episodic migraine. Headache 43:336–342
15. D'Amico D, Grazzi L, Usai S et al (2005) Disability pattern in chronic migraine with medication overuse: a comparison with migraine without aura. Headache 45:553–560
16. Silberstein SD, Lipton RB (2000) Chronic daily headache. Curr Opin Neurol 13:277–283

Neurol Sci (2008) 29:S179–S181
DOI 10.1007/s10072-008-0919-0

ORAL COMMUNICATION

Association between plasma lipid levels and migraine in subjects aged ≥50 years: preliminary data from the Zabùt Aging Project

Roberto Monastero · Carmela Pipia · Angelo B. Cefalù · Eva Turco Liveri · Rosamaria Rosano · Rosolino Camarda · Cecilia Camarda

Abstract We evaluated the association between lipid levels and migraine using cross-sectional, population-based data of 1809 subjects aged ≥50 years; 151 subjects with migraine and 1658 nonmigraineurs were included. Diagnosis of migraine was carried out using the criteria of the International Headache Society. The following plasma lipids were collected: total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG). Only TC ($p<0.003$) and LDL-C levels ($p<0.004$) were significantly higher in migraineurs than nonmigraineurs. After multiple adjustments, only elevated TC (≥220 mg/dl) was significantly associated with migraine (OR [95% CI]=1.6 [1.1–2.3]); this association increased in elderly males with migraine (OR [95% CI]=3.8 [1.4–9.9]). According to our results, TC plasma levels should be closely monitored in elderly males with migraine.

Keywords Migraine · Epidemiology · Cholesterol · Elderly

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Introduction

Migraine is a common, neurovascular, primary headache disorder, which is highly prevalent in the general population. It usually begins in the first three decades of life, with a peak in puberty. However, attacks may start at any age and there are also many active migraine patients aged ≥60 years [1].

Migraine has been associated with increased risk of several vascular disorders, including ischaemic stroke and coronary heart disease [1]. Furthermore, migraine has been associated with a more unfavourable cardiovascular risk profile [2]. Association of migraine with other vascular risk disorders, such as hypercholesterolaemia, has been proposed, but previous studies have yielded conflicting results [2, 3]. Thus, we aimed to evaluate the association between plasma lipid levels and migraine in a cross-sectional, population-based study.

Methods

Study population and case ascertainment

This study was part of the Zabút Aging Project, a comprehensive survey of neuropsychiatric disorders of all people aged ≥50 years living in a village near the city of Palermo, Italy, on 31 October 2001. As previously described [4], the detection of headache cases was conducted using a two-phase door-to-door procedure. Briefly, all participants were examined in the first phase by physicians using a screening questionnaire for the presence/absence of headache. In the second phase, neurologists examined screened positive subjects, administering a validated semi-structured headache questionnaire, which was based on the criteria of the International

Headache Society [5]. According to this information, migraine cases were then ascertained. The Ethics Committee of the Medical Faculty at the University of Palermo approved the baseline data collection and written informed consent was obtained from all participants.

Lipid measurements

Blood samples were obtained after 12 h of fasting for lipid analysis. Plasma total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were measured after phosphotungstic acid precipitation, using standard enzymatic methods [6]. Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula (TG=TC–HDLc–TG/5] [7].

Statistical analyses

Descriptive data between migraineurs and nonmigraineurs were compared with two-tail *t*-test or chi-square analysis. Lipid levels were treated as continuous and dichotomic variables. The following cut-off values, proposed by the Third Report of the National Cholesterol Education Program [8], were applied: elevated TC (≥220 mg/dl), high LDL-C (≥160 mg/dl), high TG (≥150 mg/dl), low HDL-C (<40 mg/dl for males and <50 mg/dl for females). The association between migraine and altered lipid levels was estimated using multiple logistic regression models adjusted for age, sex and education. Age was treated as a continuous and dichotomic variable (adults: 50–64 years *vs*. elderly: 65+ years). The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs) and the level of significance was $p \leq 0.05$ for all analyses.

Results

After excluding subjects with dementia, stroke-related aphasia, mental retardation and severe psychosis, 1809 individuals collected at baseline were included in this study. The mean age of participants was 73.0 years (10.1 SD), mean education was 5.3 (4.0); there were more females than males (55.1 vs. 44.9). A total of 151 (8.3%) participants were diagnosed as migraineurs. Subjects with migraine were significantly younger than nonmigraineurs (mean±SD: 68.3±8.6 vs. 73.4±10.1, $p=0.002$). Furthermore, females were more strongly represented in the migraine group as compared to nonmigraineurs (79.5% vs. 52.9%, $p<0.0001$). Concerning lipid levels, subjects with migraine showed significantly higher levels of TC (223.4±39.8 vs. 212.6±40.7, $p=0.003$) and LDL-C (146.6±36.2 vs. 136.8±37.9, $p=0.004$) than nonmigraineurs. Compared with nonmigraineurs, subjects with migraine revealed an adjusted OR (95% CI) of 1.6 (1.1–2.3) for elevated TC, while high LDL-C was not associated with migraine. The highest significant association between migraine status and elevated TC was found for elderly males (OR [95% CI]=3.8 [1.4–9.9]).

Discussion

In this large cohort of adult-to-elderly subjects, we identified a moderate cross-sectional association of migraine with elevated TC. The highest OR between migraine and elevated TC appeared in elderly males. Overall, our data propose a possible relationship between TC and migraine. In particular, our results suggest that TC might be regarded as one of the potential vascular risk factors which mediate the association between migraine and cardio- or cerebrovascular diseases [1]. It could be hypothesised that, regarding brain functioning, in adult-elderly subjects with migraine, elevated TC levels might contribute to increasing the risk for subcortical white matter lesions with subsequent increased risk of cognitive impairment [9].

The association between migraine and lipid levels has been previously evaluated in two population-based cross-sectional studies. In a Dutch study, subjects with migraine had an adjusted OR for high TC of 1.43 (95% CI, 0.97–2.1), as compared to nonmigraineurs [2]. However, in a recent British study, the authors reported that migraine in women was only slightly associated with elevated TC in their population (adjusted OR 1.09 [95% CI, 1.01–1.18]) [3]. Differences in study design and criteria used for case ascertainment may explain divergent findings between these data and ours.

Our study has several strengths, notably its large size and standardised migraine ascertainment. However, these are preliminary data, and control for potential confounders (e.g., history of cerebro- and cardiovascular disease, obesity, hypertension, etc.) should be taken into account before making appropriate conclusions. Furthermore, our study was cross-sectional, and thus we are unable to evaluate the direction of the association. Thus, generalising our results to other populations is currently limited. Our data suggest that elevated TC plasma levels in adult-to-elderly subjects with migraine, particularly in elderly males, should be closely monitored, thereby possibly reducing the risk of vascular disease.

References

1. Haan J, Hollander J, Ferrari MD (2007) Migraine in the elderly: a review. Cephalalgia 27:97–106
2. Scher AI, Terwindt GM, Picavet HS et al (2005) Cardiovascular risk factors and migraine: the GEM population-based study. Neurology 64:614–620

3. Kurth T, Ridker PM, Buring JE (2008) Migraine and biomarkers of cardiovascular disease in women. Cephalalgia 28:49–56
4. Camarda R, Monastero R (2003) Prevalence of primary headaches in Italian elderly: preliminary data from the Zabút Aging Project. Neurol Sci 24[Suppl 2]:S122–S124
5. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders cranial neuralgias and facial pain. Cephalalgia 8[Suppl 7]:1–96
6. Barbagallo CM, Polizzi F, Severino M et al (2002) Distribution of risk factors, plasma lipids, lipoproteins and dyslipidemias in a small Mediterranean island: the Ustica Project. Nutr Metab Cardiovasc Dis 12:267–274
7. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 18:499–502
8. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497
9. Camarda C, Monastero R, Pipia C et al (2007) Interictal executive dysfunction in migraineurs without aura: relationship with duration and intensity of attacks. Cephalalgia 27:1094–1100

Neurol Sci (2008) 29:S182–S185
DOI 10.1007/s10072-008-0920-7

ORAL COMMUNICATION

Patent foramen ovale detected by near-infrared spectroscopy in patients suffering from migraine with aura

William Liboni · Filippo Molinari · Giovanni Battista Allais · Ornella Mana · Emanuela Negri · Giovanni D'Andrea · Gennaro Bussone · Chiara Benedetto

Abstract There is an increased prevalence of patent foramen ovale (PFO) in women with migraine with aura (MwA) compared to controls, but the role of PFO in triggering aura is still debated. The aim of this study was to test a group of women suffering from MwA with near-infrared spectroscopy (NIRS), to assess the NIRS capability of discriminating between subjects with and without PFO. Eighty-eight MwA patients (mean age 37.4±10.7 years, range 16–62 years) underwent NIRS measurement of the cerebral variations of the oxygenated (O_2Hb) and reduced haemoglobin (HHb) during breath-holding. The prevalence of O_2Hb vs. HHb was used to assess the presence of PFO. As a gold standard, the presence of PFO was assessed by transcranial Doppler sonography (TCD). At the TCD analysis 48 patients (55%) showed PFOs, 32 of which were permanent. NIRS correctly detected 36 subjects out of 40 without PFO, and 38 subjects out of 48 having PFO: sensitivity was 79%; specificity was 90%. All the false negatives were permanent shunts. MwA patients with PFO showed a delayed increase in the O_2Hb concentration and a reduced oxygenation with respect to subjects without PFO. NIRS is effective in identifying the presence of PFO in a MwA population, but TCD achieves better diagnostic performances. The NIRS provides additional information about the cerebral vasoreactivity and highlights substantial differences between patients with latent and permanent shunts that warrant further studies.

Keywords Migraine with aura · Near-infrared spectroscopy · Patent foramen ovale · Transcranial Doppler · Vasoreactivity

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Introduction

There is a growing interest in the association of atrial septal abnormalities and migraine, particularly with aura [1]. The presence of patent foramen ovale (PFO) and the related increased number of microemboli from the heart to the brain has been related to the occurrence of the aura through a possible ischaemic/anoxic cortical mechanism [2]. This hypothesis remains undemonstrated because of the low sensitivity of the methodologies available in the evaluation of the relationship between the diameter of the shunt, the amount of microemboli and the possible cortical brain anoxia.

Transoesophageal echocardiogram is considered the gold standard for PFO detection [3], but it is uncomfortable for the patient. Patients show a better compliance with transcranial Doppler (TCD) and intravenous contrast

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saline solution, which exhibits an elevated diagnostic accuracy [4]; however, its availability is limited and it is currently not employed on a large scale.

Near-infrared spectroscopy (NIRS), which is essentially a functional technique, allows the assessment of oxygen demand in the brain tissue by measuring the concentrations of oxygenated (O_2Hb) and reduced haemoglobin (HHb). It has already been proved that this measure is a reliable index of the autoregulatory state of the subject [5], hence it could efficiently discriminate between subjects with and subjects without a right-to-left cardiac shunt.

The aim of this study was to test a group of subjects suffering from migraine with aura (MwA), to assess the NIRS capability of discriminating between subjects with and without a PFO.

Subjects and methods

Subjects

Eighty-eight women (mean age 37.4±10.7 years, range 16–62 years) were involved in the study. Inclusion criteria for the study were as follows: (1) a diagnosis of typical aura with migraine headache (ICHD-II code: 1.2.1) according to the International Headache Society criteria [6]; (2) a minimum two years' history of MwA; (3) more than 4 migraine crises in the last year; (4) no past or present disease; (5) no pregnancy or lactation; (6) no oral contraceptives intake; and (7) no genetic alterations of haemoglobin. The use of a migraine prophylaxis was not allowed during the study and in the two months before entering it. Patients were always tested in a pain-free condition and at a time when the last migraine attack had ended at least 72 h before the clinical tests.

The study was conducted following a double-blind paradigm: the women first underwent NIRS examination and then TCD. The subjects and the researchers were blinded to the presence of PFO. Data were crossed only after having tested the entire population.

NIRS and TCD recordings and processing

NIRS

Changes in the concentrations of O_2Hb and HHb were measured by a NIRO300 (Hammamatsu Photonics, Australia). Source and receiver were placed on the left frontal lobe of the subjects at a distance equal to 5 cm. The details about breath-holding, instrumental measures and subject positioning have been previously reported [5].

The O_2Hb and the HHb signals were first qualitatively analysed to derive the typical vasoreactivity pattern of the patients in response to breath holding (BH). Figure 1 depicts an example of the O_2Hb and the HHb signals in a subject without (left panel) and with (right panel) PFO.

The O_2Hb and the HHb signals were then represented after having scaled the horizontal axis in percentage to account for different BH durations. The concentration values at the beginning of the BH were set to zero. The prevalence of the O_2Hb (P_{O2Hb}) was computed as:

$$Po2Hb = \frac{O_2Hb - HHb}{O_2Hb + HHb}$$

Figure 2 shows the typical patterns of the of a subject without PFO (left panel, same subject as Fig. 1) and with PFO (right panel, same subject as Fig. 1). The observation of the O_2Hb and HHb time courses, and of the P_{O2Hb} during BH was used to assess the PFO presence: the patient was considered to have PFO if the P_{O2Hb}, after an initial dip, did not show an increasing trend before reaching 50% of the BH duration. The increase in the O_2Hb concentration due to vasodilation (Fig. 1, left panel) causes the increase of the (Fig. 2, left panel). In the presence of right-to-left cardiac shunt a mixing of the two

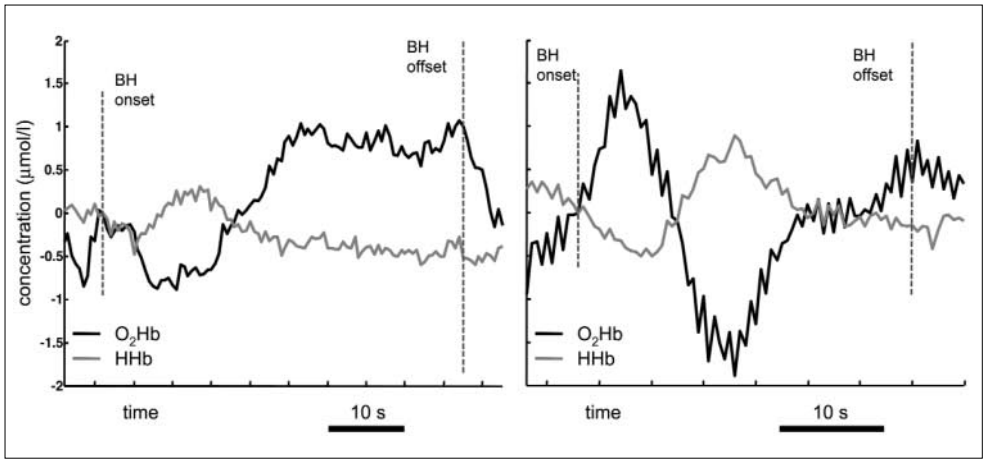

Fig. 1 Time course of the O_2Hb and HHb during BH recorded in migraineurs with aura. Left panel is relative to a subject without PFO. Right panel is relative to a subject with PFO. O_2Hb is depicted in black, HHb in grey. Vertical dashed lines represent BH onset and offset. The subject without PFO shows a vasoreactivity characterised by an abrupt increase of O_2Hb and a constant level of HHb. The vasoreactivity of the subject with PFO has a precocious O_2Hb increase and a mixture of the haemoglobin types

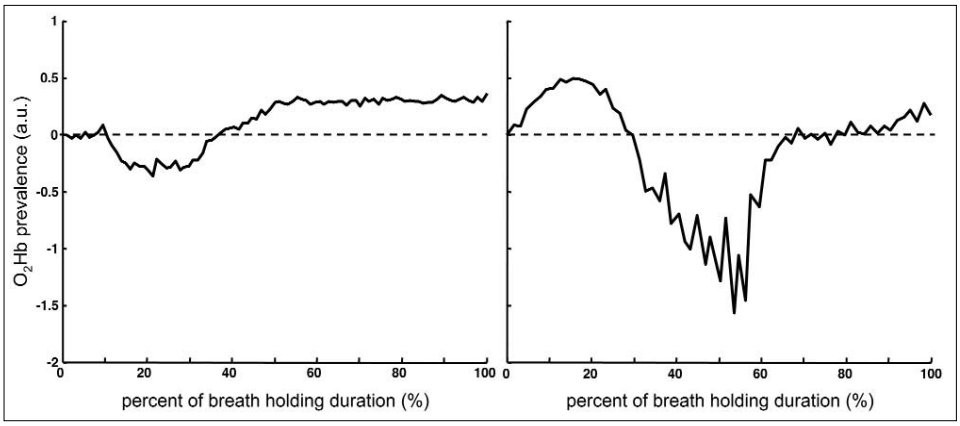

Fig. 2 Prevalence of oxygenated haemoglobin (P_{O2Hb}) during BH for a subject without PFO (left panel) and with PFO (right panel). The graphs are relative to the same subjects as Fig. 1. The horizontal axis is scaled in percent of the BH duration. Left graph: after an initial dip, the shows an increasing trend. Right graph: there is no trend and the initial dip is delayed at 40%–50% of the BH duration

haemoglobin types (Fig. 1, right panel) might cause a reduced or delayed increase of the P_{O2Hb}, or both (Fig. 2, right panel). Hence, we relied on the P_{O2Hb} signal to assess the PFO presence.

TCD

By means of a MultiDop X4 (DWL, Sipplingen, Germany) TCD device equipped with 2 MHz pulsed probes, we analysed the M1 tract of the middle cerebral arteries (MCA) of the subjects. The system was equipped with software for the automated counting of the microembolic signals (MES) that we used to detect PFO. A contrast medium (composed of 1 ml of air, 4 ml of blood and 5 ml of saline mixed together) was injected intravenously with the subject in resting conditions and the number of spontaneous MES was counted. MES detected in the MCA 5–12 s after the injection were considered indicative of right-to-left shunt at atrial level [7]. Then, another contrast agent injection was performed 5 s after the subject was asked to begin a Valsalva manoeuvre (VM).

Women with no MES were considered to be without PFO. The size of the PFO was subdivided into small (less than 10 MES), "shower" (between 11 and 25 MES) and "curtain" (not countable MES). The shunt was classified as permanent if MES were observable on the signals during the first contrast mixture injection (i.e., at rest, without performing the VM) and latent if detected only by the VM.

Statistical analysis

TCD served as the reference standard. Sensitivity and specificity of the NIRS were computed by the cross table, together with their confidence interval (CI) (α=5%). The positive predictive value was determined as the percentage of true-positive compared to the sum of the true-positive plus the false-positive findings. The negative predictive value was computed as the percentage of the true-negative compared to the sum of the true-negative plus the false-negative findings. Diagnostic accuracy was computed as the percentage of true-positive plus true-negative findings over the number of the subjects.

Results

Thirty patients (34%) presented a "curtain" pattern, 6 (7%) had a "shower" pattern and 12 (14%) were classified as having a small PFO. Thirty-two women had permanent shunt (36% of the total number of subjects and 67% of the number of subjects with PFO) and 16 had a latent shunt (18% of the total, 33% of the number of PFO). Forty patients (45%) had no MES signals during the test.

NIRS correctly identified 38 subjects out of 48 with PFO, and 36 subjects out of 40 without PFO. Sensitivity was equal to 79% (95%, confidence interval: 66%–88%) and specificity was equal to 90% (95%, confidence interval: 77%–96%). Positive predictive value was equal to 90%, negative predictive value to 78% and diagnostic accuracy to 84%.

In 10 patients NIRS was false-negative: 2 subjects with small PFO, 2 subjects with "shower" pattern of MES and 6 subjects with a "curtain" pattern.

An analysis of the diagnostic subgroups showed that all 10 false-negatives were relative to subjects having a permanent shunt. Considering only women with a latent shunt, independently of its size, sensitivity reached 100% (95% CI: 80–100%), positive predictive value 80%, negative predictive value 100% and diagnostic accuracy 93%.

Discussion

Investigating cerebral autoregulation of subjects suffering from MwA may be crucial. Our randomly chosen sample population of patients with MwA presents a PFO prevalence (55%) similar to previously reported studies [8]. The percentage of small (7%) and large shunts (48% considering both the "curtain" and the "shower" patterns) is similar to that of other studies (small 10%, large 38%) [9].

The prevalence of PFO in patients with aura is greater than in patients without aura and normal subjects [8].

We used NIRS to monitor the balancing of O_2Hb and HHb in migraineurs with aura during BH and we found that by NIRS it is possible to detect the PFO presence with good performances in terms of sensibility and specificity. Subjects without PFO showed a vasoreactivity pattern that was highly repeatable: O_2Hb concentration increases rapidly after the beginning of the BH phase, causing an increase of total O_2Hb, while the HHb remains almost constant during the entire BH phase (Fig. 1).

This abrupt increase of the O_2Hb originates the increase of the P_{O_2Hb} that, after an initial dip (between 15% and 35% of the BH duration average value), maintains positive values until the end of the BH. In the presence of PFO, the dip is evident between 40% and 60% of the BH duration (average value on the PFO subjects 52%, SD 5%); besides, does not increase with respect to the beginning of BH (Fig. 2).

This reduced increase in the oxygen prevalence observed in PFO subjects is not given by a reduced vascular reactivity. In fact, the vasoreactivity parameters these subjects show (in terms of blood flow velocity and breath-holding indexes evaluated as in [10]) are not statistically different from those of subjects without PFO. Therefore, the cause of the reduced increase in the oxygen prevalence is to be found in the mixing of the haemoglobin types caused by inter-atrial blood passage.

The impossibility of imposing a fixed BH duration is a possible drawback of this methodology. We believe it is the cause of the misclassification of the two subjects who could hold their breath only for 18 s and 15.5 s respectively.

In fact, revious studies revealed that BH is effective to trigger vasomotor reactivity provided that BH has a minimum duration of 20 s [11].

Focusing on the analysis of subjects with latent shunt, sensitivity increases to 100%. A possible explanation of this result is that subjects with a permanent PFO could have developed a compensatory mechanism in response to breath-holding stimulus by changing baseline blood composition and haemoglobin balancing. NIRS provides only a relative quantification of haemoglobin concentration in brain tissue and not an absolute one; hence in the presence of a subject with good cerebral autoregulation, the detection of PFO is precluded.

In conclusion, NIRS provides good results, but it cannot be considered an alternative to TCD, which achieves better diagnostic performances. However, we showed that migraineurs with a latent shunt depict a NIRS vasoreactivity pattern different from those with a permanent shunt. Considering these results, we suggest the joint use of TCD and NIRS to study in depth the differences between subjects with permanent and latent shunts, particularly in relation to stroke risk.

References

1. Diener HC, Kurth T, Dodick D (2007) Patent foramen ovale and migraine. Curr Pain Headache Rep 11:236–240
2. Anzola GP (2002) Clinical impact of patent foramen ovale diagnosis with transcranial Doppler. Eur J Ultrasound 16:11–20
3. Soliman OI, Geleijnse ML, Meijboom FJ et al (2007) The use of contrast echocardiography for the detection of cardiac shunts. Eur J Echocardiogr 8:S2–12
4. Blersch WK, Draganski BM, Holmer SR (2002) Transcranial duplex sonography in the detection of patent foramen ovale. Radiology 225:693–699
5. Molinari F, Liboni W, Grippi G, Negri M (2006) Relationship between oxygen supply and cerebral blood flow assessed by transcranial Doppler and near-infrared spectroscopy in healthy subjects during breath-holding. J Neuroeng Rehabil 3:16
6. Headache Classification Subcommittee of the International Headache Society (IHS) (2004) The International Classification of Headache Disorders, 2nd Edn. Cephalalgia 24:9–169
7. Markus HS, Harrison MJ (1992) Estimation of cerebrovascular reactivity using transcranial Doppler, including the use of breath-holding as the vasodilatory stimulus. Stroke 23:668–673
8. Schwerzmann M, Nedeltchev K, Lagger F et al (2005) Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 65:1415–1418
9. Tzourio C, Tehindrazanarivelo A, Iglésias S et al (1995) Case-control study and risk of ischaemic stroke in young women. BMJ 310:830–833
10. Liboni W, Molinari F, Allais G et al (2007) Why do we need NIRS in migraine? Neurol Sci 28[Suppl 2]:S222–224
11. Safonova LP, Michalos A, Wolf U et al (2004) Age-correlated changes in cerebral hemodynamics assessed by near-infrared spectroscopy. Arch Gerontol Geriatrics 39:207–225

Neurol Sci (2008) 29:S186–S190
DOI 10.1007/s10072-008-0921-6

ORAL COMMUNICATION

Oral contraceptive-induced menstrual migraine. Clinical aspects and response to frovatriptan

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Abstract Oral contraceptive-induced menstrual migraine (OCMM) is a poorly defined migraine subtype mainly triggered by the cyclic pill suspension. In this pilot, open-label trial we describe its clinical features and evaluate the efficacy of frovatriptan in the treatment of its acute attack. During the first 3 months of the study 20 women (mean age 32.2±7.0, range 22–46) with a 6-month history of pure OCMM recorded, in monthly diary cards, clinical information about their migraine. During the 4th menstrual cycle they treated an OCMM attack with frovatriptan 2.5 mg. The majority of attacks were moderate/severe and lasted 25–72 h or more, in the presence of usual treatment. Generally an OCMM attack appeared within the first 5 days after the pill suspension, but in 15% of cases it started later. After frovatriptan administration, headache intensity progressively decreased (2.4 at onset, 1.6 after 2 h, 1.1 after 4 h and 0.8 after 24 h; p=0.0001). In 55% of patients pain relief was reported after 2 h. Ten percent of subjects were pain-free subjects after 2 h, 35% after 4 h and 60% after 24 h (p=0.003 for trend); 36% relapsed within 24 h. Rescue medication was needed by 35% of patients; 50% of frovatriptan-treated required a second dose. Concomitant nausea and/or vomiting, photophobia and phonophobia decreased significantly after drug intake. OCMM is a severe form of migraine; actually its clinical features are not always exactly identified by the ICHD-II classification. However, treatment with frovatriptan 2.5 mg might be effective in its management.

Keywords Oestrogen withdrawal · Frovatriptan · Menstrual migraine · Oral contraceptives

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Introduction

Menstrual migraine (MM) appearing in patients that are on oral contraceptives (oral contraceptive-induced menstrual migraine, OCMM) is probably a quite common, albeit poorly defined, MM subtype [1] mainly caused by oestrogen withdrawal occurring during the week of pill suspension. This type of headache, codified by the ICHD-II classification [2] as oestrogen-withdrawal headache (code 8.4.3), is defined as "a headache or migraine that develops within 5 days after cessation of oestrogen use and resolves within 3 days (oestrogen use must have lasted for at least 3 weeks prior to cessation)". It is probably a severe and disabling form of migraine [3–5], but actually very few studies are tailored to define the clinical profile of this type of headache, particularly in the specific case of pure OCMM. Moreover, double-blind, randomised clinical trials have shown that MM attacks can be successfully treated [6–10] or prevented [11–13] with triptans [14]. Their efficacy in the acute management of OCMM attacks, however, has not been studied in specific trials till now. Frovatriptan is a second-generation triptan whose high selectivity for the cerebral vasculature, long elimination half-life and high persistence of therapeutic action may be useful in preventing MM [15], probably with a better safety profile than other triptans [16].

The present study was carried out in order to define the clinical features of OCMM and to test the efficacy of frovatriptan in the acute treatment of an OCMM attack.

Patients and methods

This pilot, open-label, uncontrolled study included 34 women aged 18 years or older; all of them had been taking monophasic combined oral contraceptives (21 days on/7 days off regimen) for at least 12 months and had a documented history of pure OCMM. The women selected attended our Women's Headache Center and were chosen after a careful review of their diary cards, as all patients are usually requested to regularly complete daily diary cards as part of their routine management.

The inclusion criteria were: (1) a 6-month history of pure OCMM, with attacks appearing exclusively in the pill-free week of the menstrual cycle, irrespective of the day of onset of bleeding; (2) all frovatriptan-naïve patients.

The exclusion criteria were contraindications to the use of triptans (ischaemic heart disease, multiple risk factors for coronary artery disease, cerebrovascular or other cardiovascular diseases, severe arrhythmias or conduction disturbances, uncontrolled hypertension, or history of basilar or hemiplegic migraine), severe hepatic or renal insufficiency or other clinically relevant diseases, as well as pregnancy and breast-feeding.

Our study had a length of 4 menstrual cycles and its aim was to observe the clinical features of OCMM during 3 consecutive menstrual cycles, in the presence of usual symptomatic treatment, and to test the efficacy of frovatriptan in the following menstrual cycle.

In order to achieve a correct diagnosis, we included in the study only patients showing pure OCMM in all 3 menstrual cycles taken into consideration.

After a thorough anamnestic investigation on the clinical features of their migraine, women were provided with 3 monthly diary cards. All patients were required to fill in the diaries for a period of 3 menstrual cycles (period A), recording the following information for each migraine attack as it occurred: date of onset; presence/absence of aura symptoms; quality and side of pain; peak intensity (0=no headache, 1=mild headache, 2=moderate headache and 3=severe headache); occurrence of nausea, vomiting, photophobia and phonophobia; and duration of attack in the presence of usual treatment. In the same diary patients recorded the days of pill suspension and those of menstrual bleeding.

After this observation period, patients entered the second part of the study (period B), in which they were instructed to take a single dose of frovatriptan 2.5 mg per os at the onset of a moderate or severe OCMM attack. A second dose could be taken if symptoms were alleviated but recurred within 24 h, with a 2-h lapse time between each dose. Alternatively, patients with moderate or severe headache after 2 h were allowed to take optional rescue medication in the form of standard analgesics (other than triptans or ergot derivatives).

During period B patients continued to record information about migraine attacks in the same diary used during period A. In addition, they recorded in a specific treatment card the following information about the attack treated with study medication: headache intensity at onset and at 2, 4 and 24 h after drug administration, according to the four-point anchored scale; occurrence of nausea, vomiting, photophobia and phonophobia at the same time; use of a second dose of frovatriptan or of a rescue medication.

Data analysis

We analysed the diary cards collected in period A and focused on two main aspects: the duration of OCMM attacks and the temporal window of the onset of the attack, as these are the main parameters which define the oestrogen-withdrawal headache in the ICHD-II classification.

As far as the treatment was concerned, we evaluated the following: (a) the percentage of patients with pain relief, defined as reduction of headache from moderate or severe at onset, to mild or none, (b) the percentage of patients who were pain-free, (c) the percentage of patients without associated symptoms, (d) the percentage of patients who used rescue medication, and (e) the percentage of those needing a second dose of frovatriptan. Recurrence rate (defined as the return of a severe/moderate headache within 24 h in patients who experienced relief 2 h after dosing) was also calculated. Temporal trends were explored with non-parametric Friedman's test for repeated measures.

Results

Only 20 patients (mean age 32.2±7.0 years, range 22–46) out of 34 enrolled had a positive history for pure OCMM, as documented by diary cards. Ten women out of the 14 excluded were also suffering from headache outside the pill-free week, 2 of them had not correctly filled in the diary cards and 2 of them had not suffered OCMM attacks for 3 months in a row. Final evaluation was therefore based on data obtained from the former 20 patients. All patients presented attacks with the typical features of migraine without aura; in fact, no patient reported aura symptoms. Clinical data are presented in Table 1. All OCMM attacks were of moderate (45%) or severe (55%) intensity. In the majority of patients migraine usually lasted at least 2 days in the presence of usual treatment, but 15% of attacks exceeded the 72-h upper limit proposed for migraine without aura in the IHS Classification (6). Migraine attacks appeared within the first 5 days

after the cessation of oestrogen use, irrespective of the day of onset of bleeding, though in some cases (15%) they appeared afterwards, on the 6th (n=6) or 7th (n=3) day after pill suspension.

After administration of frovatriptan, intensity progressively and significantly decreased: mean values were 2.4±0.5 at onset, 1.6±1.0 after 2 h, 1.1±0.9 after 4 h and 0.8±1.2 after 24 h (p=0.0001).

Pain relief was reported by 55% of patients after 2 h, and by 75% after 4 and 24 h (p=0.135); 10% of patients were pain-free after 2 h, 35% after 4 h and 60% after 24 h (p=0.003) (Fig. 1). Four of the 11 patients who achieved relief after 2 h relapsed within 24 h. Rescue medication was needed in 35% of the cases and a second dose of frovatriptan was taken by 50% of patients.

Concomitant nausea and/or vomiting were observed in 90%, 75%, 40% and 20% of patients at onset and after 2, 4 and 24 h respectively (p=0.0001). A similar trend was found for photophobia and phonophobia (onset: 85%; 2 h: 60%; 4 h: 35%; 24 h: 30%; p=0.001).

Discussion

The influence of oral contraception on the course of migraine is highly variable [17–20]. Increases in frequency or severity have been reported in 18%–50% of cases, with most attacks occurring during the hormone-free interval of the cycle [17, 21]. Little is known about the real incidence of OCMM, and even less in the case of pure OCMM.

Table 1 Demographic and clinical data of study population (n=20)

Age (years, mean±SD, range)	32±7 (22–46)
Systolic blood pressure (mm Hg, mean±SD, range)	111±11 (85–130)
Diastolic blood pressure (mm Hg, mean±SD, range)	72±9 (50–85)
Heart rate (bpm, mean±SD, range)	74±6 (62–84)
Intensity of OCMM attacks in the presence of usual treatment (%), in period A	
Moderate	45
Severe	55
Total duration of OCMM attacks in the presence of usual treatment (%), in period A	
<4 h	15
4–24 h	20
25–48 h	25
49–72 h	25
>72 h	15
Day of OCMM start during 7-day pill suspension (number of attacks/day), in period A	
Day 1	6
Day 2	9
Day 3	12
Day 4	15
Day 5	9
Day 6	6
Day 7	3

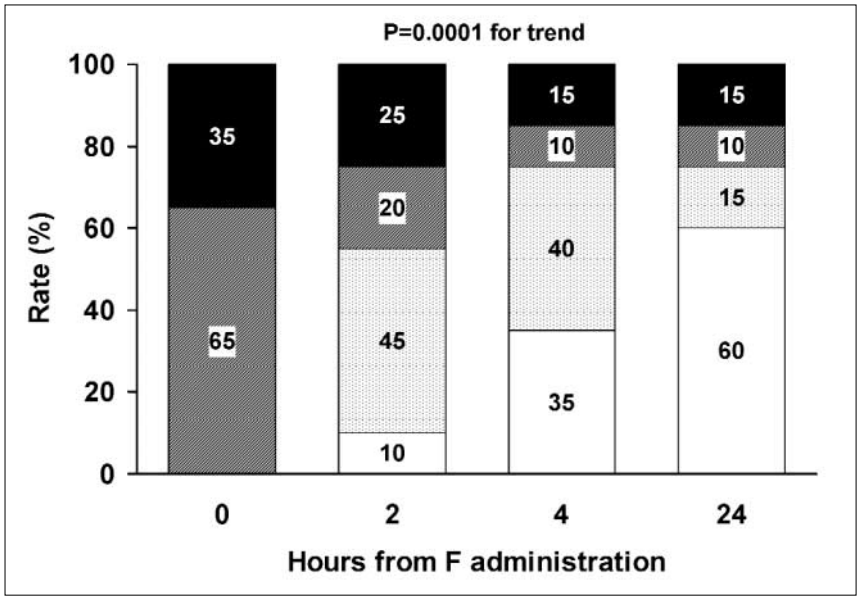

Fig. 1 Rate (%) of patients with severe (*full bars*), moderate (*striped bars*), mild (*dotted bars*) or no (*open bars*) headache at onset (*0*) and 2, 4 and 24 h after frovatriptan (*F*) administration

In the Appendix of the IHS Classification [2] it is clearly stated that "if pure menstrual migraine […] is considered to be associated with exogenous oestrogen withdrawal, both codes A1.1.1 pure menstrual migraine without aura and 8.4.3 oestrogen withdrawal headache should be used". Even though this statement implies a substantial identity of these two migraine subtypes, in the same paragraph it is also stated that "The mechanism of migraine may be different with endometrial bleeding resulting from the normal menstrual cycle and bleeding due to the withdrawal of exogenous progestogens (as occurs with combined oral contraception) […] therefore research should separate these subpopulations".

Our study tentatively describes the clinical features of OCMM, in its pure form. It highlights that the criteria established for IHS code 8.4.3 do not always adhere exactly to the real picture of this headache. In fact, 15% of patients had attacks lasting longer than 72 h. The possibility of a menstrual status migrainosus triggered by oral contraception-free interval has also been suggested by other Authors [5].

Moreover, in 15% of patients attacks developed within a temporal frame longer than 5 days after last use of the pill, suggesting that in some cases any day of pill-free interval could be the start day of the attack. In any case, the onset of OCMM attacks was irrespective of the day of bleeding onset.

The pathophysiology of OCMM and MM may partially differ; their treatment, however, is the same. Triptans are usually regarded as the most effective acute antimigraine agents [22]. Frovatriptan is a well known effective treatment for migraine [23] and useful in MM prophylaxis [11]. The present study now illustrates its clinical efficacy for the acute treatment of OCMM.

As our results show, in fact, after 2 h the rate of patients with pain relief was 55%, that of pain-free subjects was 10%, and that of patients free from nausea and/or vomiting or phonophobia and photophobia was 25% and 40%, respectively. As expected, these rates progressively increased during the period of observation, reaching 75% and 60% respectively for pain relief and pain-free at 24 h. Rescue medication or a second dose of frovatriptan was needed and recurrence was observed in no more than 50% of patients.

These are, to our knowledge, the first data on the efficacy of a triptan obtained in a trial specifically dedicated to pure OCMM. Indirect comparisons can be made with double-blind, randomised studies of oral formulations of sumatriptan, rizatriptan, almotriptan, zolmitriptan or naratriptan at usual doses in the management of MM [6–10]. In these studies, pain relief at 2 h ranged from 48% to 70% and freedom from pain ranged from 26% to 61%. Rescue medication was needed by 18%–69% of women and recurrence occurred in approximately 30%. In one of these studies [6] about 50% of the patients were under oral contraceptives, but no specific comparison can be made with our data due to the mixed nature of the study population. No direct comparisons can be made for frovatriptan, because the only published study in MM treatment was carried out to assess the efficacy of a relatively high prophylactic dose [11]. Nevertheless MacGregor and Keywood [24] reported in a congress abstract that in 82% of menstrual attacks migraine relief within 24 h was achieved and more than 40% of menstrual attacks were relieved by a single frovatriptan dose.

These studies are in line with our data, although it must be considered that response to treatment in the highly selected population of pure OCMM might be less favourable than in patients with a generic form of MM. The results may thus be adjusted accordingly [25, 26].

In summary, our study demonstrates that the clinical features of pure OCMM do not always exactly follow those established by the ICHD-II classification. In particular, OCMM is a severe form of migraine without aura that in some cases can last more than 72 h. However, our results indicate that 2.5 mg frovatriptan taken at the onset of an acute attack might be effective in the management of OCMM.

Despite its interesting results, it must be acknowledged that this is a non-randomised, open-label, uncontrolled trial on a small number of subjects. Further, double-blind, randomised, placebo-controlled studies are needed to definitely prove the efficacy of frovatriptan in this subpopulation of migrainous patients.

Moreover, in future, it would be advisable to revise and better define the diagnostic criteria of the International Headache Society for OCMM.

Acknowledgements This study was supported by Istituto Lusofarmaco d'Italia.

References

1. Allais G, Castagnoli Gabellari I, De Lorenzo C et al (2007) Menstrual migraine: clinical and therapeutical aspects. Expert Rev Neurother 7:1105–1120
2. Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache Disorders. Cephalalgia 24[Suppl 1]:1–160
3. Becker WJ (1999) Use of oral contraceptives in patients with migraine. Neurology 53[Suppl 1]:S19–S25
4. Benson MD, Rebar RW (1986) Relationship of migraine headache and stroke to oral contraceptive use. J Reprod Med 31:1082–1088
5. Nappi RE, Sances G, Brundu B et al (2005) Estradiol supplementation modulates neuroendocrine response to M-chlorophenylpiperazine in menstrual status migrainosus triggered by oral contraception-free interval. Hum Reprod 20:3423–3428
6. Nett R, Landy S, Shackelford S et al (2003) Pain-free efficacy after treatment with sumatriptan in the mild pain phase of menstrually associated migraine. Obstet Gynecol 102:835–842
7. Loder E, Silberstein SD, Abu-Shakra S et al (2004) Efficacy and tolerability of oral zolmitriptan in menstrually associated migraine: a randomized, prospective, parallel-group, double-blind, placebo-controlled study. Headache 44:120–130
8. Allais G, Acuto G, Cabarrocas X et al (2006) Efficacy and toler-

ability of almotriptan versus zolmitriptan for the acute treatment of menstrual migraine. Neurol Sci 27[Suppl 2]:S193–S197
9. Silberstein SD, Massiou H, Le Jeunne C et al (2000) Rizatriptan in the treatment of menstrual migraine. Obstet Gynecol 96:237–242
10. Massiou H, Jamin C, Hinzelin G et al (2005) Efficacy of oral naratriptan in the treatment of menstrually related migraine. Eur J Neurol 12:774–781
11. Silberstein SD, Elkind AH, Schreiber C et al (2004) A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. Neurology 63:261–269
12. Newman L, Mannix LK, Landy S et al (2001) Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. Headache 41:248–256
13. Moschiano F, Allais G, Grazzi L et al (2005) Naratriptan in the short-term prophylaxis of pure menstrual migraine. Neurol Sci 26[Suppl 2]:S162–S166
14. Mannix LK, Files JA (2005) The use of triptans in the management of menstrual migraine. CNS Drugs 19:951–972
15. Allais G, Bussone G, De Lorenzo C et al (2005) Advanced strategies of short-term prophylaxis in menstrual migraine: state of the art and prospects. Neurol Sci 26[Suppl 2]:S125–S129
16. Geraud G, Spierings EL, Keywood C (2002) Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. Headache 42[Suppl 2]:S93–S99
17. Massiou H, MacGregor EA (2000) Evolution and treatment of migraine with oral contraceptives. Cephalalgia 20:170–174
18. Loder E, Buse DC, Golub JR (2005) Headache as a side effect of combination estrogen-progestin oral contraceptives: a systematic review. Am J Obstet Gynecol 193:636–649
19. Dennerstein L, Laby B, Burrows GD et al (1978) Headache and sex hormone therapy. Headache 18:146–153
20. Martin VT, Behbehani M (2006) Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis – Part 2. Headache 46:365–386
21. MacGregor EA, Hackshaw A (2002) Prevention of migraine in the pill-free week of combined oral contraceptives using natural oestrogen supplements. J Family Planning Reprod Healthcare 28:27–31
22. Ferrari MD, Roon KI, Lipton RB et al (2001) Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 358:1668–1675
23. Poolsup N, Leelasangaluk V, Jittangtrong J et al (2005) Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. J Clin Pharm Ther 30:521–532
24. MacGregor EA, Keywood C (2000) Frovatriptan is effective in menstrually-associated migraine. Cephalalgia 20:345
25. Lay CL, Broner SW (2006) Special considerations in the treatment of migraine in women. Semin Neurol 26:217–222
26. Ashkenazi A, Silberstein SD (2006) Hormone-related headache: pathophysiology and treatment. CNS Drugs 20:125–141

Neurol Sci (2008) 29:S191–S195
DOI 10.1007/s10072-008-0923-4

This contribution has been added in proofs, and belongs to the Session "Cranial Neuralgias"

Clinical presentation of trigeminal neuralgia and the rationale of microvascular decompression

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Abstract Among the facial pain syndromes, trigeminal neuralgia has a special position for many reasons. Already described in the Romans age, the specific features of its severe symptoms, the therapeutic debate and the recent curative possibilities, make this complex pain syndrome a unique entity. The clinical onset is predominantly unilateral and is described as an electric, lancinating, focal and sharp pain. It can last seconds to minutes initially, and sometimes can last as long as 1 hour. Usually the patient is symptom-free between attacks. Later in the course of the disease, patients report dull, aching, constant pain in the same distribution as the paroxysms. The pain can be triggered by non-noxious stimuli like chewing, talking, swallowing, wind on the face, cold and light touch. Thought to be attributable to fifth cranial nerve dysfunction, the first surgical attempts aimed to interrupt nerve continuity by means of a rizothomy, with disappearance of both pain and sensory disturbances. Further investigations claimed nerve compression by vascular structures as responsible of nervous dysfunction. Hence the attempt to perform a decompression in order to relieve the symptoms and maintain physiologic nerve function. From the successful attempts of first microvascular decompression descends the now standardised and widespread technique that is commonly used today to treat trigeminal neuralgia.

Keywords Trigeminal neuralgia · Microvascular decompression · Clinical presentation · Pathogenesis · Rationale

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Introduction

Trigeminal neuralgia (TN), "tic douloureux", or Fothergill disease, is a well-known condition that neurologists and neurosurgeons are familiar with. First descriptions of this clinical entity date back to the second century AD [1], but also Arabs had some knowledge of trigeminal neuralgia during the 11th century. The first report of medical treatment is attributed to John Locke, a British physician and philosopher, who prescribed "laxatives" to an affected patient in Paris, in 1677 [2]. One century later, Nicolas André and John Fothergill collected different series of patients. The first, who named the disease "tic douloureux", grouped the disease with convulsions, tetanus and spasm, conceptualising them as a unique nosologic entity, claiming "vicious nervous liquids" as being the cause, and proposing the use of causting agents for the infraorbital nerve. The latter performed a very meticulous description of the symptoms, postulating the syndrome was caused by some sort of cancer [2]. When, finally, Sir Bell in 1820 described the fifth cranial nerve, the name trigeminal neuralgia was definitely applied [3]. Due to the lack of a pathological explanation for the pain, many therapies were initially tried, such as wine assumption, rest in a dark room, laxatives or even the assumption of hemlock, opium, arsenic [2]. None of these therapies did succeed. Among drugs, some anaesthetic agents were also employed, such as trichloroethylene or stilbamidine. In a more recent past, treatment has become surgical, ranging from dental extraction (often result of misdiagnosis) [4], to chemoneurolisis (by means of direct injection of chloroform [1] and alcohol [5] in the Gasserian ganglion, or glycerol in the trigeminal cistern [6]), from radiofrequency techniques (refined only few years ago) [7–9], to trigeminal nerve compression [10, 11]. All treatments carried significant side effects (loss of sensitivity, muscle

weakness, herpes virus infection, etc.) and early recurrence [2]. Microvascular decompression (MVD) is the treatment of choice. Radiation Therapy [1] and Stereotactic Radiosurgery [12] are a recent adjunct to the therapeutic options for trigeminal neuralgia. The latter, by means of Gamma Knife [13], assumes a peculiar interest in the light of the spreading availability of robotic frameless stereotaxy [14, 15]. Long-term results still have to be carefully evaluated with the time of long follow-up.

Physiopathology

Axons within the central nervous system are covered by myelin, which is generated by oligodendrocytes and is termed central myelin; in contrast, in the peripheral nerves, the myelin of axons is generated by Schwann cells. When a cranial nerve exits or enters the brainstem, the region of central myelin extends for a variable distance away from the brainstem and then changes into the peripheral myelin. This zone of transition is called the Obersteiner-Redlich zone. The area of the nerve that has central myelin is very vulnerable to trauma caused by the repeated pulsation of an artery in contact with the nerve. This process of nerve root injury may then cause demyelinisation [16, 17] over a focal area and an abnormal conduction or short-circuiting within the axons, which is called ephaptic transmission. This abnormality may lead to the production of a variety of hyperactive cranial nerves syndromes. Ectopic action potential generation in the sensory root of the nerve may be responsible for the typical, episodic, electric, lancinating pain of the trigeminal neuralgia [18, 19]. Relief of vascular compression leads to a permanent cure in a high percentage of patients, without permanent deficits in the distribution of the cranial nerve [20]. As shown by intraoperative electrode recordings, improvement in trigeminal nerve conduction after decompression, corroborates evidence that compression of the trigeminal nerve by a blood vessel is the major causative factor [21–23].

Clinical presentation

The diagnostic criteria for trigeminal neuralgia have to be all searched in the patient's clinical history. Pain is perceived in one or more divisions of the trigeminal nerve, mostly unilaterally. Pain is shooting, lancinating, sharp, agonising and described as an electric shock. Usually lasts seconds to minutes with repetitive bursts every few seconds. The patient is symptom-free between the attacks. A common evidence can be the trigger effect of some routinary actions involving territories innervated by the affected root, such as speaking, swallowing, chewing, brushing the teeth, or sensitive stimuli applied in these regions like simple light touch, cold, or an air blow. Even a simple position of the head can trigger the pain. Lying down over the painful area can worsen an attack; in the same manner, reversing the position can improve it. The trigger stimulus, applied to the "trigger zone", often arouses intense pain in divisions beyond the one stimulated. This allodynia is A-beta fibre activity with neuronal reorganisation at the level of dorsal root ganglion and rostrally [24]. The sensation is so discouraging that indeed even simple behaviours or activities are inhibited and social relations are compromised. A sense of despair can lead the patient to commit suicide. If untreated, or unsuccessfully treated, later in the course of the disease patients experience dull, aching, throbbing or burning, constant pain in the same distribution as the paroxysms. A long interval between the attacks is often described as a period of increasing paresthesias in the nerve distribution. In a minority of cases, pain can be experienced in the external auditory canal. Patients can describe a clicking sensation in the omolateral ear, possibly due to the motor innervation of the tensor tympani muscle.

Family history is present in about 5% of patients with trigeminal neuralgia. Up to 5% of patients can complain of bilateral, sequential pain. In our series, according to the literature, there was a female prevalence, in the sixth decade. The age range at presentation was 21 to 90 years. There is some controversy about the frequency of side of presentation and number of divisions involved [25]. In our series the right side was most frequently involved (56%) and maxillary branch was most frequently affected. Only in 13% all divisions were involved.

McGill Pain Questionnaire (MPQ) is commonly used to rank trigeminal neuralgia in affected patients. Beyond strictly evaluation of painful sensation, it can give a reliable indication of the affective stress.

Diagnostic clues

An accurate examination of the fifth cranial nerve starts exploring corneal sensitivity with a fine tip of a cotton swab, touching the cornea to elicitate the corneal reflex, considering that the upper half of the cornea is innervated by V_1, the lower by V_2. The sensory examination has to be performed on all three divisions: exploration of light touch (cotton wool), pinprick, hot/cold sensation, and deep pressure allow to discriminate a sensory deficit often present, but not described by the patient [26]. Distal small-fibre loss with neuropathy produces the feeling of burning pain. The sensory loss may not always be in the same area of the pain. Jannetta described a high incidence of hyperesthesia to cotton wool in the area of the nasolabial fold ipsilateral to the pain. Nurmikko and Eldridge in 2001 showed that electrophysiological investigations documented sensory trigeminal nerve abnormalities in the triggered zone [24]. Lunsford et al., by means

of evoked potentials, related nerve fibre dysfunction to the pain, finding that 86% of patients had nerve conduction abnormalities. Furthermore, 83% improved after microvascular decompression.

Tactile and temperature thresholds are raised in trigger areas, and hyperalgesia is often a response to normothermal stimuli [27]. There is often temporal summation (abnormal increases in intensity of pain to constant-strength stimulus, radiation of pain from the stimulus, after-sensation). Temporal summation of pain is a hallmark of central hyper-excitability to pain. Allodynia and hyperalgesia are the hallmarks of neuropathic pain. These findings implicate peripheral fibres involvement in trigeminal neuralgia [24]. Electrophysiological investigations of the trigeminal nerve have yielded consistent results, but they have not been widely used [16].

Imaging

It is well-established that typical trigeminal neuralgia is caused by a neurovascular conflict. A cornerstone in the history of trigeminal neuralgia was the possibility to visualise a tight relationship between the apparent origin of the fifth cranial nerve and some vascular structures. While the conventional T_1 and T_2 Magnetic Resonance Imaging (MRI) are useful in the differential diagnosis, excluding space-occupying lesions of the fifth nerve or close to it, specific angiographic MR algorithms allow 90.5% sensitivity with 100% specificity of vessel compression [28]. Nevertheless, the correlation of imaging with intra-operative findings has been reported to be 82,6%, 67%, 80%, 71% in various series, according to different MR sequences [29, 30]. In our series, 104 patients suspected having a neurovascular conflict for trigeminal neuralgia underwent MRI-3D CISS (constructive interference in steady state), obtaining images of the posterior fossa reconstructed using multiplanar reconstruction (MPR) algorithms. TOF (time of flight)-3D MRI angiograms of the posterior fossa were also taken and reconstructed with maximum intensity projection (MIP) algorithms. With these sequences, the vascular contact was accurately identified: the superior cerebellar artery (SCA) was compressing the trigeminal nerve in 80% of cases, the anterior-inferior cerebellar artery (AICA) was responsible in 15% of cases, in 4% of cases both SCA and AICA were involved and in 1% the vertebral artery (VA) only. MRI was negative in 1 case. In all our cases, but one, the neurovascular conflict was identified intraoperatively.

Differential Diagnosis

Typical trigeminal neuralgia is easily diagnosed. Neurological examination is usually normal in affected patients. However, there are reports in the literature of many patients with TN who experienced pain for several years before receiving an accurate diagnosis [24]. While well-acquainted by neuroscientists, trigeminal neuralgia is often referred to general practitioners or dentists who are not very familiar with such a disease, leading to misdiagnosis. Pain along one or more division/s of the fifth cranial nerve, may be an atypical trigeminal neuralgia or atypical facial pain. Indeed the term “atypical” contains the concept of multiple different clinical entities. Eller et al. [31] proposd to use the “atypical facial pain” term to indicate facial pain in the context of a somatoform pain disorder, usually bilateral, spreading outside the trigeminal distribution, often associated to multiple pain complaints in other body regions, including diagnostic clustering such as fibromyalgia or chronic fatigue syndrome. Psychological testing prior to confirmation of this diagnosis should be performed. Moreover, they proposed a classification of trigeminal neuralgia (TN) according to seven diagnostic criteria from patients’ complaints [31]. TN1 and TN2 differ only for the lasting of the pain, being episodic and brief in the first, and continuous and dull in the latter that sometimes hides a tumour, cyst, vascular malformation, etc. and demands for further imaging studies. Small infarcts and other vascular lesions in the pons or nerve root can cause pain. A different group includes pain from nervous lesioning, like in trauma or surgery, neurectomy, gangliolysis, rhizotomy, nucleotomy, tractotomy, or other denervating procedures (de-afferentation pain). Trigeminal neuralgia may be associated with Multiple Sclerosis (MS) in patients, often under 40 (1%). The supposed mechanism is similar to the real trigeminal neuralgia’s one, but the pain can be constant from the beginning. In the post-herpetic trigeminal neuralgia the first division is commonly affected and is marked by the development of allodynia superimposed on a burning, constant and deep dysesthesia. Trophic changes may be noted.

In the differential diagnosis neoplastic, inflammatory, and vascular causes can be easily ruled out. Some conditions must be accurately considered: the glossopharyngeal neuralgia which is characterised by severe, stabbing pain in the ear, throat or both while swallowing; the geniculate neuralgia with a typical severe, “ice-pick” pain deep in the ear in a constant background pain. Migraine is usually unilateral, throbbing, pulsating, usually involving cranial vault, also associated with nausea, vomiting, and photophobia, seldom with aura. Sharp-like pain has an odontogenous origin and is short-lasting. Sinusitis of the maxilla causes an aching, throbbing pain in the cheek, which gets worse in the morning and improves in head-up position. Giant cell arteritis is often accompanied by malaise, diffuse tenderness, rubor in the temporal region extending to the neck. Temporo-mandibular joint disorders cause a dull regional ache, non radicular in distribution, often worsen by pressure and movement, and limitation of jaw opening.

Surgery: Microvascular Decompression technique (MVD)

This technique has been introduced by Peter Jannetta in 1967 [32, 33]. After anaesthesia is induced and intubation is performed, the patient is placed in the lateral position with the neck minimally stretched, flexed and rotated controlateral to the pain side. The mastoid eminence, digastrics groove, and inion should be identified and an inio-meatal line drawn to define the transverse sinus. A vertical or "italic S"-shaped incision is drawn 3- to 5-cm long, approximately 0.5-cm posterior (medial) and parallel to the hair line. After soft tissues opening and bone preparation, burr hole is performed approximately on the mastoid emissary vein; the asterion can be a useful landmark. The goal of bone exposure should be to identify the edge of the junction of the transverse and sigmoid sinuses first, in order to obtain a small and safe craniectomy. The junction of the transverse and sigmoid sinuses must, then, be visualised. A T-shaped incision is made in the dura mater to expose the most superior and lateral corner of the dura adjacent to the junction of the transverse and sigmoid sinuses, to allow a direct corridor along the petro-tentorial bone. At this point the cerebellopontine angle has to be exposed. The surgeon should allow some drainage of cerebrospinal fluid (CSF) in order to minimise the cerebellar retraction. On entering the cerebellopontine angle, the first structure visualised will be the seventh-eighth nerve complex, located superficially and caudal to the trigeminal nerve. The trigeminal nerve is located in the most superior and deepest position. Decompression is relatively straightforward if the surgeon keeps in mind that the dorsal root entry or exit zone can be variable in length, particularly in the case of the nerve, and may extend to a more distal portion of the nerve itself. Therefore, the nerve should be inspected from its origin at the brainstem laterally to its exit from the cerebellopontine angle, and all vessels should be visualised. The compression may be proximal or distal, and it may be located under the ala of the cerebellum. Microvascular decompression of the trigeminal nerve requires sharp dissection of all arachnoid around the trigeminal nerve and superior cerebellar artery which usually compresses the nerve either at the brainstem or distally. Rostral compression of the nerve causes pain in the V_3, and this is most commonly due to the SCA looping downward and upward again. As the artery elongates, it compresses the middle portion of the nerve, causing pain in the V_2 in addition to the V_3. The relatively rare, isolated pain in the V_1 is caused by a vessel on the caudal side of the nerve. Isolated pain in the V_1 is most common in older men, cigarette smokers, and patients with dolichocephalic features, in whom the vertebrobasilar system arteries compress the nerve from the caudal side. Isolated pain in the V_2 is most common in younger women and is caused by a bridging vein that may be quite distal on the nerve. After the arachnoid is dissected, the looping vessel can be mobilised in order to interpose a piece of muscle or shredded Teflon felt in between. Even without evident microvascular conflict, a simple explorative procedure with mobilization of neurovascular structures of the area, may result in symptoms remission. Tight dural closure is important to ensure watertight closure. The bone edges of the mastoid air cells are accurately waxed. The deep and superficial muscles are approximated. The fascial closure must be watertight to prevent any CSF leakage. Most frequent complications are cerebellar injury, hearing loss, and CSF leakage. Rare complications of the procedure, are facial weakness or anaesthesia and lower cranial nerve dysfunction. The entire decompression procedure (from skin incision to skin closure) generally takes less than 2 hours and requires only a small corridor of exposure between the cerebellum and petrous temporal bone. This corridor is kept to a minimum by adequate exposure of the sigmoid sinus through mastoid bone removal prior to durotomy. This allows a dural incision very close to the sigmoid sinus rather than a more posterior durotomy that requires more cerebellar retraction to permit visualization along the petrous temporal bone. Avoidance of CSF leaks remains problematic after transgression of mastoid air cells and exposure of multiple overlapping tissue planes. Our incidence of CSF leaks has declined since 1990 from 3.65% to 2.15% (p0.01). Great attention must be paid to mastoid air cells: it is compulsory to fill them with abundant bone wax. The nuchal musculature has to be tightly sutured before fascia is closed. Postoperative CSF leaks usually resolve with lumbar drainage, only a minority of cases requires operative intervention, including re-exploration of the dural closure and careful inspection of the mastoid air cells. Surface veins cause a special problem, because they are prone to recollateralise if coagulated and divided. Most early recurrences are the result of these recollateralised veins. Subsequent recurrence (0.5%/year) is due to new blood vessels, especially arteries, pressing on the nerve, as a result of the continuation of the aging process.

Conclusion

The natural history of TN indicates progressive large-fibre loss, making some therapeutic options poorly effective. Many treatment strategies are available today: among them, microvascular decompression is the gold standard treatment. The commitment of neurosurgeons in this area has led to a progressive refinement of the technique over the years, with significant reduction of postoperative mortality and morbidity and indication also for elderly patients [34]. Furthermore, concerning the mechanism of the radicular damage, intra-operative electrophysiological studies allow us to exactly assess the damaged fibres, responsible of specific symptoms and signs. These elegant complementary studies allow to character-

ize patients with trigeminal neuralgia according to the damage of large-fibre, small-fibre, or mixed sensory neuropathy. This may lead to more precise surgical procedures in which the appropriate fibre group is targeted [2].

References

1. Stookey B (1959) Trigeminal Neuralgia: Its History and Treatment. Charles C. Thomas, Springfield, IL
2. Cole CD, Liu JK, Apfelbaum RI (2005) Historical perspectives on the diagnosis and treatment of trigeminal neuralgia. Neurosurg Focus 18:E4
3. Wilkins RH, Brody IA (1969) Bell's palsy and Bell's phenomenon. Arch Neurol 21:661–662
4. Tew JM Jr (1988) Percutaneous rhizotomy in the treatment of intractable facial pain (trigeminal, glossopharyngeal, and vagal nerves) 2nd Edn. Grune & Stratton, Orlando
5. Härtel F (1914) Über die intracranielle Injektionsbehandlung der Trigeminusneuralgie. Med Klinik 10:582–584
6. Hakanson S (1981) Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. Neurosurgery 9:638–646
7. Sweet WH, Wepsic JG (1974) Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. 1. Trigeminal neuralgia. J Neurosurg 40:143–156
8. Liu JK, Apfelbaum RI (2004) Treatment of trigeminal neuralgia. Neurosurg Clin N Am 15:319–334
9. Taha JM, Tew JM Jr (1996) Comparison of surgical treatments for trigeminal neuralgia: reevaluation of radiofrequency rhizotomy. Neurosurgery 38:865–871
10. Shelden CH, Pudenz RH, Freshwater DB et al (1955) Compression rather than decompression for trigeminal neuralgia. J Neurosurg 12:123–126
11. Taarnhøj P (1952) Decompression of the trigeminal root and the posterior part of the ganglion as a treatment in trigeminal neuralgia; preliminary communication. J Neurosurg 9:288–290
12. Leksell L (1971) Sterotaxic radiosurgery in trigeminal neuralgia. Acta Chir Scand 137:311–314
13. Kondziolka D, Lunsford LD, Flickinger JC et al (1996) Stereotactic radiosurgery for trigeminal neuralgia: a multiinstitutional study using the gamma unit. J Neurosurg 84:940–945
14. Lim M, Villavicencio AT, Burneikiene S et al (2005) CyberKnife radiosurgery for idiopathic trigeminal neuralgia. Neurosurg Focus 18:E9
15. Romanelli P, Heit G, Chang SD et al (2003) Cyberknife radiosurgery for trigeminal neuralgia. Stereotact Funct Neurosurg 81:105–109
16. Fromm GH (1991) Trigeminal Neuralgia: Current Concepts Regarding Pathogenesis and Treatment. Butterworth-Heinemann, Boston
17. Hilton DA, Love S, Gradidge T, Coakham HB (1994) Pathological findings associated with trigeminal neuralgia caused by vascular compression. Neurosurgery 35:299–303
18. Devor M, Amir R, Rappaport ZH (2002) Pathophysiology of trigeminal neuralgia: the ignition hypothesis. Clin J Pain 18:4–13
19. Devor M, Govrin-Lippmann R, Rappaport ZH (2002) Mechanism of trigeminal neuralgia: an ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery. J Neurosurg 96:532–543
20. Sekhar LN SD, Elahi F (2006) Microvascular decompression for cranial nerve compression syndromes. In: Sekhar LN FR (ed) Atlas of neurosurgical techniques. Thieme, New York/Stuttgart, pp 860
21. Barker FG 2nd, Jannetta PJ, Bissonette DJ et al (1996) The long-term outcome of microvascular decompression for trigeminal neuralgia. N Engl J Med 334:1077–1083
22. Leandri M, Eldridge P, Miles J (1998) Recovery of nerve conduction following microvascular decompression for trigeminal neuralgia. Neurology 51:1641–1646
23. Nurmikko TJ, Eldridge PR (2001) Trigeminal neuralgia-pathophysiology, diagnosis and current treatment. Br J Anaesth 87:117–132
24. Casey KF (2005) Role of patient history and physical examination in the diagnosis of trigeminal neuralgia. Neurosurg Focus18:E1
25. Katusic S, Beard CM, Bergstralh E, Kurland LT (1990) Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. Ann Neurol 27:89–95
26. Eide PK, Rabben T (1998) Trigeminal neuropathic pain: pathophysiological mechanisms examined by quantitative assessment of abnormal pain and sensory perception. Neurosurgery 43:1103–1110
27. Fromm GH (1989) Trigeminal neuralgia and related disorders. Neurol Clin 7:305–319
28. Patel NK, Aquilina K, Clarke Y et al (2003) How accurate is magnetic resonance angiography in predicting neurovascular compression in patients with trigeminal neuralgia? A prospective, single-blinded comparative study. Br J Neurosurg 17:60–64
29. Fukuda H, Ishikawa M, Okumura R (2003) Demonstration of neurovascular compression in trigeminal neuralgia and hemifacial spasm with magnetic resonance imaging: comparison with surgical findings in 60 consecutive cases. Surg Neurol 59:93–99
30. Yoshino N, Akimoto H, Yamada I et al (2003) Trigeminal neuralgia: evaluation of neuralgic manifestation and site of neurovascular compression with 3D CISS MR imaging and MR angiography. Radiology 228:539–545
31. Eller JL, Raslan AM, Burchiel KJ (2005) Trigeminal neuralgia: definition and classification. Neurosurg Focus 18:E3
32. Jannetta PJ (1967) Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. J Neurosurg 26[Suppl]:159–162
33. McLaughlin MR, Jannetta PJ, Clyde BL et al (2008) Microvascular decompression of cranial nerves: lesions learned after 4400 operations. J Neurosurg 90:1–8
34. Sekula RF, Marchan EM, Fletcher LH et al (2008) Microvascular decompression for trigeminal neuralgia in elderly patients. J Neurosurg 108:689–691

Neurol Sci (2008) 29:S197–S207
DOI 10.1007/s10072-008-0922-5

POSTER SESSION

Migraine, Right-to-Left shunt and focal white-matter lesions: a transcranial doppler study

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Aim of the study was to analyse the relationship among migraine characteristics, presence of Right-to-Left shunt (RLS) and of MRI focal white-matter lesions. A group of 72 patients suffering from migraine with (MwA) and without Aura (MwoA) has been studied; as a control group 20 asymptomatic, age-matched subjects have been considered. RLS was detected using Transcranial Doppler plus gaseous contrast-medium, as a standardized technique. RLS was found in a significant number of MwA patients (50% vs. 35% of control and MwoA pts); on the other side, focal MRI lesions correlated with crises frequency instead of migraine type. On the Authors' opinion these findings could shed further light on the pathophysiological mechanisms by which migraine is considered a cerebrovascular risk factor.

Patients with migraine with aura have an increased flow mediated dilation

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Nitric oxide (NO) was hypothesised to trigger migraine pain; migraineurs, in fact, share an arterial supersensitivity to NO. Previous studies demonstrated that NO donor glyceryl trinitrat (GTN) infusion can provoke headache in healthy subjects and even stronger headaches in migraineurs. Blood vessels can adjust blood flow in response to changes in the local environment. Many blood vessels respond by dilating to an increase in flow. This phenomenon is defined as flow-mediated dilatation (FMD). A principal mediator of FMD is endothelium-derived NO.

We enrolled 34 participants: 21 with migraine (10 with aura [MwA], 11 without aura [MwoA]), and 13 controls. The FMD was assessed in all subjects by measuring the change in brachial artery diameter after reactive hyperemia, compared with baseline measurements.

On average, FMD was 20.9% (SD: 11.2%), and it was not correlated with age, nor gender. Participants with MwA had a FMD of 31.0% (SD: 15%), while it was 18.2% (SD: 6.9%) in the group MwoA and 15.5% (SD: 3.9%) in the control group ($p<0.05$ for the comparison of MwA with both MwoA and controls, $p>0.05$ for the comparison between MwoA and controls). After adjustment for age and gender, the results were unchanged, with group membership being still significantly associated with FMD ($p<0.001$). Neither age and gender were associated with FMD.

The main finding of the present study is that FMD is increased in patients affected by MwA compared to controls and migraneurs without aura. These data suggest that patients affected by MwA present an increased sensitivity to the local production of NO. This phenomenon observed peripherally in the brachial artery might reflect similar characteristics in the cerebral circulation.

Increased cerebral vasomotor reactivity in migraine with aura: an autoregulation disorder? A transcranial Doppler and Near Infrared Spectroscopy study

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Migraine with Aura (MwA) is associated with a reduction in cerebral blood flow (CBF) during the cortical spreading depression. Following the passage of the oligoaemia, the vasodilatory response to hypercapnia may be impaired. The importance of the autoregulatory mechanism in patients with migraine is, however, still to be determined. Near InfraRed Spectroscopy (NIRS) derives non-invasively information about the concentrations of oxy- and deoxy-hemoglobin (Hb) measuring infrared light backscattered from the tissue. NIRS has been used to estimate cerebral blood volume (CBV) and to measure VMR.

Aim of the study was to investigate CBF and CBV in basal conditions and after CO2 inhalation in patients affected by migraine with aura. We enrolled 21 controls and 16 patients with MwA. All subjects underwent a simultaneous examination of CBF within middle cerebral arteries with TCD and of NIRS parameters (oxy% and total Hb content, THC), at rest and during CO2 reactivity test. Our results showed significant difference of cerebral VMR among migraineurs with side prevalence, without side prevalence and control subjects. Moreover, there was significant difference in terms of THC and Ox% increase, as measures of regional CBV after stimulus among the 3 groups. Consistently, VMR, THC and Ox% increases resulted significantly higher in the predominant side of migraineurs compared to their non-predominant side as well as to both sides of migraineurs without predominance and controls.

Our study demonstrates that there is an increase in cerebral VMR in patients with MwA in most usual headache side. NIRS could represent a simple and non-invasive technique complementary to TCD able to detect cerebral hemodynamic impairment in patients with migrainous aura.

Sleep-related migraine and circadian blood pressure monitoring

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Migraine attacks preferentially occurring at night time or in the early morning usually show a peak frequency between 04:00 and 09:00 a.m. This time schedule reflects a close relationship between migraine and sleep, as well as a putative impairment of circadian rhythm control systems in both episodic and chronic migraineurs. This may underlines the pivotal role of hypothalamus in the control of circadian rhythms and sleep, especially REM sleep. The role of physiological variables (e.g. aging) and pathological conditions (e.g. hypertension/hypotension and/or psychiatric disorders) in favouring the nocturnal or early morning presentation of migraine attacks is yet unknown.

The aim of this study was to assess blood pressure changes in patients with sleep-related migraine without aura (SRMwA), defined as subjects in whom at least 75% of attacks occurred at night time or on awakening. Twenty-five patients suffering from SRMwA were

compared with 30 patients with migraine without aura (MwA) who were lacking of a preferential timing of attacks. Each patient underwent a 24-hour Ambulatory Blood Pressure Monitoring (ABPM).

No significant changes of blood pressure parameters were detected in SRMwA patients as compared with MwA subjects. Data analysis of the circadian variation of blood pressure showed a reduction of the acrophase amplitude of ABPM parameters (systolic, mean, diastolic blood pressure values) in both SRMwA and MwA patient groups.

Results suggest a likely dysfunction of the circadian rhythm generator and the autonomic nervous system in either type of migraine, but do not account for the prevalent night time occurrence of attacks in SRMwA patients.

Migraine and patent foramen ovale: improvement after transcatheteral closure

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Background and Purpose: The reports on the efficacy of transcatheter PFO closure on migraine prevention are scarce. The aim of the study was to value the course of migraine assested retrospectively in migraine headache patients undergoing PFO transcatheteral closure.

Methods: We reviewed the clinical records of 42 consecutive patients who underwent successful transcatheter PFO closure at our institution because of migraine. Information about migraine before and after PFO closure was obtained by a telephonic interview using a structured questionnaire. Of the 42 patients, 28 (67%) had a diagnosis of migraine with aura (MA), and 14 (33%) migraine without aura (MoA). Migraine severity was assessed with a scale that takes into account the frequency, duration, intensity of the attacks and the occurrence of aura (score range 0 to 11).

Results: Baseline severity of migraine was higher in MA patients than MoA (p=.037). After the procedure, the overall migraine score had significantly improved: it dropped from 8.8 to 4.4 in MA patients, and from 7.5 to 4.0 in MoA patients. 11 (26%) of 42 patients had complete resolution in their migraine, 22 (52%) of 42 patients had significant improvement (reduction of migraine attack frequency by more than 50%), 9 (21%) of patients had a partial resolution (reduction of migraine attack frequency by less than 50%). In MA patients aura disappeared in 16/28 patients (57%). Multiple linear regression analysis showed that the improvement inMA and MoA was indipendent by migraine type, sex, age, cerebrovascular risk factors and previous cerebrovascular events, type of cardiac difect, thrombophilic conditions.

Conclusions: Closure of PFO brings a significant overall improvement of migraine and dramatically reduces the occurrence of aura. This seems occur irrespective of migraine type and previous cerebrovascular disease.

Parasomnias in menstrual migraine patients: a case-control study

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Background: The relationship between migraine and sleep has been known for a long time. In particular a higher incidence of parasomnias, among which bruxism, somnambulism, sleep talking and night terror, has been documented in children with migraine compared with controls. Moreover an association between headache and narcolepsy was previously reported.

Objective: The aim of the present study was to investigate the prevalence of parasomnias in women affected with menstrual migraine, a migraine sub-type with a cyclical recurrence and an evident link with biological rhythms.

Patients and Methods: 93 women (mean age 35.86±7.25 years) with a ICHD-II diagnosis of pure menstrual migraine or menstrually-related migraine, and 85 age-matched non migraineurs women were evaluated for parasomnias by mean of a semistructured interview. The χ^2 test was used to analyse differences in the frequencies of categorical variables. The odds ratio (OR) with 95% confidence interval (CI) was calculated.

Results: Significant differences between menstrual migraine patients and controls were found for the lifetime prevalence of sleep paralysis (23.7% vs. 8.2%, p=0.008; OR 3.45, CI 1.39-8.57), nightmare disorder (65% vs. 48%, p=0.021) and sleep related hallucinations (50.5% vs. 23.55, p= 0.000; OR 3.321, CI 1.74-6.33). We found no difference among groups for the lifetime prevalence of confusional arousal, somnambulism, sleep terror, rhythmic movement disorder, sleeptalking, bruxism, enuresis, hypnic jerks and REM behaviour disorder (RBD). 86% of patients had at least one parasomnias usually associated with REM sleep vs. 55% of controls (p=0.001; OR 3.35, CI 1.60-7.00).

Conclusion: Our work shows a higher prevalence of parasomnias usually associated with REM sleep, excluding RBD, in menstrual migraine and does not confirm the association between migraine and parasomnias of arousal. Those findings suggest a dysfunction in structures involved in both the pathophysiology of migraine and the control of REM sleep.

Daytime sleepiness, fatigue and sleep quality in menstrual migraine: a case-control study

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Background: Previous studies described a high prevalence of excessive daytime sleepiness and unsatisfactory sleep quality among migraine suffers.

Objectives: To evaluate prevalence of daytime sleepiness, sleep quality and fatigue in patients with menstrual migraine compared to normal female.

Material and methods: 93 patients with ICHD-II diagnosis of pure menstrual migraine and menstrually-realted migraine were recruited and compared to 83 age-matched healthy women. Daytime sleepiness was assessed by means of Epworth Sleepiness Scale (ESS) and Bologna Somnolence Questionnaire (BSQ). Sleep quality was measured using a self-rated standardized questionnaire focusing on subjective sleep quality perception and hypnotic medications intake. Berlin questionnaire on snoring was also administered. Fatigue was tested using the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS). The χ^2 test was used to analyse results.

Results: ESS and BSQ didn't show a significant difference in excessive diurnal sleepiness prevalence between the two groups. FSS and MFIS revealed a higher prevalence of fatigue among migraine women compared to controls (p=0.004) associated to a higher fatigue impact on migraineurs physical (p<0.001), cognitive (p=0.01) and psycosocial (p=0.001) performances. Migraine women resulted to be significantly unsatisfied of their nocturnal sleep with respect to controls (p=0.001) but no differences were found regarding difficulty in falling asleep, nighttime awakenings, early morning awakenings and hypnotic medications intake. Berlin questionnaire didn't show significant differences between groups.

Conclusions: The study didn't confirm the presence of excessive daytime sleepiness in a selected group of women with menstrual migraine. However, results showed a higher prevalence of fatigue

and of its impact among migraine suffers. Sleep quality was judged unsitisfactory in migraneous patients despite the absence of insomnia and sleep breathing disorders.

Sleep-related movement disorders in menstrual migraine patients: a case-control study

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Background: Migraine has been associated with periodic or restless limb movements in previous case-control studies.

Objective: The aim of the present study was to investigate the prevalence of restless legs syndrome (RLS) and sleep related legs cramps in women affected with menstrual migraine compared to healthy women.

Patients and Methods: 93 women (mean age 35.86±7.25 years) with a ICHD-II diagnosis of pure menstrual migraine or menstrually-related migraine, and 85 age-matched non migraineurs women were evaluated for RLS according to the four clinical criteria of the International Restless legs Syndrome Study Group, and for sleep related legs cramps by means of a semistructured interview. The χ^2 test was used to analyse differences in the frequencies of categorical variables. The odds ratio (OR) with 95% confidence interval (CI) was calculated.

Results: The lifetime prevalence of RLS was 32.3% in women with menstrual migraine and 14.1% in control subjects (p=0.005; OR 2.89, CI 1.36-6.13). The lifetime prevalence of sleep-related legs cramps was 35.5% in our patients and 15.3% of controls (p=0.001).

Conclusion: Our work shows a higher prevalence of sleep related movement disorders in menstrual migraine. We confirm the association between migraine and RLS and highlight a relationship between migraine and nocturnal cramps. The underlying mechanisms are still debated.

Functional-MRI (f-MRI) evaluation in chronic migraine with medication overuse before and after withdrawal

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Introduction: Withdrawal is the first step for treating patients with chronic migraine and medication overuse. Recent studies confirmed common elements in personality between these patients and subjects addicted; some neuroimaging researches showed that abnormalities revealed are related to a specific cerebral pattern and that they can return to the normal state after withdrawal.

Aim: To submit a group of patients suffering from chronic migraine and medication overuse (the diagnosis was made according to Silberstein-Lipton criteria) to a withdrawal, to evaluate by fMRI the presence of specific cerebral patterns before treatment and their possible changes after withdrawal.

Material and methods: A group of patients suffering from chronic migraine and medication overuse will be examined with a Siemens Magnetom Avanto 1.5T at time 0 and 3, 6, 12 months later. At the first exam the patients will be submitted to an initial psychophysical testing session. Mechanical pressure stimuli of 3 sec in duration will be applied to the finger of the left hand to determine threshold for just noticeable pain (level 1), moderate pain (level 4) and strong pain (level 8). The participants are exposed at the three intensity levels determinate during the previous psychophysical test.

Results: Until now three patients were submitted to this protocol. Two patients were unable to perform the tasks because the former was drowsy under the effect of the medication took at the time of testing, the latter kept moving inside the scanner during the pressure stimuli administration. In the third patient, fMRI revealed significant activations in the anterior mid-cingulate cortex (aMCC), in bilateral insula cortex (IC), and bilateral pre-central areas and particularly in the bilateral orbital cortex during the noxious stimulation (p<0.05 FDR).

Discussion: fMRI seems to be a useful technique to obtain information on particular neuronal changes of the pain network involved in this type of patients. The activated areas are congruent with some data of the literature. More subjects are needed to evaluate the possible changes after withdrawal.

Migraine with and without aura: study with transcranial doppler and brain magnetic resonance imaging

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Background: Recent studies performed by and Transcranial Doppler (TCD) with iv injection of agitate saline reported an increased prevalence of patent foramen ovale (PFO) in patients (pts) with migraine with aura compared to controls. Some PET studies reported cerebral microcirculation ipoperfusion during aura of migraine attack. Recent reports performed by Brain Magnetic Resonance Imaging (bMRI) shown that migraine with (MA+) and without aura (MA-) are at increased risk for subclinical brain lesions (infarcts and white matter lesions).

Objective: By bMRI to compare the prevalence of subclinical brain lesions in migraine cases and controls, to identify migraine characteristics associated with these lesions; by TCD to evaluate a possible correlation with patent foramen ovale and a possible cerebral microcirculation ipoperfusion during aura of migraine attack.

Patients and methods: 64 pts (10 M and 54F, mean age 38±11 s.d) 35 pts with MA+, 29 with MA- and 20 controls (mean age 42±12 s.d.) were studied by TCD (with and without iv injection of agitate saline) and bMRI (PD, T2w, T1w and FLAIR sequences).

Results: PFO was found more frequently in pts with MA+ 82 %, than in controls 20%, O.D. 18 (95% CI 0,35-0.98) p<0.0001. Pts with migraine had a higher prevalence of subclinical brain lesions than controls (EA+: O.R. 5.3 p<0.008, EA-: O.R. 15 p<0.0001). We found correlation r=0.64 p<0.0001 between subclinical brain lesions and numbers of bubbles detected by TCD only in patients with EA+ and PFO. We found no significant difference between patients with migraine and PFO and migraine without PFO in subclinical brain lesions prevalence. Pts with high frequency migraine attacks (≥ 2/month) had higher prevalence of subclinical brain lesions than pts with low frequency migraine attacks (< 2/month) O.R. 7.2 (CI 95% 0.15-0.61) p<0.001. During aura of migraine attack TCD showed a significant increase of Pulsatility Index compared with controls p<0.001 indicative of cerebral microcirculation ipoperfusion.

Conclusion: These findings suggest that PFO represents a possible risk factor for subclinical brain lesions in migraine with aura, migraine with and without aura are at increased risk for subclinical brain lesions increasing with the frequency of migraine attacks and finally cerebral microcirculation ipoperfusion probablity occurs during aura on migraine attack.

Hemicrania continua evolving from cluster headache and responding to valproate: a case report

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Hemicrania continua (HC) is a rare type of primary headache. It is classified in the group of "Other primary headaches" and is characterised by a prompt and enduring response to indomethacin. Centonze et al. described a case of cluster headache (CH) evolving into ipsilateral HC (Centonze et al. 1987). Other Authors reported a case of simultaneous occurrence of CH and HC on the same side (Saito et al. 2005). We describe a patient who suffered from CH evolving into ipsilateral HC.

A 51-year-old woman had been diagnosed with CH in our Headache Centre two years before. We recommended a prophylactic therapy with verapamil 120 mg t.i.d., but the patients took only 80 mg t.i.d. because of hypotension, with no improvement. Seven months later, the consistently unilateral headache became continuous. Pain was mild to moderate with 5-8 exacerbations a day, characterized by more severe right periorbital pain lasting from 30 min to a few hours and accompanied by ipsilateral nasal congestion, nausea and asthenia. We treated the patient with indomethacin 25 mg t.i.d. and the headache promptly disappeared. Brain MRI showed only chronic vasculopathy, seemingly due to impaired microcirculation (the patient was a heavy smoker.) We established a diagnosis of HC. The patient remained headache free for six months. As she couldn't tolerate long-term indomethacin therapy, after a few trials with other therapeutic regimens, we started a therapy with valproic acid at a dose of 750 mg/day, with significant improvement of HC at 3 months' follow-up. It is worth noting that the patient had comorbidity with other conditions, including coeliac disease, a past history of hypothyroidism (successfully treated by radiometabolic therapy), anorexia, anxiety/depression syndrome, and allergy to several drugs such as penicillin, thiamazol and amitryptilin. In our case, valproic acid had a beneficial effect on weight gain and mood improvement.

Therefore, valproic acid might represent a good alternative for HC treatment in patients who are intolerant to long-term indomethacin and also have certain comorbid conditions.

Lifestyle in cluster headache patients: does it increase the risk of head injury?

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Introduction: Several Authors have reported a significant association between cluster headache (CH) and head injury (HI).

Aims: To investigate in male patients with CH v.s. controls: a) the frequency of HI; and b) how HI occurred.

Methods: We conducted a retrospective study on 400 male patients seen at the University of Parma Headache Centre between 1 January 2004 and 1 October 2007. The study population was divided into two groups of cases and controls. The case group included 200 patients with episodic CH consecutively referred to our Headache Centre. The control group consisted of 200 patients with migraine without aura (MO). Cases were matched to controls by age at onset of headache and by age at the first visit at the Headache Centre (±2 yrs). The diagnoses were based on the International Classification of Headache Disorders (ICHD 2004, 2nd Edn). In both cases and controls, we investigated: the frequency of HI, the features of HI, and how IH occurred (e.g., in the event of road accidents, we recorded whether the patients were driving, whether they were responsible for causing the accident, etc.).

Results: Mean age of cases was 36.6 years (±9.8 yrs) and 36.7 years for controls (±9.9 yrs). Mean age at onset of headache was 24.4 years for cases (±8.9 yrs) and 23.5 years for controls (±8.7 yrs). The frequency of HI was 30.8% (123/400). In the group of CH cases, 77 (38.5%) had IH (22 with and 55 without loss of consciousness) versus only 46 (23%) in the MO control group (11 with and 35 without loss of consciousness) ($p=0.003$). A second HI without loss of consciousness was more frequent in CH cases (16/77, 20.1%) than in MO controls (6/46, 13%) ($p=0.028$). As regards the time relationship between HI and onset of CH, 47 patients had IH before CH onset (61%, mean age at HI: 14.1 yrs±8 yrs); on average, the interval of time between HI and CH onset was 10.6 years (±7.8 yrs). In this patient subgroup, 35.2% had HI on the same side on which they later developed headache, as compared with 7.4% in whom HI was contralateral to CH. Among all patients with HI, the injury occurred during a road accident in 49.4% (n=38)of CH cases vs. 58.7% (n=27) of MO controls; during a household accident in 11.7% (n=9) of cases vs. 4.3% (n=2) of controls; during a work accident in 7.8% (n=6) of cases vs. 4.3% (n=2) of controls; during a sport accident in 10.4% (n=8) of cases vs. 15.2% (n=7) of controls; or for other reasons in 18.2% (n=14) of cases vs. 13% (n=6) of controls (Data is lacking in four). In both study groups, the means of transportation more frequently involved in road accidents was the car (cases: 24/38, 63.2%; controls: 15/27, 55.6%). During road accidents, however, CH cases were more frequently driving (n=33/38, 86.8%) than MO controls (n=17/27, 63%) ($p=0.02$). Compared with MO controls, CH cases were more frequently responsible for the accident that caused HI (35/200, 17.5% vs. 16/200, 8%) ($p=0.007$), and the difference was statistically significant also for road accidents: 24/200 CH cases vs. 12/200 MO controls ($p=0.05$).

Conclusions: The results of our study demonstrate that HI is more frequent in patients with CH than in patients with MO. HI occurred more frequently during road accidents involving motor vehicles in both study groups, but in the CH group patients were more frequently driving and more frequently responsible for causing the accident than in the control group. Such data might suggest that CH patients are more prone to risky behaviour and therefore more likely to have accidents of various kinds. Lifestyle might then be considered a risk factor for HI (often, more than one injury) in CH patients.

Validation of questionnaire for diagnosis of primary headache for use in epidemiological studies in the general population

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In the absence of biological markers, the diagnosis of primary headache rests on clinical findings, as reported through ad-hoc interviews.

The aim of this study was the validation of a headache questionnaire designed to be administered by a physician, for the diagnosis of primary headaches or of probable medication overuse headache in the general population according to the International Classification of Headache Disorders (2nd Edn, 2004 – ICHD-II). The questionnaire comprises 76 questions based on the ICHD-II diagnostic criteria for migraine (code 1.1, 1.2.1, 1.2.2, 1.2.3, 1.5.1, 1.6), tension-type headache (code 2.1, 2.2, 2.3, 2.4), primary stabbing headache (code 4.1) and probable medication overuse headache (code 8.2.7) and on other clinical features (i.e. age at onset, relation between headache and pregnancy etc.). Answers to each question were: (a) numbers (i.e. age at onset); (b) "Yes" or "No" (e.g. Do you have nausea during headache?); (c) predefined answers (e.g. quality of pain). We assessed the validity and reliability of the questionnaire and its sensitivity and specificity for migraine and tension-type headache.

The study population consisted of 50 patients (37F, 13M) aged 17–76 years (mean, 40.7) seen for the first time on a consecutive basis at the University of Parma Headache Center. The questionnaire was administered independently by two trained physicians (E1 and E2) before the visit performed by a headache specialist (blind to the diagnosis made by E1 and E2). If appropriate, more than one headache subtype was considered. Questionnaire-based diagnosis was compared with

diagnosis established by the headache specialist taken as the gold standard (GS). For the first type of headache (n=50), we found an agreement of 98% (K value: 0.96; CI 95%: 0.88-1.00) between E1 and GS and between E2 and GS, and of 96% (K value: 0.91; CI 95%: 0.80-1.00) between E1 and E2. For the second type of headache (n=24) we found an agreement of 83.3% (K value 0.80; CI 95%:0.63-0.98) between E1 and GS, of 62.5% (K value: 0.62; CI 95%:0.41-0.82) between E2 and GS and of 70.8% (K value: 0.66; CI 95%:0.45-0.87) between E1 and E2.

Sensitivity and specificity were 100% and 93.3%, respectively, for migraine without aura (code 1.1) and 100% for frequent episodic tension-type headache (code 2.2). Our findings support the use of this questionnaire as a valid and reliable tool for diagnosis of headaches in epidemiological studies.

Insulin alteration in migraine and impact of proper diet on headache severity

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We recently reported [1] how about the 80% of migraineurs do have high insulin plasma levels. After that we began a prospective observational controlled study to evaluate how the treatment of this disorders could modify migraine.

Patients and methods: Patients with migraine or headache other than migraine, and healthy volunteers were included. All had general blood tests and a standard oral glucose tolerance test after a 12-hour fast, measuring both glucose and insulin. Patients with altered metabolic profile underwent a proper diet and were followed up. The group of patients with normal profile was the control group.

Results: In 2004–2005, we recruited 84 migraineurs, 25 patients with non-migraine headache, and 26 healthy controls. Multivariate analysis confirmed a significant difference between groups for glucose levels ($p<.0001$). Only in migraineurs there was a significant increase in insulin levels ($p<.0001$), both for migraine compared to other headaches ($p<.0001$) and healthy controls ($p<.0001$). From 2005 up to 2007, 319 migraineurs have been visited at our headache centre. They were 63 men and 257 women. The mean age is 40 years. The population with a normal metabolic profile was used as control group to evaluate efficacy of diet. 217 (68%) showed gluc-insulin metabolic alterations. Among these, 39 were men and 178 women. Mean age 40 years. Index of headache severity at entry did not differ between groups, such as at the end of follow-up. BMI at baseline is similar in the two groups, and did not differ significantly after diet. During follow-up the metabolic profiles improved in the majority of patients, proportionally to the clinic improvement, but with less significance.

Reference

1. Cavestro C, Rosatello A, Micca G et al (2007) Insulin metabolism is altered in migraineurs: a new pathogenic mechanism for migraine? Headache 47:1436–1442

SUNCT syndrome: a case with seasonal pattern

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SUNCT is a trigeminal autonomic cephalalgia (TAC) characterised by short unilateral attacks centred on the ophthalmic trigeminal distribution accompanied by lacrimation and redness of the ipsilateral eye. It exists in episodic and chronic form and atypical features have reported. Patients with episodic SUNCT presented attacks with a not predictable temporal pattern. SUNCT seems to share clinical and pathophysiological characteristics with the other TACs, supporting the pathogenetic hypothesis of a central origin and the predominant role of hypothalamus. Circannual periodicity is not a typical feature of SUNCT. Here, we describe the case of an episodic primary SUNCT with an exclusive seasonal pattern as previously reported in cluster headache and paroxysmal hemicrania.

"INDOTEST" in hemicrania continua: a report of three atypical cases and a review of literature

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Hemicrania continua (HC) is an indomethacin responsive headache characterised by a chronic, strictly unilateral, side-locked without side-shifting, persistent headache; however, atypical cases are reported. In two previous studies with 12 HC patients and with 7 HC patients, respectively, acute administration of indomethacin 50–100 mg intramuscularly (INDOTEST) determined complete pain relief in all cases. Here, we report a review of literature and three new cases of HC with atypical features in which an INDOTEST with 50mg intramuscularly was performed (Cephalalgia in press). The first case is a 33-year-old woman with a seasonal pattern HC. The second case is a 44-year-old man with a side-shifting HC. The last one is a 77-year-old woman with an HC and at the best of our knowledge, she is the oldest case described with an HC. In all the three cases INDOTEST predicted chronic responsiveness to indomethacin. Thus, in cases of HC with atypical features, INDOTEST could help for a correct diagnosis and therapy.

Intracranial haemorrhage due to possible postpartum cerebral angiopathy: a case report

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We describe a case of a 39-year-old woman who presented at the Emergengy Department with a 3-day history of severe, diffuse, pulse headache two weeks after spontaneous delivery of her second child. No nausea, vomiting or preceding aura were reported. Her headache worsened in spite of analgesics. Throughout her pregnancy she was normotensive, without proteinuria, oedema or seizures. No risks factor or pathologies were reported in anamnesis. Neurological examination was normal. Her blood pressure was 140/70 mmHg. Brain CT scan was normal and angio-CT was negative for venous and arterial thrombosis. Four hours later she developed decreased level of consciousness, dysarthria and left hemiparesis. A second brain CT-scan showed a right capsular haematoma. For subsequent neurological worsening and haematoma improving, neurosurgical evacuation was performed the day after. During recovery, the patient developed a severe hypertensive state treated with intravenous clonidine and nitroprussiate. All causes of secondary hypertension were excluded. Routine blood test, autoimmune and thrombophilic screening and surgical histological examination were normal. At discharge, the patient presented left severe hemiparesis with normal consciousness level and no language deficit. At cerebral angiograms follow-up (performed after 1 month and after 6 months) no evidence of venous thrombosis and vascular malformations were described.

A rare cause of intracerebral haematoma in pregnancy is postpartum cerebral angiopathy (PCA) due to large and medium size vessels vasoconstriction. Vasospastic disorder, related to hormonal changes of pregnancy, could lead to ischemic or haemorrhagic stroke. PCA clinical features include severe headache, nausea, vomiting, photophobia, transient hypertension, seizures and neurological deficits. Digital angiogram, demostrating segmental narrowing of cerebral arteries, is necessary for diagnosis. Increased cerebral blood flow velocities might be shown by transcranial doppler ultrasound in acute phase. These radiological findings are reversible within days or few weeks. History of migraine and vasocostriction drugs use are considered risk factors for this syndrome. Actually there is no established treatment for PCA.

Reversal of headache and coma from spontaneous intracranial hypotension by lumbar epidural blood patch in Trendelenburg position

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Objective: Treatment of spontaneous intracranial hypotension (SIH) resulting in coma.

Background: SIH is characterised by orthostatic headaches, low CSF pressure, distinct abnormalities on MRI.

Materials and methods: We report one case of coma from SIH.

Results: A 62-year-old man developed orthostatic headache. After 15 days he became progressively obtund. Brain CT revealed bilateral chronic subdural haematomas which were evacuated. Two days after operation he became comatose (GCS: 5 state), developed respiratory distress and was intubated. Brain MRI, showed diffuse pachymeningeal enhancement, descent of midbrain structures (MRI abnormalities of SIH). Myelo-MRI failed to demonstrate a CSF leak. He was placed in the Trendelenburg position (TP) and awoke within 8 hours. Then we performed a lumbar autologous epidural blood patch (LAEBP) with 35 cc of blood mixed with gadolinium. Spinal MRI post-LAEBP showed only a very little quantity of blood into lumbar epidural space (LES). Twentyfour hours later he became stuporous. Second LAEBP was given under fluoroscopy guidance with 30 cc of blood mixed with iopamiro. Multislice spiral spinal CT (MSSCT) post-LAEBP showed little quantity of blood in the LES, after 15 days he became stuporous again.Video-EEG showed diffuse activity theta. We performed another LAEBP with 30 cc of blood. MSSCT post-LAEBP showed blood into epidural space from L3 to C7 level. After 24 hours he improved. The patient maintained a 30 degree TP during and 24 hours after the LAEBPs. After 12 months of follow-up the patient was in good health.

Discussion and conclusions: Our case suggests: a) TP can be life saving in patients with rostrocaudal herniation by SIH. b) TP favours the spread of blood into epidural space from the lumbar to cervical level. c) LAEBP in TP is effective to treat cases of SIH resulting in coma. d) It is necessary to perform a neuroimaging examination post-LAEBP to confirm the correct execution.

High frequency of typical aura with non-migraine headache or without headache in a patient with sickle cell trait

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We report the case of a young white woman, aged 38, with a sickle cell trait, confirmed by genetic and haematological exams, free from any sickle cell disease (SCD) manifestation, that frequently complaints typical aura attacks followed by non-migraine headache or without any kind of headache after aura (1.2.2 or 1.2.3 using ICHD-2 criteria). She usually complains just fully reversible visual symptoms lasting 20–40 min without headache. In some cases she presented a complete aura with visual, sensory and dysphasic symptoms, every time fully reversible, with each symptom lasting in general from 5 to 60 min, but that in few episodes lasted more time, up to 4 h for the succession of the three symptoms. She meanly registers 8 episodes per month of aura without headache and 2 episodes of typical aura with non-migraine headache. In our patient, after more than 20 years of aura headache, Magnetic Resonance Imaging resulted normal and no persistent neurological deficit is present.

In 2006 Silva et al. [1] studied for the first time headache characteristics and frequency among SCD adult patients. They reported that 50% of SCD adult patients had severe and frequent headache, with a global prevalence of migraine without aura of about 35%. No aura patient among the 56 ones studied by them was found. They observed abnormally high blood velocities at Trans Cranial Doppler (TCD) in the headache group and they concluded that a migraine-mimicking headache occurs in SCD but not completely understandable as a primary headache because of that blood flow abnormalities observed. Bussone et al. [2] in 1984 described the case of an adult white man with sickle-cell haemoglobinopathy trait, affected by complicated migraine, who developed acute occlusion of two middle cerebral artery branches, with persistent neurological deficit. They underlined in their report that neurological manifestations have been rarely described in sickle cell trait carriers.

Headache is better studied among SCD children than in adults. Considering that the prevalence of headache in healthy children has been reported to range from 8% to 60%, depending on the population studied and the definition used [3], recently Niebanck et al. [4] concluded that the prevalence of headaches in children with SCD is similar to the general population even if younger children (<13 yrs) with SCD report headaches more frequently than control subjects. The same Authors underlined that factors associated with frequent headaches in subjects with SCD included older age, frequent vaso-occlusive pain episodes, symptoms of obstructive sleep apnea, and cerebral vessel stenosis. Palermo et al. [5] in 2005 mailed to a cohort (n=50) of children with SCD, ages 9 to 17 years, a detailed headache questionnaire using International Classification of Headache Disorders (ICHD-2): they reported that headaches had occurred over the previous 3-month period in 32 out of the 42 respondents (76.2%): 14 children (43.8%) had migraine without aura, 2 (6.2%) had migraine with aura, and 16 (50%) tension-type headache. They also found that frequent headaches were common with one attack per week or more in the 31% of cases.

Then, headache is quite typical among SCD patients, even if reliable data about adult patients and carriers are lacking. We have not found other cases of frequent typical aura manifestation with or without headache related to sickle cell trait even if we may not exclude that it should be just a case of comorbidity.

References

1. Silva GS et al (2006) Migraine-mimicking headache and sickle cell disease: a transcranial Doppler study. Cephalalgia 26:678–683
2. Bussone G, La Mantia L, Boiardi A et al (1984) Complicated migraine in AS hemoglobinopathy. Eur Neurol 23:22–25
3. Grazzi L (2004) Primary headaches in children and adolescents. Neurol Sci 25[Suppl 3]:S232–S233
4. Niebanck AE et al (2007) Headache in children with sickle cell disease: prevalence and associated factors. J Pediatr 151:67–72
5. Palermo TM et al (2005) Headache symptoms in pediatric sickle cell patients. J Pediatr Hematol Oncol 27:420–424

Botulinum toxin type A for prophylaxis of chronic daily headache associated with medication overuse: an open-label prospective trial

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Objective: To evaluate the efficacy and tolerability of Botulin Toxin Type A (BoNT-A) for prophylaxis of probable chronic migraine (pCM) and probable medication overuse headache (pMOH). Efficacy was defined by two primary endpoints: a) decrease of headache frequency; b) reduction/discontinuation of medication overuse.

Methods: 18 Caucasian adult patients (14 females; 4 males; age 31-58, mean 43) who met the International Classification of Headache Disorders (IHS 2004) criteria for pCM and pMOH were enrolled in this open-label prospective study in 7-year period between January 2001 and December 2007. All participants were asked to sign informed consent to the study. Any patient took preventive medication. Migraine disability assessment (MIDAS) and 6 months headache diary (-3 t_0/+ 3 t_0 months monitoring) were used for the evaluation of treatment efficacy and safe. A total of 400 units of European-type of BoNT-A were injected in 20 fixed sites (20 U/site) of epicranial muscles including corrugator frontalis (6), temporalis (6), parietalis (4) and occipitalis (4). Clinical evaluation and diary check was performed 4 and 12 weeks after treatment.

Results: 2 out of 18 patients were excluded from data analysis for starting preventive medications. Other 2 were dropped-out because missed clinical revaluation after treatment. 10 out of 14 patients who completed the study stated subjective improvement after the injection. Mean MIDAS score decreased significantly 4 and 12 weeks after treatment. Average of headache decrease of 48±23% days per month was registered in the 3 months following treatment (+3 t_0) in comparison with the 3 months before treatment (+3 t_0). The amount of analgesic consumption decreased of 53±39% in the 3 months after treatment (+3 t_0 vs -3 t_0: $p<0.05$). No serious adverse events were reported (1 case of transient fever, 2 cases of slight and transitory pain in the injection site).

Conclusion: BoNT-A was an effective and safe treatment for prophylaxis of migraine without aura and MOH. Clinical benefits are supposed to be related with epicranial muscle relaxation, decrease of CNS and trigeminal ganglion release of algesic peptides and psychological inferences due to the open-label study type. A randomised placebo control trial is necessary to confirm these data.

Headaches in patients with cerebral glioma and metastasis: a prospective study

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Background: The prevalence of headache associated with brain tumour ranges from 48% to 71%. Most studies come from unselected series considering both glioma (GLM) and metastasis (MTS) and are retrospective in nature. However, the growing mechanisms of GLM and MTS are different and different physiopahological mechanisms of headache may be hypothesised.

Objective: To characterise headache in both primary and secondary intracranial neoplasms and to identify possible predictable factors. To understand the uneasy relationship between headache and brain tumours. To analyse if the different pathogenetic mechanisms of GLM and MTS are related to a different pattern of headache.

Methods: Since September 2006 all hospitalised patients evaluated at the Spedali Civili Neuro-oncology Unit of Brescia for new diagnosed cerebral GLM and MTS were prospectically investigated for headache throughout the course of the disease. In all patients both family and personal history of headache, antecedent head trauma, and MRI lesion findings were considered. Headache was classified by the International Classification of Headache Disorders (ICHD 2004) criteria. The headache presence was investigated at each control during the follow-up.

Results: Until today (January 2008) 111 individuals (62 M; 49 F; age 23-88 yrs, mean 58±15, median 60 yrs) affected by GLM (45 pts) and MTS (66 pts) have been evaluated and followed at the Neuro-Oncology Unit. In 11 of them (9.9 %) headache represents the initial symptom leading to the diagnosis. Headache was reported in 5 patients with GLM, whereas patients with MTS and headache were 6. Previous headache was reported in 6 pts (54.5%), family history of headache in 5 (45.5%) and none with head trauma. Headache was pressing (7/11), of moderate intensity (7/11), bilateral (9/11), without neurovegetative symptoms (9/11) and without aura (11/11).

Conclusions: Our study confirms that headache and brain tumours are related clinically. The small size of our sample does not allow to define headache in brain tumours, yet. The prospective nature of our study will or will not confirm our feeling that a different type of headache characterize GLM and MTS.

Two cases of basilar type migraine and posterior stroke

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Basilar-type migraine (BM) is a rare form of headache generally affecting young subjects. BM is characterized by aura symptoms originating from the brainstem or from both hemispheres simultaneously. Concomitant cerebral artery anomalies should be excluded. Ischemic cerebral infarction that occurs during a migraine attack is rare and the mechanism is uncertain.

We report two patients who had cases of basilar-type migraine with posterior ischemic stroke, vascular abnormalities and concomitant cerebrovascular risk factors.

Case report 1: A 20 year-old man with BM, presented two MRI ischaemic lesions in the posterior inferior cerebellar artery territory and anatomical anomalies of the posterior circulation territory at Angio-MRI. He had concomitant cerebrovascular risk factors: mild-moderate hypertension, hyperomocysteinemia and primary antiphospholipid syndrome.

Case report 2: A 40 year-old woman with BM, presented a typical attack but with an unremitting aura phase. Neurological examination showed right hemianopsia. Brain MRI showed one subacute ischaemic lesion and several small similar lesions in the left posterior cerebral artery territory and in left cerebellar hemisphere. She had decreased folic acid level, decreased resistance to activated protein C and atrial septal aneurysm.

We wanted to describe these cases to indicate that MRI and angio-MRI studies are recommended in all cases of BM. The diagnostic protocol should also include the assessment of cerebro- and cardiovascular risk factors.

Larger cohort studies should evaluate if the IHS basilar-type migraine is a real nosologic entity or it is a diagnosis underlying a cluster of cerebrovascular pathologies.

Migraine with aura triggered by sibutramine: a case report

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The mechanisms underlying the pathophysiology of migraine are not completely understood, but the brain of a migraineur has a reduced threshold to a great number of stimuli known as trigger factors. One or

more trigger factors have been reported in 64%–90% of migraine patients. We describe a patient presenting a migraine with aura first attack two hours after treatment with a single dose of sibutramine (10 mg).

This is a drug with established efficacy in sustained weight reduction and an overall favourable safety profile. It has various neurologic adverse effects such as headache (30%), but there are not any previous cases of migraine with aura after sibutramine treatment.

Sibutramine is chemically related to the amphetamines, but its mechanism of action is different because it acts via inhibition of serotonin, norepinephrine, and dopamine reuptake rather than via direct monoamine release.

We postulate that the dopamine reuptake inhibition could result in excessive dopamine in the synaptic clefts and a consequent increased dopaminergic neurotransmission, in line with the hypothesis that monoamines are involved in migraine with aura genesis.

Migraine after syncope or atypical basilar-type migraine? A case report

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Basilar migraine was described by Bickerstaff as a rare variant of migraine which affects all age groups, particularly adolescent girls. It has been described by the HCC-IHS as "a migraine with aura symptoms clearly originating from the brainstem or from both occipital lobes." A differential diagnosis for this condition is really important and complex, having to exclude cerebrovascular disease, seizure disorders, brainstem arteriovenous malformations, posterior fossa tumors and psychiatric disorders.

Case report: A 39-year-old woman came to our ED for a reduction of consciousness followed by headache. The patient referred that during her usual work she started to notice a "shaky vision" in the both temporal sides that in few minutes involved the whole field of view. Shortly, she perceived a diffuse sweating, nausea, significant hypotension and reduction of consciousness. After 45 min began a unilateral, severe, periorbital and throbbing headache associated with photo-phonofobia and vomiting, that finished spontaneously after 6–7 h. In her anamnesis, she reported from 8-year-old other nine similar episodes characterised by bilateral visual symptoms (only in three ones), hypotension and loss of consciousness followed by a migraine-like pain. She had had no other type of headache throughout her life. Her neurological exam, EEG and EKG Holter, TTE, echocolor-doppler (ECD) of epiaortic vessels, brain TC and routine blood exams resulted normal. We suggested moreover brain angio RMN with mdc, Tilt-test, TC-ECD, TEE, thrombophilic screening and MMPI. We recommended anti-inflammatory drugs for the attack treatment, and prohibited smoke and estrogenic therapy.

Conclusions: Considering her stereotyped attacks, started since childhood and the absence of other dysautonomic symptoms without migraine, this case could be interpreted as "Basilar-type migraine" with a low frequency, even if IHS 2004 criteria do not include the loss of consciousness, but only an its reduction. An alternative hypothesis is a syncope associated with migraine: several reports evidenced that both conditions co-occur together, especially during migraine attacks

High prevalence of cluster headache and aura migraine in an Italian family

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We describe an Italian family with high prevalence of cluster headache and aura migraine. We report the history of patients distributed along four generations. In the first of these four generations (I) the grand grandfather (Ia) complained recurrent attacks of very severe head pain lasting 1–2 h, generally exploding in the evening and causing restlessness. These attacks were present during isolated periods of the year. This patient is now died and no physician formally diagnosed cluster headache even it seems the much reliable hypothesis by the history described by his daughter (IIa). She has a 60 years history of migraine with aura, characterised by high frequency of attacks (about 10–15/month), since she was 15 years old and still present. This woman has a son (IIIa) affected by cluster headache, and a daughter (IIIb), that has migraine with aura and a patent foramen ovale (PFO). She (IIIb) has two sons, one (IVa) with migraine with aura and the other (IVb) with cluster headache. In all reported patients, except Ia, the criteria of the International Headache Society were applied.

It is well known that first-degree relatives of a patient with migraine without aura, migraine with aura, chronic tension-type headache and cluster headache have a significantly increased risk of the patient's disorder if compared to the general population, [1]. A number of epidemiological studies show different possible mechanisms of inheritance for each primary headache [2–4]. De Simone et al. [5] in 2003 described a pedigree of a large kindred of four related families in which eight members were affected by cluster headache with a distribution that suggested a possible autosomal recessive mechanism of inheritance. In our family, we observed an hereditary way without skips of generation for migraine with aura (IIa, IIIb and IVa) with a direct transmission from parent to children. With regard to Cluster Headache, our family shows a transmission with generation gaps and the possible role of "healthy carrier": analysing the pedigree of this family, patients II a and III b seem to be contemporary affected by migraine with aura and healthy carrier of Cluster Headache that they transmitted respectively from Ia to IIIa and from Ia to IV b through IIa.

References

1. Russell MB (2007) Genetics in primary headaches. J Headache Pain 8:190–195
2. Leone M, Russell MB, Rigamonti A et al (2001) Familial risk of cluster headache: a study of Italian families. Neurology 56:1233–1236
3. Kudrow L, Kudrow DB (1994) Inheritance of cluster headache and its possible link to migraine. Headache 34:400–407
4. Russell MB (1997) Genetic epidemiology of migraine and cluster headache. Cephalalgia 17:683–701
5. De Simone R et al (2003) A cluster headache family with possible autosomal recessive inheritance. Neurology 61:578–579

Botulinum toxin Type A treatment in disabling migraine

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Objective: In order to evaluate the efficacy of botulinum toxin type A (BTX-A) treatment in reducing the disability associated with migraine

Background: BTX-A has shown promise for the treatment of migraine in several clinical trials; although, there has been discussion about how BTX-A should be optimally used for treating headache and which patients are best suited for treatment.

Methods: Enrolled patients had migraine headaches meeting IHS diagnostic criteria 1.1, 1.2 and 1.7 and that were severely disabling as confirmed by a > 60 Headache Impact Test (HIT-6) score and a >20 Migraine Disability Assessment Scale (MIDAS) score. Patients were randomised to receive BTX-A (200 UI Dysport) or placebo at 24

injection sites, administered after a 1-month baseline period and repeated after 4 months. Patients were assessed every 30 days.

Results: A total of 57 patients were randomised to botulinum toxin type A or placebo and 42/57 patients (73.6%) had at least 4 of 8 months of analyzable diary information. Patients receiving BTX-A reported a significant reduction in impact score, as exhibited by a decrease in HIT-6 from "severe" (66) to "some" impact (59) and a decrease in MIDAS score of 49% (74 to 38). The percentage of severe headaches in BTX-A patients decreased from 32% of all headaches at baseline to 13% over 8 months (a 40% reduction in the experience of severe headaches as a proportion of all headaches rated as mild, moderate or severe). There also appeared to be a progressive benefit from repeated BTX-A treatment after 4 months. The placebo patients experienced no changes in headache severity, minimal HIT score changes, and only a 24-point change in MIDAS. Adverse events were generally mild and transient in 7/57 patients (12.3%).

Conclusions: BTX-A appears to safely and effectively reduce the impact and disability of disabling migraine.

Long-term results of different therapeutical approaches for juvenile episodic-tension-type headache

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Introduction: Recurrent headaches are common in children and adolescents. Most current investigations have employed limited modalities (either medication or behavioural) and few have included treatment comparisons.

In this study relaxation training, amitryptiline and magnesium salts were compared for juvenile Episodic-Tension-Type Headache.

Methods: Patients were treated by behavioural therapy (limited group relaxation training) (group A) or by amitryptiline, 10 mg per day for 3 months, (group B) or by Magnesium Pidolate twice a day for 3 months (group C).

Results: The clinical improvement was significant for the 3 groups at 1 year follow-up (days of headache/month: group A 15.1 vs. 3.7; group B 18.7 vs. 2.3; group C 7.5 vs. 2.3). In group A, of the 41 initial patients, 30 (73%) achieved the 1 year follow-up. All patients came regularly for the sessions, practiced routinely, they and their parents appeared to be compliant and accepting of treatment although we did not assess this formally. In group B, 39 patients started treatment, 17 (43.5%) patients achieved the 12 months follow up; 22 (56.4%) patients did not achieve the last follow up meeting. In group C, 59 patients started to be treated leaving 26 (44%) at the last meeting, 33 (56%) patients did not complete the treatment for different reasons: no good compliance, no good taste of the medication, absence of immediate results after few weeks of therapy.

Conclusions: Although clinical significant results were obtained in the 3 groups after long-term follow-up, relaxation therapy seems to be more accepted than medication. The limited contact modality seems to be as useful as other behavioural approaches that require a greater investment of time (by patients and therapists), without unpleasant side effects.

Because the sample sizes are small, these conclusions are tentative. Data collection will continue on larger sample of patients.

Efficacy of duloxetine in patients with comorbidity of depression and chronic migraine with medication overuse

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Background and objectives: Antidepressants are often used to treat chronic daily headache (CDH) disorders mainly because of the high prevalence of associated mood disorders. Among CDH, chronic migraine with medication overuse (Silberstein and Lipton criteria) is the most frequent form. Some chronic migraine patients do not improve with current drug prophylaxis. New therapeutic strategies are needed in such cases. Duloxetine hydrochloride, a new antidepressant, is a selective serotonin and norepinephrine reuptake inhibitor. Aim of this study was to evaluate the efficacy and tolerability of duloxetine treatment in chronic migraine patients with medication overuse and concomitant depression.

Patients and methods: Fifty patients, 40 women and 10 men, aged 20 to 65 years (mean 39.4) fulfilling the Silberstein and Lipton criteria of chronic migraine with symptomatic medications overuse were included in the study. These patients had a Hamilton Depression Rating Scale (HDRS) score between 20 and 35 and a Migraine Disability Assessment Scale (MIDAS) >20 (grade IV).

Duloxetine was administered at a daily dose of 60 mg for 12 weeks. Patients had a baseline one-month period; hence, duloxetine was started and they were assessed after 4, 8 and 12 weeks. The following parameters were employed to measure outcome (clinical end-points): number of headache days per month, headache intensity, analgesic consumption, Hamilton Depression Scale and MIDAS. Number of responders (=headache frequency reduction ≥ 50% in the treatment period vs. baseline) were also evaluated.

Results: All patients completed the study; the drug was well tolerated. In our patients, number of headache days per month, analgesic consumption, headache intensity, HDRS and MIDAS were significantly reduced after duloxetine treatment (mean±SD before and after treatment 20,6±1,8 vs. 11,0±1,3; 20,0±1,8 vs. 10,5±1,3; 2,7±0,5 vs. 1,9±0,4; HDRS 26,3±2,0 vs. 14,8±1,1; MIDAS 85,66±21,4 vs. 6,7±2,05; $p< 0.0001$). Twenty-seven of the fifty (54%) patients were responders.

Discussion and conclusions: Migraine causes significant lost productivity and decreases quality of life. Part of the burden of migraine is produced by the psychiatric conditions that often coexist, such as depression or anxiety. Similar neurochemical alterations may explain comorbidity between migraine and psychiatric disorders.

Amitriptyline is a tricyclic antidepressant consistently shown to prevent migraine. Unfortunately it commonly causes side effects (such as cognitive impairment, orthostatic hypotension and cardiac abnormalities) that may limit its utility. This study shows that chronic migraine patients significantly improved after duloxetine administration. We have observed a good tolerability profile during the treatment period. Duloxetine does not bind to receptors originating tricyclic-induced side-effects and this could explain the good tolerability. Duloxetine efficacy in our patients may be explained either as a direct effect on migraine or an improvement in depression.

Headache attribuited to neurosarcoidosis

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Objectives: Neurological complications in sarcoidosis are rare (5%) and highly variable. Headache may occur in neurosarcoidosis and diagnostic criteria are given in the IHS classification. Aim of the study was to describe headache characteristics in patients diagnosed as suffering from neurosarcoidosis. The IHS criteria for "headache attribuited to neurosarcoidosis" have been applied.

Methods: Patients admitted to our Institute from 1999 to 2006 and diagnosed as suffering from neurosarcoidosis were retrospectively reviewed. Neurosarcoidosis was diagnosed according to brain or spinal MRI, thoracic CT scan, and/or gallium scintigraphy, bron-

choscopy, cerebrospinal fluid, angiotensinogen converting enzyme and response to treatment. Hystory of the patients was reviewed and headache characteristics were obtained from charts. Thirteen patients were included: 8 males, 5 females mean age at onset 48 years (29–72), illness duration 4 years (1–12).

Results: Headache was reported by six (46%) patients and was the onset symptom in five of them (38%). In two (15%) cases the headache was the only neurological symptom. In three patients (23%), the headache was associated with oculomotor palsy. In four patients headache had acute onset; in the remaining two patients headache was reported as mild at the beginning, but subsequently worsened. The IHS criteria were fulfilled in 5 (83%) patients. An intracranial lesion was observed at MRI in all the headache patients: a lesion into the ipsilateral cavernous sinus was founded; moreover, in two there was increased meningeal enhancement around the brainstem.

Conclusions: Patients included in this study fulfil the IHS criteria for headache attribuited to neurosarcoidosis.

A migraneous family with hemiplegic aspects

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Introduction: Migraine with aura (MA) is a common form of cephalalgia, with an 8% prevalence in general population. It is well known that MA is more frequent in the same family, as general Migraine without aura (MwA) has a 70% familial component. A rare genetic, autosomal dominant, with incomplete penetrance form of migraine, Familial Hemiplegic Migraine (FHM) has been described and characterized so far with 3 different genes mutations: FHM1 with CACNA1A mutations, FHM2 with ATP1A2 mutations and FHM3 with mutations on SCN1A.

Overlap in the same patients of different migraine type is a possible condition.

Materials and methods: We describe a family composed by a 12 y-old age patient affected by MA, according to IHS ICHD-II criteria, who presented two distinct, fully reversible attacks of hemiplegic migraine after strong exercise. From the paternal family tree: the father is affected by MA, and in the younghood presented several attacks of hemiplegic migraine. His other two uncles and aunt are all affected by MwA, including his father homozygotic twin brother; a first-grade cousin presents episodic Cluster Headache (CH). The paternal grandfather is affected by MwA. The young patient's mother suffers from MA. No cerebellar or epileptic aspects were found in the family anamnesis. Genetic analyses are being carried over for FHM 1-2-3 screening in the paternal family members.

Discussion: The young patient was studied with bioumoral examination, brain MRI and EEG, with normal results; he presented a normal neurological examination. He was diagnosed with Familial Hemiplegic Migraine, fulfilling HIS ICHD-II criteria, after family history and familial examination.

Conclusion: The genetic aspects of migraineous disorders are still not completely known and the family here described confirms the bond between migraine with aura-aspects subtypes and genetic inheritance.

Can prophylactic treatment improve disability and Quality of Life in migraine patients ?

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Aim: To review the main evidences in published literature on changes in the negative impact on functioning and well-being after anti-migraine prophylaxis.

Methods: the results of studies measuring disability and Health Related Quality of Life (HRQoL) caused by migraine following prophylaxis using standardised questionnaire were analysed.

Results: Two open studies have found improvement in MIDAS and-or SF-36 scores following treatment with different preventive drugs for migraine. Analysis of data deriving from double blind placebo-controlled trials with topiramate have shown significant improvement of HRQoL, both using a migraine specific tool (MSQ) and a generic tool (SF-36). Recently, the impact of topiramate (median modal dose 100 mg/day) on disability and HRQoL was evaluated in a large trial (818 patients enrolled in the 26-week open-label phase; 514 in the following 26-week double blind phase): MIDAS score at the end of the open-label phase showed a mean change vs baseline of –21.18 ($p<0.0001$). In patients who switched from topiramate to placebo after 26 weeks of treatment, the MIDAS score increased by 6 points vs. no change in patients who continued topiramate. SF-12 physical component score also deteriorated in the placebo group compared with topiramate (–3.1 vs. –0.6, $p<0.001$) while the change in mental component score did not differ between groups.

Conclusion: Emerging data suggest that prophylaxis can reduce the impact of migraine. Significant evidence exist for topiramate, which was able to induce improvement in disability and HRQoL in different trials with double blind and open label designs, also when tested in rather long (up one year) treatment periods.

Efficacy and tolerability of pregabalin and amitriptyline in the prophylaxis of chronic daily headache with medication overuse: a prospective open-label study

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Chronic daily headache (CDH), a heterogeneous group of headache disorders with attacks occurring on at least 15 days/month, represents a relevant problem in terms of health and social policies. Patients with CDH have greater disability and lower quality of life than episodic headache patients and often overuse their symptomatic drugs. An open-label prospective study was conducted to compare the efficacy and safety of pregabalin and amitriptyline in treating probable medication overuse headache (pMOH). Eligible patients received instructions to keep the daily headache diary for the 2 months prospective baseline phase and for the entire study period. One-hundred patients with pMOH were randomly assigned to receive pregabalin 150 mg/day or amitriptyline 10 mg/day. The first 4 weeks were considered the titration period and the following 4 months, the treatment period. Efficacy variables were: change in number of days with headache/month and with medication intake/month, between baseline and the last 4 weeks of the treatment period. There were no significant differences in demographic and clinical characteristic between the two groups of patients. At the end of the treatment period, a significant reduction in headache frequency with respect to baseline and a significant reduction in days with medication intake were recorded in both groups. There were no significant differences in beneficial effects between the 2 groups. Adverse effects occurred in 24 % (dizziness and somnolence) of pregabalin patients and in 31% (excessive sleepiness and mild sedation, dry mouth) of amitryptiline patients but none were severe.

Pregabalin and amitriptyline therapy seem to manage successfully CDH with medication overuse with a good tolerability. This affords clear practical advantages in treating these patients without a detoxification approach and hospitalization. Pregabalin could be a valid option in patients with contraindication for other recommended preventive therapies.

Primary headache and epilepsy comorbidity: the EPICEF Study

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Background: The association between epilepsy and headache is established. However, only the correlation between migraine and epilepsy has been carefully investigated. The aim of this study was to assess prevalence, clinical characteristics and risk factors of three major types of primary headache (migraine, tension-type headache, trigeminal autonomic cephalalgias) and two types of idiopathic/cryptogenic epilepsy (partial and generalized) in patients with comorbidity (association of the two disorders) compared to those with headache and epilepsy alone.

Materials and methods: From September 2005 to June 2007, consecutive outpatients seen in ten university and hospital epilepsy and headache centres were prospectively recruited and asked whether or not they suffered from epilepsy alone, headache alone or both. The patients were divided into three groups: headache alone, epilepsy alone, and comorbidity. An *ad hoc* questionnaire constructed according to the ICDH-2 and ILAE criteria was used to compare demographic and clinical characteristics and risk factors of headache and epilepsy in the three groups.

Results: 768 patients with available records were assessed (474 women and 293 men; mean age 40). 528 patients presented primary headache alone (migraine 83%; tension-type headache 14%; trigeminal autonomic cephalalgias 1.4%). 159 patients had idiopathic/cryptogenic epilepsy alone (partial 49%; generalised 43%). In the comorbidity group (79 patients) migraine occurred in 51% of cases and tension-type headache in 29% of cases with partial epilepsy as compared to 51% and 42% of cases with generalized epilepsy. The frequency of headache attacks in patients with migraine alone (5.3) was significantly higher than in patients with comorbidity (3.7; $p<0.05$). In contrast, the frequency of attacks in patients with tension-type headache alone and in those with comorbidity were fairly similar (5.8 vs. 7.5; $p<0.4$). Partial and generalised epilepsies were similar in patients with and without comorbidity.

Conclusion: Epilepsy characteristics are no different in patients with epilepsy alone and in those with comorbidity. Headache attacks are more frequent in patients with migraine alone compared to those with comorbidity. This is not true for tension-type headache, suggesting a possible link between migraine and chronic treatment of epilepsy. This observation may have implications for clinical practice with reference to migraine prophylaxis with antiepileptic drugs.

Short lasting lumbar CSF pressure monitoring for detecting increased intracranial pressure in chronic daily headache

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Objective: The aim of this study was to compare cerebrospinal fluid (CSF) opening pressure measurement with short lasting (one hour) lumbar CSF pressure ($LCSF_p$) monitoring for detecting increased intracranial pressure in patients suspected of having idiopathic intracranial hypertension (IIH).

Methods: In a prospective study from November 2003 to April 2007, 76 consecutive patients with chronic daily headache underwent lumbar puncture in order to record both the CSF opening pressure and short lasting (one hour) $LCSF_p$ monitoring. Increased intracranial pressure was diagnosed when CSF pressure was greater than 200 mm of H_2O. The criteria for exclusion from the study were abnormal neurological examination, presence of papilledema, or MR evidence of structural brain lesions or hydrocephalus. MR venography of the brain were also performed in all patients. Bilateral transverse sinus stenosis (BTSS) was considered present when the signal flow was poor or lacking (flow gap) in the mid-lateral portion of both transverse sinuses.

Results: Among the 76 patients with chronic daily headache who underwent CSF opening pressure measurement and short lasting (one hour) $LCSF_p$ monitoring, 61 (80 %) had normal opening pressure. Short lasting (one hour) $LCSF_p$ monitoring showed increased CSF pressure in 17 (28 %) of these 61 patients with normal opening pressure. All patients with pathological elevations of CSF pressure displayed BTSS on MR venography.

Discussion: In this study we demonstrated that about one-third of patients with normal CSF opening pressure had increased intracranial pressure when investigated with short lasting $LCSF_p$ monitoring. Our findings demonstrate the accuracy in establishing intracranial pressure of short lasting $LCSF_p$ monitoring, suggesting that patients suspected of having IIH should be evaluated with prolonged recording of CSF pressure.

Conclusions: The discrepancy between measurements of CSF opening pressure and prolonged recordings of CSF pressure indicates that short lasting $LCSF_p$ monitoring may have an important diagnostic role that should be further investigated.

A novel non sense mutation in the ATP1A2 gene associated to hemiplegic migraine

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An 11-year-old female came to our observation because, about 2 months before, she had presented migraine associated to hemiparesis, lasted 1 hour. During the attack the patient had experienced a visual aura, lasted less than 20 min, characterised by scintillating scotomas, mild right hemiparesis, hemiparesthesias and dysarthria. The headache, very intense, was accompanied by nausea, vomiting, phonophobia and photophobia. The patient underwent many investigations which were normal. The neurological examination was negative. The clinical characteristics presented by the patient here described would be compatible with a diagnosis of hemiplegic migraine with an apparently sporadic occurrence (SHM). Direct sequencing of the *ATP1A2* gene, in the patient allowed us to identify a novel heterozygous non sense mutation in exon 22, c.3027T>A leading to a premature protein truncation (p.Tyr1009Stop) within the carboxi cytoplasmic tail of the Na^+K ATPase pump alpha2 subunit. Mutation in *ATP1A2* is associated with FHM type II cases characterised by familial hemiplegic migraine. In absence of experimental data demonstrating the functional effect of the mutation, the nature of the amino acid change by itself leading to a premature protein truncation is highly suggestive of a pathogenic role of the mutation.

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