Neurological Sciences

Official Journal of the Italian Neurological Society
Founded by Renato Boeri (1979–1993) continued by Giuliano Avanzini (until 2011)

Continuation of
The Italian Journal
of Neurological Sciences

Springer

Neurological Sciences
Official Journal of the Italian Neurological Society

Aims and Scope

Neurological Sciences is intended to provide a medium for the communication of results and ideas in the field of neuroscience. The journal welcomes contributions in both the basic and clinical aspects of the neurosciences. The official language of the journal is English. Reports are published in the form of original articles, short communications, editorials, reviews and case reports. Original articles present the results of experimental or clinical studies in the neurosciences, while short communications are succinct reports permitting the rapid publication of novel results. Original contributions may be submitted for the special sections History of Neurology, Health Care and Neurological Digressions - a forum for cultural topics related to the neurosciences. The journal also publishes correspondence book reviews, meeting reports and announcements.

Manuscripts submitted for publication must contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 1965 Declaration of Helsinki. It should also be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Reports of animal experiments must state that the Principles of Laboratory Animal Care (NIH publication no. 86-23 revised 1985) were followed as were applicable national laws (e.g. the current version of the German Law on the Protection of Animals). The Editor-in-Chief reserves the right to reject manuscripts that do not comply with the above-mentioned requirements. Authors will be held responsible for false statements or for failure to fulfill such requirements.

The journal is open for publication of supplements and for publishing abstracts of scientific meetings. Conditions can be obtained from the Editor-in-Chief or the publisher.

Copyright Information

For Authors

As soon as an article is accepted for publication, authors will be requested to assign copyright of the article (or to grant exclusive publication and dissemination rights) to the publisher (respective the owner if other than Springer). This will ensure the widest possible protection and dissemination of information under copyright laws.

More information about copyright regulations for this journal is available at www.springer.com/10072

For Readers

While the advice and information in this journal is believed to be true and accurate at the date of its publication, neither the authors, the editors, nor the publisher can accept any legal responsibility for any errors or omissions that may have been made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Journal Website

www.springer.com/10072
Electronic edition: link.springer.com/journal/10072

Subscription Information

Neurological Sciences is published 12 times a year. Volume 38 (12 issues) will be published in 2017.

ISSN: 1590-1874 print
ISSN: 1590-3478 electronic

For information on subscription rates please contact Springer Customer Service Center: customerservice@springer.com

The Americas (North, South, Central America and the Caribbean)
Springer Journal Fulfillment 233 Spring Street, New York NY 10013-1578, USA
Tel.: 800-SPRINGER (777-4643) 212-460-1500 (outside North America)

Outside the Americas
Springer Customer Service Center GmbH
Tiergartenstr. 15, 69121 Heidelberg, Germany
Tel.: +49-6221-345-4303

Advertisements

Barbara Pedrotti
E-mail contact: Barbara.Pedrotti@springer.com

Disclaimer

Springer publishes advertisements in this journal in reliance upon the responsibility of the advertiser to comply with all legal requirements relating to the marketing and sale of products or services advertised. Springer and the editors are not responsible for claims made in the advertisements published in the journal. The appearance of advertisements in Springer publications does not constitute endorsement, implied or intended, of the product advertised or the claims made for it by the advertiser.

Office of Publication

Springer-Verlag Italia S.r.l Via Decembrio 28, 20137 Milan, Italy

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

ASC

STRESA HEADACHE 2017

International Multidisciplinary Seminar

Regina Palace Hotel
Stresa (VB), Italy
25-27 May 2017

UNDER THE AUSPICES OF INTERNATIONAL HEADACHE SOCIETY

PATRONAGES

Italian Minister of Health
ANIRCEF – Italian Neurological Association for Headache Research
ASC – Association for Instruction on Headaches
FICEF Onlus – Italian Headache Foundation
C. Besta Neurological Institute and Foundation
SIN – Italian Neurological Society
SNO – Society of Hospital Neurologists

ANIRCEF F.I.CEF. Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta Sistema Socio Sanitario Regione Lombardia

PROCEEDINGS

STRESA HEADACHE 2017

International Multidisciplinary Seminar

PRESIDENT OF THE CONGRESS

Gennaro Bussone (Milan)

SCIENTIFIC COMMITTEE

Elio Agostoni (Milan)
Giovanni B. Allais (Turin)
Piero Barbanti (Rome)
Vincenzo Bonavita (Naples)
Gennaro Bussone (Milan)
Bruno Colombo (Milan)
Domenico D'Amico (Milan)
Giovanni D'Andrea (Padua)
Fabio Frediani (Milan)
Licia Grazzi (Milan)
Davide Zarcone (Gallarate, VA)

ORGANIZING SECRETARIAT

EVA communication

EVA Communication S.r.l.
www.evacommunication.it

PRESS OFFICE

Cesare Peccarisi (Milan)
peccarisi@libero.it

Neurological Sciences

Volume 38 · Supplement 1 · May 2017

Continuation of table of contents

Springer

Further articles can be found at link.springer.com

Indexed in *Science Citation Index, Science Citation Index Expanded (SciSearch), PubMed/Medline, SCOPUS, PsycINFO, EMBASE, Google Scholar, EBSCO, CSA, Academic OneFile, Academic Search, Biological Abstracts, BIOSIS, Current Abstracts, Current Contents/Clinical Medicine, Gale, Health Reference Center Academic, IBIDS, Journal Citation Reports/Science Edition, Neuroscience Citation Index, OCLC, SCImago, Summon by Serial Solutions*

Impact Factor 2015: 1.783

Instructions for authors for Neurological Sciences are available at www.springer.com/10072

The Editor in Chief authorizes the publication of the Proceedings of the STRESA HEADACHE 2017 International Multidisciplinary Seminar. The authors and the Guest Editor are fully responsible for the scientific contents of the papers.

Conflict of Interest Statement
G. Bussone declares that he has no conflict of interest related to the publications of this Supplement.

Springer

Neurol Sci (2017) 38 (Suppl 1):S1–S2
DOI 10.1007/s10072-017-2949-y

GUEST EDITORIAL

Subjectivity in primary headaches: insight the causes

Gennaro Bussone[1]

There are patients who do not obtain satisfactory relief for their headache after consulting a specialist. So they take charge of their own treatment and eventually become serious analgesic abusers. Other patients are less demanding, requiring only a clear diagnosis to allay fears that may have been harboured for years: in such cases, simply giving the pain a name can improve quality of life and encourage compliance with a prescribed therapy that will satisfactorily control the headache condition.

These polarized outcomes, distilled from my own experience as a headache neurologist, are familiar, I am sure, to all headache clinicians. Before addressing them, I would like to re-emphasize something that never fails to strike me: the fundamental subjectivity of the situation—the head pain can be described by the patient but never verified by the neurologist.

In my career I have witnessed the evolution of scientific thought on the pathophysiology of headache that has changed from a peripheral vascular hypothesis to the hypothesis of an involvement of the central nervous system. However, because of this essential characteristic of subjectivity, it has still not been possible to pin down causes for primary headaches: we have not found the hope for *primum movens* and it is increasingly clear that a headache condition may have several contributing causes.

Nevertheless, functional imaging studies are providing insights into the pathophysiology of primary headaches, particularly those investigating interactions between pain, emotion, and headache, in the genesis of behaviour: they are suggesting a dysfunctional interaction between nervous system areas concerned with emotion and pain pathways. [1, 2] This dysfunction would be one of homeostasis as Bud Craig and Antonio Damasio have argued [3–5], such that altered bio-behavioural responses to head pain give rise to many of the clinical phenomena manifesting in chronic headache.

In this view, pain is part of the patient's behavioural response to his/her headache condition, with the corollary that personality traits influence whether treatment will be successful. Thus, for many patients, simply treating the pain only often leads to treatment failure. In recent years, there has been a tendency to downplay 'subjective' history taking, and physicians have become overly concerned with simply finding 'the right medication'. It is my firm opinion that the pharmaceutical treatment of head pain needs to be integrated with a bio-psychological (or cognitive-behavioural) approach predicated on the physician paying careful attention to the patient's subjective descriptions, in order to identify personality traits and develop personalized approaches that employ both pharmacological and nonpharmacological treatments. This approach will maximize the probability of clinical success and reduce the risk of chronic headache characterized by analgesic abuse.

All this implies the necessity of building a rapport of empathy with the patient. This will facilitate a collaborative approach to the problem but above all will make it easier for the physician to listen to and interpret the language of symptoms, enabling him/her to become aware of those 'mysterious functional disharmonies' that may have a major influence on treatment success, but which cannot be revealed by any 'objective' clinical examination.

✉ Gennaro Bussone
studiobussone@gmail.com

[1] Neurological Institute C. Besta, Milan, Italy

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

References

1. Bussone G, Grazzi L, Panerai AE (2012) Pain, emotion, headache. Headache 52(Suppl 2):98–101. doi:10.1111/j.1526-4610.2012.02244.x
2. Grazzi L, Chiapparini L, Ferraro S et al (2010) Chronic migraine with medication overuse pre-post withdrawal of symptomatic medication: clinical results and FMRI correlations. Headache 50(6):998–1004. doi:10.1111/j.1526-4610.2010.01695.x
3. Craig AD (2006) A new view of pain as a homeostatic emotion. Trends Neurosci 26:303–307
4. Craig AD (2009) How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci 10(1):59–70. doi:10.1038/nrn2555
5. Damasio A (2003) Feeling and emotion and self. Ann N Y Acad Sci 1001:253–261

Neurol Sci (2017) 38 (Suppl 1):S3–S6
DOI 10.1007/s10072-017-2891-z

Cost of medication overuse headache in Italian patients at the time-point of withdrawal: a retrospective study based on real data

Domenico D'Amico[1] · Licia Grazzi[1] · Marcella Curone[1] · Matilde Leonardi[2] · Alberto Raggi[2]

Abstract The objective was to assess the cost of Medication Overuse Headache (MOH) at the time-point of withdrawal treatment. We implemented a protocol in which both direct and indirect cost were directly gathered from patients and referred to the previous three months. Direct costs were calculated by medications for acute treatment and prophylaxis, diagnostic procedures, visits, complementary treatments, informal care. Indirect costs were referred to missed workdays and workdays with reduced productivity: we asked patients to refer their salaries and to rate the overall level of performance in days worked with reduced productivity, and we calculated indirect costs on this basis. A total of 135 patients were enrolled: direct costs were around 415€/month; indirect costs were 530€/month, and were mostly due to presenteeism (350€, 66.3%) rather than to absenteeism (160€, 33.7%). Our data showed higher cost than those of a previous study: this is likely due to a different approach to cost definition, to the inclusion of direct non-medical cost, and of non-pharmacological treatments.

Keywords Chronic migraine · Medication overuse · Withdrawal · Cost of disease

✉ Domenico D'Amico
domenico.damico@istituto-besta.it

[1] Headache and Neuroalgology Unit, Neurological Institute "C. Besta" IRCCS Foundation, Milan, Italy

[2] Neurology, Public Health and Disability Unit, Neurological Institute "C. Besta" IRCCS Foundation, Milan, Italy

Introduction

Chronic headaches constitute a heterogeneous group of condition whose common feature is the presence of headaches occurring for 15 days/month for at least three consecutive months. The third version of the International Classification of Headache Disorders (ICHD-3-beta) [1] identified the following among primary headache forms: Chronic Migraine (CM), Chronic Tension-Type Headache (CTTH), Hemicrania Continua, New Persistent Daily Headache and Chronic Cluster Headache. Furthermore, the ICDH-3-beta indicates a specific chronic form associated to overuse of different acute medications, i.e. Medication Overuse Headache (MOH).

Diagnosis of MOH requires headache occurring on 15 days per month or more in a patient with a pre-existing headache disorder who regularly uses for >3 months one or more drugs for acute treatment. Precise number of days with use of these symptomatic compounds for each class allows classification in different subtypes, i.e. MOH due to ergot-derivate, triptans, opioids or non-steroidal anti-inflammatories (NSAIDs). MOH patients suffer from a chronic primary form, mostly CM or CTTH. Thus, MOH is an interaction between a therapeutic agent which is used excessively and a susceptible patient. In fact, although the process of headache chronification has not been completely understood yet, there is a consensus that it might be mediated by lifestyle factors, presence of comorbidities, genetic and metabolic factors and medication overuse itself [2–5]: for this reason, withdrawal from medication overuse is the main target for MOH treatment [6]. Such a strategy is deemed to positively impact not only on patients' clinical management, but also on cost reduction.

According to the results of Eurolight study, the cost of MOH per patient in Europe is 3561€/year and is threefold

that of episodic migraine (1222€/year) and more than tenfold that of TTH (303€/year) [7]. Eurolight findings provide the most advanced information available to date on the cost of different forms of headaches, including MOH. The results are, however, biased by the cross-sectional design that neither enables to exclude casual effects in cost determination, nor to address the degree to which the return to an episodic headache corresponds to a more or less consistent cost reduction. Moreover, indirect costs have been calculated on an average nationwide salary (for Italy it was 128.7€/day) equal for men and women, which is clearly not reliable in consideration of the gender inequality, with females earning approximately 13% less than males [8], and has relevant consequences considering the higher prevalence of headaches among females. Finally, Eurolight employed a conservative assumption for the amount of used drugs, for which the category "used more than once" was interpreted as twice per month.

Here, we report preliminary data based on a project aimed to identify the value of withdrawal treatment for MOH in terms of reduction of costs. The objective of this paper is to report the baseline cost of MOH at the time-point of starting a withdrawal treatment, i.e. when MOH is not compensated by adequate therapies.

Methods

Patients herein included were adults with CM or CTTH that participated to the MOH-Cost study: they were all volunteers and signed an informed consent form prior to data collection. Patients refusing to provide data on indirect cost, and those that were submitted to a withdrawal treatment in the previous three months were excluded.

Patients were asked to fill in a protocol that included demographic and clinical issues, namely headache frequency in the previous three months and previous structured withdrawals: based on the amount of previous withdrawals in the last five years as reported by participants, we estimated a yearly withdrawal rate for each patient.

Direct cost were divided into healthcare costs, i.e. all goods and services related to the prevention, diagnosis and treatment of a disorder; e.g. physician visits, hospitalizations and pharmaceuticals—and non-medical cost, i.e. informal care for housework of caring for babies. The protocol contained a thorough list of drugs that patients could take, including NSAIDs, triptans, opioids, and prophylactic compounds used in Italy for migraine and headache treatment, including Onabotulinumtoxin-A, as well as non-pharmacological treatments such as nutraceuticals, behavioural and physical therapies. The total direct cost per patient was given by the sum of each category cost.

Indirect costs were referred to lost production due to work absence or reduced productivity at work. Patients were asked to refer how many workdays they lost in the previous three months and how many days they have been working with reduced productivity due to headache. In this case, they were requested to estimate their overall performance level on a 1–99%: the percentage needed to get to 100% was used as a coefficient to calculate the loss of productivity in days worked with headache (presenteeism). Patients were asked to refer their net salary in absolute terms or by categories (<500€; 500€–750€; 750€–1.000€; 1.000€–1.500€; 1.500€–2.000€; 2.000€–4.000€; 4.000€–7.000€; 7.000€–10.000€; >10.000€) so that a gross yearly salary could be determined: in case patients referred their salary by categories, we took the median value, and the highest and lowest categories were taken as absolute values. Once a gross yearly salary was defined, we divided it by 230 standard working days to get the daily gross salary. Finally, the indirect cost was calculated as sum of lost workdays (absenteeism) cost and sum of days worked with headache (presenteeism). For example, if a patient has a daily gross salary of 150€, lost 6 full days and worked 10 days with 60% productivity, the indirect cost will be $6 \times 150€ + 10 \times (150€ \times 0.40)$, i.e. 900€ + 600€.

Descriptive statistics (means and 95% confidence intervals) are used to report the breakdown of cost in detail by gender and for valid cases. The overall cost structure is reported for direct and indirect cost for all cases by gender. Data have been analysed with PAWS 18.0.

Results

In total, 135 patients, 22 males and 133 females, completed the protocol: they had on average more than 20 headaches per month, and had undergone withdrawal approximately once every four years. Table 1 shows the main drivers of cost by gender.

On average, those patients that were employed (69%) lost 2.5 workdays per month and had other 10 days with reduced productivity, for a total cost of 2300€ on a three-months basis (i.e. around 770€ per month). Approximately two third of this cost were due to reduced productivity, and indirect cost for males are approximately twofold of those for females. The trend is instead different for indirect costs that were approximately 35% lower for males. Finally, direct non-medical costs were reported by females only.

Table 1 also shows the subdivision of costs by gender and taking into account the three categories, i.e. indirect costs, direct healthcare costs, and direct non-medical costs. Our results showed that the total cost for patient on a 3 months basis is 2835€, with an evident gender inequality: males display a higher total cost than females (3885€ vs.

Table 1 Demographic features and cost breakdown by gender

	Males	Females	Total
Age	45.1 (38.7–51.5)	47.7 (45.6–49.7)	47.3 (45.3–49.2)
Headaches frequency	63.8 (55.9–71.7)	66.2 (62.7–69.7)	65.8 (62.6–69.0)
Years since last withdrawal	5.2 (2.3–8.1)	3.0 (2.3–3.8)	3.4 (2.6–4.2)
Yearly withdrawal rate	0.24 (0.07–0.41)	0.23 (0.16–0.30)	0.23 (0.17–0.30)
Reduction of productivity ($N = 17$ males, 76 females)			
Daily salary	203.2 (122.7–283.6)	99.5 (88.6–110.3)	118.4 (100.3–136.5)
Lost workdays	9.4 (3.1–15.6)	6.8 (4.5–9.1)	7.3 (5.1–9.4)
Days worked with reduced productivity	26.7 (17.6–35.8)	30.6 (26.5–34.8)	29.9 (26.2–33.6)
Average job performance	55% (46–65%)	56% (52–61%)	56% (52–60%)
Indirect costs			
Lost workdays	1068.0 (356.5–1779.5)	431.5 (274.1–589.0)	535.3 (360.3–710.2)
Reduced productivity	2044.8 (582.3–3507.2)	861.8 (656.5–1067.0)	1054.6 (764.1–1345.0)
Total indirect costs	3112.8 (1073.8–5151.8)	1293.3 (987.8–1598.8)	1589.8 (1172.4–2007.3)
Direct costs			
NSAIDs	22.8 (11.3–34.2)	42.9 (32.5–53.3)	39.6 (30.7–48.5)
Triptans	311.5 (167.0–456.0)	207.2 (161.2–253.2)	224.2 (179.4–268.9)
Opioids and other	2.3 (0.4–4.9)	9.7 (3.6–15.7)	8.5 (3.4–13.6)
Prophylaxis	31.4 (9.9–52.9)	58.2 (37.5–78.9)	53.8 (36.2–71.5)
Diagnostic procedures	146.0 (73.6–218.5)	358.6 (258.2–459.1)	324.0 (238.3–409.6)
Non-pharmacological treatments	258.6 (10.6–506.5)	507.4 (363.6–651.2)	466.9 (340.1–593.7)
Total direct costs	772.6 (456.2–1088.9)	1184.0 (970.9–1397.0)	1116.9 (930.8–1303.0)
Direct non-medical costs			
Informal support for housework and caring for babies	–	153.9 (88.5–219.4)	128.9 (73.4–184.3)
Total cost	3885.3 (1642.6–6128.1)	2631.2 (2205.4–3057.0)	2835.6 (2336.8–3334.4)

Data are reported as means and 95% confidence intervals

2631€), with a clear superiority of indirect costs (80%), while among females the two categories are balanced (49% indirect; 51% direct costs).

Discussion

We assessed the costs of MOH at the time-point of withdrawal, i.e. at the moment in which the disease is not adequately compensated by therapies, using a series of standardized questions investigating direct (healthcare and non-medical) and indirect costs. The main findings are that the total cost per person is around 950€ per month, 56% of which is due to indirect costs, and that there are important gender differences, as men reported a cost of around 1300€ per month, while women of around 880€, and that direct non-medical costs affect only women.

These results provide a different insight on the cost of MOH compared to the standard cost reported by the study on the cost of disorders of the brain [9, 10] and, in particular, by Eurolight [7]. In fact, the cost structure reported by our study is clearly higher than that observed by Eurolight for MOH, i.e. 3561€/year per person considering the whole study, or around 6000€ considering the case for Italy [7]. Why is it so different? There are some reasons for this. First, we based our data on a protocol where patients filled in the name and amount of each single medication that they consumed, and we used the market cost of each unit of these compounds to calculate medical costs. On the contrary, in the Eurolight study the estimates were based on an average cost per drug, that were divided between prophylactic medications and medications for acute treatment: however, in our data the cost of medication for acute treatment spanned between 0.06€ and 1.81€ for NSAIDs, between 2.69€ and 7.27€ for triptans, between 0.23€ and 16.3€ for opioids, and therefore, we think that addressing an average cost for medications for acute management is critical. Second, the conservative assumption for the amount of used drugs employed in Eurolight study, for which the category "used more than once" interpreted as twice per month cannot be applied to MOH patients—at least to those in our sample—where the average number of

NSAIDs capsules only was around 25 per month and that of triptans was 12. Third, Eurolight based its estimates on reduced productivity on the basis of average gender-specific salary levels in industry and services obtained from the Eurostat database, and loss of productivity was assessed as absence from work and by the amount of days in which the patient could do "less than half of his/her job" due to headache: in this case, days were calculated as a full lost day, while those with average reduction lower that 50% were ignored. In our data, the 95% confidence interval of productivity was 52–60%, which basically suggests that the vast majority of cost referred to reduced productivity would not have been addressed if we used Eurolight approach. Fourth, Eurolight did not take into account the cost of non-pharmacological treatments, such as nutraceuticals or behavioural approaches that are increasingly the focus of clinicians' interest [11–13], and that accounted for 16.5% of total MOH cost (19.3% among females). Fifth, our study is based on a clinical sample of patients attending a specialty centre, enrolled at the time in which the cost is maximised for productivity loss, medications intake and diagnostic procedure, and that therefore, probably had more severe headache forms compared to those enrolled in Eurolight, who were taken from the general population or among those visiting their GPs.

We can hypothesize that the annual cost of MOH per patient may be defined by four trimesters for all selected variables, with the exception to those referred to diagnostic procedures (e.g. neurological examinations, MRI, TC scans, blood tests and so on) that are likely to be compressed in the period of time that is close to the admission to a structured withdrawal treatment. Following this hypothesis, the overall per person annual cost would be around 10370€, of whom 6360€ (61%) due to indirect cost, 3495€ (34%) due to direct healthcare cost and 515€ (5%) due to direct non-medical cost.

Finally, to the best of our knowledge, this is the first study referred to the cost of a primary headache disorder in which direct non-medical costs were estimated. Considering all of this, we can presume that the cost referred to MOH as addressed by Eurolight has likely been underestimated.

The main limitation of this study is connected to the sample representativeness, as all patients were treated in a single institution and had a particularly severe disease profile being included at the time in which the cost may be maximised by disease activity. For this reasons, the cost derived from a clinical sample should not be generalized to the entire general population.

In conclusion, we reported information on costs referred to the three months prior to withdrawal treatment in patients with MOH. Our data have been derived from patients' report on the actual reduced productivity, medications intake, diagnostic procedures, non-pharmacological treatments and direct non-medical cost, rather than on population-based estimates. This approach provides new insights on the cost structure related to this disorder showing a per person monthly cost of 950€ with a clear difference between men and women (1300€ vs 880€), and an estimated per person annual cost of 10730€, which is far higher than those previously identified.

Acknowledgements The study was partially supported by FICEF Onlus.

Compliance with ethical standards

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Headache Classification Committee of the International Headache Society (2013) The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 33:629–808
2. D'Andrea G, Cevoli S, Colavito D et al (2015) Biochemistry of primary headaches: role of tyrosine and tryptophan metabolism. Neurol Sci 36:S17–S22
3. Ferraro S, Grazzi L, Muffatti R et al (2012) In Medication-overuse headache, fMRI shows long-lasting dysfunction in mid-brain areas. Headache 52:1520–1534
4. Bigal ME, Lipton RB (2011) Migraine chronification. Curr Neurol Neurosci Rep 11:139–148
5. Bigal ME, Serrano D, Buse D et al (2008) Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 48:1157–1168
6. Evers S, Jensen R (2011) Treatment of medication overuse headache—guideline of the EFNS headache panel. Eur J Neurol 18:1115–1121
7. Linde M, Gustavsson A, Stovner LJ et al (2012) The cost of headache disorders in Europe: the Eurolight project. Eur J Neurol 19:703–711
8. Mussida C, Picchio M (2014) The gender wage gap by education in Italy. J Econ Inequal 12:117
9. Gustavsson A, Svensson M, Jacobi F et al (2011) Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 201121:718–779
10. Olesen J, Gustavsson A, Svensson M et al (2012) The economic cost of brain disorders in Europe. Eur J Neurol 19:155–162
11. Orr SL (2016) Diet and nutraceutical interventions for headache management: a review of the evidence. Cephalalgia 36:1112–1133
12. Fernández-de-las-Peñas C, Cuadrado ML (2016) Physical therapy for headaches. Cephalalgia 36:1134–1142
13. Andrasik F, Grazzi L, D'Amico D et al (2016) Mindfulness and headache: a "new" old treatment, with new findings. Cephalalgia 36:1192–1205

Neurol Sci (2017) 38 (Suppl 1):S7–S10
DOI 10.1007/s10072-017-2917-6

Migraine with aura white matter lesions: preliminary data on clinical aspects

Alberto Galli[1] · P. Di Fiore[1] · G. D'Arrigo[1] · C. Uggetti[2] · S. Squarza[3] · M. Leone[4] · D. D'Amico[4] · F. Frediani[1]

Abstract A few clinic-based magnetic resonance imaging studies report an increased risk of signal abnormalities in migraineurs brain's white matter, especially in migraine with aura subjects. A vascular genesis has been hypnotized and migraine with aura was considered an independent risk factor for stroke. Available data of magnetic resonance imaging alterations are often nonspecific and sometimes controversial. The aim of our study is to investigate migraine with aura patients with standardized brain magnetic resonance imaging to detect and to quantify the presence of white matter lesions and to analyze their relation with clinical data. We report preliminary data about first 90 subjects. We did not recognize any clinical aspect in close relationship with these alterations. The only clinical feature that seems to play a role in the presence of alterations is the age, and only in migraineurs women.

Keywords Migraine · Aura · MRI · White matter lesions · WML

✉ Alberto Galli
alberto.galli@asst-santipaolocarlo.it

[1] Neurological and Stroke Unit Department, Headache Center, ASST Santi Paolo e Carlo, San Carlo Borromeo Hospital, Via Pio II, 3, 20153 Milan, Italy

[2] Neuroradiological Unit, Department of Radiology, ASST Santi Paolo e Carlo, S. Carlo Borromeo Hospital, Milan, Italy

[3] Post-graduation School in Radiodiagnostics, Università degli Studi di Milano, Milan, Italy

[4] Headache Center, Carlo Besta Neurological Institute and Foundation, Milan, Italy

Introduction

Migraine is a common neurological disorder characterized by recurrent attacks of headache. Approximately one-fourth of subjects with migraine complain of transient neurological symptoms, before or during the pain phase, constituting the so-called aura [1–5]. A few clinic-based magnetic resonance imaging (MRI) studies report an increased risk to present diffuse signal abnormalities in migraineurs brain's white matter, especially in migraine with aura subjects [6]. Different MRI alterations are described: silent posterior circulation territory infarcts, supra-tentorial deep white matter lesions, and infra-tentorial T2-hyperintense lesions. A vascular genesis has been theorized and migraine, especially with aura, has been suggested as an independent risk factor for stroke [7, 8].

Available data on MRI abnormality signal features are often nonspecific and sometimes controversial. Some authors also report the changing over time of these white matter abnormalities, sometimes even their disappearance [9, 10]. In a systematic review of literature, we did not find systematic studies about the presence of MRI white matter lesions in migraine with aura patients. In particular frequency, pathogenic significance and clinical aspects remain unclear. The aim of this perspective study is to investigate, in a large high selected group of migraine with aura patients, by a specific MRI examinations, the presence of typical white matter lesions, and then to define a correlation with clinical data.

Materials and methods

Since December 2014, we enrolled 122 consecutive patients in accordance with the study protocol approved by our Institute Ethics committee. Subjects' participant was

identified through all consecutive patients referred to the Headache Center of San Carlo Borromeo Hospital (ASST Santi Paolo e Carlo Milano) and the Headache Center of Neurological Institute "Carlo Besta" with the diagnosis of migraine with aura (MA). Trained Neurologists verified diagnosis and inclusion criteria: age 14–50 years, diagnosis based on the ICHD3-beta criteria [11], and aura's frequency of at least 1 episode/year in the last 3 years. Patients with attacks occurring only during pregnancy or induced by oral contraceptive therapy or hormonal drugs were excluded. All participants had a negative personal history for cerebrovascular disease and all had a normal neurological examination. Participants gave written informed consent. At the recruitment (T_0), all participants, after a general and neurological examination, received a face-to-face interview by one of the Neurologists of Headache Center about their habit and general clinical condition (blood pressure, smoking, lipid profile, oral contraceptive use in female, height, and weight for BMI calculation, etc.) and about aura. Next, they were subjected to a brain MRI with a standard protocol (T1, T2, FLAIR, DWI, and a specific FLAIR 3D sequence to better characterize lesions of cerebral gray and white matter). Presence, number, and localization of white matter hyperintensities in Brain MRI were analyzed by two different neuro-radiologists.

Results

We report preliminary data about the first 90 subjects.

Twenty-three (25.6%) are males and sixty-seven (74.4%) females. The mean age at T_0 was 35.8 ± 9.5 years (range 14–50 years).

White matter lesions at brain MRI are present in 27 subjects (30.0%) (positive); conversely, 63 subjects (70.0%) have no alterations at MRI imaging (negative). Only one of the positive patients has a lesion in posterior circulation compatible with an infarct. All the other positive patients have supratentorial lesions in the anterior circulation territories, with the aspect of aspecific WML.

In positive patients, 7/27 are males (26%) and 20/27 (74%) are females. In negative patients, 16/63 are males (25.4%) and 47/63 (74.6%) are females. The gender rate is the same (F:M = 3:1) for both the groups (positive and negative) and for the whole study sample.

Considering the age, the mean age in negative patients is 34.4 ± 9.6 years, with no significant different between males and females (respectively, 35.7 ± 11.0 and 34.0 ± 9.2), while the mean age in positive patients is 39.1 ± 8.5 years, with a significant difference between males and females (respectively 32.6 ± 8.8 and 41.3 ± 7.2 years, $p = 0.03$).

Onset

The mean age of onset in the whole sample is 21.8 ± 9.4 years, similar in positives (22.3 ± 9.9) and in negative (21.6 ± 9.3) subjects. No significant gender difference was observed (females 22.8 ± 8.9 vs. males 19.0 ± 10.3 in the whole sample; females 25.4 ± 9.5 vs. males 11.4 ± 5.0 in the positive group; females 21.7 ± 8.5 vs. 21.2 ± 14.0 in the negative patients).

Duration of disease

The whole sample has a mean duration of MA of 14.0 ± 9.8, with 16.8 ± 10.7 years in positive and 12.9 ± 9.2 years in negative patients. This difference is not significant. In addition, for this parameter, there is no difference between females and males, either for positive or for negative groups (see Table 1).

Mean frequency of aura, calculated as episodes/year, is 13.2 ± 18.4 in the overall sample (males 14.7 ± 24.0 and females 12.6 ± 16.0), with 14.9 ± 24.0 episodes/year in positive and 12.4 ± 15.7 episodes/year in negative. No differences between males and females in the positive or the negative groups.

Mean duration of aura is 28.0 ± 15.6 min in the whole sample (males 29.0 ± 15.5 and females 27.6 ± 15.8), with 24.9 ± 14.2 in positive (males 27.1 ± 15.2 and females 24.1 ± 14.1), and 29.2 ± 16.1 min in negative (males 29.9 ± 16.0 and females 29.0 ± 16.3). These differences are not significant.

Type of aura

57% of the sample reported exclusively visual aura, 2.2% exclusively sensitive, while the remaining 40% mixed (visual, sensitive, and aphasic). In negative subjects, 60.3% reported exclusively visual aura and 3.2% exclusively sensitive, while the remaining 36.5% mixed. In positive subjects 55.6% reported exclusively visual aura, while the remaining 44.4% mixed. No one reported an exclusively sensitive aura.

Discussion and conclusions

Until today, literature about white matter lesions in migraine with aura patients has shown controversial data. Different methodological approaches were used (i.e., diagnostic criteria; procedures for the investigational approach; mean age of population, sample number, no standardized MRI examination, etc.) resulting in non-homogeneous data. At our knowledge, there are no studies that have analyzed the clinical aspects in relationship with

Table 1 Patients of the study and clinical evaluation parameters

	Total		Females		Males		*p*
	n	%	*n*	%	*n*	%	
Sample	90	100.0	67	74.4	23	25.6	ns
RM +	27	30.0	20	74.0	7	26.0	ns
RM −	63	70.0	47	74.6	16	25.4	ns
	Years	±	Years	±	Years	±	
Age	35.8	9.5	36.2	9.3	34.8	10.3	ns
RM +	39.1**	8.5	41.5*	7.2	32.6*	8.8	0.01*
RM −	34.4**	9.6	34.0	9.2	35.8	11.0	0.03**
Onset age	21.8	9.4	22.8	8.9	19.0	10.3	ns
RM +	22.3	9.9	25.4	9.5	11.4	5.0	ns
RM −	21.6	9.3	21.7	8.5	21.2	14.0	ns
MA duration	14.0	9.8	13.4	9.1	15.9	11.6	ns
RM +	16.8	10.7	16.1	11.0	18.9	10.5	ns
RM −	12.9	9.2	12.3	8.1	14.6	12.1	ns
	Episodes years	±	Episodes years	±	Episodes years	±	
Frequency	13.2	18.4	12.6	16.0	14.7	24.0	ns
RM +	14.9	24.0	11.9	12.3	22.9	42.9	ns
RM −	12.4	15.7	12.9	17.4	11.2	9.1	ns
	Minutes	±	Minutes	±	Minutes	±	
Mean lasting of aura	28.0	15.6	27.6	15.8	29.0	15.5	ns
RM +	24.9	14.2	24.1	14.1	27.1	15.2	ns
RM −	29.2	16.1	29.0	16.3	29.9	16.0	ns

the presence or the absence of brain lesions, with standardized MRI examination, in "true" migraine with aura patients. When a migraineur can be considered a "Migraine con Aura Patient"? IHS criteria [11] state that a patient can get the diagnosis of MA when he experienced at least two attacks in his life. However, clinical experience teaches us that patients with only two aura episodes in his life or with drug-induced attacks is very different from patients who experience one or more episodes every year or every month. We did not find studies that established a minimal numbers of attacks per year in evaluating MRI of aura patients, and this may be an important bias.

The most representative study that analyzed 161 subjects with migraine with aura is the CAMERA Study (Cerebral Abnormalities in migraine, an Epidemiological Risk Analysis) [7, 8] that consider patients with migraine with and without aura, aged 30–60 years, randomly selected from another population-based study (GEM Study—Genetic Epidemiology of Migraine). The authors stated that "migraine, especially with aura, is a potential risk factor for cerebral posterior infarction". At present, our data seem to be quite different and in contrast with CAMERA statement. The only variable that appears to be related with the presence of the WML is the age. More in specific, time course seems to be a risk factor for the white matter alteration in women, whilst no effect seems to have on male population. Mean age of the patients of our study is 35.8 vs. 48.2 of MA patients in CAMERA study. We collected data from 14 to 50 year old, including the period of onset of the disease, while patients of CAMERA range from 30 to 60.

Age at onset, disease lasting, aura attacks frequency, duration, and type of aura do not increase the possibility to have WML.

Because older females are more prone to have alterations in brain white matter with the age is not clear. Considering life habits (smoke and OCT) and other diseases as comorbidity (diabetes, hypertension, dyslipidaemia, etc.), any of these aspects seem to favourite the presence of white matter either in em or in women.

These are only preliminary data and a more representative sample it is necessary, but our impression is that the pathogenesis of WML and all the alterations that can be seen in brain MRI of MA patients are still far from understanding.

Acknowledgements This study has been performed with the economical support of F.I.Cef.—Fondazione Italiana Cefalee Onlus. A special thank to Ilaria Spiezia and Virginia Invernizzi for their technical and organizing support.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this study.

References

1. Lipton RB et al (1998) Medical consultation for migraine: results from the American Migraine Study. Headache 38(2):87–96
2. Friedman BW et al (2009) Use of emergency department for severe headache. A population-based study. Headache 49:21–30
3. Ferrante T et al (2012) The PACE study: past-years prevalence of migraine in Parma's adult general population. Cephalalgia 32(5):358–365
4. Merikangas KR (2013) Contributions of epidemiology to our understanding of migraine. Headache 53(2):230–246
5. Leonardi M et al (2005) The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). J Headache Pain 6(6):429–440
6. Kruit MC et al (2004) Migraine as a risk factor for subclinical brain lesions. JAMA 291(4):427–434
7. Kruit MC et al (2005) Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. Brain 128(Pt 9):2068–2077
8. Scurks et al (2009) Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 27(339):b3914
9. Rozen TD et al (2007) Vanishing cerebellar infarcts in a migraine patient. Cephalalgia 27(6):557–560
10. Rozen TD et al (2010) Images from headache: white matter lesions of migraine are not static. Headache 50(2):305–306
11. Headache Classification Committee of the International Headache Society—HIS (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33(9):629–808

Neurol Sci (2017) 38 (Suppl 1):S11–S13
DOI 10.1007/s10072-017-2897-6

Migraine with aura and white matter lesions: an MRI study

Carla Uggetti[1] · Silvia Squarza[2] · Fabio Longaretti[3] · Alberto Galli[4] · Paola Di Fiore[4] · Paolo Filippo Reganati[1] · Adriana Campi[1] · Andreana Ardemagni[1] · Maurizio Cariati[5] · Fabio Frediani[4]

Abstract Several studies report the presence of white matter lesions on brain magnetic resonance imaging in patients with migraine. The aim of our study was to detect the entity of white matter T2-hyperintensities in 90 high selected patients affected by migraine with aura, compared to a group of 90 healthy controls. We found no significant difference of incidence of white matter alterations comparing these two groups.

Keywords Migraine · Aura · MRI · White matter · Hyperintensities

Introduction

Primary headache disorders are an important and often disabling problem in the general population. One of the most common forms is migraine [1]. Around 25% of people with migraine present transient and reversible neurological symptoms that resolve before the onset of headache (the so-called migraine aura). Once aura is resolved headache might be mild or even absent. The most frequent type of aura is characterized by visual symptoms with fortification spectra or scintillating scotoma. Sensory aura is less prevalent and almost always accompanied by visual symptoms [2].

The incidence of migraine attacks varies considerably between individuals; some have several attacks a month but others have less than one a month. In particular attacks of migraine with aura present with a lower frequency, ranging from 1 to 2 episodes in a year to one or more attacks in a month [3].

The diagnosis of migraine is based on anamnestic and clinical data. Considering magnetic resonance imaging (MRI) findings, migraine is largely considered an independent risk factor for supratentorial deep white matter lesions, silent posterior circulation territory infarcts and infratentorial T2-hyperintense lesions [4]. Lesions most frequently described in migraine patients are silent infarct-like lesions with the aspect of white matter T2-hyperintensities at MRI [5].

At our knowledge there are no systematic studies concerning the presence of MRI abnormalities in patients specifically affected by migraine with aura (MA).

The aim of our prospective protocol was to study patients affected by MA performing a brain MRI to detect and quantify the presence of typical white matter hyperintensities. Here we present our first 90 patients compared with 90 healthy controls.

Subjects and methods

Subjects recruitment was made accordingly to the following inclusion criteria.

✉ Carla Uggetti
uggetti.carla@asst-santipaolocarlo.it

[1] Neuroradiology Unit, Department of Radiology, ASST Santi Paolo e Carlo, San Carlo Borromeo Hospital, Via Pio II n. 3, 20153 Milan, MI, Italy

[2] Scuola di Specializzazione in Radiodiagnostica, Università degli Studi di Milano, Milan, Italy

[3] Department of Radiology, Policlinico San Marco and Policlinico San Pietro, Bergamo, Italy

[4] Department of Neurology, San Carlo Borromeo General Hospital, Milan, Italy

[5] Department of Radiology, San Carlo Borromeo General Hospital, Milan, Italy

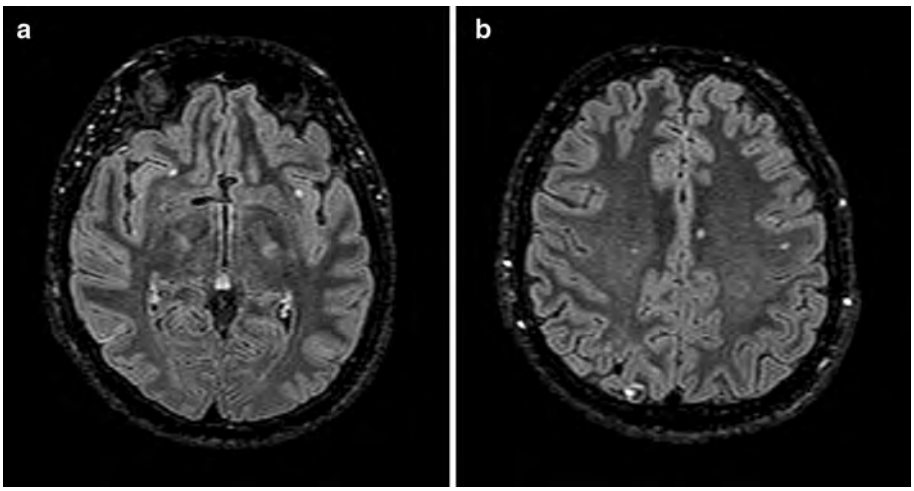

Fig. 1 **a**, **b** A 26-year-old man affected by MwA. 3D FLAIR scan shows punctate T2-hyperintensities in the white matter within the frontal lobes

Patients had a diagnosis of MA, according to ICHD-3 beta criteria of International Headache Society [6].

They were 14–50 years-old and they presented at least 1 episode/year of aura in the last 3 years.

From December 2014 to June 2016, we prospectively recruited 90 adult patients fitting these criteria, at the Headache Centre of San Carlo Borromeo Hospital (ASST Santi Paolo e Carlo, Milan). They were 28 males and 62 females, with a mean age of 36.8 years (16–50 years).

All patients were investigated with a brain MRI at the time of recruitment. MRI studied were all performed on a 1.5 T Philips Achieva, with a standard protocol including T1, T2, FLAIR and diffusion weighted sequences; an additional specific FLAIR 3D sequence was also performed to better characterize lesions of cerebral gray and white matter.

A control group of ninety adult healthy patients who performed an MRI examination for symptoms other than migraine, not suffering of headache, were retrospectively selected, matching age and sex (31 males, 59 females, mean age 38.2). They all performed brain MRI on the same Philips Achieva 1.5T tool, with the same standard brain MRI protocol without FLAIR 3D sequence, as they were selected retrospectively.

Brain MRI were read by two neuroradiologists independently who analyzed presence, number and localization of white matter T2-hyperintensities.

Statistical analysis was made using the analysis software SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Patient informed consent to be included in the study has been obtained.

Results

We detected the presence of white matter hyperintensities at brain MRI in 26/90 (29%) patients; conversely, 64/90 (61%) patients presented no white matter alterations. Lesions were all supratentorial and in particular in frontal, parietal and temporal lobes (Fig. 1). No occipital alterations were recognized. No brainstem or cerebellar lesions were detected too.

We found no association between side of aura and side of lesions.

No association was found between migraine lasting and number of lesions.

Considering the group of control patients, we found white matter hyperintensities in 24/90 (27%) patients. There was not a statistically significant difference between patients with migraine and controls ($p = 0.64$) regarding the incidence of white matter hyperintensities.

Discussion

Many reports describe the evidence that MA is related to an increased risk of cardiovascular disease [7]. Three recent meta-analyses have shown that migraine is a risk factor for ischemic stroke. Particularly a two times increased risk of ischemic stroke was reported for women with migraine, driven by the presence of aura [8].

Brain MRI alterations associated to migraine include clinically silent infarct-like lesions in the posterior circulation territory and white matter hyperintensities. White matter hyperintensities can be seen also in apparently healthy people [1].

Palm-Meinders et al. reported a higher prevalence and greater volume of MRI-measured deep white matter hyperintensities, infratentorial hyperintensities and posterior circulation territory infarct-like lesions in patients with migraine. In particular Authors described the presence of white matter hyperintensities in 33/114 (29%) patients affected by migraine with aura [9].

Particularly with respect to patients with MA, at our knowledge there is no systematic study of brain lesions in these patients. Scher et al. in a subgroup of their patients, reported an increased prevalence of posterior circulation territory infarct-like lesions in women with MA [5].

The most important recent study that analyzed a total of 295 patients, 161 affected by MA, is the CAMERA analysis (Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis). Authors detected a significant incidence of silent brain infarction in the posterior territory, the majority located in cerebellum and most pronounced in cases with MA (8%). Female with migraine also presented deep white matter lesions with a higher incidence in patients with higher attack frequency [10].

Our results are in opposition with all previous studies, as we did not find a statistically significant difference in incidence of white matter hyperintensities between patients with MA and controls.

While the CAMERA study revealed lesions of the posterior territory in 8% of patients we detected no lesions of these territories in all our 90 patients.

Furthermore, we would like to point the attention to consider that even if aura was almost always a visual aura no occipital lesions were detected. This could lead to exclude a pathogenetic vascular mechanism of white matter hyperintensities related to aura.

Moreover, we did not find a statistically significant difference either between white matter hyperintensities and duration of migraine, frequency of attacks or side of aura.

Limit of our study is the relatively small number of patients. Otherwise its strength is that patients are very well selected: we recruited only patients with defined MA and their mean age was significantly inferior compared to age of CAMERA study's patients. This could help to eliminate the bias of coexisting vascular diseases.

In conclusion, even if more patients are necessary to validate these results, our study suggests to reconsider the correlation between white matter T2-hyperintensities and MA, considered the form of migraine typically accompanied by white matter lesions. Is there a real correlation or rather these lesions are a common not specific finding in the general population?

Acknowledgements The study has been supported by a grant from F.I.CEF. (Fondazione Italiana Cefalee).

Compliance with ethical standards

The studies have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and latest revisions (the latest in 2013). The study was approved by Institutional Ethical Committee.

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Kurth T, Mohamed S, Maillard P et al (2011) Headache, migraine, and structural brain lesions and function: population based epidemiology of vascular ageing—MRI study. BMJ 342:c7357. doi:10.1136/bmj.c7357
2. Vetvik KG, MacGregor EA (2017) Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol 16:76–87. doi:10.1016/S1474-4422(16)30293-9
3. Blau JN (1987) Migraine: clinical and research aspects. Johns Hopkins University Press, p 695
4. Kamson DO, Illés Z, Aradi M et al (2012) Volumetric comparisons of supratentorial white matter hyperintensities on FLAIR MRI in patients with migraine and multiple sclerosis. J Clin Neurosci 19:696–701. doi:10.1016/j.jocn.2011.07.044
5. Scher A, Gudmundsson L, Sigurdsson S et al (2009) Migraine headache in middle age and late-life brain infarcts: the age gene/environment susceptibility—Reykjavik Study. JAMA 301:2563–2570. doi:10.1111/j.1526-4610.2009.01579.x
6. Tepper SJ (2013) Editorial: international classification of headache disorders, 3rd edition, beta version. Headache 53:1381–1382. doi:10.1111/head.12190
7. Schurks M, Rist PM, Bigal ME et al (2009) Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 339:b3914–b3914. doi:10.1136/bmj.b3914
8. Spector JT, Kahn SR, Jones MR et al (2010) Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med 123:612–624. doi:10.1016/j.amjmed.2009.12.021
9. Palm-Meinders IH, Koppen H, Terwindt GM et al (2012) Structural brain changes in migraine. JAMA 308:1889–1897. doi:10.1001/jama.2012.14276
10. Kruit MC, Van Buchem MA, Launer LJ et al (2010) Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: the population-based MRI CAMERA study. Cephalalgia 30:129–136. doi:10.1111/j.1468-2982.2009.01904.x

Neurol Sci (2017) 38 (Suppl 1):S15–S20
DOI 10.1007/s10072-017-2908-7

Community pharmacies as epidemiological sentinels of headache: first experience in Italy

Paola Brusa[1,2] · Marco Parente[1] · Gianni Allais[3,4] · Sara Rolando[3] · Giuseppe Costa[5] · Roberto Gnavi[5] · Teresa Spadea[5] · Mario Giaccone[2,6] · Andrea Mandelli[6] · Massimo Mana[7,8] · Francesca Baratta[1] · Chiara Benedetto[3] · Gennaro Bussone[4]

Abstract Migraine is a disabling neurovascular syndrome which affects 12–15% of the global population and it represents the third cause in years lived with disability in both males and females aged 15–49 years. Among migraineurs, the symptomatic drug abuse may be a risk factor in the development of medication overuse headache (MOH). Detecting cases of MOH is not straightforward; community pharmacists may, therefore, be in a strategic position to identify individuals who self-medicate, particularly with respect to prevent the development of MOH. In 2014, our group published the results of a survey conducted in Piedmont, Italy, on the patterns of use and dispensing of drugs in patients requesting assistance from pharmacists for relief of a migraine attack. We decided, now, to expand the scope of the model to a national level. The study is based on cross-sectional face-to-face interviews using questionnaires, presented in this paper, consisting of a first part regarding the socio-economic situation and a second part which aimed to classify the disease and any excessive use of drugs. Of the 610 pharmacists trained with an online course, 446 gathered a total of 4425 correctly compiled questionnaires. The participation of community pharmacies has highlighted various criticalities especially of an organisational nature; however, it also revealed the power of this method as a means of gathering epidemiological data with a capillarity which few other methods can match. The objective was also to identify each territory's requirements and facilitate the decision-making process in terms of understanding what patients/citizens actually require.

Keywords Community pharmacy · Medication overuse headache · Migraine

✉ Paola Brusa
paola.brusa@unito.it

1 Department of Scienza e Tecnologia del Farmaco, University of Turin, Via P. Giuria n. 9, 10125 Turin, Italy

2 Order of Pharmacists of Turin, Turin, Italy

3 Department of Surgical Sciences, Women's Headache Center, University of Turin, Turin, Italy

4 FI.CEF Onlus, Milan, Italy

5 Epidemiology Unit, ASL TO3, Grugliasco, Italy

6 FOFI, Federation of the Orders of Italian Pharmacists, Rome, Italy

7 ATF Informatics, Cuneo, Italy

8 Federfarma Piemonte, Turin, Italy

Introduction

Migraine headache is a disabling neurovascular syndrome which affects 12–15% of the global population; women are especially prone with a rate of 18–20% among the female population. According to a recently published study in *The Lancet* [1], migraine headache represents the third most commonly cited cause in years lived with disability in both males and females aged 15–49 years.

A *review* evaluated which other countries in Europe, and in the world, have utilised community pharmacies to identify headache sufferers as a means to make an early identification of the pathology [2].

The early identification of this pathology could potentially lead to enormous savings for the National Health System as well as a marked improvement in the quality of life for the subjects affected by this condition [3].

Among migraineurs, the overuse of medication, a reward seeking behaviour, may be a risk factor in the

development of daily migraine and chronic migraine. Indeed, while truly effective medication does exist for the treatment of migraine, its overuse, both in terms of frequency and therapy duration, may have the paradoxical effect of worsening the situation rather than improving it. This condition, called medication overuse headache (MOH), is a growing problem, with an estimated incidence of 1–2% in the general population and up to 30–50% in tertiary headache centres.

Detecting cases of MOH is not straightforward as the majority of migraineurs tend to rely on self-medication with over-the-counter (OTC) analgesics and, in the course of their lifetime, may never turn to a specialist pain centre or even consult their family doctor [2]. Community pharmacists may, therefore, be in a strategic position to identify and advise individuals who self-medicate, particularly with respect to prevention and early detection of medication overuse to prevent the development of the MOH. Furthermore, they could have an invaluable role by evaluating through simple tests the risk amongst the chronic migraine population of obesity, which leads to significant costs for the healthcare system and induces major disabilities for the affected subject.

Moreover, exploiting the network of community pharmacies makes it possible to identify those "real-life" individuals who for socio-economic reasons are unlikely to turn to a tertiary treatment centre such as a headache centre for treatment. This could help to reduce the social divide in terms of those who seek treatment for headaches.

In 2014, our group published the results of a survey conducted in Piedmont, Italy, on the patterns of use and dispensing of drugs in patients requesting assistance from pharmacists for relief of a migraine attack.

The survey was supported by the Italian Foundation for Headaches (FI.CEF), in collaboration with the Order of Pharmacists of Turin, Regional Deputy, and the Department of Scienza e Tecnologia del Farmaco, University of Turin.

The study entailed the administration of a 9-item questionnaire, the first part of which comprised items from the ID Migraine Screener test [4, 5] which investigates the different types of headache and whether the subject suffers from migraine headache according to symptom occurrence and severity. On this basis, subjects were categorized as having "Definite migraine" or "Probable migraine".

Thanks to the interesting findings of that study, both from an epidemiological perspective and a public policy viewpoint [6, 7], the decision was taken to expand the scope of the model to a national level in agreement with the Federation of the Orders of Italian Pharmacists (FOFI), the Department of Scienza e Tecnologia del Farmaco, University of Turin (DSTF), the Italian Foundation for Headaches (FI.CEF), the Epidemiology Unit, ASL TO3, (ASL S.C. a D.U. Servizio Sovrazonale di Epidemiologia), ATF Informatics Society, and the Order of Pharmacists of Turin.

Materials and methods

Design of the study: Questionnaire

The study was designed as a *cross-sectional survey* based on face-to-face interviews using questionnaires drawn up by experts and based on the scientific literature; given the unusual nature of the centres responsible for recruiting the subjects, i.e., community pharmacies, it was decided to carry out a specific training course for the data gatherers to ensure that the data were collected with the most standardised procedure possible.

Recruitment criteria

The subjects were recruited at a maximum rate of five patients per pharmacy per month amongst those entering the pharmacy requesting medicine for self-medication of a headache.

Training

The training course made use of an online platform which the pharmacists could log on to by compiling a form including their regional code; health service code and AIFA code (see "Recruitment of pharmacies in the experimental area: creation of a pharmacy database"). The training consisted of an audio file supported by explanatory slideshow. This standard training course for all territories provided through distance learning methods assured an optimised and uniform training time.

Recruitment of the pharmacies in the experimental area: creation of a pharmacy database

For this purpose, the AIFA code was used (http://www.dati.salute.gov.it/dati/dettaglioDataset.jsp?menu=dati&idPag=5—last date consulted 30/01/2017—). This is an open source system of unique identity codes for each community pharmacy made available by the Ministry of Health.

Logistics organisation

To ensure greater control at the level of the individual provinces, a provincial coordinator was appointed, who reported directly to the head of project coordination.

Results and discussion

Design of the study: Questionnaire

With respect to the previous study [6], some modifications to the questionnaire were made (Table 1). In particular, a section regarding the socio-economic situation of the recruited subjects was added (questions 1–6) to understand which were the determining factors in the prevalence of headaches.

The socio-economic questions are the product of studies carried out over an extended time span by the research group of the Epidemiology Unit, experienced in the analysis of social disparities in health treatment [8], and discussions between university, neurologists, and pharmacists. These questions have already been included in other studies carried out in community pharmacies with the aim to investigate the correlation between social factors and the pathology under investigation.

Regarding the second part of the questionnaire, which aimed to classify the pathology and any overuse of medication, some new questions were added compared to the previous version used in other studies (Table 2).

No changes were made to the ID Migraine Screener test [4] which investigates the different types of headache and whether the subject suffers from migraine headache according to symptom occurrence and severity. On this basis, subjects were categorized as having "Definite migraine" or "Probable migraine" [5].

The other questions serve to ascertain whether the subject suffering from migraine is in treatment by a medical professional and whether the MOH condition is acute [9]. The overall objective is to optimise the investigative efficiency of this questionnaire.

Recruitment criteria

Each pharmacy had the objective to recruit a maximum of 5 subjects/month for each month of the 6-month experiment.

Obviously, the maximum numerosity of the questionnaire is disproportionate compared to the potential migraineurs, considering the high prevalence of primary headache among the population.

Training

Following registration in the database of Pharmacies, the pharmacists underwent a 3-h training course with a nationally uniform structure for all areas of the country.

The online training course consisted of three 1-h sections using a slide presentation:

Table 1 "Headache and Community Pharmacies" Questionnaire part 1: Social Questionnaire

1) **Sex** M F
2) **Age** [actual age]
3) **Height** [in cm] and **weight** [in kg]
4) **Education** [the highest qualification attained]
University degree or higher
4-5-year High School Diploma valid for third-level education
2-3-year High School Diploma not valid for third-level education
Junior High School Diploma (or apprenticeship/job)
Primary school exam
No qualification
5) **Occupation**
If employed:
Manual labourer
Employee non-manual (conceptual/intellectual)
Self-employed:
Businessperson
Professional
Self-employed worker
Unemployed
Homemaker
Student
Retired
Other (military service, invalid etc.)
6) How many members are there in your family? Number of people in your household (including patient)?

Table 2 "Headache and Community Pharmacies" Questionnaire part 2

7) **ID Migraine screener test** Did you have the following with your headaches: You felt nauseated or sick to your stomach? YES/NO Light bothered you (a lot more than when you didn't have headaches)? YES/NO Your headaches limited your ability to work, study, or do what you needed to do for at least 1 day? YES/NO If the patient answers YES to at least three questions, there is a 95% probability that he/she suffers from migraines 8) **How long have you been having headaches**? <1 year; 1-4 years; 5-9 years; ≥10 years. 9) **How many days have you had a headache in the last 3 months**? ....n° 10) **How many days each month do you take pain medication for a headache**? up to 3; from 4 to 10; more than 10. 11) **Does the headache go away after you have taken pain medication?** Yes; Often; Rarely; No. 12) **Which medicines do you usually take when you have an acute attack?** NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs); ERGOT-DERIVATIVES; TRYPTANS; COMBINATION DRUGS; OTHER ANALGESICS [more than one answer is permitted]. 13) **Are you being treated by a medical professional?** [more than one answer is allowed] NOBODY; MY FAMILY DOCTOR; A SPECIALIST; A HEADACHE CENTRE 14) **Do you regard your headache as an illness?** YES/NO.

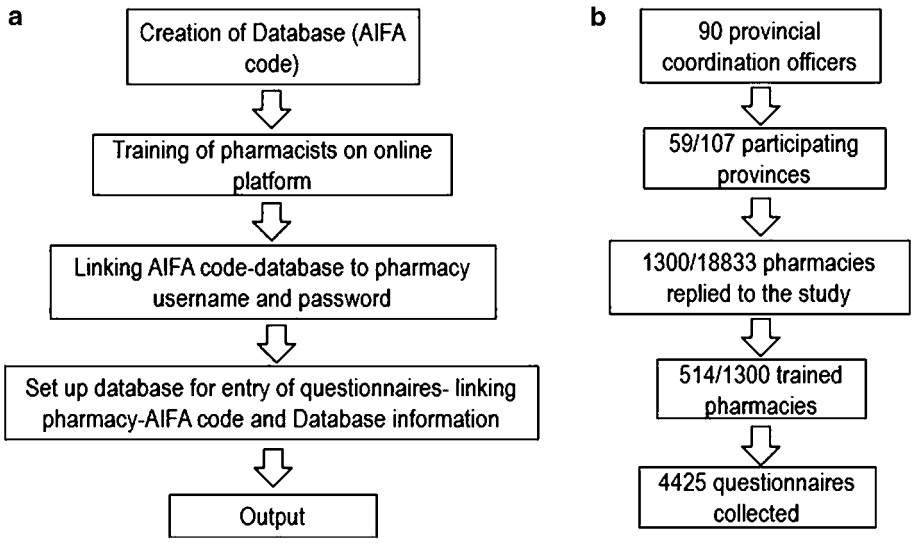

Fig. 1 **a** Organisational organogram of the database and training; **b** recruitment of pharmacies

1. Classification and epidemiological assessment of primary headaches;
2. clinical physio-pathology of primary headaches;
3. headache medication and the headache questionnaire.

After completing each section, the pharmacist had to answer three multiple-choice questions correctly to proceed to the successive section in the training course. Only after passing all three sections, the pharmacist was deemed to have completed the training course (Fig. 1a).

After completing the training procedure, each pharmacist was provided with a unique username and password linked to the Pharmacy database (AIFA code). These could be used to log on to the Questionnaire database to access the questionnaire to be filled in online (Tables 1, 2). The study was designed in such a way that it was possible to trace the location of the pharmacies and to gather questionnaires systematically so as obtain the maximum amount of location-specific information possible.

Recruitment of pharmacies in the experimental areas: creation of a pharmacy database

Utilising the AIFA code in the Pharmacy database allowed the identification of the location of the pharmacy in Italy. Through the code, it is possible to determine the region, province, city, and street address of the pharmacies present in the database.

The system was conceived to reduce the time to a minimum and this allowed rapid access to all the areas involved in the study. In addition to that, the registration process for the pharmacies did not require detailed information which would have made it time-consuming and overly complex. The information requested was, however, sufficient to enable geo-localisation; for the socio-economic stratification, by cross-checking the geographical data, and the data gathered in the questionnaires, it was possible to obtain a figure for the evaluation of the requirements.

Table 3 Training and interviews per region

Region	Trained pharmacies	Trained pharmacists	Pharmacists which gathered $\geq$1 questionnaire	Number of correctly compiled questionnaires
Piemonte	143	167	132	1362
Valle d'Aosta	20	29	19	202
Lombardia	28	34	22	239
Alto Adige (BZ)	1	1	1	2
Veneto	52	79	55	576
Friuli	54	64	52	586
Liguria	6	6	5	23
Emilia	83	91	66	696
Toscana	4	4	1	14
Umbria	9	10	6	34
Marche	12	13	9	56
Lazio	7	8	6	32
Abruzzo	2	3	1	1
Molise	6	6	4	15
Campania	3	3	2	46
Puglia	29	34	27	203
Basilicata	10	10	6	71
Sicilia	21	21	11	98
Sardegna	24	27	21	169
Total	514	610	446	4425

Logistics organisation

Ninety provincial coordination officers were appointed thanks to whom it was possible to recruit participants in 59 out of the total of 107 Italian provinces. The number of participating pharmacies was 514, with a total of 610 pharmacists trained (Fig. 1b). Of the 610 pharmacists, 446 gathered questionnaires. The total number of correctly compiled questionnaires amounted to 4425. As it is possible to note in Table 3, there is a downward gradient running from north to south of the country both in terms of participating pharmacies/trained pharmacists and the number of questionnaires returned.

Stratification based on socio-economic characteristics is essential in determining how effective the community pharmacy may be in eliminating social disparities.

Conclusions

The participation of community pharmacies, which was on an entirely voluntary basis, in an area-specific project sheds light on various criticalities especially of an organisational nature; however, it also revealed the power of this method as a means of gathering epidemiological data with a capillarity which few other methods can match.

One of the most critical points which must be evidenced is the complexity in creating a pharmacy database: in future, greater use of IT instruments must be made to prevent errors in data entry for the pharmacy and personal information.

The use of the AIFA code was an important instrument in tracing the origin of the information entered. However, it became clear that pharmacists had some difficulty in finding their own AIFA code. In any case, this code remains a powerful tool for the future mapping of a territory's requirements based on community pharmacies.

The objective, therefore, was not only to gather data, but also to identify each territory's requirements and, hence, facilitate the decision-making process in terms of understanding what patients/citizens actually require.

Acknowledgements The authors would like to thank Federation of the Orders of Italian Pharmacists (FOFI) that funded the national project.

Compliance with ethical standards

Conflict of interest All the authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388(10053):1545–1602

2. Giaccone M, Baratta F, Allais G, Brusa P (2014) Prevention, education and information: the role of the community pharmacist in the management of headaches. Neurol Sci 35:S1–S4
3. Camarda R, Monastero R (2003) Prevalence of primary headaches in Italian elderly: preliminary data from the Zabút Aging Project. Neurol Sci 24:S122–S124
4. Lipton RB, Dodick D, Sadovsky R et al (2003) A self-administered screener for migraine in primary care. The ID Migraine™ validation study. Neurology 61:375–382
5. Rapoport AM, Bigal ME (2004) ID-migraine. Neurol Sci 25:S258–S260
6. Brusa P, Allais G, Bussone G et al (2014) Migraine attacks in the pharmacy: a survey in Piedmont, Italy. Neurol Sci 35:S5–S9
7. Brusa P, Allais G, Rolando S et al (2015) Migraine attacks in the pharmacy: a gender subanalysis on treatment preferences. Neurol Sci 36:S93–S95
8. Costa G, Marinacci C, Spadea T (2010) Social inequalities in health: challenges and current priorities in a European context. Epidemiol Prev 34(5–6):31–34
9. Saracco MG, Allais G, Tullo V et al (2014) Efficacy of frovatriptan and other triptans in the treatment of acute migraine of normal weight and obese subjects: a review of randomized studies. Neurol Sci 35:S115–S119

Neurol Sci (2017) 38 (Suppl 1):S21–S25
DOI 10.1007/s10072-017-2918-5

KEY LECTURE

Our Headache Fellowship: a 10-year history

Paul Rizzoli[1]

Abstract There has been a clear trend in American medical education after World War II toward training specialization and subspecialization. After some early specialization efforts by the American Board of Psychiatry and Neurology, further efforts were undertaken by the United Council for Neurologic Subspecialties (UCNS), leading to the introduction of the neurologic subspecialty of Headache Medicine in March, 2005. The training program at our center at the Brigham and Women's Hospital Department of Neurology, Harvard Medical School, in Boston, Massachusetts, was accredited in 2008 and has graduated 14 trainees since its inception. Our experience is reviewed.

Keywords Neurologic subspecialty · Headache Medicine · Graduate medical education · Fellowship · Curriculum · United Council for Neurologic Subspecialties

Introduction

There has long been a perception that developing knowledge and treatment advances in headache care were not filtering down to the many patients who could benefit from them. There were too many patients and too few adequately trained physicians. Studies [1, 2] suggested that as many as 50% of individuals meeting criteria for migraine in the US population had never even entered the healthcare system for headache care.

Coupled with a clear need for improved access and quality of care was the trend in American medical education after World War II toward training specialization and subspecialization. After some early specialization efforts by the American Board of Psychiatry and Neurology, progress in neurologic subspecialization slowed. This in part led to the development of The United Council for Neurologic Subspecialties, formed to stimulate the development of neurologic subspecialities with the goal of improving patient care and preserving and enhancing individual subspecialty practices [3].

The neurologic subspecialty of Headache Medicine was added by UCNS in March, 2005. Academic centers with headache faculty, including ours at the Brigham and Women's Hospital Department of Neurology, Harvard Medical School, in Boston, Massachusetts, soon began to apply for accreditation. Today, some 10 years later, there are approximately 32 accredited Headache Medicine training programs in the US. This is the story of our center.

The Headache Medicine Fellowship

Training programs in headache existed in the US and elsewhere long before the neurologic subspecialty of Headache Medicine was inaugurated. Physicians would serve essentially as apprentices in centers dedicated to the management of headache. In 1998, in response to an increase in interest in the development of neurologic subspecialties, and in part driven by an explosion of neuroscience research, the American Academy of Neurology (AAN) appointed a commission on subspecialty certification. This led to the formation of the separate nonprofit

✉ Paul Rizzoli
prizzoli@partners.org

[1] Department of Neurology, John R. Graham Headache Center, Brigham and Women's Faulkner Hospital, No. 1153 Centre Street, Suite 4H, Boston, MA 02130, USA

organization, the UCNS [4], to help oversee the process of both the accreditation of subspecialty training programs and of the certification of trainees who, through examination, have demonstrated competence in their subspecialty area. UCNS provides no funding to fellowships [5].

The original idea for a formal headache fellowship was advanced by the American Headache Society beginning in 2003. This proposal was endorsed as well by the American Academy of Neurology, the American Neurological Association and other organizations that would ultimately come together to form UCNS, which was given the mandate to develop mechanisms for accreditation and credentialing of subspecialty training programs [3].

The John R. Graham Headache Medicine Fellowship

I arrived at the Faulkner Hospital, a well-respected academic community hospital, in 1999 just before the hospital merged with the much larger Brigham and Women's Hospital several miles down the road. Faulkner had had a long history of excellence in headache care and education during the tenure of John Graham and later that of Egligius Spierings. Interest in headache was at a low ebb when I arrived, however, and my efforts therefore were concentrated in general neurology.

As the merger progressed, I became part of the Brigham Neurology Department in 2004 and my focus of interest changed as I was charged with reinvigorating headache care at Faulkner. The effort was directly encouraged by the department chair, Martin Samuels, with great foresight and a level of support for headache that was uncommon among neurology department chairs at the time. The headache clinic, renamed for John Graham, would now be under the Department of Neurology.

To reinvigorate the clinic, the first step was to bring on board a known headache expert. Elizabeth Loder was not only well known throughout the headache world, she had previously trained in headache medicine at Faulkner and was the perfect choice. One little-known wrinkle was that Dr. Loder, like Dr. Graham, was an internist, not a neurologist. Another wrinkle was that she has never actually worked for us fulltime. When we first approached her with the idea of working at the center, she was in the process of negotiating a position as an editor for the *British Medical Journal*, a job that very much interested her. After some reflection, her decision was to accept both jobs on a part time basis and, during her time at the center, she has always worked two jobs. Over the years her expertise in editing, writing and scientific research has been a great benefit to our department and our trainees.

Adding fellowship training was a natural extension of our mission. Planning for this took place as soon as the subspecialty of Headache Medicine was announced in 2005. Our program was one of the first accredited in 2008. Our first certification-eligible graduate was in 2009.

The initial application process

The application process stipulates that all fellowships must have an ACGME-accredited sponsoring institution which takes overall responsibility for the quality of the training. The primary institution or site, generally a dedicated headache clinic, is expected to provide both adequate facilities and resources, and adequate faculty and personnel, in order to provide a quality longitudinal training experience for the fellow.

Training is for a minimum of 12 continuous months. To apply, candidates must be licensed in the United States or Canada and must have graduated from an ACGME or Royal College of Physicians and Surgeons of Canada (RCPSC)—accredited residency training program in neurology or other specialty. By intention, application is not restricted only to neurology residency graduates. Training programs are expected to provide fellows the opportunity to evaluate, under supervision, a minimum of 200 patients per year. The program's academic structure is based on the *Headache Medicine Core Curriculum* [6].

Compliance with all the stated requirements is documented in a lengthy on-line application which, together with payment of the application fee begins the process of accreditation.

Fellowship funding

An early and ongoing issue has been funding of the training program. UCNS provides neither funding nor guidelines on funding, leaving programs to fend for themselves. Various options have been employed. One, the use of grants, gifts or awards, is not guaranteed year after year and does not promote continuity or allow planning. The only option that appeared available initially was to derive funds from ongoing patient care activity of the clinic, including that of the fellows. This has proved a durable funding source that has covered the costs of training at the center and has allowed us to participate within the department without concern for our financial survival. This plan though, in contrast to other training arrangements, requires the full licensing, accreditation and credentialing of fellows as staff physicians so that they may be enrolled in the insurance programs that cover our patients. While remaining under supervision, they become the attending physician for their patients and "own" the cases. Conceived by necessity, this financial arrangement produced an unexpected value. Exit interviews have uniformly suggested strong support among

the trainees for this system. Trainees note that the "real world" experience during training provides a strong foundation and confidence for their future clinical activities. One downside is the time, cost and effort required to obtain all the necessary approvals. Also, ethical concerns have been raised by some over this financial structure. Patients are fully aware of how the system works, however, and who they are scheduled to see; and no trainee has reported feeling coerced, used or unsupported.

More recently another concern has arisen. This current financial structure, for all practical purposes, restricts the fellowship to accepting only US-trained neurologists. This limits the pool of available applicants and restricts the enrichment of the program by limiting exposure to other disciplines. Whether a fully precepted model, where care of the trainee's patient is billed under a supervising provider, is as viable as the current system is being investigated.

Working with GME

UCNS recommends, where possible, that in structuring their fellowship, programs work with their local graduate medical education (GME) office. These offices coordinate and monitor the quality of graduate medical education activities at their individual institutions. However, not all institutions have a GME office and working with GME was not explicitly required, at least in the early days of the fellowship. As a result, our program was accredited by UCNS and began operation without reference to GME, a fact that came to light in rather stark fashion about 2 years into our operation when we were advised that we were not in compliance with our institution's GME requirements. This deficiency was remedied by yet another round of applications and review, this time by our GME office that ultimately led to their approval of our fellowship. We now operate in a fairly integrated fashion through GME to UCNS to keep everyone updated on the status of the program.

A word about administrative efforts. The administrative work required to start and maintain a program is not insubstantial. We have now been re-accredited twice, not including the initial UCNS application and the subsequent GME review. Both groups have a policy of periodic re-evaluation and UCNS has recently instituted an additional annual review that amounts to a mini-reaccreditation. We have just recently begun to receive some administrative assistance; however, for those contemplating this process, be prepared to devote hours of administrative time in addition to that required to actually run the program.

Applicant recruiting

After training one fellow per year for 2 years we applied for and were accredited to train two fellows per year. Initial interest in our fellowship seemed strong. Inquiries were received year round and the selection process for a given year was completed more than 1.5 years before the start date. We always knew who was scheduled to start training and had ample time to plan. All trainees to date have been neurologists. For some individuals, completion of their prior training coincided with their start date in the fellowship. Others adjusted their postgraduate activities in anticipation of their start date. Those with prior specialty training in stroke or behavioral neurology have been able to provide special insight from these disciplines.

Other programs reported difficulty with this 'open' application process and, in the past two application cycles, the subspecialty has moved to a match process administered through the National Resident Matching Program [7]. This, it was thought, would be more fair to the programs and more familiar and acceptable to candidates. It also shortened the admission process timeframe considerably. The review and interview process begins in late summer, concludes in the fall and results are announced in December for a start date the following July. The last two years have seen a significant reduction in the number of applicants, an experience that is atypical for other programs in the Match. At present the explanation is unclear.

The clinic day

The UCNS mandates that 80% of the fellowship consist of direct patient contact. Thus the outpatient clinic is at the core of the training experience. Clinic weeks are divided into 5 days, ten sessions; each session is 4 h. Each fellow is assigned eight sessions per week of direct patient care, most of that time spent in the Graham Center clinic. Each session has an assigned preceptor. Two sessions, or one day per week is devoted to research and teaching.

In addition to the core clinical experience, each fellow spends one session per week of direct patient care divided between a Boston Children's Hospital pediatric headache experience and at the Fish Center, a women's health center in the Brigham Health system.

Short observerships in orofacial pain medicine and in anesthesia/pain are also included in the clinical experience.

In addition to learning from clinic patients, conversations with preceptors, and case discussions at noon meeting, we present a series of didactic discussions. The curriculum topics are pre-specified and suggested readings

are available. Attending discussants rotate, so that each attending covers a topic every month to 6 weeks.

Ample opportunities exist for fellows to prepare, practice and deliver presentations to a variety of audiences, from a teaching conference to medical students to a grand rounds presentation in the neurology department. Presentations at regional and national meetings are also common. We stress preparation and practice.

Over the course of the fellowship, fellows are expected to complete a guided research project and publish the results. Of necessity these are short and expected to be completed within a 6-month time frame. The goal is to provide familiarity with study design, institutional review board approval, compiling statistical material and writing and submitting a final paper for publication.

All staff and fellows are typically in the Graham Center site on Tuesdays. Noon conference on Tuesdays is a meeting of the entire clinic, and evening headache activities tend to be on Tuesday nights. These include periodic Journal Club, Research Meeting and any outside headache meetings. Fellows are encouraged to participate in the activities of our regional society, the Headache Cooperative of New England, including both the fall meeting in Boston and winter meeting in March at Stowe, Vermont.

A periodic Visiting Scholar Program, administered by Paul Mathew, brings speakers in several times per year for an afternoon and evening of discussion, presentations, article review and socialization.

As of the end of this academic year, 2017, we will have graduated 14 Headache Medicine specialists. The overwhelming majority are practicing headache medicine today, most of them in academic positions and four run headache centers. One, Rebecca Burch, has remained on staff with us. It has been very rewarding to get to know and work with these colleagues. Each has left a mark on the program, helping over time to develop a rich history and tradition.

Graduation ceremonies, often held in Dr. Loder's garden in the late spring, draw faculty, spouses, children and others as we celebrate a year that seems to have passed too quickly.

The future of the Headache Medicine Fellowship—what have we learned?

Some reasons given in support of fellowship training are that it provides the trainee with personal satisfaction and professional recognition, shows commitment to maintenance of the best quality care, and sets trainees on the path of academic advancement [8]. Further, subspecialty training is generally supported by neurology graduates [5].

From our perspective the efforts to build and maintain a subspecialty training program have been more than repaid by the rewarding experience of being involved in the shaping of the early careers of young physicians and of the impact that these efforts are expected to have on the specialty of Headache Medicine and ultimately upon improvements in patient care.

General and program-specific challenges remain. Maintaining any subspecialty career track requires ongoing effort, financial support and growth [5]. The success of any particular subspecialty is not guaranteed. The initial enthusiastic interest in training and certification in some subspecialties may have slowed [8], and how various healthcare issues are decided in the future may in part determine whether some subspecialties survive long term. In Headache Medicine, continued growth of the applicant base is essential. Expanding recruiting efforts beyond the neurology training graduate could be helpful since the discipline of headache should appeal to a wide range of medical, surgical and dental training graduates. Also, reducing any barriers to access to headache fellowships occasioned by the admissions policies should be addressed. One example is setting application dates late in the year prior to training, creating uncertainty and potentially forcing applicants into other fellowships that match earlier. Such a policy may make the Headache Medicine Fellowship less competitive with other subspecialty programs.

Challenges within our program include, first, continued questions about the best methods to finance the training. A switch to an ACGME-based fellowship it is argued would open up the possibility of federal funding of fellows. In our institution, at least, this is not the case since we are already over budgeted on the number of residents/fellows we have compared with the calculated number upon which the federal support is based. Thus, such a switch would not change our financial situation. Next, attempts to reduce or avoid unnecessary administrative tasks and financial burdens on both the program and the applicants should be considered. Lastly, we experience the usual time and space limitations that seem a chronic and constant fact of academic life.

Though the manpower shortages and disparities that exist [9–11] in Headache Medicine cannot be resolved simply through an increase in fellowship training positions, it is nonetheless suspected that the 32 fellowship training programs in Headache Medicine provide incalculable impact beyond simply the number of graduates they produce.

Conclusions

We are proud of our fellowship training program. The extra efforts to develop and maintain the program are balanced by a sense of enrichment of all of us. We believe that the program and its graduates benefit the specialty of Headache Medicine and, as we honor the past contributions of John

Graham, we eagerly await the future contributions of our graduates.

Compliance with ethical standards

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF (2002) Migraine in the United States: epidemiology and patterns of health care use. Neurology 58:885–894
2. Solomon S, Diamond S, Mathew N, Loder E (2008) American headache through the decades: 1950 to 2008. Headache 48(5):671–677. doi:10.1111/j.1526-4610.2008.01120.x
3. Finkel AG (2008) The legitimization of headache medicine. Headache. 48(5):711–713. doi:10.1111/j.1526-4610.2008.01111.x
4. https://www.ucns.org/go/about
5. Vespa PM, Sergay SM, Kohring JH (2011) Subspecialization in neurology: the role of the United Council for Neurologic Subspecialties. Neurology 77(18):1702–1705. doi:10.1212/WNL.0b013e3182364918
6. https://www.ucns.org/globals/axon/assets/3672.pdf
7. https://www.nrmp.org
8. Faulkner LR, Juul D, Pascuzzi RM, Aminoff MJ, Crumrine PK, Dekosky ST, Jozefowicz RF, Massey JM, Pirzada N, Tilton A (2010) Trends in American Board of Psychiatry and Neurology specialties and neurologic subspecialties. Neurology 75(12):1110. doi:10.1212/WNL.0b013e3181f39a41
9. Rizzoli P, Weizenbaum E, Loder T, Friedman D, Loder E (2014) The evolution and geographic distribution of headache medicine fellowship programs and graduates: an observational study. Headache 54(10):1591–1600. doi:10.1111/head.12476
10. Mauser ED, Rosen NL (2014) So many migraines, so few subspecialists: analysis of the geographic location of United Council for Neurologic Subspecialties (UCNS) certified headache subspecialists compared to United States headache demographics. Headache 54(8):1347–1357. doi:10.1111/head.12406
11. Loder S, Sheikh HU, Loder E (2015) The prevalence, burden, and treatment of severe, frequent, and migraine headaches in US minority populations: statistics from National Survey studies. Headache 55(2):214–228. doi:10.1111/head.12506

Neurol Sci (2017) 38 (Suppl 1):S27–S30
DOI 10.1007/s10072-017-2875-z

NEUROBIOLOGY OF HEADACHE

The prokineticin system: an interface between neural inflammation and pain

Silvia Franchi[1] · Paola Sacerdote[1] · Alberto Panerai[1]

Abstract Prokineticins (PK) 1 and 2 belong to a new family of chemokines capable to interact with two different G coupled receptors: Prokineticin receptor (PKR)1 and 2. Both prokineticins and their receptors are widely distributed in different tissues and regulate several biological functions. In particular, a role of the PK system in inflammation and nociception has been established. PKRs are expressed in regions of the nervous system associated with pain and in primary sensitive neurons they colocalize with transient potential receptor vanilloid–TRPV1 providing an anatomical interaction in nociceptor sensitization. Moreover, PKs are strongly upregulated in immune and glial cells and sustain a proinflammatory loop in inflamed tissues. Recent evidences indicate that the block of the PK system represents a promising strategy to contrast inflammation and pain.

Keywords Prokineticins · Neuroinflammation · Pain

Prokineticins

What are they? and why are they becoming popular?

Prokinetincins belong to a family of small peptide discovered about twenty years ago in the skin secretions of *Bombina Variegata* frog, from which the alternative denomination Bv8 derives [1], and in the venum of *Black Mamba* snake and were initially described for their ability to induce gastrointestinal motility in rodents. Soon the mammal homologs of Bv8: the prokineticin 1 (PK1 or endocrine gland derived vascular endothelial growth factor, EG-VEGF) and PK2 (mammalian Bv8) were also described. All members of the PK family weigh approximately 8 kDa and have a structural conserved motif characterized by an N-terminal AVITGA sequence, a Trp residue in position 24 and the presence of five disulfide bridges. These peptides activate two closely related G-protein coupled receptors: prokineticin receptor 1 and 2 (PKR1 and PKR2) that belong to the family of neuropeptide Y receptor and have an amino acid identity of 85%.

PKs and their receptors are widely distributed in many human tissues such as ovary, testis, adrenal gland, placenta, uterus, brain, intestinal tract, heart, bone marrow and peripheral blood. This wide and strategic presence in the body tissues allows them to be involved in many biological activities and to coordinate complex behaviors like feeding, drinking, circadian rhythm, neurogenesis, angiogenesis, haematopoiesis [2–4] activating multiple intracellular signals such as mitogen activated protein kinase (MAPK), AKT and STAT3. Moreover, the presence of PK members (PK and PKRs) in immune cells and in the main stations involved in pain transmission makes PK important players in inflammation and pain pathophysiology.

Prokineticins as regulators of inflammation

A parallelism between the structure, size, signaling and biological activities of prokineticins and chemokine superfamily was soon suggested [5] and PKs are now recognized in all respects as chemokines. Lymphoid organs, circulating leukocytes and hematopoietic cells, synoviocytes and dendritic cells constitutively express

✉ Alberto Panerai
alberto.panerai@unimi.it

[1] Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi Milano, Milan, Italy

moderate levels of prokineticins [6, 7] and their levels are increased in inflamed tissues [7].

We demonstrated that the administration of Bv8 (a valuable research tool to study PK system) in mice induced a proinflammatory phenotype stimulating macrophage chemotaxis and proinflammatory cytokine release [8] and skewing a Th1/Th2 balance towards a Th1 response [9]. A similar effect was also described for human monocytes. Our studies demonstrated that these effects are mediated by PKR1 receptor with the involvement of a Gq protein [8]. Moreover, the literature suggests that multiple pathways are involved in PK signaling and PKRs can also couple to Gi and Gs proteins [6, 10].

In the last years, several papers described in animals and humans a direct correlation between alterations in PK system and the development of different inflammatory and autoimmune diseases suggesting that the PK antagonism could ameliorate the pathological condition. The involvement of PK system was described in a mice model of arthritis (collagen-induced arthritis, CIA) where the expression levels of PK2 and PKR2 were found to be elevated in the CIA joints due to the presence of macrophage cells in the synovial membrane and these levels correlated with the arthritis severity. The administration of a prokineticin receptor antagonist decreased or suppressed the severity of arthritis by inhibiting PK2-PKR2 signaling in macrophages and reducing the levels of proinflammatory cytokines [11].

Pedotti' group recently demonstrated a role of the PK system in multiple sclerosis, in an animal model (experimental autoimmune encephalomyelitis, EAE) and patients and showed how the use of a PKR antagonist could inhibit proinflammatory T cell responses and reduce neurologic signs and central nervous system damage in mice [12]. The role of PK was also suggested in the development of Psoriasis, a chronic systemic inflammatory and autoimmune skin disease [13]. The author demonstrated a positive PK2/IL-1 proinflammatory loop which sustained chronic inflammation and keratinocyte hyperproliferation. The knock-down of PK2 improved the inflammatory condition while PK2 overexpression aggravated psoriasis [13].

These results suggest that prokineticins appear strongly upregulated in inflammatory cells and sustain a positive inflammatory loop at the basis of the development of pathological condition.

Prokineticins in nociceptive pain

The first evidences of a pronociceptive role of PK were derived from the observation that systemic injection of Bv8 and PK2 in rodents induces hyperalgesia to mechanical and thermal stimuli [1, 14] by activating PKRs receptors localized in the main stations of pain pathway. Both PKR1 and PKR2 are expressed in the superficial layers of the spinal cord, dorsal root ganglia (DRG) and peripheral terminal of nociceptors. The release of the neuropeptides like calcitonine gene related peptide (CGRP) and substance P in the spinal cord [1, 15] together with TRPV1 sensitization in primary dorsal root ganglia (DRG) neurons [16] was primarily involved in the development of hyperalgesia. Experiments of co-localization indicated that the majority of PKR1-positive DRG neurons also express TRPV1 and a reduced response to Bv8 is observed in TRPV1 deficient mice. Moreover, 50% of the Bv8-responding DRG neurons also express neuromediators involved in pain processing such as substance P and CGRP and release them after Bv8/PK exposure.

It was suggested that PKs are also able to modulate central pain mechanism. Maione and collaborators demonstrated that the microinjection of Bv8/PK into the periaqueductal grey (PAG) exerted a pronociceptive effect increasing the intrinsic GABAergic tone which, in turn, was responsible for the inhibition of PAG antinociceptive output neurons impinging on rostro ventromedial medulla (RVM) neurons [17].

Further studies conducted in mice lacking pkr1 or pkr2 or pk2 genes demonstrated a direct role of the prokineticin system in pain perception in fact all these genotypes were characterized by higher thermal, mechanical and tactile pain threshold in comparison to normal wild type mice [18, 19].

Prokineticines in chronic pain (inflammatory and neuropathic pain)

It has recently emerged that pathological pain development and maintenance are not confined only to changes in the activity of neuronal systems, but involve interactions between neurons, inflammatory immune cells, glial cells, as well as a wide cascade of pro- and anti-inflammatory cytokines [20]. In this view, PKs can be considered important modulators capable to interfere both with peripheral and central pain mechanism. Consistently in the last years, a role of the PK system was suggested in the development and maintenance of inflammatory and neuropathic pain. Negri [21] demonstrated in an animal model of chronic inflammation, Complete Freund Adjuvant (CFA), that inflammation was highly correlated with an overexpression of PK2 in the granulocytes that infiltrate the inflamed tissue and the up-regulation was responsible for inflammation-associated hyperalgesia [21]. The authors showed how the hyperalgesia induced by CFA was abolished by PC1, a non-peptidic PKR1 preferred antagonist.

Regarding neuropathic pain (NP), the involvement of prokineticins was investigated in different experimental animal models: NP derived from an injury of sciatic nerve:

chronic constriction injury model (CCI) [22] and spared nerve injury [23], diabetes [24] and cancer-induced NP [25]. In all these models, the presence of aberrant pain well correlates with an increase of the levels of PK2 in the spinal cord, especially in activated astrocytes [22–24]. The treatment with a PK system antagonist like PC1 or with PK neutralizing antibody [25] was able to counteract thermal hyperalgesia and allodynia, reduce the injury-induced overexpression of PK2 and restore the physiological levels of proinflammatory and anti-inflammatory cytokines both in periphery and spinal cord.

Conclusions

The above presented evidences suggest that PK system plays a central role in the development and maintenance of inflammation and acute and chronic pain and indicate that the antagonism of the PKRs could represent a new pharmacological strategy to control pathological pain, acting at different levels. The PKR block may contrast the pronociceptive role of endogenous PK, reduce immune cells infiltration and neuroinflammation in the main pain stations, and prevent the release of CGRP and TRPV1 sensitization.

Perspective: what about a possible role of prokineticins in migraine?

Abundant evidences accumulated from animal and human have demonstrated that the activation of meningeal afferents, neuropeptide release, and neurogenic inflammation plays a pivotal role in the generation of pain in migraine headache. CGRP is no doubt a crucial player and upon stimulation, it is released not only at the nerve endings, where it mediates vasodilation via smooth muscle cell receptors and plasma extravasation [26] but also from the neuronal cell bodies in the trigeminal ganglia. It is now recognized that CGRP represents a regulator of the intraganglionic crosstalk between neurons and glial cells prompting an inflammatory cascade that could lead to sensitization throughout the release of proinflammatory cytokines and chemokines which in turn activate TRPV1 or purinergic P2X receptors. Moreover, recent evidences suggested that also in migraine a significant neuronal, glia, immune interaction exists and an involvement of proinflammatory cytokines in the pathophysiology of primary headaches is probable. As previously described, prokineticins induce CGRP release in the spinal cord and DRG and recent findings demonstrated that also the trigeminal ganglia can be a target for prokineticins. In fact the application of Bv8/PK to trigeminal ganglia significantly elevated their heat-induced CGRP release and immunohistochemistry experiments revealed a co-localization of PK2 and CGRP in the same trigeminal neurons [27]. It was also suggested that PK2 suppressed GABA activated current in trigeminal ganglion neurons [28]. All these evidences support the idea of the presence of prokineticin receptors in the vascular trigeminal system. In the same way, we cannot exclude the possibility that PKs may also directly sensitize meningeal nociceptors also by inducing proinflammatory cytokines release. Finally, we can speculate that PK may also sustain a central nervous system origin of migraine acting on PAG-RVM circuit [29].

Future studies aimed at identifying novel targets, such as PK system, in migraine will be of great importance, also considering that the treatment of this condition is still far from being satisfactory.

Compliance with ethical standards

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Mollay C, Wechselberger C, Mignogna G, Negri L, Melchiorri P, Barra D, Kreil G (1999) Bv8, a small protein from frog skin and its homologue from snake venom induce hyperalgesia in rats. Eur J Pharmacol 374(2):189–196
2. Negri L, Lattanzi R, Giannini E, De Felice M, Colucci A, Melchiorri P (2004) Bv8, the amphibian homologue of the mammalian prokineticins, modulates ingestive behaviour in rats. Br J Pharmacol 142(1):181–191
3. Cheng MY, Bullock CM, Li C, Lee AG, Bermak JC, Belluzzi J, Weaver DR, Leslie FM, Zhou QY (2002) Prokineticin 2 transmits the behavioural circadian rhythm of the suprachiasmatic nucleus. Nature 417(6887):405–410
4. Ferrara N, Frantz G, LeCouter J, Dillard-Telm L, Pham T, Draksharapu A, Giordano T, Peale F (2003) Differential expression of the angiogenic factor genes vascular endothelial growth factor (VEGF) and endocrine gland-derived VEGF in normal and polycystic human ovaries. Am J Pathol 162(6):1881–1893
5. Monnier J, Quillien V, Piquet-Pellorce C, Leberre C, Preisser L, Gascan H, Samson M (2008) Prokineticin 1 induces CCL4, CXCL1 and CXCL8 in human monocytes but not in macrophages and dendritic cells. Eur Cytokine Netw 19(4):166–175
6. LeCouter J, Zlot C, Tejada M, Peale F, Ferrara N (2004) Bv8 and endocrine gland-derived vascular endothelial growth factor stimulate hematopoiesis and hematopoietic cell mobilization. Proc Natl Acad Sci USA 101(48):16813–16818
7. Dorsch M, Qiu Y, Soler D, Frank N, Duong T, Goodearl A, O'Neil S, Lora J, Fraser CC (2005) PK1/EG-VEGF induces monocyte differentiation and activation. J Leukoc Biol 78(2):426–434
8. Martucci C, Franchi S, Giannini E, Tian H, Melchiorri P, Negri L, Sacerdote P (2006) Bv8, the amphibian homologue of the mammalian prokineticins, induces a proinflammatory phenotype of mouse macrophages. Br J Pharmacol 147(2):225–234
9. Franchi S, Giannini E, Lattuada D, Lattanzi R, Tian H, Melchiorri P, Negri L, Panerai AE, Sacerdote P (2008) The prokineticin

receptor agonist Bv8 decreases IL-10 and IL-4 production in mice splenocytes by activating prokineticin receptor-1. BMC Immunol 9:60
10. Lin DC, Bullock CM, Ehlert FJ, Chen JL, Tian H, Zhou QY (2002) Identification and molecular characterization of two closely related G protein-coupled receptors activated by prokineticins/endocrine gland vascular endothelial growth factor. J Biol Chem 277(22):19276–19280
11. Ito H, Noda K, Yoshida K, Otani K, Yoshiga M, Oto Y, Saito S, Kurosaka D (2016) Prokineticin 2 antagonist, PKRA7 suppresses arthritis in mice with collagen-induced arthritis. BMC Musculoskelet Disord 17:387
12. Abou-Hamdan M, Costanza M, Fontana E, Di Dario M, Musio S, Congiu C, Onnis V, Lattanzi R, Radaelli M, Martinelli V, Salvadori S, Negri L, Poliani PL, Farina C, Balboni G, Steinman L, Pedotti R (2015) Critical role for prokineticin 2 in CNS autoimmunity. Neurol Neuroimmunol Neuroinflamm 2(3):e95
13. He X, Shen C, Lu Q, Li J, Wei Y, He L, Bai R, Zheng J, Luan N, Zhang Z, Rong M, Lai R (2016) Prokineticin 2 plays a pivotal role in psoriasis. EBioMedicine 13:248–261
14. Negri L, Lattanzi R, Giannini E, Metere A, Colucci M, Barra D, Kreil G, Melchiorri P (2002) Nociceptive sensitization by the secreted protein Bv8. Br J Pharmacol 137(8):1147–1154
15. De Felice M, Melchiorri P, Ossipov MH, Vanderah TW, Porreca F, Negri L (2012) Mechanisms of Bv8-induced biphasic hyperalgesia: increased excitatory transmitter release and expression. Neurosci Lett 521(1):40–45
16. Vellani V, Colucci M, Lattanzi R, Giannini E, Negri L, Melchiorri P, McNaughton PA (2006) Sensitization of transient receptor potential vanilloid 1 by the prokineticin receptor agonist Bv8. J Neurosci 26(19):5109–5116
17. de Novellis V, Negri L, Lattanzi R, Rossi F, Palazzo E, Marabese I, Giannini E, Vita D, Melchiorri P, Maione S (2007) The prokineticin receptor agonist Bv8 increases GABA release in the periaqueductal grey and modifies RVM cell activities and thermoceptive reflexes in the rat. Eur J Neurosci 26(11):3068–3078
18. Negri L, Lattanzi R, Giannini E, Colucci M, Margheriti F, Melchiorri P, Vellani V, Tian H, De Felice M, Porreca F (2006) Impaired nociception and inflammatory pain sensation in mice lacking the prokineticin receptor PKR1: focus on interaction between PKR1 and the capsaicin receptor TRPV1 in pain behavior. J Neurosci 26(25):6716–6727
19. Hu WP, Zhang C, Li JD, Luo ZD, Amadesi S, Bunnett N, Zhou QY (2006) Impaired pain sensation in mice lacking prokineticin 2. Mol Pain 2:35
20. Austin PJ, Moalem-Taylor G (2010) The neuro-immune balance in neuropathic pain: involvement of inflammatory immune cells, immune-like glial cells and cytokines. J Neuroimmunol 229(1–2):26–50
21. Giannini E, Lattanzi R, Nicotra A, Campese AF, Grazioli P, Screpanti I, Balboni G, Salvadori S, Sacerdote P, Negri L (2009) The chemokine Bv8/prokineticin 2 is up-regulated in inflammatory granulocytes and modulates inflammatory pain. Proc Natl Acad Sci USA 106(34):14646–14651
22. Maftei D, Marconi V, Florenzano F, Giancotti LA, Castelli M, Moretti S, Borsani E, Rodella LF, Balboni G, Luongo L, Maione S, Sacerdote P, Negri L, Lattanzi R (2014) Controlling the activation of the Bv8/prokineticin system reduces neuroinflammation and abolishes thermal and tactile hyperalgesia in neuropathic animals. Br J Pharmacol 171(21):4850–4865
23. Guida F, Lattanzi R, Boccella S, Maftei D, Romano R, Marconi V, Balboni G, Salvadori S, Scafuro MA, de Novellis V, Negri L, Maione S, Luongo L (2015) PC1, a non-peptide PKR1-preferring antagonist, reduces pain behavior and spinal neuronal sensitization in neuropathic mice. Pharmacol Res 91:36–46
24. Castelli M, Amodeo G, Negri L, Lattanzi R, Maftei D, Gotti C, Pistillo F, Onnis V, Congu C, Panerai AE, Sacerdote P, Franchi S (2016) Antagonism of the prokineticin system prevents and reverses allodynia and inflammation in a mouse model of diabetes. PLoS One 11(1):e0146259
25. Hang LH, Luo H, Li SN, Shu WW, Chen Z, Chen YF, Yuan JF, Shi LL, Shao DH (2015) Involvement of spinal Bv8/prokineticin 2 in a rat model of cancer-induced bone pain. Basic Clin Pharmacol Toxicol 117(3):180–185
26. Schlereth T, Schukraft J, Krämer-Best HH, Geber C, Ackermann T, Birklein F (2016) Interaction of calcitonin gene related peptide (CGRP) and substance P (SP) in human skin. Neuropeptides 59:57–62
27. Hoffmann T, Negri L, Maftei D, Lattanzi R, Reeh PW (2016) The prokineticin Bv8 sensitizes cutaneous terminals of female mice to heat. Eur J Pain 20(8):1326–1334
28. Xiong YC, Li XM, Wang XJ, Liu YQ, Qiu F, Wu D, Gan YB, Wang BH, Hu WP (2010) Prokineticin 2 suppresses GABA-activated current in rat primary sensory neurons. Neuropharmacology 59(7–8):589–594
29. Panerai AE (2013) Is migraine a disorder of the central nervous system? Neurol Sci 34(Suppl 1):S33–S35

Neurol Sci (2017) 38 (Suppl 1):S31–S35
DOI 10.1007/s10072-017-2907-8

NEUROBIOLOGY OF HEADACHE

The role of anti-CGRP antibodies in the pathophysiology of primary headaches

Piero Barbanti[1] · Cinzia Aurilia[1] · Luisa Fofi[1] · Gabriella Egeo[1] · Patrizia Ferroni[2]

Abstract Calcitonin gene-related peptide (CGRP), a potent vasodilator and pain-signaling neuropeptide, is a validated therapeutic target for migraine and cluster headache. Four anti-CGRP monoclonal antibodies (mAbs) have been developed, representing the first specific, mechanism-based, migraine prophylactic treatment. CGRP mAbs demonstrated good efficacy coupled to excellent tolerability and safety in 5 phase II clinical trials. Notably, CGRP mAbs induced complete migraine remission in a patients' subset. To date, more than 20 phase III trials using CGRP mAbs for of episodic and chronic migraine and cluster headache prevention are ongoing. Future investigations will shed light on migraine endophenotypes predictive of good CGRP mAbs responsiveness and provide answers on their long-term cardiovascular safety.

Keywords CGRP · Monoclonal CGRP antibodies · Migraine · Headache · Treatment

Introduction

The calcitonin gene-related peptide (CGRP), a neuropeptide crucially involved in the neurobiology of neurovascular headaches, is currently considered the best treatment target for migraine (M) and cluster headache (CH) [1]. The development of monoclonal antibodies against CGRP or its receptor (CGRP mAbs) is paving the way to a new era for M and CH prevention, giving rise to effective disease-specific prophylactic treatments characterized by improved safety, tolerability, and therapeutic adherence [2, 3].

In this review, we will outline how CGRP intervenes in M and CH pathophysiology, detailing recent CGRP mAbs phase II clinical trials.

CGRP

Synthesis

CGRP is a 37 amino-acid neuropeptide with an N-terminal disulfide bond and amidated C terminus, predominantly localized to C and Aδ sensory fibers. CGRP exists in two isoforms, αCGRP (also known as CGRP I) and βCGRP (also known as CGRP II) that are produced by two different genes, both located on chromosome 11 [4, 5]. αCGRP is synthesized by alternative splicing of the CALC I gene and is primarily expressed in the nervous system, while βCGRP is encoded by the CALC II gene and is prevalent in the enteric neurons. The two isoforms are characterized by a high degree of homology (>90%), differing by three amino acids only. In addition to α and βCGRP, calcitonin, adrenomedullin, adrenomedullin 2, and amylin also belong to the CGRP gene family.

Stored in dense-core vesicles within sensory nerve terminals, CGRP is released via calcium-dependent exocytosis by means of SNARE (soluble N-ethylmalemide-sensitive factor attachment protein receptor) proteins [4, 5]. Experimental studies further demonstrated that CGRP release may be induced by activation of transient receptor

✉ Piero Barbanti
piero.barbanti@sanraffaele.it

[1] Headache and Pain Unit, Department of Neurological, Motor and Sensorial Sciences, IRCCS San Raffaele Pisana, Via della Pisana 235, 00163 Rome, Italy

[2] Department of Human Sciences and Quality of Life Promotion, San Raffaele Roma Open University, Rome, Italy

potential non-selective ion channels (TRPV1 and TRPA1) located in dural nociceptive afferents [6].

Receptors

The CGRP receptor is a G protein-coupled receptor that consists of 3 parts [4]:

- *Calcitonin-like receptor* (*CLR*), a 461 amino-acid, 7-transmembrane domain receptor belonging to class B "secretin-like" family of G protein-coupled receptors.
- *Receptor activity-modifying protein 1* (*RAMP1*), which interacts with CLR to form a heterodimer, representing the true CGRP receptor.
- *Receptor component protein* (*RCP*), a small membrane-associated protein needed for optimal CGRP receptor functioning and signal transmission.

Transient CGRP receptor stimulation is characterized by its internalization followed by prompt recycling back to plasma membrane, whereas chronic stimulation induces lysosome degradation of the internalized receptor (desensitization). CGRP acts not only on CGRP receptors but also on calcitonin, amylin, and adrenomedullin receptors. Combination of calcitonin receptor with RAMP1, RAMP2, and RAMP3 gives rise to amylin 1 (AMY1), AMY2, and AMY3 receptors, whereas combination of CLR with RAMP2 and RAMP3 originates adrenomedullin 1 (AM1) and AM2 receptor [5].

Physiological functions

Nervous system

CGRP-containing fibers are widely distributed throughout the brain and are believed to play a role in olfaction, audition, vision, autonomic and motor function, learning, feeding, behavior, and, above all, nociception. CGRP is primarily released from sensory nerves and is implicated in neurovascular pain [5].

Cardiovascular system

CGRP is the most potent microvascular dilating agent currently known with a potency which is tenfold higher than prostaglandins and up to 100-fold higher than other vasodilators [4]. CGRP induces vasodilation either directly, acting on vascular smooth muscles, or indirectly, stimulating nitric oxide formation. Accordingly, it has been hypothesized that CGRP may contribute to cardiovascular system protection [5].

Other systems

CGRP is likely to facilitate tissue repair and influence metabolic health and aging [5, 7]. As such, it has been involved in various pathological conditions such as arthritis, diabetes, and obesity [4].

CGRP in primary headaches

CGRP and experimental M models

CGRP seems involved in the pathophysiology of neurovascular headaches at both central and peripheral levels [1]. CGRP, in fact, is highly expressed in trigeminal neurons (especially in unmyelinated C and small myelinated Aδ fibers) where is often co-localized with other neuropeptides (e.g., substance P). CGRP-positive trigeminal nociceptive fibers originating from the trigeminal ganglion form a rich plexus on intracranial blood vessels and centrally project to trigemino-cervical complex neurons in a somatotopic fashion [7]. When released peripherally from activated trigeminal nociceptive endings, CGRP induces edema, increases blood flow, and recruits inflammatory cells, promoting neurogenic inflammation and leading to M pain. At synapses in the trigemino-cervical complex, CGRP transmits nociceptive inputs centrally, via the brainstem, to thalamus and somatosensory cortex, generating hyperalgesia [1, 2, 5, 8].

CGRP is also capable of exerting neuromodulatory effects on central pain circuitry, as it promotes glutamatergic neurotransmission by increasing discharge frequency of wide-dynamic range neurons in the spinal cord [9], contributes to cholinergic fine-tuning nicotinic synaptic transmission [10], and increases neuronal trafficking of P2X purinoceptor 3 involved in chronic pain [11]. As a consequence, during M, CGRP could sensitize neuronal circuits decreasing the filtering of sensory inputs, leading not only to pain but also to allodynia, nausea, photophobia, and phonophobia [12].

CGRP levels in M and CH

CGRP levels are markedly increased into external jugular venous blood ipsilateral to pain during the headache phase of M with or without aura [13]. Serum and saliva CGRP levels are elevated during spontaneous and nitric oxide-induced M attacks [14, 15] and also interictally in patients with chronic M (CM) [16]. During spontaneous CH attacks, CGRP blood levels are increased in the external jugular vein ipsilateral to pain and reduced by both oxygen and subcutaneous (sc) sumatriptan [17]. Furthermore,

patients suffering from episodic CH show higher jugular vein CGRP plasma levels interictally during the bout compared to the remission period due to ongoing hyperactivity of the trigeminal nociceptive pathway [18].

CGRP as a headache trigger

IV administration of human αCGRP (2 μg/ml for 20 min) induces M-like disorders and M without aura headache in migraineurs without aura [19], triggers (1.5 μg/ml for 20 min) experimentally induced M attack in 57% of patients and typical aura symptoms in 28% in migraineurs with aura [20], but does not induce any M attacks in patient affected by familial hemiplegic M [21]. To date, no CGRP provocation test has been performed in CH.

CGRP targeting in primary headache treatment

From the aforementioned findings, it emerges that CGRP, or its receptor, is a well-validated therapeutic target for M and CH. Current CGRP-targeted treatments include CGRP receptor antagonists and CGRP mAbs [3].

Small molecule CGRP receptor antagonists

These compounds, called *gepants*, have demonstrated to be effective in M treatment in phase II and III trials. However, the development of 4 out of 7 molecules has been stopped due to safety concerns, formulation issues, or unknown reasons.

- *Telcagepant* (*MK0974*), it was demonstrated to be more effective than placebo for 2-h pain freedom (2-hPF) ($p < 0.001$) and 2-h pain relief (2-hPR) ($p < 0.001$), but inferior to triptans for 2-hPF ($p < 0.001$) and equal to triptans for 2-hPR ($p = 0.061$). Telcagepant induced more adverse events than placebo, but less than triptans. Its clinical development was stopped due to liver toxicity [22].
- *Olcegepant* (*BIBN4096*) at the dose of 2.5 mg (iv), olcegepant was superior to placebo for 2-hPR (66 vs 27%) and for most secondary endpoints, with minimal adverse events. Nonetheless, the drug was discontinued due to its poor oral bioavailability [23].
- *MK-3207* at the dose of 200 mg, it was three times more effective than placebo for 2-hPF (36.2 vs 9.8%; $p < 0.001$). Unfortunately, the drug was discontinued for liver toxicity concerns [24].
- *BI 44370 TA* at a dose of 400 mg, its 2-hPF rate was superior to that of placebo (27.4 vs 8.6%; $p = 0.0016$) and similar to that achieved with eletriptan 40 mg (34.8%). Tolerability was excellent. Unexpectedly, no further trials have followed [25].
- *BMS-846372,* it demonstrated superiority in 2-hPF over placebo (15.3%) at the doses of 75 mg (31.4%, $p = 0.002$), 150 mg (32.9%, $p < 0.001$), and 300 mg (29.7%, $p = 0.002$), with an efficacy similar to sumatriptan (35%, $p < 0.001$) and an excellent tolerability profile [26].
- *Ubrogepant* (*MK-1602*) at the dose of 100 mg, it was superior to placebo in achieving 2-hPF (25.5 vs 8.9%, $p = 0.003$)—but not 2-hPR—with a similar incidence of adverse events [27]. Two phase III trials are ongoing (ClinicalTrials.gov identifiers: NCT02828020, NCT02867709).
- *Atogepant* (*AGN241689/MK8301*) a phase II/III RCT study aimed to evaluate its efficacy, safety, and tolerability at multiple dosing regimens in episodic M (EM) prevention is underway (ClinicalTrials.gov identifier: NCT02848326).

CGRP mAbs

CGRP mAbs are believed to target smooth muscle cells on blood vessels and neurons and glial cells located outside the blood–brain barrier, probably in the trigeminal ganglion and brainstem paraventicular structures [2]. Four mAbs blocking CGRP or its receptor are currently being developed for M prevention.

- *Eptinezumab* (ALD-403, humanized CGRP mAb). In a phase II trial for prevention of frequent EM (5–14 days/month) performed on 163 patients, a single dose of eptinezumab (1000 mg iv) induced a significant M days reduction from months 1–2 compared to placebo (5.6 vs 4.6; $p = 0.0306$).
  At the same timepoint, a 50% M day reduction was achieved by 75% of patients receiving eptinazumab, whereas 75 and 100% M day reduction was achieved by 44 and 16% of patients, respectively. Eptinezumab was safe and well tolerated and no differences emerged in adverse events compared to placebo [28]. Four clinical trials (1 phase II and 2 phase III in CM; 1 phase III in frequent EM) are ongoing (ClinicalTrials.gov identifiers: NCT02275117, NCT02985398, NCT02974153, and NCT02559895).
- *Galcanezumab* (LY-2951742, humanized CGRP mAb). In a phase II proof-of-concept study, 218 patients with EM (4–14 days/month) were randomly treated with galcanezumab 150 mg or placebo given sc once every 2 weeks for 12 weeks. Patient treated with galcanezumab showed a greater reduction in M days from baseline to week 12 compared to placebo (−4.2 vs −3.0 days; $p = 0.003$). Adverse events occurred in 72% of patients receiving galcanezumab and in 67% of those taking placebo [29]. Ten clinical trials are ongoing: 2 phase II and 3 phase III in EM, 1 phase

III in EM or CM, 1 phase III in CM, 1 phase III in chronic CH, 1 phase III in episodic CH, and 1 phase III in episodic or chronic CH (ClinicalTrials.gov identifiers: NCT02163993, NCT02959177, NCT02614261, NCT02614183, NCT02614196, NCT02614287, NCT02959190, NCT02438826, NCT02397473, and NCT02797951).

- *Erenumab* (AMG-334, fully human mAb targeting CGRP receptor). This antibody has been tested for the prevention of EM (4–14 days/month) in a phase II trial. Patients ($n = 483$) were assigned to monthly sc placebo or erenumab at three different doses (7, 21, 70 mg). At week 12, patients treated with erenumab 70 mg (but not those taking lower doses) showed a greater reduction in monthly M days from baseline compared to placebo (-3.4 vs -2.3 days; $p = 0.021$). Adverse events frequency was the same (54%) in the different groups [30]. Three phase II clinical trials (2 in CM, 1 in EM) and 2 phase III trials in EM are underway (ClinicalTrials.gov identifier: NCT02174861, NCT02066415, NCT02456740, and NCT02630459).
- *Fremanezumab* (TEV-48125, fully humanized CGRP mAb). A randomised, double-blind, double-dummy, placebo-controlled study designed to compare safety, tolerability, and efficacy of two doses of fremanezumab (675/225 mg and 900 mg, sc once every 28 days for 3 months) versus placebo in 264 patients with CM showed that during the third treatment cycle (weeks 9–12), the mean change from baseline in the number of headache hours was significantly larger in the 675/225 mg (-59.84; $p = 0.0386$) and in the 900 mg groups (-67.51; $p = 0.0057$) compared to placebo (-37.10). The drug was safe and well tolerated: adverse events were reported by 40% of patients on placebo, 53% on fremanezumab 675/225 mg, and 47% on fremanezumab 900 mg [31].

  Fremanezumab was also studied in the prevention of frequent EM (8–14 migraine days/month) in a multicentre, randomised, double-blind, placebo-controlled phase II study where 297 patients were randomly assigned to three 28 day treatment cycles of sc fremanezumab 225 mg, fremanezumab 675 mg, or placebo. The least square mean difference in the reduction of M days (primary endopoint) between the placebo and fremanezumab was -2.81 days for the 225 mg group ($p < 0.0001$) and -2.64 days for the 675 mg group ($p < 0.0001$). Adverse events were equally distributed in the different treatment groups [32]. Five phase III clinical trials are ongoing: 1 on EM and CM, 1 on EM, 1 on CM, 1 on episodic CH, and 1 on chronic CH (ClinicalTrials.gov identifiers: NCT02638103, NCT02629861, NCT02621931, NCT02945046, and NCT02964338).

Conclusions

Blocking CGRP or its receptor with mAbs represents a novel, promising, disease-specific strategy for M (and possibly CH) prevention. Five phase II clinical trials with CGRP mAbs in M prevention enrolling 1425 migraineurs have been published so far: 1 focused on CM, 3 on EM, and 1 on high-frequency EM. In all studies, CGRP mAbs met the primary endpoints, being significantly more effective than placebo in reducing M days or hours from baseline to observation period and revealing 50% responder rates ranging from 53 to 75% (placebo 28–54%). Tolerability and safety were excellent. Notably, CGRP mAbs induced complete M remission in some patients: this is of extreme interest for future tailored treatments and prompts for a more detailed characterization of M endophenotypes in next trials, as individuals with unilateral pain, for example—especially those with associated unilateral cranial autonomic symptoms—are more responsive than others to trigeminal-targeted treatments [33]. Similarly, the availability of dedicated headache biobanks could contribute to shed light on the different CGRP mAbs responsiveness by correlating it to specific M biotypes [34].

Twenty-three phase II/III clinical trials on CGRP mAbs in episodic and chronic M and CH are now underway. Answers on long-term cardiovascular safety are awaited from future investigations, as CGRP mAbs might theoretically increase the risk of hypertension and transformation of transient mild into full-blown brain or myocardial infarction, especially in women [35]. Yet, available data support the hypothesis that CGRP mAbs may provide a valuable option to relieve the burden of episodic or chronic migraine.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Edvinsson L (2015) The journey to establish CGRP as a migraine target: a retrospective view. Headache 55(9):1249–1255
2. Edvinsson L (2015) CGRP receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. Br J Clin Pharmacol 80(2):193–199
3. Schuster NM, Rapoport AM (2016) New strategies for the treatment and prevention of primary headache disorders. Nat Rev Neurol 12(11):635–650
4. Russell FA, King R, Smillie SJ et al (2014) Calcitonin gene-related peptide: physiology and pathophysiology. Physiol Rev 94(4):1099–1142
5. van Rossum D, Hanisch UK, Quirion R (1997) Neuroanatomical localization, pharmacological characterization and functions of CGRP, related peptides and their receptors. Neurosci Biobehav Rev 21(5):649–678

6. Dussor G, Yan J, Xie JY, Ossipov MH et al (2014) Targeting TRP channels for novel migraine therapeutics. ACS Chem Neurosci 5(11):1085–1096
7. Riera C, Huising MO, Follett P et al (2014) TRPV1 pain receptors regulate longevity and metabolism by neuropeptide signaling. Cell 157(5):1023–1036
8. Edvinsson L, Fredholm BB, Hamel E (1985) Perivascular peptides relax cerebral arteries concomitant with stimulation of cyclic adenosine monophosphate accumulation of release of an endothelium derived relaxing factor in the cat. Neurosci Lett 58:213–217
9. Yu Y, Lundeberg T, Yu LC (2002) Role of calcitonin gene-related peptide and its antagonist on the evoked discharge frequency of wide dynamic range neurons in the dorsal horn of the spinal cord in rats. Regul Pept 103:23–27
10. Di Angelantonio S, Giniatullin R, Costa V (2003) Modulation of neuronal nicotinic receptor function by the neuropeptides CGRP and substance P on autonomic nerve cells. Br J Pharmacol 139:1061–1075
11. Giniatullin R, Nistri A, Fabbretti E (2008) Molecular mechanisms of sensitization of pain-transducing P2X3 receptors by the migraine mediators CGRP and NGF. Mol Neurobiol 37:83–90
12. Ho TW, Edvinsson L, Goadsby PJ (2010) CGRP and its receptors provide new insights into migraine pathophysiology. Nat Rev Neurol 6(10):573–582
13. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 28(2):183–187
14. Bellamy JL, Cady RK, Durham PL (2006) Salivary levels of CGRP and VIP in rhinosinusitis and migraine patients. Headache 46(1):24–33
15. Tfelt-Hansen P, Le H (2009) Calcitonin gene-related peptide in blood: is it increased in the external jugular vein during migraine and cluster headache? A review. J Headache Pain 10:137–143
16. Cernuda-Morollón E, Larrosa D, Ramón C et al (2013) Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. Neurology 81:1191–1196
17. Goadsby PJ, Edvinsson L (1994) Human in vivo evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attacks therapies. Brain 117(Pt 3):427–434
18. Neeb L, Anders L, Euskirchen P et al (2015) Corticosteroids alter CGRP and melatonin release in cluster headache episodes. Cephalalgia 35(4):317–326
19. Lassen LH, Haderslev PA, Jacobsen VB et al (2002) CGRP may play a causative role in migraine. Cephalalgia 22(1):54–61
20. Hansen JM, Hauge AW, Olesen J, Ashina M (2010) Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia 30(10):1179–1186
21. Hansen JM, Thomsen LL, Olesen J et al (2011) Calcitonin gene-related peptide does not cause migraine attacks in patients with familial hemiplegic migraine. Headache 51:544–553
22. Cui XP, Ye JX, Lin H et al (2015) Efficacy, safety, and tolerability of telcagepant in the treatment of acute migraine: a meta-analysis. Pain Pract 15(2):124–131
23. Olesen J, Diener HC, Husstedt IW et al (2004) Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. N Engl J Med 350(11):1104–1110
24. Hewitt D, Aurora SK, Dodick DW et al (2011) Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine. Cephalalgia 31(6):712–722
25. Diener HC, Barbanti P, Dahlöf C et al (2011) BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. Cephalalgia 31(5):573–584
26. Marcus R, Goadsby PJ, Dodick D et al (2014) BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia 34(2):114–125
27. Voss T, Lipton RB, Dodick DW et al (2016) A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. Cephalalgia 36(9):887–898
28. Dodick DW, Goadsby PJ, Silberstein SD et al (2014) Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol 13(11):1100–1107
29. Dodick DW, Goadsby PJ, Spierings EL et al (2014) Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol 13(9):885–892
30. Sun H, Dodick DW, Silberstein S et al (2016) Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol 15(4):382–390
31. Bigal ME, Edvinsson L, Rapoport AM et al (2015) Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol 14(11):1091–1100
32. Bigal ME, Dodick DW, Rapoport AM et al (2015) Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol 14(11):1081–1090
33. Barbanti P, Egeo G (2015) Pharmacological trials in migraine: it's time to reappraise where the headache is and what the pain is like. Headache 55(3):439–441
34. Palmirotta R, Barbanti P, Ludovici G et al (2013) Establishment of a biorepository for migraine research: the experience of Interinstitutional Multidisciplinary BioBank (BioBIM). Neurol Sci 34:1659–1663
35. MaassenVanDenBrink A, Meijer J, Villalón CM, Ferrari MD (2016) Wiping out CGRP: potential cardiovascular risks. Trends Pharmacol Sci 37(9):779–788

Neurol Sci (2017) 38 (Suppl 1):S37–S43
DOI 10.1007/s10072-017-2862-4

Pathogenesis of chronic cluster headache and bouts: role of tryptamine, arginine metabolism and α_1-agonists

G. D'Andrea[1] · G. Bussone[2] · P. Di Fiore[2] · F. Perini[3] · A. Gucciardi[4] · A. Bolner[1] · M. Aguggia[5] · G. Saracco[5] · E. Galloni[3] · G. Giordano[6] · A. Leon[1]

Abstract The aim of this study was to explore the possible role of tryptamine in the pathogenesis of chronic cluster headache along with that of adrenaline and noradrenaline (α-agonists) together with arginine metabolism in the origin of cluster bouts. Plasma levels of tyramine, tryptamine, serotonin, 5-hydroxyindolacetic acid, noradrenalin, adrenalin and the markers of arginine metabolism such as arginine, homoarginine, citrulline, ADMA and NMMA, were measured in 23 chronic cluster headache patients (10 chronic cluster ab initio and 13 transformed from episodic cluster) and 28 control subjects. The plasma levels of tyramine, tryptamine, noradrenalin and adrenalin were found several times higher in chronic cluster headache patients compared to controls, whereas the plasma levels of arginine, homoarginine and citrulline were significantly lower. No differences were found in the plasma levels of serotonin, 5-hydroxyindolacetic, ADMA and NMMA between chronic cluster headache patients and control subjects. These results provide support for a role of tryptamine in the pathogenesis of chronic cluster headache and, in particular, in the duration of the cluster bouts. In addition, the low levels of the nitric oxide substrates together with the high levels of noradrenalin and adrenalin suggest an activation of endothelial TAAR1 receptors followed by the release of nitric oxide in the circulation that may constitute the final step of the physiopathology of cluster crisis.

Keywords Tryptamine · Cluster headache · Trace amines · Arginine metabolism · Noradrenaline

✉ G. D'Andrea
giovidavi@virgilio.it

[1] Research and Innovation (R&I) s.r.l., Padua, Italy

[2] C. Besta Neurological Institute IRCCS Foundation, Milan, Italy

[3] Neurology Department, Headache Center, Vicenza Hospital, Vicenza, Italy

[4] Mass Spectrometry and Metabolomic Laboratory, Institute of Pediatric Research IRP Città della Speranza, Padua, Italy

[5] Neurology Department, Headache Center, Asti Hospital, Asti, Italy

[6] Women's and Children's Health Department, University of Padova, Padua, Italy

Introduction

A cluster headache (CH) is a trigeminal autonomic cephalalgia (TAC) primary headache characterized by unilateral pain attacks. The bouts are, in comparison to those of migraine and tension-type headache, brief: they last from minutes to 3 h, typically characterized by sudden excruciating pain from the onset that quickly disappears after the end of the crisis. Accompanying features invariably include miosis, ptosis, lacrimation, nasal stiffness and secretion, sweating, all signs that suggest a dysfunction of the sympathetic system [1].

In the majority of patients, CH occurs in an episodic form in which the painful attacks are present, with variable frequency, every day or week. The active period may last weeks or months. The remission period follows when the bouts disappear for a period of time, generally for months or years. In chronic cluster headache (CCH), unlike the episodic form, the bouts occur, without remission periods, continuously from at least 1 year. At times, the chronic form develops in episodic cluster headache patients in which the remission period becomes shorter followed by complete disappearance with time of remission. The

features of the crisis are similar in both forms. The pathogenesis of chronic cluster and the process that transforms the episodic into the chronic form are unknown [2]. It is also unknown why the cluster crisis is characterized by an abrupt onset, short duration, excruciating pain and sudden disappearance.

Tryptophan (TRP) is the amino acid precursor of indoles: 5-hydroxytryptamine (5-HT), 5-hydroxyindolacetic acid (5-HIAA) and tryptamine (TRY). TRY is a biogenic amine structurally related to 5-HT and is generated in neural and peripheral tissues in minute amounts and, for this reason, is considered an elusive amine. The enzymes that govern the synthesis of 5-HT, 5-HIAA and TRY are TRP hydroxylase and TRP decarboxylase, respectively [3, 4].

Migraine and cluster headache types have been shown to be relieved by psilocybin, a component of magic mushrooms, whose active metabolite, psilocybin is a tryptamine analogue (*N,N*-dimethyltryptamine) [5]. However, the specific functions of tryptamine were unknown until a few years ago when it was discovered that TRY is an agonist of 5-HT1A, 5-HT2A and trace amine-associated (TAARs) receptors [6]. The 5-HT1A receptor is abundant in corticolimbic regions, hippocampus, amygdala and hypothalamus. 5-HT1A is the major somatodendritic autoreceptor on 5-HT neurons where it acts in an inhibitory manner. 5-HT2A receptors are located in neurons of the raphe nuclei of the brain stem. These neurons project widely throughout the brain regulating many functions, including the pain threshold [7]. TAARs receptors, on the other hand, represent a family of G-protein coupled receptors. TAAR1 is a receptor widely distributed in many organs and tissues including brain and endothelium. In brain TAAR1 modulates, in an inhibitory manner, the release of catecholamines from noradrenergic and dopaminergic fibers, including those of the pain matrix [8, 9]. TAAR1 on endothelial cells modulates the activity of the constitutive nitric oxide synthase (NOS) enzyme, therein affecting the synthesis of nitric oxide (NO) [10]. In normal conditions, TAAR1 activation determines an inhibition of NOS activity and vasoconstriction. In conditions of high levels of circulating α_1-agonists, such as phenylephrine and/or adrenaline (E) and noradrenaline (NE), stimulation of TAAR1 by high levels of TRY, tyramine (TA) or other elusive amines causes an activation of NOS activity, release of NO, and intense vasodilatation [10].

The role of TRY in the pathogenesis of chronic cluster headache and its relationship with NO synthesis in the endothelium are unknown. Since TRY, together with TA, elusive amine of tyrosine metabolism [11], is an agonist of TAAR1 receptors located, together with α_1-receptors, on the endothelium, it is possible that in certain pathological circumstances the activation of TAAR1 determines NO production in the arterial bed. An increased synthesis and release of NO has been reported during and after painful attacks in episodic cluster headache sufferers [12]. To explore this issue, we measured levels of 5-HT, 5-HIAA, TRY together with TA in plasma of a group of CCH patients and controls. In addition, to explore the possible interaction of TRY, tyramine and endothelial TAAR1, we measured the levels in plasma of arginine (Arg), homoarginine (H-Arg), citrulline (Cit), N^G,N^G-asymmetric dimethyl-L-arginine (ADMA), N^G-monomethyl-L-arginine (NMMA), all products related to NO metabolism, together with those of E and NE in CCH patients versus control subjects.

Methods

Study population and sampling

A sample of consecutive patients presenting at the Headache Centers of Neurology Departments in three Italian hospitals (Vicenza, Milan and Asti) from January 2014 to December 2014 were enrolled in the study. The inclusion criteria consisted of a history of cluster headache lasting at least 1 year or more. The diagnosis of CCH was made according to ICHD-3 beta criteria [13]. Thirteen patients were chronic cluster ab initio and ten patients with cluster shifted from episodic into the chronic form (ECCH). All patients were in prophylactic treatment: 13 subjects received verapamil with doses ranging between 400 and 800 mg/daily, five subjects were given 900 mg daily of sodium valproate (Depakin) and five patients were treated with different antiepileptic drugs (Topamax, Gabapentin). All these patients were under cortisone therapy except two who were treated with Verapamil and Depakin alone. The demographic patient characteristics are shown in Table 1.

The control group consisted of 28 subjects matched for age and sex with CCH patients. To assure for adequate sample amounts for the biochemical assessments, 16 of these samples were employed for assessment of the TRP metabolites and α-agonists. Samples from the remaining controls (12 subjects) were used to verify statistical differences in compounds related to the Arg pathway between the two groups. All control subjects were free from headaches, diabetes, hypertension or other relevant pathological disorders.

Peripheral venous blood (20 ml) was drawn from the antecubital vein at 9 a.m. from patients after 10 min of resting in the supine position, at least 4 h after the last bout. Ten ml of blood were drawn from healthy subjects. The blood was drawn by an expert operator and collected into tubes with EDTA as an anticoagulant. The blood was centrifuged at 3500 rpm for 15 min and obtained poor platelet plasma was stored at −80 °C until analysis.

Table 1 Demographic and clinical characteristics of CH patient and control groups

Subjects (*n*)	Controls	16
	CH patients	23
Age, years ± SD (range)	Controls	54.0 ± 10.1 (34–80)
	CH patients	50.8 ± 11.4 (31–67)
Sex, male [*n* (%)]	Controls	15 (54%)
	CH patients	18 (78%)
Age of symptoms onset (mean ± SD)		36.7 ± 11.2
Years of disease duration (mean ± SD)		14.1 ± 8.9
Chronic cluster (*n*)	From episodic	13
	Ab initio	10
CH lateralization (*n*)	Right side	13
	Left side	8
	Side-altering	2

Sample analysis

The levels of 5-HT, 5-HIAA, TRY, E, NE, TA, together with Arg, H-Arg, Cit, ADMA and NMMA were measured in the plasma of all patients.

Tryptamine assay was performed by HPLC with fluorescence detection. The analytical detection was performed by a fluorometer Jasco FP920 with excitation and emission lambda fixed at 285 and 340 nm, respectively. Levels of 5-HT, 5-HIAA and TA were assessed using HPLC methodology equipped with a multi-channel electrochemical detector system (Coulochem II ESA, Bedford, MA, USA) as previously described [14, 15].

Plasma concentrations of Arg, H-Arg, Cit, ADMA, NMMA were determined by ultra-performance liquid chromatography tandem mass spectrometry (UPLC–ESI–MS/MS) method, as previously reported [16]. Metabolites were chromatographically separated on a BEH C18 column in the Acquity UPLC (Waters Milford, MA, USA) system coupled with a Xevo TQ-S triple quadrupole tandem mass spectrometry (Waters, Milford, MA, USA). Data were acquired with related metabolites were expressed as μmol/l while trace amines, 5-HT and 5-HIAA were expressed as ng/ml. Mass Lynx 4.1 and processed with TargetLynx (Waters, Milford, MA, USA).

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 23, SPSS IBM, New York, USA) and Prism 4 (GraphPad Inc., San Diego, CA) software packages. Plasma levels of all quantified metabolites were first tested for normality using Shapiro–Wilk test and for equality of variance by Levene's test. All groups displayed a parametric distribution with equal variance; therefore, the differences between groups were tested using the independent samples *t* test. Evaluation of differences between the CCH and ECCH patients was performed for plasmatic levels of all metabolites. Pearson's correlations were performed between concentration levels and also with clinical variables assessed during a clinical interview. Differences in the plasma levels of all markers between males and females were also evaluated. The results were expressed as the mean ± SD and level of significance was assumed for a p value <0.05.

Results

CCH and control subjects displayed a similar age distribution, with the CCH group including more men than the control subjects. Detectable levels of 5-TH, 5-HIAA, Try, TA, adrenalin, NE, H-arginine, arginine, citrulline, ADMA and NMMA and were found in the plasma levels of all subjects. Table 2 reports the mean levels of TA and metabolites of tryptophan hydroxylase and decarboxylase found in the plasma of CCH and control subjects. The plasmatic concentrations of α_1-agonists and arginine metabolites in control and cluster subjects are reported in Tables 3 and 4 respectively. The plasma levels of 5-HT, 5-HIAA, ADMA and NMMA were in the similar range in the two group of subjects. The levels of TRY, NE, E and TA found in CCH

Table 2 Plasma levels of tyramine and metabolites of tryptophan hydroxylase and decarboxylase in control and cluster subjects

	CTRL ($n = 16$)	Cluster ($n = 23$)	p value*
Serotonin	0.35 ± 0.3795	0.2182 ± 0.1682[a]	0.1614
5-HIAA	6.455 ± 5.612	5.777 ± 2.495[a]	0.6108
Tryptamine	1.838 ± 1.01	4.363 ± 4.896[a]	0.0039
Tyramine	2.06 ± 1.61	12.51 ± 3.83[a]	<0.0001

* Values are expressed as mean ± SD. p value was obtained by unpaired *t* test

[a] ng/ml

Table 3 Plasma levels of α_1-agonists in control and cluster subjects

	CTRL ($n = 16$)	Cluster ($n = 23$)	p value*
Norepinephrine	72.29 ± 33.9	214.4 ± 110.4[a]	0.0001
Epinephrine	11.65 ± 2.015	21.63 ± 13.46[a]	0.0162

* Values are expressed as mean ± SD. p value was obtained by unpaired t test

[a] ng/ml

Table 4 Plasma levels and ratios of arginine metabolites in cluster and control subjects

	CTRL ($n = 12$)	Cluster ($n = 23$)	p value*
Arginine	84.82 ± 16.94	53.26 ± 17.57[a]	0.0032
Homoarginine	1.69 ± 0.67	1.10 ± 0.48[a]	0.0043
ADMA	0.77 ± 0.11	0.90 ± 0.24[a]	0.1008
NMMA	0.08 ± 0.01	0.08 ± 0.02[a]	0.1801
Citrulline	41.10 ± 5.71	31.13 ± 10.81[a]	0.0134
Arg/ADMA ratio	2.23 ± 1.03	1.22 ± 0.43[a]	0.0008
Cit/Arg ratio	0.49 ± 0.09	0.61 ± 0.23[a]	0.2567

* Values are expressed as mean ± SD. p value was obtained by unpaired t test

[a] μmol/l

patients were higher whereas those of H-Arg (Tables 2, 3), Arg and Cit were significantly lower compared with those of controls (Table 4). There was no significant statistical difference in the levels of elusive amines and α_1-agonists in patients suffering from chronic CH evolved from the episodic form compared with those with a history of the chronic form ab initio (Table 5). Comparison between males and females in all groups of subjects did not show significant differences, as well as correlations between metabolites and clinical parameters (age, sex, side affected, age of beginning of the bouts and duration of disease).

Discussion

One aim of this study was to assess the plasmatic levels of 5-HT, 5-HIAA and TRY, products of TRP hydroxylase and decarboxylase enzyme activities respectively, in CCH and control subjects. The levels of TRY resulted significantly more elevated in plasma of CCH patients whereas those of 5-HT, 5-HIAA were in the same range. The normal levels of 5-HT and 5-HIAA in CCH sufferers are in line with previous results in episodic CH, in which the plasma levels of 5-HT were found only slightly more elevated with respect to controls [17]. Together this suggests that the TRP hydroxylase dependent metabolic pathway is not affected in CCH, whereas that of TRP decarboxylase is increased in CCH patients.

The serotoninergic system play a pivotal role in the regulation of pain threshold, in particular in the brain stem nuclei that discriminate and modulate the incoming pain sensations from the spinal cord [18]. 5-HT1A and 5-HT2A receptors are localized in cortical serotoninergic neurons, the descending fibers of which activate the Rafè magnum and other serotoninergic nuclei of the brain stem, including those of the pain matrix [19]. 5-HT1A receptors are expressed in GABAergic interneurons of the orbitofrontal cortex and other cortical brain regions including the limbic centres. In these circuits, the activation of 5-HT1A receptors reduces the release of GABA and activates the serotonergic orbitofrontal descending outputs to the periaqueductal gray (PAG) [20]. 5-HT2A receptors, on the other hand, are densely distributed throughout the cortex, including the prefrontal cortex, as well as in the ventral tegmental area, substantia nigra and striatum. In the orbitofrontal cortex, 5-HT2A induces excitation of serotonergic neurons connected to the PAG and, at the level of the extrapyramidal system, regulates dopamine synthesis and release [21].

TRY is an agonist of 5-HT1A, 5-HT2A, and, as such, plays an important role in the modulation of the pain threshold. This amine, by acting on 5-HT1 receptors, reduces the release of GABA from the interneurons in the cortex, resulting in firing of the cortical and sub-cortical serotonergic neurons and consequent release of 5-HT [22]. The activation of the 5-HT2A receptor by TRY, on the other hand, directly activates these same serotoninergic systems resulting in an increase of the inhibitory control on PAG and other related centers of the pain matrix [20]. Should the high plasma levels of TRY, here observed in CCH, mirror similar changes in the CNS, this may result in activation, both indirectly (through of 5-HT1A) and directly (through 5-HT2A), of the inhibitory control of the 5-HT system on PAG and its related centers. This effect may constitute an attempt to counteract the abnormal activation of the hypothalamus and trigeminal system and, in doing so, limit the number of bouts in CCH patients. The high level of TRY may, also, explain why the length of CH attacks are shorter than those of a migraine and chronic tension-type headache in which the levels of TRY are reported to be significantly lower than those of control subjects and CCH patients [15].

TRY, together with TA, octopamine and β-PEA, is an agonist of TAAR1 and 5-HT2A receptors located on the endothelium of the arterial wall together with α_1-receptors. Stimulation of 5-HT2A by TRY determines a vasoconstriction. This action is a consequence of a release of prostaglandin PGE2, a cyclooxygenase product, since indomethacin (a non-selective inhibitor of COX-1/2) and nimesulide (an inhibitor of COX-2), reduce the vasoconstriction [23]. In contrast, activation of the endothelial

Table 5 Plasma levels of catecholamines, trace amines and of chronic CH patients evolved from the episodic form and those with the chronic form ab initio

	Chronic ab initio ($n = 13$)	Episodic ($n = 10$)	p value
Serotonin	0.19 ± 0.14	0.24 ± 0.19	0.56
5-HIAA	5.51 ± 2.37	5.95 ± 2.67	0.71
Tryptamine	5.98 ± 6.19	3.24 ± 3.60	0.20
Tyramine	12.55 ± 4.434	12.48 ± 3.48	0.96
Norepinephrine	245.2 ± 139.8	194.7 ± 86.7	0.29
Epinephrine	23.08 ± 13.31	20.51 ± 14.02	0.66
Arginine	46.74 ± 13.54	59.24 ± 19.22	0.09
Homoarginine	1.05 ± 0.55	1.15 ± 0.43	0.64
ADMA	0.88 ± 0.24	0.91 ± 0.24	0.77
NMMA	0.09 ± 0.018	0.09 ± 0.03	0.75
Citrulline	28.57 ± 8.149	33.48 ± 12.68	0.29

5-HT2A by TRY, in conditions of high levels of circulating α_1-receptor agonist (phenylephrine, norepinephrine or adrenaline) determines vasodilatation [23]. Current evidence suggests that this vasodilatation is a consequence of the concomitant stimulation of TAAR1, located on the endothelium of the vessel wall, by TRY and other circulating elusive amines as TA. It has been demonstrated that, in this biochemical milieu, the activation of this receptor determines activation of constitutive endothelial NOS and consequent release of NO in the arterial circulation resulting in intense vasodilatation [10, 24]. In order to ascertain if such pathological conditions are present in the circulation of our patients, we assessed the metabolism of arginine, the circulating levels of the α_1-agonist NE and E along with that of TRY. The circulating levels of arginine regulate the activity of NOS and NO synthesis [25].

NO is a gaseous transmitter produced from the amino acid L-arginine by the enzymatic action of NOS in the Arg–NO pathway. Arginine is an important substrate for enzymes such as NOS and arginases whose activities are regulated by Arg availability. NOS converts Arg to Cit in a reaction that simultaneously produces NO, whereas arginases convert Arg to ornithine (Orn) and urea [26]. NO generation by NOS is inhibited by ADMA and NMMA. ADMA and NMMA are metabolized to Cit and methylamines, through a reaction catalyzed by dimethylarginine dimethylaminohydrolase (DDAH). L-homoarginine, a homologous of Arg with one extra methyl group on carbon chain, is formed from lysine by the urea cycle enzymes and by arginine:glycine amidinotransferase (AGAT). H-Arg serves as NOS substrate, competing with Arg for NOS, arginase, and for the cationic amino acid transport (CAT) and thus can potentially modulate intracellular Arg bioavailability [25].

To verify if the metabolism of arginine is involved in chronic cluster bouts, we measured the levels of Arg, H-Arg, Cit, ADMA and NMMA along with those of NE, E and TA, in plasma of CCH patients, within 4 h after the bout, and controls. The levels of NE, E and TA were found very high in plasma of our patients whereas those of Arg, H-Arg and Cit were very low. The low levels of Arg and H-Arg, may reflect the high rate of substrate consumption for the synthesis and release of NO that occurred during the bouts. The lower levels of Cit, precursor of endogenous arginine synthesis, could indicate the high recycling of Cit to Arg, that may represent a compensatory mechanism as suggested by similar Cit/Arg ratios [27] in patients and controls. Not significantly differences were found between patients and controls in ADMA and NMMA levels, whereas Arg/ADMA ratio was about 50% lower in CCH group suggesting the possibility of a lower degree of endogenous inhibition of NOS activity. Together this suggests that, in the circulation of CCH patients, there occurs biochemical scenario that favour the activation of endothelial TAAR1 resulting in NO release and vasodilatation. The intense release of NO from the endothelium may be the cause of the cluster bouts.

In conclusion, we here provide evidence that the high plasma levels of TRY in CCH may reflect an attempt in the CNS to increase the top-down control of the central 5-HT system on the pain matrix to limit the number of painful attacks. One consequence may be that the length of the cluster bouts that last minutes to few hours, instead of days as occurs in migraine and tension chronic headaches [15]. In the circulation, on the other hand, there occur biochemical changes that result in endothelial TAAR1 activation and NO release during the cluster bouts. The low levels of arginine substrates, precursors of NO synthesis, support this hypothesis. The sudden artery dilatation of the trigeminovascular system, due to a release of NO, may constitute the final step of the pathophysiology of the cluster headache attacks.

One limitation of our study is that Arg, H-Arg and related metabolites along with NO levels were not measured during the bouts and in episodic cluster headache patients. In addition, Arg availability could be reduced in

CCH patients due to increased arginase activity assessed by evaluating the ratio of arginine to ornithine. Unfortunately, we did not measure Orn levels in the available samples. We can, however, exclude confounding effects of differences in L-arginine food intake because all subjects were studied under fasting conditions for at least 12 h before the blood sampling.

Clinical implications

The high plasma levels of tryptamine in CCH patients suggest that this elusive amine may, in the CNS, constitute a compensatory mechanism involved in the regulation of the cortical and subcortical serotoninergic centers, the result of which leads to a containment of the duration of the CH attacks. At the same time, the high levels of α_1-agonists (adrenaline and noradrenaline) together with that of tyramine and tryptamine found in the circulation may result in endothelial TAAR1 activation that, in turn, results in NO production and intense vasodilation and pain. In support of this hypothesis, the low levels of arginine, homoarginine and citrulline, found in the plasma of patients, hours after of the bouts, indicate that the high rate of arginine metabolism and NOS activation occurred during the bouts. Treatment(s) that modulate the function of vascular TAAR1 together with agents that inhibit NOS activity may beneficial in the prevention of the occurrence of CH crisis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest with the publication of this article.

Funding The authors disclosed receipt of the following financial support for the research, authorship and/or publication of the article. The research was partially funded by the F.I.CEF Charity (Italian Headache Foundation).

References

1. Altiokka O, Mutluay B, Koksal A, Ciftci-Kavaklioglu B, Ozturk M, Altunkaynak Y, Baybas S, Soysal A (2016) Evaluation of interictal autonomic function during attack and remission in cluster headache. Cephalalgia 36(1):37–43
2. Mitsikostas DD, Edvinson L, Jensen HR, Katsarava Z, Lampl C, Negro A, Osipova V, Paemeleire K, Siva A, Valade D, Martelletti P (2014) Refractory chronic cluster headache: a consensus statement on clinical definition from the European Headache Federation. J Headache Pain 15:79
3. Wollman H, Nilson E, Antonin KH, Reiderer P (1985) Tryptamine kinetics in human volunteers. In: Bolton AA, Maite L, Beick PR (eds) Neuropsychopharmacology of trace amines. Humana Press, Clifton, pp 361–378
4. Borowsky B, Adham N, Jones KA et al (2001) Traces amines: identification of a family of mammalian G protein-coupled receptors. Proc Natl Acad Sci USA 98:8966–8971
5. Curran DA, Lance JW (1964) Clinical trials of methysergide and other preparations in the management of migraine. J Neurol Neurosurg Psychiatry 27:463–469
6. Albert PR, Le Francois B, Millar AM (2011) Transcriptional dysregulation of 5-HT1A autoreceptors in mental illness. Mol Brain 4:21
7. Huo FQ, Qu CL, Li YQ, Tang JS, Jia (2008) Gabaergic modulation is involved in ventrolateral orbital cortex 5-HT1 receptor activation-induced antinociception in the rat. Pain 139(2):398–405
8. D'Andrea G, Nordera GP, Pizzolato G et al (2010) Trace amine metabolism in Parkinson's disease: low circulating levels of octopamine in early disease stage. Neurosci Lett 469:348–351
9. Revel FG, Moreau JL, Gainetdinov RR, Bradaia A, Sotnikova TD et al (2011) TAAR1 activation modulates monoaminergic neurotransmission, preventing hyperdopaminergic and hypoglutamatergic activity. Proc Natl Acad Sci USA 108(20):8485–8490
10. Anwar MA, Ford WR, Broadley KJ, Herbert AA (2012) Vasoconstrictor and vasodilator responses to tryptamine of rat-isolated perfused mesentery: comparison with tyramine and β-phenylethylamine. Br J Pharmacol 165(7):2191–2202
11. D'Andrea G, D'Arrigo A, Dalle Carbonare M, Leon A (2012) Pathogenesis of migraine: the role of the neuromodulators. Headache 52(7):1155–1163
12. D'Andrea G, Granella F, Cadaladini M (2003) Platelet aggregation profiles in cluster headache Headache 43(3):272–275
13. The international classification of headache disorders: 3-beta edition (2013) Cephalalgia 33(9):629–808
14. D'Andrea G, D'Amico D, Bussone G et al (2013) The role of tyrosine metabolism in the pathogenesis of chronic migraine. Cephalalgia 33(11):932–937
15. D'Andrea G, D'Amico D, Bussone G et al (2014) Tryptamine levels are low in plasma of chronic migraine and chronic tension-type headache. Neurol Sci 35:1941–1945
16. Di Gangi IM, Chiandetti L, Gucciardi A et al (2010) Simultaneous quantitative determination of *N*(G),*N*(G)-dimethyl-L-arginine or asymmetric dimethylarginine and related pathway's metabolites in biological fluids by ultrahigh-performance liquid chromatography/electrospray ionization-tandem mass spectrometry. Anal Chim Acta 677(2):140–148
17. D'Andrea G, Granella F, Alecci M et al (1998) Serotonin metabolism in cluster headache. Cephalalgia 18(2):94–96
18. Viguer E, Michot B, Hamon M et al (2013) Multiple roles of serotonin in pain mechanism-implications of 5-HT_7 and other receptor types. Eur J Pharmacol 716(1–3):8–16
19. Qu GL, Huo FQ, Huang FS (2008) The role of 5-HT receptors in medial prefrontal cortex of 5-HT induced antinociception in the rat. Neuroscience 152:487–494
20. Huo FQ, Qu GL, Ly YQ et al (2008) GABAergic modulation is involved in the ventrolateral orbital cortex 5-HT_{1A} recept activation-induced antinociception in the rat. Pain 139(2):398–405
21. Pockros AL, Pentkowski NS, Swinford SE et al (2011) Blockade of 5-HT_{2A} in medial prefrontal cortex attenuates reinstatement of cue-elicited cocaine-seeking behaviour in rats. Psycopharmacology (Berl) 213(2–3):307–320
22. Huo FQ, Huang FS, Lu BC et al (2010) Activation of serotonin 1A receptors in ventrolateral orbital cortex depresses persistent nociception: a presynaptic inhibition mechanism. Neurochem Int 57(7):749–755
23. Anwar MA, Ford WR, Herbert AA et al (2013) Signal transduction and modulating pathways in tryptamine-evoked responses of the rat isolated mesenteric bed. Vascul Pharmacol 58(1–2):140–149
24. Broadley PB (2010) The vascular effects of trace amines and amphetamines. Pharmacol Ther 125:363–375

25. Tsikas D, Guoyao W (2015) Homoarginine, arginine and relatives: analysis, metabolism, transport, physiology and pathology. Amino Acids 47:1697–1702
26. Böger RH, Bode-Böger SM (2001) The clinical pharmacology of L-arginine. Annu Rev Pharmacol Toxicol 41:79–99
27. Flam BR, Eichler DC, Solomonson LP (2007) Endothelial nitric oxide production is tightly coupled to the citrulline-NO cycle. Nitric Oxide 17(3–4):115–122

Neurol Sci (2017) 38 (Suppl 1):S45–S50
DOI 10.1007/s10072-017-2924-7

Cluster headache: present and future therapy

Massimo Leone[1] · Alessandro Giustiniani[1] · Alberto Proietti Cecchini[1]

Abstract Cluster headache is characterized by severe, unilateral headache attacks of orbital, supraorbital or temporal pain lasting 15–180 min accompanied by ipsilateral lacrimation, rhinorrhea and other cranial autonomic manifestations. Cluster headache attacks need fast-acting abortive agents because the pain peaks very quickly; sumatriptan injection is the gold standard acute treatment. First-line preventative drugs include verapamil and carbolithium. Other drugs demonstrated effective in open trials include topiramate, valproic acid, gabapentin and others. Steroids are very effective; local injection in the occipital area is also effective but its prolonged use needs caution. Monoclonal antibodies against calcitonin gene-related peptide are under investigation as prophylactic agents in both episodic and chronic cluster headache. A number of neurostimulation procedures including occipital nerve stimulation, vagus nerve stimulation, sphenopalatine ganglion stimulation and the more invasive hypothalamic stimulation are employed in chronic intractable cluster headache.

Keywords Cluster headache · Treatment · Neurostimulation · Drugs · CGRP

Introduction

Cluster headache (CH) is considered the most severe primary headache form. According to the International Headache Society diagnostic criteria, cluster headache attacks are strictly unilateral, severe or very severe, the pain is felt in the orbital, supraorbital or temporal regions, its duration is 15–180 min [1] and the pain is accompanied by at least one of the following symptoms ipsilateral to the pain: conjunctival injection or lacrimation, nasal congestion, rhinorrhea, eyelid edema, forehead and/or facial sweating, miosis, or ptosis. A sense of restlessness and agitation is often present during attacks [1]. These recur with circadian rhythmicity at fixed hours of the day or night [2, 3]. In episodic CH, attacks usually occur in periods, cluster periods, lasting 6–12 weeks followed by periods of remission of various durations [2, 3]. In chronic CH attacks occur without remission [1].

Discovery of relevant pathophysiological mechanisms, both in the peripheral and central nervous system, allowed discovery of new treatments and others are under investigations.

To prevent recurrent attacks during cluster periods patients need adequate prophylactic treatments while acute treatments are needed to abort single attacks.

In the last 16 years, a number of neurostimulation procedures have been tried to treat CH and some have been shown to improve the condition when it is intractable.

Acute treatment

A fast-acting treatment is necessary because attacks peak at their maximum intensity in few minutes after onset. Patients have to treat the attack as soon as possible after onset.

About 60–70% of CH patients respond to inhalation of 100% oxygen via a non-rebreathing face mask [4, 5] while hyperbaric oxygen does not prevent CH [5].

✉ Massimo Leone
leone@istituto-besta.it

[1] Department of Neurology and Headache Centre, Fondazione Istituto Nazionale Neurologico 'Carlo Besta', Via Celoria 11, 20133 Milan, Italy

Sumatriptan, a 5-$HT_{1B/D}$ agonist, is considered the gold standard to abort ongoing CH attacks both from data reported in double-blind, placebo-controlled trials and from clinical practice [6, 7]. Rarely repeated injections are necessary. Usually there is neither evidence of tachyphylaxis nor rebound in most patients and it is contraindicated in patients with cardiovascular or cerebrovascular disorders or arterial hypertension. Chest pain and/or discomfort and distal paresthesia are the most uncomfortable adverse effects of sumatriptan [8]. The most effective sumatriptan formulation in CH is the injectable form [9], there are also oral and nasal-spray formulations.

Another 5-HT_1 agonist zolmitriptan is effective but to a less extent compared to sumatriptan injections.

Some authors have reported a certain efficacy of the preemptive use of triptans ('short-term prophylaxis') for CH treatment.

Probably the oldest treatment for CH is oral ergotamine; [10] but in one trial, intranasal application of dihydroergotamine was shown to be no superior to placebo [11]. It has beenshown that intravenous dihydroergotamine can stop attacks in 3 days in about two-thirds of patients [12].

Even if octreotide a somatostatin analog has been shown to improve acute CH, it is not in the common therapeutic armamentarium because of its low cost:benefit ratio [13].

Preventive treatment

Before start with drug therapy some factors have to be considered: alcohol intake and napping can trigger attacks and should be avoided [2, 3]. Also nitroglycerin and some vasodilating antihypertensives can precipitate CH and should be avoided whenever possible [2, 3].

Prevention has the aim to stop or reduce attack recurrence.

Once obtained a satisfying attack-free period, preventive agents can be gradually tapered, slowly and also with caution to find the lowest effective dose.

A number of general rules have to be considered when choosing preventive pharmacotherapies for CH. The therapeutic approach may vary according to the chronic or episodic course of CH, pain intensity, attack frequency and duration, and patient's characteristics.

Only few randomized clinical trials have investigated preventive drugs in CH and much of preventive therapy is based on clinical experience.

Verapamil and lithium are considered as first-line medications, methysergide—methylergonovine in the United States—and ergotamine as second-line medications, and pizotifen, topiramate and valproic acid as third-line drugs. Other drugs can be of some help.

Corticosteroids are the most effective preventive agents but because of their adverse effects should be administered with great caution particularly in long-term treatment.

First-line medications

Verapamil is considered as first choice in CH prophylaxis in both episodic and chronic CH [14, 15]. Headache frequency was reduced by 50% or more in 80% of patients in a double-blind study verapamil employing 360 mg per day [15]. In refractory patients higher doses of verapamil have been used with some success but since the drug can cause atrioventricular block, electrocardiograms to check for PR interval prolongation are needed to disclose impending heart block [16]. In this respect each dose increase can be done after a normal electrocardiogram result [15, 16]. Constipation, distal limb edema, hypotension dizziness, nausea, fatigue and bradycardia are the most common adverse events [14, 15]. Concomitant use of antihypertensive drugs may lead to arterial hypotension and faints.

When a single drug is not effective, administration of two or more drugs can be considered.

Lithium is effective in the prophylactic of CH [17, 18]. Common effective dosage is 900 mg (600–1200 mg) per day. Patients should be started at 300 mg once or twice a day; the dose has to be increased in steps of 150–300 mg per day. Disappearance of headaches or adverse effects onset indicate to stop increase. Postural tremor of the hands, nausea, abdominal discomfort, agitation, insomnia, weakness, thirst, slurred speech, and blurred vision are among the commonest adverse events and toxicity is witnessed with the appearance of nausea and vomiting, diarrhea, confusion, nystagmus, ataxia and seizures. Long-term use of lithium can provoke hypothyroidism and kidney dysfunction leading to polyuria due to diabetes insipidus: renal and thyroid function have to be periodically checked. Lithium can also induce polymorphonuclear leukocytosis that can be diagnosed as an occult infection. Dehydration increases the probability of adverse events induced by the drug, thus patients have to be warned to have an appropriate water intake particularly in warm weather.

Second-line medications

In open studies, methysergide has been demonstrated to exert some preventive effect both in episodic and chronic CH headache [19, 20].

Methysergide dosage can be increased to as much as 12 mg per day, starting from 1 mg per day, and then with of 1 mg every 3–5 days. After 6–8 months a 1-month drug holiday is necessary to prevent adverse effects. Common adverse effects are nausea, vomiting, dizziness, muscle cramps, abdominal pain, and peripheral edema.

Methysergide is contraindicated with coronary or peripheral arterial insufficiency. In past years prolonged treatment with methysergide was reported to cause retroperitoneal, pulmonary, pleural, or cardiac fibrosis in a few patients. When methysergide is administered for prolonged periods periodic electrocardiogram, chest X-ray and abdominal MRI is highly desirable. Sumatriptan and methysergide should not be administered at the same time because of the increased risk of vasoconstriction. In the United States, methylergonovine, an active metabolite of methysergide, is used as an alternative to methysergide. Ergotamine is another option at a dose of 2–4 mg per day and when headache onset is at given times of the day or night the drug can be administered 30–60 min before the expected time of the attack or bedtime for nocturnal attacks. Special caution in hypertensive patients should be considered when prescribing ergot-type alkaloids and only if arterial blood pressure values are fully controlled. The starting of limb-paresthesia can suggest the onset of a dangerous condition, ergotism: the drug must be stopped. As for methysergide concomitant triptan use is not recommended.

Dihydroergotamine also seems a promising agent for patients with chronic cluster headache who do not respond to other preventive medications. In an open-label study of 54 patients with intractable cluster headache (23 episodic, 31 chronic),

Repeated intravenous administration of dihydroergotamine has been shown to produce a headache free condition in 83% of patients with episodic CH and 39% of patients with chronic CH persisting 12 months later [21].

Topiramate has shown a good efficacy in open-label trials in the range of 25–200 mg per day in 70% of patients [22, 23]. The drug should be started at 25 mg per day and increased by 25 mg every week to minimize adverse effects, Adverse effects occur in about 40% of patients but these are rarely severe and include paresthesia of distal extremities, dizziness, cognitive symptoms, somnolence, imbalance and ataxia [22, 23]. Marked weight loss, mood changes and psychosis indicate the urgent need to stop the treatment. Glaucoma and nephrolithiasis are much less common and, in order to prevent nephrolithiasis, patients have to drink at least 2 l of water per day.

Pizotifen has been reported to exert some effect in one open-label study and one controlled trial [24]. Common dosage is 0.5 mg two or three times a day. Sedation, dry mouth, drowsiness, increased appetite and weight gain are the most frequent adverse effects.

Sodium valproate or divalproex sodium has been reported to be effective in 54–73% of CH patients [25], but in a randomized controlled double-blind study no efficacy was observed [26].

Gabapentin at a dose of 900 mg per day produced pain free state in eight episodic and four chronic CH within 8 days in an open-label study [27]. This effect was long lasting, months after discontinuation of the agent.

Reduced serum melatonin in CH prompted its use as a preventive agent CH. In a double-blind pilot study comparing melatonin to placebo, 20 patients were randomly assigned to either 10 mg melatonin or placebo for 2 weeks [28]. In the melatonin group, five patients had their attacks ceased after 5 days of treatment. Unfortunately similar findings were not reported in subsequent studies.

Other drugs including botulinum toxin, chlorpromazine, naratriptan, eletriptan, baclofen, and transdermal clonidine have been tried in open-label studies, but controlled trials are necessary to establish their efficacy.

Corticosteroids

Corticosteroids as prednisolone, prednisone, and dexamethasone are employed in the treatment of CH and must be used with caution because of potentially serious adverse event particularly in long-term treatment. Common dosage of oral prednisone or prednisolone is 60 mg once daily for 5–10 days or until the attacks stop; the dose should then be reduced by 5–10 mg every 4–10 days but tapering could be slower in chronic CH because relapse may occur. Transitional therapy is indicated when attacks are frequent, in the meantime other preventive medication takes effect: dexamethasone 8 mg daily intramuscularly or orally can be given for 5–10 days. Blockade of greater occipital nerve ipsilateral to the pain is effective in CH [29]. A mixture of corticosteroid plus local anesthetic is injected into the area.

Blockade of sphenopalatine ganglion has certain effectiveness in CH [30]. It is performed by nasal application of local anesthetic lidocaine (1 ml 4–10% preparation) ipsilateral to the pain. It is thought to reduce pain traffic in the trigeminal fibers at that level.

Calcitonin gene-related peptide (CGRP) antagonists

The observation of increased (CGRP) plasma levels in the external jugular vein blood on the pain side during spontaneous CH attacks confirmed a role of CGRP in CH pathophysiology [31]. Another indirect proof of such CGRP involvement is its normalization after high dose corticosteroids course in CH [32]. CGRP is a potent vasodilator with a prominent role in pain transmission particularly in trigeminal primary neurons. BOLD-signal in the brain of healthy subjects evoked by noxious heat stimuli of the trigeminal nerve is modulated by intravenous infusion of CGRP with contemporary headache induction. [33] All these effects were antagonized by sumatriptan [34]. How CGRP induces head pain is a matter of discussion. CGRP could induce headache by gating the sensory

process without a direct effect: in fact it does not trigger any pain when it is injected into temporal muscle or skin [34]. When CGRP is released by trigeminal nerve, it activates glial cells and NO release, thus, initiating inflammatory cascade in the tissue [35]. This produces peripheral sensitization associated with allodynia. A similar observation has been reported in CH [36].

In the last few years, monoclonal antibodies (mAbs) targeting the free CGRP peptide [37] or the CGRP receptor [38] have been found to have a certain efficacy in migraine and are under investigation as a treatment for both episodic and chronic CH (LY2951742 and TEV-48125) [39, 40]. There is great hope because of their specificity, prolonged half-lives, and up to now, a good tolerability profile.

Neurostimulation

When all pharmacological options fail, invasive or semi-invasive procedures can be considered.

A number of destructive procedures on the trigeminal or autonomic (cranial parasympathetic) pathways were tried in past years.

Trigeminal sensory rhizotomy via the posterior fossa, percutaneous radiofrequency trigeminal gangliorhizolysis, microvascular decompression of the trigeminal nerve have been tried in CH with unsatisfying results in the long-term evaluation [41, 42]. Adverse effects of these procedures claim caution and contralateral recurrence of the attacks after surgery is high [41, 42].

Neurostimulation procedures have been tried to treat intractable CH with the advantage of being less invasive than traditional surgery with encouraging results.

Vagal nerve stimulation (VNS)

In a prospective open-label randomized study VNS efficacy was evaluated as adjunctive prophylactic and compared to standard of care (SoC) [43]. A significantly higher reduction in the mean number of CH attacks per week was observed with SoC plus nVNS (40% of responders) vs controls (8.3%) in the four-week randomized phase followed by a four-week extension phase. The stimulation was well tolerated.

In an another open-label study VNS (gammaCore) was used as acute treatment: it reduced attacks duration in 47% of cases: 11 vs 75 min [44] in 19 CH patients. VNS can thus be employed in CH patients suffering many attacks per day in order to reduce risks related to triptans overuse.

Hoarseness, skin irritation, a certain muscle discomfort and paraesthesia are reported side effects.

Occipital nerve stimulation (ONS)

Published data of open-label studies support ONS efficacy in the long term prevention of intractable chronic CH. So far 126 CH patients from ten open studies show an overall average efficacy of 67% reduction of headache attack frequency [45, 46]. The European Headache Society commission published criteria on the use of ONS as well as other invasive neurostimulation procedures. ONS should be used in drug refractory CH [47].

Sphenopalatine ganglion (SPG) stimulation

SPG implanted stimulator has been used as treatment for ongoing CH attacks in a multicentre trial on 28 patients: it improved 67% of CH at 15 min vs 7% of sham group [48]. In a 24 months open-label follow-up study 5956 CH attacks were evaluated and 45% of patients were responders (acute effectiveness in $\geq$50% of attacks) [49]. A $\geq$50% reduction in headache frequency was also reported in 11 patients (33%).According to an expert consensus [50] SPG neurostimulator should be placed only when all available medical treatments have failed: the procedure is indicated in strictly unilateral CH.

Hypothalamic stimulation

Sixteen years after the introduction of deep brain stimulation (DBS) of the hypothalamus as treatment of intractable chronic CH, there is only one randomized placebo-controlled trial in 11 chronic CH patients treated with this invasive procedure. Unfortunately the duration of the double-blind observation period was only 1-month [51]. This duration does not allow a proper evaluation of efficacy because it takes weeks to months to take place [52, 53]. Results from more than 90 chronic CH patients treated by hypothalamic DBS have been reported and the overall proportion of responders ($\geq$50% headache frequency reduction) is of about 66% [52].

Acute hypothalamic stimulation is not effective. Taken together, these observations point to a complex mechanism of action instead of the hypothesized mere inhibition of the stimulated area.

A modulatory effect on the antinociceptive system could mediate the efficacy as shown by the increased ipsilateral cold pain threshold in V1 territories in these patients [54].

Another mechanism could be a modulating action on pain matrix signalling as indicated by the increased blood flow in pain matrix brain areas in hypothalamic stimulated patients [55].

The normal parasympathetic system activity [56] in these patients also suggests that the hypothalamic

stimulation could improve CH by restoring parasympathetic control in the superior salivatory nucleus (SSN).

The ipsilateral trigeminal nucleus and ganglion are activated in these patients during active hypothalamic stimulation [55]. It is possible that DBS exert its action on pain circuits involving trigeminal system activity [57].

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

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. Kudrow L (1980) Cluster headache, mechanism and management, 1st edn. Oxford University Press, Oxford
3. Sjaastad O (1992) Cluster headache syndrome. Saunders Companu Ltd., London, Philadelpia, Toronto
4. Nilsson Remahl AIM, Ansjön R, Lind F, Waldenlind E (2002) Hyperbaric oxygen treatment of active cluster headache: a double-blind placebo-controlled cross-over study. Cephalalgia 22:730–739. doi:10.1046/j.1468-2982.2002.00450.x
5. Bennett MH, French C, Schnabel A et al (2015) Normobaric and hyperbaric oxygen therapy for the treatment and prevention of migraine and cluster headache. Cochrane Database Syst Rev. doi:10.1002/14651858.CD005219.pub3
6. The Sumatriptan Cluster Headache Study Group (1991) Treatment of acute cluster headache with sumatriptan. N Engl J Med 325:322–326. doi:10.1056/NEJM199108013250505
7. Ekbom K, Monstad I, Prusinski A et al (1993) Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. The Sumatriptan Cluster Headache Study Group. Acta Neurol Scand 88:63–69
8. Dodick DW, Martin VT, Smith T, Silberstein S (2004) Cardiovascular tolerability and safety of triptans: a review of clinical data. Headache 44(suppl 1):S20–S30. doi:10.1111/j.1526-4610.2004.04105.x
9. van Vliet JA, Bahra A, Martin V et al (2003) Intranasal sumatriptan in cluster headache: randomized placebo-controlled double-blind study. Neurology 60:630–633
10. Horton BT, Ryan R, Reynolds JL (1948) Clinical observations on the use of E.C. 110, a new agent for the treatment of headache. Proc Staff Meet Mayo Clin 23:105–108
11. Andersson PG, Jespersen LT (1986) Dihydroergotamine nasal spray in the treatment of attacks of cluster headache. A double-blind trial versus placebo. Cephalalgia 6:51–54. doi:10.1046/j.1468-2982.1986.0601051.x
12. Magnoux E, Zlotnik G (2004) Outpatient intravenous dihydroergotamine for refractory cluster headache. Headache 44:249–255
13. Matharu MS, Levy MJ, Meeran K, Goadsby PJ (2004) Subcutaneous octreotide in cluster headache: randomized placebo-controlled double-blind crossover study. Ann Neurol 56:488–494. doi:10.1002/ana.20210
14. Gabai IJ, Spierings EL (1989) Prophylactic treatment of cluster headache with verapamil. Headache 29:167–168
15. Leone M, D'Amico D, Frediani F et al (2000) Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. Neurology 54:1382–1385
16. Cohen AS, Matharu MS, Goadsby PJ (2007) Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. Neurology 69:668–675. doi:10.1212/01.wnl.0000267319.18123.d3
17. Ekbom K (1981) Lithium for cluster headache: review of the literature and preliminary results of long-term treatment. Headache 21:132–139
18. Bussone G, Leone M, Peccarisi C et al (1990) Double blind comparison of lithium and verapamil in cluster headache prophylaxis. Headache 30:411–417
19. Curran DA (1967) Methysergide. Res Clin Stud Headache 1:74–122
20. Krabbe A (1989) Limited efficacy of methysergide in cluster headache: a clinical experience. Cephalalgia 9(Suppl 10):S404–S405
21. Mather PJ, Silberstein SD, Schulman EA, Hopkins MM (1991) The treatment of cluster headache with repetitive intravenous dihydroergotamine. Headache 31:525–532
22. Leone M, Dodick D, Rigamonti A et al (2003) Topiramate in cluster headache prophylaxis: an open trial. Cephalalgia 23:1001–1002. doi:10.1046/j.1468-2982.2003.00665.x
23. Pascual J, Láinez MJA, Dodick D, Hering-Hanit R (2007) Antiepileptic drugs for the treatment of chronic and episodic cluster headache: a review. Headache 47:81–89. doi:10.1111/j.1526-4610.2007.00653.x
24. Speight TM, Avery GS (1972) Pizotifen (BC-105): a review of its pharmacological properties and its therapeutic efficacy in vascular headaches. Drugs 3:159–203
25. Hering R, Kuritzky A (1989) Sodium valproate in the treatment of cluster headache: an open clinical trial. Cephalalgia 9:195–198. doi:10.1046/j.1468-2982.1989.0903195.x
26. El Amrani M, Massiou H, Bousser MG (2002) A negative trial of sodium valproate in cluster headache: methodological issues. Cephalalgia 22:205–208. doi:10.1046/j.1468-2982.2002.00349.x
27. Tay BA, Ngan Kee WD, Chung DC (2001) Gabapentin for the treatment and prophylaxis of cluster headache. Reg Anesth Pain Med 26:373–375. doi:10.1053/rapm.2001.24404
28. Leone M et al (1996) Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. Cephalalgia 16:494–496
29. Ambrosini A, Vandenheede M, Rossi P et al (2005) Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain 118:92–96. doi:10.1016/j.pain.2005.07.015
30. Costa A, Pucci E, Antonaci F et al (2000) The effect of intranasal cocaine and lidocaine on nitroglycerin-induced attacks in cluster headache. Cephalalgia 20:85–91. doi:10.1046/j.1468-2982.2000.00026.x
31. Goadsby PJ, Edvinsson L (1994) Human in vivo evidence for trigeminovascular activation in cluster headache Neuropeptide changes and effects of acute attacks therapies. Brain 117:427–434
32. Neeb L, Anders L, Euskirchen P et al (2015) Corticosteroids alter CGRP and melatonin release in cluster headache episodes. Cephalalgia. doi:10.1177/0333102414539057
33. Asghar MS, Becerra L, Larsson HBW et al (2016) Calcitonin gene-related peptide modulates heat nociception in the human brain—an fMRI study in healthy volunteers. PLoS One. doi:10.1371/journal.pone.0150334
34. Asghar MS, Hansen AE, Kapijimpanga T et al (2010) Dilation by CGRP of middle meningeal artery and reversal by sumatriptan in normal volunteers. Neurology 75:1520–1526. doi:10.1212/WNL.0b013e3181f9626a
35. Li J, Vause CV, Durham PL (2008) Calcitonin gene-related peptide stimulation of nitric oxide synthesis and release from trigeminal ganglion glial cells. Brain Res. doi:10.1016/j.brainres.2007.12.028

36. Ashkenazi A (2010) Allodynia in cluster headache. Curr Pain Headache Rep 14:140–144. doi:10.1007/s11916-010-0097-7
37. Bigal ME, Edvinsson L, Rapoport AM et al (2015) Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol 14:1091–1100. doi:10.1016/S1474-4422(15)00245-8
38. Sun H, Dodick DW, Silberstein S et al (2016) Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol 15:382–390. doi:10.1016/S1474-4422(16)00019-3
39. https://clinicaltrials.gov/ct2/results?term=LY2951742
40. https://clinicaltrials.gov/ct2/show/NCT02945046
41. 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
42. O'Brien M (1999) Trigeminal nerve section for chronic migraine neuralgia. In: Olesen JGP (ed) Clust. Headache Relat. Cond. Oxford University Press, Oxford, pp 291–295
43. Gaul C, Diener H, Solbach K et al (2014) EHMTI-0364. Non-invasive vagus nerve stimulation using gammacore® for prevention and acute treatment of chronic cluster headache: report from the randomized phase of the preva study. J Headache Pain 15:I7. doi:10.1186/1129-2377-15-S1-I7
44. Nesbitt AD, Marin JCA, Tompkins E et al (2015) Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. Neurology 84:1249–1253. doi:10.1212/WNL.0000000000001394
45. Magis D, Schoenen J (2012) Advances and challenges in neurostimulation for headaches. Lancet Neurol 11:708–719. doi:10.1016/S1474-4422(12)70139-4
46. Leone M, Proietti Cecchini A, Messina G, Franzini A (2016) Long-term occipital nerve stimulation for drug-resistant chronic cluster headache. Cephalalgia. doi:10.1177/0333102416652623
47. Martelletti P, Jensen RH, Antal A et al (2013) Neuromodulation of chronic headaches: position statement from the European Headache Federation. J Headache Pain 14:86. doi:10.1186/1129-2377-14-86
48. Schoenen J, Jensen RH, Lantéri-Minet M et al (2013) Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. Cephalalgia 33:816–830. doi:10.1177/0333102412473667
49. Jürgens TP, Barloese M, May A et al (2016) Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache. Cephalalgia. doi:10.1177/0333102416649092
50. Jürgens TP, Schoenen J, Rostgaard J et al (2014) Stimulation of the sphenopalatine ganglion in intractable cluster headache: expert consensus on patient selection and standards of care. Cephalalgia 34:1100–1110. doi:10.1177/0333102414530524
51. Fontaine D, Lazorthes Y, Mertens P et al (2010) Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. J Headache Pain 11:23–31. doi:10.1007/s10194-009-0169-4
52. Leone M, Proietti Cecchini A (2016) Deep brain stimulation in headache. Cephalalgia 36:1143–1148. doi:10.1177/0333102415607176
53. Akram H, Miller S, Lagrata S et al (2016) Ventral tegmental area deep brain stimulation for refractory chronic cluster headache. Neurology 86:1676–1682. doi:10.1212/WNL.0000000000002632
54. Jürgens TP, Leone M, Proietti-Cecchini A et al (2009) Hypothalamic deep-brain stimulation modulates thermal sensitivity and pain thresholds in cluster headache. Pain 146:84–90. doi:10.1016/j.pain.2009.07.006
55. May A, Leone M, Boecker H et al (2006) Hypothalamic deep brain stimulation in positron emission tomography. J Neurosci 26:3589–3593. doi:10.1523/JNEUROSCI.4609-05.2006
56. 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. doi:10.1111/j.1468-1331.2007.01850.x
57. Leone M, Franzini A, Cecchini AP, Bussone G (2013) Success, failure, and putative mechanisms in hypothalamic stimulation for drug-resistant chronic cluster headache. Pain 154:89–94. doi:10.1016/j.pain.2012.09.011

Neurol Sci (2017) 38 (Suppl 1):S51–S55
DOI 10.1007/s10072-017-2909-6

FACIAL PAIN

Treatments of glossopharyngeal neuralgia: towards standard procedures

Andrea Franzini[1] · Giuseppe Messina[1] · Angelo Franzini[1] · Marcello Marchetti[2] · Paolo Ferroli[1] · Laura Fariselli[2] · Giovanni Broggi[1]

Abstract The degree of disability due to glossopharyngeal neuralgia (GN) refractory to conservative treatments justifies surgical procedures as second-line treatments. Since the first description of this facial pain disorders, many surgical options have been described either via a percutaneous or an open surgical way. Actually, when a neurovascular conflict on root entry zone (REZ) or cisternal portion of the ninth and tenth cranial nerves is identified, microvascular decompression (MVD) is the first surgical option to consider. Many studies have demonstrated its efficacy and safety for the treatment of GN. Recently, stereotactic radiosurgery has gained space in the treatment of selected cases of GN. We provide an overview of the surgical procedures for the treatment of GN and of our own experience.

✉ Andrea Franzini
andrea.franzini1@hotmail.it

Giuseppe Messina
Giusmex@gmail.com

Angelo Franzini
bsvjf@tin.it

Marcello Marchetti
marcello.marchetti@istituto-besta.it

Paolo Ferroli
pferroli@istituto-besta.it

Laura Fariselli
lfariselli@istituto-besta.it

Giovanni Broggi
gbroggi@gmail.com

[1] Neurosurgery Department, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via Celoria 11, 20133 Milan, Italy

[2] Radiosurgery Department, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

Keywords Glossopharyngeal neuralgia · Microvascular decompression · Percutaneous thermorizotomy · Radiosurgery

Introduction

First described by Weisenburg in 1910 in a patient with a cerebellopontine angle tumor [1] glossopharyngeal neuralgia (GN) is a rare facial pain syndrome which overall incidence is estimated to be between 0.2 and 0.7 per 100,000 individuals per year [2, 3]. It is characterized by severe paroxysmal episodes of electric shock-like lancinating pain referred to the external ear canal, the base of the ipsilateral tongue, the tonsil, or the area beneath the angle of the jaw. Pain usually starts in the region of the ear, and then irradiates to the ipsilateral throat region or vice versa; it is triggered by yawning, swallowing, talking, and coughing. It may be accompanied by severe cardiovascular issues, such as life-threatening syncopal episodes, hypotension, bradycardia, or even asystole due to the concomitant involvement of the vagal nerve (which supplies the carotid sinus [4, 5]).

The majority of GN patients have no underlying cause or associated neurological deficit and the syndrome in this case is termed "classic" or idiopathic, while a smaller group is "symptomatic", due to the presence of a structural lesion affecting the distribution of the ninth and tenth cranial nerves [6].

Since the first attempts of sectioning the glossopharyngeal nerve extracranially by Sicard and Rubineau in 1920 [7], many different pharmacological and surgical treatment modalities have been applied to treat GN. In particular, surgery should be considered when a situation of drug intolerance or refractoriness develops [8, 9].

Conservative treatment

Several drugs are used to treat or prevent GN. The pharmacological lines of treatment include anticonvulsants, analgesics, steroids, and antidepressants, which can be helpful as a single agent or in combination [4]. Carbamazepine is recognized as the best available drug for GN and is the first-line agent used by most physicians. Among other anticonvulsants, the most frequently used is phenytoin, lamotrigine, oxcarbazepine, gabapentin, or pregabalin. However, the efficacy of these drugs is variable and could decline over time [4, 10]. When an important cardiovascular component is associated to pain, the administration of atropine can be considered to prevent the possible life-threatening cardiac phenomena [4].

Percutaneous surgical methods

The first percutaneous radiofrequency thermocoagulation for GN has been reported in 1974 by Lazorthes and Verdie [11, 12]. Since then, many authors have described series of patients treated for GN with percutaneous radiofrequency coagulation of the petrous ganglion and nerves inside the jugular foramen [3, 13–18]. The aim of this procedure is to selectively destroy the pain fibers through an inserted electrode by thermocoagulation at, or, above 65 °C. As described by Giorgi and Broggi, the entry site for cannulation of the jugular foramen is a point 3.5 cm lateral to the labial commissure. The rigid electrode is then introduced along a trajectory at 12° laterally to the sagittal plane and at 40° inferior to a plane passing through the internal auditory meatus and the inferior margin of the orbit [13]. Lateral fluoroscopic images in this procedure are important to track the advancing of the needle, and to avoid entering other cranial foramina with possible devastating consequences due to the lesion of vascular and nervous structures. When the electrode tip has reached the jugular foramen, electrophysiology is important to check that the "pars nervosa" of the foramen has been correctly cannulated. If it occurs, low-voltage stimulation elicits paraesthesias in the distribution of the ninth cranial nerve. A continuous monitoring of the systemic pressure and heart rate during the procedure is important to interrupt the coagulation in case that signs of tenth nerve involvement (such as bradycardia or hypotension) appear. This technique was adopted at our institution in a series of 14 patients with medically refractory GN, which was published in 1984 by one of the senior authors (G.B.). This report shows that the procedure was efficacious in abolishing pain, even though all patients had permanent reduction of touch sensation in the pharynx and tonsillar pillar, reduction or abolition of gag reflex, dryness of the oral cavity, and ageusia on the affected side. In one case, persistent swallowing impairment was present after surgery [13].

Even if efficacious in relieving pain, percutaneous radiofrequency thermocoagulation can be hampered by severe morbidity (in particular lower cranial nerves deficits), and could imply significant discomfort for the patient, who is awake during the procedure. Some recent reports disagree with this statement and demonstrate its safety and efficacy, if performed with CT guidance, in a large population and with a long follow-up [3].

Nevertheless, due to the high incidence of side effects and variable effectiveness, this technique has been progressively abandoned in favor of surgical microvascular decompression (MVD) and, more recently, of radiosurgical procedures [19].

Open surgical methods

As well as percutaneous procedures, most open surgical treatments for GN focused on the lesion of the ninth and tenth cranial nerve fibers and nuclei [9]. Following the first surgical experience of Sicard and Rubineau of extracranial nerve avulsion [7], many other open surgical procedures have been described, both at central and peripheral sites, in an intracranial or extracranial location (direct extracranial surgical neurotomies, direct section of glossopharyngeal or vagal nerve in the cerebellopontine angle, and open trigeminal tractotomy-nucleotomy) [9, 12, 19–28].

All these surgical approaches are based on the lesioning of the glossopharyngeal and vagus nerves' neural pathways, and can be hindered by severe side effects, in particular, when upper vagal rootlets are included in the rhyzotomy (dysphagia, dysphonia, dysarthria, hoarseness, and other lower cranial nerves disorders) [29]. As a general principle, lesional procedures for pain should be avoided when alternative and safer treatments are available. Today, the refinement of microsurgical and anesthesiological techniques made microvascular decompression (MVD) one of the most widely used surgical options for GN. So far, this surgical option can be performed with a very low complication rate [9, 29–31].

The first description of an anomalous arterial loop in a patient affected by GN was produced by Lillie and Craig in 1936 [32], but it was Jannetta who recognized that GN was caused by vascular compression and popularized MVD for treating cranial neuralgias [33, 34]. Since then, MVD has become a standard surgical treatment for cranial nerves' compression syndromes, such as trigeminal neuralgia (TN), GN, or hemifacial spasm [35]. MVD is a surgical procedure which purpose is to separate an offending vessel from a compressed nerve. This conflict is a well-established

cause of TN and hemifacial spasm, though controversies still exist on the role of neurovascular conflict in the pathogenesis of GN [35].

The procedure described here has also been described in previous reports [9, 19]. The patient is placed in a supine position with the head rotated to the opposite side of the neuralgia and the ipsilateral shoulder slightly elevated. Exposure of the ipsilateral cerebellopontine and cerebellomedullary cisterns is performed through a retromastoid craniectomy centered on the asterion and extended in a way to be able to expose the medial margin of sigmoid sinus and the inferior margin of transverse sinus. Dura is opened inferior and medially to these sites, and subsequent microsurgical opening of the arachnoid of the cerebellomedullary cistern allows to expose vagal and glossopharyngeal nerves including their root entry zone in the retroolivar sulcus. The vessel that most commonly is found to be responsible of the compression is the posterior-inferior cerebellar artery, followed by vertebral artery (Fig. 1). Paying attention to respect the perforating vessels, compressive arteries are kept away and fixed far from the nerves as well as their root entry zone in the brainstem by interposing little pieces of muscle or fibrillar surgicel, veins are electrocoagulated and cut.

We critically reviewed 20 patients with idiopathic GN who received MVD at our institution between 1990 and 2017.

Experience at our institution

In our institution, 20 consecutive patients with GN have been treated with MVD since 1990. All of these patients were refractory to medications or experienced persistent side effects at the effective dosage. In all cases, contrast-enhanced MRI or CT showed neurovascular compression and excluded cerebellopontine angle masses and signs of demyelinating disease. Duration of pre-operative symptoms ranged between 45 days and 20 years. One patient received section of stylomastoid ligament for suspected Eagle's syndrome, whereas another patient had undergone two percutaneous rhizotomy of the ninth nerve with no result. The follow-up period after MVD ranged from 11 months to 20 years. In 18 patients out of 20, pain

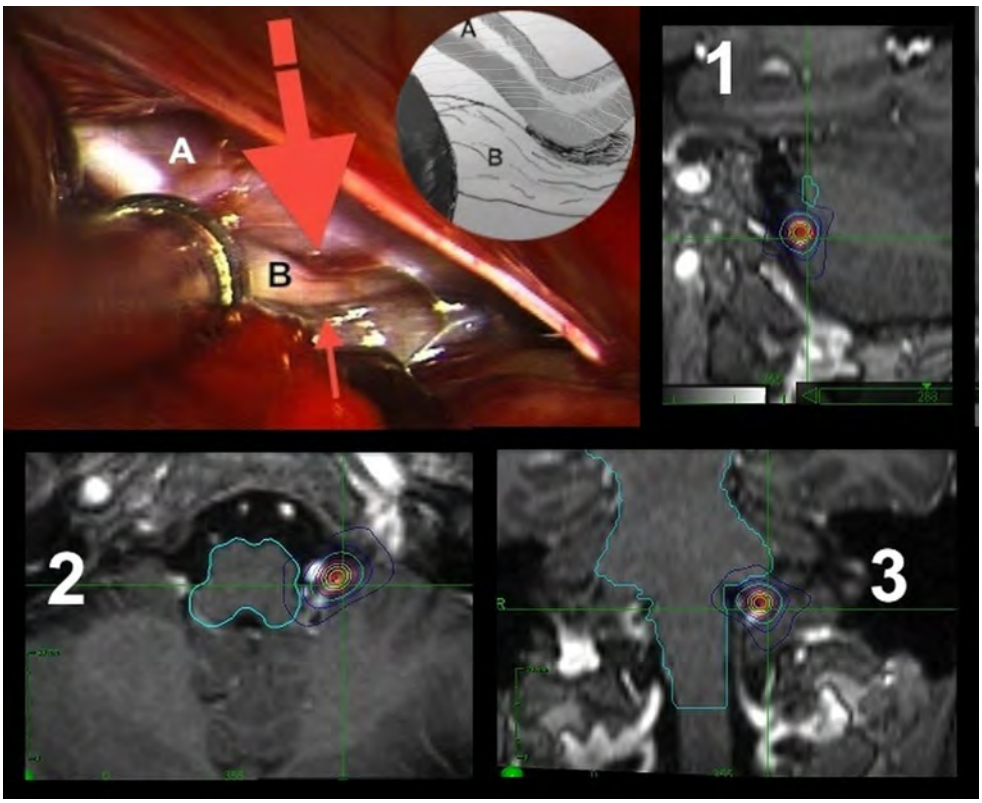

Fig. 1 *Upper left* microsurgical view of the neurovascular conflict between the glossopharyngeal nerve and the vertebral artery; in the *black* and *white circle,* the schematic drawing of the conflict with surgifoam inserted to separate the artery from the nerve sheat (the tip of the microsurgical suction device is included in the *left* of both *pictures*). *Upper right* relationship between the radiosurgical target on the glossopharyngeal nerve and the cerebellum in sagittal MRI picture (T1). *Lower left* and *lower right* the radiosurgical target on the glossopharyngeal nerve in axial (*2*) and coronal (*3*) MRI pictures (T1) showing the relationships with the brainstem

disappeared immediately after surgery. In the two remaining patients, it faded in the following 2 weeks. After 2 and 5 years, two patients required repeated surgery for recurrence of pain. In one patient, pain recurred 11 months following MVD after a laryngitis. He was treated with Cyberknife radiosurgery and actually is pain free. A total of 17 patients were pain free at long-term follow-up (11 months–20 years). We did not observe mortality or long-term surgical morbidity in our series, although about one-third of patients had transitory cranial nerve deficit. Of three patients experiencing CSF rhinorrhea, two were successfully treated with few days of external lumbar drainage, and one developed a meningitis, thus requiring revision surgery to seal the fistula. Cephalea and nausea were common in the immediate post-operative period, due to deliquoration and intracranial hypotension.

Our experience is in agreement with a recent literature review on 28 patient series which shows that MVD is a safe and effective procedure to treat GN with a overall relief from pain varying from 50 to 100% of patients, and with lower recurrences and morbidity rates than percutaneous thermorizotomy [12]. An experienced team and intra-operative neurophysiological monitoring and endoscopic assistance could be useful to achieve excellent results with MVD [36].

Radiosurgery

Stereotactic gamma knife radiosurgery (GKR) was first reported for the treatment of TN by Leksell in 1971 [37]. Its use, however, became widely used only after the mid-1990s in conjunction with advancements in neuroimaging, such as MRI. Since then, the efficacy of GKR for TN, as reported in the literature, has resulted to be comparable to that of MVD. As far as the pathophysiology of GN is considered to be similar to that of TN, the use of GKR was extended to the treatment of GN. Some series have been reported concerning the radiosurgical treatment of GN with radiosurgery devices with satisfactory results despite a higher recurrence rate than in MVD is observed [12, 38–41].

Indications to radiosurgery (RS) are mainly clinical. Contrary to MVD, the presence of an MRI evidence of a neurovascular conflict is not mandatory. Particularly RS would be indicated for all the patients who are less than ideal candidates for open surgery, due to the age or relevant comorbidity. Moreover, the patient's preference can also be considered.

In general, the RS target is a little portion of the intracisternal portion of the glossopharyngeal nerve. The glossopharyngeal meatus of the foramen lacerum could also be considered [38].

The precise radiation dose to obtain a pain relief is not defined yet, and it may widely change according to the considered device. In general, the dose ranges from 55 to 90 Gy, delivered in single fraction [38–41].

At our institution, Cyberknife has been available since March 2004 and it is commonly and effectively used so far to treat patients suffering for a trigeminal neuralgia [42].

Three patients with refractory GN have been treated with CK so far. Our results are still to b considered preliminary. However, the potential of this treatment modality (together with the observed absence of toxicities and the patients comfort) suggests a concrete future development.

Discussion and conclusions

Because of the high incidence of side effects, such as dysphagia, vocal cord paralysis, and impaired gag reflex [12], and the high risk of lesioning important vascular structures (such as the internal carotid artery and the internal jugular vein, in proximity to the foramen lacerum), percutaneous thermal rhizotomy is too dangerous and unpredictable and should not be recommended anymore. Otherwise, in the future, better imaging techniques and technology to accurately track instruments according to images, such as frameless stereotaxy, may favor the resurgence of this procedure.

As stated, MVD is a functional, safe, and efficacious procedure, and according to the pain treatment policy of our institution, it is the first treatment of choice for patients, whose age is under 70, and who can tolerate open surgery in general anesthesia.

Cyberknife and stereotactic radiosurgery should be reserved to patients who are unable to tolerate intracranial procedures because of old age or comorbidities, who refuse open surgery, or who did not benefit from MVD, or to recurrent patients.

Acknowledgements This work was supported by IRCCS Fondazione Istituto Neurologico Carlo Besta, Milan, Italy.

Compliance with ethical standards

Conflict of interest This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Weisenburg TH (1910) Cerebello-pontine tumor diagnosed for six years as tic doloureux. The symptoms of irritation of the ninth and twelfth cranial nerves. JAMA 54:1600–1604
2. Pearce JM (2006) Glossopharyngeal neuralgia. Eur Neurol 55:49–52

3. Wang X, Tang Y, Zeng Y, Ni J (2016) Long-term outcomes of percutaneous radiofrequency thermocoagulation for glossopharyngeal neuralgia. Medicine 95(48):e5530
4. Blumenfeld A, Nikolskaya G (2013) Glossopharyngeal neuralgia. Curr Pain Headaches Rep 17:343
5. Ori C, Salar G, Giron GP (1985) Cardiovascular and cerebral complications during glossopharyngeal nerve thermocoagulation. Anaesthesia 40:433–437
6. The international classification of headache disorders, 2nd edn. (2004) Cephalalgia, pp 1–160
7. Sicard R, Robineau J (1920) Communications et presentations: Algie vèlo-pharyngèe essentielle. Traitement chirurgical. Rev Neurol 36:256–257
8. Ma Y, Li YF, Wang Q, Wang B, Huang H (2016) Neurosurgical treatment of glossopharyngeal neuralgia: analysis of 103 cases. J Neurosurg 124:1088–1092
9. Ferroli P, Fioravanti A, Schiariti M, Tringali G, Franzini A, Calbucci F, Broggi G (2009) Microvascular decompression for glossopharyngeal neuralgia: a long-term retrospectic review of the Milan-Bologna experience in 31 consecutive cases. Acta Neurochir 151:1245–1250
10. O'Neill F, Nurmikko T, Sommer C (2017) Other facial neuralgias. Cephalalgia 0(0):1–12
11. Lazorthes Y, Verdie JC (1979) Radiofrequency coagulation of the petrous ganglion in glossopharyngeal neuralgia. Neurosurgery 4:512–516
12. Jianqing C, Sindou M (2015) Vago-glossopharyngeal neuralgia: a literature review of neurosurgical experience. Acta Neurochir 157:311–321
13. Giorgi C, Broggi G (1984) Surgical treatment of glossopharyngeal neuralgia and pain from cancer of the nasopharynx. J Neurosurg 61:952–955
14. Arias MJ (1986) Percutaneous radio-frequency thermocoagulation with low temperature in the treatment of essential glossopharyngeal neuralgia. Surg Neurol 25:94–96
15. Isamat F, Ferran E, Acebes JJ (1981) Selective percutaneous thermocoagulation rhizotomy in essential glossopharyngeal neuralgia. J Neurosurgery 55:575–580
16. Sindou M, Henry JF, Blanchard P (1991) Idiopathic neuralgia of the glossopharyngeal nerve. Study of a series of 14 cases and review of the literature. Neurochirurgie 37:18–25
17. Oris C, Salar G, Giron G (1983) Percutaneous glossopharyngeal thermocoagulation complicated by syncope and seizures. Neurosurgery 13:427–429
18. Salar G, Ori C, Baratto V, Iob I, Mingrino S (1983) Selective percutaneous thermolesions of the ninth cranial nerve by lateral cervical approach: report of eight cases. Surg Neurol 20:276–279
19. Franzini A, Ferroli P, Messina G, Broggi G (2010) Surgical treatment of cranial neuralgias. Handb Clin Neurol 97:679–692
20. Bernard EJ, Nashold BS, Caputi F, Moossy JJ (1987) Nucleus caudalis DREZ lesions for facial pain. Br J Neurosurg 1:81–92
21. Crue BL, Carregal JA, Felsoory A (1972) Percutaneous stereotactic radiofrequency: trigeminal tractotomy with neurophysiological recordings. Confin Neurol 34:389–397
22. Hitchcock E (1970) Stereotactic trigeminal tractotomy. Ann Clin Res 2:131–135
23. Isamat F, Ferran E, Acebes JJ (1981) Selective percutaneous thermocoagulation rhizotomy in essential glossopharyngeal nevralgia. J Neurosurg 55:575–580
24. Kanpolat Y, Savas A, Batay F, Sinav A (1998) Computer tomography-guided trigeminal tractotomy–nucleotomy in management of vagoglossopharyngeal and geniculate neuralgias. Neurosurgery 43:484–489
25. Kunz Z (1965) Treatment of essential neuralgia of the 9th nerve by selective tractotomy. J Neurosurg 23:494–500
26. Rushton JG, Stevens JC, Miller RH (1981) Glossopharyngeal (vagoglossopharyngeal) neuralgia: a study of 217 cases. Arch Neurol 38:201–205
27. Taha JM, Tew JM Jr (1995) Long-term results of treatment of idiopathic neuralgias of the glossopharyngeal and vagal nerves. Neurosurgery 36:926–931
28. Tew JM Jr, Tobler WD, Van Loveren H (1982) Percutaneous rhizotomy in the treatment of intractable facial pain. In: Schmidek HH, Sweet WH (eds) Operative neurosurgical techniques, vol 2. Grune and Stratton, New York, pp 1083–1106
29. Rey-Dios R, Cohen-Gadol AA (2013) Current neurosurgical management of glossopharyngeal neuralgia and technical nuances for microvascular decompression surgery. Neurosurg Focus 34:E8
30. Kandan SR, Khan S, Jeyaretna DS et al (2010) Neuralgia of the glossopharyngeal and vagal nerves: long-term outcome following surgical treatment and literature review. Br J Neurosurg 24:441–446
31. Patel A, Kassam A, Horowitz M et al (2002) Microvascular decompression in the management of glossopharyngeal neuralgia: analysis of 217 cases. Neurosurgery 50:705–711
32. Lillie H, Craig WM (1936) Anomalous vascular lesion in the cerebellopontine angle. Arch Otolaryngol 23:642–645
33. Laha RK, Jannetta PJ (1977) Glossopharyngeal neuralgia. J Neurosurg 47:316–320
34. Jannetta PJ (1977) Observation on the aetiology of trigeminal neuralgia, hemifacial spasm, acoustic nerve dysfunction and glossopharyngeal neuralgia. Definitive microsurgical treatment and result in 117 patients. Neurochirurgia (Stutt) 20:145–154
35. Xiong N, Zhao H, Zhang FC, Liu RE (2012) Vagoglossopharyngeal neuralgia treated by microvascular decompression and glossopharyngeal rhizotomy: clinical results of 21 cases. Stereotact Funct Neurosurg 90(1):45–50
36. Broggi G, Scaioli V, Brock S et al (1995) Neurophysiological monitoring of cranial nerves during posterior fossa surgery. Acta Neurochir Suppl 64:35–39
37. Leksell L (1971) Stereotaxic radiosurgery in trigeminal neuralgia. Acta Chir Scand 137(4):311–314
38. Stieber VW, Bourland JD, Ellis TL (2005) Glossopharyngeal neuralgia treated with gamma knife surgery: treatment outcome and failure analysis. Case report. J Neurosurg 102(Suppl):155–157
39. Leveque M, Park MC, Melhaoul A, Yomo S, Donnet A, Règis J (2011) Gamma knife radiosurgery for glossopharyngeal neuralgia: marseille experience. J Radiosurg SBRT 1:41–46
40. Martinez-Alvarez R, Martinez-Moreno N, Kusak ME, Rey-Portoles G (2014) Glossopharyngeal neuralgia and radiosurgery. J Neurosurg 121(Suppl):222–225
41. Kano H, Urgosik D, Liscak R, Pollock BE et al (2016) Stereotactic radiosurgery for idiopathic glossopharyngeal neuralgia: an international multicenter study. J Neurosurg 125(Suppl 1):147–153
42. Fariselli L, Marras C, De Santis M, Marchetti M, Milanesi I, Broggi G (2009) Cyberknife radiosurgery as a first treatment for idiopathic trigeminal neuralgia. Neurosurgery 64(2 Suppl):A96–A101

Neurol Sci (2017) 38 (Suppl 1):S57–S61
DOI 10.1007/s10072-017-2863-3

FACIAL PAIN

Usefulness of an occlusal device in the treatment of medication overuse headache and persistent idiopathic facial pain: preliminary results

H. A. Didier[1] · M. Curone[2] · V. Tullo[2] · A. H. Didier[3] · R. Cornalba[4] · A. B. Giannì[5] · G. Bussone[2,6]

Abstract There is a debate in literature about the therapeutic usefulness of oral devices in patients suffering from Medication Overuse Headache (MOH) or in patients suffering from Persistent Idiopathic Facial Pain (PIFP). From the case histories of 3356 patients, referred to us with a diagnosis of chronic craniofacial pain for assessment of the eventual application of an occlusal device to correct an impaired neuromuscular relationship between the mandible and the maxilla, we selected, following the criteria of the International Classification of Headache Disorders (ICHD-3beta), two groups of patients suffering from MOH and PIFP. All patients of the two groups underwent a Kinesiographic exam and an EMG to evaluate the freeway space (FWS). Patients presenting an impaired FWS were placed in treatment with the application of an occlusal device. At the follow-up after 6 months and after 1 year, we found a significant decrease in pain with regard to the intensity resulting in the reduction of clinical disability. The preliminary data collected using the VAS scale and the MIDAS questionnaire confirm that the neuromuscular cranio-mandibular system can have an important role in the diagnostic process of the MOH and the PIFP, suggesting the usefulness of treatment with an occlusal device, where there is adequate FWS.

Keywords Freeway space (FWS) · TENS · Medication overuse headache (MOH) · Persistent idiopathic facial pain (PIFP) · Orthosis

✉ H. A. Didier
henri.didier@unimi.it

[1] Dental and Oral Surgery, University of Milan and Headache and Facial Pain Center, Maxillo-facial and Dental Unit, IRCCS Foundation Ca' Granda, Maggiore Policlinico Hospital, University of Milan, Milan, Italy

[2] Igea Healthcare Institute, Milan, Italy

[3] U.O.C. Hospital Pharmacy, ASST Melegnano Martesana, Milan, Italy

[4] School of Orthodontics, University of Milan, Milan, Italy

[5] Maxillo-facial and Dental Unit, Department of Biomedical, Surgical and Dental Sciences, IRCCS Foundation Ca' Granda, Maggiore Policlinico Hospital, The University of Milan, Milan, Italy

[6] C. Besta Neurological Institute Foundation and Igea Healthcare Institute, Milan, Italy

Introduction

The freeway space between the dental arches (FWS) is the distance that the mandible performs about once a minute, during swallowing, to pass from the rest position to the maximum intercuspation.

This freeway space between the two dental arches is to be considered normal when it is between 1.4 and 2.5 mm. It is important to distinguish the habitual mandibular rest position in which agonistic and antagonistic muscles are not involved but is maintained by muscle tone, and the physiological rest position which corresponds to the state of minimal activity of the masticatory muscles achieved through the use of transcutaneous electrical nerve stimulation (TENS).

The habitual rest position is often conditioned by stress, by parafunctions (grinding and clenching) or occlusal problems. The role of the TENS is to identify, through the use of the EMG–Kinesiograph, the discrepancies between the habitual rest position and the physiological position and between the habitual closing trajectory and the

physiological–neuromuscular trajectory, through the deprogramming of the masticatory muscles [1–3].

For this reason, the EMG exam and the Kinesiograph were chosen as fundamental instruments for the study of the neuromuscular component of patients suffering from chronic craniofacial pain.

Materials and methods

In recent years, as part of the activity of the Craniofacial Pain Center of the University Hospital of Milan, 3356 patients (1118 male and 2238 female) with an average age of 40, suffering from chronic craniofacial pain of various origins, underwent Kinesiography and EMG [5–8]. We assessed the FWS of all patients and the advancement or retrusion of the mandible in habitual rest and in habitual occlusion, comparing it with that obtained after neurostimulation with TENS. The instrumentation used (Myotronics/Normed Inc. Tukwila, Washington, USA) consists of a K7/EMG electromyograph, a K7/CMS Kinesiograph with its magnet and a J4 Myomonitor TENS unit with Myotrode SG mono-polar electrodes.

From the entire case histories, we selected two groups of patients: the first group of 88 suffering from Medication Overuse Headache (MOH) and the second of 49 suffering from Persistent Idiopathic Facial Pain (PIFP). The diagnosis for the two groups was made according to ICDH—3rd edition criteria (beta version 2013) [4]. All patients underwent Kinesiographic and EMG investigation and from these 60 suffering from MOH and 38 suffering from PIFP were selected because they presented a FWS adaptable for the application of an oral device in acrylic resin called "Orthosis" to be worn 20/22 h a day for 1 year.

The aim of the study was to evaluate the efficiency of the oral treatment paying particular attention to the disability and to the patients' perception of pain, using the MIDAS questionnaire for disability and the VAS scale for perception of pain, at the beginning of the treatment (TO), at 6 months (T1) and after 12 months (T2).

With regard to the data obtained from Kinesiographic and EMG examination of the two groups of patients, the habitual values of FWS were considered, measured on scan 3 (Fig. 1), compared with those measured after neurostimulation with TENS on scan 4 (Fig. 2) and the mandibular advancement or retrusion values measured on scan 5 (Fig. 3). The TENS used is characterized by a pulse duration of 500 μs, with a frequency of 40 pulses per minute and with a variable intensity from 0 to 25 mA, depending on the threshold of each individual patient. The electrodes for the neurostimulation, monopolar and disposable, were applied for 45 min on the coronoid notch of the mandible in the depth of which pass the branches of the V° and VII° pairs of cranial nerves [9–13].

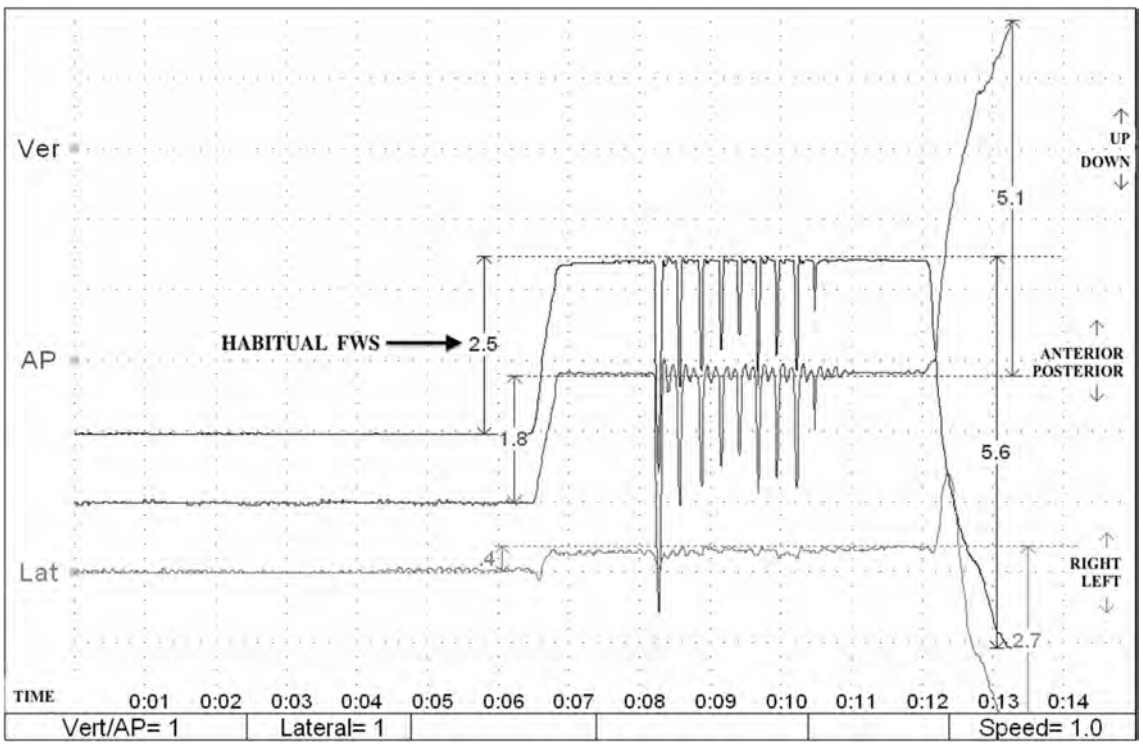

Fig. 1 Analysis of habitual FWS values

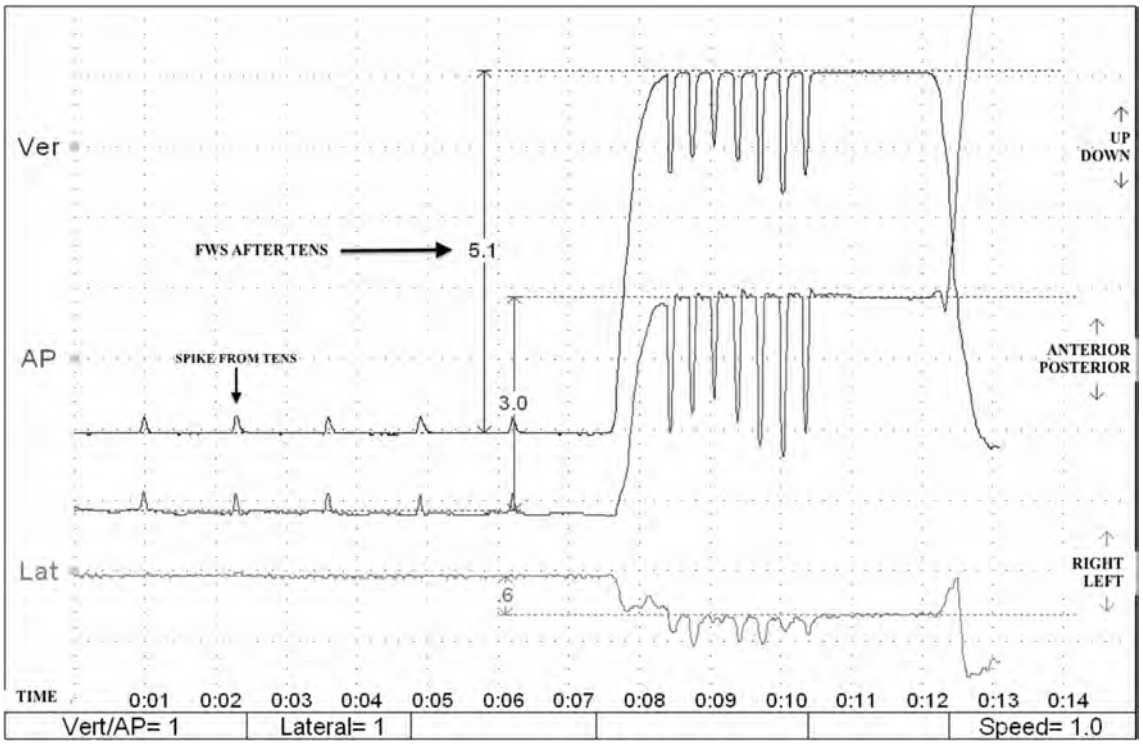

Fig. 2 Analysis of FWS values after TENS

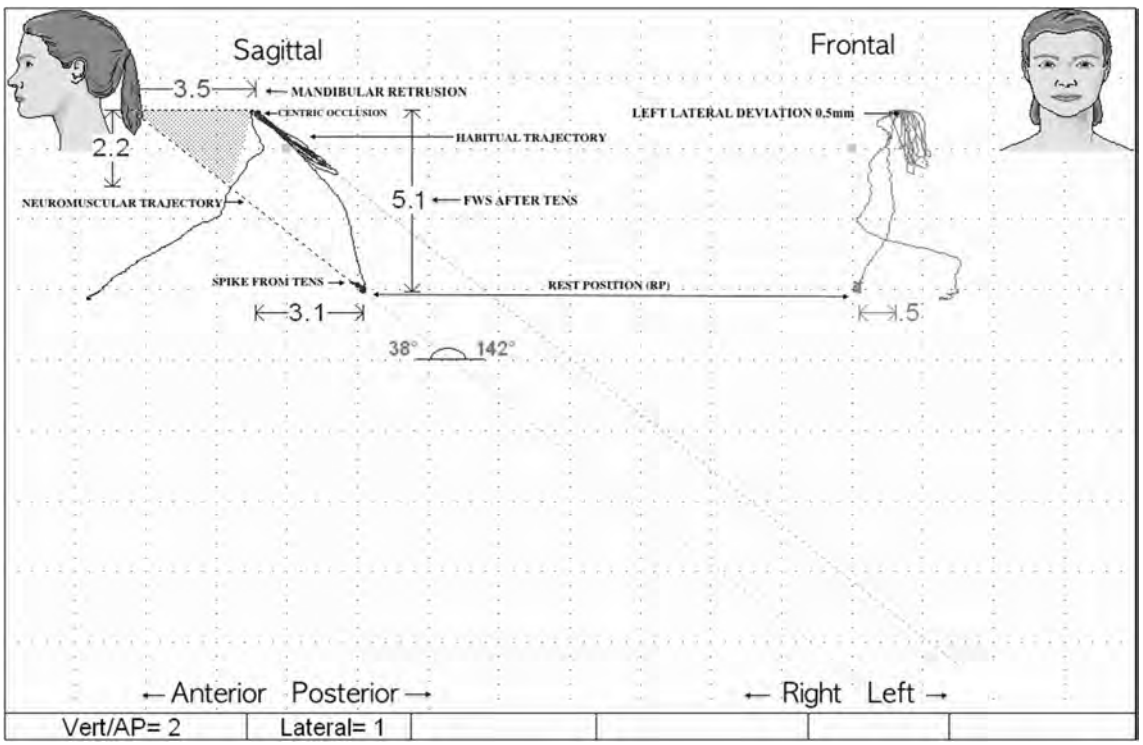

Fig. 3 Example of the registration of the discrepancy between the habitual closing trajectory compared to that induced from TENS (neuromuscular trajectory) on the sagittal and *frontal planes* which in this patient proves to be retruded by 3.5 mm and have a FWS of 5.1 mm. It also shows a *left* lateral deviation of 0.5 mm. All these alterations can be corrected with the application of an 'orthosis'

Results

The follow-up study at 6 months and at 12 months revealed a significant decrease in pain regarding the intensity, which resulted in a reduction of clinical disability. Within the selected groups of patients the mean values of VAS showed a reduction in pain from 5.05 to 2.18 (S.D. 0.98) for the patients with MOH and from 6.21 to 3.52 (S.D. 1.33) for the patients with PIFP and an average disability improvement from the questionnaire MIDAS for MOH from 3.31 to 1.49 (S.D. 0.78) and for PIFP from 2.65 to 1.44 (S.D. 0.86). The patients with PIFP from the questionnaire MIDAS showed a reduction in lost working days from 180 to 80 per year at the follow-up at one year and regarding the patients with MOH from 240 to 100 lost working days. The relative graphs show the mean values of the MIDAS and the VAS before and after the application of the orthosis at 6 and 12 months (Figs. 4, 5, 6, 7). For all the samples analyzed (PIFP and MOH), the data were processed using the Student *t* test for paired data.

The test showed that the mean values before and at 12 months from the application of the orthosis were statistically significant for $P < 0.05$.

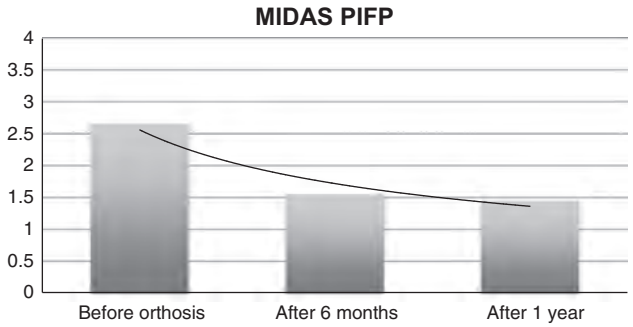

Fig. 4 Degrees of disability: average from I° to IV°

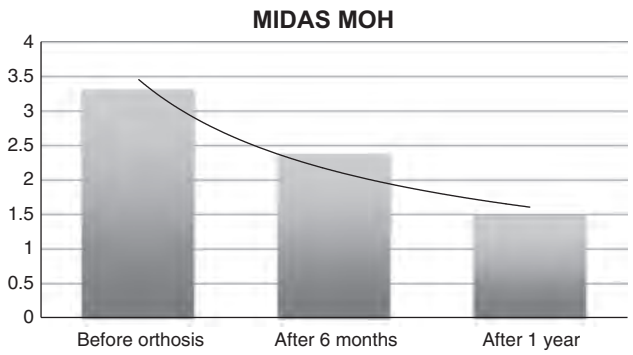

Fig. 5 Degrees of disability: average from I° to IV°

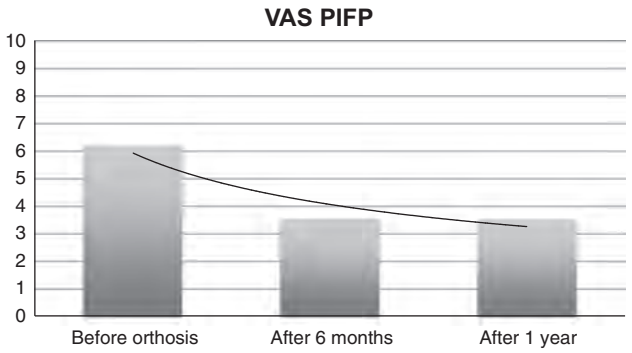

Fig. 6 *Scale* of perceived pain: average from 1 to 10

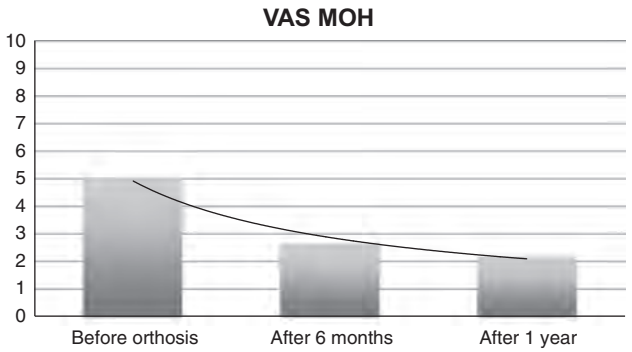

Fig. 7 *Scale* of perceived pain: average from 1 to 10

Conclusions

The alteration of the FWS may be secondary to iatrogenic injury (prosthetic or orthodontic), to parafunctions (grinding and clenching), to causes related to chronic stress, to multiple deviations from normal functional development in the first few years of life as well as a phylogenetic developmental component that can determine structural modifications of the splanchnocranium in respect to the neurocranium.

The application of TENS is indicated to properly assess such information coming from the study of the patient's neuromuscular system enabling discrimination on the use of occlusal therapy that can return the (FWS) to conditions of physiological rest.

In the two groups of patients studied, the clinical benefit confirmed by the significant reduction in the intensity of pain from the VAS scale and the improvement of disability from the MIDAS questionnaire suggest that the therapeutic approach with an occlusal device is safe, well tolerated and effective in the therapy for MOH and PIFP. These encouraging preliminary findings suggest that further research is warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to the publication of this article.

References

1. Konchak Peter A, Thomas Norman R, Lanigan Dennis T, Devon Richard M (1988) Freeway space measurement using mandibular Kinesiograph and EMG before and after TENS. Angle Orthod 58(4):343–350
2. G. Ferronato, R. Peretta M. Franco, G. Borgo (1993) La recidiva nella chirurgia ortognatica delle terze classi. Nota I: l'ipotesi dell'eziologia neuro-muscolare. Revisione della letteratura. Cattedra di Chirurgia Maxillo-Facciale Università di Padova
3. Jankelson B, Radke JC (1978) The Myo-monitor: its use and abuse (I). Quintessence Int Dent Dig 9(2):47–52
4. Prosthet Dent J (1979) A clinical study of rest position using the Kinesiograph and Myomonitor. George JP Boone M 41(4):456–462
5. Headache Classification Committee of the International Headache Society (2013) The international classification of headache disorders, 3rd edition (beta version). Cephalgia 33(9):629–808
6. Didier H, Marchetti C, Borromeo G, D'Amico D, Tullo V, Bussone G, Santoro F (2011) Chronic daily headache: suggestion for the neuromuscular oral therapy. Neurol Sci 32(Suppl 1):S161–S164
7. Didier H, Marchetti C, Marchetti A, D'Amico D, Tullo V, Bussone G, Santoro F (2012) Implementing gnathological and neuromuscolar concepts in patients with chronic migraine. Neurol Sci 33(Suppl 1):S177–S180
8. Didier H, Marchetti C, Marchetti A, D'Amico D, Tullo V, Proietti Cecchini A, Di Fiore P, Bussone G, Santoro F (2013) Positive outcome of occlusal freeway space restablishment in patients with medication overuse due to chronic migraine. Neurol Sci 34(Suppl 1):S171–S173
9. Didier H, Marchetti C, Borromeo G, Tullo V, Bussone G, Santoro F (2010) Persistent idiopathic facial pain: multidisciplinary approach and assumption of comorbidity. Neurol Sci 31(Suppl 1):S189–S195
10. Jankelson B (1969) Electronic control of muscle contraction—a new clinical era in occlusion and prostodontics. Sci Educ Bull 2(1):29–31
11. Jankelson B (1980) Measurement accuracy of the mandibular Kinesiograph: a computerized study. J Prosthet Dent 44(6): 656–666
12. Tingey EM, Buschang PH, Throckmorton GS (2001) Mandibular rest position: a reliable position influenced by head support and body posture. Am J Orthod Dentofac Orthop 120(6):614–624
13. Cooper Barry C, Kleinberg Israel (2008) Establishment of a temporomandibular physiological state with neuromuscular orthosis treatment affects reduction of TMD symptoms in 313 patients. J Craniomandib Pract 26(2):104–117

Neurol Sci (2017) 38 (Suppl 1):S63–S65
DOI 10.1007/s10072-017-2892-y

VIEW AND PERSPECTIVES

The role of radiosurgery in trigeminal neuralgia

Laura Fariselli[1] · Francesco Ghielmetti[2] · Davide Bosetti[1] · Angelo Franzini[1] · Marcello Marchetti[1]

Abstract A short review of clinical use of radiosurgery in trigeminal neuralgia is offered.

Keywords Trigeminal neuralgia · Radiosurgery

Trigeminal neuralgia (TN) is a neurological condition related to recurrent episodes of severe pain irradiated in trigeminal territory. It is the most frequently encountered type of craniofacial neuralgia. It is usually the foremost consideration in the differential diagnosis when a patient reports intermittent, paroxysmal pain confined to the distribution of the trigeminal nerve. The incidence is of 2–5 cases/100,000 inhabitants per year [1]. The etiology is not very well known and as a consequence the treatment schedule is inconsistent with the etiology [2]. Drugs relieve pain in approximately 75% of patients and are the first treatment of choice. However, in 25–50% of cases, higher doses or several drugs are needed, or medication becomes contraindicated. In such cases, it may be necessary to give patients other approaches; for example, surgery. In the past, different surgical approaches have been proposed: Gasserectomy with Roos, in 1890, Retrogasserian Neurotomy with Frazier in 1901, Retrogasserian Neurotomy with Dandy in 1920, Trigeminal Tractotomy with Sjoqvist, in 1938, Temporal Intradural Decompression with Taarnhoj in 1952 [3]. At present microvascular decompression (MVD) and percutaneous rhizotomy are the commonly used surgical procedures [3]. Nevertheless, surgery has high rates of recurrence and MVD has also high risk in terms of posterior fossa complications; other procedures are associated with relevant rates of numbness [4].

Radiosurgery (RS) was introduced for the first time in 1951 by Leksell as a possible alternative to surgery: the first TN patient was treated by Leksell using Gamma Knife, irradiating the trigeminal ganglion [3]. Other possible targets were analyzed to obtain the best result in terms of pain relief with decreased risk of complications, overall numbness or anesthesia dolorosa [5, 6]. Targeting the retrogasserian region of the nerve and dose escalation studies resulted in improved pain resolution in 70–90% of treated patients with doses of at least 70 Gy [6, 7]. In our experience CT and MR were used to target the retrogasserian portion of the trigeminal nerve (Fig. 1) for a length of 3–6 mm (4 mm in 85% of cases); FIESTA protocol (Fast Imaging Employing Steady-state Acquisition) is the most useful sequence to the best definition of trigeminal nerve in all planes (axial, sagittal and coronal) [8–10]. This selected point has been considered eligible following the publication of Regis' prospective trial [11].

The results in terms of pain local control are interesting; nevertheless, a complete durable pain-free status cannot be achieved compared to the result obtained with MVD. 20–30% of patients reported immediate improvement; faster response is observed in patients without previous surgery. At 2 years, 83% of patients keep a good response to radiosurgery with some medication [4–6, 8, 10]. Worse results are observed in patients with multiple sclerosis [12]. The rate of neurological new toxicity is quite low when doses less than 85 Gy are used; larger pre-pontine cisternae offer the possibility of good dose distribution with marginal brainstem total doses lower than 14 Gy [13]. Different pain scale for the correct evaluation of treatment

✉ Marcello Marchetti
marcello.marchetti@istituto-besta.it

[1] Neurosurgery Department, Neurological Institute "Carlo Besta" IRCCS Foundation, Milan, Italy

[2] Health Department, Neurological Institute "Carlo Besta" IRCCS Foundation, Milan, Italy

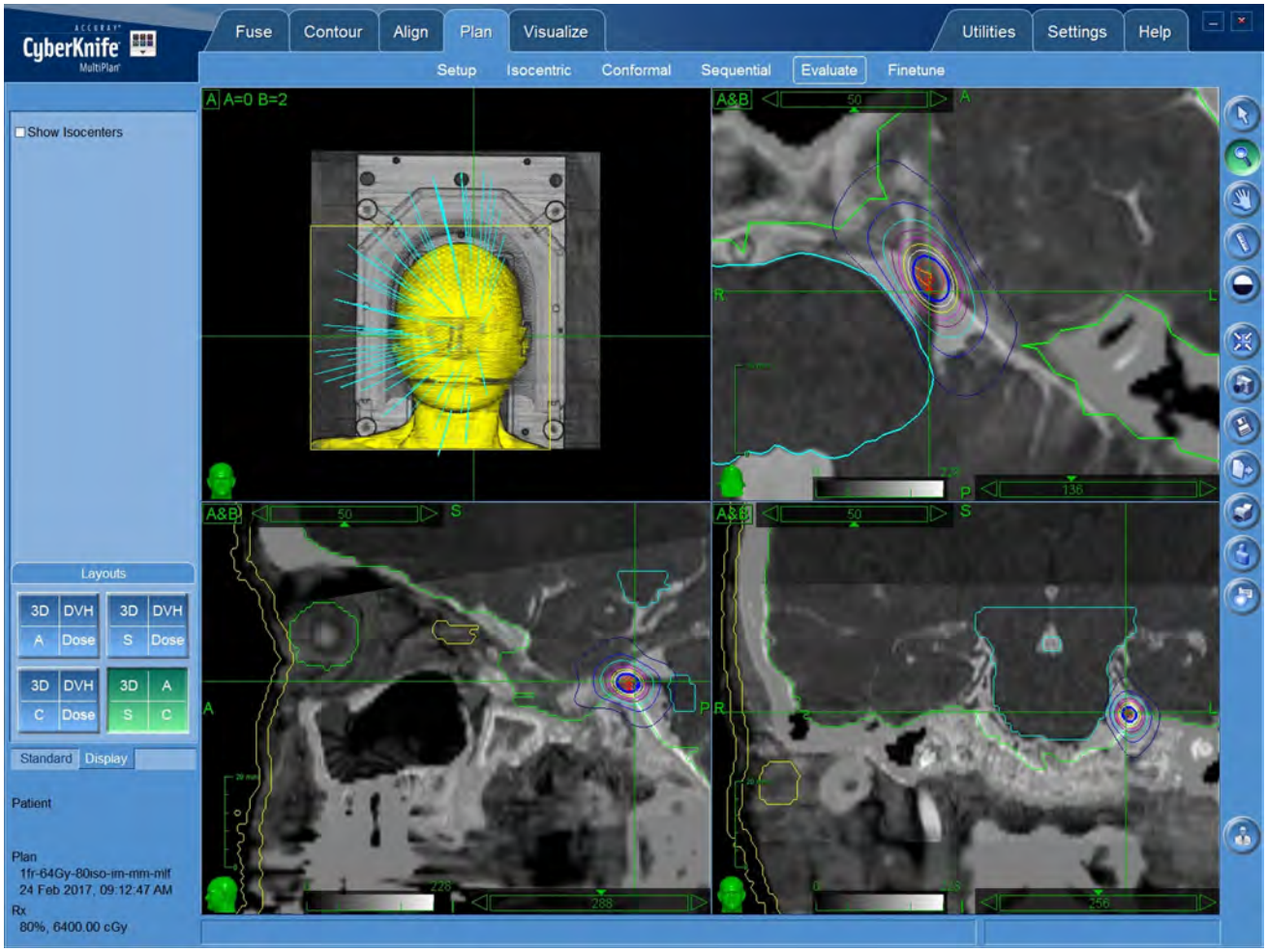

Fig. 1 Radiosurgery treatment, dose distribution in different planes

results is used and this makes the comparison of results difficult.

In conclusion, SRS has become a consolidated tool in the neurosurgeon–radiation oncologist armamentarium; it could be considered as first-line approach in aged patients, in patients with multiple sclerosis or in case of surgical failure.

Compliance with ethical standards

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

Ethical standards This article does not contain any study with human subjects performed by any of the authors.

References

1. Manzoni C, Torelli P (2005) Epidemiology of typical and atypical craniofacial neuralgias. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol 26(Suppl. 2):s65–s67
2. Gorgulho A (2012) Radiation mechanisms of pain control in classical trigeminal neuralgia. Surg Neurol Int 3:S17–S25
3. Patel SK, Liu JK (2016) Overview and history of trigeminal neuralgia. Neurosurg Clin N Am 27(3):265–276. doi:10.1016/j.nec.2016.02.002 **(review)**
4. Pagni CA, Fariselli L, Zeme S (2008) Trigeminal neuralgia. Non-invasive techniques versus microvascular decompression. It is really available any further improvement? Acta Neurochir Suppl 101:27–33 **(review)**
5. Guo S, Chao ST, Reuther AM, Barnett GH, Suh JH (2008) Review of the treatment of trigeminal neuralgia with gamma knife radiosurgery. Stereotact Funct Neurosurg 86:135–146
6. Massager N, Lorenzoni J, Devriendt D, Levivier M (2007) Radiosurgery for trigeminal neuralgia. Prog Neurol Surg 20:235–243
7. Tuleasca C, Carron R, Resseguier N, Donnet A, Roussel P, Gaudart J et al (2012) Patterns of pain free response in 497 cases of classic trigeminal neuralgia treated with gamma knife surgery and followed up for least 1 year. J Neurosurg 117(Suppl.):181–188
8. Fariselli L, Marras C, De Santis M, Marchetti M, Milanesi I, Broggi G (2009) Cyberknife radiosurgery as a first treatment for idiopathic trigeminal neuralgia. Neurosurgery 64(suppl 2):A84–A90

9. Tarricone R, Aguzzi G, Musi F, Fariselli L, Casasco A (2008) Cost-effectiveness analysis for trigeminal neuralgia: cyberknife vs microvascular decompression. Neuropsychiatr Dis Treat 4(3):647–652
10. Villavicencio AT, Lim M, Burneikiene S, Romanelli P, Adler JR, McNeely L, Chang SD, Fariselli L, McIntyre M, Bower R, Broggi G, Thramann JJ (2008) Cyberknife radiosurgery for trigeminal neuralgia treatment: a preliminary multicenter experience. Neurosurgery 62(3):647–655 **(discussion 647–655)**
11. Régis J, Metellus P, Hayashi M, Roussel P, Donnet A, Bille-Turc F (2006) Prospective controlled trial of gamma knife surgery for essential trigeminal neuralgia. J Neurosurg 104(6):913–924
12. Montano N, Papacci F, Cioni B, Di Bonaventura R, Meglio M (2013) What is the best treatment of drug-resistant trigeminal neuralgia in patients affected by multiple sclerosis? A literature analysis of surgical procedures. Clin Neurol Neurosurg 115(5):567–572
13. Régis J (2002) High-dose trigeminal neuralgia radiosurgery associated with increased risk of trigeminal nerve dysfunction. Neurosurgery 50(6):1401–1402 **(author reply 1402–1403)**

Neurol Sci (2017) 38 (Suppl 1):S67–S72
DOI 10.1007/s10072-017-2893-x

COMORBIDITY

Headache and arterial hypertension

Cinzia Finocchi[1] · **Davide Sassos**[1]

Abstract Elevated blood pressure (BP) and headache have long been linked in the medical literature. Headache associated with arterial hypertension is a main concern in emergency department. It is believed that headache may be a symptom attributed to arterial hypertension only if the BP values are very high or rise quickly. Many studies support the hypothesis that migraine patients have an increased risk of developing hypertension, while hypertensive subjects do not seem to have an increased risk of migraine or other types of headache. Conversely many studies found an inverse association. Hypertension has been identified as one of the most important factors of chronic transformation of episodic migraine and increases the cerebrovascular and cardiovascular risk of migraine patients. Migraine and arterial hypertension may share common mechanisms like endothelial dysfunction, deficiency of autonomic cardiovascular regulation and renin angiotensin system involvement. Preventive effects of migraine were described by several antihypertensive agents traditionally beta-blockers, and more recently angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers.

Keywords Arterial hypertension · Headache · Migraine · Vascular risk factors · Blood pressure

✉ Cinzia Finocchi
cfinocchi@neurologia.unige.it

[1] Clinica Neurologica IRCCS Azienda Ospedaliera Universitaria San Martino, IST, Largo Daneo 3, 16132 Genoa, Italy

Introduction

Elevated BP and headache have long been linked in the medical literature [1], with complex and various inferences. First of all headache is probably one of the most classical symptom in relation to arterial hypertension and current hypertension guidelines recommend questioning for headache during the work-up of a hypertensive patient. This condition is considered by the International Classification of Headache Disorders (ICHD) 3rd edition (beta version) as headache attributed to arterial hypertension, with different subtypes [2]. Then, many studies highlighted the possible association and reciprocal influences between hypertension and one of the more frequent types of primary headache, migraine. Finally, we will discuss about possible common pathophysiological mechanisms and shared therapies.

Headache attributed to arterial hypertension

International guidelines establish that headache should be attributed to elevated BP if the systolic BP rises quickly to 180 mmHg or higher, or if the diastolic BP rises to 120 mmHg or higher, and if the headache resolves with normalization of BP [2]. Mild (140–159/90–99 mmHg) or moderate (160–179/100–109 mmHg) chronic arterial hypertension does not appear to cause headache. Ambulatory blood pressure monitoring in patients with mild and moderate hypertension has shown no convincing relationship between blood pressure fluctuations over a 24-h period and presence or absence of headache. In many acute conditions, headaches are associated with various disorders that lead to abrupt, severe, and paroxysmal elevations in BP. Elevated BP is common among patients who access an

emergency department with a chief complaint of headache, more frequently than among patients with other chief complaints [3]. In these subjects, however, improvement in blood pressure is not associated with improvement in headache. In general elevated BP at baseline is associated with less headache relief. Migraineurs with hypertension tend to be less responsive than migraineurs without hypertension to triptans therapy [4].

In the ICHD-3 (beta) classification [2], the headache attributed to arterial hypertension is located in the group of headaches attributed to disorders of homeostasis. When a headache occurs for the first time in close temporal relation to a disorder of homoeostasis, it is coded as a secondary headache attributed to that disorder. This remains true even if the new headache has the characteristics of any of the primary headache disorders classified in Part One of ICHD-3 (beta). When a pre-existing headache with the characteristics of a primary headache disorder becomes chronic, or significantly worsens (usually meaning a twofold or greater increase in frequency and/or severity), in close temporal relation to a disorder of homoeostasis, both the initial headache diagnosis and a diagnosis of headache attributed to disorders of homeostasis are given. Headaches attributed to arterial hypertension are discussed under five major categories and for each one definite criteria have been validated (see Tables 1, 2). Regardless of the specific category, headache attributed to arterial hypertension is often bilateral and pulsating, usually during an acute rise in systolic (to $\geq$180 mmHg) and/or diastolic (to $\geq$120 mmHg) BP and improves after BP normalization.

Table 1 Classification of headaches attributed to disorders of homeostasis (IHS Classification ICHD-3 Beta [2])

10. Headache attributed to disorder of homoeostasis
10.1 Headache attributed to hypoxia and/or hypercapnia
10.1.1 High-altitude headache
10.1.2 Headache attributed to aeroplane travel
10.1.3 Diving headache
10.1.4 Sleep apnoea headache
10.2 Dialysis headache
10.3 Headache attributed to arterial hypertension
10.3.1 Headache attributed to phaeochromocytoma
10.3.2 Headache attributed to hypertensive crisis without hypertensive encephalopathy
10.3.3 Headache attributed to hypertensive encephalopathy
10.3.4 Headache attributed to pre-eclampsia or eclampsia
10.3.5 Headache attributed to autonomic dysreflexia
10.4 Headache attributed to hypothyroidism
10.5 Headache attributed to fasting
10.6 Cardiac cephalalgia
10.7 Headache attributed to other disorder of homoeostasis

Headache/hypertension co-morbidity

Many studies focused on the question if migraine patients have an increased risk of developing arterial hypertension. The results were variable, many studies finding a positive association and others with negative results. In recent years most studies pointed out a positive association. Contradictory results may be partially explained by different relationship between migraine and diastolic and systolic BP values, respectively. Gudmundsson et al. [5], in a large population-based longitudinal study found that migraine patients had lower systolic but higher diastolic BP compared with controls. In particular, a one standard deviation (SD) increase in diastolic BP raises the probability of having migraine of 14% in men (non statistically significant) and 30% in women, while a one SD increase in systolic BP decreases the probability of having migraine of 19% in men and 25% in women. In the same study migraine patients were also found to have lower pulse pressure compared with controls. Bigal et al. [6] pointed

Table 2 Diagnostic criteria for headache attributed to arterial hypertension (IHS Classification ICHD-3 Beta [2])

Description
Headache, often bilateral and pulsating, caused by arterial hypertension, usually during an acute rise in systolic (to $\geq$180 mmHg) and/or diastolic (to $\geq$120 mmHg) blood pressure. It remits after normalization of blood pressure
Diagnostic criteria
A. Any headache fulfilling criterion C
B. Hypertension defined as systolic pressure $\geq$180 mmHg and/or diastolic pressure $\geq$120 mmHg has been demonstrated
C. Evidence of causation demonstrated by either or both of the following
1. Headache has developed in temporal relation to the onset of hypertension
2. Either or both of the following:
(a) headache has significantly worsened in parallel with worsening hypertension
(b) headache has significantly improved in parallel with improvement in hypertension
D. Not better accounted for by another ICHD-3 diagnosis

out that migraine with and without aura were associated with both occurrence of cardiovascular disease and risk factors for cardiovascular disease. Subjects with migraine had a 1.4-fold increased risk of hypertension as compared with subjects without migraine. Scher et al. [7] obtained similar results and underlined that patients with migraine with aura and women have a stronger risk elevation. In a large cohort of hypertensive patients followed for up to 30 years [8], the presence of all headache types studied (episodic migraine, daily headache, nonspecific headache) was predicted by female gender, diastolic BP, and secondary hypertension. Another longitudinal study [9] explored whether self-reported migraine predicted hypertension in a Finnish working-age population during a follow-up, 5 years later. Subjects with migraine at baseline had 1.4-fold significantly increased risk of hypertension as compared with subjects without migraine. Migraine remained a significant independent predictor for hypertension after adjustments for other confounding variables as gender, age, occupational training, living alone, an index of physical activity, body max index and alcohol consumption. Principal limitation was self-reported diagnosis of migraine, that involves the possibility of misdiagnosis, (for example headache attributed to hypertension), conducing to a circular conclusion. Finally, migraine is known to be a risk factor for the development of hypertension during pregnancy in normotensive women (OR 2.87) [10].

Other studies focused on the other side of headache/hypertension comorbidity: whether hypertension increases the risk of different types of headache. In this field too, the results are controversial, with many studies finding an inverse association. In a prospective study on 22,685 adults in Norway [11], high systolic and diastolic BP were associated with reduced risk of non-migrainous headache. For migraine, a similar relation was found only in women. Another large prospective population-based study [12] confirmed the inverse relationship between systolic, diastolic and pulse BP at baseline and any headache. The date was more evident for systolic blood pressure (OD 0.90 per 10 mmHg increase in systolic BP), and pulse pressure (OR 0.84 per 10 mmHg increase in pulse pressure). The strongest evidence was that increased pulse pressure was associated with a lower prevalence of both migraine and tension-type headache. This observation could be related to the so-called hypertension-associated hypalgesia, according to which hypertensive individuals have a higher pain threshold than normotensive ones. The authors link this mechanism to a role of the baroreflex system in modulating nociceptive impulses. However, the inverse relationship between systolic and pulse BP and headache may be explicated too on the basis of the pathological autonomic cardiovascular regulation mainly observed in migraine (see later). Conversely, in a large multi-ethnic urban population study [13], hypertension was found associated with migraine, both with and without aura. The ethnicity did not influence the association. The cross-sectional nature of the study makes difficult to determine the direction of the association.

The last question is whether hypertension has a potential negative effect on primary headaches natural history. Hypertension has been identified as one of the most important factor of chronic transformation of episodic migraine. Mathew et al. [14] reported that patients with chronic daily headache, transformed from originally episodic migraine, had a higher possibility of hypertension. Bigal et al. [15] carried out a randomised case–control study to identify the factors associated with induction and transformation from episodic to chronic migraine. They found a strong association between hypertension and chronic migraine with and without analgesic overuse, when the study group was compared with episodic migraine and chronic posttraumatic headache.

Gipponi et al. [16] studied the risk factors for headache chronicity in three groups of patients with different types of headache: episodic migraine, episodic tension-type headache and chronic daily headache. According Silberstein and Lipton criteria [17] chronic daily headache included transformed migraine, chronic tension-type headache, and medication overuse headache. Hypertension prevalence in chronic daily headache group (16.2%) was significantly higher than both episodic migraine (7.3%) and episodic tension-type headache (6.6%). In this study, hypertension prevalence did not differ between chronic daily headache patients with and without medication overuse, while Huang et al. [18] found that in chronic daily headache the frequency of elevated BP was higher in patients with analgesic overuse than in those without analgesic overuse ($P = 0.011$), with only systolic BP being significantly higher ($P = 0.04$). In the subgroup chronic daily headache not chronic migraine, patients with analgesic overuse were significantly older than those without analgesic overuse. This might be a confounding factor. Acetaminophen that has been linked with a higher incidence of hypertension, was one of the most used drug in this population.

Headache and hypertension common mechanisms

Many observations support the occurrence of an endothelial dysfunction in migraine, with a reduction of vasodilator substances and an increase of endothelium derived contracting factors [19]. Endothelium dysfunction may be both one of the factors that increase the cerebrovascular and cardiovascular risk in migraine subjects and a determinant of hypertension development. On the other hand

hypertension is one of the medical conditions causing endothelial dysfunction and by this mechanism may increase migraine susceptibility and migraine frequency. Nitric oxide (NO) is a very important molecule in the regulation of cerebral and extra-cerebral cranial blood flow and arterial diameters. In migraine, the arteries (in particular cerebral and meningeal) are hypersensitive to NO; this is believed one of the mechanism of migraine attack trigger [20]. Endothelial dysfunction, with impairment of NO, is an important risk factor for both hypertension and cardiovascular disease [21] and may represent a major link between these two conditions and migraine.

Brainstem regions that control the cardiovascular system also have a role in migraine pathophysiology and pain modulation. Hypothalamus and insula have an increasingly recognized role in migraine pathophysiology and control autonomic pathways important for blood pressure. Both subjects with arterial hypertension [22] and migraine patients have pathological autonomic cardiovascular regulation. The deficiency of autonomic cardiovascular regulation may contribute to the onset and persistence of headache [23]. Migraine patients in young age often have low basal values of systolic and diastolic pressure [24]; their autonomic cardiovascular reactivity shows a vagal hyperactivity and a deficiency of the sympathetic system. The basal concentrations of catecholamines (and in particular noradrenaline) have been found low in migraine patients out of the attacks, while, immediately before the attack, the catecholamines levels increase. This sympathetic activation causes platelet aggregation and vasoconstriction. Therefore, migraine patients show an increased sensitivity to catecholamines, [25]. Babayan et al. [26] studied autonomic regulation in migraine patients with and without hypertension. They did not observe significant differences between migraine patients with and without arterial hypertension and controls in the neurogenic heart rate regulation, while migraine patients showed higher values of the vasomotor reactivity independently from their hypertension status. Therefore, the subgroup of migraine hypertensive patients showed arterial baroreflex reduction and orthostatic hypertension. The authors believe that the reduction of arterial baroreflex contributes to the development of arterial hypertension in migraine.

The renin angiotensin system could be another factor responsible for the association between migraine and hypertension. This might explain because some angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers are shown to be effective in preventing migraine, regardless of the presence or not of associated hypertension (see later).

Does hypertension comorbidity influence vascular risk and life expectancy in migraine patients?

Whether migraine in general represents a risk factor for cardiovascular and cerebrovascular disease is still under debate. The risk seems to be limited to particular subtypes of migraine and subgroups of patients. In particular, individuals (especially women) with a history of migraine with aura have a twofold increased risk of ischemic stroke, while individuals with migraine without aura do not show an increased risk of ischemic stroke, myocardial infarction or death due to cardiovascular disease [27].

The occurrence of hypertension in a migraine subject may have a strong effect in increasing vascular risk. Common risk factors (tobacco use, hypertension, hyperlipidemia, obesity and diabetes) increase the risk of vascular events in migraine with and without aura women and must be carefully considered and treated when prescribing combined oral contraceptives [28]. An Italian cross-sectional survey [29] pointed out that migraine patients with hypertension have more frequently a history of stroke/transient ischemic attack (4.4%) in comparison to migraine patients without hypertension (0.7%) or hypertensive patients without migraine (3.1%). However, the number of cerebrovascular events was limited and the causality link between cerebrovascular events and hypertension was not analysed. Courand et al. [8] found that in moderate to severe hypertensive subjects, headache (migraine included) is more frequently associated with subclinical target organ damage, namely hypertensive retinopathy. However, in spite of the presence of a high-risk profile, hypertensive patient with all types headache (migraine patients included) do not have, paradoxically, a worse prognosis over the long term. The study recruited a large cohort of hypertensive patients which are followed for up to 30 years. The authors think that headache in hypertensive subjects should be considered as a warning sign that can provide the patients are correctly monitored.

Use of antihypertensive drugs in migraine prophylaxis

Preventive effects of migraine were described for several antihypertensive agents traditionally beta-blockers, which are recommended as first line preventive therapy by several guidelines, and more recently angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs).

Among beta-blockers, the efficacy of propranolol, atenolol, nadolol, timolol, bisoprolol and nebivolol is supported by controlled studies [30]. The mechanisms underlined the

prophylactic efficacy of beta-blocker treatment in migraine are not fully known, but some data suggest that modified central excitability may be one of the factors [31].

Among ACEIs and ARBs, efficacy in migraine preventive therapy was reported for lisinopril [32], candesartan, telmisartan, olmesartan, irbesartan and valsartan [33], both in hypertensive and normotensive patients. Preventive migraine mechanisms of ACEIs and ARBs remain unclear. ARBs block the renin–angiotensin system as direct antagonist of angiotensin II type I receptors. The anti-migraine effect seems independent from BP lowering. ARBs are found to restore vasoreactivity, attenuate inflammatory and oxidative stress, and regulate the nitric oxide synthase isoenzymes in the brain [33]. Blocking the activation of angiotensin II type I receptors in the caudal ventro-lateral medulla seems attenuate hyperalgesia and play a role in descending pain modulation and nociception [34].

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

Ethical standards This article does not contain any study with human subjects performed by any of the authors.

References

1. Janeway TC (1913) A clinical study of hypertensive cardiovascular disease. Arch Intern Med 12:755–798
2. Headache Classification Committee of the International Headache Society (IHS) (2014) The International Classification of Headache Disorders, 3rd edition (beta version) Cephalalgia 33(9):629–808
3. Friedman BW, Mistry B, West JR, Wollowitz A (2014) The association between headache and elevated blood pressure among patients presenting to an ED. Am J of Em Med 32:976–981
4. Tullo V, Bussone G, Omboni S, Barbanti P, Cortelli P, Curone M, Peccarisi C, Benedetto C, Pezzola D, Zava D, Allais G (2013) Efficacy of frovatriptan and other triptans in the treatment of acute migraine of hypertensive and normotensive subjects: a review of randomized studies. Neurol Sci 34(Suppl 1):S87–S91
5. Gudmundsson LS, Thorgeirsson G, Sigfusson N et al (2006) 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
6. Bigal ME, Kurth T, Santanello N et al (2010) Migraine and cardiovascular disease: a population-based study. Neurology 74:628–635
7. Scher AI, Terwindt GM, Picavet HS et al (2005) Cardiovascular risk factors and migraine: the GEM-population-based study. Neurology 64:614–620
8. Courand PY, Serraille M, Girerd N, Demarquay G, Milon H, Lantelme P, Harbaoui B (2016) The Paradoxical Significance of Headache in Hypertension. Am J Hypert 29:1110–1116
9. Entonen AH, Suominen SB, Korkeila K, Mantyselka PT, Sillanmaki LH, Ojanlatva A, Rautava PT, Koskenvuo MJ (2013) Migraine predicts hypertension—a cohort study of the Finnish working-age population. Eur J Pub Health 24(2):244–248
10. Facchinetti F, Allais G, Nappi RE et al (2009) Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. Cephalalgia 29:286–292
11. Hagen K, Stovner LJ, Vatten L, Holmen J, Zwart JA, Bovim G (2002) Blood pressure and risk of headache: a prospective study of 22 685 adults in Norway. J Neurol Neurosurg Psychiatry 72:463–466
12. Fagernæsa CF, Heuchb I Zwartb, Winsvoldb BS, Lindea M, Hagena K (2015) Blood pressure as a risk factor for headache and migraine: a prospective population-based study. Eur J Neurol 22:156–162
13. Gardener H, Monteith T, Rundek T, Wright CB, Elkind MSV, Sacco RL (2016) Hypertension and Migraine in the Northern Manhattan Study. Ethn Dis 26:323–330
14. Mathew NT (2011) Pathophysiology of chronic migraine and mode of action of preventive medications. Headache 51(Suppl. 2):84–92
15. Bigal ME, Sheftell FD, Rapoport AM et al (2002) Chronic daily headache: identification of factors associated with induction and transformation. Headache 42:575–581
16. Gipponi S, Venturelli E, Rao R, Liberini P, Padovani A (2010) Hypertension is a factor associated with chronic daily headache. Neurol Sci Suppl 1:S171–S173
17. Silberstein SD, Lipton RB (2000) Chronic daily headache. Curr Opin Neurol 3:277–283
18. Huang Q, Li W, Li N, Wang J, Tan G, Chen L, Qin G, Liang X, Zhou J (2013) Elevated blood pressure and analgesic overuse in chronic daily headache: an outpatient clinic-based study from China. J Head Pain 14:51–59
19. Tietjen GE (2009) Migraine as a systemic vasculopathy. Headache 29:989–996
20. Olesen J (2008) The role of nitric oxide (NO) in migraine, tension-type headache and cluster headache. Pharmacol Ther 20:157–171
21. Hermann M, Flammer A, Lüscher TF (2006) Nitric oxide in hypertension. J Clin Hypertens (Greenwich) 8(Suppl 4):17–29
22. Palatini P, Julius S (2009) The role of cardiac autonomic function in hypertension and cardiovascular disease. Curr Hypertens Rep 11:199–205
23. Matei D, Constantinescu V, Corciova C, Ignat B, Matei R, Popescu CD (2015) Autonomic impairment in patients with migraine. Eur Rev Med Pharmacol Sci 19:3922–3927
24. Benjelloun H, Birouk N, Slaoui I, Coghlan L, Oulad Amar Bencheikh B, Jroundi I, Benomar L (2005) Profil autonomique des patients migraineux Autonomic profile of patients with migraine. Neurophysiol Clin 35:127–134
25. Cortelli P, Pierangeli G, Parchi P, Contin M, Baruzzi A, Lugaresi E (1991) Autonomic nervous system function in migraine without aura. Headache 31:457–462
26. Babayan L, Oleg V, Mamontov OV, Amelin AV, Bogachev M, Kamshilin AA (2017) Arterial hypertension in migraine: role of familial history and cardiovascular phenotype. Autonom Neurosci Basic Clin 203:103–107
27. 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
28. Allais G, Gabellari C, De Lorenzo C, Mana O, Benedetto C (2009) Oral contraceptives in migraine. Expert Rev Neurother 9(3):381–393
29. Mancia G, Rosei EA, Ambrosioni E, Avino F, Carolei A, Daccò M, Di Giacomo G, Ferri C, Grazioli I, Melzi G, Nappi G, Pinessi L, Sandrini G, Trimarco B, Zanchin G. MIRACLES Study Group (2011) Hypertension and migraine comorbidity: prevalence and risk of cerebrovascular events: evidence from a large,

multicenter, crosssectional survey in Italy (MIRACLES study). J Hypertens 29:309–318
30. Sarchielli P, Granella F, Prudenzano MP et al (2012) Italian guidelines for primary headaches: 2012 revised version. J Headache Pain 13(Suppl 2):S31–S70
31. Gerwig M, Niehaus L, Stude P, Katsarava Z, Diener HC (2012) Beta-blocker migraine prophylaxis affects the excitability of the visual cortex as revealed by transcranial magnetic stimulation. J Headache Pain 13(1):83–89
32. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G (2001) Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ 322:19–22
33. Disco C, Maggioni F, Zanchin G (2015) Angiotensin II receptor blockers: a new possible treatment for chronic migraine? Neurol Sci 36(8):1483–1485
34. Zhang R, Bai YG, Lin LJ, Bao JX, Zhang YY, Tang H, Cheng JH, Jia GL, Ren XL, Ma J (2009) Blockade of AT1 receptor partially restores vasoreactivity, NOS expression, and superoxide levels in cerebral and carotid arteries of hindlimb unweighting rats. J Appl Physiol 106(1):251–258
35. Marques-Lopes J, Pinto M, Pinho D, Morato M, Patinha D, Albino-Teixeira A, Tavares I (2009) Microinjection of angiotensin II in the caudal ventrolateral medulla induces hyperalgesia. Neuroscience 158(4):1301–1310

Neurol Sci (2017) 38 (Suppl 1):S73–S76
DOI 10.1007/s10072-017-2902-0

COMORBIDITY

Shared mechanisms of epilepsy, migraine and affective disorders

Davide Zarcone[1] · **Simona Corbetta**[1]

Abstract Since the nineteenth century several clinical features have been observed in common between migraine and epilepsy (such as episodic attacks, triggering factors, presence of aura, frequent familiarity), but only in recent years researchers have really engaged in finding a common pathogenic mechanism. From studies of disease incidence, we understand how either migraine among patients with epilepsy or epilepsy among migraine patients are more frequent than in the general population. This association may result from a direct causality, by the same environmental risk factors and/or by a common genetic susceptibility. Ischemic events are the most frequent direct causes, especially among women and elderly people: migraine can lead to silent or clinically considerable strokes, and these ones could explain the increased risk of developing epilepsy in people with a history of migraine. Head injuries can lead headache, often with migraine characteristics, and seizures. But there are also many idiopathic cases. The comorbidity migraine–epilepsy might be explained in these cases by a neuronal hyperexcitability, which increases the risk of both diseases: a higher concentration of extracellular glutamate, the main excitatory neurotransmitter, leads in fact as a result a Cortical Spreading Depression (the pathophysiological mechanism at the base of aura) and convulsions; antiepileptic drugs such as topiramate are, therefore, used also in migraine prophylaxis. A genetic link between these two diseases is particularly evident in familial hemiplegic migraine: mutations of ATP1A2, SCN1A and CACNA1A genes, identified in this disease, have also been involved in different types of epilepsy and febrile seizures. The channelopathies, especially engaging sodium and potassium ions, can be the common pathogenic mechanism of migraine and epilepsy. Both migraine and epilepsy also have, compared to the general population, a higher prevalence and incidence of affective disorders such as anxiety, depression and suicidal ideation. Anxiety and depression can be part of symptoms that accompany migraine or seizures. Female patients with a long history of illness and frequent attacks are the most at risk. The impact of these diseases on the quality of life is the most obvious cause of these disorders, furthermore some antiepileptic drugs can have depressive effects on mood; the anxious–depressive disorders often result from the interaction between iatrogenic and psychosocial factor with common neurobiological pathogenesis. A chronic lowering of 5-HT (serotonin) levels has been demonstrated both in migraineurs and in depressed patients; amitriptyline and venlafaxine are the most indicated drugs in the treatment of migraine with comorbid depression currently. Likewise imbalance in dopamine levels has been also demonstrated: a D2 receptor genotype has been directly related to comorbidity migraine–depression. In women, hormonal fluctuations are also crucial, especially in the post-partum and late luteal phase, when the estrogenic reduction, associated with up-regulation of SNPs and down-regulation of serotonergic and GABAergic systems, increases the risk of migraine and depression. Furthermore, central sensitization phenomena have been highlighted in both diseases, and result in a progressive increase in the frequency of attacks up to chronicity and the consequent development of drug resistance and overuse. Further studies will be necessary to deepen the close relationship between these three diseases.

Keywords Epilepsy · Migraine · Affective disorders · Common mechanisms

✉ Davide Zarcone
davide.zarcone@asst-valleolona.it

[1] U.O. Neurologia e Stroke Unit, Gallarate Hospital, ASST Valle Olona, Gallarate, Italy

Since the nineteenth century some overlap of symptoms between migraine and epilepsy has been observed:

- both disorders are manifested by periodic attacks and return to normality between crisis
- they are precipitated by the same factors, such as exposure to bright flash, stress, sleep deprivation and menstrual cycle
- they are often present in several members of the same family and in identical twins
- they can be characterized by the presence of transient neurological symptoms (aura), although in epilepsy positive symptoms are more frequent, instead of negative ones in migraine
- frequent association with autonomic and psychological symptoms
- brain nonspecific electrical faults, observable during EEG, can be present in both disorders
- possible occurrence of headache before, during or after seizures
- possible unleashing of a seizure by a typical migraine aura
- patients with migraine during the attacks may experience mental confusion or narrowing of consciousness similar to those with seizure.

For these reasons we can sometimes have problems in differential diagnosis.

Overlaps in clinical symptomatology might indicate pathophysiological overlaps.

Only in recent years researchers have really engaged in finding a common pathogenic mechanism and the number of studies are still small.

Then the purpose of this article is to try to clarify a topic that is still under discussion.

From studies of disease incidence we understand how either migraine among patients with epilepsy or epilepsy among migraine patients are more frequent than in the general population: depending on the considered studies, we can see that the incidence of headache in the general population is between 5 and 10%, while in patients with epilepsy is 8–23%; in the same way, the incidence of epilepsy in the general population is 0.5–1%, but in migraine patients it can be up to 5.9%.

This association may result from:

- a direct causality
- same environmental risk factors
- a common genetic susceptibility.

The most frequent direct cause is represented by ischemic strokes: it is known that migraine can lead to silent or clinically considerable strokes, and these ones could explain the increased risk of developing epilepsy in people with a history of migraine.

However, this association is valid only for elderly people and women who suffer from migraine with aura: there is not a significant association in men and in people affected by migraine without aura.

Moreover, head injuries can cause both headache, often with migraine characteristics, and seizures.

But, obviously, there are also many idiopathic cases, and particularly for those last ones a genetic susceptibility has been suspected.

The results of a study, made by Columbia University Medical Center in New York and published on Epilepsia, indicated for the first time that a strong family history of epilepsy increases the chances of suffering from migraine with aura: by analyzing data from participants in the genetic study "Epilepsy Phenome/Genome Project", which had involved 730 patients with epilepsy and 501 families from 27 US clinical centers, this study demonstrated that people who have more epileptic relatives have a double chance to suffer from migraine with aura compared with those who have less epileptic relatives; this is the evidence that there are genes that cause simultaneously epilepsy and migraine [1].

The comorbidity migraine–epilepsy might be explained in these cases by a neuronal hyperexcitability, which increases the risk of both diseases: a higher concentration of extracellular glutamate, the main excitatory neurotransmitter, leads in fact as a result of a Cortical Spreading Depression (slow wave of neuronal hyperexcitability that spreads at a speed of 3–5 mm/min, followed by a cortical electrical activity depression: the pathophysiological mechanism at the base of aura) and convulsions (Fig. 1).

In migraine, an initial excess of neuronal activity leads to CSD and aura, with the subsequent recruitment of the trigeminal nucleus leading to central sensitization and pain; in epilepsy, neuronal overactivity leads to the recruitment of larger populations of neurons firing in a rhythmic manner that constitutes an epileptic seizure. Both migraine aura and headaches may act as a trigger for epileptic seizures [2].

This is the reason because some antiepileptic drugs such as topiramate are, therefore, used also in migraine prophylaxis.

The channelopathies (especially engaging sodium and potassium ions, which can trigger a CSD) can be the common pathogenic mechanism of migraine and epilepsy.

A genetic link between these two diseases is particularly evident in a mendelian transmission type of migraine, the familial hemiplegic migraine: mutations of ATP1A2, SCN1A and CACNA1A genes, identified in this disease, have also been involved in different types of epilepsy and febrile seizures [3].

Of course, the ultimate goal of genetic research is to get targeted drugs for specific diseases.

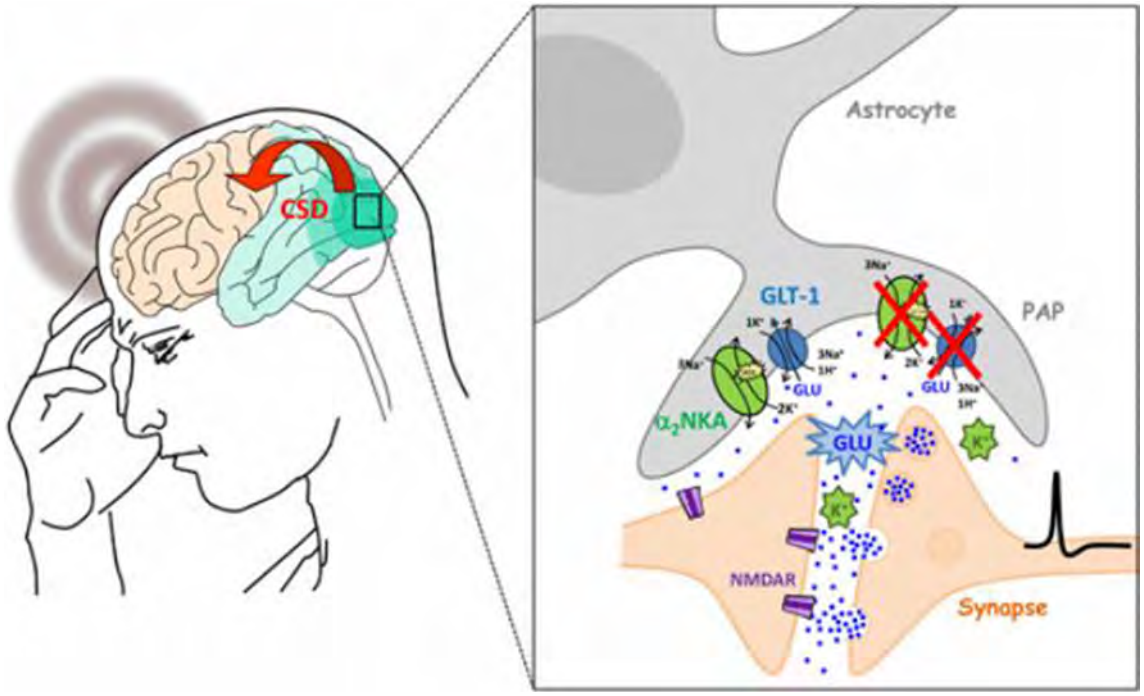

Fig. 1 Cortical spreading depression in migraine

However, the hypothesis of a common genetic susceptibility has not yet been demonstrated clearly, because it is probably a complex polygenic multifactorial inheritance and the gene–environment interaction plays an essential role: so further studies must be done.

Affective disorders can be part of symptoms that accompany migraine or seizures, in a bidirectional relationship.

Both migraine and epilepsy also have, compared to the general population, a higher prevalence and incidence of anxiety, somatization, depression, fear, anguish during dreaming and suicidal ideation.

These comorbidities increase disease burden, may complicate the treatment of the combined disorders and interfere with possible rehabilitation [4].

The impact of the affective disorders on the quality of life (social life and productivity) is the most obvious cause of these diseases; female patients with a long history of illness, frequent attacks and medication overuse are the most at risk [5].

In patients with epilepsy, it is reported that headache overall was significantly related to depression and anxiety; interictal headache was correlated with depression only, and postictal headache was related with depression as well as suicidality, separately.

These results show that investigating and controlling headaches may relieve affective symptoms and ultimately improve the quality of life of patients with epilepsy [6].

Furthermore, some antiepileptic drugs can have depressive effects on mood; the anxious–depressive disorders often result from the interaction between iatrogenic and psychosocial factor with common neurobiological pathogenesis.

A chronic lowering of 5-HT (serotonin) levels is well known both in migraineurs and in depressed patients; amitriptyline and venlafaxine are the most indicated drugs in the treatment of migraine with comorbid depression currently.

Likewise imbalance in dopamine levels has been also highlighted: a D2 receptor genotype has been directly related to comorbidity migraine–depression.

In women hormonal fluctuations are also crucial, especially in the post-partum and late luteal phase, when the estrogenic reduction, associated with up-regulation of SNPs and down-regulation of serotonergic and GABAergic systems, increases the risk of migraine and depression.

Furthermore, central sensitization phenomena have been discovered in both diseases, and result in a progressive increase in the frequency of attacks up to chronicity and the consequent development of drug resistance and overuse.

Chronic pain in idiopathic headaches is, in part, an emotional response induced by alterations in the homeostasis of the interoceptive system, a system that integrates nociceptive information with the emotional network (mediating emotional awareness): these findings suggest that idiopathic headaches are probably due to both an altered

pain matrix on the one hand, and an altered affective–cognitive state on the other [7].

Although, these relationships remain unclear in many cases: routine screening for psychiatric disorders in neurological illnesses is infrequent. Much more needs to be done to improve the detection and treatment of patients affected by neurological and psychiatric disorders: understanding the scope of this overlap may inspire collaborations to improve the lives of people affected by both disorders [8].

Further studies will be necessary to deepen the close relationship between these three diseases.

Compliance with ethical standards

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

Ethical standards This article does not contain any study with human subjects performed by any of the authors.

References

1. Winawer MR, Connors R, EPGP Investigators (2013) Evidence for a shared genetic susceptibility to migraine and epilepsy. Epilepsia 54(2):288–295. doi:10.1111/epi.12072 **(epub 2013 Jan 7)**
2. Kramer DR, Fujii T, Ohiorhenuan I, Liu CY (2017) Interplay between cortical spreading depolarization and seizures. Stereotact Funct Neurosurg 95(1):1–5. doi:10.1159/000452841 **(epub ahead of print)**
3. Nye BL, Thadani VM (2015) Migraine and epilepsy: review of the literature. Headache 55(3):359–380. doi:10.1111/head.12536 **(epub 2015 Mar 7)**
4. Castelnuovo G, Giusti EM, Manzoni GM, Saviola D, Gatti A, Gabrielli S, Lacerenza M, Pietrabissa G, Cattivelli R, Spatola CA, Corti S, Novelli M, Villa V, Cottini A, Lai C, Pagnini F, Castelli L, Tavola M, Torta R, Arreghini M, Zanini L, Brunani A, Capodaglio P, D'Aniello GE, Scarpina F, Brioschi A, Priano L, Mauro A, Riva G, Repetto C, Regalia C, Molinari E, Notaro P, Paolucci S, Sandrini G, Simpson SG, Wiederhold B, Tamburin S (2016) Psychological considerations in the assessment and treatment of pain in neurorehabilitation and psychological factors predictive of therapeutic response: evidence and recommendations from the Italian consensus conference on pain in neurorehabilitation. Front Psychol 7:468. doi:10.3389/fpsyg.2016.00468 **(eCollection 2016)**
5. Lampl C, Thomas H, Tassorelli C, Katsarava Z, Laínez JM, Lantéri-Minet M, Rastenyte D, Ruiz de la Torre E, Stovner LJ, Andrée C, Steiner TJ (2016) Headache, depression and anxiety: associations in the Eurolight project. J Headache Pain. 2016(17):59. doi:10.1186/s10194-016-0649-2 **(epub 2016 Jun 1)**
6. Seo JH, Joo EY, Seo DW, Hong SB (2016) Correlation between headaches and affective symptoms in patients with epilepsy. Epilepsy Behav 60:204–208. doi:10.1016/j.yebeh **(epub 2016 May 25)**
7. Bussone G, Grazzi L (2013) Understanding the relationship between pain and emotion in idiopathic headaches. Neurol Sci 34(Suppl 1):S29–S31. doi:10.1007/s10072-013-1362-4
8. Hesdorffer DC (2016) Comorbidity between neurological illness and psychiatric disorders. CNS Spectr 21(3):230–238. doi:10.1017/S1092852915000929 **(epub 2016 Feb 22)**

Neurol Sci (2017) 38 (Suppl 1):S77–S80
DOI 10.1007/s10072-017-2880-2

COMORBIDITY

Headache and endovascular procedures

Stefano de Biase[1] · Marco Longoni[2] · Gian Luigi Gigli[1] · Elio Agostoni[2]

Abstract The International Classification of Headache Disorders (ICHD-3 beta) includes headache attributed to intracranial endovascular procedures (EVPs). The aim of this review is to describe the clinical and pathophysiological aspects of headache related to vascular lesions and EVPs. Current studies regarding this issue are contradictory, although generally favouring headache improvement after EVPs. Further large studies are needed to adequately assess the effect of EVPs on headache.

Keywords Angiography · Arteriovenous malformation · Cerebral aneurysm · Endovascular procedures · Headache

Introduction

Nowadays cerebral endovascular procedures (EVPs) are performed routinely and their benefits and risks are well documented in terms of mortality and neurological morbidity, but large series fail to document minor symptoms related to these procedures, such as headaches [1]. The ICHD-3 beta includes headache attributed to intracranial EVPs [2].

Headache occurs among 19–72% of patients undergoing EVPs, either therapeutic embolizations or diagnostic angiography [3, 4]. Headache is usually described as brief, stabbing or pressure-like pain, felt ipsilaterally to the manipulated vessel. Factors associated with headache during EVPs are female sex, therapeutic procedures, psychiatric comorbidities of anxiety/depression, tobacco use and previous headache frequency more than four attacks per month [3, 4]. Migraine is not a risk factor on its own, although the injection of contrast was reported to trigger a migraine attack in a person who had migraine [5].

The pathogenesis of pain associated with EVPs includes:

- mechanical stimulation of the arterial wall by traction, stretching and distortion from materials used (balloons, catheters, coils, glue, stent) with subsequent triggering of the trigeminovascular pathway;
- local toxicity or chemical reaction (dye, glue);
- inflammatory changes caused by intra-arterial injection of embolic or contrast materials;
- hemodynamic changes;
- parenchymal ischemia;
- vasogenic edema;
- thrombosis and hemorrhage within the aneurysmal vessel wall;
- physical and psychological stress from pain or fear [4].

Cerebral dural arteriovenous fistula (DAVF), headache and EVPs

The ICHD-3 beta classification includes headache attributed to DAVF [2]. DAVF is a rare but potentially treatable cerebrovascular pathology resulting from abnormal connection between meningeal arteries and dural sinuses. DAVFs can be clinically grouped into benign (asymptomatic, bruit, headache, tinnitus or ocular symptoms) and

✉ Elio Agostoni
elioclemente.agostoni@ospedaleniguarda.it

[1] Neurology Unit, Department of Experimental and Clinical Medical Sciences, University of Udine Medical School, Udine, Italy

[2] Neurology and Stroke-Unit, Department of Neurosciences, Niguarda Ca' Granda Hospital, Piazza Ospedale Maggiore, 3, 20162 Milan, Italy

aggressive (hemorrhage or dementia). A painful pulsatile tinnitus can be a presenting symptom, as well as headache with features of intracranial hypertension due to decrease in venous outflow and sometimes to sinus thrombosis. DAVFs involving the cavernous sinus (CS) may present as painful ophthalmoplegia [2]. CS-DAVF causes periorbital aching with ocular symptoms due to high venous pressure in the CS, while headache is caused by arterial dilatation-stimulating trigeminal nerves around the vessels that could cause migraine-like symptoms. The vasoconstrictive properties of triptans have been reported to be efficacious in these cases [6]. Triptans are known to contract carotid and cerebral arteries via the 5-HT1B receptor. Shunting blood flow through the fistula is very likely decreased by triptans leading to headache improvement. Most of the cerebral fistulas can now be treated by EVPs, however, surgery is still an option. Several case reports concerning headache improvement after DAVFs treatment are described in the literature [6, 7].

Brain arteriovenous malformations (AVMs), headache and EVPs

AVMs of the brain are complex tangles of abnormal vessels that result in the direct arteriovenous shunting of blood due to lack of an intervening capillary bed. The ICHD-3 beta outlines the diagnostic criteria for headaches attributable to AVMs and indicates that AVMs can cause attacks of migraine [2]. It is noted that up to 58% of women with AVMs have migraine with aura as the presenting symptom. Evidence linking AVMs to other headache disorders is less robust.

An occipital location appears to increase the risk of concurrent migraine-like headaches in AVM patients [8]. These patients typically have concurrent visual symptoms. Several explanations involving the activation of trigeminovascular nerve afferents are plausible. Among the proposed mechanisms, increased intracranial pressure, brain ischemia due to a steal phenomenon and cortical spreading depression are commonly cited [9].

The usefulness of pharmacotherapies in treating AVM-associated headache has not been rigorously studied. In those patients, lesion eradication is a reasonable treatment goal. Most case series suggest that interventional therapy is capable of achieving symptomatic resolution in those with intractable headaches [9].

Intracranial aneurysms, headache and EVPs

Headache is the presenting symptom in approximately one third of patients with unruptured intracranial aneurysms (UIAs) [10]. The ICHD-3 beta outlines established criteria for the diagnosis of headache secondary to UIA [2]. With the exception of thunderclap headache, which requires investigation for subarachnoid hemorrhage, headache related to UIAs usually has no specific features and may be accompanied by focal symptoms or signs. When patients present in this fashion, there is a high suspicion for a direct relationship between the presenting symptoms and UIAs. However, when a patient presents with recurrent headaches with characteristics of migraine or tension-type headache (TTH), the relationship with UIAs is usually unclear. Several studies have reported that the prevalence of migraine and TTH in patients with UIAs is higher compared to the general population [11, 12].

The mechanisms that cause headache associated with UIAs include local thrombosis, localized meningeal inflammation, expansion of the aneurysm and bleeding within the vascular wall [13].

In the last years, EVPs of UIAs have evolved significantly and currently represent the first line of treatment. Following treatment of UIAs, there may be a change in headache patterns, with some patients improving, some worsening and others having the onset of new headaches. Coil embolization may reduce the pulsatile expansion of the aneurysm sac which leads to relief of headache. In addition, the development of a fibrotic response within the embolized aneurysm may result in reduction of the volume of the aneurysms [14].

Worsening or development of new headache may be attributed to increase in the size of the aneurysm after placement of coils: coil mass itself and thrombosis in coiled aneurysms cause distension of the aneurysmal wall, which can induce headache. However, the most important mechanism may be the inflammatory response invoked by coils within the aneurysm sac. Aneurysm occlusion following coil embolization is described as following the biological pattern of wound healing in a vessel wall [15]. Asymptomatic wall enhancement can be seen after embolization with all coil types and probably represents a normal healing response to the coils. Almost 20% of aneurysms treated with bare platinum coils demonstrate mural enhancement [16].

In a recent study, Berge et al. reported that 7 of 17 patients (41%) had neurologic worsening after flow-diverter treatment for UIAs [17]. All seven patients had headache and four also an aggravation of pre-existing compressive symptoms. This clinical deterioration was transient; it was observed between 3 and 15 days post-treatment and resolved by day 30. MR imaging revealed signs highly suggestive of perianeurysmal inflammation with vasogenic edema and blood–brain barrier breakdown. The association between MR imaging inflammatory features and clinical aggravation was statistically significant. Large aneurysmal size and its proximity to surrounding

brain tissue were predictive of this inflammatory reaction after flow diversion.

Existing studies on post-EVP headache in patients with aneurysms and AVMs showed diverging results, generally favouring improvement of headache after treatment. When an exacerbation was found, it was typically reported to be temporary and to resolve within days or months. Qureshi et al. reported that coil embolization of UIAs was associated with reduction in the severity of headaches in the majority of patients with pre-procedural headaches (59%). On the contrary, 33.3% (5/15) of the patients without headache before coil embolization reported an onset of headache, and 6% (2/32) reported worsening in chronic headache severity [14]. Kong et al. retrospectively analyzed 81 patients who had undergone surgical clipping or EVPs of UIAs over a 5-year period. 49 had recurrent headaches prior to aneurysm treatment. Following treatment, 44/49 (89.8%) had headache improvement, four had no change, and one patient had headache worsening [18]. In a prospective study of 44 patients, Schwedt et al. reported reduced headache frequency in 68% of patients, while 9% had new or worsened headaches following aneurysm treatment during 6 months of follow-up. Pre-treatment migraine, more severe pre-treatment headaches, anxiety and stent-assisted aneurysm coiling were associated with a lack of headache improvement [19]. On the contrary, side of headache ipsilateral to the aneurysm and aneurysm size >10 mm resulted significant predictors of headache relief [10].

Regarding patients with no history of headache previous EVPs, Hwang et al. reported that 50 of 90 patients (55.6%) experienced post-embolization headache at 7.9 h (range 0–72) that resolved within an average of 73 h (range 3–312) [20]. In another study, in 32 of 130 patients (24.5%) headache occurred or was exacerbated after embolization of UIAs. Of these, 30 patients showed improvement within days, but two patients with previous migraine history complained of intermittent headache over 3 months after embolization [21]. Stent-assisted coiling, a packing attenuation of >25% and no history of hypertension were significantly associated with post-embolization headache [20, 21].

In a recent study of Khan et al., 59 patients underwent treatment of aneurysms ($n = 43$), FAVDs ($n = 11$), and AVMs ($n = 5$) [22]. There was a significant increase in overall headache and TTH within the first 3 months after EVPs compared to 1 month before EVP. However, at interview time (median 2.5 years post-EVP), the increase in overall headache, migraine and TTH was not statistically significant. The result of the study suggested a temporary increase in headache in the first 3 months after EVPs, which normalizes over time. In a sub-group analysis, post-EVP headache resulted more prevalent after coiling of aneurysms, followed by stent placements. Although aneurysms were overrepresented, it also seemed that post-EVP headache was more prevalent in patients treated for aneurysms compared to AVMs.

Baron et al. retrospectively conducted a study on 372 patients, of who 263 underwent intracranial coil embolizations, 21 acrylic glue embolizations, and 88 stent placements. Post-EVP headache occurred in 72% of coil patients, 33% of glue patients and 14% of stent patients [4].

Headache and cervical stent and angioplasty

Headache attributed to carotid or vertebral angioplasty and stenting has been previously reported [23].

Headache is usually mild, ipsilateral, fronto-temporal in location and commonly arise in a short period after the procedure and resolves within 10 min. Moreover, headache might also be a part of the cerebral hyperperfusion syndrome (CHS) [2]. CHS is a critical complication after carotid and vertebral artery stenting (CAS) and carotid endarterectomy (CEA), with a reported incidence ranging from 0.2 to 18.9% [24]. CHS represents a spectrum of clinical symptoms that might include severe unilateral headache, seizures, focal neurologic defects and intracerebral hemorrhage in its most severe form. Impaired cerebral autoregulation and post-revascularization changes in cerebral blood flow are the main mechanisms involved in the development of CHS [25, 26].

Discussion

In the last years, EVPs of vascular lesions has evolved significantly and often represent the first line of treatment. However, functional outcomes such as headache after EVPs have received only little attention.

Vascular lesions may predispose to headache in their own and headache may be the presenting symptom. What is less known, is how headache is affected by EVPs and the expected time frame of headache resolution. Current studies in this field are contradictory, some showing headache improvement after EVPs, others aggravation or new development of headache. Further large studies are needed to adequately assess the effect of EVPs on headache. It would also be interesting to quantify the strength of association between several risk factors and post-EVP headache. These findings may help to predict those most likely to develop post-EVP headache; treating possible contributing comorbidities could provide an opportunity for preventing post-EVP headache in some patients. Predicting who will develop post-EVP headache would be clinically useful and potentially could assist in reducing the

excessive diagnostic testing so often obtained in these patients. Moreover, this may help in reducing the time to reach discharge criteria and would be cost effective. Guidelines or algorithms concerning the management of patients after EVPs are still lacking.

The current ICHD-3 beta definition of headache attributed to EVPs appear suboptimal, since in different studies headache following EVPs lasted more than the allowed 24 h [2, 4, 22].

In a recent study, post-EVP headache was most likely to be associated with aneurysmal coiling, followed by acrylic glue embolization and then stenting [4]. An inflammatory reaction may aggravate, transiently, clinical symptoms after aneurysm treatment. A large-sized aneurysm and close contact with adjacent parenchyma are risk factors associated with perianeurysmal brain inflammation [17]. Steroid administration in the periprocedural period may decrease the inflammatory risk. Some patients respond to steroid therapy, a feature that supports an inflammatory etiology, however, complete symptomatic improvement is not always guaranteed. Further research is needed to better understand the underlying mechanisms as well as to achieve better prevention strategies.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Agostoni E, Zagaria M, Longoni M (2015) Headache in subarachnoid hemorrhage and headache attributed to intracranial endovascular procedures. Neurol Sci 36(Suppl 1):67–70
2. Headache Classification Committee of the International Headache Society (IHS) (2013) The international classification of headache disorders: 3rd edition (beta version). Cephalalgia 33:629–808
3. Gil-Gouveia RS, Sousa RF, Lopes L et al (2007) Headaches during angiography and endovascular procedures. J Neurol 254:591–596
4. Baron EP, Moskowitz SI, Tepper SJ et al (2011) Headache following intracranial neuroendovascular procedures. Headache 52:739–747
5. Shuaib A, Hachinski VC (1988) Migraine and the risks from angiography. Arch Neurol 45:911–912
6. Osaka M, Shibata M, Oki K et al (2015) Clinical utility of triptans in the management of headache attributed to dural arteriovenous fistula involving the cavernous sinus. J Neurol Sci 349:260–261
7. Nomura M, Mori K, Tamase A et al (2016) Cavernous sinus dural arteriovenous fistula patients presenting with headache as an initial symptom. J Clin Med Res 8:342–345
8. Galletti F, Sarchielli P, Hamam M et al (2011) Occipital arteriovenous malformations and migraine. Cephalalgia 31:1320–1324
9. Ellis JA, Mejia Munne JC, Lavine SD et al (2016) Arteriovenous malformations and headache. J Clin Neurosci 23:38–43
10. Ji W, Liu A, Yang X et al (2016) Incidence and predictors of headache relief after endovascular treatment in patients with unruptured intracranial aneurysms. Interv Neuroradiol 23(1):18–27
11. Esmanhotto BB, Piovesan EJ, Lange MC (2016) Brazilian experience of the influence of endovascular treatment on headache in patients with ruptured intracranial aneurysms. Acta Neurol Scand 135(3):377–381
12. Lebedeva ER, Gurary NM, Sakovich VP et al (2013) Migraine before rupture of intracranial aneurysms. J Headache Pain 14:15
13. Raps EC, Rogers JD, Galetta SL et al (1993) The clinical spectrum of unruptured intracranial aneurysms. Arch Neurol 50:265–268
14. Qureshi AI, Suri MF, Kim SH et al (2003) Effect of endovascular treatment on headaches in patients with unruptured intracranial aneurysms. Headache 43:1090–1096
15. Raymond J, Desfaits AC, Roy D (1999) Fibrinogen and vascular smooth muscle cell grafts promote healing of experimental aneurysms treated by embolization. Stroke 30:1657–1664
16. Fanning NF, Willinsky RA, ter Brugge KG (2006) Wall enhancement, edema, and hydrocephalus after endovascular coil occlusion of intradural cerebral aneurysms. J Neurosurg 108:1074–1086
17. Berge J, Tourdias T, Moreau JF et al (2011) Perianeurysmal brain inflammation after flow-diversion treatment. AJNR Am J Neuroradiol 32:1930–1934
18. Kong DS, Hong SC, Jung YJ et al (2007) Improvement of chronic headache after treatment of unruptured intracranial aneurysms. Headache 47:693–697
19. Schwedt TJ, Gereau RW, Frey K, Kharasch ED (2011) Headache outcomes following treatment of unruptured intracranial aneurysms: a prospective analysis. Cephalalgia 31:1082–1089
20. Hwang G, Jeong EA, Sohn JH et al (2012) The characteristics and risk factors of headache development after the coil embolization of an unruptured aneurysm. AJNR Am J Neuroradiol 33:1676–1678
21. Choi KS, Lee JH, Yi HJ et al (2014) Incidence and risk factors of postoperative headache after endovascular coil embolization of unruptured intracranial aneurysms. Acta Neurochir (Wien) 156:1281–1287
22. Khan S, Amin FM, Hauerberg J et al (2016) Post procedure headache in patients treated for neurovascular arteriovenous malformations and aneurysms using endovascular therapy. J Headache Pain 17:73
23. Gündüz A, Göksan B, Koçer N et al (2012) Headache in carotid artery stenting and angiography. Headache 52:544–549
24. van Mook WN, Rennenberg RJ, Schurink GW et al (2005) Cerebral hyperperfusion syndrome. Lancet Neurol 4:877–888
25. Adhiyaman V, Alexander S (2007) Cerebral hyperperfusion syndrome following carotid endarterectomy. QJM 100:239–244
26. Buczek J, Karliński M, Kobayashi A et al (2013) Hyperperfusion syndrome after carotid endarterectomy and carotid stenting. Cerebrovasc Dis 35:531–537

Neurol Sci (2017) 38 (Suppl 1):S81–S84
DOI 10.1007/s10072-017-2881-1

CLINICAL ASPECTS OF HEADACHE

Neurobiology of chronicization

Gian Camillo Manzoni[1] · Marco Russo[2] · Arens Taga[2] · Paola Torelli[2]

Abstract In the past few years, research on chronicization of headache has focussed primarily on migraine, even though there are other types of primary headache that over time can turn into chronic forms. Only a minority of migraine sufferers will develop a chronic condition, with attacks that are likely to vary in their clinical features. As a result, in chronic migraine the specific diagnostic criteria for this headache type do not always exhibit the typical features of migraine. Among the factors that play a major role in favouring chronicization are a high frequency of migraine attacks since the beginning, overuse of symptomatic medication and onset of depression or arterial hypertension. Several neurophysiology, biochemistry and functional neuroimaging studies suggest that chronic migraine may be associated with structural, functional and metabolic changes in the brain, especially involving the brainstem.

Keywords Chronic migraine · Chronic headache · Medication overuse headache · International Classification of Headache Disorders

✉ Paola Torelli
paolatorelli@libero.it

[1] Poliambulatorio Dalla Rosa Prati, Centro Diagnostico Europeo, Parma, Italy

[2] Dipartimento di Medicina e Chirurgia, Centro Cefalee, Università di Parma, Parma, Italy

Introduction

Clinically, the most common types of primary headache—migraine (M), tension-type headache (TTH) and cluster headache (CH)—are characterized by a fitful time pattern, consisting of attacks that may vary greatly in frequency and duration depending not only on the headache type, but also, within the same headache type, on the subject and the life period in which they occur.

In these most common types of primary headache, the attacks generally continue to recur for many years; "chronic" may then be a suitable term to describe them regardless of their frequency of occurrence. Recently, however, M, TTH and CH have increasingly been described as chronic headache types based on patterns of recurrence over periods of a quarter (M and TTH) or a year (CH).

Thus, according to the diagnostic criteria set by the current International Classification of Headache Disorders (ICHD-3) [1], if M occurs on 15 or more days per month for more than 3 months and on at least 8 days per month has the features of M headache, it can be termed as chronic migraine (CM); if TTH occurs on $\geq$15 days per month on average for >3 months ($\geq$180 days per year), it can be termed as chronic TTH (CTTH); and if CH occurs without a remission period, or with remissions lasting <1 month, for at least 1 year, it can be termed as chronic CH (CCH).

A major difference between the chronic forms of M, TH and CH is that while CTTH and CCH can be chronic ab initio, CM is never chronic since the beginning, but it becomes so only as an evolution of M over time.

Perhaps it is precisely for that reason that, when talking about chronicization of primary headache, neurologists basically refer to CM, and that most of the studies aimed at

understanding the neurobiological mechanisms underlying chronicization have focussed on M.

In this article, too, we will not deal with CTTH and CCH, but only with CM. In our three-step discussion, we will start by reviewing the possible forms that M may evolve into over the years; we will then consider the changes that M exhibits in its clinical features when it becomes chronic and the possible factors contributing to transforming episodic M into chronic M; finally, we will investigate the possible neurobiological bases underlying chronicization of M.

Natural history of M

The true natural history of M is mostly unknown for two main reasons. First, the fact that almost all M sufferers sooner or later in their lifetime will use some treatment to relieve it is a big hindrance to reconstructing the "true" natural history of the disease. Secondly, data are currently available for M patients followed at headache clinics and not for migraineurs in the general population.

Therefore, it is more correct to speak of, and perhaps even more interesting from a medical point of view to deal with, a possible evolution of M over time, rather than a true natural history of M.

Having clarified that, we can say that there is agreement between the opinions of expert headache clinicians and the epidemiological data published in the literature—which indicate a markedly lower prevalence of M in the elderly compared with the young and the middle aged [2] without a shorter survival [3]—about how M evolves over time.

Most patients develop M in their second and third life decades and continue to suffer from it with varying degrees of severity for a good part of their life. However, after around age 50, M generally evolves in two possible and very different ways: in most migraineurs, M will significantly improve or even disappear altogether; conversely, in a minority it will markedly worsen or even occur daily or almost daily.

Thus, while about 70–80% of M cases have a favourable evolution, there are about 20–30% that undergo chronicization. By contrast, patients who in their old age continue to have the same frequency of recurring attacks as they had in previous decades are very few.

We should be very careful not to confuse true chronicization of M with two other evolved forms of M: one is a true association of M with another type of headache, either primary (particularly TTH) or secondary; the other is the result of M being replaced over time by another type of headache. In the latter case, onset of the new headache type is generally not preceded by a progressive worsening of M as always happens when M becomes chronic; indeed, there may even be a more or less long M-free interval.

Chronicization of M will not occur suddenly, but through a gradual worsening in the frequency of M attacks, which in many cases is associated with overuse of symptomatic medication. This may further compound the patient's clinical picture and make successful treatment more difficult to achieve. In most cases of M chronicization, as attacks progressively increase in frequency, they undergo changes in their clinical features.

Clinical features of M when it becomes chronic

Changes in the clinical features of M when it becomes chronic have been known since the 1980s. In those years, when interest began to surge about this particular type of headache, Mathew et al. [4] perspicaciously introduced the fitting term "transformed migraine" to describe such condition. The phenomenological changes that M undergoes when it becomes chronic have been officially, though somewhat belatedly, recognized in the diagnostic criteria of ICHD-3 of 2013 [1]. Unlike the 2004 edition [5], in which CM attacks had to always have the clinical features of M headache, the current ICHD-3 classification establishes that, of the 15 or more days of headache per month required for a diagnosis of CM, up to 7 may not have the clinical features of M headache.

In the absence of any conclusive evidence from literature reports, the diagnostic criteria of ICHD-3 fail to provide sufficient elements to characterize CM headache when it does not exhibit the typical features of M.

However, from clinical practice we do know that the majority of migraineurs who over the years show an increase in the frequency of attacks until they become chronic report changes in their M features compared with the past: pain is less severe on average, most often starts in the posterior regions of the head and only later does it extend to the fronto-temporal region, is less frequently unilateral and not as often accompanied by nausea and/or vomiting.

Possible factors transforming episodic M into CM

Several studies have tried to identify the factors that can worsen the natural history of M to a point that it will evolve into CM. It is very important to be able to recognize predictive elements of M chronicization, because this could lead to the adoption of M prevention strategies in patient management.

The first transforming factor that was singled out—and the one that still seems to play the most prominent role—is overuse of symptomatic medication [4], in particular combination drugs containing sedative agents in addition to

the active ingredient that has a painkilling effect or acts on the typical mechanisms of M attacks [6]. Other factors that have been known for several years are stressful events in a patient's life, arterial hypertension, early physiological or surgical menopause and depression [4]. A possible role of hypothyroidism, obesity and obstructive sleep apnoea syndrome has also been reported [7]. More recently, it has been suggested that M chronicization may be related to the occurrence of idiopathic intracranial hypertension without papilledema following cerebral venous sinus stenosis [8].

Unfortunately, most studies on the possible factors of M chronicization have been conducted on subjects who have already developed CM and therefore their results are not entirely reliable. In addition, for some of the factors mentioned above—such as obesity, which may be associated with headache attributed to idiopathic intracranial hypertension or pseudotumor cerebri [1], and obstructive sleep apnoea syndrome, which can be responsible for a particular and specific form of headache [1]—it may be difficult to distinguish between a factor of M chronicization and another symptomatic headache overlapping with M itself.

More conclusive data may come from a review of the results of a study investigating the relationship between the different evolutions of M over the years and the possible onset of a variety of conditions [9]. This study was conducted on 348 subjects who were diagnosed with M without aura when they were first seen at our University of Parma Headache Centre and were then followed up at this centre for at least 10 years. Thirty-three of the 348 patients in the initial sample showed a very inconsistent M pattern, with intervals of M alternating with intervals of CM. In the remaining 315 (257 women and 58 men), M was unchanged, improved or disappeared altogether in 243 (195 women and 48 men, Group A) and became steadily chronic in 72 (62 women and 10 men, Group B). From the comparison of a number of parameters related to the patient's family, physiological, past and recent medical history, and to the history of any conditions occurring after the first observation in the two groups we found that Group B showed the following statistically significant differences over Group A: increased average number of days with M per month at the first observation; increased presence of depression in men at the first observation; onset of arterial hypertension and of depression in women during follow-up.

Therefore, in addition to the obvious role played by overuse of at least some symptomatic drugs in M chronicization, the factors that may be primarily involved are a high frequency of attacks, depression and arterial hypertension.

Possible neurobiological bases of M chronicization

Several neurophysiology [10], biochemistry [11] and functional neuroimaging [12] studies suggest that CM may be associated with structural, functional and metabolic changes in the brain, especially involving the brainstem.

On the other hand, other studies indicate the presence of cortical hyperexcitability and rostral brainstem activation even in episodic M [13].

As proposed by Aurora and Brin [14] in a recent review of CM, "Taken together, findings from studies using a range of techniques suggest persistent changes in certain brain structures among chronic migraineurs, while fewer or transient changes occur in individuals with episodic migraine, supporting the spectrum model of migraine. It is not clear whether any of these changes were present before clinical symptoms and reflect a fundamental biology of susceptibility, or alternatively, are the signature of consequent abnormalities in pain signaling".

Current literature reports concern subjects with episodic M or subjects with CM, but unfortunately there are no prospective studies, which are the only ones that could clarify whether the changes found in the two types of M may represent a continuum of severity and may or may not be reversible.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

Ethical approval This article does not contain any study with human subjects performed by any of the authors

References

1. Headache Classification Committee of the International Headache Society (2013) The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 33:629–808
2. Manzoni GC, Stovner LJ (2010) Epidemiology of headache. In: Nappi G, Moskowitz MA (eds) Handbook of clinical neurology (3rd series), vol 97. Elsevier BV, Amsterdam, pp 3–22
3. Schürks M, Rist PM, Shapiro RE, Kurth T (2011) Migraine and mortality: a systematic review and meta-analysis. Cephalalgia 31:1301–1314
4. Mathew NT, Stubits E, Nigam MP (1982) Transformation of episodic migraine into daily headache: analysis of factors. Headache 22:66–68
5. Headache Classification Subcommittee of the International Headache Society (2004) The international classification of headache disorders, 2nd edn. Cephalalgia 24(suppl 1):1–160
6. Saper JR, Hamel RL, Lake AE (2005) Medication overuse headache (MOH) is a biobehavioural disorder. Cephalalgia 25:545–546
7. Bigal ME, Gironda M, Tepper SJ, Feleppa M, Rapoport AM, Sheftell FD, Lipton RB (2006) Headache prevention outcome and body mass index. Cephalalgia 26:445–450

8. De Simone R, Ranieri A, Montella S, Cappabianca P, Quarantelli M, Esposito F, Cardillo G, Bonavita V (2014) Intracranial pressure in unresponsive chronic migraine. J Neurol 261:1365–1373
9. Manzoni GC, Lombardi LL, Lana S, Maffezzoni M, Camarda C, Torelli P (2012) Detection of possible factors favouring the evolution of migraine without aura into chronic migraine. Neurol Sci 33:S165–S167
10. Aurora SK, Barrodale PM, Tipton RL, Khodavirdi A (2007) Brainstem dysfunction in chronic migraine as evidenced by neurophysiological and positron emission tomography studies. Headache 47:996–1003
11. D'Andrea G, Cevoli S, Colavito D, Leon A (2015) Biochemistry of primary headaches: role of tyrosine and tryptophan metabolism. Neurol Sci 36(suppl 1):17–22
12. Matharu MS, Bartsch T, Ward N, Frackowiak RS, Weiner R, Goadsby PJ (2004) Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain 127:220–230
13. Cao Y, Aurora SK, Nagesh V, Patel SC, Welch KM (2002) Functional MRI-BOLD of brainstem structures during visually triggered migraine. Neurology 59:72–78
14. Aurora SK, Brin MF (2017) Chronic migraine: an update on physiology, imaging, and the mechanism of action of two available pharmacologic therapies. Headache 57:109–125

Neurol Sci (2017) 38 (Suppl 1):S85–S89
DOI 10.1007/s10072-017-2906-9

CLINICAL ASPECTS OF HEADACHE

Treating migraine with contraceptives

Gianni Allais[1] · Giulia Chiarle[1] · Silvia Sinigaglia[1] · Gisella Airola[1] · Paola Schiapparelli[1] · Fabiola Bergandi[1] · Chiara Benedetto[1]

Abstract At least 18% of women suffers from migraine. Clinically, there are two main forms of migraine: migraine with aura (MA) and migraine without aura (MO) and more than 50% of MO is strongly correlated to the menstrual cycle. The high prevalence of migraine in females, its correlation with the menstrual cycle and with the use of combined hormonal contraceptives (CHCs) suggest that the estrogen drop is implicated in the pathogenesis of the attacks. Although CHCs may trigger or worsen migraine, their correct use may even prevent or reduce some forms of migraine, like estrogen withdrawal headache. Evidence suggested that stable estrogen levels have a positive effect, minimising or eliminating the estrogenic drop. Several contraceptive strategies may act in this way: extended-cycle CHCs, CHCs with shortened hormone-free interval (HFI), progestogen-only contraceptives, CHCs containing new generation estrogens and estrogen supplementation during the HFI.

Keywords Combined hormonal contraceptives · Extended regimen contraceptives · Hormone-free interval · Migraine · Progestogen-only contraceptives

✉ Gianni Allais
gb.allais@tiscali.it

[1] Department of Surgical Sciences, Women's Headache Center, University of Turin, Via Ventimiglia 3, 10126 Turin, Italy

Introduction

About 18% of women, which rises to 24% between 30 and 39 years of age, and 6% of men suffers from migraine [1], with a female/male prevalence ratio of around 3 to 1 [2]. Clinically, there are two main forms of migraine: migraine with aura (MA) and migraine without aura (MO) [3]. More than 50% of MO is strongly correlated to the menstrual cycle and the consequent hormonal fluctuations [4–6] in two forms: pure menstrual migraine (PMM) and menstrually related migraine (MRM). The former affects around 10% of migrainous women, only in the perimenstrual period (from 2 days before to 3 days after menses), the latter may also occur at other times of the cycle [7].

Migraine and hormonal fluctuations

The high prevalence of migraine in females and its correlation with the menstrual cycle suggests that the estrogen drop during the last few days of the cycle is implicated in the pathogenesis of the attacks [8]. Other supporting evidence is that women on combined hormonal contraceptives (CHCs) for at least 3 weeks have frequent attacks during the hormone free interval (HFI) [9]: a condition defined as Estrogen-withdrawal headache. The migraine attack, occurring with the estrogen drop, must have been preceded by exposure to high hormonal levels in the previous few days, like in the luteal phase or in women on contraceptives [10]. This estrogen drop may increase the vascular susceptibility to other factors, including prostaglandins [11]. Moreover, estrogen variation may play a role in the modulation of the neuronal excitability, pain perception, in the neuro-endocrine axis adjustment and serotonergic tone [7, 12, 13].

The use of CHCs and their negative effects on migraine

Although the use of a safe and efficacious contraception is a must for women in fertile age, this population is the one most affected by migraine: therefore interaction between migraine and CHCs needs a deepened evaluation. The percentage of women using contraceptive methods increased from 54 to 62% worldwide, between 1990 and 2010. The most commonly reversible contraceptive used in the USA is hormonal contraception (34%) [14] as in Europe (30%), followed by condoms (20%), intrauterine devices (11%) and sterilisation (11%).

Both components and doses in CHCs have been markedly reduced over the last decade, ethinylestradiol (EE) dropped from 50 to 30 μg/day and even less in ultralow-dose formulations (20 or 15 μg); also natural estrogen (micronized 17β estradiol) and estradiol valerate are currently marketed. There are numerous formulations of CHCs, with different types of estrogen and hormone concentrations in a single pill and varying HFI lengths. Currently, there are monophasic, biphasic, triphasic and quadriphasic pills that simulate the hormonal fluctuation in the natural menstrual cycle and pills that foresee less than the traditional 7-day HFI.

Formulations other than the oral one are available, like the patch or vaginal ring. The transdermal patch releases 20 μg of EE plus 150 μg of norelgestromin over 24 h, while the vaginal ring releases 15 μg of EE and 120 μg of etonogestrel.

Progestogen only contraceptives include the progestogen-only pill (POP), sub-dermal implants (levonorgestrel or the newer etonogestrel), depot progestins (medroxyprogesterone acetate, norethindrone enanthate) and the levonorgestrel-releasing intrauterine system.

It has been established that CHCs may worsen or even trigger migraine, meaning that hormonal assumption may be stopped by the physician or patient, due to migraine worsening during pill assumption or the HFI period [15–17]. The IHS classification has defined these two different types of migraine according to the assumption/interruption of CHC [3]: headache attributed to exogenous hormones and estrogen-withdrawal headache (Table 1).

Contraceptives to prevent migraine

Although CHCs may trigger or worsen migraine, their correct use may even prevent or reduce some forms of migraine, like estrogen withdrawal headache. Evidence suggested that stable estrogen levels have a positive effect [18], making minimising or eliminating the estrogenic drop [19]. Two hypotheses underlie this affirmation: the "residual threshold hypothesis" and the "magnitude of decline hypothesis" [20]. The former states there must be a minimum blood estrogen concentration (60–80 pg/ml), to prevent the migraine onset. The latter, that an EE drop of <10 μg cannot trigger an attack. These can be evaluated by comparing two different commercially available products that maintain the minimum EE level at 60–80 pg/ml: Seasonique® and LoSeasonique®. The former leads to a 20 μg estrogen drop during HFI and the latter only a 10 μg drop. A longer migraine has been associated to Seasonique® during the cycle [20].

Although randomized control trials have still to demonstrate these hypotheses, hormonal strategies have reduced the hormonal drop-related menstrual migraine by 77–81% in the population studied.

It has been hypothesised that contraceptives which induce amenorrhea are more efficacious in reducing menstrual migraine attacks. Vetvik et al. evaluated 141 women affected by menstrual migraine and 49 took hormonal contraceptives. Amenorrhea had been induced in 23/49 for 10–32 months, that led to a significantly higher migraine reduction than those with deprivation bleeding (OR 3.5 CI 95% 1.1–11.4, $p = 0.04$). All the amenorrhoeic women were on progestogens (19 levonorgestrel intrauterine system, 3 desogestrel only-pill, 1 depot medroxyprogesterone acetate). It seems that the amenorrhea was connected more to a local effect on the endometrium than to anovulation, as it is associated to a reduced prostaglandin level [11, 21].

Several contraceptive formulations can reduce estrogen drop.

Extended-cycle CHCs

Sulak et al. administered an oral formulation with 3 mg of drospirenone (DRSP) and 30 μg of EE to 114 women. The 1st cycle was 21 days on a hormonal pill, followed by 7 days of placebo, an extended regimen was then adopted for 168 days at the end of the 1st month. There was a significant reduction in the headache score ($p < 0.001$) between the 28 days of the cycle of the 21/7 of DRSP/EE and the 1st 28 days of the extended cycle, a benefit that remained over the entire 168 days of the extended cycle. Moreover, there was a further reduction in the headache score ($p = 0.009$) when the first and last 28 days of the extended cycle were compared. This benefit was confirmed by a reduction in non-productive days ($p = 0.004$). There was also a reduction in headache duration ($p = 0.003$) and number of episodes that did not respond to treatment ($p = 0.008$) [22]. The same authors continued their observations for a year: 73/80 women who completed the cycle wished to continue on the extended regimen. Comparing the baseline conditions, 69 women (86%) reported a higher quality of life, 10 no changes and 1 a worsening. Six

Table 1 Diagnostic criteria for estrogen withdrawal headache and headache attributed to exogenous hormones, following the ICHD-3 beta

Estrogen withdrawal headache (8.3.3)	Diagnostic criteria
	A. Headache or migraine fulfilling criterion C
	B. Daily use of exogenous estrogen for ≥3 weeks, which has been interrupted
	C. Evidence of causation demonstrated by both of the following
	1. Headache or migraine has developed within 5 days after the last use of estrogen
	2. Headache or migraine has resolved within 3 days of its onset
	D. Not better accounted for by another ICHD-3 diagnosis
Headache attributed to exogenous hormones (8.1.12)	Headache developing as an adverse event during regular intake of exogenous hormones, usually for contraception or as hormone replacement therapy
	Diagnostic criteria
	A. Any headache fulfilling criterion C
	B. Regular intake of one or more exogenous hormones
	C. Evidence of causation demonstrated by both of the following
	1. Headache has developed in temporal relation to the commencement of hormone intake
	2. One or more of the following
	(a) Headache has significantly worsened after an increase in dosage of the hormone
	(b) Headache has significantly improved or resolved after a reduction in dosage of the hormone
	(c) Headache has resolved after cessation of hormone intake
	D. Not better accounted for by another ICHD-3 diagnosis

months after study completion, 83% were still taking CHC and 75% the extended regimen [23].

The use of the vaginal ring in extended regimen was evaluated in women affected by MA. The authors hypothesized that a constant, stable, low estrogen dose that blocked ovulation would have avoided both painful episodes and the onset of aura caused by peaks of high hormonal levels. MA was reduced ($p < 0.0005$) and aura frequency dropped (0.23 vs 3.23) in the 23 women under observation for 7.8 months; 18 had used the ring without interruption, 15/18 for 12 consecutive weeks, eliminating menstrual migraine in 91.3% of cases, even if 3 cases (10.7%) of aura were reported during menstruation [24].

A 2014 Cochrane Review compared cyclic and extended regimen contraceptives, reporting that the headache improved in subjects on long-term contraception without interruption, although the doses and administration periods studied differed greatly [25].

CHC with shortened HFI

There are monophasic formulations with 24 active pills and 4 placebo and multiphasic ones with 22 and 26 active pills, followed by an HFI, which ranges from 6 to 2 days, respectively. These formulations are associated with a higher ovary suppression and less hormonal fluctuation, laying the basis for their rational use in menstrual migraine prevention [26].

De Leo et al. studied 60 women affected by PMM and evaluated two therapeutic approaches after randomization: EE 20 μg/DRSP 3 mg in formulations of 21/7 or 24/4 were administered for 3 months. Although both groups had a significant reduction in both intensity and duration of attacks, the group on the 24/4 regimen had the most benefits as from the first cycle [27].

CHC containing new generation estrogen

Nappi et al. evaluated the effects of CHCs containing estradiol valerate and dienogest in women suffering from MRM: the number of migraine attacks, their severity and duration were reduced at the 3rd and 6th cycle ($p < 0.001$), compared to the run-in period, as were the analgesics used ($p < 0.001$). Indeed, this particular formulation provides more stable estrogen plasma concentrations and could reduce withdrawal headache [28].

Progestogen-only contraceptives

This type of contraception may be proposed for women with risk factors that exclude the use of CHCs (e.g., age over 35 years, tobacco use, hypertension, obesity, diabetes, presence of MA) or that have worsening of estrogen-related symptoms (e.g., migraine attacks during HFI). Progestogen seems to be protective against migraine attacks because of its increased during medium-luteal phase and the induction of anovulatory cycles in continuous formulations [29, 30]. Progesteron may also affect the central nervous system, by reducing the nociceptive activation in the trigeminal-vascular system and down-regulating the estrogen receptors [31, 32].

The effect of a 3-month administration of desogestrel-only contraception (75 μg) on the quality of life and headache attack frequency in 37 women with MO or MA was evaluated. The participants answered the Migraine Disability Assessment (MIDAS) questionnaire before and at 3 months after taking the POP. Improvement was observed in both the MIDAS score (27.4–11.1) after 90 therapy days and the MIDAS grade (68% of subjects) ($p = 0.001$). There was a decrease in the number of lost workdays by 79% and impeded social life days by 71%. Moreover, migraine days decreased from 22.7 in the 3 months before therapy to 13.5 days after ($p = 0.001$), with a significant pain intensity decrease ($p = 0.006$) [33].

A second study evaluated the decrease in migraine attack frequency and intensity after desogestrel-only contraception. The follow-up was completed by 38 women (32 MO and 6 MA) who had final assessment. After 3 months of POP intake, there was a significant reduction in the number of migraine days per month ($p = 0.001$) and days of any headache type ($p = 0.002$), headache intensity ($p = 0.0001$), severe headache pain days ($p = 0.0001$) and the number of days on analgesics ($p = 0.007$) [34].

POP was tested against an extended combined oral regimen in 53 MO women: 22 in the CHC group and 31 in the POP group. Fewer migraine days were reported in the POP group after 3 and 6 months compared to baseline ($p = 0.012$ and $p < 0.001$, respectively) as did headache days in both the CHC and the POP groups ($p = 0.029$ and $p = 0.010$, respectively), at 6 months. The POP group had a drop in headache intensity at 6 months ($p = 0.002$) and in severe headache pain at 3 and 6 months ($p = 0.01$ and $p < 0.001$, respectively). Analgesic use was reduced in the POP group at 3 and at 6 months compared to baseline ($p = 0.001$ and $p < 0.001$, respectively) and in the CHC group at 6 months ($p = 0.037$), when the POP group had a significant improvement ($p = 0.04$). Only the POP group reported a significant improvement in the quality of life at 6 months ($p < 0.001$) [35].

Nappi et al. evaluated 30 MA patients (15 had never taken a CHC and 15 diagnosed with MA while taking a CHC). All patients were started on POP (desogestrel 75 μg) after 3 months of observation and a decrease in the average number of migraines was observed in all subjects compared to baseline ($p < 0.001$ and $p < 0.02$, respectively), although visual aura and total aura duration reduced only in previous CHC users ($p < 0.03$ and $p < 0.02$, respectively) [36].

Estrogen supplementation during the HFI

The migraine risk may be reduced by estrogen supplementation during the HFI. The estroprogestinic formulations with supplementary estrogen doses in the 7-day interval were first devised to maximize the potential contraceptive effect and only later were the non-contraceptive effects evaluated. A study on 11 women with menstrual migraine reported that a daily administration of 0.9 mg of conjugated equine estrogen during the 7-day HFI envisaged by CHCs led to a reduction in headache days by at least 50% (average 77%) [37]. The use of transdermal EE formulations were also evaluated, but only doses of >0.05 mg obtained a prophylactic effect. Migraine duration was reduced ($p < 0.002$) when 2 mg of concentrated estradiol gel was given during the 7-day HFI period, as impeding pain ($p < 0.001$), vomiting episodes ($p < 0.04$) and analgesic use ($p < 0.001$), compared to placebo [12].

Conclusions

Treating menstrual migraine and migraine during the HFI period with various contraceptive formulations or providing a safe contraception also to women with migraine with aura by using tailored hormonal formulations is surely both safe and advantageous. However, a close team collaboration between the headache specialist and the gynaecologist is a must. The task of these two professionals is that of evaluating the pros and cons of hormonal contraception, so as to determine the most suitable formulation based on the needs and characteristics of the individual patient and the trend the migraine takes with CHC administration, aimed at early detection of any side-effects that may lead to therapy modification or suspension.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Lipton RB, Bigal ME, Diamond M et al (2007) Migraine prevalence, disease burden and the need for preventive therapy. Neurology 68:343–349
2. Buse DC, Loder EW, Gorman JA et al (2013) Sex differences in the prevalence, symptoms and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) study. Headache 53:1278–1299
3. Headache Classification Committee of the International Headache Society (IHS) (2013) The International Headache Classification, 3rd edition (beta version). Cephalalgia 33:629–808
4. Mannix LK, Calhoun AH (2004) Menstrual migraine. Curr Treat Options Neurol 6:489–498
5. MacGregor EA, Igarashi H, Wilkinson M (1997) Headaches and hormones: subjective versus objective assessment. Headache Q 8:126–136

6. Couturier EG, Bomhof MA, Neven AK et al (2003) Menstrual migraine in a representative Dutch population sample: prevalence, disability and treatment. Cephalalgia 23:302–308
7. Silberstein SD, Merriam GR (1993) Sex hormones and headache. J Pain Symptom Manag 8:243–259
8. MacGregor EA, Frith A, Aspinall LA et al (2006) Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. Neurology 67:2154–2158
9. Machado RB, Pereira AP, Coelho GP et al (2010) Epidemiological and clinical aspects of migraine in users of combined oral contraceptives. Contraception 81:202–208
10. MacGregor EA (2004) Oestrogen and attacks of migraine with and without aura. Lancet Neurol 3:354–361
11. Nattero G, Allais G, De Lorenzo C et al (1989) Relevance of prostaglandins in true menstrual migraine. Headache 29:233–238
12. Nappi RE, Sances G, Brundu B et al (2005) Estradiol supplementation modulates neuroendocrine response to M-chlorophenylpiperazine in menstrual status migrainous triggered by oral contraception-free interval. Hum Reprod 20:3423–3428
13. MacGregor A (2000) Migraine associated with menstruation. Funct Neurol 15:143–153
14. Alkema L, Kantorova V, Menozzi C et al (2013) National, regional and global rates and trends in contraceptive prevalence and unmet need for family planning between 1990 and 2015: systematic and comprehensive analysis. Lancet 381:1642–1652
15. Granella F, Sances G, Zanferrari C et al (1993) Migraine without aura and reproductive life events: a clinical epidemiological study in 1,300 women. Headache 33:385–389
16. Aegidius K, Zwart JA, Hagen K et al (2006) Oral contraceptives and increased headache prevalence: the Head-HUNT Study. Neurology 66:349–353
17. Lieba-Samal D, Wober C, Frantal S (2011) Headache, menstruation and combined oral contraceptives: a diary study in 184 women with migraine. Eur J Pain 15:852–857
18. Magos AL, Zilkha KJ, Studd JW (1983) Treatment of menstrual migraine by oestradiol implants. J Neurol Neurosurg Psychiatry 46:1044–1046
19. Calhoun A (2004) Four hypotheses for understanding menstrual migraine. Female Patient 29:38–44
20. Calhoun A (2012) Combined hormonal contraceptive: is it time to reassess their role in migraine? Headache 52:648–660
21. Vetvik KG, MacGregor EA, Lundqvist C et al (2014) Contraceptive-induced amenorrhoea leads to reduced migraine frequency in women with menstrual migraine without aura. J Headache Pain 15:30
22. Sulak P, Willis S, Kuenl T et al (2007) Headaches and oral contraceptives: impact of eliminating the standard 7-day placebo interval. Headache 47:27–37
23. Coffee AL, Sulak PJ, Kuehl TJ (2007) Long- term assessment of symptomatology and satisfaction of an extended oral contraceptive regimen. Contraception 75:444–449
24. Calhoun A, Ford S, Pruitt A (2012) The impact of extended-cycle vaginal ring contraception on migraine aura: a retrospective case series. Headache 52:1246–1253
25. Edelman A, Micks E, Gallo MF et al (2014) Continuous or extended cycle vs cyclic use of combined hormonal contraceptives for contraception. Cochrane Database Syst Rev 7:CD004695. doi:10.1002/14651858.CD004695.pub3
26. Klipping C, Duijkers I, Trummer D et al (2008) Suppression of ovarian activity with a drospirenone-containing oral contraceptive in a 24/4 regimen. Contraception 78:16–25
27. De Leo V, Scolaro V, Musacchio MC et al (2011) Combined oral contraceptives in women with menstrual migraine without aura. Fertil Steril 96:917–920
28. Nappi RE, Terreno E, Sances G et al (2013) Effect of a contraceptive pill containing estradiol valerate and dienogest [E2V/DNG] in women with menstrually-related migraine [MRM]. Contraception 88:369–375
29. Martin VT, Wernke S, Mandell K et al (2005) Defining the relationship between ovarian hormones and migraine headache. Headache 45:1190–1201
30. Somerville BW, Carey HM (1970) The use of continuous progestogen contraception in the treatment of migraine. Med J Aust 1:1043–1045
31. Martin VT, Behbehani M (2006) Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis-part II. Headache 46:365–386
32. Jayaraman A, Pike CJ (2009) Progesterone attenuates oestrogen neuroprotection via downregulation of oestrogen receptor expression in cultured neurones. J Neuroendocrinol 21:77–81
33. Merki- Feld GS, Imthurn B, Seifert B et al (2013) Desogestrel-only contraception may reduce headache frequency and improve quality of life in women suffering from migraine. Eur J Contracept Reprod Health Care 18:394–400
34. Merki- Feld GS, Imthurn B, Langner R et al (2013) Headache frequency and intensity in female migraineurs using desogestrel-only contraception: a retrospective pilot diary study. Cephalalgia 33:340–346
35. Morotti M, Remorgida V, Venturini PL et al (2014) Progestin-only contraception compared with extended combined oral contraceptive in women with migraine without aura: a retrospective pilot study. Eur J Obstet Gynecol Reprod Biol 183:178–182
36. Nappi RE, Sances G, Allais G et al (2011) Effects of an estrogen-free, desogestrel-containing oral contraceptive in women with migraine with aura: a prospective diary-based pilot study. Contraception 83:223–228
37. Calhoun AH (2004) A novel specific prophylaxis for menstrual-associated migraine. South Med J 97:819–822

Neurol Sci (2017) 38 (Suppl 1):S91–S93
DOI 10.1007/s10072-017-2915-8

CLINICAL ASPECTS OF HEADACHE

Chiari malformation type 1-related headache: the importance of a multidisciplinary study

Marcella Curone[1,2] · L. G. Valentini[1] · I. Vetrano[1] · E. Beretta[1] · M- Furlanetto[1] · L. Chiapparini[3] · A. Erbetta[3] · G. Bussone[2]

Abstract Chiari type 1 Malformation (CM 1) is a structural defect consisting of a displacement of the cerebellar tonsils through the foramen magnum causing obstruction of cerebrospinal fluid (CSF) outflow. CM 1 has a variety of presentation with headache being the most common symptom. The evaluation and treatment of headache related to CM 1 are often difficult, because the pain in the occipital-suboccipital region or headache that is of cough-type suggests symptomatic CM 1, but patients suffering from CM 1 can also report migraine or tension-type headache. In 2015 we started a collaborative project in which our group of neurologists, neurosurgeons and neuroradiologists contribute to create a Chiari Special Outpatient Service; this was set up to provide a multidisciplinary evaluation, treatment and follow-up of patient suffering from CM 1. 201 patients (58 males, 143 females) suffering from CM 1 were multidisciplinary evaluated. Headache characteristics, clinical features, and treatment of patients are discussed. Further progress in multidisciplinary care of headache and CM 1 should be performed to define guidelines.

Keywords Chiari type I malformations · Headache related to Chiari malformation

✉ Marcella Curone
marcella.curone@istituto-besta.it

[1] Neurosurgery III, C. Besta Neurological Institute and Foundation, Via Celoria 11, 20133 Milan, Italy

[2] Igea Healthcare Clinic, Via Marcona 69, 20129 Milan, Italy

[3] Neuroradiology, C. Besta Neurological Institute and Foundation, Via Celoria 11, 20133 Milan, Italy

Introduction

Chiari type 1 malformation (CM 1) is a structural defect consisting of a displacement of the cerebellar tonsils through the foramen magnum causing obstruction of cerebrospinal fluid (CSF) outflow. CM 1 has a variety of presentation with headache being the most common symptom [1, 2]. CM can cause also dizziness, nausea, tinnitus, gait impairment, neck pain, numbness, and dysphagia. Although the prevalence of common primary headache disorders in patients with Chiari malformation is similar to that of the general population, a particular type of occipital headache occurs more frequently in patients with CM 1 [2]. A suboccipital–occipital headache of variable quality and duration aggravated by Valsalva's maneuver, effort, cough, or postural changes, laughing, crying, sneezing, or straining is frequently described [3]. Headache is reported as either dull, throbbing, bursting, or occasionally lancinating [2, 3]. Cervicogenic headache may resemble CM type 1 headache [4] (Table 1). Headache triggered by coughing is often reported by patients affected by CM 1, and both Stovner and Pascual [3, 4] describe the pain associated with the Chiari type 1 malformation as short-lasting "cough headache" attacks lasting less than 5 min. The pathophysiology of cough headache is associated with an increased intracranial pressure caused by coughing; this is due to an increase in the intra-thoracic and intra-abdominal pressure, subsequently leading to an increase in the central venous pressure [5]. In patients with a Chiari malformation type 1, this seems to be caused by the sagging of the cerebellar tonsils below the foramen magnum [6, 7]. Williams [6] described cases with cough headache and tonsillar herniation where a difference in pressure between the ventricles and the lumbar subarachnoidal space after performing a Valsalva manoever was

demonstrated. This craniospinal pressure dissociation displaces the tonsils further into the foramen magnum and pain by coughing could, therefore, be caused by compression or tracking on pain-sensitive structures in the arachnoid space or blood vessels surrounding the tonsils [6, 7]. This mechanism is supported by the fact that, after surgery, both the craniospinal pressure dissociation and cough headache disappear [6]. Neck pain, pain in the arm, and restriction of neck movement often accompany the headache. Dizziness is also a distinguishing feature in the Chiari patients [2–4]. The evaluation and treatment of headache related to CM 1 are often difficult, because the pain in the occipital-suboccipital region or headache that is of cough-type suggests symptomatic CM 1, but patients suffering from CM 1 can also report migraine or tension-type headache. Many patients referring to Headache Centers with the previous CM 1 diagnosis are chronic at admission and had undergone plenty of examinations and visits. To perform a quality headache treatment in patient with CM 1, the approach should be based on multidisciplinary teamwork. Most patients with CM 1 have not surgical indication and they need to be treated by neurologist or pain specialist.

Objective

In 2015 started a collaborative project in which our group of neurologists, neurosurgeons and neuroradiologists contribute to create a Chiari Special Outpatient Service; this was set up to provide a multidisciplinary evaluation, treatment and follow-up of patient suffering from CM 1.

This project was based upon the observation that many patients with headache and diagnosis of CM 1 were again and again visited by different specialists, especially neurologist for treatment of headache, with different and often discordant conclusions that leaded to frustration of patients and their relatives. A major focus of our group was to develop a coherent multidisciplinary approach to the CM 1. A particular attention was paid to headache features. We reported our experience.

Patients and methods

Patients with diagnosis of CM 1 were evaluated in the same visit both from neurologist and neurosurgeon. During the multidisciplinary evaluation, the clinical history, charts, and neuroimaging of the patient were reviewed and a neurological examination was performed. At the end of the visit, after a brief discussion of the case, the two specialists suggest the treatment. Patients without indication for surgical treatment were prescribed drugs with particular focus of prophylaxis of headache and further exams. Patient with surgery indication was discussed in a new following meeting with neuroradiologists and the surgical treatment was defined.

Results

From September 2015 to December 2016, 201 patients (58 males, 143 females) suffering from CM I were multidisciplinary evaluated. All patients referred headache. 52 patients (25.8%) had a previous history of migraine. 134 (67%) had tension-type headache. 58 (28.8%) had migraine headache. 93 (46%) had both migraine and tension-type headache. 176 (88%) had neck pain. 59 (29%) described a suboccipital-occipital binding headache. Diffuse/non-pulsating headache was present in 149 (%). A pulsating headache was present in 46 (%). In 174 (87%), headache was worsened by Valsalva's maneuver, effort, cough, sneezing, or straining. In 27 (13.4%), headache onset was only during Valsalva's maneuver, effort, cough, sneezing, and laughing. 68 patients (34%) reported short-lasting cough headache attacks. Long-lasting (from 3 h to 3 days) headache attacks were reported in 82 (41%). In 85 (42%), the headache was severe, in 101 (50%) was moderate to severe, and in 15 (7%) the headache was mild. 32 patients (16%) had continuous headache. Migrainous-associated symptoms were reported in 77 (38%), nausea was described in 48 (23.8%), photophobia in 41 (20%). Dizziness was present in 179 (89%). 21 (10.4%) had medication overuse (MO) due to chronic pain. 3 of them had MO involving drugs of dependence. 20 patients on 21 with MO underwent an inpatient detoxification program at our institute with pharmacological prophylaxis after withdrawal from MO with highly significant improvement and reduction in headache with 52%. 11 patients (5.4%) had surgical indication and 4 of them underwent a posterior fossa decompression with improvement of headache. 106 (52.7%) are still in follow-up for adjustment of prophylactic treatment of headache and had reduction in headache with 46% (Tables 1, 2).

Discussion

Patient with headache and CM 1 may be difficult to treat, and in these cases, multidisciplinary approach can be the best choice. Most patients with chronic headache and CM 1 are generally referred to many specialists with waste of time and delay in the treatment. Neurological or neurosurgical evaluation alone cannot be conclusive. Moreover, many patients receive surgical indication without fitting surgical criteria, especially because there is still

Table 1 Headache characteristics in CM I patients

Tension-type	134 (67%)
Migraine-type	58 (28.8%)
Migraine and tension-type	93 (46%)
Binding	59 (29%)
Diffuse/non-pulsating	149 (74%)
Worsened by Valsalva's maneuver	174 (87%)
Pulsating headache	46 (22.8%)
Short-lasting cough-related	68 (34%)
Long-lasting (from 3 h to 3 days)	82 (41%)
Severe	85 (42%)
Moderate to severe	101 (50%)
Mild	15 (7%)
Continuous	32 (16%)
Migrainous-associated symptoms	77 (38%)
Nausea	48 (23.8%)
Fotofobia	41 (20%)

Table 2 Headache attributed to Chiari malformation type 1 (CM 1) IHS diagnostic criteria

Description
Headache caused by Chiari type I malformation, usually occipital or suboccipital, of short duration (less than 5 min), and provoked by cough or other Valsalva-like maneuvers. It remits after the successful treatment of the Chiari malformation
Diagnostic criteria
A. Headache fulfilling criterion C
B. Chiari malformation type 1 (CM1) has been demonstrated
C. Evidence of causation demonstrated by at least two of the following
1. Either or both of the following:
(a) Headache has developed in temporal relation to the CM1
(b) Headache has resolved within 3 months after successful treatment of the CM1
2. Headache has at least one of the following three characteristics:
(a) Precipitated by cough or other Valsalva-like maneuver
(b) Occipital or suboccipital location
(c) Lasting < 5 min
3. Headache is associated with other symptoms and/or clinical signs of brainstem, cerebellar, lower cranial nerve, and/or cervical spinal cord dysfunction
D. Not better accounted for by another ICHD-3 diagnosis

controversy on the indication and selection of decompression procedures [8] Our results suggest that headache is the most common symptom observed in patients with CM 1 but as we apply IHS diagnostic criteria for "headache attributed to CM 1" [9, Table 2], while the worsening of headache cough or other Valsalva-like maneuver was present in high percentage (87%), the headache strictly precipitated by cough or other Valsalva-like maneuver was present in a very small group (only 13.4%). To understand and define more clearly headache due to CM 1, we found out in our clinical sample that these patients had different types of headache and the pain merely provoked by Valsalva-like maneuver, that is to say the real headache due to CM 1 is about rare. The pain observed in our patients resembled features of both primary headaches and cervicogenic pain and the overuse of symptomatic drugs also complicated the headache. This survey suggests that pain associated with CM 1 should be seen in a wide vision and needs to be managed by a neurologist or pain specialist regardless from surgical indication. In our experience, the outcome and the satisfaction of the patient are better when the care is provided by different disciplines at the same time with focus on the same problem. Further progress in multidisciplinary care of headache and CM I should be performed to define guidelines.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential no conflict of interest in relation to this article.

References

1. Victorio MC, Khoury CK (2016) Headache and Chiari I malformation in children and adolescents. Semin Pediatr Neurol. 23(1):35–39
2. Kesler R, Mendizabal JE (1999) Headache in Chiari malformation: a distinct clinical entity? J Am Osteopath Assoc 99(3):153–156
3. Pascual J, Oterino A, Berciano J (1992) Headache in type I Chiari malformation. Neurology 42(8):1519–1521
4. Stovner LJ (1993) Headache associated with the Chiari type I malformation. Headache 33(4):175–181
5. Cordenier A, De Hertogh W, De Keyser J, Versijpt J (2013) Headache associated with cough: a review. J Headache Pain 14:42
6. Williams B (1980) Cough headache due to craniospinal pressure dissociation. Arch Neurol 37(4):226–230
7. Sansur CA, Heiss JD, DeVroom HL, Eskioglu E, Ennis R, Oldfield EH (2003) Pathophysiology of headache associated with cough in patients with Chiari I malformation. J Neurosurg 98(3):453–458
8. Fan T, Zhao H, Zhao X, Liang C, Wang Y, Gai Q (2017) Surgical management of Chiari I malformation based on different cerebrospinal fluid flow patterns at the cranial-vertebral junction. Neurosurg Rev 9:1–8
9. Headache Classification Committee of the International Society (2013) The international classification of headache disorders 3rd edition (Beta version) Cephalalgia 33(9):629–808

Neurol Sci (2017) 38 (Suppl 1):S95–S98
DOI 10.1007/s10072-017-2950-5

CLINICAL ASPECTS OF HEADACHE

Chiari malformation-related headache: outcome after surgical treatment

Elena Beretta[1] · Ignazio G. Vetrano[1] · Marcella Curone[2] · Luisa Chiapparini[3] · Marika Furlanetto[1] · Gennaro Bussone[2] · Laura G. Valentini[1]

Abstract The outcome of headache in a series of 135 operated CM1 is presented. Favorable results were obtained in 85% of atypical and 93% typical headache with the support of a multidisciplinary approach that restricted the indications for surgery.

Keywords Cerebrospinal fluid · Chiari 1 malformation · Headache · Occipital-cervical decompression · Syringomyelia

Introduction

Chiari 1 malformation (CM1) is defined as cerebellar tonsils descend of at least 5 mm into the spinal canal below the plane of the foramen magnum. The brainstem may be occasionally involved; if bony anomalies of the craniovertebral junction are associated as well, the picture is defined CM 1.5. In many instances, tonsil herniation is an incidental finding on neuroradiological imaging and, if asymptomatic, surgical treatment is not necessary. The prevalence in general population is 0.6–0.9% [1]. On the contrary, CM1 may be associated with syringomyelia, obstructive hydrocephalus, or neurological signs and symptoms [2]; in these cases, surgery is the treatment of choice. In rare cases, CM1 patients may experience syncope [3]. Symptoms usually start in the second-third decade of life, but there is increased recognition of symptomatic cases in children [4–6]. Headache is the most common initial symptom, leading to diagnosis in 25–50% [2]. The malformation may reduce the free pulsatile movement of cerebrospinal fluid (CSF) through the foramen magnum during the cardiac cycle, creating a partially entrapped spinal subarachnoid space and causing high cervical subarachnoid pressure waves, enhancing transmural CSF movement into the spinal cord, which is the pathophysiological base of syrinx. The obstruction of the CSF circulation may likewise be important in the origin of headache. The typical CM1-related headache is usually severe and paroxysmal, induced or exacerbated by Valsalva maneuvers such as laughing, sneezing, and coughing [7], in relation to waves of increased intracranial pressure that impact on cerebellar tonsils. However, many other types of headache have been reported including migraine, tension-type headache, and cluster headache [8, 9] but the role of CM1 in the genesis of these "atypical" headaches is still debated. We present a series of patient that underwent foramen magnum decompression (FMD) for CM1 associated with syringomyelia or symptoms, focusing on the impact of surgical treatment on preoperative headache both typical and non-typical.

Drs. Beretta and Vetrano equally contributed to all aspect of this work.

✉ Laura G. Valentini
laura.valentini@istituto-besta.it

[1] Department of Neurosurgery, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Via G. Celoria 11, 20133 Milan, Italy

[2] Center for the diagnosis and treatment of headache, Casa di Cura Igea, Milan, Italy

[3] Neuroradiology, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy

Material and methods

Between 1998 and 2017, 143 adult patients affected by CM1 were admitted at our institution for surgical treatment. The malformation was documented in all patients by MRI imaging scans on the sagittal plane; CM1 was confirmed with a tonsil descent of 5 mm in relation to the basion-ophistion plane. Spine MRI scans were also performed to detect syrinx, and flow study in posterior fossa was done to confirm the

constraint to CSF passage posteriorly. All patients had neurological symptoms attributable to the CM1 (i.e., Chiari-type headache, bulbar, or cerebellar dysfunction) or harbored progressive syringomyelia. Patients with an associated congenital syndrome for skeletal dysplasia, such as Klippel–Feil syndrome, were excluded from this study ($n = 4$). Age at surgery ranged between 19 and 73 years old (mean 40.6 years old) with a female prevalence ($n = 90$). The most common indication for surgery was syringomyelia ($n = 67$), syringomyelia associated to typical-CM1 headache ($n = 30$), typical headache ($n = 27$), bulbar, and cerebellar symptoms ($n = 9$), Four patients presented also hydrocephalus; four other patients were lost at follow-up. Typical headache was defined as occipital or suboccipital pain of short duration (less than 5 min) and provoked by cough or other Valsalva-like maneuvers [7]. All types of headache that did not fulfill criteria for typical-CM1 headache were defined as atypical. Taking in account the global series (135 pts), 97 (71.8%) had a syrinx, 29 (21.5%) had just typical headache, and 9 (6.7%) had neurological signs and symptoms. Regarding to the 97 patients in which surgical indication was due to progressive syringomyelia, 34 of them were also affected by non-typical headache, 64 by typical headache, and the remaining 33 never complained for headache. So the total number of patients complaining for preoperative headache was 93 (70%), the great majority affected by typical headache ($n = 89$) and a small number of atypical ($n = 30$). Short-term (<3 months) and long-term (12 months) outcomes were evaluated. Headache improvement was defined as a reduction in the frequency or intensity of the headache at follow-up. Because the end point of the present study was to evaluate the impact of surgical treatment on preoperative headache, the patients with motor impairments and dysphagia ($n = 2$), ataxia ($n = 2$), ataxia plus dysphagia ($n = 1$), apnea and dysphagia ($n = 1$), limb pain ($n = 1$), visual disturbances ($n = 1$), and tinnitus ($n = 1$) were excluded from the final analysis, due to absence of headache. The final analysis about the results of surgery on headache was therefore performed on 93 CM1-operated patients. The clinical data and demographic details of the series are summarized in Table 1. The surgical treatment by FMD was carried out in the prone position. After occipital bone craniectomy with high-speed drill, the posterior arch of the atlas was routinely removed, but C2 and related muscle attachments were preserved. In all cases, the dura was opened under microscopic vision with a midline linear incision. The arachnoid plane was preserved whenever possible, and tonsil resection or coagulation was performed only when the tonsil extended behind the posterior arch of the axis or in case of arachnoiditis. A dural patch was therefore tightly sutured, widening much more just at the craniovertebral passage. The graft was cut to the size of the dural defect and secured with a monofilament non-absorbable suture. Fibrin glue and different sealant products were applied on the suture to prevent cerebrospinal fluid leak. In four patients presenting an hydrocephalus due tonsil herniation, the ventricular dilatation was treated before the CM1 to prevent CSF leakage due to increased intracranial pressure (ICP); in three of them, the first surgical choice was to perform an endoscopic ventriculocisternostomy and in the remaining one, a ventriculoperitoneal shunt was placed.

Table 1 Patient series ($n = 135$)—surgery and symptoms

Males	45		
Females	90		
Age range	19–73 years		
Mean	40.6 years		
Median	41 years		
	Syrinx	No syrinx	Other symptoms
	97 (72%)	29 (21%)	9 (7%)
No headache 42	33 (24%)	–	9 (7%)
Headache 93			
Typical	30 (22%)	29 (21%)	–
Atypical	34 (25%)	–	–

Results

There was no major morbidity neither mortality.

One hundred thirty-two patients were submitted to FMD and 9 (6.8%) of them had different degrees of CSF collections; 8 were treated conservatively with evacuations and compression bandages. Other postoperative complications included hydrocephalus ($n = 2$) and wound infections ($n = 1$). One case of hydrocephalus had ventriculo-peritoneal shunt (VPS) and one patient with a CSF leak underwent reoperation for re-do duroplasy (0.75%). The global favorable response of preoperative headache to surgery for CM1 in our series was 70%. More in detail, 64 patients who were operated for syrinx also had headache. Of them, 29 (85%) patients out of 34 affected by atypical headache experienced an improvement, 2 had no change, 1 temporarily worsened (due to CSF leak that required a second surgery), while 27 (96%) patients out of 30 with typical headache had an improvement. About the 29 patients operated on just for typical headache, without any syrinx, 27 (93%) of them had an improvement, only one had remained stable, and another one temporary worsened due to the occurrence of postoperative hydrocephalus that required a shunt placement. All the 132 patients submitted to FMD were treated in the postoperative period by a protocol aimed to prevent "relative hypotension" occurrence, by overhydration and prolonged supine positioning with recovery of the upright in a couple of weeks. Despite this precaution, 18 patients experienced prolonged intracranial hypotension syndrome

with orthostatic headache and walking difficulties that solved prolonging overhydration and bed rest for 4 weeks.

Discussion

The clinical presentation of CM1, which typically begins in young adults, can include headaches, visual disturbances, neuro-otological complaints, lower cranial nerve dysfunction, and sleep apnea [5, 6, 10]. Those clinical manifestations are related to direct compression syndromes (brainstem or spinal cord) or to cerebrospinal fluid (CSF) disturbances (hydrocephalus, pseudotumor-like episodes, headache). Headache is the most common symptom, occurring in 30–80% of patients [11]. This is true also in the pediatric population, with a frequency of headache ranging from 15 to 75% [12]. By the way, the patients in which cerebellar tonsil displacement is present report a wild spectrum of headache. The typical headache in CM1 is described as occipital or suboccipital pain, brief in duration and triggered by cough, Valsalva maneuver, or physical activity [7]. Also, different types of headache have been associated with CM1, including intracranial hypotension-like headache, long-lasting headache with cervicogenic features, and continuous headache. Pascual [13, 14] reported that all symptomatic cases of cough headache were associated to CM1, and most of them had also other posterior fossa signs and symptoms. This type of headache is supposed to be a consequence to the compression of C1 and C2 roots by further tonsillar descent occurring during Valsalva-like maneuvers. Moreover, the pain could be the result of dissociation of the craniospinal pressure or due to sudden increase in intracranial pressure caused by obstruction of the CSF [15]. In that kind of patients, headache usually remits or improves after successful treatment of CM1 [7]. It is also important to remember that patients with CM1 have the same risk for the common headache disorders as normal population, including migraine and tension-type headache; if these headache disorders are present, they should not be confused with CM1 headache or be considered as an indication for surgery [16]. Other patients with CM1 may present with signs and symptoms of interruption of CSF flow, brainstem, or cerebellar dysfunction including visual disturbances, dysphonia, dysphagia, sleep apnea, incoordination, and sensory disturbances. Motor and sensory difficulties, pain, and scoliosis may be associated with syringomyelia. According to the literature, there is poor correlation between entity of symptoms and radiological severity of tonsil descent. So it is difficult to attribute radiological findings to different types of headache [17]. Despite many debates about the appropriate technique for surgery, there is a consensus between neurosurgeons about the fact that treatment is indicated just in patients with symptomatic CM1 and progressive syringomyelia. A watch and see management is also a reasonable option in patients with mild, non-disabling symptoms, in absence of neurological deficits. The problem rises with the symptom "headache" is taken into account, for the difficulty to discriminating whether or not it depends on the tonsil descent.

Conservative management is generally proposed for atypical headache rather than for the typical one, with specific occipital–suboccipital pain with significant disability and concurrent cough headache. The decision for non-surgical treatment should be taken in consultation with neurosurgeon, neuroradiologist, and neurologist [18]. Surgery is recommended to patients with signs and symptoms of brainstem or cerebellar dysfunction, large or progressive syringomyelia, or with a poorly controlled, typical CM1 headache disorder [19]. Patients should be considered as surgical candidates if the headache is suboccipital, precipitates by Valsalva-like maneuvers, and is refractory to medical therapy and affect everyday life. Moreover, in patients with non-typical CM1 headache, additional signs or symptoms might indicate surgery, in particular bulbar dysfunction (ocular movement disorder, central sleep apnea, swallowing disturbances) or syrynx. The present series is a selection of highly symptomatic cases, with a restrict indication for surgery, offered just in case of progressive syrinx, disabling typical headache of neurological deterioration. The results of surgery on headache in these selected cases was quite good: 93% of patients with typical headache improved, regardless to the association with syringomyelia or less. By the way, also atypical headache had benefits of surgical treatment, with improvement in 85% of cases, even if the surgical indication was due to progressive syringomyelia. Consequently, some role of symptomatic CM1 in facilitation if not in the genesis of other types of headache may be hypnotized. This study present several important limitations. First, headache is a subjective symptom that is difficult to assess. Second, there were few details on headache because the patients were evaluated just by the neurosurgeon in some steps of their clinical pathway; moreover, the diagnostic criteria for headache related to CM1 require validation [7]. It has been hypnotized that when surgical treatment for CM1 fails, we need to evaluate if tonsil herniation is secondary to other predisposing factors such as raised intracranial pressure associated with idiopathic hypertension or occult craniosynostosis [20]. No cases in our series presented such a picture; on the contrary, many of our patients experienced an intracranial hypotension-like headache, quite different from the headache they had before surgery. The self-limiting duration and the good response to hypotension protocols confirm its genesis: a transient passage of relative intracranial hypotension due to CSF loss along surgery and underproduction in the change from a chronic hypertension due to CM1 to a normal range of intracranial pressure. Based on this, it may be hypnotized that the FMD technique applied in the present series was effective in treating headache related to chronic intracranial hypertension due to CM1. The multidisciplinary approach that

we propose, with the aid of the neurologist, increased the percentage of successful surgery by the mean of a more tight indication, excluding from surgery the patients with incidental CM1 affected by different neurological syndromes and headache responsive to medical treatment.

Conclusions

CM1 patients may present a range of neurological signs and symptoms, including different types of headache. Our study reports that headaches will improve after surgery if the indication is correct. A multidisciplinary approach is mandatory to obtain this result.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Meadows J, Kraut M, Guarnieri M, Haroun RI, Carson BS (2000) Asymptomatic Chiari type I malformations identified on magnetic resonance imaging. J Neurosurg 92(6):920–926
2. Taylor FR, Larkins MV (2002) Headache and Chiari I malformation: clinical presentation, diagnosis, and controversies in management. Curr Pain Headache Rep 6(4):331–337
3. Ziegler DK, Mallonee W (1999) Chiari-1 malformation, migraine, and sudden death. Headache 39(1):38–41
4. Milhorat TH, Chou MW, Trinidad EM, Kula RW, Mandell M, Wolpert C, Speer MC (1999) Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. Neurosurgery 44:1005–1017
5. Nohria V, Oakes WJ (1990) Chiari I malformation: a review of 43 patients. Pediatr Neurosurg 16:222–227
6. Tubbs RS, Lyerly MJ, Loukas M, Shoja MM, Oakes WJ (2007) The pediatric Chiari I malformation: a review. Childs Nerv Syst 23: 1239–1253
7. Headache Classification Committee of the International Headache Society (IHS) (2013) The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 33(9):629–808
8. Grazzi L, Andrasik F (2012) Headaches and Arnold Chiari syndrome: when to suspect and how to investigate. Curr Pain Headache Rep 16:350–353
9. Kao YH, Hsu YC (2015) Chiari malformation type I presenting as cluster-like headache. Acta Neurol Taiwanica 24(4):122–124
10. Dyste GN, Menezes AH, Van Gilder JC (1989) Symptomatic chiari malformations. An analysis of presentation, management and long-term outcome. J Neurosurg 71:159–168
11. Stovner LJ (1993) Headache associated with the Chiari type I malformation. Headache 33:175–181
12. Victorio MC, Khoury CK (2016) Headache and Chiari I malformation in children and adolescents. Semin PediatrNeurol 23:35–39
13. Pascual J, Iglesias F, Oterino A, Vázquez-Barquero A, Berciano J (1996) Cough, exertional, and sexual headaches: an analysis of 72 benign and symptomatic cases. Neurology 46(6):1520–1524 Review
14. Pascual J, Oterino A, Berciano J (1992) Headache in type I chiari malformation. Neurology 42:1519–1521
15. Sansur CA, Heiss JD, DeVroom HL, Eskioglu E, Ennis R, Oldfield EH (2003) Pathophysiology of headache associated with cough in patients with. Chiari I malformation J Neurosurg 98(3):453–458
16. Abu-Arafeh I, Campbell E (2017) Headache, Chiari malformation type 1 and treatment options. Arch Dis Child 102(3):210–211
17. Raza-Knight S, Mankad K, Prabhakar P, Thompson D (2017) Headache outcomes in children undergoing foramen magnum decompression for Chiari I malformation. Arch Dis Child 102(3): 238–243
18. Novegno F, Caldarelli M, Massa A, Chieffo D, Massimi L, Pettorini B, Tamburrini G, Di Rocco C (2008) The natural history of the Chiari type I anomaly. J Neurosurg Pediatr 2(3):179–187
19. Imperato A, Seneca V, Cioffi V, Colella G, Gangemi M (2011) Treatment of Chiari malformation: who, when and how. Neurol Sci 32(Suppl 3):S335–S339
20. Frič R, Eide PK (2016) Comparative observational study on the clinical presentation, intracranial volume measurements, and intracranial pressure scores in patients with either Chiari malformation type I or idiopathic intracranial hypertension. J Neurosurg 24:1–11

Neurol Sci (2017) 38 (Suppl 1):S99–S102
DOI 10.1007/s10072-017-2890-0

CLINICAL ASPECTS OF HEADACHE

The role of visual system in migraine

Stefania Bianchi Marzoli[1] · **Alessandra Criscuoli**[1]

Abstract The visual system is involved in different ways in migraine. Visual auras are the most common form of migraine aura. It may consist of positive or negative visual symptoms and cortical spreading depression is felt to be the phenomenon that underlies it. Even in migraine without aura, vision it is not totally excluded given that one of the major criteria for the diagnosis of migraine is photophobia. In persistent visual aura, patients refer symptoms defined as visual snow and television static. In retinal migraine unilateral decreased vision or complete visual loss occurs. Ophthalmoplegic migraine is characterized by palsy of one among the three ocular motor nerves. Migraine visual aura, particularly when occurring without headache, is a diagnosis of exclusion. Imaging studies and laboratory tests should exclude neurologic disease, included seizures and central nervous system tumor, ocular pathologies, carotid or cardiac disease, thrombosis and connective tissue disease.

Keywords Migraine aura · Photophobia · Visual snow · Retinal migraine · Ophthalmoplegic migraine

✉ Stefania Bianchi Marzoli
s.bianchimarzoli@auxologico.it

[1] Neuro-ophthalmology Service and Ocular Electrophysiology Laboratory, Scientific Institute Capitanio Hospital, IRCCS Istituto Auxologico Italiano, via Mercalli, 28, 20122 Milan, Italy

Introduction

In 60% of migraineurs, warning signs occur and they can begin insidiously hours to days before the onset of headache. Among the migraine auras, visual auras are the most common (99%) followed by somatosensory (40%), motor (18%) and speech difficulties (20%), symptoms that may be present in the same or different moments of the attack [1].

The visual system can be involved in different ways and different forms of migraine.

The visual system in migraine

Migraine with visual aura affects about 8% of the population and it is about three times less common than migraine without aura. Migraine with or without aura may coexist in 13% of migraineurs and about 19% of patients had aura symptoms with every headache attack [1, 2]. Headache generally follows the aura in 93% of patients.

The visual aura may be unilateral (70%) or bilateral (30%) and may consist of positive or negative visual phenomena. It commonly begins in the centrolateral area of the visual field with alteration of visual perception due to visual loss or presence of bright spots and may evolve into a small scotoma [3]. This symptom may progress over a period of 5 min to 1 h to involve a hemifield or a quadrant of visual field with the expanding margin that may have the appearance of zigzagging lines or geometric shapes known as fortification spectra or teichopsia. Positive visual phenomena may assume a C-shape or a crescent with shimmering edges (scintillations) with or without color. Simple flashes (phosphenes), white or colored dots, bean-like forms, bright bars of light may also be seen. The presence

of scintillations distinguishes auras from transient ischemic attacks. Other visual auras such as foggy vision, looking through water and complex visual hallucinations and negative phenomena such as hemianopsia or quadrantanopsia, scotomas, tunnel vision and complete blindness can also occur. Normal central vision returns as the disturbance migrates peripherally, usually in less than 30 min, with a total duration of less than 60 min.

"Alice in wonderland" syndrome typically affect young children who refer micropsia and telopsia (objects appear smaller and further away than they are), condition often associated with acute bilateral occipital pole lesion, seldom at the onset of migraine attack [4].

The primary striatal visual cortex may be the site of origin of the negative visual phenomena, although the visual unimodal association areas and other extrastriate areas can also be involved. With the exception of phosphenes, the migraine positive visual phenomena seem related to involvement not only of the primary visual area but also of the associative heteromodal zones adjacent to the parieto-occipital fissures and to the superior temporal sulci and the pre-occipital notch. The participation of white matter tracts linking the visual areas to the frontal lobes may generate atypical symptoms [5]. The evidence that visual evoked potentials (VEPs) seem to not differ in migraineurs and healthy subjects, may indicate that there is not an anatomical permanent damage along the visual pathway. However, VEPs may not be the most reliable neurophysiological hallmark in migraine [3, 4, 6].

Involvement of the retina and optic nerve structures, as a consequence of a vasospastic etiology in migraine with aura, has been investigated with Spectral Domain Optical Coherence Tomography although data from different studies are not homogeneous. Reduction of peripapillary retinal nerve fiber layer (pRNFL) thickness in the temporal or in the upper optic nerve quadrants that have been reported by some authors was not confirmed by others [7–11]. On comparing migraineurs with aura and chronic headache patients we also did not identify differences in pRNFL and ganglion cell layer [12].

Cortical spreading depression (CSD) is felt to be the phenomenon that underlies migraine aura. It is a wave of hyper-excitation followed by suppression spreads at a speed of around 3–6 mm/min across areas of contiguous parenchyma without respecting specific neurovascular boundaries of functional cortex. CSD causes release of excitatory and pro-inflammatory mediators which are capable of activating meningeal and perivascular nociceptive neurons causing trigeminovascular activation and dural mast cell degranulation, culminating in a sterile neurogenic inflammation which may prolong headache pain [1, 5]. In patients with spontaneous and evoked migraine auras, hemodynamic alterations, not always respecting specific vascular territory, were reported by multimodal MRI techniques including perfusion-weighted imaging and blood oxygen level dependent (BOLD) imaging [1].

A recent fMRI study reported an abnormal resting-state visual network functional connectivity in the absence of structural or microstructural abnormalities not related to clinical parameters of migraine severity [13]. In the same study, the resting-state fMRI data are in line with recent EEG findings suggesting a close relationship between the aura phenomenon and neural connectivity in migraine during photic stimulation, supporting that lingual gyrus is crucial in photophobia and in trigeminal pain multisensory integration also in patients with migraine without aura.

Persistent migraine visual aura can also occur and it is supposed that it may be due to recurrent waves of CSD. Positive visual phenomena are the typical manifestation in persistent migraine visual aura most commonly consisting of formed or unformed visual hallucinations sometimes covering the entire visual field of both eyes. Metamorphopsia and palinopsia are rarely reported. The diagnosis of persistent migraine visual aura should be made if seizures, toxic-metabolic conditions, retinal inflammatory conditions and psychiatric disease have been excluded. For the International Headache Society, persistent migraine aura may fulfill criteria for migraine with aura and one or more aura symptoms persisting for more than 2 weeks. The condition is associated with absence of neuroimaging finds suggesting infarction or EEG abnormalities and with normal ophthalmological examination. Two descriptive patterns have been common in these patients: visual snow, sometimes referred to as primary persistent visual disturbance, and television static. Schankin and colleagues performed a PET study on patients with visual snow and found metabolic hyper activation at the lingual gyrus without any abnormality on diffusion or perfusion-weighted MRI [14]. In some patients persistent visual aura may resolve spontaneously in a period of weeks to months, in some others it decreased with antiepileptic agents including lamotrigine and valproate while in there are patients who poorly respond to treatment with migraine prophylactics or antiepileptic medication [15].

Not all typical migraine aura episodes are followed by or associated with migraine headache. Among migraineurs with aura, 38% of patients may show also typical migraine aura without headache while exclusive aura without headache can occurs in 4% of subjects [16]. The pathophysiologic explanation might suggest existence of some silent-pain areas that can be involved in the migraine attack before the adjacent cortical pain regions so that patients refer only visual symptoms and not headache. The fact that not all patients with aura developed headache suggest that both are still separate phenomena. Therefore, some drugs

(e.g. lamotrigine) are effective in preventing migraine with aura without great advantage in migraine without aura attacks.

Even in migraine without aura, vision is not totally excluded given that one of the major criteria for the diagnosis of migraine is photophobia and it can occur as a premonitory symptom being present in around 50% of patients [17]. The causes of this hypersensitivity to light is unknown: a PET study suggested that activations in the extrastriate visual cortex are directly linked to increased sensitivity to light in the premonitory phase [18]. It is unclear whether photophobia is photosensitivity, as in pain worse with light, as opposed to photo-allodynia, where light is bothersome in and off itself. Light may exacerbate headache through involvement of photosensitive retinal ganglion cells, those cells that do not have image-forming functions but are involved in the regulation of the circadian rhythm and the adaptation of pupillary size to light, then the visual pathway from the optic chiasm to the pulvinar and progressively towards the somatosensitive cortex and the visual and visual-associated cortex [19]. Complete cessation of migraine visual aura was showed in a study of 26 migraineurs with post-geniculate or visual cortex lesion [5].

In the retinal migraine, patient reports unilateral decreasing vision or complete visual loss, flashes, and a shade over a portion of the visual field. In most patients visual symptoms last less than 30 min. It may be difficult to differentiate monocular transient visual loss (TVL) or retinal migraine from a migraine aura because patients have difficulties in distinguishing monocular visual loss from visual loss occurring within the same hemifield of both eyes. The mechanism in common between migraine and TVL is the transient loss of perfusion related to vasospasm that may cause an impairment of the circulation to the choroid and/or optic nerve, but there is not a conclusive evidence cause-effect, even if in migraine-associated anterior ischemic optic neuropathy the onset of visual loss is often temporally related to the episode of migraine headache.

Treatment of migraine can have side effects on visual system structure. Ergotamine derivatives are known to cause vasoconstriction and may cause unwanted ischemic side effects such as stroke and myocardial infarction or ischemic optic neuropathy .

A possible link between migraine and normal tension glaucoma was evoked and the pathophysiology of both could be substained from a disregulation of the vascular system, as it is the Raynaud's phenomenon which sometimes coexists [20].

Ophthalmoplegic migraine is a rare subtype of migraine in which only one among the three ocular motor nerves is involved, often the third cranial nerve characteristically with sparing of pupil activity. The oculomotor palsy begins at the peak of a migraine attack and persists for days to weeks after the headache phase. The resolution is complete even if, rarely, a residual paresis may persist after repeated attacks. In the acute stage, MRI may show thickening and enhancement of the oculomotor nerve at its exit from the midbrain and the signal becomes less intense during the quiescent phase. Early treatment with steroids can accelerate the resolution of headache and ophthalmoplegia from weeks to few days. The pathogenesis of ophthalmoplegic migraine is still unknown and the hypothesis includes compression, ischemia, demyelination and vascular anomaly. It has been also proposed an involvement of the trigeminovascular system since neuropeptides released during the migraine attack cross the relatively open blood–brain barrier at the oculomotor nerve exit inducing a sterile inflammation and causing ophthalmoplegia [3].

Among migraineurs, 10–24%, mainly adolescent girls, are affected from basilar migraine, the so-called symptoms arise from the territory supplied by the basilar artery, the brainstem, cerebellum and the occipital cortex. Bilateral visual disturbance, diplopia, vertigo, dizziness, dysarthria, ataxia, paresthesias, fainting and loss of consciousness precede headache. The typical aura goes on for around 60 min. Individuals reporting migraine with brainstem aura have been found to carry mutations in the CACNA1A or ATP1A2 genes in some cases, but no causative mutation has been found across all subjects [21].

Another migraine manifestation can be isolated pupil dilation, occurring usually in young women sometimes alternating the side in different episodes. In some patients anisocoria increases in bright light and is associated with accommodation impairment suggesting a parasympathetic paresis; while in others can be due to sympathetic overactivity. The pupil may remain dilated for hours or weeks. There is no ptosis or ocular motility disorder differentiating this condition from oculomotor nerve palsy.

Differential diagnosis

The migraine aura, particularly when not associated with headache, is a diagnosis of exclusion. Imaging studies and laboratory tests should exclude neurologic disease, included seizures and central nervous system tumor, ocular pathologies, carotid or cardiac disease, thrombosis and connective tissue disease.

Persistent visual loss may occur as a result from stroke involving the posterior visual pathways. The precise relationship between migraine and stroke remains unclear, even if migraine with aura, oral contraceptives and smoke may increase the risk of stroke in female patients with migraine [22].

Conclusions

Visual and ophthalmologic signs and symptoms are commonly reported by patients with migraine. The relationship between the migraine aura and headache is not clear: the majority of patients with migraine never experience visual aura, many patients who have migraine with aura may also have attacks of headache without aura and sometimes aura without headache is reported. Ophthalmologists have a fundamental role in the differential diagnosis and establishing the amount of visual system involvement in migraine. Susceptibility to migraine seems to be caused by a hyper-excitability of the brain, lowering the threshold for the induction of CSD, a wave of spreading cortical hyperexcitation followed by depression, a process that most likely thought to be the underlying cause of aura. Different phenotypes of migraine may be possible and combined since during the attack some no-pain areas with visual activities may be involved in the CSD before or without the commitment of adjacent cortical pain regions so that some patients may complain only visual symptoms but not headache. Structural, functional and metabolic abnormalities within the visual system are on the basis of this hyperexcitability and imaging investigations are required to better diagnose and treat migraine.

Compliance with ethical standards

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to the publication of this article.

References

1. DeLange JM, Cutrer FM (2014) Our Evolving Understanding of Migraine with Aura. Curr Pain Headache Rep 18(10):453
2. Foroozan R (2009) Visual Dysfunction in Migraine. Intern Ophthalmol Clin 49(3):133–146
3. Arunagiria G, Santhib S (2003) Migraine: an ophthalmologist's perspective. Curr Opin Ophthalmol 14:344–352
4. Liu AM, Liu JG, Liu GW (2014) "Alice in wonderland" syndrome: presenting and follow up characteristics. Ped Neurol 51:317–320
5. Kowacs PA, Utiumi MA, Piovesan EJ (2015) The visual system in migraine: from the bench side to the office. Headache 55(S1):84–98
6. Omland PM, Uglem M, Hagen K, Linde M, Trovnik E, Sand T (2016) Visual evoked potentials in migraine: is the neurophysiological hallmark concept still valid? Clin Neurophysiol 127:810–816
7. Martinez A, Proupim N, Sanchez M (2008) Retinal nerve fiber layer thickness measurements using optical coherence tomography in migraine patients. Br J Ophthalmol 92:1069–1075
8. Tan FU, Akarsu C, Gullu R (2005) Retinal nerve fiber layer thickness is unaffected in migraine patients. Acta Neurol Scand 112:19–23
9. Sorkhabi R, Mostafaei S, Ahoor M, Talebi M (2013) Evaluation of retinal nerve fiber layer thickness in migraine. Iran J Neurol 12(2):51–55
10. Gipponi S, Scaroni N, Venturelli E, Forbice E, Rao R, Liberini P, Padovani A, Semeraro F (2013) Reduction in retinal nerve fiber layer thickness in migraine patients. Neurol Sci 34:841–845
11. Ekingi M, Ceylan E, Cagatay HH, Keles S, Huseyinoglu N, Tanyildiz B, Cakici O, Kartal B (2014) Retinal nerve fibre layer, ganglion cell layer and choroid thinning in migraine with aura. BMC Ophthalmol 14:75
12. Bianchi Marzoli S, Criscuoli A (2015) Normal RNFL and OCT Thickness in migraine with and without aura. Neurol Sci. 36(S1):85–88
13. Tedeschi G, Russo A, Conte F, Corbo D, Caiazzo G, Giordano A, Conforti R, Esposito F, Tessitore A (2016) Increased interictal visual network connectivity in patients with migraine with aura. Cephalalgia 36(2):139–147
14. Schankin CJ, Maniyar FH, Sprenger T, Chou DE, Eller M, Goadsby PJ (2014) The relation between migraine, typical migraine aura and visual snow. Headache 54:957–966
15. Schankin CJ, Viana M, Goadsby PJ (2017) Persistent and repetitive visual disturbances in migraine. Headache 57:1–16
16. Russell MB, Olesen J (1996) A nosographic analysis of the migraine aura in a general population. Brain 119:355–361
17. Lovati C, Mariotti C, Giani L, D'Amico D, Sinelli A, De Angeli F, Capiluppi E, Bussone G, Mariani C (2013) Central sensitization in photophobic and non-photophobic migraineurs: possible role of retino nuclear way in the central sensitization process. Neurol Sci 34(S1):133–135
18. Maniyara FH, Sprengera T, Schankina C, Goadsbya PJ (2014) Photic hypersensitivity in the premonitory phase of migraine: a positron emission tomography study. Eur Jour Neurol 21:1178–1180
19. Purdy RA (2011) The role of the visual system in migraine: an update. Neurol Sci 32(Suppl 1):89–93
20. Nguyen BN, Lek JJ, Vingrys AJ, McKendrick AM (2016) Clinical impact of migraine for the management of glaucoma patients. Progr Retin Eye Res 51:107–124
21. Kirchmann M, Thomsen LL (2006) Basilar type migraine: clinical epidemiologic, genetic features. Neurology 75:967–972
22. Linstra KM, Ibrahimi K, Terwindt GM, MaassenVanDenBrink A (2017) Migraine and cardiovascular disease in women. Maturitas 97:28–31

Neurol Sci (2017) 38 (Suppl 1):S103–S106
DOI 10.1007/s10072-017-2865-1

CLINICAL ASPECTS OF HEADACHE

From 0° to 18°: how headache changes over time

Vincenzo Guidetti[1] · **Noemi Faedda**[1]

Abstract Recognize the presence of headache at early age is essential to prevent that the disorder interferes with physical, psychological and social functioning. However, there are several differences between adults and children in the clinical manifestation of headache such as quality and severity of pain, trigger, associated symptoms, gender, duration of attacks, number of daytime attacks, comorbidities and red flags of secondary headache. These differences can make the diagnosis more complex in early ages than in adults, so it is essential to know how headache changes over time to identify its presence in the earliest phases of childhood.

Keywords Headache · Children · Adolescents · Triggers · Red flags

Introduction

Although headache is one of the most frequently reported somatic complaints by children and adolescents [1] and it affects about 60% of children and adolescents all over the world [2], its presence is still underestimated in the earliest phases of childhood [3]. For a long period, headache was considered only a problem for adults and many people, also healthcare professionals, denied its existence in children. The diagnosis of headache is indeed more difficult in early ages than in adults [4, 5]: for children below the age of 12, the headache history may be difficult to obtain. Children may not be able to describe the features of the onset of pain, trigger, or associated symptoms. Furthermore, there are several differences between adults and children in the diagnosis of headache and only as children move through adolescence, their attacks became similar to attacks in adults. So, it is fundamental to learn about several differences between headache in children and adults, to avoid underestimating this disorder also in younger patients.

✉ Vincenzo Guidetti
vincenzo.guidetti@uniroma1.it

[1] Department of Paediatrics and Child and Adolescent Neuropsychiatry, Sapienza University of Rome, Via dei Sabelli 108, 00185 Rome, Italy

Headache in children vs adults: which are the differences?

Headache features in early childhood

Battistella et al. [6] made a retrospective study comparing preschool age and pubertal age children with headache. Results showed that:

- Greater male gender prevalence and earlier onset of the attacks;
- The attack duration was shorter in preschool children, it can last as little as 30 min;
- Lower symptom association such as photo- or phonophobia, nausea;
- No pain increase during physical activity;
- TTH was more frequent in preschool children;
- Migraine was more frequent in pubertal subjects.

A recent research found that the frequencies of the main migraine features in the younger children were similar to those of children older than 7 years, except for a shorter duration of migraine and reduced frequency of attacks [7].

Headache clinical features

There are several differences between adults and children in the clinical features of primary headache: children seem to have fewer attacks per month, a higher number of daytime attacks than adults; their attacks tend to be of shorter duration, less severe and easier to treat [8, 9]. They are often relieved by sleep and are more easily controlled [10]. Paediatric headache is more often bilateral, frontal and temporal than unilateral (35 vs 60% in adults); occipital pain, whether unilateral or bilateral, is rare; there is a higher incidence of light or noise sensitivity than in adults.

For these reasons, some authors supported the idea that IHS classification criteria are not fully adequate for juvenile headaches. For example, in Battistella's study [6] the headaches of more than 10% of preschool patients still remained unclassifiable, while those of all the pubertal subjects were properly classifiable.

This could be due to [11]:

- Child inability to describe features of the headache;
- Limited verbal and language skills;
- Failure to meet the criterion for minimum duration;
- The presence of migraine-like symptoms in some patients with tension headache;
- In very young children is often a nonspecific complaint.

Gender

Vast differences are present according to age and gender: in the sample of Benbir et al. [12], while 60% of patients with migraine were male among the group of children, about 80% of patients were females among the adults. The prevalence of headache is higher in girls with menarche at 12 years or younger than in those with menarche after the age of 12 years [13]. It is well known that before puberty migraine is more common in males [14] and that after puberty women are twice as likely to experience headache than men, but the mechanisms behind these differences are still poorly understood [15]. This is most likely due to hormonal changes during puberty but may also be related to gender differences in cognitive and social reactions to pain [16]). Faria et al. [15] found that older females with migraine had more grey matter in the S1, amygdala, and caudate compared to older males with migraine and matched healthy controls. These sex and developmental differences in paediatric migraineurs in brain regions provided insight into the neural mechanisms underlying distinct migraine sex phenotypes.

Triggers

Most common headache triggers in early childhood are: stress, weather, holiday, week-end, season, external temperature, food, quality of sleep, bright light, noises, smells, skipping of meals, display, and physical activity.

In adolescence also smoke (tobacco), menstrual cycle, alcohol, other drugs, computer and mobile phone (Table 1).

Primary and secondary headache: how do they differ?

History and physical examination are the major tools for differentiating primary headache disorders from symptomatic headaches caused by defined pathologies, but in children under 12, headache history could be difficult to obtain. So, a precise profile of the headache aspects during the time might be achieved with the compilation of a headache diary (intensity, timing, lasting, frequency, triggers, associated symptoms) (Fig. 1).

Comorbidity

In a review article, Bellini et al. [18] showed that the most frequent psychiatric and neurological comorbidities in children and adolescents are: anxiety, epilepsy, sleep disorders, attention hyperactive disorder and Tourette syndrome. Some longitudinal studies on psychiatric and neurological comorbidities found that the presence of psychiatric disorders is predictive of bad outcome for headache; anxiety disorders are negative prognostic factors, they are related to the persistence of headaches and to the subsequent onset of depression; the remission of headaches is related to the absolute absence of psychiatric disorders after 8 years, supporting the notion of syndromic relationship (migraine, anxiety and mood disorders) [19–21].

Table 1 Triggers, differences between young and adult patients with headache

Trigger	Young	Adults
Stress	75.5%	59–79%
Lack of sleep	69.6%	44–57%
Climate	68.6%	53.2–71%
Bright lights	52.9%	29–61%
Food	3.9–11.8%	15%

Source: Neut et al. [17]

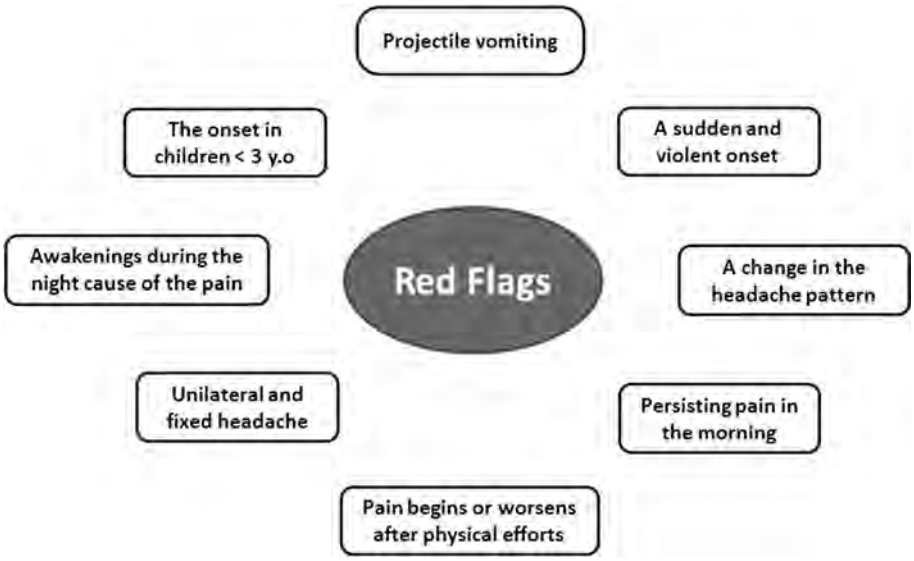

Fig. 1 Red flags for secondary headache in children

Genetic vs epigenetic

The risk of developing migraine depends on a balance between the genetic inheritance and the environmental effects that contribute to the phenotypic expression. The best-fitting model showed a genetic influence of 60–70%, with the remaining risk derived from a non-shared environmental influence. This model indicates that migraine is a genetic disease, but that environmental factors can substantially contribute to its expression [22]. A recent meta-analysis [23] of 375,000 individuals identified 38 susceptibility loci for migraine and it estimated heritability for migraine to be about 40%. That means that approximately 60% of migraine is probably non-genetic and, very well, could have something to do with lifestyle or environment. Furthermore, several studies found a relationship between adverse childhood experiences including abuse (emotional, physical, sexual), parental separation, etc., and an increased prevalence and risk of frequent headache in adults [24]. The study of Malter Cohen et al. [25] provides evidence of early and persistent alterations in anxious behaviour and amygdala function following the early life stress of disorganised parental care. These changes in both brain and behaviour are not diminished when the stressor is removed nor diminished with the development of prefrontal regulatory regions. So, early life stress can lead to altered brain circuitry and emotion dysregulation that may increase the risk for psychopathology and chronic disease [25].

Conclusion

Recognizing the presence of headache at early age is essential to prevent the disorder interfering with the individual's functioning in a variety of domains such as physical, psychological and social functioning.

A multidisciplinary approach is essential for the treatment of headache, especially in children and adolescents. A psychological evaluation is mainly recommended when the following conditions are met: multiple somatizations, psychopathological comorbidities, irritability, boredom, important life changes (e.g. separation of parents), changes in school achievement, recurrent primary headache not relieved by drug therapy and suspicion for secondary gain.

Compliance with ethical standards

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Casucci G, Terlizzi R, Cevoli S (2014) Headache in school age. Neurol Sci 35(Suppl 1):31–35
2. Abu-Arafeh I, Razak S, Sivaraman B, Graham C (2010) Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol 52(12):1088–1097
3. Balottin U, Nicoli F, Pitillo G, Ferrari Ginevra O, Borgatti R, Lanzi G (2004) Migraine and tension headache in children under 6 years of age. Eur J Pain 8(4):307–314
4. Al-Twaijri WA, Shevell MI (2002) Pediatric migraine equivalents: occurrence and clinical features in practice. Pediatr Neurol 26:365–368
5. Bille B (1996) Migraine and tension-type headache in children and adolescents. Cephalalgia 16(2):78
6. Battistella PA, Fiumana E, Binelli M, Bertossi E, Battista P, Perakis E, Soriani S (2006) Primary headaches in preschool age children: clinical study and follow-up in 163 patients. Cephalalgia 26(2):162–171
7. Raieli V, Pitino R, Giordano G, Spitalieri C, Consolo F, Puma D, Santangelo G, Vanadia F, D'Amelio M (2015) Migraine in a pediatric population: a clinical study in children younger than 7 years of age. Dev Med Child Neurol 57(6):585–588
8. Winner P (2008) Pediatric headache. Curr Opin Neurol 21(3):316–322

9. Evans RW (2007) Handbook of headache. Headache during childhood and adolescence, Philadelphia, pp 209–299
10. Guidetti V, Canitano R (1994) Diagnostic criteria of childhood migraine. Cephalalgia 14(5):381
11. Antonaci F, Voiticovschi-Iosob C, Di Stefano AL, Galli F, Ozge A, Balottin U (2014) The evolution of headache from childhood to adulthood: a review of the literature. J Headache Pain 15(1):15
12. Benbir G, Karadeniz D, Göksan B (2012) The characteristics and subtypes of headache in relation to age and gender in a rural community in Eastern Turkey. Agri 24(4):145–152
13. Aegidius KL, Zwart JA, Hagen K, Dyb G, Holmen TL, Stovner LJ (2011) Increased headache prevalence in female adolescents and adult women with early menarche. The Head-HUNT Studies. Eur J Neurol 18(2):321–328
14. Stewart WF, Linet MS, Celentano DD, Van Natta M, Ziegler D (1991) Age- and sex-specific incidence rates of migraine with and without visual aura. Am J Epidemiol 134(10):1111–1120
15. Faria V, Erpelding N, Lebel A, Johnson A, Wolff R, Fair D, Burstein R, Becerra L, Borsook D (2015) The migraine brain in transition: girls vs boys. Pain 156(11):2212–2221
16. Waldie KE, Thompson JM, Mia Y, Murphy R, Wall C, Mitchell EA (2014) Risk factors for migraine and tension-type headache in 11 year old children. J Headache Pain 15:60
17. Neut D, Fily A, Cuvellier JC, Vallée L (2012) The prevalence of triggers in paediatric migraine: a questionnaire study in 102 children and adolescents. J Headache Pain 13(1):61–65
18. Bellini B, Arruda M, Cescut A, Saulle C, Persico A, Carotenuto M, Gatta M, Nacinovich R, Piazza FP, Termine C, Tozzi E, Lucchese F, Guidetti V (2013) Headache and comorbidity in children and adolescents. J Headache Pain 14:79
19. Blaauw BA, Dyb G, Hagen K, Holmen TL, Linde M, Wentzel-Larsen T, Zwart JA (2015) The relationship of anxiety, depression and behavioral problems with recurrent headache in late adolescence: a Young-HUNT follow-up study. J Headache Pain 16:10
20. Arruda M, Arruda R, Guidetti V, Bigal M (2015) Psychosocial adjustment of children with migraine and tension-type headache: a nationwide study. Headache 55(Suppl 1):39–50
21. Guidetti V, Galli F, Fabrizi P, Giannantoni AS, Napoli L, Bruni O, Trillo S (1998) Headache and psychiatric comorbidity: clinical aspects and outcome in an 8-year follow-up study. Cephalalgia 18(7):455–462
22. Hershey AD (2010) Current approaches to the diagnosis and management of paediatric migraine. Lancet Neurol 9(2):190–204
23. Gormley P, Anttila V, Winsvold BS, Palta P et al (2016) Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet 48(8):856–866
24. Anda R, Tietjen G, Schulman E, Felitti V, Croft J (2010) Adverse childhood experiences and frequent headaches in adults. Headache 50(9):1473–1481
25. Malter Cohen M, Jing D, Yang RR, Tottenham N, Lee FS, Casey BJ (2013) Early-life stress has persistent effects on amygdala function and development in mice and humans. Proc Natl Acad Sci USA 110(45):18274–18278

Neurol Sci (2017) 38 (Suppl 1):S107–S110
DOI 10.1007/s10072-017-2882-0

CLINICAL ASPECTS OF HEADACHE

Vestibular migraine: who is the patient?

Bruno Colombo[1] · Roberto Teggi[2] · On behalf of NIVE Project

Abstract Vestibular migraine has been classified as a specific entity in which vestibular symptomatology is defined as part of the migrainous disorder. New and appropriate diagnostic criteria have been proposed by the Barany and International Headache Societies. The diagnosis of vestibular migraine mainly depends on the patient history. The NIVE project is a prospectic multicentric study on vestibular migraine. The aim of this project is to evaluate demographics, epidemiology, clinical manifestations of migraine and vertigo in a large cohort of Caucasian patients affected by vestibular migraine.

Keywords Vestibular migraine · Migraine · Vertigo · Prospectic study

Introduction

The relationship between migraine and vertigo is frequently observed in clinical practice both by clinical neurologists and otorhinolaryngologists (ENT) specialists. Up to 50% of patients affected by migraine reported at least occasionally dizziness or vertigo [1]. A large mass of studies over the last thirty years have described the association of migraine and vestibular symptoms both in adults as well in pediatric patients [2, 3]. Vestibular migraine (VM) is the ultimate term (firstly used by Boenheim in 1917 and then reintroduced by Dieterich in 1999) accepted to describe the vestibular symptomatology related to migraine spectrum disorders [4]. VM is now considered a specific and distinct nosological entity by both the International Headache Society (IHS) and the Barany Society. A consensus document jointly formulated by the two academic panels and the inclusion of diagnostic criteria for VM in the appendix of the beta version of IHS (ICHD-3 beta) confirmed VM as an emerging entity needing further research for fully validation. Diagnosis of VM is included in ICHD-3 beta as a subchapter in "Episodic syndromes that may be associated with migraine" [5]. Referring to VM, other outdated terms such as migrainous vertigo, migraine-associated vertigo or dizziness, migraine-related vestibulopathy have to be no longer used.

Diagnostic criteria

The ICDHD-3 beta criteria for a definite diagnosis of VM depend completely on patient history. According to the accepted definition of VM (if no other better diagnostic explanation is found and other etiologies are ruled out), to establish the diagnosis at least five episodes fulfilling the following criteria are required: (a) current or past history of migraine, either with or without aura, considering the ICHD criteria, (b) moderate or severe vestibular symptoms, lasting 5 min to 72 h, (c) at least half of episodes are associated with at least one of migrainous features. In particular: (1) headache with at least two of the following characteristics (unilateral location/pulsating quality/moderate or severe intensity/aggravation by routine physical activity), (2) photophobia and phonophobia, (3) visual

All Participants of the NIVE Project are listed in "Appendix".

✉ Bruno Colombo
colombo.bruno@hsr.it

[1] Headache Unit, Department of Neurology, IRCCS Ospedale San Raffaele, Vita-Salute University, Milan, Italy

[2] ENT Department, IRCCS Ospedale San Raffaele, Vita-Salute University, Milan, Italy

aura. The vestibular symptoms needed for a correct diagnosis of VM, and reported by several authors during vestibular attacks are: spontaneous vertigo, positional vertigo that occurs when changing head position, visually induced vertigo due to a large or complex moving visual stimulation, head-motion-induced vertigo and head-motion-induced dizziness with nausea. According to these criteria, VM has to be defined as a chronic recurrent disturbance and should not to be diagnosed in occasional episodes of dizziness or vertigo in migraine patients. Nonetheless VM diagnosis mainly relies on clinical history. It is important to underline that the temporal relation between migraine and vertigo is not fixed, so this relationship is variable and vertigo can be present between migraine attacks or during an headache attack (preceding, occurring with or after).

Epidemiology

The prevalence of VM is variable according to study population used and clinical context. Historical data reveal a prevalence of 9–11.9% in a tertiary headache clinic and 4.7–29.3% in an ENT clinic [6, 7]. A more recent multicenter study according to ICHD-3 beta criteria found the prevalence of VM to be 10.3% in migraine patients [8]. The one-year prevalence in the general population is 0.9% [9]. VM is likely the most common neuro-otologic disorder presenting to headache clinics and outpatients departments. Despite these epidemiological data, VM is still an underdiagnosed entity, probably due to the poor knowledge both in neurological and ENT scientific communities. In a study completed in a tertiary vertigo center, VM was suspected by referring physicians only in less than 2% of patients, whereas a correct diagnosis was eventually made in 20.2% of patients [10].

Differential diagnosis

VM has to be differentiated particularly from Meniere disease (MD) and benign paroxysmal peripheral vertigo (BPPV). At the very beginning of the clinical history, most symptoms can be quite similar. Some clues have to be considered for a more detailed differential diagnosis. For example, VM can occur at any time in life, whereas MD has a peak in 3rd–5th decade and BPPV in 5th decade. Family history is better characterized in VM. Vertigo symptoms are positional in BPPV and monosymptomatics in MD, whereas in VM are polysymptomatics too. Vertigo attacks duration is very short in BPPV (seconds, but recurrent positional paroxysms are present for days or weeks). Otherwise, in MD the duration of attacks ranges from 20 min to 12 h, and generally they occur over the course of a few weeks or months. In VM duration is variable from minutes to days. During several years, in MD the progressive hearing loss can worsen without or with vertigo and low-frequency audiometric disturbances became evident. Nevertheless, it has to be considered that the prevalence of migraine in patients affected by MD is reported to be twice as high as in a control group [11, 12]. Phono- or photophobia is instead strictly correlated to VM. Vertigo is specifically also present in two others migraine subtypes, according to ICHD-3 beta classification of headaches: Migraine with brainstem aura (MBA) and hemiplegic migraine (HM). In MBA at least two of brainstem symptoms have to be present during aura (vertigo, tinnitus and hearing loss are part of these symptomatology). Each aura symptom develops in more than 5 and less than 60 min. In HM vertigo can occur associated with episodic ataxia and a totally reversible motor weakness. These entities are quite rare, particularly HM (about 200 families with familial HM have been identified, the same number is for the sporadic form), and diagnostic criteria are adequate for an accurate differential diagnosis although sometimes an overlap is possible.

Pathophysiology

The complex mechanisms underlying VM dysfunction are still under debate. Recent MRI studies are focusing on activity of overlapping vestibular and pain pathways from brainstem to cortical levels with particular attention on thalamus. Previous studies showed an increased thalamic activation in VM patients during vestibular stimulation if compared with healthy controls [13]. In a more recent work, VM patients (studied using a 3.0 Tesla scanner) had a selective gray matter volume increase in occipital and frontal regions compared both to controls and migraineurs (with or without aura). Furthermore, VM patients had increased gray matter volume of the left thalamus, without correlation with attack frequency or disease duration. This study demonstrates a distinct pattern of regional gray matter abnormalities in VM patients located in multisensory vestibular and nociceptive brain areas, supporting the hypothesis of a dismodulation of multimodal sensory integration and processing areas in VM patients [14]. Another recent functional MRI study detected different patterns of activated and deactivated areas as a possible result of an incomplete central adaptive mechanisms during recurrent vertigo. In particular, brain areas related to integration of visual and vestibular cues resulted activated. In addition, a decreased activation of brain regions functionally involved in space memory and navigation was detected [15]. These recent data confirm that the dismodulation of

thalamo-cortical regions processing vestibular and nociceptive informations could be assumed as a possible pathophysiological indication.

The NIVE project

NIVE (Network Italiano Vertigine Emicranica) proposed in 2015 a prospectic multicentric study on VM. The first aim is to assess clinical presentation of VM using the new classification in a large cohort of Caucasian patients. The secondary objectives are to study the clinical relationship between VM and migraine outside vertigo, the rate of familial cases for both migraine and vertigo and the rate of people referring childhood periodic syndromes. A specific validated questionnaire has been produced by investigators for this purpose. Expected benefits include a better knowledge of VM phenotypes according to new criteria, and possible correlations with phenotypes of migraine per se. The NIVE project is a work in progress, here we report some very preliminary results and considerations about the first data on VM phenotypes particularly regarding migraine aspects.

Up to now, 252 consecutively patients were enrolled by different Italian and European Centers (tertiary headache or vestibology centers). In our knowledge, this is the first cooperative study (neurologists and ENT specialists) devoted to VM. Expert neurologists or vestibologists made a correct diagnosis of VM according to new ICHD criteria (Lempert–Olesen criteria) during outpatient activity. Data were included in an "ad hoc" database, specifically devoted to NIVE project. Age at inclusion was 45.8 (range 19–76), with a female sex predominance (85%). Age of the first headache was 22.9 years, age of the first vertigo attack was 37.9 years. Migraine characteristics are summarized in Table 1.

The intensity of migraine pain was similar (7.2 in a VAS scale vs 7) both in the presence of vertigo or without vertigo symptoms. Patients are bothered more for vertigo than for headache (7 vs 7.8 in a VAS scale).

Interestingly, VM patients reported motion sickness during childhood in 43% of cases, cyclic vomiting in 9.5%, episodic abdominal pain in 7.1% and episodic vertigo or torticollis in 4.8%.

A familiarity for the first and/or second degree relatives was found: 73% for migraine and 66.2% for vertigo.

As far as vertigo is concerned, in comparison to previous data based on telephone interviews or records from outpatient headache clinic, our group of patients reported a prevalence of internal vertigo (brief duration in less than 50% of cases, moderate intensity), positional dizziness, unsteadiness.

Table 1 absefns

Duration of migraine attacks in VM patients	
No more than 2 h (%)	5.1
3–4 h (%)	14.7
5–12 h (%)	21.4
12–24 h (%)	37.7
24–72 h (%)	21.1
Migraine accompanying symptoms in VM patients	
Photophobia (%)	Always 44
Visual aura (%)	8.3
Diplopia (%)	9.1
Phonophobia (%)	Always 38.9
Tinnitus (%)	Always 10.7
Fullness (%)	Always 8.7
Hearing loss (%)	Always 4

Our work-in-progress data confirm that VM is a specific form of headache and an opportunity both for neurologists and ENT specialists for cooperative studies in order to improve the knowledge on clinical expression, epidemiology, pathophysiology and treatment. Data are still under analysis for a better definition of VM phenotypes in this increasing group of patients (NIVE project), under the auspices of FICEF (Fondazione Italiana Cefalee).

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

Appendix

NIVE Project is sustained by: Albera R (Torino, Italy), Asprella Libonati G (Matera, Italy), Casani A (Pisa, Italy), Colombo B (Milano, Italy), Guidetti G (Modena, Italy), Lucisano S (Torino, Italy), Mandalà M (Torino, Italy), Manfrin M (Pavia, Italy), Marcelli V (Napoli, Italy), Messina A (Palermo, Italy), Neri G (Chieti, Italy), Nuti D (Siena, Italy), Pecci R (Firenze, Italy), Tedeschi G (Napoli, Italy), Teggi R (Milano, Italy) Torelli P (Parma, Italy), Vannucchi P (Firenze, Italy) and Batuecas-Caletrio A, Espinoza-Sanchez JM, Lopez-Escamez A, Sanz EM (Spain).

References

1. Colombo B (2014) Migraine: pathophysiology and classification. In: Colombo B, Teggi R (eds) Vestibular migraine and related syndromes. Springer, New York, pp 1–17
2. Luzeiro I, Luis L, Goncalves F et al (2016) Vestibular migraine: clinical challenges and opportunities for multidisciplinarity. Behav Neurol. doi:10.1155/2016/6179805

3. Langhagen T, Landgraf M, Huppert D et al (2016) Vestibular migraine in children and adolescents. Curr Pain Headache Rep 20:67
4. Furman JM, Balaban CD (2015) Vestibular Migraine. Ann N Y Acad Sci 1343:90–96
5. Headache Classification Committee of the International Headache Society (IHS) (2013) The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 33(9):629–808
6. Neuhauser H, Leopold M, Von Brevern G et al (2001) The interrelations of migraine, vertigo and migrainous vertigo. Neurology 56(4):436–441
7. Vukovic V, Plavec D, Galinovic A et al (2007) Prevalence of vertigo, dizziness and migrainous vertigo in patients with migraine. Headache 47(10):1427–1435
8. Cho SJ, Kim BK, Kim BS et al (2016) Vestibular migraine in multicenter neurology clinics to the appendix criteria in the third beta edition of the International Classification of headache disorders. Cephalalgia 36(5):454–462
9. Neuhauser H, Radtke A, Von Brevern M et al (2006) Migrainous Vertigo: prevalence and impact on quality of life. Neurology 67:1028–1033
10. Geser R, Straumann D (2012) Referral and final diagnoses of patients assessed in an academic vertigo center. Front Neurol. doi:10.3389/fneur.2012.00169 **(Article 169)**
11. Shepard NT (2006) Differentiation of Meniere's disease and migraine-associated dizziness: a review. J Am Acad Audiol 17(1):69–80
12. Lopez-Escamez JA, Dlugaiczyk J, Jacobs J et al (2014) Accompanying symptoms overlap during attacks in Meniere's disease and vestibular migraine. Front Neurol. doi:10.3389/fneur.2014.00265 **(Article 265)**
13. Russo A, Marcelli V, Esposito F et al (2014) Abnormal thalamic function in patients with vestibular migraine. Neurology 82(23):2120–2126
14. Messina R, Rocca MA, Colombo B et al (2017) Structural brain abnormalities in patients with vestibular migraine. J Neurol 264:295–303
15. Teggi R, Colombo B, Rocca MA et al (2016) A review of recent literature on functional MRI and personal experience in two cases of definite vestibular migraine. Neurol Sci 37:1399–1402

Neurol Sci (2017) 38 (Suppl 1):S111–S115
DOI 10.1007/s10072-017-2889-6

SYMPOSIUM - NUTRACEUTICS AND HEADACHE

Ketogenic diet in migraine: rationale, findings and perspectives

Piero Barbanti[1] · Luisa Fofi[1] · Cinzia Aurilia[1] · Gabriella Egeo[1] · Massimiliano Caprio[2,3]

Abstract Ketogenic diet (KD) is an established treatment for refractory pediatric epilepsy and a promising therapy for diverse neurological diseases. Clinical data on KD in migraine—obtained from 150 patients investigated in case reports and prospective studies—suggest that KD may be a rapid onset effective prophylaxis for episodic and chronic migraine. KD would contribute to restore brain excitability and metabolism and to counteract neuroinflammation in migraine, although its precise mechanism is still unclear. Randomized controlled studies are needed to confirm the usefulness of KD in migraine and to investigate its optimal duration, repeatability, feasibility in normal weight subjects, efficacy in pediatric population and association to conventional migraine prophylaxis.

Keywords Migraine · Ketogenic diet · Treatment · Prevention · Disability

✉ Piero Barbanti
piero.barbanti@sanraffaele.it

[1] Headache and Pain Unit, Department of Neurological, Motor and Sensorial Sciences, IRCCS San Raffaele Pisana, via Della Pisana 235, Rome 00163, Italy

[2] Laboratory of Cardiovascular Endocrinology, IRCCS San Raffaele Pisana, Rome, Italy

[3] Department of Human Sciences and Promotion of the Quality of Life, San Raffaele Roma Open University, Rome, Italy

Introduction

Diet has long been being considered crucial in migraine due to the belief that certain foods might trigger an attack, leading to dietetic restrictions in absence of proven scientific evidence [1].

Ketogenic diet (KD) is a therapeutic tool for epilepsy and a fascinating treatment opportunity for other neurological disorders [2]. Several evidence suggests that KD may be helpful in the preventive treatment of migraine, a disorder characterized by recurrent neurovascular pain attacks triggered by a hyperexcitable and hypometabolic brain [3].

This review outlines rationale, findings and perspectives of KD in migraine treatment.

What is KD?

KD is a very-low-carbohydrate diet based on a dramatic reduction in carbohydrate intake (usually <50 mg/day) coupled to a relative increase in protein and fat proportion which forces the metabolism to obtain its energy needs from lipids by free fatty acids mitochondrial beta-oxidation [2]. During KD, in absence of exogenous glucose as energy source, fatty acids are mobilized from adipose tissue depots and subsequently transported to the liver for conversion to ketone bodies (KB, i.e. acetoacetate, β-hydroxybutyric acid and acetone), a phenomenon naturally occurring during fasting. KB are then distributed to metabolically active tissues, i.e. skeletal muscle, brain and heart, where they represent an important energy source since they are converted to acetyl-CoA, the substrate of Krebs cycle [2].

KS has been used since the 1910s for epilepsy treatment [4]. Nowadays, there is strong evidence that KD have

important therapeutic implications in weight reduction, diabetes, and cardiovascular diseases. Moreover, emerging data suggest its beneficial role in cancer, polycystic ovary syndrome, acne and different neurological diseases [2].

KD in neurological disorders

KD affects neuronal plasticity, influences the balance between inhibitory and excitatory neurotransmitters and exerts neuroprotective effects via KB production and blood glucose reduction. Presently, KD is being considered "the most notable example of a dietary treatment with proven efficacy against a neurological condition" [5].

Human clinical evidence hints KD beneficial effects in diverse neurological disorders:

- *Epilepsy* Used to reduce seizures frequency since 1920s, KD is now a recognized treatment for children with medically refractory epilepsy [6].
- *Parkinson's disease* A small feasibility study on diet induced hyperketonemia showed an improvement in Unified Parkinson's Disease Rating Scale scores in all the 5 subjects studied [7].
- *Alzheimer's disease* Three-month daily administration of AC-1202, a ketogenic compound, significantly improved Alzheimer's Disease Assessment Scale-Cognitive subscale in APOE4 (−) subjects in a randomized, double-blind, placebo-controlled trial, on 152 patients affected by mild to moderate Alzheimer's disease [8].
- *Malignant brain tumors* Following case reports suggesting that KD may be efficacious in brain tumors, a number of clinical trials on KD in patients with primary and recurrent glioma are now under way [9].
- *Autism* A pilot study showed an improvement of Childhood Autism Rating Scale in 60% of children with autistic behavior adherent to KD for 6 months [10].
- *Others* Experimental preclinical studies indicate that KD could be helpful also in the treatment of multiple sclerosis, stroke, amyotrophic lateral sclerosis and head trauma [5].

KD in migraine

Rationale

Migraine is a primary disorder of brain excitatory–inhibitory balance leading to the periodic activation and sensitization of the trigemino-vascular pain pathway. Migraine pain is considered to be caused by a sterile neurogenically driven dural inflammation [11]. Migraine brain is hypometabolic, as revealed by low phosphocreatine, increased adenosine diphosphate, and decreased phosphorylation potential in migraineurs [12].

Experimental evidence indicates that KD may favorably act at different stages of migraine pathophysiology restoring brain metabolism and excitability and counteracting neuroinflammation and redox mechanisms.

Cortical spreading depression (CSD)

In experimental models, short-term medium- and long-chain triglyceride KD reduces the propagation of CSD, the neurophysiological event underpinning migraine aura [13].

Glutamate and GABA

KD could activate astrocyte metabolism facilitating glutamate conversion to glutamine, allowing efficient glutamate removal and glutamine conversion to GABA. This would in part compensate migraine unbalance between excitatory and inhibitory neurotransmission, decreasing brain cortical excitability [14].

Neuroinflammation

Migraine is an inflammatory disorder, characterized by a sterile meningeal neurogenic inflammation which stimulates trigeminal afferent nociceptive neurons innervating intracranial meninges and related large blood vessels and activates mast cells and macrophages which in turn release cytokines, serotonin, histamine and proteases [15].

KD protects against neuroinflammation. In a mouse hippocampus seizure model using kainic acid, KD decreases TNFα (tumor necrosis factor alpha) levels and NFκB (nuclear factor κ B) nuclear translocation, inhibits COX2 (cyclooxygenase 2) and microsomal prostaglandin E(2) synthase-1 expression [16].

Oxidative stress

Migraineurs are more susceptible to oxidative stress [17]. KB may prevent mitochondrial permeability transition and oxidative injury in neocortical rat neurons exposed to hydrogen peroxide or diamide, probably reducing mitochondrial reactive oxygen species production [18].

Mitochondrial free radicals

KB reduce glutamate-induced free radical formation by increasing the NAD+/NADH ratio and enhancing mitochondrial respiration in rat neocortical neurons, suggesting a neuroprotective activity [19].

Brain metabolism

KD significantly enhances brain metabolism. A microarrays study on hippocampal gene expression in adolescent rats demonstrated that KD induces an upregulation of transcripts encoding energy metabolism enzymes/mitochondrial proteins and increases the number of mitochondrial profiles and the phosphocreatine/creatine ratio [20].

Findings

Case reports

The first report on the usefulness of KD in migraine dates back to 1928 when Schnabel described "some improvement" in 9 out of 23 migraineurs [21]. Seventy-eight years later, R. Scott Strahlman, a pediatrician, reported the case of his wife who had a dramatic migraine improvement (from almost daily headache to headache freedom) using KD suggesting "further research to confirm the benefits of a ketogenic diet on migraines" [22]. A meaningful migraine improvement using KD was observed in monozygotic twins (11 years) affected by glucose transporter deficiency syndrome [23]. De Lorenzo et al. described a marked migraine frequency reduction (from 15–16 days/month to headache disappearance) 3 days after KD was started or resumed in two female twins treated for weight-loss purpose. Both patients adopted KD for repeated 4-weeks cycles, following transitional low-calorie, non-ketogenic low-carbohydrate diet during the 2-month interval periods. Their rapid migraine improvement was interpreted as a direct consequence of KD metabolic changes more than an effect of weight loss [24].

Prospective studies

One small prospective open label study using a modified Atkins diet (a high fat, very low-carbohydrate diet) to treat chronic daily headache in eight adolescents (mean age 14.9 years, range 13–16), unsuccessfully treated with at least 2 pharmacological prophylaxis, failed to demonstrate any diet efficacy. However, the study had several limitations, including a small sample, normal weight at baseline in most patients and a headache diagnosis ("daily chronic headache") which might have hidden concomitant headaches or psychological comorbidities [25].

A prospective observational study described the effects of KD in 96 overweight female migraineurs who referred themselves to a dietician for weight loss [26]. Migraine patients had a headache frequency ranging from 1 attack to 14 days/month, did not overuse analgesic nor had been on migraine prophylaxis during the last 3 months. Patients were blindly treated with KD or non-ketogenic standard weight-loss diet (SD) over the first 3 months and with SD over months 4, 5 and 6. Patients in the KD treatment arm received during the first month a very low calorie diet (VLCKD, $\leq$800 kcal) consisting of 4 meals with ad hoc developed dietary products (30 g/day carbohydrates, 15 g lipids, 1.0–1.4 g/kg proteins), during the second month a transitional diet supplemented by nutraceutical integrators (TD1) and during the third month a transitional diet without nutraceutical integrators (TD2). SD (1200–1500 kcal) was composed by 46% carbohydrates, 24% protein and 30% lipids. Neurologists were unaware of patients' diet type and weight modifications. Migraineurs treated with KD showed a significant improvement in attack frequency, headache days and analgesic use during the first month (corresponding to VLCKD), followed by a modest worsening—despite being improved compared with baseline—during TD1, and TD2 and subsequent SD period, whereas those treated with SD had a slower migraine improvement (significant reduction in headache days and analgesic intake at month 3 and in attack frequency at month 6). Migraine worsening (following the initial improvement) when patients were shifted from KD to TD1 (at the end of the first treatment month) indicates that ketogenesis is helpful in migraine treatment independently from weight loss.

A neurophysiological multimodal evoked potentials study assessed the cortical functional correlates of responsiveness to short-lasting preventive treatment with KD in migraine [27]. Eighteen migraineurs (14 without aura, 4 with aura) were treated with a 4-week KD: 10 overweight patients received VLCKD ($\leq$800 kcal) in 5 ad hoc meals supplemented by 1 daily meal of fish or meat plus salad and nutritional supplements, whereas 8 normal weight patients received a normocaloric KD (modified Atkins diet). Patients, who did not assume any prophylactic treatment, were studied interictally using visual (VEPs) and median nerve somatosensory (SSEPs) evoked potentials before and after 1 month of KD. After 1-month of KD, migraine frequency and duration significantly improved ($p < 0.001$). KD induced a normalization of the interictally reduced VEPs and SSEPs (all $p < 0.01$) habituation during the subsequent blocks, indicating that KD seems to restore the habituation deficit on evoked potentials during stimulus repetition in parallel with migraine clinical improvement, probably by balancing cortical excitation and inhibition events.

Conclusions and perspectives

We identified seven studies on the effects of KD in headache including 150 patients: 3 case reports (5 pts) [22–24], 2 case series (31 pts) [21, 25] and 2 prospective studies

Table 1 Overview of studies on KD in headache treatment

References	Study design	Pts (*n*)	KD type	KD duration	Control diet	Headache diagnosis	Results
Schnabel [21]	Case series	23	"A diet at least relatively high in fats and low in carbohydrates"	Not specified	No	Migraine	Improvement in 39% of cases
Strahlman [22]	Case report	1	VLCKD (600-800 kcal)	7 months	No	CM, MOH	Migraine freedom even following KD discontinuation
Kossoff [25]	Case series	8	Modified Atkins diet	0.1–7 months	No	DCH	No effect on migraine frequency
Urbizu [23]	Case reports	2	3:1 proportion of fat (supplemented with long-chain triglyceride mix) to carbohydrates	6 months	No	MwA, MA	No severe headache
Di Lorenzo [24]	Case reports	2	<1 g/kg/day carbohydrates 1.2–1.6 g/kg/day proteins + 1 daily meal of meat or fish and nutraceutical supplements	repeated 4-weeks cycles, following transitional low-calorie, non-ketogenic low-carbohydrate diet during the 2-month interval periods	No	High frequency MwA	Transient migraine disappearance as soon as 3 days after KD was started or resumed
Di Lorenzo [26]	Prospective	96	1°month: VLCKD (≤800 kcal: 30 g/day carbohydrates, 15 g lipids, 1.0–1.4 g/kg proteins) 2 months: transitional diet + nutraceutical supplements 3 months: transitional diet without nutraceutical supplement	3 months	SD (1200-1500 kcal: 46% carbohydrates, 24% protein and 30% lipids)	MwA, MA	Significant improvement in attack frequency, headache days and analgesic use during the 1° month ($p < 0.0001$) followed by a modest worsening during transitional diet and subsequent SD period
Di Lorenzo [27]	Prospective	18	VLCKD (≤800 kcal) MAD	1 month	No	MwA, MA	Significant improvement in attack frequency and duration ($p < 0.001$); normalization of the interictally reduced VEPs and SSEPs ($p < 0.01$) habituation

KD ketogenic diet, *VLCKD* very-low-calorie KD, *SD* standard diet, *MAD* modified Atkins diet, *CM* chronic migraine, *MOH* medication overuse headache, *DCH* daily chronic headache, *MA* migraine with aura, *MwA* migraine without aura, *VEPs* visual evoked potentials, *SSEPs* somatosensory evoked potentials

(114 pts) [26, 27]. Three studies used VLCKD [22, 26, 27], only 1 study was controlled versus standard diet [26]. Five studies focused on migraine in adults [21, 22, 24, 26, 27], 1 on daily chronic headache in adolescents [25], 1 on monozygotic twins affected by glucose transporter deficiency syndrome [23]. Six out of seven studies showed that KD is effective in migraine prophylaxis, the benefit ranging from reduction in attack frequency and intensity to migraine disappearance [21–24, 26, 27] (Table 1). In almost all cases, KD started to be effective in a few days.

Given these limitations, the aforementioned data suggest that KD is a promising therapeutic tool for migraine prevention. However, there is a clear need for well-designed randomized controlled trials on large populations to confirm these data and to provide answers to some relevant clinical points.

Is KD feasible in normal weight migraineurs? Efforts are needed to adapt KD dietary regimen to non-obese individuals providing them the required daily calories intake and increasing patients' adherence to KD. Furthermore, it has to be clarified if KD may be of help also in pediatric population.

Future researches should specify what is the optimal KD duration, establish criteria for repeating KD cycles, verify KD effects duration and identify migraine endophenotypes more sensitive to KD.

Studies are also awaited to elucidate the unexpected very rapid KD onset of action in migraine which markedly contrasts with the delayed prophylactic effect of preventative migraine drugs. Is this due to KD combined effect on brain excitability/metabolism and neuroinflammation? This issue needs to be clarified with biochemical, neurophysiological and neuroimaging studies. Finally, it has to be tested if KD may increase the efficacy of conventional pharmacological prophylaxis when used as add-on therapy, or their tolerability, especially when taking preventive drugs at risk for weight gain.

Compliance with ethical standards

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Martin VT, Vij B (2016) Diet and headache: part 2. Headache 56(9):1553–1562
2. Paoli A, Rubini A, Volek JS, Grimaldi KA (2013) Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. Eur J Clin Nutr 67(8):789–796
3. Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine–current understanding and treatment. N Engl J Med 346(4):257–270
4. Guelpa G, Marie A (1911) La lutte contre l'epilepsie par la disintoxication et par la reeducation alimentaire. Rev Ther Med Chir 78:8–13
5. Stafstrom CE, Rho JM (2012) The ketogenic diet as a treatment paradigm for diverse neurological disorders. Front Pharmacol 3(59):1–8
6. Martin K, Jackson CF, Levy RG, Cooper PN (2016) Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev 2:CD001903. doi:10.1002/14651858
7. Vanitallie TB, Nonas C, Di Rocco A et al (2005) Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. Neurology 64(4):728–730
8. Henderson ST, Vogel JL, Barr LJ et al (2009) Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. Nutr Metab 6:31. doi:10.1186/1743-7075-6-31
9. Woolf EC, Syed N, Scheck AC (2016) Tumor metabolism, the ketogenic diet and β-hydroxybutyrate: novel approaches to adjuvant brain tumor therapy. Front Mol Neurosci 9(122):1–11
10. Evangeliou A, Vlachonikolis I, Mihailidou H et al (2003) Application of a ketogenic diet in children with autistic behavior: pilot study. J Child Neurol 18:113–118
11. Vecchia D, Pietrobon D (2008) Migraine: a disorder of brain excitatory–inhibitory balance? Trends Neurosci 8:507–520
12. Montagna P, Cortelli P, Monari L et al (2004) 31P-magnetic resonance spectroscopy in migraine without aura. Neurology 44(4):666–669
13. de Almeida Rabello Oliveira M, da Rocha Ataìde T, de Oliveira S et al (2008) Effects of short-term and long-term treatment with medium- and long-chain triglycerides ketogenic diet on cortical spreading depression in young rats. Neurosci Lett 434:66–70
14. Yudkoff M, Daikhin Y, Horyn O, Nissim I (2008) Ketosis and brain handling of glutamate, glutamine, and GABA. Epilepsia 8:73–75
15. Waeber C, Moskowitz MA (2005) Migraine as an inflammatory disorder. Neurology 64:S9–S15
16. Jeong EA, Jeon BT, Shin HJ et al (2011) Ketogenic diet-induced peroxisome proliferator-activated receptor-γ activation decreases neuroinflammation in the mouse hippocampus after kainic acid-induced seizures. Exp Neurol 232(2):195–202
17. Borkum JM (2016) Migraine triggers and oxidative stress: a narrative review and synthesis. Headache 56(1):12–35
18. Kim D, Davis L, Sullivan P et al (2007) Ketone bodies are protective against oxidative stress in neocortical neurons. J Neurochem 101:1316–1326
19. Maalouf M, Sullivan P, Davis L et al (2007) Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation. Neuroscience 145:256–264
20. Bough K, Wetherington J, Hassel B et al (2006) Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. Ann Neurol 60:223–235
21. Schnabel TG (1928) An experience with a ketogenic dietary in migraine. Ann Intern Med 2:341–347
22. Strahlman RS (2006) Can ketosis help migraine sufferers? Headache 46:182
23. Urbizu A, Cuenca-León E, Raspall-Chaure M et al (2010) Paroxysmal exercise-induced dyskinesia, writer's cramp, migraine with aura and absence epilepsy in twin brothers with a novel SLC2A1 missense mutation. J Neurol Sci 295(1–2):110–113
24. Di Lorenzo C, Currà A, Sirianni G et al (2013) Diet transiently improves migraine in twin sisters: possible role of ketogenesis? Funct Neurol 28(4):305–308
25. Kossoff EH, Huffman J, Turner Z, Gladstein J (2010) Use of the modified Atkins diet for adolescents with chronic daily headache. Cephalalgia 30(8):1014–1016
26. Di Lorenzo C, Coppola G, Sirianni G et al (2015) Migraine improvement during short lasting ketogenesis: a proof-of-concept study. Eur J Neurol 22(1):170–177
27. Di Lorenzo C, Coppola G, Bracaglia M et al (2016) Cortical functional correlates of responsiveness to short-lasting preventive intervention with ketogenic diet in migraine: a multimodal evoked potentials study. J Headache Pain 17:58. doi:10.1186/s10194-016-0650-9

Neurol Sci (2017) 38 (Suppl 1):S117–S120
DOI 10.1007/s10072-017-2901-1

SYMPOSIUM - NUTRACEUTICS AND HEADACHE

Usefulness of nutraceuticals in migraine prophylaxis

Florindo D'Onofrio[1] · Simona Raimo[2] · Daniele Spitaleri[1] · Gerardo Casucci[3] · Gennaro Bussone[4]

Abstract Several studies have supported the efficacy of complementary and alternative medicine approaches (physical, behavioral and nutraceutical therapies) in the treatment of headache disorders. Nutraceutical treatment consists of taking vitamins, supplements (magnesium, riboflavin, coenzyme Q10, and alpha lipoic acid) and herbal preparations (feverfew and butterbur), and its usage is frequently determined by dissatisfaction with conventional medical therapies. There is a growing body of research on nutraceutical use for migraine prophylaxis. This brief overview provides information about the potential efficacy and side effects of various nutraceutical products summarizing randomized controlled trials of some of the most commonly used non-pharmacological treatments for the prophylaxis and treatment of migraine, including magnesium, coenzyme Q10, riboflavin (vitamin B_2), petasites, and feverfew.

Keywords Nutraceuticals · Vitamin · Migraine · Headache

Introduction

Nutraceutic is a term derived from "nutrition" and "pharmaceutics" [1]. A nutraceutical product is defined as "a substance, which brings physiological benefit or provides protection against chronic diseases" [1]. Nutraceutical treatment consists of taking vitamins, supplements (magnesium, riboflavin, coenzyme Q10, and alpha lipoic acid) and herbal preparations (feverfew and butterbur), and its usage is frequently motivated by dissatisfaction with conventional medical therapies [2]. Recently, there has been a growing interest for natural supplements such as vitamins and herbal preparations in trying to control migraine headaches [3] and a variety of natural treatments have provided evidence of their efficacy in migraine prophylaxis [4]. In addition to evidence of efficacy, there is a tendency to prefer nutraceutical treatment because of the false perception that "all natural medicines are good" compared to drug treatment of which patients fear contraindications, side effects and cost [1]. In view of this, the use of nutraceutical treatment should be taken into account by physicians to enhance patient acceptance and adherence to long-term prophylaxis therapy [5], and the treatment plan should be constructed considering patient preference and expectations.

Nutraceutical approach for the treatment of migraine

Magnesium

Magnesium deficiency has been associated with migraine attack [6]. Studies on the use of magnesium supplement showed improvement of migraine symptoms [7], decrease

✉ Simona Raimo
simonaraimo.sun@gmail.com

[1] Institute of Neurology San G. Moscati Hospital, Avellino, Italy

[2] Department of Psychology, University of Campania Luigi Vanvitelli, Viale Ellittico 31, 81100 Caserta, Italy

[3] San Francesco Hospital, Telese Terme, Benevento, Italy

[4] C. Besta Neurological Institute and Foundation, Milan, Italy

of migraine frequency [8] and burden of disease [7], in addition to their effectiveness in the short-term prevention of menstrual migraine. A recent meta-analysis of randomized controlled trials [9] showed that intravenous magnesium significantly reduced acute migraine and oral magnesium significantly alleviated the frequency and intensity of migraine. Meta-analysis results indicated that intravenous and oral magnesium should be adopted as a part of multimodal approach to reduce migraine; however, optimal dosages were not reported and the effective formulations of magnesium treatment varied widely across investigated studies. Different evidences were provided by an evidence-based review [10] on oral magnesium supplementation in the preventive treatment of migraine that showed although dietary magnesium intake was inadequate in a large percentage of migraine patients, the evidences supporting oral magnesium supplementation were quite limited at this time and magnesium deficiency was associated with multiple conditions that were risk factors for migraine (such as obesity, metabolic syndrome, caffeine overuse).

Riboflavin

A deficit of mitochondrial energy metabolism and abnormalities in cortical information processing might play a role in migraine pathogenesis and might be modified by prophylactic drug therapy. Studies on riboflavin treatment showed its efficacy for the prevention of migraine reporting a significant reduction of headache attack frequency, a good treatment adherence and an excellent tolerability [11–13], even if it did not change the cortical information processing significantly as measured by the auditory evoked cortical potentials [12] and had no efficacy in children preventing migraine treatment [14].

Petasites hybridus (butterbur)

Also the efficacy of butterbur treatment in migraine prevention has been shown in several studies both in adults [15–17] and in children [18, 19], where there was a significant reduction of migraine attacks through its anti-spasmodic, anti-inflammatory effects and blocking of calcium channel.

Feverfew

While the evidences for magnesium, riboflavin and butterbur are fairly good, other nutraceutical substances reported inconsistent results. In particular, some studies on feverfew reported its safety and clinical efficacy in migraine prevention [20], whereas other studies reported lack of clinically relevant reduction in migraine frequency, likely due to strength of the parthenolides and differences in the stability of feverfew preparations [21]. In addition, a Cochrane review of double-blind randomized clinical trials (2004; 2015) assessed the clinical efficacy and safety of feverfew in migraine prevention, concluding that there was insufficient evidence to suggest that feverfew was more effective than placebo (difference of reduced migraine attacks per month of 0.6).

Coenzyme Q10

Coenzyme Q10 improves energy metabolism similarly to riboflavin [22]. Several studies [22–24] have shown benefits in migraine prophylaxis with a significant reduction in the frequency, duration and intensity of attacks, even if these effects have been not demonstrated in pediatric and adolescent migraine patients [25].

Daily dose and effectiveness of nutraceutical substances described above are listed in Table 1.

Nutraceutical combination

More recent studies [7] evaluated the efficacy of proprietary nutritional supplement containing a nutraceutical combination as prophylactic treatment for migraine. For instance, a fixed combination of magnesium, riboflavin and Q10 [7] showed a significant impact on migraine frequency, symptoms and burden of disease. Another nutraceutical combination of feverfew and ginger [26] showed positive effect on migraine attack frequency and pain relief. Moreover, other

Table 1 Nutraceutical treatments in migraine prophylaxis

Agents	Daily dose	Comments
Intravenous magnesium sulphate	1–2 g	Reduction in migraine attacks
Intravenous magnesium chloride	32 mg	
Oral magnesium citrate	400–600 mg	Reduction in frequency and severity of migraine attacks
Riboflavin	400 mg	Reduction in migraine attacks
Petasites hybridus	50–150 mg	Reduction in frequency and severity of migraine attacks
Feverfew	50–300 mg	Controversial results
Coenzyme Q10	300 mg	Reduction in frequency, duration and severity of attacks

studies [27] showed the efficacy of a combination of ginkgo biloba, coenzyme Q10 and vitamin B_2 in reducing the frequency and duration of migraine with aura.

Adverse effects

Patients tend to perceive nutraceutical supplements as safe for a variety of reasons, including their non-prescription availability and their natural properties; whereas, mild and transient adverse events, most commonly gastrointestinal complaints and mouth ulcers, have been reported in nutraceutical trials [11, 17, 18]. Therefore, as with pharmaceutical agents, patients should be aware of the potential toxicities and side effects of these interventions. Cases of hepatotoxicity linked to butterbur illustrate the need for ongoing caution and long-term monitoring of safety data in relation to nutraceuticals [28].

Concluding remarks

In conclusion, this brief overview underlined that nutraceutical treatment was useful in decreasing headache frequency, intensity and burden and in increasing the sense of self-efficacy in individuals with headache. However, further researches should investigate this alternative therapeutic option and how this might influence the course and outcome of headache disorders.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Kalra EK (2003) Nutraceutical—definition and introduction. AAPS Pharm Sci 5:27–28
2. Sun-Edelstein C, Mauskop A (2011) Alternative headache treatments: nutraceuticals, behavioral and physical treatments. Headache 51(3):469–483
3. Daniel O, Mauskop A (2016) Nutraceuticals in acute and prophylactic treatment of migraine. Curr Treat Options Neurol 18(4):14
4. Kandasamy AD (2014) Nutraceuticals for the treatment of migraine prophylaxis. Discov Phytomed 1:16–21
5. D'Amico D, Tepper SJ (2008) Prophylaxis of migraine: general principles and patient acceptance. Neuropsychiatr Dis Treat 4(6):1155–1167
6. Rybicka JM, Balce DR, Chaudhuri S, Allan ERO, Yates RM (2012) Phagosomal proteolysis in dendritic cells is modulated by NADPH oxidase in a pH-independent manner. EMBO J 31(4):932–944
7. Gaul C, Diener HC, Danesch U; Migravent® Study Group (2015) Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-blind, multicenter trial. J Headache Pain 16:516
8. Mauskop A, Altura BT, Altura BM (2002) Serum ionized magnesium levels and serum ionized calcium/ionized magnesium ratios in women with menstrual migraine. Headache 42:242–248
9. Chiu HY, Yeh TH, Huang YC, Chen PY (2016) Effects of intravenous and oral magnesium on reducing migraine: a meta-analysis of randomized controlled trials. Pain Physician 19(1):E97–E112
10. Teigen L, Boes CJ (2015) An evidence-based review of oral magnesium supplementation in the preventive treatment of migraine. Cephalalgia 35(10):912–922
11. Schoenen J, Jacquy J, Lenaerts M (1998) Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. Neurology 50(2):466–470
12. Sandor PS, Afra J, Ambrosini A, Schoenen J (2000) Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials. Headache 40:30–35
13. Boehnke C, Reuter U, Flach U, Schuh-Hofer S, Einhäupl KM, Arnold G (2004) High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. Eur J Neurol 11(7):475–477
14. MacLennan SC, Wade FM, Forrest KM, Ratanayake PD, Fagan E, Antony J (2008) High-dose riboflavin for migraine prophylaxis in children: a double-blind, randomized, placebo-controlled trial. J Child Neurol 23(11):1300–1304
15. Grossmann M, Schmidramsl H (2000) An extract of *Petasites hybridus* is effective in the prophylaxis of migraine. Int J Clin Pharmacol Ther 38(9):430–435
16. Diener HC, Rahlfs VW, Danesch U (2004) The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. Eur Neurol 51(2):89–97
17. Lipton RB, Göbel H, Einhäupl KM, Wilks K, Mauskop A (2004) *Petasites hybridus* root (butterbur) is an effective preventive treatment for migraine. Neurology 63(12):2240–2244
18. Pothmann R, Danesch U (2005) Migraine prevention in children and adolescents: results of an open study with a special butterbur root extract. Headache 45(3):196–203
19. Utterback G, Zacharias R, Timraz S, Mershman D (2014) Butterbur extract: prophylactic treatment for childhood migraines. Complement Ther Clin Pract 20(1):61–64
20. Diener HC, Pfaffenrath V, Schnitker J, Friede M, Henneicke-von Zepelin HH (2005) Efficacy and safety of 6.25 mg t.i.d. feverfew CO_2-extract (MIG-99) in migraine prevention—a randomized, double-blind, multicentre, placebo-controlled study. Cephalalgia 25(11):1031–1041
21. Pittler MH, Ernst E (2004) Feverfew for preventing migraine. Cochrane Database Syst Rev 1:CD002286
22. Sandor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, Seidel L, Agosti RM, Schoenen J (2005) Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology 64(4):713–715
23. Rozen TD, Oshinsky ML, Gebeline CA, Bradley KC, Young WB, Shechter AL, Silberstein SD (2002) Open label trial of coenzyme Q10 as a migraine preventive. Cephalalgia 22(2):137–141
24. Shoeibi A, Olfati N, Soltani Sabi M, Salehi M, Mali S, Akbari Oryani M (2016) Effectiveness of coenzyme Q10 in prophylactic treatment of migraine headache: an open-label, add-on, controlled trial. Acta Neurol Belg 117:103–109
25. Slater SK, Nelson TD, Kabbouche MA, LeCates SL, Horn P, Segers A, Manning P, Powers SW, Hershey AD (2011) A randomized, double-blinded, placebo-controlled, crossover, add-on

study of CoEnzyme Q10 in the prevention of pediatric and adolescent migraine. Cephalalgia 31(8):897–905
26. Cady RK, Goldstein J, Nett R, Mitchell R, Beach ME, Browning R (2011) A double-blind placebo-controlled pilot study of sublingual feverfew and ginger (LipiGesic^{TM} M) in the treatment of migraine. Headache 51(7):1078–1086
27. D'Andrea G, Bussone G, Allais G, Aguggia M, D'Onofrio F, Maggio M, Moschiano F, Saracco MG, Terzi MG, Petretta V, Benedetto C (2009) Efficacy of Ginkgolide B in the prophylaxis of migraine with aura. Neurol Sci 1:S121–S124
28. Orr SL, Friedman BW, Christie S, Minen MT, Bamford C, Kelley NE, Tepper D (2016) Management of adults with acute migraine in the emergency department: the American Headache Society evidence assessment of parenteral pharmacotherapies. Headache 56(6):911–940

Neurol Sci (2017) 38 (Suppl 1):S121–S124
DOI 10.1007/s10072-017-2896-7

The use of nutraceutics in children's and adolescent's headache

R. Sangermani[1] · A. Boncimino[2]

Abstract Nutraceutics are the most used non-pharmacological remedies for migraine's prophylaxis in children and adolescents. Doctors interested in use of nutraceuticals for a complete treatment of children's headache should be adequately informed on this treatments' efficacy and safety. Actually there is a lack of official guidelines about use of nutraceuticals in migraine's prevention in children and adolescent and there are few studies with limited efficacy evidences. The most used nutraceuticals for adolescent's and children's headache prophylaxis are: magnesium, coenzyme Q10, riboflavin, butterbur, feverfew and melatonin. Further Randomised Controlled Trials are needed for a better effectiveness evaluation in nutraceuticals' use for migraine treatment in child and adolescent.

Keywords Pediatric · Adolescent · Headache · Prophylaxis · Nutraceutical

Introduction

In last years the use of complementary and alternative medicine (CAM) in disease's treatment and in health maintenance is expanding and their use is increasing even in children's and adolescents' diseases. The most frequent indications are pain, migraine, ADHD disease, asthma, neonatal colics and sleep problems [1]. Due to the low collateral effects of natural treatments, patients' and doctor's interest on these approach is growing in the last years.

In USA 12% of children and adolescents use CAM and in particular nutraceuticals in most of cases [1]. An Italian study shows CAM use, in prevalence nutraceuticals use, in 76% of children and adolescents with headache, in large part with self prescription [2].

However, its use could be particularly dangerous in pediatric population due to the self choice of the patients and their families without doctor's advice. On the other side pediatricians who have interest on CAM use for an integrative approach on children diseases and/or who are ready to ask for advice with families choices, should have appropriate information on treatments' efficacy and safety.

Despite nutraceuticals are largely used for prophylactic treatment of children's headache, there is a lack of official guideline and even the few disposable studies have limited evidences of efficacy [3]. In fact indications on migraine therapies descend on adult patients' experience.

Efficacy evaluation of nutraceuticals in children studies feels the negative effect of the substantial response to placebo (as for pharmacological therapies). Since in children's and adolescent's migraine we expect a placebo efficacy among 10–50% of cases, a suitable comparison's evaluation between nutraceuticals vs placebo needs RCT studies with a wide number of patient [4].

Most used nutraceuticals for headache's prevention in children and adolescents are: magnesium, Coenzyme Q10 (Cq10), riboflavin, butterbur, melatonin and preparations of feverfew, magnesium, Cq10, riboflavin or of ginkolide B, magnesium, Cq10, riboflavin [3, 5].

✉ R. Sangermani
roberto.sangermani@gmail.com

[1] Neurology Department, S.Carlo Borromeo Hospital, Milan, Italy

[2] Local health authority, Lodi, Italy

Magnesium

Magnesium's indication for migraine's therapy rests on the hypothesis of its role on migraine's pathogenesis and on evidence indicating its deficiency in a part of adult's and children's migraineurs [6]. Magnesium is involved in a large part of enzymatic reactions and has a role in ATP production and function, in the control of vascular tone and it binds to NMDA receptors.

The American Academy of Neurology (AAN) Guidelines rate magnesium supplementation for the adult's prophylactic therapy as having level B evidence for its efficacy [6]. Attack frequency was reduced by 41.6% in the magnesium group, compared to only by 15.8% in the placebo group in a RCT vs placebo study [6].

A RCT trial Mg oxide (9 mg/kg tid) vs placebo in 118 migraineurs children and adolescents (3–17 years) showed a limited evidence of efficacy after 4 months treatment. After 6 weeks therapy there was a statistically significant downward trend in migraine frequency ($p = 0.037$) and in its severity ($p = 0029$) in magnesium group but not in the placebo group ($p = 086$). However, regression analyses did not confirm any statistically significant difference [5]. Side effects (soft stools e/o diarrhea) were significantly more frequent in the magnesium group compared with the placebo group (19 vs 7%) [5]. Authors conclude that demonstration of Mg efficacy is not univocal for children's and adolescent's migraine.

In a small open-label study, magnesium was given to 40 children with periodic syndrome (of whom 25 had migraine). After 1 month of treatment, 75% of patients had a reduction in symptoms [5]. The value of these results is limited by the model of study itself and by the heterogeneous population. The available trial did not tested pretreatment magnesium level thus avoiding an evaluation of efficacy difference in magnesium-deficient patients vs non deficient ones.

Coenzyme Q10

A lot of evidences show that migraineurs patients have difficulties in energy production and that mitochondria play a role in migraine pathogenesis. Coenzyme Q10 (Cq10) is pivotal in sustaining mitochondrial energy stores given that it is an electron carrier in the mitochondrial electrons transport chain; furthermore it has antioxidant proprieties. Due to these roles it could have an efficacy in migraine's prevention. The American Academy of Neurology Guidelines considers Cq10 to be possibly effective in migraine prevention as having level C evidence [6].

Hershey et al. suggested that Cq10 supplementation might be particularly beneficial in migraine's treatment, finding a Cq10 deficiency in 32% of adolescents (13.3 ± 3.5 years) with frequent migraine [3, 5]. A first open label trial after 3 months of Cq10 supplementation (1–3 mg Kg/die) in patients with coenzyme deficiency show Cq10 levels increase with a decrease of migraine frequency ($p < 001$) and of pediatric migraine disability index (PedMIDAS) ($p < 001$)(3)(5). The same group later published a double bind RCT trial evaluating the efficacy of Cq10 (100 mg/daily for 4 months regardless of coenzyme plasmatic level) in 120 children and adolescents (6–17 years) with chronic and episodic migraine [5]. After 4 weeks of treatment, patients receiving Cq10 felt better than placebo, while at the end of the trial there was a significant decrease in frequency ($p < 0.001$), in severity ($p < 0.006$) and in duration ($p < 0.016$) of the episodes in both groups (Cq10 and placebo) [5].

The studies associated a psychological and educational trial to the treatment. The same authors conclude that children's and adolescent's migraine could improve with a standardized multidisciplinary treatment indifferently by the use of Cq10 or placebo. Adverse effects of Cq10 treatment (anorexia, dyspepsia, nausea and diarrhea) are rare (<1%) [5].

Riboflavin (B2 vit)

Riboflavin (B2 vit) is a vital component of mitochondrial energy production. It has two active coenzyme forms cofactors in oxidation–reduction reaction of flavoproteins and seems to reduce symptoms in patients with mitochondrial dysfunction. Riboflavin should correct the theoretical role of mitochondrial malfunction in migraine [6].

The American Academy of Neurology Guidelines has concluded that riboflavin is probably effective for the prophylactic treatment of migraine in adults with a level B of evidence [6].

Riboflavin's efficacy in children and adolescent with migraine has been evaluated by two RCT and one observational trial. The RCT studies did not show differences between riboflavin and placebo in terms of frequency, severity and duration of migraine attacks while the observational one showed a statistically significant decrease on frequency and severity of migraine [5]. An RCT compared riboflavin 200 mg/daily to placebo in 48 children (5–15 years) with migraine. After 4 months treatment, there was a decrease of attacks in 44% of the riboflavin treated patients and in 66% of placebo children [3, 5]. The evaluation of these results is invalidated by the small sample size and by the high response to placebo in pediatric population. A second double blind cross-over RCT study compared placebo with 42 patients (6–13 years) with migraine and tension-type headache treated with 16 weeks

riboflavin (50 mg/daily). There was no statistically significant difference between the groups when comparing frequency, duration and intensity of migraine's attacks. Otherwise the difference was significant ($p = 0.004$) in reducing the frequency of tension-type headache [3, 5].

Considering that the recommended riboflavin's dose in mitochondrial dysfunctions is 100–300 mg for children, the lower dose of riboflavin used in this study could influence the efficacy of the therapy [5]. An open label trial evaluate the response to 200–400 mg/daily riboflavin given for 6 months to an heterogeneous group of children and adolescents (7–18 years) affected by headache (migraine with and without aura, frequent tension-type headache, basilar migraine and paroxysmal benign vertigo) not responding to pharmacological prophylaxis. After 3 and 4 months treatment riboflavin efficacy was statistically significant in terms of decrease of frequency and intensity ($p < 0.01$); otherwise after 6 months there was no difference between group and placebo. Riboflavin has been well-tolerated in all trial [3, 5].

Butterbur

Butterbur (Petasites Hybridus) role in migraine prophylaxis is due to its antihistamine properties, inhibition of leukotrienes production and to its block in calcium channels. The AAN Guidelines consider Petasites to be effective in adult's migraine prevention with a level A evidence [6].

The presence in Petasites Hybridus (Phy) of pyrrolizidine alkaloids (PA), which have known hepatotoxic properties, limits the use in children over all [5, 6]. A lot of countries advise against the use of preparation with Phy. Phy products are available with the recommendation to use only the PA-free treatments (Petadolex) monitoring liver function during the therapy [5, 6]. There is a low evidence of efficacy in children when compared with adults. A RCT compared placebo and music therapy to Petadolex (50–150 mg) bid given to 63 migraineurs children (8–12 years).All patients received educational advice to deal with migraine. The results were evaluated at the post-treatment and after a 6 months follow-up period. At the end of treatment, music therapy was more efficient than placebo ($p < 0.005$), while after the 6 months follow-up both music therapy ($p < 0.018$) and Petadolex ($p < 0.044$) had a better efficacy than placebo. All groups showed an important decrease in terms of migraine frequency compared to the previous 8 weeks. The authors postulated that both music therapy and Butterbur root extract have promising properties in children's migraine prophylaxis [5].

Ginkgolide B

Ginkgolide B (GB) is an extract from the leaves of the Ginkgo Biloba tree and it is a platelet-activating factor (PAF) receptor antagonist, so having a pro-inflammatory role modulating the cytokine release and increasing the serotonin secretion from platelets during migraine attack [6]. Therefore, PAF inhibition may play a role in the prophylaxis of migraine attacks.

There are only open label trial evaluating GB efficacy associated with other elements with anti-migraine proprieties in children and adolescents [5, 6].

An open label trial assessed the efficacy of a 6 months treatment combination of GB (80 mg/d), coenzyme Q10 (20 mg/d), B1 vitamin (6 mg/d) and magnesium (300 mg/d) in 24 children (8–18 years) with migraine. Headache frequency had a statistically reduction ($p < 0.0015$) [5]. Another open label trial compared the same preparation with GB (preparation A) with a complex of Griffonia simplicifolia (5-hydroxytriptophan), L-tryptophan, vitamin PP and vitamin B6 (preparation B) in 374 children with migraine without aura (10.7 ± 1.8 years) [7]. After a 6-month treatment period there was a statistically significant reduction (more than 50%) in headache's frequency in all patients with the A preparation showing significant superiority ($p < 0.001$) over the other preparation. The efficacy was confirmed for duration, intensity, PedMIDAS and Behavior Index as well [7]. It is difficult to establish if the increase of Behavior Index depends on treatment or if it is himself one of the reasons of the headache's improvement in all the groups. Only 4.27% of children treated with GB experimented minor and transient side effects (nausea and abdominal pain). Because of the presence in these products of other anti-migraine components and the lack of study RCT-placebo, we cannot say that GB is effective in isolation in children's and adolescent's migraine prophylaxis.

Feverfew

The extract from the leaves of Tenacetum Partheniunim (Feverfew) tree contain parthenolides, substances with probably anti-migraine activity [6]. This action is probably related to the inhibition of oxide nitric synthesis, to the cytokines induction, to the release of serotonin from the platelets and to the inhibition of the Calcitonin Gene-Related Peptide (CGRP) release from the trigeminovascular system [6]. The ANN Guidelines consider feverfew to be possibly effective in adult's migraine prevention with level B evidence [6].

Adult's trial with variable dose of Feverfew showed contradictory evidence of efficacy [6]. A recent RCT trial in adults treated for migraine with 6.23 mg/tid with Feverfew showed a significant ($p = 0.053$) decrease of attacks ($\geq$50%) after 3 months therapy when compared with placebo. Side effects were rare and the treatment was in general well-tolerated [6]. Caution should be taken in patients with daisy family trees allergy. Actually there is a lack of study on Feverfew efficacy in children and adolescents with migraine, testing the substance alone or in association with other components.

Melatonin

A recent open label trial tested the efficacy of 3 months Melatonin treatment (0.3 mg/kg/d) in children (10.31 ± 2.39 years) with migraine with and without aura. The author showed a significant ($p < 0.05$) decrease in frequency and duration of attacks and in disability [3]. Melatonin is commonly used in sleep's disturbance of children and the lack of night restore is considered a trigger for migraine A RCT study in adults compared melatonin (3 mg), amitriptyline (25 mg) and placebo. Melatonin and amitriptyline had the same efficacy, with a statistical significance ($p = 0.009$) when compared to placebo. Melatonin was better tolerated than amitriptyline. Side effects in child and adolescent could be daily drowsiness and hypotension [3].

Polyunsatured fatty acid

Polyunsatured fatty acid (PUFAs) have anti-vasopressor effects and anti-inflammatory properties which should have anti-migraine functions. A RCT study in adolescents with chronic migraine did not showed significant difference in frequency and severity of migraine when comparing PUFAs and placebo (olive oil) [3].

Conclusions

Only 1/3 of migraineurs children and adolescents receive a prophylactic therapy and often the proposed treatment has low demonstration of efficacy [8].

The non pharmacological option of treatments includes behavioral and physical therapies and nutraceuticals including vitamins, minerals and herbal preparations.

CAM is used alone or in association with drugs in a multidisciplinary approach to increase the efficacy on migraine prophylaxis. Nutraceuticals are often considered a natural remedy more accepted by the parents for the treatment of their sons.

Considering the increase in nutraceuticals use for children's migraine treatment, is important to have high-quality evidence supporting their use. Otherwise there is a lack on efficacy data at the moment.

The evaluation of nutraceutical's efficacy (and of pharmacological treatment in general) is difficult in children and adolescents with migraine because of the high response to placebo in this population. In the future, we hope for RCT studies with an adequate number of patients, giving the force of conclusions.

Anyway nutraceuticals are a very requested, used and well-tolerated resource for migraine's prevention. Migraine's treatment in children and adolescent should be a "tailor-made" intervention with nutraceuticals, other CAM (music therapy, ago puncture…) and/or pharmacy resting on a global evaluation and living educational advises to face up migraine and daily stress to maximize the resource change behavior and habits having a role on migraine genesis.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. John Snyder, Brown P (2012) Complementary and alternative medicine in children: an analysis of the recent literature. Curr Opin Pediatr 24:539–546
2. Dalla Libera D, Colombo B, Pavan G et al (2014) Complementary and alternative medicine (CAM) use in Italian cohort of pediatric headache patients: the tip of the iceberg. Neurol Sci 35(suppl1):145–148
3. Kedia S (2016) Complementary and Integrative Approaches for Pediatric Headache. Semin Pediatr Neurol 23:4–52
4. Mac Lennan SC, Wade M et al (2008) High dose riboflavin for migraine prophylaxis in children. J Child Neurol 23(11):1300–1304
5. Orr S, Venkateswaran S (2014) Nutraceuticals in the prophylaxis of pediatric migraine: evidence-based review and recommendations. Cephalalgia 34(8):568–583
6. Oved D, Mauskop A (2016) Nutraceuticals in acute and prophylactic treatment of migraine. Curr Treat Options Neurol 18:14
7. Esposito M, Ruberto M, Pascotto A (2012) Nutraceutical preparations in childhood migraine prophylaxis: effects on headache outcomes including disability and behavior. Neurol Sci 33:1365–1368
8. Kacperski J, Hrershey AD (2014) Preventive drugs in childhood and adolescent migraine. Curr Pain Headache Rep 18:422–429

Neurol Sci (2017) 38 (Suppl 1):S125–S130
DOI 10.1007/s10072-017-2866-0

KEY LECTURE

Understanding migraine as a cycling brain syndrome: reviewing the evidence from functional imaging

Arne May[1]

Abstract Due to the clinical picture and also based on early imaging data (Weiller et al. Nat Med 1:658–660, 1995), the brainstem and midbrain structures have been intensely discussed as possible driving or generating structures in migraine. The fact that the brainstem activation persisted after treatment makes it unlikely that this activation was only due to increased activity of the endogenous anti-nociceptive system. It was consequently (and somewhat simplifying) coined the "migraine generator". Since then several studies have focussed on this region when investigating episodic, but also chronic migraine. Denuelle et al. were the first to not only demonstrate significant activations in the midbrain and pons but also in the hypothalamus, which, just like the brainstem activation in the first study, persisted after headache relief with sumatriptan. Expanding these studies into f-MRI studies, refined the involvement of rostral parts of the pons in acute migraine attacks. However, they also focused on the preictal stage of NO-triggered and native human migraine attacks and suggested a predominant role of the hypothalamus shortly before the beginning of migraine headaches as well as alterations in hypothalamic functional connectivity. Additionally, changes in resting-state functional connectivity of the dorsal pons and the hypothalamus in interictal migraineurs has recently been found. The pathophysiology and genesis of migraine attacks is probably not just the result of one single "brainstem generator". Spontaneous oscillations of complex networks involving the hypothalamus, brainstem, and dopaminergic networks lead to changes in activity in certain subcortical and brainstem areas, thus changing susceptibility thresholds and not only starting but also terminating headache attacks.

Keywords Migraine · Attack · Brainstem · Hypothalamus · Network

Introduction

Migraine is a multiphasic disorder and understanding of its pathophysiology starts with the acknowledgment that migraine is not simply a disease of intermittently occurring pain, but that it involves processes that affect the brain over time. These processes seem to lead to increased sensitivity or hyperexcitability of different brain regions, facilitating paroxysmal headache and aura [1]. Effects on the brain (structure, neurochemistry, function) and neurovascular system have been widely documented during the different phases of migraine, and neuroimaging has played a significant role in the current understanding of pathophysiologic processes behind migraine [2]. However, these processes are still only partially understood, are likely multifactorial, and involve several brain structures. If one wants to interpret the most recent findings in migraine pathophysiology, it is important to again discuss the clinical presentation of all phases of a migraine attack.

The clinical presentation of migraine

Migraine is clinically characterized by various symptoms which are defined by the IHS classification [3]. What is not expressed by this classification is the fact that most of these symptoms follow a specific succession over time [4], and

✉ Arne May
a.may@uke.de

[1] Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

that the headache is just the most salient of these symptoms. The accompanying symptoms of nausea and photo-, and phonophobia are usually simultaneous to the headache. However, quite some symptoms start before the headache. Around 70–80% of migraine patients experience at least in some of these attacks, so-called migraine premonitory symptoms, including changes in appetite (food craving or nausea) and sleep–waking rhythms (yawning, fatigue, sleep disturbances). Other symptoms comprise hypersensitivity to certain stimuli (photo-, osmo-, phonophobia) or mood changes, changes in liquid tolerance and others [5–11]. And just as there are *prodromal* symptoms, a great percentage of patients experience a *postdromal* phase characterized as occurring after headache remission: fatigue and tiredness but also euphoria or dysphoria are frequent, next to alterations in appetite or osmoregulation [12–14].

Blau was the first to not only focus on the headache phase in migraine, but also to describe the clinical characteristics of a migraine attack in a timely order [4]. If one follows this line of thought, migraine appears to be not an isolated event of headache but an oscillating up-and-down of sensory and bodily functions, where headache appears to be just one of many symptoms.

There are three clinical features of migraine which point towards the limbic system and hypothalamus as attack-generating brain structures. The first one is that almost all symptoms of the premonitory phase including yawning, tiredness and mood changes [11] point towards hypothalamic involvement. Secondly, the circadian rhythmicity of attacks [15] and thirdly the association of attacks with hormonal status and the menstrual cycle [16]. Some of the typical premonitory symptoms (e.g., yawning and nausea) additionally suggest dopaminergic involvement [17].

The migraine attack: focusing on the brainstem

In contrast to earlier hypotheses of migraine attacks being of vessel or vascular origin, evidence of the past 20 years supports the existence of central processes leading to the evolution of migraine pain [18]. The first brain region to be identified using neuroimaging in spontaneous human migraine attacks was a region of the dorsal pons [19]. Attributing these activations to distinct anatomical nuclei was difficult at that time, given the poor spatial resolution of PET scanners.

Moreover, these activations spanned brainstem structures over several planes. These structures were towards the midline but contralateral to the headache side and have most recently been refined in their localization to the dorsal pons [20]. The injection of sumatriptan relieved the patients from headache while still being in the scanner. Immediately after becoming headache free due to sumatriptan medication showed that the activation of brain stem and midbrain structures persisted when compared to the headache-free interval. Therefore, it was considered unlikely that this activation was only due to increased activity of the endogenous anti-nociceptive system. The persistence of brainstem and midbrain activation after successful treatment with sumatriptan could also explain the phenomenon of headache recurrence after initial efficacy of a triptan [21].

The results by Weiller et al. were replicated in a case study where the authors wanted to study a patient with cluster headache using $H_2^{15}O$-activation PET and triggering the attack using glyceryl titrate [20]. However, the patient developed a typical migraine attack and during this attack activation in the dorsal rostral brainstem was detected. Further PET studies showed a similar region being more active during migraine pain than within the pain-free interval both in spontaneous [20, 22, 23] and NO-triggered migraine headaches [24, 25].

A strong indicator for an attack-generating function of this area is the fact, that a specific activation of this region could be shown for the premonitory phase of nitro-glycerine-triggered migraine attacks even before onset of migraine-like headaches in a recent PET study [25]. Task-related f-MRI studies further replicated stimulus-dependent pons activations during spontaneous migraine attacks [26–28], which is functionally stronger coupled to the hypothalamus during spontaneous migraine attacks [28].

Given the overwhelming evidence the important role of this region for the pain phase of migraine is undisputed; however, there are still many questions as how this region might be involved in migraine attack generation [29]. The commonly reported sustained activation of this area even after pain relief by sumatriptan strongly suggests attack-sustaining properties and that triptans do not terminate migraine attacks, but merely lead to a headache relief for a certain time. The exact anatomical correlate corresponding to such activations has to date not been clearly identified. Likely candidates are the caudal part of the PAG, the cuneiform nucleus, the locus coeruleus, the lateral parabrachial nucleus and the dorsal Raphe—areas that are commonly involved in trigeminal pain processing and are thought to be parts of the descending pain modulating system. Although the original study by Weiller et al. did not report the PAG specifically as the brainstem region showing activation during attacks [19], the PAG was much discussed due to an earlier clinical study in which implementation of stimulating electrodes in the PAG of intractable pain patients resulted post-operative migraine-like headache in some patients [30]. It was thought that altered function of these brainstem areas might indicate a deficit in descending pain control and possibly disinhibition of lower pain processing areas such as the spinal

trigeminal nucleus. This theory has rightly been challenged [29] and several other brainstem regions have been brought into focus. The locus coeruleus and the lateral parabrachial nucleus are important relay stations for dopaminergic projections from the mesostriatal and the mesocorticolimbic dopaminergic systems. The dorsal raphe is involved in regulation of arousal and sleep—altered activation of this area even before headache onset might thus explain the changes in alertness often experienced in the premonitory phase of migraine—activation of the same area during headache might account for similar changes in the headache phase. At the moment where we stand now, the brainstem has been proven to be crucially involved in migraine attacks, but the exact nuclei involved are unknown. The question also arises whether the activation in the dorsal pons is connected to migraine, the migraine attack or indeed in the generation of attacks. Single activation changes in specific brain regions may be the correlate of specific symptoms of headache, but do not easily explain any cycling change over time or indeed the generation of attacks. Recent evidence as well as the clinical presentation of migraine nowadays suggests other parts of the central nervous system to play a more prominent role in migraine attack generation—among these the central dopaminergic system and the hypothalamus.

Migraine attacks mediated by the hypothalamus

The hypothalamus has various neuroanatomical connections to pain modulating systems and also to the spinal trigeminal nuclei [31–33]. The orexinergic system, which is known to regulate arousal and nociceptive processing as well as thermoregulation and autonomic functions, has only recently become a site of interest in migraine research [34, 35]. The orexinergic processing was suggested to be involved in migraine attack generation and/or sustainment of migraine pain. Pharmacological blockade of orexin receptors inhibited cortical spreading depression in rats and attenuated meningeal artery dilation caused by nociceptive afferent trigeminal activation [36]. Another neurotransmitter system involving the hypothalamus is the central dopaminergic system. Typical premonitory symptoms such as yawning and fatigue but also changes in appetite and nausea involve the dopaminergic system [17, 37]. Dopaminergic agonists such as apomorphine increase yawning, dizziness, nausea and vomiting in migraine patients [17, 38–41]. Dopamine antagonists such as metoclopramide, which is usually given against nausea in migraine, has been proven to be also effective in the treatment of the headache itself [42–47]. A specific cell group within the posterior hypothalamus has been shown to inhibit trigeminonociceptive firing of the trigeminocervical complex and this effect was blocked by application of the dopamine-receptor antagonist eticlopride [48]. Ascending projections from this cell group to thalamic regions possibly involved in photophobia and allodynia (posterior and latero-posterior thalamus) indicate another possible role of hypothalamic–thalamic interactions in migraine. This could also explain some accompanying symptoms such as craving or anorexia, given that the hypothalamus is involved in regulation of food intake [48].

Recent neuroimaging studies in migraine patients undermine hypothalamic involvement in the premonitory and acute pain phase of migraine [23, 49]. Interestingly, this activation persisted even after pain relief by sumatriptan, thus suggesting a role of the hypothalamus going beyond simple pain processing [23]. Maniyar et al. investigated the (pain free) interval between initial headache after administration of NO as a human model of the premonitory phase and found increased activity of the hypothalamus and the dorsal rostral pons [25]. Most recently, one migraine patient went into the scanner daily over a whole month which included three spontaneous untreated headache attacks. Increased hypothalamic activation was seen in the prodromal phase (within the last 24 h before migraine headache onset) as compared to the interictal state [28]. More importantly, the pain-related hypothalamic functional connectivity between the hypothalamus and the spinal trigeminal nuclei was significantly increased during the preictal phase as compared to the interictal phase [28]. These data strongly suggest that the hypothalamus plays not only a crucial role in generating premonitory symptoms, but also the migraine attack itself.

Migraine attacks as a change in network architecture?

Comparing the brain activity with different stages of the migraine cycle has had tremendous impact on our understanding of migraine pathophysiology. Recent evidence from neuroimaging draws a complex picture of the evolution of a migraine attack: distinct changes within the dopaminergic system account for typical premonitory but also accompanying migraine symptoms. These changes involve certain networks including the hypothalamus and the dorsal rostral pons with a rather specific pattern during different stages of the migraine cycle. The premonitory symptoms can be mainly explained by changes in dopaminergic and hypothalamic networks, whereas (later) changes in pontine activity and hypothalamic and brainstem networks probably maintain specific migraine symptoms and sustainment of migraine pain. Thus the current understanding of migraine attack generation is developing from the hypothesis of one single migraine generator to a

more complex perspective of oscillating neurotransmitter networks and time-dependent changes in network connectivity.

Various studies have investigated network architecture in interictal migraineurs and have found alterations in common resting-state networks and seed-based connectivity [50–62]. Connectivity studies using areas as seeds that are known to play an important role in migraine pathophysiology are especially apt to contribute to a deeper understanding of the interictal state of this disease: The dorsal pons showed increased functional connectivity with the anterior insula [61], the PAG showed stronger coupling to various brain areas involved in somatosensation and nociception [52] and the hypothalamus was functionally strongly connected to the locus coeruleus, the parahippocampal gyrus and other brain areas [63]. Regarding BOLD-changes, a very recent study from our own group on one migraine patient scanned for 30 consecutive days including three untreated migraine attacks revealed alteration in pain-related hypothalamic functional connectivity. Whereas in the preictal phase the hypothalamus was functionally coupled with the spinal trigeminal nuclei, it showed increased functional coupling with the dorsal rostral pons during the ictal phase. These data strongly point towards alterations in functional connectivity between the hypothalamus and other brain regions as an independent oscillating system which lowers the susceptibility threshold for incoming sensory signals. However, these data are based on a single subject and will need confirmation in an adequate study sample. Taken together the available data suggest that the pathophysiology and genesis of migraine attacks is probably not just the result of one single "brainstem generator". A more complex picture of migraine attack generation is likely: spontaneous oscillations of complex networks involving the hypothalamus, brainstem, and dopaminergic networks lead to changes in activity in certain subcortical and brainstem areas, thus changing susceptibility thresholds and not only starting but also terminating headache attacks.

Compliance with ethical standards

Conflict of interest The author has no financial conflict of interest with any content of this manuscript.

Funding sources This work was supported by the German Research Foundation, SFB936/A5 to A.M.

References

1. Sprenger T, Borsook D (2012) Migraine changes the brain: neuroimaging makes its mark. Curr Opin Neurol 25:252–262. doi:10.1097/WCO.0b013e3283532ca3
2. May A, Goadsby PJ (1999) The trigeminovascular system in humans: pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. J Cereb Blood Flow Metab 19:115–127
3. International Headache Society HCC of the IHS (2013) The International Classification of Headache Disorders 3rd edition (beta version). Cephalalgia 33:629–808. doi:10.1177/0333102413485658
4. Blau JN (1992) Migraine: theories of pathogenesis. Lancet Lond Engl 339:1202–1207
5. Laurell K, Artto V, Bendtsen L et al (2016) Premonitory symptoms in migraine: a cross-sectional study in 2714 persons. Cephalalgia Int J Headache 36:951–959. doi:10.1177/0333102415620251
6. Giffin NJ, Ruggiero L, Lipton RB et al (2003) Premonitory symptoms in migraine: an electronic diary study. Neurology 60:935–940
7. Kelman L (2004) The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. Headache 44:865–872. doi:10.1111/j.1526-4610.2004.04168.x
8. 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. doi:10.1111/j.1468-2982.2006.01157.x
9. Schoonman GG, Evers DJ, Terwindt GM et al (2006) The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. Cephalalgia Int J Headache 26:1209–1213. doi:10.1111/j.1468-2982.2006.01195.x
10. Cuvellier J-C, Mars A, Vallée L (2009) The prevalence of premonitory symptoms in paediatric migraine: a questionnaire study in 103 children and adolescents. Cephalalgia Int J Headache 29:1197–1201. doi:10.1111/j.1468-2982.2009.01854.x
11. Schulte LH, Jürgens TP, May A (2015) Photo-, osmo- and phonophobia in the premonitory phase of migraine: mistaking symptoms for triggers? J Headache Pain 16:14. doi:10.1186/s10194-015-0495-7
12. Giffin NJ, Lipton RB, Silberstein SD et al (2016) The migraine postdrome: an electronic diary study. Neurology 87:309–313. doi:10.1212/WNL.0000000000002789
13. Bose P, Goadsby PJ (2016) The migraine postdrome. Curr Opin Neurol 29:299–301. doi:10.1097/WCO.0000000000000310
14. Kelman L (2006) The postdrome of the acute migraine attack. Cephalalgia Int J Headache 26:214–220. doi:10.1111/j.1468-2982.2005.01026.x
15. Alstadhaug K, Salvesen R, Bekkelund S (2007) Insomnia and circadian variation of attacks in episodic migraine. Headache 47:1184–1188. doi:10.1111/j.1526-4610.2007.00858.x
16. Silberstein S, Merriam G (1999) Sex hormones and headache 1999 (menstrual migraine). Neurology 53:S3–S13
17. Charbit AR, Akerman S, Goadsby PJ (2010) Dopamine: what's new in migraine? Curr Opin Neurol 23:275–281. doi:10.1097/WCO.0b013e3283378d5c
18. May A (2013) Pearls and pitfalls: neuroimaging in headache. Cephalalgia Int J Headache 33:554–565. doi:10.1177/0333102412467513
19. Weiller C, May A, Limmroth V et al (1995) Brain stem activation in spontaneous human migraine attacks. Nat Med 1:658–660
20. Bahra A, Matharu MS, Buchel C et al (2001) Brainstem activation specific to migraine headache. Lancet 357:1016–1017
21. Pascual J, Mateos V, Roig C et al (2007) Marketed oral triptans in the acute treatment of migraine: a systematic review on efficacy and tolerability. Headache 47:1152–1168
22. Afridi SK, Giffin NJ, Kaube H et al (2005) A positron emission tomographic study in spontaneous migraine. Arch Neurol 62:1270–1275. doi:10.1001/archneur.62.8.1270

23. Denuelle M, Fabre N, Payoux P et al (2007) Hypothalamic activation in spontaneous migraine attacks. Headache 47:1418–1426. doi:10.1111/j.1526-4610.2007.00776.x
24. Afridi SK, Matharu MS, Lee L et al (2005) A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. Brain J Neurol 128:932–939. doi:10.1093/brain/awh416
25. Maniyar FH, Sprenger T, Monteith T et al (2014) Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain J Neurol 137:232–241. doi:10.1093/brain/awt320
26. Stankewitz A, Aderjan D, Eippert F, May A (2011) Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. J Neurosci Off J Soc Neurosci 31:1937–1943. doi:10.1523/JNEUROSCI.4496-10.2011
27. Stankewitz A, May A (2011) Increased limbic and brainstem activity during migraine attacks following olfactory stimulation. Neurology 77:476–482. doi:10.1212/WNL.0b013e318227e4a8
28. Schulte LH, May A (2016) The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. Brain J Neurol 139:1987–1993. doi:10.1093/brain/aww097
29. Borsook D, Burstein R (2012) The enigma of the dorsolateral pons as a migraine generator. Cephalalgia Int J Headache 32:803–812. doi:10.1177/0333102412453952
30. Raskin NH, Hosobuchi Y, Lamb S (1987) Headache may arise from perturbation of brain. Headache 27:416–420
31. Mayanagi Y, Hori T, San K (1978) The posteromedial hypothalamus and pain, behavior, with special reference to endocrinological findings. Appl Neurophysiol 41:223–231
32. Buller KM (2003) Neuroimmune stress responses: reciprocal connections between the hypothalamus and the brainstem. Stress 6:11–17
33. Bartsch T, Levy MJ, Knight YE, Goadsby PJ (2005) Inhibition of nociceptive dural input in the trigeminal nucleus caudalis by somatostatin receptor blockade in the posterior hypothalamus. Pain 117:30–39
34. Holland P, Goadsby PJ (2007) The hypothalamic orexinergic system: pain and primary headaches. Headache 47:951–962. doi:10.1111/j.1526-4610.2007.00842.x
35. Tso AR, Goadsby PJ (2014) New targets for migraine therapy. Curr Treat Options Neurol 16:318. doi:10.1007/s11940-014-0318-1
36. Hoffmann J, Supronsinchai W, Akerman S et al (2015) Evidence for orexinergic mechanisms in migraine. Neurobiol Dis 74:137–143. doi:10.1016/j.nbd.2014.10.022
37. Akerman S, Goadsby PJ (2007) Dopamine and migraine: biology and clinical implications. Cephalalgia Int J Headache 27:1308–1314. doi:10.1111/j.1468-2982.2007.01478.x
38. Cerbo R, Barbanti P, Buzzi MG et al (1997) Dopamine hypersensitivity in migraine: role of the apomorphine test. Clin Neuropharmacol 20:36–41
39. Del Zompo M, Lai M, Loi V, Pisano MR (1995) Dopamine hypersensitivity in migraine: role in apomorphine syncope. Headache 35:222–224
40. Blin O, Azulay JP, Masson G et al (1991) Apomorphine-induced yawning in migraine patients: enhanced responsiveness. Clin Neuropharmacol 14:91–95
41. Del Bene E, Poggioni M, De Tommasi F (1994) Video assessment of yawning induced by sublingual apomorphine in migraine. Headache 34:536–538
42. Eken C (2015) Critical reappraisal of intravenous metoclopramide in migraine attack: a systematic review and meta-analysis. Am J Emerg Med 33:331–337. doi:10.1016/j.ajem.2014.11.013
43. Ellis GL, Delaney J, DeHart DA, Owens A (1993) The efficacy of metoclopramide in the treatment of migraine headache. Ann Emerg Med 22:191–195
44. Factor SA, Jankovic J, Friedman BW et al (2014) Randomized trial of IV valproate vs metoclopramide vs ketorolac for acute migraine. Neurology 83:1388–1389. doi:10.1212/01.wnl.0000455698.16732.0a
45. Gaffigan ME, Bruner DI, Wason C et al (2015) A randomized controlled trial of intravenous haloperidol vs. intravenous metoclopramide for acute migraine therapy in the Emergency Department. J Emerg Med 49:326–334. doi:10.1016/j.jemermed.2015.03.023
46. Talabi S, Masoumi B, Azizkhani R, Esmailian M (2013) Metoclopramide versus sumatriptan for treatment of migraine headache: a randomized clinical trial. J Res Med Sci Off J Isfahan Univ Med Sci 18:695–698
47. Tek DS, McClellan DS, Olshaker JS et al (1990) A prospective, double-blind study of metoclopramide hydrochloride for the control of migraine in the emergency department. Ann Emerg Med 19:1083–1087
48. Kagan R, Kainz V, Burstein R, Noseda R (2013) Hypothalamic and basal ganglia projections to the posterior thalamus: possible role in modulation of migraine headache and photophobia. Neuroscience 248C:359–368. doi:10.1016/j.neuroscience.2013.06.014
49. Denuelle M, Fabre N, Payoux P et al (2008) Posterior cerebral hypoperfusion in migraine without aura. Cephalalgia Int J Headache 28:856–862. doi:10.1111/j.1468-2982.2008.01623.x
50. Liu J, Zhao L, Lei F et al (2015) Disrupted resting-state functional connectivity and its changing trend in migraine suffers. Hum Brain Mapp 36:1892–1907. doi:10.1002/hbm.22744
51. Colombo B, Rocca MA, Messina R et al (2015) Resting-state fMRI functional connectivity: a new perspective to evaluate pain modulation in migraine? Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol 36(Suppl 1):41–45. doi:10.1007/s10072-015-2145-x
52. Mainero C, Boshyan J, Hadjikhani N (2011) Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. Ann Neurol 70:838–845. doi:10.1002/ana.22537
53. Russo A, Tessitore A, Giordano A et al (2012) Executive resting-state network connectivity in migraine without aura. Cephalalgia Int J Headache 32:1041–1048. doi:10.1177/0333102412457089
54. Schwedt TJ, Larson-Prior L, Coalson RS et al (2014) Allodynia and descending pain modulation in migraine: a resting state functional connectivity analysis. Pain Med Malden Mass 15:154–165. doi:10.1111/pme.12267
55. Schwedt TJ, Schlaggar BL, Mar S et al (2013) Atypical resting-state functional connectivity of affective pain regions in chronic migraine. Headache 53:737–751. doi:10.1111/head.12081
56. Tessitore A, Russo A, Conte F et al (2015) Abnormal connectivity within executive resting-state network in migraine with aura. Headache 55:794–805. doi:10.1111/head.12587
57. Xue T, Yuan K, Cheng P et al (2013) Alterations of regional spontaneous neuronal activity and corresponding brain circuit changes during resting state in migraine without aura. NMR Biomed 26:1051–1058. doi:10.1002/nbm.2917
58. Xue T, Yuan K, Zhao L et al (2012) Intrinsic brain network abnormalities in migraines without aura revealed in resting-state fMRI. PLoS One 7:e52927. doi:10.1371/journal.pone.0052927
59. Yuan K, Qin W, Liu P et al (2012) Reduced fractional anisotropy of corpus callosum modulates inter-hemispheric resting state functional connectivity in migraine patients without aura. PLoS One 7:e45476. doi:10.1371/journal.pone.0045476
60. Yuan K, Zhao L, Cheng P et al (2013) Altered structure and resting-state functional connectivity of the basal ganglia in migraine patients without aura. J Pain 14:836–844. doi:10.1016/j.jpain.2013.02.010

61. Tso AR, Trujillo A, Guo CC et al (2015) The anterior insula shows heightened interictal intrinsic connectivity in migraine without aura. Neurology 84:1043–1050. doi:10.1212/WNL.0000000000001330
62. Hadjikhani N, Ward N, Boshyan J et al (2013) The missing link: enhanced functional connectivity between amygdala and visceroceptive cortex in migraine. Cephalalgia Int J Headache 33:1264–1268. doi:10.1177/0333102413490344
63. Moulton EA, Becerra L, Johnson A et al (2014) Altered hypothalamic functional connectivity with autonomic circuits and the locus coeruleus in migraine. PLoS One. doi:10.1371/journal.pone.0095508

Neurol Sci (2017) 38 (Suppl 1):S131–S140
DOI 10.1007/s10072-017-2884-y

Action mechanisms of Onabotulinum toxin-A: hints for selection of eligible patients

Carlo Lovati[1] · **Luca Giani**[1]

Abstract In the past few decades, the so-feared botulinum toxin has conversely acquired the role of a ever more versatile therapeutic substance, used in an increasing number of pathological situations, including chronic headache and more precisely in the prophylaxis of chronic migraine. The medical use of botulinum toxin allowed to better understand its multiple mechanisms of action. Investigations about the pathophysiology of primary and secondary headaches has shown a series of common biological elements that frequently are also targets of the action of botulinum toxin. These increasing evidences allowed to identify some biochemical, neurophysiological and radiological markers that may be useful in the individuation of patients which probably will respond to the treatment with Onabotulinum toxin-A among chronic migraineurs. These predictors include CGRP plasmatic levels, specific laser-evoked potential responses, peculiar brain MRI and fMRI and characteristic clinical manifestations. Unfortunately, at now, these predictors are still not available for the clinical practice. Furthermore, the better knowledge about biology of headaches and regarding botulinum toxin activities may also help in directing investigations on the possible use of Onabotulinum toxin-A in other headaches different from migraine. This review tries to show in detail these biological mechanisms and their implication in selecting patients eligible for the treatment with Onabotulinum toxin-A.

✉ Carlo Lovati
carlo.lovati@asst-fbf-sacco.it

[1] Neurology Unit, Headache Center, Osp. L.Sacco, University of Milan, Via G.B. Grassi 74, 20157 Milan, Italy

Keywords Onabotulinum toxin-A · Migraine · CGRP · TRP · Headache

Introduction: botulinum toxin (BTX) and Onabotulinum toxin-A

Botulinum toxin (BTX) is the neurotrophic protein produced by the *Clostridium botulinum* that primarily prevents the release of acetylcholine from axon endings at the neuromuscular junction. BTX is the most acutely lethal toxin known, with an estimated human median lethal dose of 1.3–2.1 ng/kg intravenously or intramuscularly. BTX exists in seven different structurally similar forms, named as A, B, C, D, E, F and G, which are antigenically and serologically distinct. Types A and B cause disease in humans and are commercially and medically used. Also types E and F may be noxious in humans. BTX induces its effect by cleaving proteins required for nerve activation. The BTX active form consists in a two-chain protein composed of a 100-kDa heavy chain and a 50-kDa light chain polypeptide. The light chain is a zinc endopeptidase, while the heavy chain gives cholinergic specificity: the toxin binds specifically to cholinergic nerves by connecting presynaptically to high-affinity recognition sites. Once bound to the nerve terminal, the neuron confines the toxin into a vesicle. As the vesicle moves into the cell, it acidifies, activating a portion of BTX which triggers it to exit from the vesicle to the cytoplasm where the toxin cleaves SNARE proteins avoiding the cell from releasing vesicles of neurotransmitter. In this way BTX stops the nerve signaling. Different BTXs target different SNARE proteins. A component of the SNARE complex, named SNAP-25, is central to synaptic vesicle exocytosis and seems to be relevant in BTX mechanism of action.

Medical uses

BTX is utilized to treat many pathological conditions. First of all, it is used in muscle spasticity, including spasms of the head and neck, eyelid, limbs, jaw, vocal cords. It is useful in strabismus, blepharospasm, hemifacial spasm but also in dystonias. Similarly, BTX is useful to relax clenching of muscles, including those of the esophagus, lower urinary tract and bladder, or the anus. BTX is also active in the therapy of disorders of hyperactive nerves as excessive sweating or neuropathic pain. BTX is used for a series of chronic pain problems including chronic migraine: this was initially thought to be an indirect effect of reduced muscular tension, but it is now known that the toxin acts also in other ways including the inhibition of the release of peripheral nociceptive neurotransmitters and the modulation of pain-linked receptors with the consequent, at least partial, suppression of the central pain processing systems. A major clinical advantage of type A toxin (Onabotulinum toxin-A or BoNT-A) arises from its prolonged duration of action due to the longevity of its protease (90 days in rats and probably much longer in human neurons) and from its prevalently local effect.

Pain management

Notwithstanding the exact analgesic mechanism of action of Onabotulinum toxin-A is only partially known, BoNT-A is largely used in the management of multiple pain disorders. It was shown [1] that BoNT-A inhibits calcium-dependent release of substance P in dorsal root ganglia and, consequently, that it may produce an analgesic effect through peripheral inhibition of C and A delta fibers. BoNT-A in peripheral nociceptive neurons plays a direct peripheral and an indirect central analgesic effect due to the retrograde transport. It has been demonstrated able to treat efficaciously different neuropathic pain disorders such as postherpetic and trigeminal neuralgias, and diabetic neuropathic pain. A Cochrane review on low back pain concluded that BoNT-A injections may have a certain effect in reducing pain [2].

Chronic migraine

Headaches may be labeled as episodic (<15 headache days per month) or chronic (≥15 days per month for more than 3 months). When, for at least 3 months, headache is present for 15 or more days per month and it has migraine characteristics on at least 8 days per month, chronic migraine (CM) may be diagnosed. To treat this chronic headache, BoNT-A is injected into the scalp and neck. BoNT-A received FDA approval for treatment of CM in 2010: since then, several RCTs have confirmed that BoNT-A may reduce headache symptoms and frequency and may improve quality of life of chronic migraineurs when used prophylactically, also when present medication overuse. Clinical studies suggest that BoNT-A is a safe treatment, efficacious for the prevention of chronic migraine and perhaps high-frequency episodic migraine [3]. Two large RCT studies (PREEMPT 1 trial and PREEMPT 2 trial) allowed to obtain solid evidences about its efficacy and safety and to define a valid paradigm of inoculation in terms of sites of injection and timing for successive treatments [4, 5]. In the Phase III REsearch Evaluating Migraine Prophylaxis Therapy 1 (PREEMPT 1), no significant between-group difference for BoNT-A versus placebo was observed for the primary endpoint (change from baseline in headache episode frequency at week 24), but significant between-group differences for BoNT-A emerged for headache days and migraine days [4]. The PREEMPT 2 added that BoNT-A was statistically significantly superior to placebo for frequency of headache days per 28 days relative to baseline [5]. Both PREEMPT 1 and 2 found that BoNT-A was safe and well tolerated and successful inducing reductions from baseline for headache and migraine days, cumulative hours of headache on headache days and frequency of moderate/severe headache days, which in turn reduced the burden of illness in chronic migraineurs.

Headache physiopathological elements related to BoNT-A activity

A series of biological elements involved in the pathophysiology of migraine and other primary headaches have been recognized as target of the BoNT-A action in preventing headache recurrency and manifestations. The understanding of their role in different headaches and their involvement in BoNT-A action may improve patient selection for treatment and may help to recognize other possible kinds of headache in which BoNT-A should have a possible role.

CGRP

Calcitonin gene-related peptide (CGRP) is a vasodilator and a pronociceptive neuropeptide produced in both peripheral and central neurons. It is locally released by motor neurons, and it is overexpressed in response to surgical or pharmacological blockage of neuromuscular transmission.

The main source of CGRP in the trigeminal vascular system is represented by the cell bodies in the trigeminal ganglion. CGRP is above all involved in the communication of pain messages in the body. It acts on a specific

receptor composed of a G protein-coupled receptor called calcitonin receptor-like receptor (CALCRL) and a receptor activity-modifying protein (RAMP1). CGRP receptors are present throughout the body because CGRP modulates a variety of physiological functions in all major systems (cardiovascular, respiratory, etc.). As it will be described in detail in the paragraph, CGRP plasma levels are altered in a variety of different diseases including migraine, temporomandibular joint disorder, complex region pain syndrome, cardiac failure, hypertension, diabetes and sepsis.

CGRP exists in two forms, alpha-CGRP and beta-CGRP. In pain conditions, including migraine, it mainly derive from the peptidergic peripheral innervations, principally as alpha-CGRP, and it was observed that alpha-CGRP-positive neurons of the dorsal root ganglia respond to agonists that evoke pain [6]. The beta-CGRP is expressed among epidermal keratinocytes, and its keratinocytic expression is increased in chronic pain conditions: keratinocyte-derived beta-CGRP may modulate epidermal homeostasis through autocrine/paracrine signaling and may contribute to chronic pain under pathological conditions [7]. The beta-CGRP is also expressed among enteric neurons of the gut and seems to be implicated in mechanisms of visceral pain disorders, such as irritable bowel syndrome. CGRP is also involved in peripheral nerve injury-induced behavioral hypersensitivity and in chemokine production: it was demonstrated that CGRP plays its pronociceptive role through stimulating glial response inducing the increase of CCL5 which in turn potentiate behavioral hypersensitivity following spinal nerve damage as observed in the L5 transection (L5Tx) in a mouse model of neuropathic pain [8].

Among its multiple biological functions, CGRP acts also on skeletal muscle excitation–contraction (EC) coupling [9].

CGRP in migraine and other primary headache

Multiple data sustain the relationship between CGRP and headache. Primarily, it was observed that CGRP is released in migraine, cluster headache and paroxysmal hemicranias and the increase of CGRP during migraine and cluster headache attacks in the extracerebral circulation is an established fact. Similarly, it is known that CGRP can induce migraine. Conversely, CGRP antagonists, like olcegepant and telcagepant, are effective in the treatment of migraine attacks: CGRP receptor blockade stops the attack with a non-vasoconstricting mechanism of action (interestingly reinforcing that migraine is eminently a neurological disorder) [10]. Also triptans activity supports the CGRP–headache relationship: they induce a reduction of CGRP levels by increasing intracellular calcium, which in turn cause decreases in CGRP promoter activity. Paradoxically there is only some uncertainty as to whether CGRP is effectively increased in all migraine patients or not [11]. During a migraine attack, activated primary sensory neurons (meningeal nociceptors) in the trigeminal ganglion release CGRP from their endings situated within the meninges where it binds to and activates CGRP receptors located around meningeal vessels, inducing vasodilation, mast cell degranulation and plasma extravasation [12, 13]. Furthermore, CGRP levels tend to be higher in migraineurs all the time, and not only during the attack, especially among chronic migraineurs, particularly the ones with aura [14]. CGRP levels are significantly increased in chronic migraine also if compared with episodic cluster headache patients, and increased CGRP level outside migraine attacks and in the absence of symptomatic medication seems to be so specific of chronic migraine that it was proposed as a biomarker in the differential diagnosis of chronic migraine [14].

Notwithstanding in the last years CGRP has progressively reached a key role in migraine, the mechanisms underlying the elevation of CGRP levels of some migraineurs are not known. A candidate mechanism is cortical spreading depression (CSD) [15]. Experimental data in rat models showed that multiple, but not single, CSD events significantly increase CGRP mRNA levels at 24 h post-CSD in the ipsilateral rat cerebral cortex. The study concluded that repeated CSD provides a mechanism for prolonged elevation of CGRP in the cerebral cortex, which may contribute to migraine headache [15]. Further studies with experimental models should reveal whether CGRP provocation experiments could also be used to predict efficacy of CGRP modulating treatments in migraine patients [16], BoNT-A included.

All these data about CGRP in migraine open also several questions: Why different levels of CGRP are in migraineurs, also among chronic migraine patients? Exactly what role do CGRP levels play in migraine? Is it possible the existence of "different migraines," with different treatment options even if with similar symptoms, and neurological manifestations? Furthermore, the observation of different levels of CGRP in apparently similar patients induces to consider whether the role of CGRP in migraine is accessory or unavoidable.

But CGRP, as seen, seems to be involved also in the pathophysiology of other primary headaches. To what extent CGRP is involved in tension-type headache and cluster headache is still unknown [16]. In cluster headache, the activation of trigeminal afferents and cranial parasympathetic efferents (trigemino–parasympathetic reflex) can explain both pain and autonomic phenomena. Both migraine and cluster headache involve activation of the trigeminovascular system, and in support, there is a clear association between the head pain and the release of

CGRP from the trigeminovascular system [17]. Pain in cluster headache is attributed, at least in part, to the increased CGRP plasma levels released by activated trigeminal system [18]. These elevated CGRP plasma levels in a cluster headache bout are normalized after a course of high-dose corticosteroids. It was demonstrated that methylprednisolone suppresses cytokine (IL-1β)-induced CGRP release from trigeminal ganglia cells and it may represent a potential mechanism of action that mediates the preventive effect of methylprednisolone on cluster headache and recurrent migraine attacks [19]. In cluster headache, there is, in addition, release of the parasympathetic neuropeptide vasoactive intestinal peptide (VIP) that is coupled to facial vasomotor symptoms [17].

CGRP in the cranial circulation is, as described, one of the best marker for trigeminovascular activation, and with this aim, it was used to evaluate a possible trigeminovascular activation in cervicogenic headache (CEH) that sometimes may be confused with a primary headache: it was shown that in CEH there is no evidence for an activation of the trigeminovascular system and the dosage of CGRP levels was proposed as a biological marker to distinguish CEH from other primary headache [20] and to address consequently specific treatments.

BoNT-A and CGRP in migraine prophylaxis

A series of studies evaluated the effect of BoNT-A on migraine in relationship with its effects on CGRP. It was evidenced that BoNT-A is able to lower interictal plasma CGRP concentrations in chronic migraineurs and it was shown that pretreatment CGRP levels in responders were significantly higher than in non-responders [21]. The lowering effect needs time: one month after treatment, the CGRP levels significantly decreased in responders, while it did not change in non-responders. These results suggest that BoNT-A in chronic migraineurs may reverse sensitization as a result of the inhibition of CGRP release [21] obtained through the cleavage of SNAP-25 protein. These evidences were reinforced by another recent study [22] that investigated the reactivity of cranial dura to trigeminal pain and the mechanism of BoNT-A action on dural neurogenic inflammation (DNI) in a rat model. Authors demonstrated that a treatment with BoNT-A is able to reduce both mechanical allodynia and DNI. BoNT-A prevented inflammatory cell infiltration and inhibited the increase of CGRP levels in dura [22]. They also described that BoNT-A, injected pericranially, is taken up by local sensory nerve terminations, axonally transported to the trigeminal ganglion and then transcytosed to dural afferents. Additionally, they individuated a colocalization of cleaved SNAP-25 and CGRP in dura suggesting that BoNT-A may prevent DNI by suppressing transmission by CGRP. In fact, when BoNT-A exits from the vesicle to the cytoplasm, it cuts SNARE proteins avoiding the cell from releasing vesicles of neurotransmitters and stopping nerve signaling. SNAP-25 is a component of the SNARE complex which not only controls exo-/endocytic processes at the presynaptic terminal, but also regulates postsynaptic receptor trafficking, spine morphogenesis and plasticity [23]. This effect of BoNT-A on SNAP-25 may then modify migraine in a CGRP-mediated way but possibly also interfering with synapses and brain plasticity.

TRP channels

Nociception is a chemical sense, as archaic as vision and older than smell and taste. Most of the animals have highly conserved systems for detecting noxious agents, including ion channel receptors [24]. The transient receptor potential (TRP) family is a heterogeneous group of non-selective cation channels [25]. Their activation by external stimuli, such as light, temperature, mechanical and osmotic stimuli, electrical charge and endo- and xenobiotic substances, modifies the permeability to particular ions and subsequently modifies the cell membrane potential. TRP is encoded by at least 21 channel subunit genes and is divided into 6 subfamilies: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin) and TRPV (vanilloid). TRP is widely expressed throughout the nervous system and also by non-neuronal cells, such as keratinocytes, bladder urothelium and smooth muscle, liver, polymorphonuclear granulocytes, pancreatic β-cells, endothelial cells, lymphocytes and macrophages [26]. TRPV in particular is activated by chemical, mechanical and thermal stimuli. In fact, 5 heat-activated TRP channels (TRPV1–4, TRPM3) and 2 cold-activated channels (TRPM8 and TRPA1) have been identified to date. TRPV4 is activated by variations in osmolarity and by stretching of the cell membrane [27]. TRPV1, TRPV2, TRPV3, TRPV4 are expressed on primary nociceptive neurons. TRPA1 is highly expressed in the dorsal root ganglia, in the trigeminal ganglia and in the sensory ganglia of the vagus nerve. At these sites, TRPA1 is colocalized with TRPV1 in primary sensory neurons with small-to-medium-diameter unmyelinated C and Aδ sensory fibers. TRPA1 can be activated by noxious cold (18–25 °C) and various chemical stimuli, such as oxidative stress, prostaglandins, bradykinin and mustard [28]. TRPA1-expressing neurons produce the proinflammatory neuropeptides substance P and calcitonin gene-related protein (CGRP). The calcium influx mediated by the stimulated TRPA1 determines the release of these peptides, which cause vascular (arterial vasodilation, plasma extravasation) and non-vascular responses (e.g., contraction or relaxation of smooth muscles, glandular secretion), at the peripheral

terminal of the sensory axon. This phenomenon is called "neurogenic inflammation" [29]. TRPA1 knockout models do not display reaction to painful stimuli and objective signs (edema, hyperalgesia) at the site of application of the irritant (TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents, cell 124, 1269–1282, 2006). TRPV1 was first identified due to its responsiveness to the pungent compound capsaicin isolated from hot chili peppers [30]. TRPV1 also responds to hot temperatures in the noxious range (>43 °C) and acid, to low pH and inflammatory factors, such as nerve growth factor, bradykinin, lipids, prostaglandins, protein kinases A (PKA) and C (PKC) and ATP. TRPV1 is also expressed throughout the central nervous system, where it is thought to be involved in long-term depression (LTD) and thus synaptic plasticity [31].

TRP channels and migraine

As described before, TRP channels are principally involved in pain induction and modulation and they seem to be involved also in migraine pathophysiology, especially TRPV1 and TRPA1 that are present in peripheral trigeminovascular neurons, in the trigeminal ganglion and in meningeal nociceptors [32]. Several evidences sustain their importance in migraine: the intranasal administration of the TRPV1 agonist civamide induces a beneficial effect in migraine attack [33], and an improvement in chronic migraine has been described after repeated intranasal administration of capsaicin [34] able to desensitize the TRPV1 receptor. Furthermore, a number of well-known migraine triggers, like cigarette smoke and formaldehyde, are also TRPA1 activators [35]. Interestingly, the activation of TRPA1 channels by intranasal umbellulone was demonstrated able to stimulate meningeal nociceptors and to induce CGRP release and meningeal vasodilation, typical of migraine attack [35]. The stimulation of TRPV1 and TRPA1 channels activates meningeal nociceptors that start the headache attack, while the inhibition of TRPV1 and TRPA1 channels with specific antagonists may block their activation [36] and the consequent effect on head pain: in fact, desensitizing agonists active on TRPA1 and TRPV1 channels reduce their sensitivity and inhibit headache perception [37–39].

BoNT-A and TRP

The activation of meningeal nociceptors by cortical spreading depression or by neurogenic inflammation may involve one or more dural receptors including TRPV1, TRPA1 and the calcitonin gene-related peptide (CGRP) receptor. A series of studies evidenced that BoNT-A can alter the processing of nociceptive signals by meningeal nociceptors. It was shown that administration of BoNT-A to extracranial sutures renders mechanically insensitive the suture branches of the meningeal nociceptors [40]. This capacity of BoNT-A to inhibit meningeal nociceptors is different in relationship with their sensitization state: applied to non-sensitized C-units BoNT-A inhibits responses to mechanical supra-threshold stimuli, while, when applied to sensitized units, it reversed mechanical hypersensitivity and, when applied before sensitization, it prevents development of mechanical hypersensitivity. These effects of BoNT-A may depend on its interference with neuronal surface expression of high-threshold mechanosensitive ion channels linked to mechanical pain by preventing their fusion into the nerve terminal membrane [40]. In fact BoNT-A may block (SNARE)-dependent cell surface expression of TRPV1 and TRPA1 channels in the dura [42] and is able to inhibit mechanical nociception [40] and to prevent CGRP release and its effect on peripheral sensitization of nociceptors in response to inflammation [41].

Because the headache phase of the migraine attack seems to be induced by the activation of meningeal nociceptors by endogenous stimuli (mechanical, as changes in intracranial pressure, or chemical), it was to be determined how extracranial injections of BoNT-A may modify the chemosensitivity of meningeal nociceptors to stimulation of their intracranial receptive fields. The administration of BoNT-A to peripheral sites outside the calvaria is able to modify migraine intracranial pathways probably via a network of sensory fibers that origins from intracranial meningeal nociceptors and reach extracranial tissues such as periosteum and pericranial muscles by crossing the skull from inside to outside through the sutures [42]. A recent study evaluated the effects of extracranially administered BoNT-A, on the responses of intracranial meningeal nociceptors to dural stimulation obtained with mechanical stimuli and with chemical agents like capsaicin (selective TRPV1 agonist) and mustard oil (agonist of TRPA1, partially active on TRPV1). It was demonstrated that extracranial injected BoNT-A was able, in few days, to inhibit responses of C-type meningeal nociceptors to stimulation of their intracranial dural receptive fields with the capsaicin and mustard oil. In other words, it was demonstrated that extracranial administration of BoNT-A suppresses the responses of meningeal nociceptors to stimulation of their intracranial dural receptive fields suggesting that surface expression of TRPV1 and TRPA1 channels in dural nerve endings of meningeal nociceptors is reduced by the extracranial administration of BoNT-A. In chronic migraineurs it may reduce the sensitivity to molecules that activate meningeal nociceptors through the TRPV1 and TRPA1 channels, suggesting another possible way important for the prophylactic activity of BoNT-A [43]. Summarizing, extracranial injection of BoNT-A may reduce migraine frequency and intensity by acting also on TRP channels: it inhibits responses of C-type meningeal

nociceptors to stimulation of their intracranial dural receptive field with TRPV1 and TRPA1 agonists, and this process requires a time of some days for producing an effective inhibition of intracranial dural receptive fields [43]. Injections of BoNT-A near extracranial nerve endings of suture branches of intracranial meningeal nociceptors may reduce the sensitivity of these nociceptors by the reduction of TRPV1 and TRPA1 receptors on the membrane of the dural collateral branches of the same axon [40].

The observation of the effect of BoNT-A on this "transsutural way" may also suggest to add other sites of inoculation near suture to improve the currently approved injection paradigm that is directed to several muscle groups adjacent to sutures and to other muscle regions that are innervated by relevant nociceptors.

CGRP-TRP receptor relationship

Experimental activation of TRPA1 channels may stimulate meningeal nociceptors and can cause CGRP release and meningeal vasodilation [35]. The sole TRPA1 receptor channel activation releases CGRP and increases the activation threshold of meningeal afferents causing local effects like vasodilatation but not pain generation. Per contrast, the combined TRPA1 and TRPV1 activation may be pronociceptive supporting headache generation. These data reinforced the idea that peripheral TRPA1 receptors may have a pronociceptive function in trigeminal nociception only in combination with TRPV1 and through CGRP release [44]. Furthermore, it is known that the proalgesic sensitization of peripheral nociceptors in painful syndromes involves mobilization of thermosensory receptors (thermo-TRP channels) to the neuronal surface. Sensitization of TRPV1 receptors to the neuronal membrane is a mechanism specifically used by peptidergic nociceptors to potentiate their excitability. Also this mechanism is influenced by CGRP: in fact, deletion or silencing of αCGRP gene expression drastically reduced proalgesic TRPV1 potentiation in peptidergic nociceptors by abrogating its calcium-dependent exocytotic recruitment [45].

Other effects of botulinum toxin A in primary headache patients

BoNT-A and habituation

It is consolidated that the habituation to sensory stimuli of different modalities is reduced in migraine patients [46] as comparatively demonstrated with laser-evoked potentials in migraineurs versus healthy controls and patients with tension-type headache: the latency and amplitude of registered responses were similar in all the groups but, while controls and CTTH patients showed a significant habituation of the N2/P2 response, in migrainous patients this LEP component did not develop any habituation at all after face stimulation and showed a significantly lower habituation than in controls after hand stimulation [46]. This reduced habituation of migraineurs probably reflects an abnormal excitability of the cortical areas involved in pain processing [46]. This peculiar habituation may be influenced by BoNT-A as demonstrated in chronic migraine patients (CM) by laser-evoked potentials (LEPs) [47]: the study revealed, after seven days of BoNT-A treatment, a normalization of the trigeminal habituation index that is altered in a large proportion of migraineurs [50]. Furthermore, responders displayed trigeminal LEPs facilitation at T0 time [47]. BoNT-A may consequently exert a modulating effect on trigeminal nociception, normalizing central neurotransmission and possibly reverting the described pain processing alterations [47]. Moreover, the better clinical response to BoNT-A in those patients with a trigeminal LEPs facilitation before treatment might be used as predictor of BoNT-A efficacy.

BoNT-A and neuroradiological changes

It was observed that the transition from chronic to episodic migraine following prophylactic treatment with BoNT-A is accompanied by structural and functional brain changes in treated CM patients responsive to the prophylaxis compared to non-responders. The two groups showed differences in cortical thickness as measured by surface-based morphometry: responders showed a significant cortical thickening in the right primary somatosensory cortex (SI) and anterior insula (aINS) and left superior temporal gyrus (STG) and pars opercularis (ParsOp) compared to non-responders [48]. Differences emerged also in the resting-state functional connectivity (RS-FC) that revealed anticorrelations between the SI seed and lateral occipital (LOC) and dorsomedial prefrontal cortices (DMPFC) in responders, whereas non-responders showed increased connectivity between the ParsOp seed and LOC [48]. The comparison of structural and functional MRI before treatment could represent another useful way to predict the response to BoNT-A and possibly to follow patients establishing if there is only a delay in the response or a lack of any favorable effect. Potentially it may be also useful to program when retreatment is necessary in this specific patient.

BoNT-A and non-migraine primary headaches

BoNT-A has been tried for the treatment of various head, neck and face pain syndromes. The end result of controlled clinical trials was that there was not clear evidence for use

in many of the common primary and secondary headaches [49]. With regard to BoNT-A in hemicrania continua, only few case reports and small open-label experiences are present in scientific literature [50, 51]. In some case the treatment with BoNT-A was tried because the patient had developed side effect to indomethacin and did not respond to other pharmacological treatments: in a certain proportion of these few cases, a complete resolution of all of symptoms was obtained, but data are still anecdotic. In our experience (unpublished data), two out of three treated patients obtained a significant reduction in indomethacin consumption and the treatment is consequently still ongoing.

Botulinum toxin has been evaluated for the treatment of tension-type headaches in patients who were unable to tolerate or cannot benefit from standard therapies. Most of the open design studies seem to present positive results. However, the randomized, double-blind, placebo-controlled studies present contradictory results [52] and when compared with chronic migraineurs, effects in chronic tension-type headache are always lower [53].

BoNT-A toward the sphenopalatine ganglion (SPG) was used in a small group of intractable chronic cluster headache. The number of cluster headache attacks was statistically significantly reduced, and five out of ten patients had at least 50% reduction of attack frequency compared to baseline. The cluster attack frequency was significantly reduced for five out of six month post-treatment [54].

Predicting BoNT-A response for chronic migraine

In the NY headache blog, few years ago, Alexander Mauskop evidenced that when a patient asks whether Botox will help him, the usual response is "Quite possibly, but you'll have to try it to find out." This sentence unfortunately is still true even if a series of predictors are potentially available, even if in general they are available only at a research level or without definitive results and consequently, for now, unusable for routinely clinical use. In the clinical practice, about 30% of chronic migraineurs do not respond to BoNT-A: it would be very useful to know beforehand which patients will respond and which will not. Besides the cost, it would also save patients time, during which they could be trying other treatments.

CGRP plasmatic levels

As seen, the dosage of CGRP blood levels could predict whether a chronic migraineur will respond to BoNT-A with an estimated 95% accuracy. Patients with a CGRP level above a certain threshold were largely more prone to respond to BoNT-A than those with CGRP levels below that threshold. Unfortunately, at the moment, the measurement of CGRP is taken only by research institutions and is not yet offered by commercial laboratories. This evidence has been recently confirmed [21] by determining CGRP levels outside a migraine attack and without symptomatic medication in the previous 24 h. CGRP levels before BoNT-A treatment were significantly higher in responders than those seen in non-responders. The same study evaluated also CGRP level changes one month after the treatment: post-treatment CGRP levels were significantly lower as compared with CGRP levels obtained before BoNT-A treatment, but only in responders. Another work evaluated in parallel plasmatic CGRP and VIP levels and found they were both significantly increased in the chronic migraineurs vs controls and that CGRP and, to a lesser degree, VIP levels were significantly increased in responders vs non-responders [55]. For now the assessment of CGRP plasmatic levels seems to be the better biological way to guide the selection of patients for BoNT-A treatment.

Neurophysiological predictors

A neurophysiological tool to predict BoNT-A response may be a laser-evoked potential examination: the better clinical response to BoNT-A was observed in patients with a trigeminal LEPs facilitation before treatment that may consequently be used as predictor of BoNT-A efficacy [47].

Possible MRI predictors

Before the treatment with BoNT-A, a significant cortical thickening in several cortical areas (right primary somatosensory cortex, anterior insula, left superior temporal gyrus, pars opercularis) was observed in responders compared to non-responders [49]. A cutoff of the thickening size should be obtained to propose this parameter as predictor of BoNT-A efficacy in migraine treatment.

Clinical or demographic predictor: the possible role of pain directionality

The most reliable predictor is probably a correct diagnosis. Since quite two decades Mathew observed that a greater percentage of patients with CM responded to BoNT-A than patients with CTTH, especially when headache is prevalently unilateral and associated with scalp allodynia [53].

Pain directionality seems to be a possible clinical predictor. Pain directionality is whether the pain feels like it is exploding, imploding or ocular. Exploding headache is when the pain is felt pushing from the inside out. People with imploding or ocular pain are more likely to

find relief from BoNT-A than those with exploding pain. Multiple studies have explored this possible connection between pain directionality and BoNT-A response. One of these researches supports the hypothesis that patients with imploding and ocular migraines are more responsive to BoNT-A than those with exploding migraines [56]. Another study evidenced that patients with imploding and ocular migraines are more responsive to BoNT-A than those with exploding migraines (but the same work hypothesized that injections of BoNT-A at doses appropriate for cosmetic purposes might be sufficient to prevent migraine attacks) [56]. To test the validity of these findings, a retrospective study was conducted at two other headache clinics, in which patients who were already undergoing prophylactic treatments with BoNT-A were interviewed. Again, the only factor that distinguished those who responded from those who did not respond was the description and directionality of their headaches. Pain directionality (exploding, imploding or ocular) seems consequently to be another possible predictor: people with imploding or ocular pain are more likely to find relief from BoNT-A than those with exploding pain. Notwithstanding, pain directionality seems to be not a very reliable predictor because the categorization of pain in this way is not so easy.

Also a number of demographic factors, clinical features and comorbidities were tested to differentiate responders from non-responders, but no difference was found [20]. A recent study [57] evaluated in parallel a number of possible clinical predictive factors including unilateral location of headache, pericranial muscular tension, directionality of pain, duration of migraine history (> or < of 10 years) and medication overuse, comparing responders vs non-responders to BoNT-A treatment, but no significant difference emerged.

Conclusive remarks

Benefits of BoNT-A treatment in migraine and other headaches

- Local effect and consequent reduction of adverse events and pharmacological interactions.
- Better in chronic migraine with a long history of headache: the typical combination of refractory migraines.
- It acts directly on multiple mechanisms that are involved in pathophysiology of migraine, migraine transformation, plasticity.
- The effect on biological elements common in the genesis and modulation of different kinds of pain and headaches (CGRP, SNAP-25, TRP channels) offer the realistic possibility to treat also other primary headaches different from chronic migraine.

Prediction of BoNT-A effect in chronic migraine

BoNT-A is able to act on multiple biological steps involved in pathophysiology of migraine. It may:

- Modify CGRP release and interrupt its central and peripheral effects.
- Interfere with TRP channels modifying their activity.
- Influence in multiple ways neuronal plasticity (SNAP-25, TRP, etc.).
- Ameliorate sensitization/habituation imbalance as evidenced by the normalization of the trigeminal habituation index.
- Structurally and functionally model brain circuitry involved in migraine transformation.

Responders to BoNT-A treatment show:

- Elevated CGRP levels between attacks.
- A prevalent pain direction (imploding and ocular pain).
- A trigeminal LEPs facilitation before treatment.
- MRI thickening in specific cortical areas is present in responders, but a cutoff is lacking.

The possibility to determine at least one of these predictors should increase the percentage of responders and may prevent the loss of time and money spent in treating probable non-responders.

Enlargement of indication of BoNT-A for non-migraine headache

Primary and secondary headaches in which BoNT-A might be a useful treatment may be hypothesized, and possibly predicted, analyzing their biological characteristics: if a specific kind of headache shows one or more elements known to be targets of BoNT-A, a positive response to the treatment is probable and consequently it could be experimented with the hope of success. On the contrary, when those biological elements are absent in a specific type of headache (as observed for cervicogenic headache), a positive response seems to be improbable and the treatment is predictably useless.

In conclusion, it is desirable that the described possible predictors will reach a good standard of applicability that allows their use also in the clinical practice, because at the moment the only fundamental element to select patients is still the correct diagnosis.

Compliance with ethical standards

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Welch MJ, Purkiss JR, Foster KA (2000) Sensitivity of embryonic rat dorsal root ganglia neurons to *Clostridium botulinum* neurotoxins. Toxicon 38(2):245–258 **(PMID: 10665805)**
2. Waseem Z, Boulias C, Gordon A, Ismail F, Sheean G, Furlan AD (2011) Botulinum toxin injections for low-back pain and sciatica. Cochrane Database Syst Rev CD1:008257. doi:10.1002/14651858.CD008257.pub2 **(Review, PMID: 21249702)**
3. Silberstein SD. (2016) The use of botulinum toxin in the management of headache disorders. Semin Neurol. Thieme Medical Publishers, 333 Seventh Avenue, New York, NY 10001, USA **(PMID 26866501)**
4. Aurora SK, Dodick DW et al (2010) PREEMPT 1 Chronic Migraine Study Group. Onabotulinum toxin A for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 30(7):793–803. doi:10.1177/0333102410364676 **(Epub 2010 Mar 17)**
5. Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, Silberstein SD, Brin MF (2010) PREEMPT 2 Chronic Migraine Study Group. Onabotulinum toxin A for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 30(7):804–814. doi:10.1177/0333102410364677 **(Epub 2010 Mar 17)**
6. McCoy ES, Taylor-Blake B, Zylka MJ (2012) CGRPα-expressing sensory neurons respond to stimuli that evoke sensations of pain and itch. PLoS One 7(5):e36355. doi:10.1371/journal.pone.0036355 **(PMID: 22563493)**
7. Hou Q et al (2011) Keratinocyte expression of calcitonin gene-related peptide β: implications for neuropathic and inflammatory pain mechanisms. Pain 152(9):2036–2051. doi:10.1016/j.pain.2011.04.033 **(PMID: 21641113)**
8. Malon JT, Cao L (2016) Calcitonin gene-related peptide contributes to peripheral nerve injury-induced mechanical hypersensitivity through CCL5 and p38 pathways. J Neuroimmunol 15(297):68–75. doi:10.1016/j.jneuroim.2016.05.003 **(PMID: 27397078)**
9. Vega AV, et al. (2010) CGRP, a vasodilator neuropeptide that stimulates neuromuscular transmission and EC coupling. Curr Vasc Pharmacol 8(3):394–403
10. Goadsby PJ (2005) Calcitonin gene-related peptide antagonists as treatments of migraine and other primary headaches. Drugs 65(18):2557–2567
11. Tfelt-Hansen P et al (2009) Calcitonin gene-related peptide in blood: is it increased in the external jugular vein during migraine and cluster headache? A review. J Headache Pain 10(3):137–143. doi:10.1007/s10194-009-0112-8
12. Arulmani U et al (2004) Calcitonin gene-related peptide and its role in migraine pathophysiology. Eur J Pharmacol 500(1–3):315–330
13. Durham P (2006) Calcitonin gene-related peptide (CGRP) and migraine. Headache 48(Suppl 1):S3–S8. doi:10.1111/j.1526-4610.2006.00483.x **(PMC 3134175, freely accessible, PMID 16927957)**
14. Cernuda-Morollón E (2013) Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. Neurology 81(14):1191–1196. doi:10.1212/WNL.0b013e3182a6cb72
15. Wang Y et al. (2016) Induction of calcitonin gene-related peptide expression in rats by cortical spreading depression. Cephalalgia. doi:10.1177/0333102416678388
16. Ashina H et al. (2016) CGRP in human models of primary headaches. Cephalalgia. doi:10.1177/0333102416684344
17. Edvinsson L et al. (2005) Neurobiology in primary headaches. Brain Res Brain Res Rev 48(3):438–456
18. Leone M et al. (2017) Advances in the understanding of cluster headache. Expert Rev Neurother 17(2):165–172. doi:10.1080/14737175.2016.1216796
19. Neeb L et al. (2016) Methylprednisolone blocks interleukin 1 beta induced calcitonin gene related peptide release in trigeminal ganglia cells. J Headache Pain 17:19. doi:10.1186/s10194-016-0609-x
20. Frese A et al. (2005) Calcitonin gene-related peptide in cervicogenic headache. Cephalalgia 25(9):700–703
21. Cernuda-Morollón E et al. (2015) Onabotulinum toxin A decreases interictal CGRP plasma levels in patients with chronic migraine. Pain 156(5):820–824. doi:10.1097/j.pain.0000000000000119
22. Lacković Z et al. (2016) Activity of botulinum toxin type A in cranial dura: implications for treatment of migraine and other headaches. Br J Pharmacol 173(2):279–291. doi:10.1111/bph.13366
23. Antonucci F et al (2016) SNAP-25, a known presynaptic protein with emerging postsynaptic functions. Front Synaptic Neurosci 24(8):7. doi:10.3389/fnsyn.2016.00007 **(review, PMID: 27047369)**
24. Garrity P (2010) Analysis of Drosophila TRPA1 reveals an ancient origin for human chemical nociception. Nature 464:25. doi:10.1038/nature08848597 **(Macmillan Publishers Limited, all rights reserved © 2010)**
25. Clapham DE (2003) TRP channels as cellular sensors. Nature 426(6966):517–524 **(review, PMID: 14654832)**
26. Starowicz K, Nigam S, Di Marzo V (2007) Biochemistry and pharmacology of endovanilloids. Pharmacol Ther 114(1):13–33
27. Blair NT et al (2015) Transient receptor potential channels. Last modified on 21 May 2015. IUPHAR/BPS guide to pharmacology
28. Story GM et al (2003) ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell 112(6):819–829 **(PMID: 12654248)**
29. Geppetti P, Holzer P (1996) Neurogenic inflammation. CRC Press, Boca Raton
30. Caterina MJ, Schumacher MA et al (1997) The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 389:816–824
31. Gibson HE, Edwards JG et al (2008) TRPV1 channels mediate long-term depression at synapses on hippocampal interneurons. Neuron 57(5):746–759. doi:10.1016/j.neuron.2007.12.027
32. Huang D, Li S, Dhaka A et al (2012) Expression of the transient receptor potential channels TRPV1, TRPA1 and TRPM8 in mouse trigeminal primary afferent neurons innervating the dura. Mol Pain 8:66. doi:10.1186/1744-8069-8-66
33. Diamond S, Freitag F, Phillips SB et al (2000) Intranasal civamide for the acute treatment of migraine headache. Cephalalgia 20(6):597–602
34. Fusco BM, Barzoi G, Agro F (2003) Repeated intranasal capsaicin applications to treat chronic migraine. Br J Anaesth 90(6):812
35. Nassini R, Materazzi S, Vriens J et al (2012) The 'headache tree' via umbellulone and TRPA1 activates the trigeminovascular system. Brain 135:376–390
36. Edelmayer RM, Le LN, Yan J et al (2012) Activation of TRPA1 on dural afferents: a potential mechanism of headache pain. Pain 153:1949–1958
37. Materazzi S, Benemei S, Fusi C et al (2013) Parthenolide inhibits nociception and neurogenic vasodilatation in the trigeminovascular system by targeting the TRPA1 channel. Pain 154:2750–2758
38. Zhong J, Minassi A, Prenen J et al (2011) Umbellulone modulates TRP channels. Pflugers Arch 2011(462):861–870

39. O'Neill J, Brock C, Olesen AE et al (2012) Unravelling the mystery of capsaicin: a tool to understand and treat pain. Pharmacol Rev 64:939–971
40. Burstein R, Zhang X et al (2014) Selective inhibition of meningeal nociceptors by botulinum neurotoxin type A: therapeutic implications for migraine and other pains. Cephalalgia 34(11):853–869. doi:10.1177/0333102414527648 **(Epub 2014 Apr 2)**
41. Amaya F, Oh-hashi K et al (2003) Local inflammation increases vanilloid receptor 1 expression within distinct subgroups of DRG neurons. Brain Res 963:190–196
42. Schueler M, Messlinger K et al (2013) Extracranial projections of meningeal afferents and their impact on meningeal nociception and headache. Pain 154:1622–1631
43. Zhang X, Strassman AM, Novack V (2016) Extracranial injections of botulinum neurotoxin type A inhibit intracranial meningeal nociceptors' responses to stimulation of TRPV1 and TRPA1 channels: are we getting closer to solving this puzzle? Cephalalgia 36(9):875–886. doi:10.1177/0333102416636843 **(Epub 2016 Mar 16 PMID: 26984967)**
44. Denner AC et al. (2016) Role of transient receptor potential ankyrin 1 receptors in rodent models of meningeal nociception—experiments in vitro. Eur J Pain. doi:10.1002/ejp.986
45. Devesa I, Ferrándiz-Huertas C et al (2014) αCGRP is essential for algesic exocytotic mobilization of TRPV1 channels in peptidergic nociceptors. Proc Natl Acad Sci USA 111(51):18345–18350. doi:10.1073/pnas.1420252111 **(Epub 2014 Dec 8)**
46. Valeriani M et al. (2003) Reduced habituation to experimental pain in migraine patients: a CO(2) laser evoked potential study. Pain 105(1–2):57–64
47. de Tommaso M et al. (2016) Effects of OnabotulintoxinA on Habituation of LaserEvoked Responses in Chronic Migraine. Toxins (Basel) 8(6). doi:10.3390/toxins8060163
48. Hubbard CS, Becerra L, Smith JH et al (2016) Brain changes in responders vs. non-responders in chronic migraine: markers of disease reversal. Front Hum Neurosci 10:497 **(eCollection 2016, PMID: 27766076)**
49. Finkel AG (2015) Botulinum toxin and the treatment of headache: a clinical review. Toxicon 107(Pt A):114–119. doi:10.1016/j.toxicon.2015.09.008
50. Miller S, Correia F, Lagrata S, Matharu MS (2015) Onabotulinum toxin A for Hemicrania continua: open label experience in 9 patients. J Headache Pain 16:19. doi:10.1186/s10194-015-0502-z
51. Khalil M et al. (2013) Hemicrania continua responsive to botulinum toxin type a: a case report. Headache 53(5):831–833, doi:10.1111/head.12086
52. Rozen D et al. (2006) Treatment of tension-type headache with botox: a review of the literature. Mt Sinai J Med 73(1):493–498
53. Mathew NT et al. (2008) Predictors of response to botulinum toxin type A (BoNTA) in chronic daily headache. Headache 48(2):194–200
54. Bratbak DF et al (2016) Pilot study of sphenopalatine injection of onabotulinum toxin A for the treatment of intractable chronic cluster headache. Cephalalgia 36(6):503–509. doi:10.1177/0333102415597891 **(PMID: 26232105)**
55. Cernuda-Morollón E et al (2014) CGRP and VIP levels as predictors of efficacy of onabotulinum toxin type A in chronic migraine. Headache 54(6):987–995. doi:10.1111/head.12372 **(Epub 2014 May 6)**
56. Kim CC et al (2010) Predicting migraine responsiveness to botulinum toxin type A injections. Arch Dermatol 146(2):159–163. doi:10.1001/archdermatol.2009.356
57. Pagola I et al. (2014) Predictive factors of the response to treatment with onabotulinum toxin A in refractory migraine. Rev Neurol 58(6):241–246

Neurol Sci (2017) 38 (Suppl 1):S141–S143
DOI 10.1007/s10072-017-2864-2

Onabotulinumtoxin A for chronic migraine with medication overuse: clinical results of a long-term treatment

Licia Grazzi[1]

Abstract The use of Onabotulinumtoxin A as treatment for different neurological conditions is more common in the last decades; its application has been consolidated on the basis of significant clinical results. The clinical experiences with Onabotulinumtoxin A for chronic migraine are on the increase in Italy: at the moment, clinical results are encouraging and enforce the application of the toxin for chronic migraine, according to the results of the PREEMPT studies. The possibility for the patients to be treated with a second cycle of therapy after the first year of treatment is under discussion, in particular for patients who obtained significant clinical benefit from the first period of treatment. In this report, a group of patients treated with Onabotulinumtoxin A for 1 year, according to the PREEMPT protocol, has been retreated for one more year in order to confirm the clinical benefit obtained after the first year of treatment.

Keywords Chronic migraine · Medication overuse · Onabotulinumtoxin A · PREMPT · Retreatment

Introduction

Chronic migraine is a very disabling condition; it is estimated to affect approximately 2% of the general population with a considerable burden for the individuals [1, 2]. These patients experience headache >15 days per month for >3 months and they often overuse medications for aborting pain with more than 15 tablets per month (generally triptans or NSAIDS) [3].

An effective prophylactic treatment after an adequate withdrawal from the offending medications can significantly improve the clinical condition of these patients by reducing the medication intake [4].

In the last decades, efficacy of Onabotulinumtoxin A for the treatment of different neurological conditions has been consolidated on the basis of the significant clinical results [5–7].

In particular, the application and the efficacy of Onabotulinumtoxin A Botox to treat chronic migraine has been demonstrated by the PREEMPT studies which confirmed definitely that Onabotulinumtoxin A is a safe, well-tolerated and effective treatment as prophylaxis for chronic migraine and significant clinical results were obtained [8–10].

Although the clinical results are encouraging, the specific mechanism of action of Onabotulinumtoxin A is not clear yet. One of the possible explanation, as demonstrated in some studies, is that Onabotulinumtoxin A inhibits the release of nociceptive mediators (glutamate and substance P, CGRP) from peripheral terminals of primary afferents [11, 12].

Blocking the release of these neurotransmitters, it inhibits neurogenic inflammation and consequently the peripheral sensitization of nociceptive nerve fibers. As a result, peripheral pain signals to the central nervous system are reduced and central sensitization is blocked [11–13].

Since the problem of managing patients with chronic migraine is challenging in clinical practice, new alternatives for prophylaxis are needed for helping these patients. Onabotulinumtoxin A has been revealed a potential effective treatment for chronic migraine and the results collected in the last years, also in Italian clinical experiences

✉ Licia Grazzi
licia.grazzi@istituto-besta.it

[1] Headache Unit, "C. Besta" Neurological Institute and Foundation, Via Celoria, 11, 20133 Milan, Italy

[14–16], have been encouraging. Also, Onabotulinumtoxin A seems to be well tolerated and safe for patients.

A problem under discussion concerns the possibility to retreat patients after the first year of treatment: specific guidelines to continue the treatment more than a period of 1 year do not exist yet, even if the international literature report different clinical experiences [17–20].

In this report, we consider a clinical experience of a small group of chronic migraine patients with medication overuse treated with Onabotulinumtoxin A for a period of 1 year according to the PREEMPT study protocol and after that, on the basis of clinical significant results, they were submitted to a second period of therapy by using the same protocol of treatment to enforce or to maintain the clinical results obtained after the first year of therapy.

Methods

A first group of 50 patients, 8 male; 42 females, mean age 51.2 ± 9.0; onset of migraine 18.2 ± 8.3, suffering from chronic migraine with medication overuse according to HIS criteria [3], was treated by Onabotulinumtoxin A for a period of 1 year according to the PREEMPT study protocol [8–10], at the Headache Center of the Neurological Institute C. Besta in Milan. All patients underwent a withdrawal program in a day hospital regimen for 5 days in order to stop the overuse of symptomatic medications.

After 1 year of treatment with the application of therapy every 3 months, 16/50 patients asked to continue the treatment as they recorded a significant clinical improvement. Patients were treated by a second period of therapy according to the PREEMPT protocol, with the same treatment schedule previously applied: 5 sessions, one session every 3 months, at the dosage of 155 UI per 31 sites.

Clinical indexes, number of headache days per month, symptomatic medications per month were recorded by using a headache daily diary during both periods of treatment.

Results

Data concerning the small group of 16 patients, 15 females, 1 male, (mean age 52.5 ± 9.9; onset of migraine 15.4 ± 3.9) submitted to a second period of treatment for one more year, are encouraging: they evidenced a significant decrease of days of headache per month at 1 year and the results were confirmed after 2 years of treatment: (25.3 ± 6.1 baseline vs 15.1 ± 7.8 at 1 year vs 15.5 ± 8.7 at 2 years) and also a significant decrease of medication intake per month (23.8 ± 6.8 baseline vs 13.8 ± 7.68 at 1 year vs 15.8 ± 8.48 at 2 years). Patients did not report any side effect and they considered the treatment safe and well tolerated, although we did not record these indexes specifically.

Discussion

In the past, basic science data strongly support an analgesic effect of Onabotulinumtoxin A. In accordance with the past evidences, many headache clinicians have seen patients with chronic migraine who have responded dramatically to Onabotulinumtoxin A treatment. As chronic migraine is a serious clinical condition for patients, highly disabling with risk of medication overuse and moderate response to treatment so common for this category of patients, the possibility of using this new therapeutic option is crucial.

The selection of patients is the key to the successful use of Onabotulinumtoxin A in chronic migraine management [8, 9].

In the past, data from different studies were not conclusive due to the erroneous selection of patients. On the other side, the most recent clinical trials have shown more positive results as more selective criteria for inclusion of patients were used [8, 9].

Moreover, the pharmacological profile of Onabotulinumtoxin A makes it a good candidate for migraine prevention at the adequate dosage as proposed in the PREEMPT study. Its long duration of action (3 months) makes it particularly attractive for patients who are not compliant with the daily use of preventive medications, or if they cannot tolerate them or when they are refractory to preventive medications [16].

In preceding studies it has been demonstrated the efficacy and safety of Onabotulinumtoxin A in chronic migraine with medication overuse over a period of 24 months and also at different dosages, higher than 155 U is well tolerated [17, 20].

In terms of mean reduction of days of migraine and medication consumption, our clinical experience shows significant results even if the dosage was limited to 155 over a period of 24 months. The treatment was safe and well tolerated. Patients adherence to treatment was high, no missed appointments and side effects (usually reported from oral prophylaxis as weight gain, somnolence, fatigue, hypotension) were not recorded during the course of treatment.

All patients were able to manage the medication intake, without relapses of medication overuse in absence of other prophylaxis for their migraine.

In conclusion, data from recent studies show encouraging results: Onabotulinumtoxin A seems to be effective for patients with chronic migraine, in particular the long

duration of action and favorable adverse events make it a suitable therapeutic alternative for those patients not compliant with oral preventive medications. The application of Onabotulinumtoxin A is indicated also in the early stage of the disease and this may result in a better treatment outcome. Although our results are preliminary, as the limited group of patients retreated, they led to intense efforts to evaluate analgesic properties of Onabotulinumtoxin A and to assess its clinical applicability for longer period than 1 year to confirm the preceding data [17–20], by reinforcing the clinical benefit obtained from the first year of treatment.

Future studies have to be performed to better understand the mechanism of action of Onabotulinumtoxin A and to identify possible predictors of response to this innovative treatment.

Compliance with ethical standards

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Bigal ME, Serrano D, Reed M, Lipton RB (2008) Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. Neurology 71:559–566
2. Manack AN, Buse DC, Lipton RB (2011) Chronic migraine: epidemiology and disease burden. Curr Pain Headache Rep 15:70–78
3. International Headache Society (2013) International classification of headache disorders, 3rd edition (beta version). Cephalalgia 33:628–808
4. Grazzi L, Andrasik F, Usai S, Bussone G (2009) Treatment of chronic migraine with medication overuse: is drug withdrawal crucial? Neurol Sci 30(Suppl 1):85–88
5. Ranoux D, Attal N, Morain F, Bouhasira D (2008) Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurol 64:274–283
6. Simpson DM, Hallett M, Ashman EJ, Comella CI, Green MW, Gronseth GS, Armostrong MJ, Gloss D, Potrebic S, Jankovic J, Karp BR, Naumann M, So YT, Yablon SA (2016) Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. Neurology 86:1818–1826
7. Colosimo C, Tiple D, Berardelli A (2012) Efficacy and safety of long-term botulinum toxin treatment in craniocervical dystonia: a systematic review. Neurotox Res 22:265–273
8. Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, Diener HC, Brin MF, PREEMPT 1 Chronic Migraine Study Group (2010) Onabotulinumtoxin A for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 30:793–803
9. Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, Silberstein SD, Brin MF, PREEMPT 2 Chronic Migraine Study Group (2010) Onabotulinumtoxin A for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 30:804–814
10. Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, DeGryse RE, VanDenburgh AM, Nolan ME, Turkel CC (2011) Onabotulinumtoxin A for treatment of chronic migraine: pooled analyses of the 56-week PRE-EMPT clinical program. Headache 51:1358–1373
11. Aoki KR (2003) Evidence for antinociceptive activity of botulinum toxin type A in pain management. Headache 43(Suppl):S9–S15
12. Aoki KR (2005) Review of a proposed mechanisms for the antinociceptive action of botulinum toxin type A. Neurotoxicology 26:785–793
13. Gazerani P, Pedersen NS, Staahl C, Drewes AM, Arendt-Nielsen L (2009) Subcutaneous botulinum toxin type A reduces capsaicin-induced trigeminal pain and vasomotor reactions in human skin. Pain 141:60–69
14. Sandrini G, Perrotta A, Tassorelli C, Torelli P, Brighina F, Sances G, Nappi G (2011) Botulinum toxin type-A in the prophylaxis treatment of medication-overuse headache: a multi center, double blind, randomized, placebo-controlled, parallel group study. J Headache Pain 12:427–433
15. Grazzi L, Usai S (2015) Onabotulinumtoxin A (Botox) for chronic migraine treatment: an Italian experience. Neurol Sci 36(Suppl1):S33–S35
16. Farinelli I, Coloprisco G, De Filippis S, Martelletti P (2006) Long-term benefits of Botulinum Toxin A (BOTOX) in chronic daily headache: a five-year long experience. J Headache Pain 7:407–412
17. Cernuda-Morollon E, Ramon C, Larrosa D, Alvarez R, Riesco N, Pascual J (2015) Long-term experience with Onabotulinumtoxin A in the treatment of chronic migraine: what happens after one year? Cephalalgia 35:864–868
18. Kollewe K, Escher CM, Wulff DU, Fathi D, Paracka L, Mohammadi B, Karst M, Dressler D (2016) Long-term treatment of chronic migraine with Onabotulinumtoxin A: efficacy, quality of life and tolerability in a real-life setting. J Neural Transm 123:533–540
19. Guerzoni S, Pellesi L, Beraldi C, Pini LA (2016) Increased efficacy of regularly repeated cycles with Onabotulinumtoxin A in MOH patients beyond the first year of treatment. J Headache Pain 17:48
20. Negro A, Curto M, Lionetto L, Martelletti P (2016) A two years open-label prospective study of Onabotulinumtoxin A 195U in medication overuse headache: a real-world experience. J Headache Pain 17:1–9

Neurol Sci (2017) 38 (Suppl 1):S145–S156
DOI 10.1007/s10072-017-2910-0

New treatments for headache

Kasra Maasumi[1] · Stewart J. Tepper[2] · Alan M. Rapoport[3]

Abstract Headache disorders are common worldwide and often disabling. Until recently, treatments were borrowed from other branches of neurology and medicine. Monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) ligand and receptor, small molecule CGRP receptor antagonist gepants, serotonin$_{1F}$ agonists, new devices to deliver currently available drugs, and neuromodulation devices have recently been in the forefront of headache treatments that are rather specific for various headache disorders. These novel therapies are changing the field of headache medicine. Herein, we update the latest data available for these therapies.

Keywords Calcitonin gene-related peptide (CGRP) · Monoclonal antibodies · Headache treatment · Neuromodulation · Neurostimulation · Magnetic stimulation

Introduction: epidemiology of primary headache disorders

Headache disorders are among the most common and debilitating conditions with which physicians deal. Prevalence data show that tension-type headache is the second most prevalent disorder worldwide [1, 2]. After dental caries, tension-type headache was among the eight diseases affecting more than 10% of the world population in 2013. Tension-type headache affects 1.6 billion people worldwide. Among all neurological conditions, migraine, tension-type headache, and medication overuse headache were among the most prevalent. The 1-year prevalence rate for migraine is 10%, ranging from 4.5 to 6% in men and 14.5–18% in women [3, 4]. The prevalence distribution for migraine has an inverted U shape, i.e., low prevalence in young and old people. The highest prevalence (23.5%) is among females between the ages of 18 and 44 [5–7].

There are various oral medications for the acute and preventive treatment of primary headache disorders. Patients, however, generally do not remain on their medications for long. Hepp et al. reviewed over 8000 patients and reported that adherence to the initial oral migraine preventive medication prescribed was only 25% at 6 months and 14% at 12 months [8]. They further concluded that switching between oral medications is common, but adherence worsens as the patients' cycle through various treatments. It is also known that most patients do not stay on the first triptan prescribed, nor get total relief from these medications [9, 10].

In this review, we will detail some of the latest treatment options in the pipeline for the primary headache disorders. We will focus on the monoclonal antibodies, non-triptan serotonin receptor agonists, and devices that use triptans and ergots with novel delivery systems. Finally, we will discuss the use of neuromodulation.

✉ Kasra Maasumi
Kmaasumi@gmail.com

[1] Neurology, Headache, University of California San Francisco (UCSF), 2330 Post Street Unit 610, San Francisco, CA 94115, USA

[2] The Giesel School of Medicine at Dartmouth, Hanover, NH, USA

[3] University of California Los Angeles, Los Angeles, CA, USA

New oral and injectable treatment options

Some of the most exciting advances in headache prevention are attributed to modulating the effect of CGRP. The development of small molecule CGRP receptor antagonist gepants and monoclonal antibodies that target either the CGRP ligand or its receptor has proceeded for more than 10 years. Early treatments by the small molecule CGRP receptor antagonist gepants either showed signs of liver toxicity or were not commercialized. Today, other gepants are being tested both for acute care and prevention of migraine. There are several pharmaceutical companies working on their development.

Why target CGRP?

CGRP is a 37 amino acid neuropeptide that is a potent vasodilator present ubiquitously in the body. Lars Edvinsson of Lund University, Sweden, performed the early studies on CGRP and then the effect of blocking CGRP on arteries [11]. CGRP mediates neurogenic inflammation and modulates nociceptive input [12]. It is found in trigeminal sensory afferents, other sensory neurons, and the spinal trigeminal nucleus [13]. In 1990s, Goadsby, Edvinsson, and others reported elevated levels of CGRP in the jugular outflow during migraine attacks [14, 15]. It was also found abundantly in the saliva during migraine attacks [15]. Furthermore, levels of CGRP were attenuated by administration of triptans, associated with pain relief [16]. It has also been shown that intravenous injection of CGRP can cause a headache [16]. Interestingly, migraine-like headache occurred only in patients with a history of migraine, while non-migraineurs had a sensation of fullness in the head [17].

Small molecule CGRP receptor antagonists, the gepants

There have been numerous small molecule CGRP receptor antagonists, called gepants, studied so far for the acute treatment of migraine. All were found effective with positive primary outcomes in phase 2 and 3 trials. The earlier animal studies did not show that they constrict blood vessels. There was no sign of liver toxicity in these early trials. When a preventive trial was done with the daily use of one of these antagonists, telcagepant, which had already shown acute care efficacy in two-phase 3 trials, liver toxicity was noted. A follow-up trial requested by the US Food and Drug Administration (FDA), done in patients with menstrually associated migraine, also showed liver toxicity and further work on telcagepant was halted [18–22].

Early studies of gepants

The first gepant described in clinical trials was olcegepant [22, 23]. The trial was a multi-center, double-blind, randomized trial for the acute relief of a migraine attack; it revealed that at 2 h, the 2.5 mg intravenous dose of olcegepant provided 66% of the patients with pain relief compared to 27% for the placebo ($p = 0.001$). The adverse event rate was 25% compared to the placebo, which was 12.5%. The most common side effect was paresthesia; there were no CNS or triptan-like side effects. It was concluded that it was effective in treating migraine acutely. It has not yet been commercialized.

Telcagepant (MK0974), at 300 mg, achieved pain relief at 2 h of 68%, at 400 mg 48.2%, and at 600 mg 67.5% versus rizatriptan 10 mg 69.5% and placebo 46.3% ($p = 0.015$) [24]. In a randomized, parallel-group, placebo-controlled, double-blind, international trial of 1380 patients, telcagepant 300 mg was as effective at treating migraine acutely as zolmitriptan 5 mg but with fewer adverse events [25, 26]. Cui et al. performed a meta-analysis on the efficacy of telcagepant versus placebo and triptans (zolmitriptan or rizatriptan) in 2015. Eight trials were included in the analysis. Pain freedom at 2 h favored telcagepant over placebo (odds ratio = 2.70, 95% confidence interval = 2.27–3.21, $p < 0.001$) There was non-inferiority for telcagepant versus triptans (odds ratio = 0.68, 95% confidence interval = 0.56–0.83, $p < 0.001$). Pain relief at 2 h was better for telcagepant compared to placebo (odds ratio = 2.48, 95% confidence interval = 2.18–2.81, $p < 0.001$; this was not the case when telcagepant was compared with triptans (odds ratio = 0.76, 95% confidence interval = 0.57–1.01, $p = 0.061$) [27]. The development of telcagepant was halted due to an increase in aminotransferases in two patients. A randomized, double-blind, placebo-controlled, multi-center trial by Ho et al. showed that although telcagepant taken daily reduced headache by 1.4 days per month compared to placebo, but there was a 2.5% risk of increased alanine aminotransferase (ALT) [18].

Current studies of gepants

BMS-92771 is an oral gepant in which the phase 2 trial was completed; however, the company that developed it is offering to sell it [21]. It is superior to placebo and is well tolerated. In the double-blind, randomized, placebo-controlled, dose-ranging trial, the authors showed that at 2 h, pain freedom for the 75 mg dose was 31.4% ($p = 0.002$), for the 150 mg dose was 32.9% ($p < 0.001$), and for the 300 mg dose was 29.7% ($p = 0.002$) compared to placebo,

which was 15.3%. A secondary endpoint, sustained pain freedom from 2 to 24 h post dose, demonstrated statistically significant results compared to placebo.

Another oral gepant for which phase 2 dose-ranging data were published is BI 44370 TA. The study was done on 341 subjects with migraine who were treated with 50, 200, and 400 mg of study drug, eletriptan 40 mg or placebo [28]. The primary endpoint was 2 h pain freedom. For the 400 mg dose, the results were 27.4% compared to eletriptan, which was 34.8% and placebo, which was 8.6% ($p = 0.0016$). There are apparently no current plans to proceed with this gepant into phase 3.

Voss et al. performed a phase IIb randomized, double-blind, placebo-controlled trial of oral ubrogepant for the acute treatment of migraine attacks in 2016 [29]. The dose range finding study of 1, 10, 25, 50, and 100 mg compared to placebo was performed for efficacy and tolerability. There were 527 subjects who received the drug and 113 that received placebo. Ubrogepant 100 mg showed superiority over placebo for 2-h pain freedom, 25.5% compared to 8.9%, $p < 0.001$) but no superiority for pain relief at any time point. The failure to show benefit for pain relief was either due to a relatively high placebo response rate, a somewhat low number of patients in the 100 mg dose, or the dose selected, which may have been too low in this dose-ranging study.

Atogepant, antoher oral gepant, is currently being studied in the phase 2 trials as a preventive treatment of episodic migraine (Clinicaltrials.gov NCT02848326).

The development of monoclonal antibodies to CGRP or its receptor

Monoclonal antibodies to CGRP and its receptor have been developed for migraine prevention. They are highly specific for their target. They are not metabolized in the liver and therefore devoid of liver toxicity. They have very long half-lives compared to currently available oral migraine preventive medications. Because of their large molecular size, they cannot cross the blood brain barrier and must be injected intramuscularly, subcutaneously, or infused intravenously [30]. Currently there are four monoclonal antibodies to CGRP or its receptor that are being developed. At the time of this writing (March 2017), they all have completed phase 2 trials and are currently in phase 3 studies: erenumab (Amgen 334) [31, 32] eptinezumab (ALD 403) [33], galcanezumab (LY2951742) [34], and fremanezumab (TEV48125) [35]. These will be described individually in detail.

Erenumab (AMG 334)

The trials for Erenumab (AMG 334) are for episodic and chronic migraine; this is the only antibody of the four that targets the CGRP receptor, not the ligand. Erenumab is a fully human CGRP immunoglobulin G2 (IgG) antibody that binds selectively to the CGRP receptor. It is the only one of the four migraine preventive monoclonal antibodies that is fully human; the other three are humanized. The target is a G protein coupled receptor composed of calcitonin receptor-like receptor and receptor activity modifying protein 1 subunits (RAMP1). At 70 mg, the half-life of erenumab is 21 days, allowing for monthly subcutaneous injections [31, 32]. In a multi-center, randomized, double-blind, placebo-controlled phase 2 trial, the safety and efficacy of erenumab were assessed for prevention of migraine attacks [31]. There were 483 patients enrolled at 59 centers between the ages 18–60 with 4–14 migraine days per month. The primary endpoint was the change in monthly migraine days from baseline for 12 weeks. The mean change in monthly migraine days was 3.4 days fewer at 12 weeks with erenumab at 70 mg compared to 2.3 days fewer with placebo ($p = 0.021$). Adverse events occurred in 54% who received placebo, and 54% of those who received erenumab 70 mg.

There is also a phase 3 randomized, double-blind, placebo-controlled trial for the evaluation of the efficacy and safety of erenumab in migraine prevention (Clinicaltrial.gov NCT02483585). The primary outcome measure is change from baseline in mean monthly migraine days at 3 months. This is for episodic migraine patients with or without aura who have headaches more than 12 months. The erenumab at dose of 70 mg subcutaneously once a month or placebo was administered for the first 12 weeks then followed by open-label phase for 28 weeks.

Phase 2/3 data on Erenumab were presented at the European Headache Federation/Migraine Trust meeting in September 2016 in Glasgow, Scotland. Erenumab 70 and 140 mg were both superior to placebo at reducing migraine days at 12 weeks, showing a 6.6 decrease in migraine days versus a 4.2 decrease in migraine days for placebo, $p < 0.001$. About 40% of patients treated with active drug had at least a 50% decrease in migraine days compared with 24% for placebo. Tolerability was good and comparable to placebo.

Currently, we are awaiting other results of trials pertaining to erenumab. There is an open-label extension study to assess the long-term safety and efficacy of erenumab (Clinicaltrial.gov NCT02174861). There is a randomized, double-blind, placebo-controlled, study on the effect of AMG 334 on exercise time during a treadmill test in patients with stable angina (Clinicaltrial.gov NCT02575833). There is a phase 1 randomized controlled trial (RCT) on the effect of a single dose erenumab on blood pressure given concomitantly with subcutaneous sumatriptan in healthy subjects (Clincialtrial.gov NCT02741310). There is a phase 1 RCT to evaluate the

blockade of CGRP receptor using a single dose of erenumab in preventing PCAP-38-induced migraine, such as attacks (Clinicaltrial.gov NCT 02542605). Another phase 1 RCT evaluates the efficacy, safety, tolerability and pharmacokinetics of erenumab in women with hot flashes associated with menopause (Clinicaltrial.gov NCT 01890109).

Eptinezumab (ALD 403)

The eptinezumab trials are for episodic and chronic migraine attacks, and the only ones looking at an intravenous dose. The current data available for this drug are from a phase 2 trial. Eptinezumab is a humanized CGRP IgG1 antibody that binds to both alpha and beta forms of the human CGRP [33]. It has a half-life of 31 days at 1000 mg dose, given intravenously.

In a randomized, double-blind, placebo-controlled exploratory proof of concept phase 2 trial, Dodick et al. assessed the safety, tolerability, and efficacy of eptinezumab in patients with 5–14 migraine days per 28-day period who were between the ages 18–55. The trial enrolled 163 patients, 81 of whom received 1000 mg of eptinezumab, while 82 received placebo only once in 3 months. After 5–8 weeks, the mean change in migraine days compared to baseline was 5.6 days fewer for the eptinezumab group and 4.6 days fewer for the placebo group ($p = 0.0306$). There were no safety concerns noted. A post hoc analysis showed that 16% of the subjects had a 100% responder rate for pain relief, 24% had a 75% responder rate, and 28% had a 50% responder rate during the 12 weeks of the trial.

The current trial in progress is entitled "A Parallel Group, Double-Blind, Randomized, Placebo-Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of ALD 403 Administered Intravenously in Patients With Chronic Migraine" (Clinicaltrials.gov NCT02974153). Results may be available in 2017. An open-label trial is also under way titled "An Open Label Trial to Evaluate the Safety of ALD403 Administered Intravenously in Patients With Chronic Migraine" (Clinicaltrials.gov NCT02985398).

Galcanezumab (LY2951742)

The clinical trials for galcanezumab are for episodic and chronic migraine as well as cluster headaches. The treatment is given as a single subcutaneous injection twice a month. Galcanezumab is a humanized monoclonal antibody selectively binding to CGRP ligand with a half-life of 28 days [34]. In a phase 2 RCT, the efficacy and safety of galcanezumab were assessed at 35 centers in patients between the ages of 18–65 with 4–14 migraine days per month. The dose was 150 mg galcanezumab in comparison with placebo. The primary endpoint was the mean change in number of migraine headache days per 28-day period between baseline and 12 weeks. Safety was assessed over 24 weeks. Of the 218 patients, 108 of them received galcanezumab, and the rest received placebo. The mean change in headache days after 12 weeks compared to baseline was 4.2 fewer days for those receiving the drug and 3 days fewer for those receiving placebo ($p = 0.0030$). Adverse events occurred in a small percentage of the patients.

RCTs in phase 3 evaluating galcanezumab for episodic and chronic cluster headaches are underway (Clinicaltrial.gov NCT02438826 and NCT02397473).

Fremanezumab (TEV48125)

The trials for fremanezumab are for episodic and chronic migraine and also for cluster headache. It was the first of the monoclonals to be reported in a phase 2 trial for chronic migraine. It is given as a monthly subcutaneous injection and targets the CGRP ligand. In a phase 2b multi-center, randomized, double-blind, placebo-controlled trial on episodic migraineurs, the efficacy and safety of fremanezumab were assessed in patients between the ages of 18 and 65 with 8–14 headache days per month, which is high-frequency episodic migraine [35]. The primary endpoints for episodic migraine were change in migraine days from baseline to 12 weeks as well as safety and tolerability. There were 297 patients evaluated, 95 of them received the 225 mg dose and 96 received the 675 mg dose. The change in number of migraine days after 12 weeks was 6.09 days fewer in the 675 mg dose group, 6.27 days fewer in the 225 mg dose group, and 3.46 fewer days in the placebo group ($p < 0.0001$). Adverse events occurred in 59% in the group who received 675 mg dose, 46% in the 225 mg dose group, and 56% of the placebo group.

Fremanezumab was also evaluated at the same time for chronic migraine [36]. This was a multi-center, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, phase 2b trial. The participants were patients between the age of 18 and 65 with chronic migraine who received three 28-day treatment cycles of subcutaneous fremanezumab at doses of 675 mg in the first treatment cycle, 225 mg in the second and third treatment cycles each. This dosage was compared to 900 mg in all three treatment cycles as well as placebo. The primary endpoints were change from baseline in total headache hours during weeks of 9–12, which are the third treatment cycle, along with safety and tolerability. Overall, there were 264 participants. The mean change from baseline in terms of the number of headache hours during the third treatment cycle was 67.51 h fewer in the 900 mg group, 59.84 h fewer in the groups that received 675/225 mg injections, and finally 37.10 h fewer in the placebo group.

Adverse events were 47% in the 900 mg group, 53% in the 675/225 mg group, and 40% in the placebo group.

There are also ongoing phase 3 studies of fremanezumab on episodic and chronic cluster headaches (Clinicaltrial.gov NCT02945046 and NCT02964338).

Lasmiditan: a Serotonin$_{1F}$ receptor agonist

The 5-HT$_{1F}$ receptor agonists are alternatives to the triptans, which are mostly agonists at the 5-HT$_{1B/1D}$ receptors. The unique features of pure 5-HT$_{1F}$ receptor agonists are that they are anti-inflammatory, centrally active, and do not constrict vessels. Some triptans have minor 1F activity but are also vasoconstrictors as they have 1B activity.

Ferrari et al. evaluated lasmiditan in a randomized, multi-center, placebo- controlled, double-blind proof of concept trial in 130 patients using IV lasmiditan versus placebo [37]. The primary outcome was headache response, defined as improvement from moderate or severe headache at baseline to mild or no headache at 2 h post infusion. Of those that received lasmiditan, 54–75% showed 2 h headache response compared to 45% for the placebo ($p = 0.0126$). They concluded that at 20 mg IV and higher, lasmiditan proved effective in the acute treatment of migraine. Studies were then planned for an oral form of the drug.

In a phase 2 trial, the efficacy and safety of oral lasmiditan for acute treatment of migraine were assessed [38]. Doses of 50, 100, 200, or 400 mg of lasmiditan or placebo were tested on 512 patients with assessment of 2-h pain relief. The percentage of patients improving on 50 mg dose compared to placebo showed a difference of 17.9% ($p = 0.022$), for 100 mg, the difference was 38.2% ($p < 0.0001$), for 200 mg, the difference was 28.8% ($p < 0.0018$), and for 400 mg, the difference was 38.7% ($p < 0.0001$). The most common side effects were dizziness and paresthesia along with fatigue and nausea, and the rates were fairly high. The authors concluded that the oral lasmiditan is safe and effective in treatment of acute migraine, but tolerability was an issue.

In the phase 3 trial of oral lasmiditan, the primary outcome measure was the proportion of subjects being pain free at 2 h post dose; it was 32.2% for 200 mg versus 15.3% for placebo ($p < 0.001$). The doses tested were 50, 100 and 200 mg. A key secondary endpoint was freedom of the most bothersome symptom. At 100 mg, the results were 40.9%, at 200 mg 40.7%, and placebo was 29%. ($p < 0.001$). Tolerability was better in the phase 3 than in the phase 2 trial, but there remain questions on the methodology used in phase 3 and the technique used for collection of adverse event data (Clinicaltrials.gov NCT02605174).

New devices for currently approved medications

Sumatriptan 3 mg subcutaneous injection (Zembrace SYMTOUCH)

This device made by Promius Pharma LLC, the American arm of Dr. Reddy's Laboratory Ltd, India, provides a disposable auto-injector prefilled with 3 mg of sumatriptan. In a recent trial, Cady et al. attempted to justify the use of the 3 mg dose subcutaneous sumatriptan as opposed to the 6 mg dose in a randomized, double-blind, cross-over study [39]. They compared the efficacy and tolerability of the 3 mg SC sumatriptan (DFN-11) with the 6 mg SC sumatriptan in 20 adults who had rapidly escalating migraine attacks. None of the results was statistically significant. They reported that at 1 h post injection, 50% of patients experienced pain relief with the 3 mg dose and 52.6% with the 6 mg dose. Similar types and numbers of adverse events were found for both doses including paresthesia, neck pain, flushing, and involuntary muscle contractions of the neck.

Another phase 2 trial is also in progress titled "Pilot Study of DFN-11 Injection in Medication Overuse Headache" (Clinicaltrials.gov NCT02583425). The advantage of using the 3-mg dose injection may be mainly for those who cannot tolerate the higher doses of 4 and 6 mg. It may also be helpful to lower the total daily or weekly dose of sumatriptan in cluster patients and those with frequent migraine attacks, although it was not studied for these indications.

Sumatriptan breath-powered intranasal powder (Onzetra Xsail)

This device from Avanir pharmaceuticals, Inc. is a nasal powder formulation of sumatriptan that is blown into each nostril, for acute treatment of migraine in adults. The amount of sumatriptan used is 11 mg in each nostril, although slightly less is actually delivered. When the device was under development, it was called AVP-825 or Optinose.

Obaidi et al. assessed the pharmacokinetic profile of 22 mg sumatriptan powder given intranasally [40]. In an open-label, cross-over, comparative bioavailability study, they compared it with 20 mg sumatriptan liquid nasal spray, a 100 mg tablet, and a 6 mg subcutaneous injection. They concluded that the breath-powered intranasal delivery is more efficient form of drug delivery providing a higher peak and earlier exposure with a lower dose than the nasal spray and faster absorption that either nasal spray or oral form.

The efficacy and safety of the device were assessed by Cady et al. in a phase 3 study comparing it to an identical

device containing lactose powder (placebo) [41]. This was a double-blind, placebo-controlled, parallel-group study with the primary endpoint of 2-h pain relief. They enrolled 223 patients into the study. There were 68% of the patients on verum who had 2 h pain relief compared to 45% on placebo ($p = 0.002$). At 2 h, 38% of the patients on verum achieved pain freedom compared to 17% on placebo ($p = 0.008$). There were no serious adverse effects (AE) and few triptan AEs.

Tepper et al. compared the efficacy, tolerability and safety of the AVP-825 with 100 mg oral sumatriptan for the acute treatment of migraine in a comparative effectiveness trial across at least five attacks in a double-dummy design [42]. They enrolled total of 275 subjects in the trial. The primary endpoint was the mean value of the summed pain intensity differences through 30-min post dose, comparing the oral with the nasal sumatriptan. The secondary endpoints were pain relief, pain freedom, and pain reduction as well as safety across multiple times. There was a significant reduction in migraine pain intensity in the first 30 min ($p < 0.001$) for the powder, which continued for 2 h. At 2 h, the tablet caught up with the nasal form. However, in the first 2 h, the dry nasal powder was consistently superior to the tablet for efficacy despite the lower dose of the nasal formulation with lower adverse events. The main complaints were nasal discomfort and abnormal taste. This device has been marketed in the US since May 2016. This formulation would be appropriate for patients requiring a non-oral formulation, those with quick onset to peak headaches, and for those with triptan sensations from conventional oral triptan doses.

Dihydroergotamine (DHE) Oral Inhaler (Semprana)

Shrewsbury et al. conducted a randomized, double-blind, placebo-controlled trial of two doses of inhaled DHE on 19 subjects in 2008 [43]. They concluded that it resulted in rapid and efficient systemic absorption. There were no clinically relevant safety issues observed. In another study, Shrewsbury also investigated the pulmonary absorption of DHE and compared its safety, pharmacokinetic, and metabolic profile in various doses using the Tempo Inhaler from MAP Pharmaceuticals Inc, in 18 healthy volunteers [44]. They concluded that its delivery of 1 mg was slightly lower than IV administration.

Tepper et al. also conducted a post hoc sub-analysis using data from the Freedom-301 study, which had enrolled 903 patients in a randomized, double-blind, placebo-controlled phase 3 trial in 2008. It evaluated the efficacy of orally inhaled DHE for the acute treatment of migraine between 1 and 8 h post migraine onset [45]. They concluded that the orally inhaled DHE is effective in treating migraine irrespective of the time of the treatment.

In a review, Tepper further elaborated that DHE has persistent receptor binding that may account for its use in treating allodynia and central sensitization in prolonged migraine and status migrainosus among the many subtypes of migraine [46]. The inhaled formulation has a lower maximal serum concentration than the IV formulation resulting in markedly decreased nausea and vomiting.

In the Freeedom-301 phase 3 study, 903 adults with episodic migraine had superior 2 h results from DHE compared to the placebo for pain relief (58.7 versus 34.5%, $p < 0.0001$), phonophobia free (52.9 versus 33.8%, $p < 0.0001$), photophobia free (46.6 versus 27.2%, $p < 0.0001$), and nausea free (67.1 versus 58.7%, $p = 0.0210$). In addition, more patients were pain free at 2-h post treatment compared to placebo (28.4 versus 10.1%, $p < 0.0001$) [47]. Tolerability was good, and no pulmonary signal was reported.

There have been concerns noted by the FDA with chemistry, manufacturing, and controls (CMC) for the DHE inhaler, but not with efficacy or safety. If these CMC issues are resolved, the brand name of the DHE inhaler is anticipated to be Semprana (formerly Levadex).

Zolmitriptan microneedle patch (ZP)

A randomized, double-blind, multi-center, parallel-group, dose-ranging comparison trial has just been reported by press release from Zosano for the safety and efficacy of the ZP-zolmitriptan intracutaneous microneedle system for the acute treatment of migraine (Clinicaltrial.gov NCT02745392). This small patch, the size of a coin, is placed by an applicator and contains numerous microneedles impregnated with zolmitriptan. The primary endpoint was pain freedom at 2 h using 1, 1.9, and 3.8 mg single patch administration compared to placebo. The results were all statistically significant. There were 77 patients on placebo, 79 on 1 mg, 83 on 1.9 mg, and 82 on 3.8 mg. Pain freedom at 2 h was 14.3% for placebo, 30.4% for the 1 mg dose ($p = 0.0149$), 27.7 for the 1.9 mg dose ($p = 0.0351$), and 41.5% for the 3.8 mg ($p = 0.0001$). The secondary endpoint was freedom from most bothersome symptom at 2 h. The only result that was statistically significant was for the 3.8 mg dose, which was 68.3%, compared to placebo, which was 42.9% ($p = 0.0009$). Tolerability was good.

Neuromodulation

Neuromodulation is a rapidly growing branch of headache medicine therapy, whereby non-invasive or minimally invasive techniques are used to modulate pain by targeting specific areas of the central and peripheral nervous system [48].

Non-invasive neuromodulation

Non-invasive forms of neuromodulation include single pulse transcranial magnetic stimulation (sTMS), transcutaneous supraorbital nerve stimulation (tSNS), non-invasive vagal nerve stimulation (nVNS), and caloric vestibular stimulation (CVS). Both sphenopalatine ganglion stimulation and occipital nerve stimulation are more invasive, and transcranial direct current stimulation (tDCS) has not been studied in the United States for headache disorders.

Single pulse transcranial magnetic stimulation (sTMS)

Single pulse TMS, from eNeura, Inc., is effective and FDA approved for acute treatment for migraine with aura [49]. Both sTMS and repetitive TMS (rTMS) are being studied for migraine prevention [50–56]. The magnet generates an electrical field penetrating the cortex up to 3 cm deep. It is believed that the sTMS works on migraine with aura by inhibiting occipital cortical spreading depression. It is approved in Europe for the acute treatment of migraine with and without aura and for migraine prevention.

To evaluate the responses of patients to sTMS in clinical practice, Bhola et al. surveyed 190 patients with migraine with and without aura over a 3-month treatment period using the device in an open-label study [49]. She found that 62% of the patients reported pain relief, 52% reported less nausea, 55% reported less photophobia, and 53% reported less phonophobia. At 3 months, there was a reduction in headaches days from 12 to 9 among those with episodic migraine and a reduction from 24 to 16 among those with chronic migraine. A larger open-label study, the ESPOUSE study, for prevention of migraine, has been completed in the United States, and preliminary positive data were presented at the European Headache Federation/Migraine Trust meeting in September, 2016 in Glasgow, Scotland.

Transcutaneous supraorbital nerve stimulation (tSNS)

The frontal nerve is a part of the ophthalmic division of the trigeminal nerve and it terminates in the supraorbital and supratrochlear nerves. These two nerves provide sensation to the front and top of the head. By inhibiting the nociceptive transmission via transcutaneous electrical stimulation, it is believed that the nociceptive activity can be modulated more centrally. A device named Cefaly made by Cefaly Technology, Belgium has been approved for migraine prevention in the United States [57, 58].

Schoenen and colleagues published the only RCT on tSNS [59]. In 67 patients with episodic migraine, the 50% responder rate after 3 months was 38.2% compared to the sham group, which was 12.1%. The acute migraine medication intake was reduced by 36.7% in the active group. A study on the acute treatment of migraine is underway.

Non-invasive vagal nerve stimulation (nVNS)

The vagus or 10th cranial nerve has mixed sensory and motor nerve components [48]. It is both an afferent and efferent nerve, which is about 70% sensory. It carries parasympathetic preganglionic fibers and also cutaneous sensory and visceral afferent traffic.

A transcutaneous, non-invasive device has been developed by electro-Core LLC, NJ USA called GammaCore. It stimulates the cervical part of the vagal nerve. It is under consideration by the FDA for the indication of acute treatment of cluster headache. They have also applied for migraine acute care and prevention indications. It is a hand held device that is approved for treatment of migraine and cluster headaches in many countries in the world.

The device clearly stimulates just the afferent vagal fibers, preferentially activating afferent A and large B fibers, not C or efferent pathways that mediate bradycardia and bronchoconstriction in data presented by Nonis and colleagues at the American Academy of Neurology meeting in 2016. nVNS suppresses rat cortical spread depression (CSD) and inhibits central trigeminovascular and thalamocortical pathways without affecting blood pressure or pulse [60].

Several open-label studies on nVNS in acute and preventive treatment of migraine have been published. In one by Barbanti et al., open-label data on treatment of high-frequency episodic migraine and chronic migraine in 48 patients showed at 2 h, the proportion of patients with pain freedom was 39.6%, and the proportion of patients with pain relief was 64.6% [61–64].

In another open-label trial, Grazzi and colleagues studied the nVNS in mini-prevention for menstrually related migraine. They reported, "The number of menstrual migraine/menstrually related migraine days per month was significantly reduced from baseline (mean $\pm$ standard error, 7.2 ± 0.7 days) to the end of treatment (mean $\pm$ standard error, 4.7 ± 0.5 days; $p < 0.001$) (primary end point). Of all subjects, 39% (95% confidence interval: 26%, 54%) (20/51) had a $\geq$ 50% reduction (secondary end point). For the other secondary end points, clinically meaningful reductions in analgesic use (mean change $\pm$ standard error, -3.3 ± 0.6 times per month; $p < 0.001$), 6-item Headache Impact Test score (mean change $\pm$ standard error, -3.1 ± 0.7; $p < 0.001$), and Migraine Disability Assessment score (mean change $\pm$ standard error, -11.9 ± 3.4; $p < 0.001$) were observed, along with a modest reduction in pain intensity (mean change $\pm$ standard error, -0.5 ± 0.2;

$p = 0.002$). There were no safety/tolerability concerns." [65].

In an RCT for chronic migraine, with two 90s pulses delivered three times daily, the primary endpoint of reduced headache days at 2 months was not significant. However, there appeared to be reduction of headache days per month clinically evident over 6 months of open-label use [66].

There are two published RCTs for the treatment of cluster headache (CH) published at the time of this writing (March 2017). In the first, nVNS + standard of care was compared with standard of care alone for the CH prevention. The PREVA study showed reduced CH attacks per week from baseline, significant for the nVNS group and positive secondary endpoints of the 50% responder rate and reduced use of rescue medications including oxygen compared with standard of care alone [67].

In the first of two planned RCTs for the acute treatment of CH, the nVNS failed to relieve CH attacks in all comers at 15 min, the primary endpoint. There were significant methodologic problems with the study. However, the ACT1 study clearly showed nVNS could relieve episodic CH attacks at 15 min, while was unsuccessful stopping attacks in chronic CH [68].

Caloric vestibular stimulation (CVS)

Caloric vestibular stimulation (CVS) is a new technique for inhibitory central neuromodulation. The contiguity of the vestibular and trigeminal systems at the point of entry and in transit within the brainstem offers the opportunity for cross-talk and down regulation of central pain conditions, such as migraine.

A device which delivers fluctuating thermal changes in the vestibular pathways, tightly controlled to avoid vertigo and nausea but set with inhibitory parameters, has been studied in prevention of episodic migraine, with reports presented at the American Headache Society annual scientific meeting in San Diego and the European Headache Federation/Migraine Trust meetings in Glasgow 2016. Black et al. showed evidence that CVS treatment can elicit changes in cerebral blood flow physiology consistent with the neuromodulation of brainstem centers [69].

The data presented were from a placebo controlled, blinded, home-use protocol trial (Clinicaltrials.gov NCT02866084), which was completed at six sites enrolling patients with 4–14 headache days per month. Primary and secondary endpoints were positive. Per protocol for headache days at 3 months versus baseline results were: active ($n = 28$); placebo ($n = 18$); active: -3.6 headache days vs. baseline ($p < 0.0001$). That is, active versus sham showed a -2.7 headache day decrease ($p = 0.012$). In the Intention To Treat (ITT) analysis, active ($n = 34$); placebo ($n = 18$): active: -3.2 HA days versus baseline ($p < 0.0001$). That is, active versus sham showed a -2.4 headache day decrease ($p = 0.034$). Secondary endpoints reported as positive were 50% responder rates, use of acute medications, mood, cognition, and balance.

Adverse events were essentially the same as sham. Adverse events reported in >1 patient included nausea, dizziness, ear symptoms, and tinnitus. Both placebo and active groups reported dizziness in four patients each.

Minimally invasive neuromodulation

Minimally invasive neuromodulation forms involve sphenopalatine ganglion (SPG) stimulation and occipital nerve stimulation (ONS).

Sphenopalatine ganglion stimulation (SPGs)

The sphenopalatine or pterygopalatine ganglion (SPG) receives preganglionic parasympathetic fibers originating in the superior salivatory nucleus (SSN). These fibers synapse in the SPG and then postganglionic parasympathetic pathways exit and terminate in autonomic and secretory glands of the face. Postganglionic sympathetic fibers traverse the SPG without synapse on their course to similar destinations. Afferent trigeminal pathways also pass through the SPG.

For many years, physicians have tried to block the SPG to treat migraine and especially cluster headache. It has been chemically inactivated, surgically altered or removed, anesthetized with cocaine and with 4% lidocaine. It can be stimulated at low frequency to activate cluster headache and at high frequency to block it.schy [70]. A small SPG stimulator, without wires or batteries, has been designed and is being tested by Autonomic Technologies, Inc., in Silicon Valley, California. The stimulator is implanted over the ganglion via an oral entry done under anesthesia, and it is remotely activated at the start of each cluster attack. In data from a published RCT by Schoenen et al., later expanded to a larger number of patients and presented at international headache meetings, pain relief was achieved by 67% of the 566 acute attacks of cluster headache at 15 min compared to 7% of the placebo and sham patients. In addition, the device showed preventive effects, with 42% of patients manifesting an 89% decreased attack frequency [71–73].

Barloese et al. monitored the self-reported attack frequency, headache disability, and medication intake in 33 patients with refractory chronic cluster headache [74]. It was an open-label follow-up study in which patients were followed for 2 years after the insertion of the SPG stimulator. They reported that 30% of the patients experienced at least one period of complete attack remission.

This wireless, remote controlled stimulator is currently approved in Europe for treatment of chronic cluster headache and has been studied for migraine, with a submission for CE mark at the time of this writing (March 2017). The registration study in the US for chronic cluster headache is underway,

Occipital nerve stimulation (ONS)

As an alternative treatment for prevention of intractable chronic migraine and cluster headache, ONS stimulation has been under investigation. The idea is to stimulate the large sensory afferents to cause pain reduction by inhibiting nociceptive activity in c-fibers and a-delta fibers as well as possible central inhibition. There have been three RCTs for ONS for prevention of chronic migraine, two of which have been published in peer-reviewed papers. Neither of the two studies which had primary endpoints reached the primary endpoint, and the third negative study was exploratory. One of the three, by Lipton and colleagues, was presented at the International Headache Congress in 2012 but never published fully. The other two studies, as noted, were negative [75, 76]. There are open-label reports of effectiveness, and open-label studies that look at the efficacy of ONS combined with supraorbital and supratrochlear nerve stimulation, but it is well to remember the negative RCTs [77, 78].

Adverse events for ONS include electrode migration, intolerance to paresthesias, cable breakage, pain, muscular spasm, infection, and battery depletion. In 2014, the EU rescinded the CE Mark approval for the St Jude Genesis ONS device for headaches because of these issues.

Maximally invasive neuromodulation

Deep brain stimulation (DBS)

The suprachiasmatic nucleus of the posterior hypothalamus is involved in the pathogenesis of cluster headache [79]. In cases of medically refractory cluster headaches, DBS has been investigated as a treatment option [50, 80–84]. Overall, about 60% of the published cases in the literature report at least 50% reduction in their cluster attack frequency [85]. The first group to refer a patient for this operation was headed by Dr. Gennaro Bussone and Massimo Leone at the Istituto Neurologico C Besta in Milan, Italy. The neurosurgeons performing the operation were Drs. Broggi and Franzini. They had excellent results with very few major complications putting the electrode in the hypothalamic/rostral midbrain area. Some patients are getting excellent relief many years later, even with bilateral implants. Other groups had major complications, and enthusiasm for the procedure has waned.

Conclusions

Headaches are some of the most painful and disabling disorders affecting many people worldwide. So far, for migraine prevention, we have been utilizing medications that were initially developed for other disorders, such as antiepileptic drugs, antihypertensive drugs, or antidepressants. However, new medications and devices have been developed that are targeting primary headache disorder treatment, including migraine and cluster headache. These include CGRP monoclonal antibodies, small molecule CGRP receptor antagonist gepants, $5HT_{1F}$ receptor agonists, and neuromodulation. We also have new acute care treatments in the form of medications, stimulators, and devices with better delivery of older drugs. These new medications and tools will not only help many patients in the near future, but will further open the door to new treatment trials so we can hone the results of treatment of primary headache disorders.

Compliance with ethical standards

Conflict of interest Kasra Maasumi: none. Stewart Tepper: Research grants (no personal compensation): Alder, Allergan, Amgen, ATI, Avanir, Dr. Reddy's, Scion Neurostim, Teva, Zosano; Consultant: Acorda, Alder, Allergan, Amgen, ATI, BioVision, Dr. Reddy's, Eli Lilly, Kimberly-Clark, Pernix, Pfizer, Scion Neurostim, Teva, Zosano; Royalties: Springer; Salary: Dartmouth-Hitchcock Medical Center, American Headache Society; Stock Options: ATI. Alan Rapoport: Is on the Speakers Bureau of Avanir and Depomed. He has consulted for Acorda, Amgen, Autonomic Technologies, Avanir, Depomed, Promius, Impax, Lilly, Pernix, Teva and Zosano.

References

1. Global Burden of Disease Study 2013 Collaborators (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386:743–800
2. Leonardi M, Raggi A (2013) Burden of migraine: international perspectives. Neurol Sci 34(Suppl 1):S117–S118
3. Stewart WF, Lipton RB, Celentano DD, Reed ML (1992) Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. JAMA 267:64–69
4. Maasumi K, Tepper SJ, Kriegler JS (2017) Menstrual migraine and treatment options: review. Headache. 57:194–208
5. Burch RC, Loder S, Loder E, Smitherman TA (2015) The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. Headache. 55:21–34
6. Lipton RB, Bigal ME (2005) Migraine: epidemiology, impact, and risk factors for progression. Headache 45(Suppl 1):S3–s13

7. Smitherman TA, Burch R, Sheikh H, Loder E (2013) The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 53:427–436
8. Hepp Z, Dodick DW, Varon SF, Chia J, Matthew N, Gillard P, Hansen RN, Devine EB (2016) Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: a retrospective claims analysis. Cephalalgia. doi:10.1177/0333102416678382
9. Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A, Peterson J, Coyle D, Skidmore B, Gomes T, Clifford T, Wells G (2015) Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. Headache. 55(Suppl 4):221–235
10. Cady RK, Maizels M, Reeves DL, Levinson DM, Evans JK (2009) Predictors of adherence to triptans: factors of sustained vs lapsed users. Headache 49:386–394
11. Edvinsson L, Chan KY, Eftekhari S, Nilsson E, de Vries R, Saveland H, Dirven CM, Danser AH, MaassenVanDenBrink A (2010) Effect of the calcitonin gene-related peptide (CGRP) receptor antagonist telcagepant in human cranial arteries. Cephalalgia 30:1233–1240
12. Russo AF (2015) Calcitonin gene-related peptide (CGRP): a new target for migraine. Annu Rev Pharmacol Toxicol 55:533–552
13. Kageneck C, Nixdorf-Bergweiler BE, Messlinger K, Fischer MJ (2014) Release of CGRP from mouse brainstem slices indicates central inhibitory effect of triptans and kynurenate. J Headache Pain 15:7
14. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 28:183–187
15. Ho TW, Edvinsson L, Goadsby PJ (2010) CGRP and its receptors provide new insights into migraine pathophysiology. Nat Rev Neurol 6:573–582
16. Asghar MS, Hansen AE, Amin FM, van der Geest RJ, Koning P, Larsson HB, Olesen J, Ashina M (2011) Evidence for a vascular factor in migraine. Ann Neurol 69:635–645
17. Petersen KA, Lassen LH, Birk S, Lesko L, Olesen J (2005) BIBN4096BS antagonizes human alpha-calcitonin gene related peptide-induced headache and extracerebral artery dilatation. Clin Pharmacol Ther 77:202–213
18. Ho TW, Connor KM, Zhang Y, Pearlman E, Koppenhaver J, Fan X, Lines C, Edvinsson L, Goadsby PJ, Michelson D (2014) Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology 83:958–966
19. Ho TW, Ho AP, Ge YJ, Assaid C, Gottwald R, MacGregor EA, Mannix LK, van Oosterhout WP, Koppenhaver J, Lines C, Ferrari MD, Michelson D (2016) Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine. Cephalalgia 36:148–161
20. Hewitt DJ, Aurora SK, Dodick DW, Goadsby PJ, Ge YJ, Bachman R, Taraborelli D, Fan X, Assaid C, Lines C, Ho TW (2011) Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine. Cephalalgia 31:712–722
21. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ (2014) BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia 34:114–125
22. Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko LM (2004) Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. N Engl J Med 350:1104–1110
23. Yao G, Yu T, Han X, Mao X, Li B (2013) Therapeutic effects and safety of olcegepant and telcagepant for migraine: a meta-analysis. Neural Regen Res 8:938–947
24. Ho TW, Mannix LK, Fan X, Assaid C, Furtek C, Jones CJ, Lines CR, Rapoport AM (2008) Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. Neurology 70:1304–1312
25. Ho TW, Ferrari MD, Dodick DW, Galet V, Kost J, Fan X, Leibensperger H, Froman S, Assaid C, Lines C, Koppen H, Winner PK (2008) Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. Lancet 372:2115–2123
26. Connor KM, Shapiro RE, Diener HC, Lucas S, Kost J, Fan X, Fei K, Assaid C, Lines C, Ho TW (2009) Randomized, controlled trial of telcagepant for the acute treatment of migraine. Neurology 73:970–977
27. Cui XP, Ye JX, Lin H, Mu JS, Lin M (2015) Efficacy, safety, and tolerability of telcagepant in the treatment of acute migraine: a meta-analysis. Pain Pract 15:124–131
28. Diener HC, Barbanti P, Dahlof C, Reuter U, Habeck J, Podhorna J (2011) BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. Cephalalgia 31:573–584
29. Voss T, Lipton RB, Dodick DW, Dupre N, Ge JY, Bachman R, Assaid C, Aurora SK, Michelson D (2016) A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. Cephalalgia 36:887–898
30. Wang W, Wang EQ, Balthasar JP (2008) Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 84:548–558
31. Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, Saper J, Cady R, Chon Y, Dietrich J, Lenz R (2016) Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol 15:382–390
32. Shi L, Lehto SG, Zhu DX, Sun H, Zhang J, Smith BP, Immke DC, Wild KD, Xu C (2016) Pharmacologic characterization of AMG 334, a potent and selective human monoclonal antibody against the calcitonin gene-related peptide receptor. J Pharmacol Exp Ther 356:223–231
33. Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, Wilks K, Kudrow D, Kroll R, Kohrman B, Bargar R, Hirman J, Smith J (2014) Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol 13:1100–1107
34. Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS (2014) Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol 13:885–892
35. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, Loupe PS, Burstein R, Newman LC, Lipton RB (2015) Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol 14:1081–1090
36. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings EL, Diener HC, Burstein R, Loupe PS, Ma Y, Yang R, Silberstein SD (2015) Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 14:1091–1100
37. Ferrari MD, Farkkila M, Reuter U, Pilgrim A, Davis C, Krauss M, Diener HC (2010) Acute treatment of migraine with the

selective 5-HT1F receptor agonist lasmiditan–a randomised proof-of-concept trial. Cephalalgia 30:1170–1178
38. Farkkila M, Diener HC, Geraud G, Lainez M, Schoenen J, Harner N, Pilgrim A, Reuter U (2012) Efficacy and tolerability of lasmiditan, an oral 5-HT(1F) receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. Lancet Neurol 11:405–413
39. Cady RK, Munjal S, Cady RJ, Manley HR, Brand-Schieber E (2017) Randomized, double-blind, crossover study comparing DFN-11 injection (3 mg subcutaneous sumatriptan) with 6 mg subcutaneous sumatriptan for the treatment of rapidly-escalating attacks of episodic migraine. J Headache Pain 18:17
40. Obaidi M, Offman E, Messina J, Carothers J, Djupesland PG, Mahmoud RA (2013) Improved pharmacokinetics of sumatriptan with breath powered nasal delivery of sumatriptan powder. Headache 53:1323–1333
41. Cady RK, McAllister PJ, Spierings EL, Messina J, Carothers J, Djupesland PG, Mahmoud RA (2015) A randomized, double-blind, placebo-controlled study of breath powered nasal delivery of sumatriptan powder (AVP-825) in the treatment of acute migraine (The TARGET Study). Headache 55:88–100
42. Tepper SJ, Cady RK, Silberstein S, Messina J, Mahmoud RA, Djupesland PG, Shin P, Siffert J (2015) AVP-825 breath-powered intranasal delivery system containing 22 mg sumatriptan powder vs 100 mg oral sumatriptan in the acute treatment of migraines (The COMPASS study): a comparative randomized clinical trial across multiple attacks. Headache 55:621–635
43. Shrewsbury SB, Kori SH, Miller SD, Pedinoff A, Weinstein S (2008) Randomized, double-blind, placebo-controlled study of the safety, tolerability and pharmacokinetics of MAP0004 (orally-inhaled DHE) in adult asthmatics. Curr Med Res Opin 24:1977–1985
44. Shrewsbury SB, Cook RO, Taylor G, Edwards C, Ramadan NM (2008) Safety and pharmacokinetics of dihydroergotamine mesylate administered via a Novel (Tempo) inhaler. Headache 48:355–367
45. Tepper SJ, Kori SH, Goadsby PJ, Winner PK, Wang MH, Silberstein SD, Cutrer FM (2011) MAP0004, orally inhaled dihydroergotamine for acute treatment of migraine: efficacy of early and late treatments. Mayo Clin Proc 86:948–955
46. Tepper SJ (2013) Orally inhaled dihydroergotamine: a review. Headache 53(Suppl 2):43–53
47. Aurora SK, Silberstein SD, Kori SH, Tepper SJ, Borland SW, Wang M, Dodick DW (2011) MAP0004, orally inhaled DHE: a randomized, controlled study in the acute treatment of migraine. Headache 51:507–517
48. Puledda F, Goadsby PJ (2016) Current approaches to neuromodulation in primary headaches: focus on vagal nerve and sphenopalatine ganglion stimulation. Curr Pain Headache Rep 20:47
49. Bhola R, Kinsella E, Giffin N, Lipscombe S, Ahmed F, Weatherall M, Goadsby PJ (2015) Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: evaluation of outcome data for the UK post market pilot program. J Headache Pain 16:535
50. Schwedt TJ, Vargas B (2015) Neurostimulation for treatment of migraine and cluster headache. Pain Med 16:1827–1834
51. Clarke BM, Upton AR, Kamath MV, Al-Harbi T, Castellanos CM (2006) Transcranial magnetic stimulation for migraine: clinical effects. J Headache Pain 7:341–346
52. Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, Fischell RE, Ruppel PL, Goadsby PJ (2010) Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 9:373–380
53. Brighina F, Piazza A, Vitello G, Aloisio A, Palermo A, Daniele O, Fierro B (2004) rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. J Neurol Sci 227:67–71
54. Conforto AB, Amaro E Jr, Goncalves AL, Mercante JP, Guendler VZ, Ferreira JR, Kirschner CC, Peres MF (2014) Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. Cephalalgia 34:464–472
55. Misra UK, Kalita J, Bhoi SK (2013) High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: a randomized, placebo-controlled study. J Neurol 260:2793–2801
56. Teepker M, Hotzel J, Timmesfeld N, Reis J, Mylius V, Haag A, Oertel WH, Rosenow F, Schepelmann K (2010) Low-frequency rTMS of the vertex in the prophylactic treatment of migraine. Cephalalgia 30:137–144
57. Magis D, Sava S, d'Elia TS, Baschi R, Schoenen J (2013) Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly(R) device in headache treatment: a survey of 2,313 headache sufferers in the general population. J Headache Pain. 14:95
58. Schoenen J, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gerard P, Magis D (2013) Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology. 80:697–704
59. Riederer F, Penning S, Schoenen J (2015) Transcutaneous supraorbital nerve stimulation (t-SNS) with the Cefaly(R) device for migraine prevention: a review of the available data. Pain Ther 4:135–147
60. Oshinsky ML, Murphy AL, Hekierski H Jr, Cooper M, Simon BJ (2014) Noninvasive vagus nerve stimulation as treatment for trigeminal allodynia. Pain 155:1037–1042
61. Kinfe TM, Pintea B, Muhammad S, Zaremba S, Roeske S, Simon BJ, Vatter H (2015) Cervical non-invasive vagus nerve stimulation (nVNS) for preventive and acute treatment of episodic and chronic migraine and migraine-associated sleep disturbance: a prospective observational cohort study. J Headache Pain 16:101
62. Nesbitt AD, Marin JC, Tompkins E, Ruttledge MH, Goadsby PJ (2015) Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. Neurology. 84:1249–1253
63. Barbanti P, Grazzi L, Egeo G, Padovan AM, Liebler E, Bussone G (2015) Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: an open-label study. J Headache Pain 16:61
64. Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA (2014) Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. Cephalalgia 34:986–993
65. Grazzi L, Egeo G, Calhoun AH, McClure CK, Liebler E, Barbanti P (2016) Non-invasive vagus nerve stimulation (nVNS) as mini-prophylaxis for menstrual/menstrually related migraine: an open-label study. J Headache Pain 17:91
66. Silberstein SD, Calhoun AH, Lipton RB, Grosberg BM, Cady RK, Dorlas S, Simmons KA, Mullin C, Liebler EJ, Goadsby PJ, Saper JR (2016) Chronic migraine headache prevention with noninvasive vagus nerve stimulation: the EVENT study. Neurology. 87:529–538
67. Gaul C, Diener HC, Silver N, Magis D, Reuter U, Andersson A, Liebler EJ, Straube A (2016) Non-invasive vagus nerve stimulation for prevention and acute treatment of chronic cluster headache (PREVA): a randomised controlled study. Cephalalgia 36:534–546
68. Silberstein SD, Mechtler LL, Kudrow DB, Calhoun AH, McClure C, Saper JR, Liebler EJ, Rubenstein Engel E, Tepper SJ (2016) Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. Headache 56:1317–1332
69. Black RD, Rogers LL, Ade KK, Nicoletto HA, Adkins HD, Laskowitz DT (2016) Non-invasive neuromodulation using time-

varying caloric vestibular stimulation. IEEE J Transl Eng Health Med 4:2000310
70. Schytz HW, Barlose M, Guo S, Selb J, Caparso A, Jensen R, Ashina M (2013) Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. Cephalalgia 33:831–841
71. Schoenen J, Jensen RH, Lanteri-Minet M, Lainez MJ, Gaul C, Goodman AM, Caparso A, May A (2013) Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. Cephalalgia 33:816–830
72. Tepper SJ, Rezai A, Narouze S, Steiner C, Mohajer P, Ansarinia M (2009) Acute treatment of intractable migraine with sphenopalatine ganglion electrical stimulation. Headache. 49:983–989
73. Ansarinia M, Rezai A, Tepper SJ, Steiner CP, Stump J, Stanton-Hicks M, Machado A, Narouze S (2010) Electrical stimulation of sphenopalatine ganglion for acute treatment of cluster headaches. Headache. 50:1164–1174
74. Barloese MC, Jurgens TP, May A, Lainez JM, Schoenen J, Gaul C, Goodman AM, Caparso A, Jensen RH (2016) Cluster headache attack remission with sphenopalatine ganglion stimulation: experiences in chronic cluster headache patients through 24 months. J Headache Pain 17:67
75. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ (2011) Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia 31:271–285
76. Silberstein SD, Dodick DW, Saper J, Huh B, Slavin KV, Sharan A, Reed K, Narouze S, Mogilner A, Goldstein J, Trentman T, Vaisman J, Ordia J, Weber P, Deer T, Levy R, Diaz RL, Washburn SN, Mekhail N (2012) Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia 32:1165–1179
77. Reed KL, Black SB, Banta CJ 2nd, Will KR (2010) Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: initial experience. Cephalalgia 30:260–271
78. Reed KL, Will KR, Conidi F, Bulger R (2015) Concordant occipital and supraorbital neurostimulation therapy for hemiplegic migraine; initial experience; a case series. Neuromodulation 18:297–303 **(discussion 304)**
79. May A, Goadsby PJ (2001) Hypothalamic involvement and activation in cluster headache. Curr Pain Headache Rep 5:60–66
80. Bartsch T, Pinsker MO, Rasche D, Kinfe T, Hertel F, Diener HC, Tronnier V, Mehdorn HM, Volkmann J, Deuschl G, Krauss JK (2008) Hypothalamic deep brain stimulation for cluster headache: experience from a new multicase series. Cephalalgia 28:285–295
81. Fontaine D, Lazorthes Y, Mertens P, Blond S, Geraud G, Fabre N, Navez M, Lucas C, Dubois F, Gonfrier S, Paquis P, Lanteri-Minet M (2010) Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. J Headache Pain 11:23–31
82. 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 **(discussion 1099–1101)**
83. Leone M, Franzini A, Broggi G, Bussone G (2003) Hypothalamic deep brain stimulation for intractable chronic cluster headache: a 3-year follow-up. Neurol Sci 24(Suppl 2):S143–S145
84. Piacentino M, D'Andrea G, Perini F, Volpin L (2014) Drug-resistant cluster headache: long-term evaluation of pain control by posterior hypothalamic deep-brain stimulation. World Neurosurg 81:442.e411–442.e445
85. Magis D, Schoenen J (2012) Advances and challenges in neurostimulation for headaches. Lancet Neurol 11:708–719

Neurol Sci (2017) 38 (Suppl 1):S157–S161
DOI 10.1007/s10072-017-2928-3

Behavioral therapy: emotion and pain, a common anatomical background

Lauren A.-M. Dahlke[1] · Jeffrey J. Sable[1,2] · Frank Andrasik[1]

Abstract Emotion and pain are closely intertwined in the brain, as the human experience of pain includes both affective and nociceptive components. Although each of these components relies on a different system in the brain, the two systems converge on the anterior cingulate and insular cortices, which interact with the prefrontal cortex and other frontal structures to influence behavior. Both emotional and physical pain elicit activity in these common areas, and conditions that affect one system (e.g., drugs, neural plasticity) may affect the function of the other—ultimately altering the experience of pain. Changes in these areas and their connections may even contribute to the chronification of pain. This relationship should not be overlooked in the treatment of painful conditions, including headache. Nonpharmacological therapies, such as cognitive behavioral therapy, yoga, biofeedback, and meditation, that are often used for enhancing emotional regulation, are increasingly being turned to for augmenting management of migraine and pain. Because of the overlap between emotion and pain, these therapies are likely acting through similar mechanisms, and emotional cues can be sensitive indicators of treatment-related changes in patients.

Keywords Behavioral therapy · Brain · Emotion · Headache · Pain

✉ Frank Andrasik
fndrasik@memphis.edu

[1] Department of Psychology, University of Memphis, 400 Innovation Drive, Memphis, TN 38152, USA

[2] Department of Behavioral Sciences, Christian Brothers University, 650 East Parkway South, Memphis, TN 38104, USA

Introduction

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," and notes that "pain is always subjective" [1]. However, this definition may not capture the full complexity of pain, as many chronic pain conditions cannot be explained in terms of tissue pathology; headache being a case in point. Individuals' behaviors can provide just as much, if not more, information as their subjective self-reports of pain [2–4]. To effectively treat pain, we must understand that it involves a complex interaction between biological and psychological components that should be addressed concurrently.

The idea that pain is more than a physical sensation is not new; Melzack and Casey [5] long ago presented a conceptual model of pain as physical sensation followed by affective and cognitive responses to said sensation. Yet, this subjective, emotional component of pain is often overlooked in clinical practice and research, and we believe that failure to do so leads to incomplete understanding and limits treatment options. Both patients and health-care professionals may benefit greatly from a better understanding of the emotional aspects of pain.

A growing body of research is showing the benefits of behavioral therapy for pain management, which is likely due in part to successful management of both pain-related behavior and emotions [6, 7] and neurophysiological changes to the brain [8]. Our chief goal in this brief, selective review is to highlight common links between pain and emotion, and to introduce why and how health service professionals can capitalize on these links to better manage headache pain. Readers seeking more comprehensive reviews may wish to consult the following sources,

realizing they devote less attention to behavioral aspects [9–12]. Although there is substantial evidence for functional overlap between emotion and acute pain [13, 14], our focus is restricted to recurrent forms of headache and chronic pain.

Comorbidity of pain and mental illness

To begin to see the link between emotion and pain, it is important to note the high rates of comorbidity of pain-related conditions and psychiatric disorders. In general, migraineurs have increased risk for anxiety and affective disorders—even more so if the condition is chronic [15]. In a more recent review, common psychiatric comorbidities with migraine included depression, anxiety, post-traumatic stress disorder, childhood trauma, and substance abuse in adulthood, with prevalence rates ranging from 9 to 58% [16]. Additionally, in a study of 500 patients with chronic musculoskeletal pain, nearly half of patients also reported depression (20%), anxiety (3%), or both (26%) [17]. Patients having both anxiety and depression alongside chronic pain showed the most severe pain and pain-related disability. Though causal factors are unclear (i.e., do psychiatric disorders cause development of pain, does development of pain cause psychiatric disorders, or is it a complex co-occurrence?), some evidence exists that psychiatric conditions could lead to chronic health conditions, such as chronic pain. A longitudinal study of individuals who experienced childhood abuse or neglect found that, although childhood trauma alone could not predict pain symptoms, PTSD in young adulthood and childhood trauma together produced a robust prediction of pain in middle adulthood [18]. These findings suggest pain may be exacerbated by unresolved psychological trauma.

It, thus, seems clear that a close relationship exists between emotional processing and the experience of pain. One explanation is that the physical and emotional aspects of pain engage overlapping neural pathways and common structures in the brain.

Dual systems theory of pain

Two systems are ultimately involved in the human experience of pain [3, 4, 9] (see Fig. 1). The first of these systems is the lateral pain system, or neospinothalamic tract, which gives rise to nociception. This system contains projections from the spinal cord to the thalamus, and on to the primary somatosensory cortex, and is involved in the physical sensation of pain [11].

The second system is the medial pain system, or paleospinothalamic tract, which passes through the periaqueductal gray and structures of limbic system [11]. This system elicits the affective experiences of pain [19].

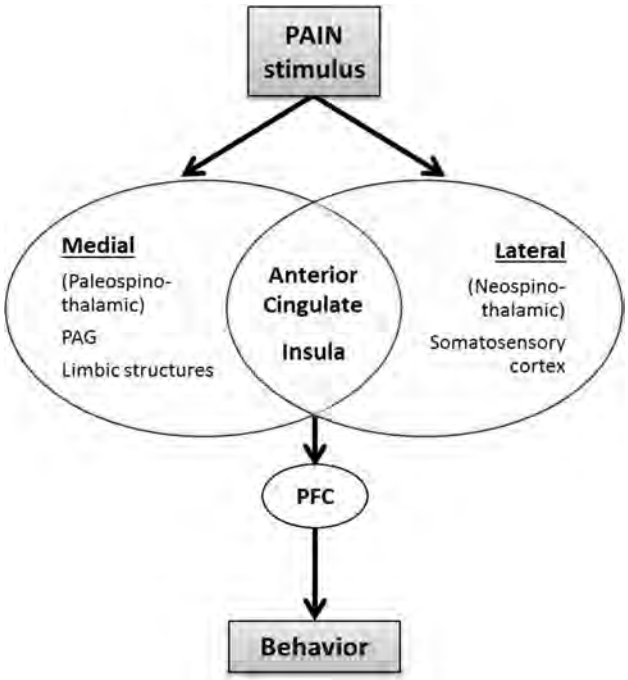

Fig. 1 A single painful stimulus is processed through parallel neural pathways [9]. The medial system gives rise to the emotional aspects of pain, while the lateral system gives rise to nociception. These systems converge on the anterior cingulate and insular cortices, which interact with the prefrontal cortex (PFC) to plan responses and produce behavior. Although the figure shows the flow of information from inputs to outputs, information flows in both directions (e.g., regulation of pain input by descending fibers). *PAG* periaqueductal gray

Information from both pathways comes together in the anterior cingulate cortex (ACC) and insular cortices. Thus, it is the combination of nociceptive and affective input to these areas—elicited by the same stimulus—that influences interoceptive homeostasis [20] and response prioritization [9, 11]. Hence, both types of information about pain contribute to our subjective experience and, ultimately, our response to it. It is from this theory that we seek to establish the anatomical links between emotion and pain.

Areas of the brain and emotion as a factor in pain

Several areas are consistently activated in PET and fMRI studies when pain is involved. The second somatosensory (S2) and insular regions, as well as the ACC, are the areas most consistently activated during the experience of pain [21]. The thalamus is often activated as well, but less consistently so. These areas reflect activation of the medial and lateral pain systems, especially where they converge on the insula and ACC. In a more recent paper [22], meta-

analytic connectivity modeling was utilized to identify areas that were active across multiple types of stimuli, as well as attentional, emotional, and reward tasks. The insula, dorsal ACC (dACC), and thalamus were again consistently activated. The authors suggest that activity in this system reflects both external input of pain and internal reflection on pain, much in line with Melzack and Casey's [5] two-stage theory of pain described previously in brief.

The ACC appears to be particularly important in the affective interpretation of pain. One study that dissociated the circuitry involved in emotional and attentional modulation of pain showed that the ACC was the largest modulator of mood and influenced pain unpleasantness, but not pain intensity [23]. Attentional modulation associated with pain intensity was not as robust, but activated the anterior insular cortex. The ACC likely acts as a mediator between cognition and emotion, with connections to the limbic system and prefrontal cortex (PFC), as well as somatosensory areas [24]. Because the ACC is so closely linked with affective processing and it is consistently activated during the experience of pain, it is likely that the ACC plays a role in affective regulation during the experience of pain. A review of analgesia effects of placebos supports this notion [25].

Due to this close link, emotional pain appears to mimic certain aspects of physical pain in terms of brain activity and pain perception. For example, social rejection elicits similar activation in the same areas as physical pain, and greater sensitivity to physical or social pain is associated with greater sensitivity to physical pain [14]. Interestingly, daily administration of acetaminophen compared to placebo in two studies showed reduced self-reports of social pain, as well as reduced activity in both dACC and anterior insula, when experiencing social exclusion [26].

Additionally, as pain shifts from acute to chronic conditions, more emotional components come into play in pain processing. For example, although both medial and lateral pain systems were found to be active in patients with arthritic pain while experiencing both arthritic pain and experimentally induced pain, the medial system was significantly more active during the experience of arthritic pain [27]. Preliminary data discussed by Bussone, Grazzi, and Panerai [3, 4] also indicate that changes are not seen in the lateral pain system in chronic migraineurs, suggesting chronification of migraine may be influenced more by emotional factors than somatic factors. Furthermore, it has been shown that, as pain moves from acute to chronic, areas associated with emotion become more involved [28].

There is existing evidence of alterations in the ACC and insula, as well as the PFC, that may accompany pain [25, 29]. Decreased gray matter, white matter integrity, and opioid binding in these areas are associated with chronic pain. These alterations may impact the function in pathways that descend from these areas, reducing cognitive and emotionally mediated analgesic effects. Synaptic mechanisms may underlie the involvement of the ACC in chronification of pain as well [29]. In particular, NMDA-mediated long-term potentiation in the ACC (and resistance to subsequent long-term depression) appears to sustain the affective experience in chronic pain. Thus, pain ultimately may perpetuate itself through neural changes to areas affected by the emotional aspects of pain.

These changes may manifest in altered emotional processing. In migraineurs, for example, pain catastrophizing has been positively correlated with insular activity (measured with fMRI) elicited by acute pain stimuli, but negatively correlated with PFC and dorsal cingulate activity [30]. Migraineurs also show heightened attention-related brain responses (the visual N1 component of the event-related brain potential) specifically to angry faces [31].

In summary, emotion and pain are clearly intertwined in the human brain. A single painful stimulus activates parallel pathways. One results primarily in an awareness of the nature and location of the stimulus. The other elicits sensations of emotion and arousal. The two converge in the ACC and insular cortices, which give rise to our subjective interpretation and, ultimately, behavioral plans to cope (or not) with the painful stimulus. Changes to these areas, in turn, may alter the incoming information and our affective experience of it. It thus becomes critical to consider emotional factors in the treatment of pain. Failing to do so ignores a substantial part of the neural system that gives rise to pain and the dynamics that occur in that system.

Effect of behavioral therapy on pain

Behavioral therapy is traditionally used for the treatment of mental health disorders, and broadly refers to therapies that target changes in behavior and ways of thinking for more positive outcomes. Behavioral approaches such as cognitive behavioral therapy (CBT), yoga, meditation, and biofeedback are increasingly being used to treat pain disorders as well. Having established that pain and emotion processing are entangled in the brain, we posit here that behavioral therapies in actuality target some of the same mechanisms in both pain and psychological disorders. Because pain perception is affected by cognition and emotion, we see positive effects of behavioral therapies on both emotional and pain outcomes. Changing thought processes regarding pain alters the brain, and in turn the brain alters the experience of pain.

The body of literature on effects of behavioral therapies on neuroanatomy is small, but expanding. This literature is even smaller in specific regard to pain, but there is growing evidence that these therapies are working to alter pain

perception through neural mechanisms. After an 11-week CBT program, gray matter volume was increased in areas that included the dorsolateral PFC, ACC, and sensorimotor cortices in patients with a variety of chronic pain conditions, and these areas were associated with a decrease in pain catastrophizing [32]. This finding could be especially important in migraine treatment, as reduced gray matter in these areas has been found in migraineurs [33]. In patients with fibromyalgia, CBT led to increased PFC activation and PFC-thalamus functional connectivity during induced pain, as well as reported improvement in condition despite no improvement on clinical measures of pain [34]. Such findings lend support to the notion that greater control of cognitive and emotional factors related to pain subsequently reduces perceived pain.

Treatments incorporating mindfulness, a practice of non-judgmental awareness, are becoming more popular and appear to be promising for the treatment of headache [35]. Mindfulness meditation has been shown to affect mainly the medial pain system, with meditation-induced increases in ACC and anterior insula activation associated with reduced ratings of pain intensity and pain unpleasantness [36]. However, mindfulness increases pain-evoked PFC activity [37, 38]. Mindfulness meditation also has been shown to reduce anticipatory anxiety of pain [38], supporting ACC modulation of pain processing and mindfulness as a viable therapy for pain reduction.

Pain treatment may even benefit from something as simple as an increased awareness of emotional states in patients. As described above, for example, heightened emotional reactivity in migraineurs, such as catastrophizing [30] and sensitivity to negative emotion [31] may parallel changes in pain-related processing. Monitoring such emotions may improve the efficacy of treatment in these patients.

Conclusions

The authors of numerous reviews of emotional factors in the experience of pain [11, 25] advocate for consideration of these factors in pain treatment, even targeting emotions specifically. We have attempted to further explicate that emotion and pain processing share common anatomical bases that can and often do affect one another. Given the bidirectional influence between emotion and pain, it should come as no surprise that the few treatments that have targeted both aspects (by combining pharmacological and behavioral approaches) with patients experiencing varied forms of recurrent headache, found a multiplicative effect on pain outcomes [39, 40]. Evidence is mounting that behavioral therapies are influencing functional and structural changes in the brain; changes that may be beneficial in combatting deficits that may be inherent in a multitude of chronic pain conditions, including headache and migraine. How best to implement and integrate emotional factors into the treatment of headache and pain remains fertile ground for further study. We urge researchers to embrace the clarion call to include a greater focus on understanding neuroanatomical changes as a function of behavioral therapy when intervening with patients experiencing chronic headache and pain.

Compliance with ethical standards

Conflict of interest The authors of this article certify that there is no actual or potential conflict of interest in relation to this article.

Ethical standards This article does not contain any study with human subjects performed by any of the authors.

References

1. IASP Task Force on Taxonomy (1994) Part III: pain terms, a current list with definitions and notes on usage. In: Merskey H, Bruyn GW (eds) Classification of chronic pain, 2nd edn. IASP Press, Seattle, pp 209–214
2. Williams AC, Craig KD (2016) Updating the definition of pain. Pain 157(11):2420–2423
3. Bussone G, Grazzi L, Panerai AE (2012) Pain, emotion, headache. Headache 52(S2):98–101
4. Bussone G, Grazzi L (2013) Understanding the relationship between pain and emotion in idiopathic headaches. Neurol Sci 34(S1):S29–S31
5. Melzack R, Casey KL (1968) Sensory, motivational and central control determinants of pain: a new conceptual model. In: Kenshalo DR (ed) The skin senses. Thomas, Springfield, pp 423–443
6. Sturgeon JA (2014) Psychological therapies for the management of chronic pain. Psychol Res Behav Manag 7:115–124
7. Jensen MP, Turk DC (2014) Contributions of psychology to the understanding of treatment of people with chronic pain: why it matters to all psychologists. Am Psychol 69(2):105–118
8. Flor H (2014) Psychological pain interventions and neurophysiology: implications for a mechanism-based approach. Am Psychol 69(2):188–196
9. Price DD (2000) Psychological and neural mechanisms of the affective dimension of pain. Science 288(5472):1769–1772
10. Elman I, Zubieta J-K, Borsook D (2012) The missing "p" in psychiatric training: why is it important to teach pain to psychiatrists? Arch Gen Psychiatry 68(1):12–20
11. Lumley MA, Cohen JL, Borszcz GS, Cano A, Radcliffe AM, Porter LS, Schubiner H, Keefe FJ (2011) Pain and emotion: a biopsychosocial review of recent research. J Clin Psychol 67(9):942–968
12. Simons L, Elman I, Borsook D (2014) Psychological processing in chronic pain: a neural systems approach. Neurosci Biobehav Rev 39:61–78
13. MacDonald G, Leary MR (2005) Why does social exclusion hurt? The relationship between social and physical pain. Psychol Bull 131(2):202–223
14. Eisenberger NI (2012) The neural bases of social pain: evidence for shared representations with physical pain. Psychosom Med 74(2):126–135
15. Antonaci F, Nappi G, Galli F, Manzoni GC, Calabresi P, Costa A (2011) Migraine and psychiatric comorbidity: a review of clinical findings. J Headache Pain 12(2):115–125

16. Minen MT, Begasse De Dhaem O, Kroon Van Diest A, Powers S, Schwedt TJ, Lipton R, Silbersweig D (2016) Migraine and its psychiatric comorbidities. J Neurol Neurosurg Psychiatry 87(7):741–749
17. Bair MJ, Wu J, Damush TM, Sutherland JM, Kroenke K (2008) Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Pyschosom Med 70(8):890–897
18. Raphael KG, Widom CS (2011) Post-traumatic stress disorder moderates the relation between documented childhood victimization and pain 30 years later. Pain 152(1):163–169
19. Vogt BA, Sikes RW, Vogt LJ (1993) Anterior cingulate cortex and the medial pain system. In: Vogt BA, Gabriel M (eds) Neurobiology of cingulate cortex and limbic thalamus: a comprehensive handbook. Brikhäuser, Boston, pp 313–344
20. Craig AD (2003) A new view of pain as homeostatic emotion. Trends Neurosci 26(6):303–307
21. Peyron R, Laurent B, Garcia-Larrea L (2000) Functional imagining of brain responses to pain: a review and meta-analysis. Neurophysiol Clin 30(5):263–288
22. Cauda F, Torta DME, Sacco K, Geda E, D'Agata F, Costa T, Duca S, Geminiani G, Amanzio M (2012) Shared "core" areas between the pain and other task-related networks. PLoS One 7(8):e41929. doi:10.1371/journal.pone.0041929
23. Villemure C, Bushnell MC (2009) Mood influences supra-spinal pain processing separately from attention. J Neurosci 29(3):705–715
24. Stevens FL, Hurley RA, Taber KH (2011) Anterior cingulate cortex: unique role in cognition and emotion. J Neuropsychiatry Clin Neurosci 23(2):120–125
25. Bushnell MC, Čeko M, Low LA (2013) Cognitive and emotional control of pain and its disruption in chronic pain. Nature Rev Neurosci 14:502–511
26. DeWall CN, MacDonald G, Webster GD, Masten CL, Baumeister RF, Powell C, Combs D, Schurtz DR, Stillman TF, Tice DM, Eisenberger NI (2010) Acetaminophen reduces social pain: behavioral and neural evidence. Psychol Sci 21(7):931–937
27. Kulkarni B, Bentley DE, Elliot R, Julyan PJ, Boger E, Watson A, Boyle Y, El-Deredy W, Jones AK (2007) Arthritic pain is processed in brain areas concerned with emotions and fear. Arthritis Rheum 56(4):1345–1354
28. Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, Schnitzer TJ, Apkarian AV (2013) Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain 135(Pt 9):2751–2768
29. Bliss TV, Collingridge GL, Kaang BK, Zhuo M (2016) Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. Nature Rev Neurosci 17(8):485–496
30. Mathur VA, Moayedi M, Keaser ML, Khan SA, Hubbard CS, Goyal M, Seminowicz DA (2016) High frequency migraine is associated with lower acute pain sensitivity and abnormal insula activity related to migraine pain intensity, attack frequency, and pain catastrophizing. Front Hum Neurosci 10:489. doi:10.3389/fnhum.2016.00489
31. Andreatta M, Puschmann AK, Sommer C, Weyers P, Pauli P, Mühlberger A (2012) Altered processing of emotional stimuli in migraine: an event-related potential study. Cephalalgia 32(15):1101–1108
32. Seminowicz DA, Shpaner M, Keaser ML, Krauthamer GM, Mantegna J, Dumas JA, Newhouse PA, Filippi C, Keefe FJ, Naylor MR (2013) Cognitive behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. J Pain. doi:10.1016/j.pain.2013.07.020
33. Jin C, Yuan K, Zhao L, Yu D, von Deneen KM, Zhang M, Qin W, Sun W, Tian J (2012) Structural and functional abnormalities in migraine patients without aura. NMR Biomed 26(1):58–64
34. Jensen KB, Kosek E, Wicksell R, Kemani M, Olsson G, Merle JV, Kadetoff D, Ingvar M (2012) Cognitive behavioral therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgeia. Pain 153(7):1495–1503
35. Andrasik F, Grazzi L, D'Amico D et al (2016) Mindfulness and headache: a "new" old treatment, with new findings. Cephalalgia 36(12):1192–1205
36. Zeidan F, Martucci KT, Kraft RA, Gordon NS, McHaffie JG, Coghill RC (2011) Brain mechanisms supporting modulation of pain by mindfulness meditation. J Neurosci 31(14):5540–5548
37. Grant JA, Courtemanche J, Rainville P (2011) A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. Pain 152(1):150–156
38. Gard T, Hölzel BK, Sack AT et al (2012) Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain. Cereb Cortex 22(11):2692–2702
39. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW (2001) Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. JAMA 285(17):2208–2215
40. Holroyd KA, Cottrell CK, O'Donnell FJ, Cordingley GE, Drew JB, Carlson BW, Himawan L (2010) Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimized acute treatment in frequent migraine: randomised controlled trial. BMJ 341:c4871. doi:10.1136/bmj.c4871

Neurol Sci (2017) 38 (Suppl 1):S163–S167
DOI 10.1007/s10072-017-2883-z

Intravenous mannitol in status migrainosus treatment: a clinical case series

Roberto De Simone[1] · Angelo Ranieri[2] · Guido Ferra[1] · Federico Cautiero[1]

Abstract Status migrainosus (SM) is defined as a severe migraine attack, usually poorly responsive to treatments, lasting more than 72 h. Recurrent SM predicts chronic migraine (CM) development in 83.7% of cases. There is evidence that in most unresponsive CM patients a sinus stenosis-associated raised intracranial pressure is causatively involved in migraine chronification. To test the hypothesis that SM may reflect a sustained rise in intracranial pressure, we tested the efficacy of a 3-day treatment with intravenous mannitol 18% 250 ml b.i.d. in seven subjects presenting with a SM unresponsive to common treatments, showing unilateral or bilateral sinus stenosis at magnetic resonance venography. Mannitol infusion induced the abrupt reduction or the disappearance of pain in all patients, at least along the 3 days of treatment. While the benefit was only observed during the days of treatment in two subjects, in the remaining five patients the time to the next headache was delayed between 20 days to 5 weeks after mannitol infusion. Due to the lack of any analgesic property of mannitol, our data indicate that in this series a rise in intracranial pressure was involved in SM causative mechanisms.

Keywords Status migrainosus · Mannitol · Idiopathic intracranial hypertension · Chronic migraine · Sinus venous stenosis

✉ Roberto De Simone
rodesimo@unina.it

[1] Department of Neuroscience, Reproductive Sciences and Odontostomatology, Headache Centre, University of Naples "Federico II", Via Pansini 5, 80131 Naples, Italy

[2] Istituto di Diagnosi e Cura Hermitage Capodimonte, Naples, Italy

Background

Status migrainosus (SM) is a complication of migraine defined as a severe pain attack lasting more than 72 h [1]. The diagnostic criteria do not define the upper time limit for SM; however, a continuous pain lasting more than three months without remission matches the diagnostic criteria for New Daily Persistent Headache (NDPH) [1]. Therefore, the diagnostic boundaries of SM are migraine on the one hand and NDPH, migraine variant, on the other. The latter is a condition quite comparable to chronic migraine (CM) except for the sudden onset, clearly remembered by the patient, and for a daily course since the beginning, without remission [2]. SM is usually observed in patients with episodic forms of migraine, but it is not uncommon in patients with CM [3]. Recurrent SM has been recently found to predict CM in up to 87.3% of the cases in a retrospective series [4].

Intracranial sinus venous stenosis is a sensitive (93%) and specific (93%) predictor of intracranial hypertension [5]. Sinus stenosis has recently been included in IIH diagnostic criteria [6] among the neuroradiological signs that may support the diagnosis in cases without papilledema (IIHWOP). In CM patients, sinus stenosis is much more prevalent than expected (about 50% in clinical series of CM [7, 8] versus 23% of a large community of patients without signs and symptoms of intracranial hypertension [9]). In CM subjects with documented unresponsiveness to treatments, sinus stenosis has been found in more than 90% of cases, a prevalence close to that found in IIH [10]. Also based on a number of other observations, we have proposed that an intracranial hypertension without papilledema associated with venous stenosis, although quite common in subjects without sign and symptoms of intracranial hypertension, in migraine predisposed subjects may

represents a powerful risk factor for pain chronification [11]. This hypothesis has been subsequently supported by the finding [10] that the 77% of a series of consecutive patients with documented refractory CM and sinus stenosis reported the abrupt disappearance of chronic pain soon after a lumbar puncture with cerebrospinal fluid (CSF) withdrawal, maintained for a very variable length of time, ranging between a few days to several months.

Intravenous infusions of mannitol are promptly effective in reducing raised intracranial pressure (ICP) [12–14] with an effect observable within 20 min after its administration [14]. Mannitol acts as an osmotic agent, but the exact mechanism by which it lowers ICP is debated [15]. Studies on normal brain in animal models and on traumatic injured brain in humans have indicated that the reducing of brain water content [12, 13] and the reduction of CSF production rate [12] may account for the ICP reduction induced by mannitol. Mannitol infusion is generally well tolerated; however, high daily doses or excessive infusion speed is associated with relevant side effects, included hyponatremia and dehydration, congestive heart failure, pulmonary oedema and acute kidney injury [16].

Objective

To test the hypothesis that SM may reflect a sustained rise in ICP, we tested the efficacy of a short-lasting treatment with intravenous mannitol in subjects presenting with a SM refractory to common treatments, showing unilateral or bilateral sinus stenosis.

Study population

We have retrospectively recruited the study group among outpatients presenting with a SM referred to our Headache Centre between 2014 and 2016. Patients were consecutively included if:

- presented with an uninterrupted severe migrainous pain since more than 4 days,
- multiple acute treatments in the previous days had failed,
- the neurological examination was normal, and papilledema was excluded,
- a normal magnetic resonance (MR) of the brain and a MR venography (MRV) documenting significant unilateral or bilateral sinus stenosis were available,
- no history of any other relevant acute or chronic disease,
- the data of follow-up visit were available.

Study protocol and data collection

All patients underwent a 3-day treatment (in add-on if on prophylactic treatment) with an intravenous infusions of 250 ml of mannitol 18% (infusion speed 125 ml/h) every 12 h (6 infusions in total). All patients were asked to keep a diary of headache. Clinical data were reviewed and collected at the subsequent follow-up, after 2–4 months. The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and latest revisions (the latest in 2013). Patient informed consent to be included in the study has been obtained.

Case series

We found seven patients who met the criteria, five women and two men. Because of substantial heterogeneity of patients clinical histories, we will shortly summarize each case.

Case 1

Sixty-eight-year-old man, normal weight, arterial hypertension controlled with metoprolol 100 mg/die, migraine without aura (MWOA) since the age of 6 with attack frequency less than monthly in adult life. Status migrainosus since 4 weeks, no known precipitant factors, poorly or not responsive to ibuprofen 600 mg per os; naproxen 550 mg per os and intramuscular ketorolac 10 mg. The MR and MRV showed partial empty sella and left transverse sinus (TS) hypoplasia (Fig. 1, case 1). A complete efficacy was reported since the second day of mannitol infusion. Time to the next headache: 5 weeks. No adverse event or side effect was reported.

Case 2

Seventeen-year-old obese (BMI 30.12) woman. General good health. MWOA since the age of 12 (about 1 per month, not related to menses). Status migrainosus since 8 weeks, associated with an overlapping stabbing headache (12 days per month, 4–5 attacks per day). No known precipitant factors. Prophylactic treatment with topiramate 100 mg/die plus flunarizine 5 mg/die without appreciable effects after 45 days. Repeated acute treatments with common analgesics included rectal indomethacin 50 mg had failed. The MRV showed a right TS hypoplasia with proximal apparent flow gap (Fig. 1, case 2). The mannitol administration was followed, since the first infusion, by a 60% reduction of pain intensity, subjectively estimated. The incomplete benefit suddenly ceased at the 4th day, 24 h after the interruption of mannitol infusion. No adverse reaction or side effect was reported.

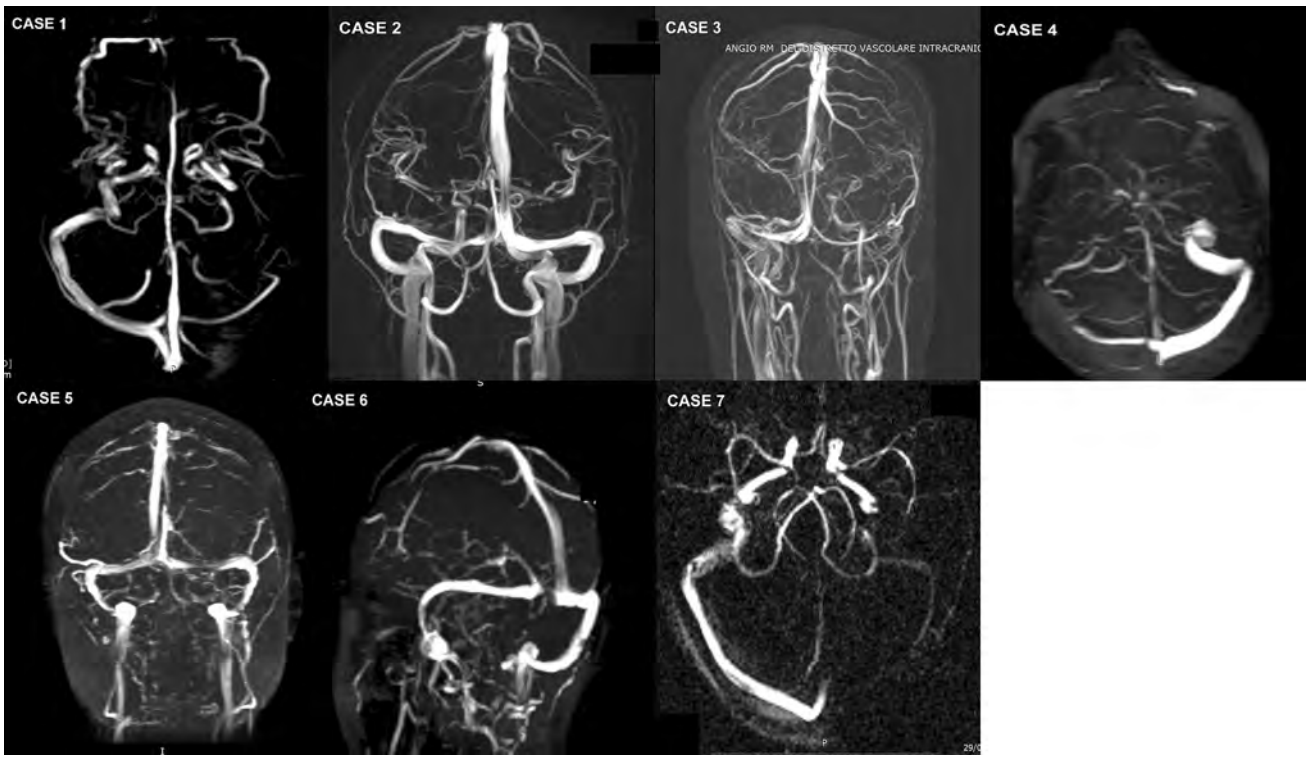

Fig. 1 Magnetic resonance venography of each clinical case showing unilateral or bilateral abnormalities of the dural sinuses

Case 3

Twenty-eight-year-old woman, normal weight, hypothyroidism (subclinic) treated with 25 μg of levothyroxine daily. MWOA since age of 16, about 1 attack per month, often menstrually related. Onset of migraine with aura (MWA) at age of 20 occurring less than 1 per month. She presented with a continuous severe migrainous pain (without aura) since 20 days. The MRV showed bilateral narrowing of TS with apparent bilateral flow gaps (Fig. 1, case 3). A prophylaxis with topiramate 100 mg/die and flunarizine 5 mg/die had no effects on continuous pain after 4 weeks. The 3-day infusion of mannitol was proposed as add-on therapy. The pain ameliorated during the first of the six infusions and completely stopped after the second one, within the first day of intravenous treatment. The pain remitted completely for about 4 weeks. Prophylaxis therapy was progressively stopped. At a 4-month follow-up, she reported 1–2 attacks per month, responsive to common analgesics. The patient reported no side effects and no adverse reaction to the treatment.

Case 4

Sixty-eight-year-old woman, normal weight, major depression in treatment with lamotrigine 100 mg/die; escitalopram 20 mg/die; clotiazepam 5 mg/die; arterial hypertension controlled with captopril 50 mg/die and amlodipine 5 mg/die. MWOA since the age of 13, MWA since the age of 58. At first observation, she complained about ten attacks per month of moderate to severe migraine pain of which 2–3 attacks per month with typical aura, associated with a subcontinuous tension-type headache. The patient was diagnosed with a typical aura with headache and CM. A MRV showed the aplasia of right TS (Fig. 1, case 4). A prophylactic treatment with topiramate 100 mg/die and propranolol 80 mg/die resulted in about 50% reduction of moderate or severe headache days without effects on subcontinuous mild pain. After 2 years of continuous prophylactic treatment, the patient requested a consultation for an uninterrupted severe migraine pain (without aura) since 20 days, poorly responsive to repeated oral ibuprofen 600 mg and intramuscular ketorolac 10 mg. A 3-day infusion of mannitol was proposed as add-on therapy. The patient experienced the sudden and complete disappearance of the pain since the first day of mannitol infusion. The benefit lasted for about 20 days before the relapse of the daily severe pain. Subsequently, the patient reported that she had self-prescribed the repetition of the mannitol infusion at SM recurrence, every 1–2 months, reporting each time a new extended benefit. She did not reported any adverse event or side effect after the mannitol infusions.

Case 5

34 year-old woman, normal weight and general good health. MWOA since age of 11. A fluctuating migraine frequency ranging 1–5 attacks per month, prolonged up to 2 days and poorly responsive to symptomatics was reported at first visit, while she was 29. The headache significantly improved with topiramate 200 mg/die. The patient was then lost to follow-up but after 4 years she asked a new consultation for a sudden worsening of her headache, despite the prosecution of topiramate treatment at the same doses. At presentation, she complained the sudden onset of a continuous and severe migraine pain, with nighttime worsening, since 12 days. The MRV showed the proximal narrowing of left TS, with apparent bilateral flow gaps (Fig. 1, case 5). A 3-day infusion of mannitol was proposed as add-on therapy. The pain completely ceased already during the first day of mannitol infusions. The patient reported no further recurrence of headache for about 3 weeks, and then the pain returned to the previous episodic pattern. After about 1 year, a new SM occurred. The repetition of the 3-day mannitol infusion replicated the identical abrupt disappearance of the pain, starting at the end of the first mannitol administration. Similarly to the previous experience, the benefit was maintained for about 2 weeks and was followed by the return to the previous episodic headache pattern. The patient reported no side effects and no adverse reaction.

Case 6

This patient is the son of RDS. Fifteen-year-old man, normal weight, general good health, pubertal timing. MWOA since the age of 6, presenting with infrequent (less than monthly) short-lasting (15–60 min) attacks of severe unilateral migraine pain. He had also experienced 1–2 episodes per month of short-lasting abdominal migraine until the age of 10. In the previous 2 years, headache attacks had become longer (several hours up to half day) and occurring with a frequency of 1–3 per month. In coincidence with a flu (presenting with cold, cough and a minor hyperthermia), he developed a migraine attack, identical to others but poorly controlled by repeated oral ketoprofen 80 mg per os. In the six subsequent days, the throbbing pain becomes holocranic and continuous, with intense vegetative symptoms, fatigue, and periodic excruciating exacerbations of the pain, mainly in the recumbent position. To lie in bed also triggered an ejective and repeated vomiting, not always accompanied by a nausea of a comparable degree. Besides oral ketoprofen, the condition resulted poorly responsive to: repeated oral doses of sodic naproxen 550 mg; indomethacin suppositories 50 mg, and to dexamethasone 4 mg intramuscularly, repeated after 8 h.

At the sixth day, the patient was admitted to a paediatric clinic and performed an MR of the brain with angiographic MR of intracranial vessels. The MRV showed a moderate, diffuse narrowing of dural sinuses, more relevant at the junction of the right sigmoid sinus with the jugular bulb, and an almost complete separation of the transverse sinuses at the torcular level (Fig. 1, case 6). The brain MR also showed a partial empty sella and a mild enlargement of optical nerves calibre. The mannitol infusion was started at the end of the seventh days of continuous severe SM. The patient was not able to sleep since several days but fell asleep 30 min after the first infusion, because of the sudden amelioration of pain and of related vegetative symptoms. He waked up, after a quite nighttime sleep, completely pain free. The 3-day infusion cycle was completed, as scheduled. The time to the next head pain was about 5 weeks. Subsequently, his habitual frequency pattern of 1–3 attacks per month returned. No side effect and no adverse reaction were reported.

Case 7

Forty-seven-year-old woman, normal weight. Homozygous for C677T polymorphism of MTHFR with normal homocysteine. MWOA onset at 16, with monthly attacks of severe pain of less than 24 h of duration. At the age of 39, she started to experience recurrent "episodic status migrainosus" (a condition highly predictive of CM development in a recent series [4]) of about 3–4 weeks of duration, with intervals of up to 2 years. SM onsets and remissions were apparently spontaneous. Duration of recurrent SM increased over time up to about 8 weeks. These events did not modified the usual low monthly frequency of migraine without aura attacks. The patient presented in the late 2016 for the recurrence of a SM. A MRV showed the severe hypoplasia of the left TS (Fig. 1, case 7). She accepted to undergo a 3-day cycle of intravenous mannitol as first therapeutic attempt. The headache reduced significantly in the course of any single mannitol infusion, but she was not pain free between the administrations because of a mild tight pressing holocranic pain associated with occasional stabbing headache. Unfortunately, the pain returned with the same severity at the end of the 3-day mannitol cycle. No adverse reaction or side effect was reported. The patient was shifted to standard prophylactic treatments.

Discussion

In this series, a 3 days of intravenous 250 ml mannitol 18% b.i.d. at 125 ml/h infusion speed were very well tolerated in all subjects. Mannitol infusion induced the abrupt reduction

or disappearance of the pain in all patients, at least along the 3 days of treatment. While the benefit was only observed during the days of treatment in two subjects, in the remaining five patients the time to the next headache was delayed between 20 days to 5 weeks after mannitol infusion. Moreover, the replication of a new long-lasting benefit was observed in both the cases in which the treatment was repeated. Because of the lack of any intrinsic analgesic properties of mannitol, our data indicate that SM was sustained by an intracranial pressure increase in all the patients of this series.

The sudden onset of pain in SM and its abrupt remission after mannitol, maintained, in most cases, much longer than expected, fully complies with the newly proposed pathogenetic model of IIH based on a causative role of sinus stenosis [17, 18]. According to the model, the excessive collapsibility of one or more segments of dural sinus, especially when combined with the anatomical restriction of total dural sinus cross section, allows the existence of a second possible balance point between ICP and sinus venous pressures, at higher values. The new balance state is the consequence of a *self-limiting collapse* (SVC) feedback loop [17] between intracranial pressure that compress the excessively compliant sinus, and the rise of sinus venous pressure that increase the intracranial pressure. This loop leads to the coupled ascent of the ICP and dural venous pressure, and a phenomena not expected in the presence of adequately rigid and normally sized dural sinuses [18]. Once the abnormal venous compliance is exhausted, the loop stabilizes and a new balance state is maintained, at higher pressure values. The new high-pressure balance state is self-sustained, but it may revert under adequate perturbations [17]. It is possible that mannitol infusion that reduce the CSF production rate in experimental models up to 49% [12] may breaks the SVC feedback loop leading, at least in some patients, to the sustained restoration of a normal balance state between intracranial pressure and sinus venous pressure. We propose that this mechanism may be involved in SM pathophysiology. A randomized controlled trial confirming the efficacy of mannitol infusion in status migrainosus is required before such a treatment could be translated into clinical practice. Further studies aimed to clarify the role of raised intracranial pressure in SM mechanisms are urgently needed.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Headache Classification Committee of the International Headache Society (2013) The International Classification of Headache Disorders, 3rd Edition (beta version). Cephalalgia 33(9):629–808
2. Nierenburg H, Newman LC (2016) Update on new daily persistent headache. Curr Treat Options Neurol 18(6):25
3. Modi SY, Dharaiya D, Katramados AM et al (2016) Predictors of prolonged hospital stay in status migrainosus. Neurohospitalist 6(4):141–146
4. Singh TD, Cutrer FM, Smith JH (2017) Episodic status migrainosus: a novel migraine subtype. Cephalalgia. doi:10.1177/0333102416686341
5. Farb RI, Vanek I, Scott JN et al (2003) Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. Neurology 60:1418–1424
6. Friedman DI, Liu GT, Digre KB (2013) Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology 81(13):1159–1165
7. Fofi L, Giugni E, Vadala R et al (2012) Cerebral transverse sinus morphology as detected by MR venography in patients with chronic migraine. Headache 52(8):1254–1261
8. Bono F, Salvino D, Tallarico T et al (2010) Abnormal pressure waves in headache sufferers with bilateral transverse sinus stenosis. Cephalalgia 30(12):1419–1425
9. Bono F, Cristiano D, Mastrandrea C et al (2010) The upper limit of normal CSF opening pressure is related to bilateral transverse sinus stenosis in headache sufferers. Cephalalgia 30:145–151
10. De Simone R, Ranieri A, Montella S et al (2014) Intracranial pressure in unresponsive chronic migraine. J Neurol 261(7):1365–1373
11. De Simone R, Ranieri A, Cardillo G et al (2011) High prevalence of bilateral transverse sinus stenosis-associated IIHWOP in unresponsive chronic headache sufferers: pathogenetic implications in primary headache progression. Cephalalgia 31(6):763–765
12. Donato T, Shapira Y, Artu A et al (1994) Effect of mannitol on cerebrospinal fluid dynamics and brain tissue edema. Anesth Analg 78(1):58–66
13. Albright AL, Latchaw RE (1985) Effects of osmotic and oncodiuretic therapy on CT-brain density and intracranial pressure. Acta Neurochir (Wien) 78(3–4):119–122
14. Mendelow AD, Teasdale GM, Russell T et al (1985) Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury. J Neurosurg 63(1):43–48
15. Tang SC, Lin RJ, Shieh JS et al (2015) Effect of mannitol on cerebrovascular pressure reactivity in patients with intracranial hypertension. J Formos Med Assoc 114(9):842–848
16. Lin SY, Tang SC, Tsai LK et al (2015) Incidence and risk factors for acute kidney injury following mannitol infusion in patients with acute stroke: a retrospective cohort study. Medicine (Baltimore) 94(47):e2032
17. De Simone R, Ranieri A, Montella S et al (2014) The role of dural sinus stenosis in idiopathic intracranial hypertension pathogenesis: the self-limiting venous collapse feedback-loop model. Panminerva Med 56(3):201–209
18. De Simone R, Ranieri A, Bonavita V (2017) Starling resistors, autoregulation of cerebral perfusion and the pathogenesis of idiopathic intracranial hypertension. Panminerva Med 59(1):76–89

Neurol Sci (2017) 38 (Suppl 1):S169–S171
DOI 10.1007/s10072-017-2894-9

BRIEF COMMUNICATION

Clinical and psychosocial features of frequent relapsers (FR) among patients with chronic migraine and medication overuse

Alberto Raggi[1] · Licia Grazzi[2] · Roberta Ayadi[1] · Matilde Leonardi[1] · Alberto Proietti[2] · Silvia Schiavolin[1] · Chiara Scaratti[1] · Susanna Usai[2] · Domenico D'Amico[2]

Abstract The objective was to characterize frequent relapsers (FR)—i.e. those requiring two or more withdrawals in a 3-year period—in a sample of 188 patients with chronic migraine with medication overuse (CM-MO). We tested differences between FR and non-FR for age, gender, employment status, days with headache, headache severity, type of overused medication, BDI-II, WHODAS 2.0 and MSQ. 30.8% of participants were FR: they were more frequently treated as inpatients and living alone, had a lower education, higher disability and lower QoL, higher frequency and intensity of headaches, and higher depression scores. Clinicians should address whether CM-MO patients submitted to withdrawal had recently underwent other similar interventions.

Keywords Chronic migraine · Medication overuse · Disability evaluation · Withdrawal · Relapse rate

Introduction

Approximately 14% of migraineurs in clinical samples progress to chronic migraine with medication overuse (CM-MO), a negative evolution of migraine course characterized by >45 headache days/3 months and by the overuse of symptomatic medications, which is a driver for chronification itself [1, 2]. Treatment for CM-MO requires withdrawal of overused drugs, prescription of prophylaxis, and education to prevent relapses, and is successful when at one year headaches frequency is reduced by 50% or more [3]. However, some patients seem to be more prone to relapse into CM-MO than others, and 12-month relapse rates peak up to 41% [4–7]. Despite this common phenomenon, there is no literature highlighting the features of these "frequent relapsers" (FR), i.e. those requiring two or more structured withdrawals within three years.

The objective of this study is, therefore, to characterize FR patients in terms of disease features and associated mood problems.

Methods

Patients herein included were adults with CM-MO that participated to DIS.CHRONIC study [8], and for whom information on previous withdrawals was available. They were volunteers and signed an informed consent form prior to data collection.

The research protocol comprised the Migraine-Specific Quality of Life Questionnaire (MSQ) [9], the WHO-Disability Assessment Schedule (WHODAS 2.0) [10], the Beck Depression Inventory (BDI-II) [11], headache frequency in the past three months and average pain intensity defined on a 0–10 scale. The type of MO was defined as overuse of triptans, alone or with other medications vs. overuse of other drugs (i.e. non-triptans).

Baseline differences between FR and non-FR was tested with Chi-Squared test for treatment setting (DH vs. ward), gender, employment status (employed/student vs. not employed), education (secondary or less

✉ Alberto Raggi
alberto.raggi@istituto-besta.it

[1] Neurology, Public Health and Disability Unit, Neurological Institute "C. Besta" IRCCS Foundation, Via Celoria 11, 20133 Milan, Italy

[2] Headache and Neuroalgology Unit, Neurological Institute "C. Besta" IRCCS Foundation, Milan, Italy

vs. high or academic), living situation (alone vs. with others), and type of overused medication, and with Student's t test for age, headache frequency and pain intensity, BDI-II, WHODAS 2.0, MSQ. Significance was set at $P < 0.05$.

Results

The analyses were based on 188 patients: of them, 58 (30.8%) were FR. Table 1 reports differences between FR and non-FR patients. FR patients were more often treated as inpatients (+18%), they were living alone (+12%), had lower education (+17%), higher headaches frequency (+16%) and pain intensity (+8%), lower MSQ (−24%), higher WHODAS 2.0 (+20%) and BDI-II scores (+27%).

Discussion

Our results show that FR patients generally had a worse clinical and psychosocial situation: compared to non-FR, they were more frequently treated as inpatients, living alone, had lower education, higher disability and lower QoL, higher frequency and intensity of headaches, and higher depression scores.

We did not find any difference connected to the kind of overused medication, which is in line with the inconsistency of literature findings. In fact, two prospective studies showed some protective effect of triptans compared to NSAIDs [6, 7], while other reports showed that the use of triptans is associated to an increased risk of chronification among high frequency episodic migraineurs, while NSAIDs seem to be protective in low-frequency migraine sufferers [12, 13].

Table 1 Baseline features of FR compared to non-FR patients

Categorical variables	Non-FR ($N = 130$) (%)	FR ($N = 58$) (%)	χ^2
Treatment setting			5.3 ($P = 0.021$)
Inpatient ($N = 93$)	43.8	62.1	
DH ($N = 95$)	56.2	37.9	
Gender			0.01 ($P = 0.940$)
Males ($N = 33$)	17.7	17.2	
Females ($N = 155$)	82.3	82.8	
Employment status			0.3 ($P = 0.610$)
Employed/students ($N = 138$)	72.3	75.9	
Unemployed ($N = 50$)	27.7	24.1	
Education			4.9 ($P = 0.027$)
Up to secondary ($N = 75$)	34.6	51.7	
High or academic ($N = 113$)	65.4	48.3	
Living situation			5.2 ($P = 0.023$)
Living alone ($N = 26$)	10.0	22.4	
Living with others ($N = 162$)	90.0	77.6	
Overuse of			0.9 ($P = 0.764$)
Triptans ($N = 110$)	59.2	56.9	
NSAIDs or other ($N = 78$)	40.8	43.1	

Continuous variables	Non-FR ($N = 130$)	FR ($N = 58$)	t test
Age	43.4 (41.2–45.6)	45.8 (43.2–48.4)	1.37 ($P = 0.173$)
Days with headache	55.1 (51.5–58.7)	63.9 (57.9–69.9)	2.61 ($P = 0.010$)
Headache intensity	7.5 (7.3–7.7)	8.1 (7.7–8.5)	2.75 ($P = 0.006$)
BDI-II	15.3 (13.8–16.8)	19.4 (16.6–22.3)	2.82 ($P = 0.005$)
WHODAS 2.0	29.1 (26.7–31.5)	34.8 (31.6–37.9)	2.86 ($P = 0.005$)
MSQ-RR	35.1 (32.1–38.1)	26.9 (22.8–31.0)	3.09 ($P = 0.002$)
MSQ-RP	51.4 (47.8–55.1)	39.1 (33.1–45.0)	3.63 ($P < 0.001$)
MSQ-EF	46.0 (41.8–50.2)	35.1 (28.5–41.8)	2.82 ($P = 0.005$)

FR frequent relapser, *DH* day-hospital, *NSAIDs* nonsteroidal anti-inflammatory drugs, *BDI-II* Beck Depression Inventory, 2nd version, *WHODAS 2.0* WHO Disability Assessment Schedule, 2nd version, *MSQ* Migraine-Specific Quality of Life Instrument, *MSQ-RR* MSQ role restriction, *MSQ-RP* MSQ role prevention, *MSQ-EF* MSQ emotional functioning

The issue of headaches frequency and intensity among FR patients deserves a comment. There are in fact studies showing a modification of the pain network connected to MO [14, 15] and others suggesting that an altered metabolism of tyrosine plays a role in the transformation of episodic migraine without aura into CM-MO [16]: as tyrosine modulates the function of pain matrix serotoninergic system, the authors concluded that this might affect modulation of incoming nociceptive inputs. It would be of interest to evaluate whether there are difference in pain networks, through neuroimaging and tyrosine metabolism studies, between FR and those patients in which MO is "occasional": this would further on add elements on CM-MO pathogenesis and could support the development of new treatment options. It has to be acknowledged that in our study FR patients were mostly treated as inpatients, a setting where generally patients with higher headaches frequency and severity are treated [17]: it is, therefore, likely to suppose that both the history of recent withdrawals and the higher disease severity have an impact on disability and QoL profiles.

The main limitation of this study is connected to sample representativeness: all patients had MO very high headache frequency and considerable mood impairment. Therefore, the ratio of FR compared to the whole group of headache sufferers may be influenced by the fact that patients with higher complexity are more likely attended to specialty centres.

In conclusion, compared to "occasional" medication overusers, FR patients had a worse clinical and psychosocial profile. Being a FR patient exposes to the risk of falling again into MO and thus to being in need of other structured withdrawals [18]. Clinicians should be aware of the utility of assessing whether CM-MO patients submitted to withdrawal recently underwent similar procedures: their specific psychosocial and clinical features should be assessed in planning post-withdrawal clinical follow-up.

Acknowledgements This paper is based on the results of DIS.-CHRONIC Project, sponsored by the Neurological Institute C. Besta IRCCS Foundation.

Compliance with ethical standards

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Bigal ME, Lipton RB (2011) Migraine chronification. Curr Neurol Neurosci Rep 11:139–148
2. Natoli JL, Manack A, Dean B et al (2010) Global prevalence of chronic migraine: a systematic review. Cephalalgia 30:599–609
3. Evers S, Jensen R (2011) Treatment of medication overuse headache–guideline of the EFNS headache panel. Eur J Neurol 18:1115–1121
4. Rossi P, Faroni JV, Nappi G (2008) Medication overuse headache: predictors and rates of relapse in migraine patients with low medical needs. A 1-year prospective study. Cephalalgia 28:1196–1200
5. Biagianti B, Grazzi L, Usai S et al (2014) Dependency-like behaviors and pain coping styles in subjects with chronic migraine and medication overuse: results from a 1-year follow-up study. BMC Neurol 14:181
6. Katsarava Z, Limmroth V, Finke M et al (2003) Rates and predictors for relapse in medication overuse headache: a 1-year prospective study. Neurology 60:1682–1683
7. 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
8. D'Amico D, Grazzi L, Bussone G et al (2015) Are depressive symptomatology, self-efficacy, and perceived social support related to disability and quality of life in patients with chronic migraine associated to medication overuse? Data from a cross-sectional study. Headache 55:636–645
9. Raggi A, Giovannetti AM, Schiavolin S et al (2014) Validating the Migraine-Specific Quality of Life Questionnaire v2.1 (MSQ) in Italian Inpatients with Chronic Migraine with a history of Medication Overuse. Qual Life Res 23:1273–1277
10. Federici S, Bracalenti M, Meloni F et al (2016) World Health Organization disability assessment schedule 2.0: an international systematic review. Disabil Rehabil. doi:10.1080/09638288.2016.1223177
11. Beck AT, Steer RA, Brown GK (1996) Beck depression inventory manual, 2nd edn. The Psychological Corporation, San Antonio
12. Bigal ME, Lipton RB (2009) Overuse of acute migraine medications and migraine chronification. Curr Pain Headache Rep 13:301–307
13. Starling AJ, Hoffman-Snyder C, Halker RB et al (2011) Risk of development of medication overuse headache with nonsteroidal anti-inflammatory drug therapy for migraine: a critically appraised topic. Neurologist 17:297–299
14. Grazzi L, Chiapparini L, Ferraro S et al (2010) Chronic migraine with medication overuse pre-post withdrawal of symptomatic medication: clinical results and FMRI correlations. Headache 50:998–1004
15. Ferraro S, Grazzi L, Mandelli ML et al (2012) Pain processing in medication overuse headache: a functional magnetic resonance imaging (fMRI) study. Pain Med 13:255–262
16. D'Andrea G, Cevoli S, Colavito D et al (2015) Biochemistry of primary headaches: role of tyrosine and tryptophan metabolism. Neurol Sci 36:S17–S22
17. Raggi A, Schiavolin S, Leonardi M et al (2015) Approaches to treatments of chronic migraine associated with medication overuse: a comparison between different intensity regimens. Neurol Sci 36:S5–S8
18. Raggi A, Giovannetti AM, Leonardi M et al (2017) Predictors of 12-months relapse after withdrawal treatment in hospitalized patients with chronic migraine associated with medication overuse: a longitudinal observational study. Headache 57:60–70

Neurol Sci (2017) 38 (Suppl 1):S173–S175
DOI 10.1007/s10072-017-2874-0

BRIEF COMMUNICATION

Mindfulness and pharmacological prophylaxis have comparable effect on biomarkers of inflammation and clinical indexes in chronic migraine with medication overuse: results at 12 months after withdrawal

Licia Grazzi[1] · Domenico D'Amico[1] · Alberto Raggi[2] · Matilde Leonardi[2] · Emilio Ciusani[3] · Elena Corsini[3] · Giovanni D'Andrea[4] · Andrea Bolner[4] · Francisco Salgado-García[5] · Frank Andrasik[5] · Emanuela Sansone[1]

Abstract Chronic migraine (CM) is a disabling condition arising from a complex mixture of interconnected biological, psychological and social factors, and is often associated with medication overuse (MO). Mindfulness is emerging as a helpful treatment for pain, and one study showed that the longitudinal 12 months' course of CM-MO patients that attended mindfulness-based treatment alone was similar to that of patients receiving medical prophylaxis alone; in this study, we describe the course of biomarkers of inflammation. Our results provide initial evidence of sustained similar effects on reduced concentration of biomarkers of inflammation, although not sizeable enough to reach statistical significance. Whether more intensive treatment and/or larger samples would lead to greater changes is unknown, but these encouraging preliminary findings suggest further research is warranted.

Keywords Chronic migraine · Medication overuse · Mindfulness · Biomarkers · Interleukin-6

✉ Licia Grazzi
licia.grazzi@istituto-besta.it

[1] Headache and Neuroalgology Unit, Neurological Institute "C. Besta" IRCCS Foundation, Via Celoria 11, 20133 Milan, Italy

[2] Neurology, Public Health and Disability Unit, Neurological Institute "C. Besta" IRCCS Foundation, Milan, Italy

[3] Laboratory of Clinical Pathology and Medical Genetic, Neurological Institute "C. Besta" IRCCS Foundation, Milan, Italy

[4] Research & Innovation (R&I), Padua, Italy

[5] Department of Psychology, University of Memphis, Memphis, TN, USA

Introduction

Headache disorders are common disabling conditions that, in the last Global Burden of Disease study, have been rated as the sixth cause of disability [1]. Chronic migraine (CM) is a negative evolution of episodic migraine: it has a prevalence of approximately 2 and 2.5% of episodic migraineurs progress to CM each year [2]. CM is diagnosed when headache episodes occur more than 15 days/month for more than 3 months [3], and is frequently associated with overuse of acute medications. Medication overuse (MO) is one of the factors contributing to migraine chronification [4] and it further complicates CM making it particularly difficult to manage. Patients with CM-MO present therapeutic challenges and require multidisciplinary care, including pharmacological and non-pharmacological therapeutic approaches [5]. The medication withdrawal is a "reset" that gives patients a greater likelihood of positively responding to appropriate prophylaxis, and is most helpful when it is accompanied by support and education about proper use of medications [6, 7].

Among the wide array of available non-pharmacological treatments, mindfulness has been recently included in rehabilitation programs for chronic pain conditions [8, 9], and researchers in the field of headache started to turn their attention to mindfulness training as viable approach for supplementing patient care. Literature findings suggest that various mindfulness-based approaches may be helpful for headache sufferers [10], and one study showed that patients that attended mindfulness-based treatment, and not receiving medical prophylaxis, underwent a clinical improvement that was comparable to that of patients receiving medical prophylaxis [11]. The mechanism behind is not completely explored yet and, in particular, we are not aware of any study pointing at the biological aspects that

might be associated to the changes in headaches frequency, with specific reference to the inflammatory hypothesis beyond migraine pathogenesis [12, 13].

The aim of this paper is to complement the information on the clinical course with that on the trend of biomarkers of inflammation in patients with CM-MO submitted to withdrawal treatment, with the hypothesis that mindfulness-based approach would be similar in effectiveness when compared to conventional prophylactic treatment not only for reducing headache frequency and medication intake, but also for improving the pattern of hematological biomarkers.

Methods

Here we reported a secondary analysis on the course of CM-MO patients that participated to a study on the course of headache and that compared patients that receive "medication alone" or "mindfulness training alone" (Med-Group or MT-Group) [11]. Briefly, 44 patients with CM-MO according to the ICHD-3-beta [3], aged 18–65 years and with had a history of CM lasting for at least ten years, associated with overuse of Triptans and/or non-steroidal anti-inflammatory drugs (NSAIDs) for a minimum of the past five years were included. They underwent structured withdrawal [14] and then were followed up for 12 months. Patients participating in the Med-Group received only prophylactic medications. Patients included in the MT-group, participated to six mindfulness training sessions on a weekly basis and were instructed to self-practice every day for 7–10 min, as previously reported [11].

Here we reported the follow-up at 12 months for headache frequency and medication intake, as well as for the following biomarkers of inflammation: white blood cell (WBC) count, interleukin-6 (IL-6), neutrophils and lymphocyte subsets CD3, CD4, CD8, CD19. We tested between-group baseline differences using Mann–Whitney U test, and tested within-group longitudinal differences using Wilcoxon's paired sample test. Significance was set at $P < 0.05$ level.

Results

Twenty patients in the MT-Group and 19 in the Med-Group completed the 12-month follow-up assessment.

Table 1 reports the average decrease between baseline and follow-up for each variable. Patients were comparable at baseline for all variables with the exclusion of IL-6, that was significantly higher among those in the MT-Group. Besides the known and significant improvement in headaches frequency and medications intake, our analysis show an overall decrease in all biomarkers, that in most cases were not significant. Significant changes were observed for IL-6 and neutrophils among patients in the MT-Group, and for CD4 lymphocyte subset among patients in the Med-Group.

Discussion

Our preliminary data show that the degree of 12 months' improvement herein observed among patients receiving mindfulness-based intervention is basically comparable to that of patients receiving medical prophylaxis with regard to headache frequency, medication intake and selected biomarkers of inflammation.

Mindfulness is designed to promote the ability to focus on present situations and accept the difficulties of every day. As demonstrated by Kabat-Zinn [15], patients who have been educated to use mindfulness may manage stressful situations, increase their self-efficacy, and learn to manage pain more adequately. The result is that they avoid the compulsion between pain and medication intake which easily sets in motion the vicious cycle leading to medication overuse. Our findings are encouraging and complement the hypothesis of the independent value of mindfulness for headache care that we already pointed out [11]. Although some improvements occurred with respect to hematological parameters, they were not sizeable enough to reach statistical significance for most parameters. It is interesting to note that IL-6—which is deemed to play a significant role in the regulation of pain threshold, trigeminal nerve fiber sensitization and to facilitate pain signaling during the development of migraine headaches [16–18]—underwent a marked reduction among patients in the MT-Group: it has however to be noted that, for unknown reasons, the baseline concentration was significantly higher among these patients.

Limitations to this study include the relatively small sample size, the absence of randomization and the lack of blinding. Our results have to be taken as preliminary and a cautious interpretation is suggested.

In conclusion we report initial evidence on the benefit of mindfulness-based treatment compared to standard pharmacological prophylaxis: the longitudinal course of patients in the two conditions was similar not only for main clinical outcomes, but also for the concentration of biomarkers of inflammation.

Compliance with ethical standards

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

Table 1 Longitudinal course of headache frequency, medication intake and concentration of biomarkers

	MT-group			Med-group		
	Baseline	12 Months	% Decrease (%)	Baseline	12 Months	% Decrease (%)
Headache frequency	18.5 ± 7.2	12.4 ± 8.5	33[b]	18.5 ± 7.2	10.4 ± 7.2	43.8[b]
Medication intake	17.7 ± 5.9	10.3 ± 5.4	26.6 [b]	15.4 ± 4.4	8.6 ± 4.8	44.2[b]
WBC	7037 ± 2316	6082 ± 1971	13.6	7549 ± 2542	6282 ± 1298	16.8
IL-6[a]	2.52 ± 4.14	0.70 ± 2.00	72[b]	0.75 ± 1.91	0.50 ± 1.16	33.3
Neutrophils	4809 ± 2011	3759 ± 1668	21.8[b]	4792 ± 1953	3757 ± 1121	21.6
Lymphocytes	1901 ± 731	1711 ± 451	10	2137 ± 680	1894 ± 490	11.4
CD3	1474 ± 668	1291 ± 363	12.4	1680 ± 545	1443 ± 417	14.1
CD4	830 ± 528	722 ± 284	13	1133 ± 419	896 ± 291	20.9[b]
CD8	556 ± 220	499 ± 166	10.2	580 ± 228	532 ± 148	8.3
CD19	194 ± 71	175 ± 56	9.8	242 ± 109	197 ± 102	18.6

[a] $P < 0.05$ for between-group comparison (Mann–Whitney U test)

[b] $P < 0.05$ in longitudinal analysis (Wilcoxon's paired test)

Ethical standards The studies have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and latest revisions (the latest in 2013). Patient informed consent to be included in the study has been obtained.

References

1. Global Burden of Disease Study 2013 Collaborators (2015) (2013) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386:743–800
2. Manack AN, Buse DC, Lipton RB (2011) Chronic migraine: epidemiology and disease burden. Curr Pain Headache Rep 15:70–78
3. Headache Classification Committee of the International Headache Society (2013) The International Classification of Headache Disorders, 3rd edn (beta version). Cephalalgia 33:629–808
4. Bigal M (2009) Migraine chronification-concept and risk factors. Discov Med 8:145–150
5. Andrasik F, Grazzi L, Usai S et al (2009) Non-pharmacological approaches to treating chronic migraine with medication overuse. Neurol Sci 30:89–99
6. Grazzi L, Andrasik F, Usai S et al (2009) Treatment of chronic migraine with medication overuse. Is drug withdrawal crucial? Neurol Sci 30:S85–S88
7. Candy R, Farmer K, Beach ME et al (2008) Nurse-based education: an office-based comparative model for education of migraine patients. Headache 48:564–569
8. Rosenzweig S, Greeson JM, Reibel DK et al (2010) Mindfulness based stress reduction for chronic pain condition: variation in treatment outcomes and role of home meditation practice. J Psychosom Res 68:29–36
9. Castelnuovo G, Giusti EM, Manzoni GM, et al (2016) Psychological considerations in the assessment and treatment of pain in neurorehabilitation and psychological factors predictive of therapeutic response: evidence and recommendations from the Italian consensus conference on pain in neurorehabilitation. Front Psychol 7:468
10. Wells RE, Burch R, Paulsen RH et al (2014) Meditation for migraines: a pilot randomized controlled trial. Headache 54:1484–1495
11. Grazzi L, Sansone E, Raggi A et al (2017) Mindfulness and pharmacological prophylaxis after withdrawal from medication overuse in patients with chronic migraine: an effectiveness trial with a one-year follow-up. J Headache Pain 18:15
12. Tietjen GE, Khubchandani J (2015) Vascular biomarkers in migraine. Cephalalgia 35:95–117
13. Durham P, Papapetropoulos S (2013) Biomarkers associated with migraine and their potential role in migraine management. Headache 53:1262–1277
14. 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
15. Kabat-Zinn J (2003) Mindfulness-based interventions in context: past, present, and future. Clin Psychol Sci Pract 10:144–156
16. Uzar E, Evliyaoglu O, Yucel Y et al (2011) Serum cytokine and pro-brain natriuretic peptide (BNP) levels in patients with migraine. Eur Rev Med Pharmacol Sci 15:1111–1116
17. Yan J, Melemedjian OK, Price TJ et al (2012) Sensitization of dural afferents underlies migraine-related behavior following meningeal application of interleukin-6 (IL-6). Mol Pain 8:6
18. Wang F, He Q, Ren Z et al (2015) Association of serum levels of intercellular adhesion molecule-1 and interleukin-6 with migraine. Neurol Sci 36:535–540

Neurol Sci (2017) 38 (Suppl 1):S177–S179
DOI 10.1007/s10072-017-2898-5

BRIEF COMMUNICATION

Raven coloured progressive matrices in migraine without aura patients

Giovanna Viticchi[1] · Lorenzo Falsetti[2] · Marco Bartolini[1] · Laura Buratti[1] · Lara Pistelli[1] · Leandro Provinciali[1] · Mauro Silvestrini[1]

Abstract Conflicting results emerged from studies investigating cognitive performances in migraine patients. Based on clinical and neuroradiological aspects, the possible involvement of executive functions has been especially taken into consideration. The aim of this study was to evaluate, in a population of subjects affected by migraine without aura (MwoA), frontal lobe cognitive functions. We enrolled all the consecutive patients affected by MwoA referred to our headache centre for a first evaluation. Each patient underwent a neuropsychological evaluation including Raven coloured progressive matrices (CPM). We collected variables as age, education, years of migraine, frequency of attacks and CPM scores. Relationship between continuous variables was explored with multiple regression lines, selecting the best-fitting trendline for each relationship. We obtained a final sample of 36 subjects (females: 62.5%; mean age: 42.25 ± 10.21 years). Patients had mean length of migraine history of 12.25 ± 11.00 years and a mean frequency of attacks of 8.06 ± 7.15 per month. Linear regression underlines a progressive decrease of CPM score with the increase of the migraine history's length ($R^2 = 0.8871$; $p < 0.001$), and the frequency of migraine attacks ($R^2 = 0.3122$; $p < 0.05$). Our findings suggest that pathological CPM scores can be associated with the severity of migraine. These data seem to confirm the hypothesis of an impairment of executive functions in MwoA. Different hypotheses to explain cognitive impairment in migraine have been postulated including the impact of the typical white matter lesions and a long history of drug abuse. The possible relevant clinical consequence of a full comprehension of this particular aspect related to migraine deserves further attention and consideration.

Keywords Migraine without aura · Executive functions · Cognitive impairment

Introduction

Several studies investigated and underlined the presence of cognitive alterations in migrainous patients, particularly during the attack period. On the other hand, there are contrasting data regarding the interictal intervals: most of the studies showed only a weak evidence of deficits in attention, working memory and sustained attention in migrainous subjects [1], while other studies did not evidence any significant difference with respect to healthy controls [2]. The aim of this study was to evaluate frontal lobe cognitive functions, particularly the executive ones, in a population of subjects affected by migraine without aura (MwoA).

Methods

We enrolled, in a six-month period, all the consecutive patients affected by MwoA referring to our headache centre for a first visit. Each patient underwent a neuropsychological evaluation including Raven coloured progressive matrices (CPM). This is a validated test and it is usually employed to assess nonverbal reasoning [3].

✉ Giovanna Viticchi
viticchi.g@gmail.com

[1] Neurological Clinic, Marche Polytechnic University, Via Conca 1, 60020 Ancona, Italy

[2] Internal and Subintensive Medicine, Ospedali Riuniti Ancona, Ancona, Italy

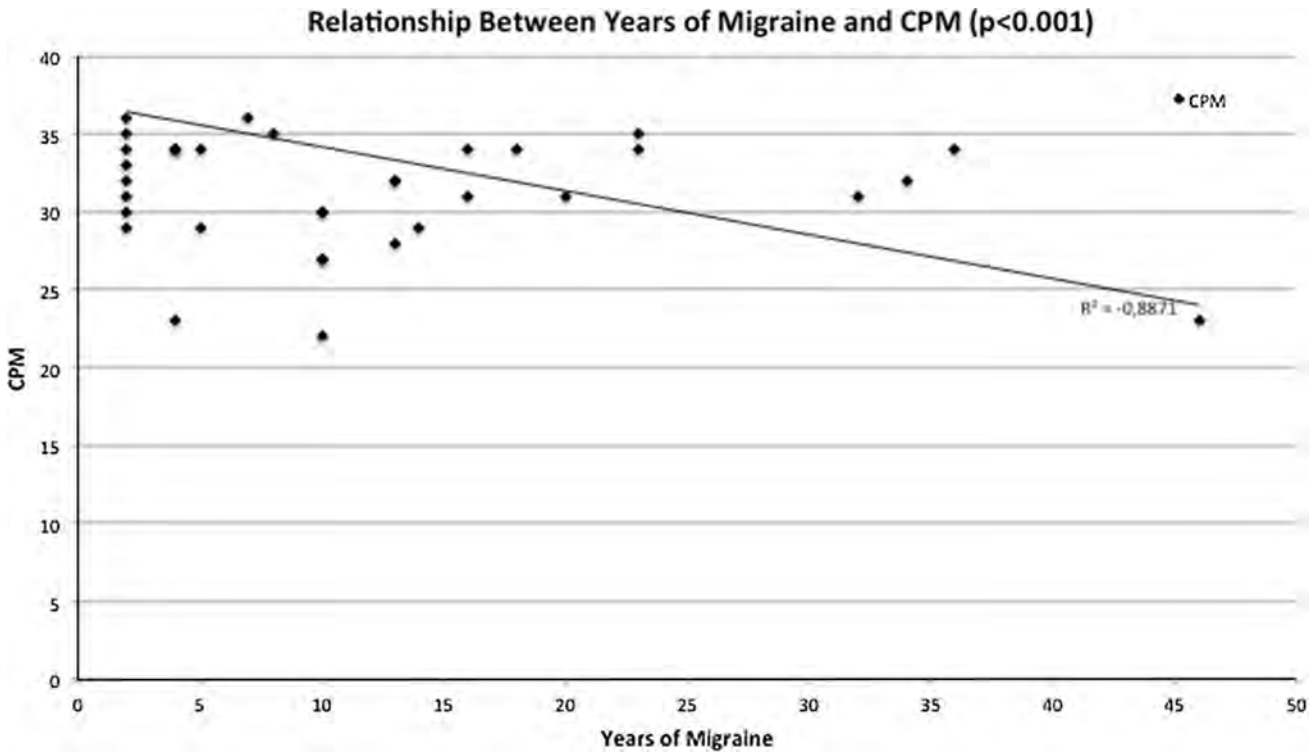

Fig. 1 Relationship between years of migraine and CPM

We collected variables as age, education, years from migraine onset, frequency of attacks and CPM scores. Relationship between continuous variables was explored with multiple regression lines, selecting the best-fitting trendline for each relationship.

Results

We obtained a final sample of 36 subjects (women 62.5%), mean age: 42.25 ± 10.21 years. Patients had a mean length of migraine history of 12.25 ± 11.00 years and a mean monthly frequency of attacks of 8.06 ± 7.15. Linear regression underlined a progressive decrease of CPM scores with the increase of the migraine history's length ($R^2 = 0.8871$; $p < 0.001$) (Fig. 1). A similar result was obtained for the frequency of migraine attacks ($R^2 = 0.3122$; $p < 0.05$) (Fig. 2).

Discussion

Our data suggest that a pathological CPM can be associated with a longer history of migraine and to a higher frequency of attacks. Accordingly, subjects with severe and disabling headache seem to present an increased probability of developing deficits in reasoning and executive functions. These findings strengthen the hypothesis of the presence of executive functions impairment in MwoA.

Different possible explanations for alteration in executive abilities have been postulated. Among the most interesting ones, we underline the possible role of the typical white matter lesions, especially when these vascular alterations affect strategic areas in cognition, such as the frontal lobe. Several authors also hypothesized that a long history of drug abuse could impair cognitive abilities, especially frontal functions, as the decision making [4].

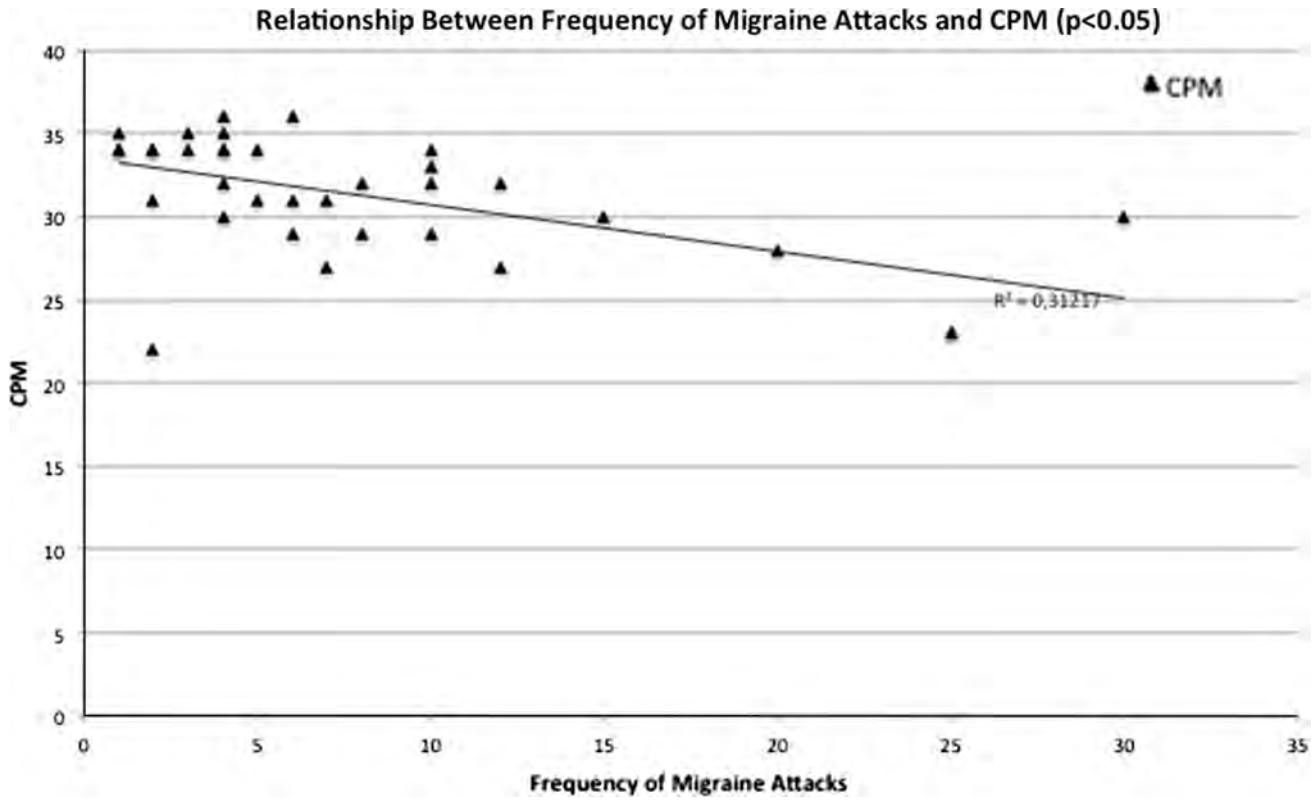

Fig. 2 Relationship between frequency of migraine attacks and CPM

Larger studies are necessary to better understand the complex cognitive assessment of migrainous patients. A full comprehension of this particular aspect of migraine could help to understand new aspects of the illness, and could be useful in severe conditions as chronic migraine or medication-overuse headache.

Compliance with ethical standards

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

Ethical standards The studies have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and latest revisions (the latest in 2013). Patient informed consent to be included in the study has been obtained.

References

1. Suhr JA, Seng EK (2012) Neuropsychological functioning in migraine: clinical and research implications. Cephalalgia 32:39–54
2. Gil-Gouveia R, Oliveira AG, Martins IP (2016) Sequential brief neuropsychological evaluation of migraineurs is identical to controls. Acta Neurol Scand 134:197–204
3. Raven J, Court JH, Raven JC (1998) Raven Manual, Section 1 (General overview) and Section 2 (Coloured Progressive Matrices). Oxford Psychologist Press, Oxford
4. Biagianti B, Grazzi L, Gambini O et al (2012) Decision-making deficit in chronic migraine patients with medication overuse. Neurol Sci 33:S151–S155

Neurol Sci (2017) 38 (Suppl 1):S181–S184
DOI 10.1007/s10072-017-2929-2

BRIEF COMMUNICATION

Personality disorders in cluster headache: a study using the Millon Clinical Multiaxial Inventory-III

Sylvie Hélène Marie Jeanne Piacentini[1] · Lara Draghi[1] · Alberto Proietti Cecchini[2] · Massimo Leone[2]

Abstract A great deal of studies suggests that cluster headache (CH) patients are usually comorbid to anxiety-mood spectrum disorders and psychopathological symptoms; however, the personality profiles reported in the literature strictly depend on type of assessment used. Psychiatric comorbidities have been extensively studied in migraine and they are recognized to represent a major risk factor associated with poorer outcome, playing a role in the headache chronification process at once as cause and consequence of it. By contrast the incidence and role of psychopathological aspects in CH is still not clarified, insufficiently explored as the striking severity of such a physical pain apparently leaves no room to psychological explanations. The aim of the present study is to describe psychopathological aspects of CH patients by means of the Millon Clinical Multiaxial Inventory-III (MCMI-III), a psychological assessment tool compatible to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) that correlates personality disorders (PDs) and clinical syndromes. We included all consecutive inward patients with CH between January 2014 and December 2016. Patients were evaluated using the MCMI-III a validated inventory assessing 14 PDs Scales (coordinate with DSM-IV Axis II disorders) and ten Clinical Syndrome Scales (coordinate with DSM-IV Axis I disorders). Twenty-six CH patients (24 chronic CH) were tested. Personality disorders were present in 92% of the patients. The most frequent PDs were: obsessive–compulsive (30.8%), histrionic (26.9%), narcissistic (11.5%), paranoid (11.5%) and avoidant (11.5%). According to the MCMI-III, patients with CH showed a high prevalence of personality disorders (Axis II-DSM-IV). PDs in CH patients can play an important role in determining CH course toward chronification. These preliminary results suggest that behavioral treatments can find room to support more conventional drug and neurostimulation therapies in these patients. In addition, the very high prevalence of PDs in our patients suggests that CH could in some cases be considered among the spectrum of somatoform and pain syndromes in patients with PDs.

Keywords Cluster headache · Personality disorders · Millon Clinical Multiaxial Inventory-III · Clinical syndromes

Background

Cluster headache (CH) is commonly cited as the most painful of the primary headache disorders.

According to the International Classification of Headache Disorders (ICHD-3, beta) [1], CH is characterized by attacks of severe pain, lasting 15–180 min and occurring from once every other day to eight times a day. The pain is often associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea and/or with restlessness or agitation. Cluster headache belongs to Trigeminal Autonomic Cephalalgias (TACs) group and can be divided into episodic or chronic, who can be distinguished by the frequency of the attacks, while the pain experienced by both groups is similar. The majority of patients suffering CH are men (3:1) and the attacks usually

✉ Sylvie Hélène Marie Jeanne Piacentini
sylvie.piacentini@istituto-besta.it

[1] Clinical Neuropsychological Service, IRCCS Foundation "Carlo Besta" Neurological Institute, Via Celoria, 11, 20133 Milan, Italy

[2] Headache and Neuroalgology Unit, IRCCS Foundation "Carlo Besta" Neurological Institute, Milan, Italy

start between the age of 20 and 40 [2]. Generally, CH attacks have a striking circadian rhythm, with the attacks taking place at the same time each day, commonly in the afternoon or evening and during the night. In addition, episodic CH tends to have a circannual rhythm, with active periods reappearing at the same time of the year [3].

Unlike migraine, CH has not been the focus of a great deal of research investigating correlations between headaches and psychopathological factors. Horton firstly [4] explained clearly the intolerable pain suffered by CH patients, and it is then referred as "suicide headache". The pain is described as a knife being pushed into the eye, the eye being crushed or ripped from the orbit. A recent review of the literature revealed that the actual act of suicide amongst CH patients is reasonably uncommon [5], also due to the greatly improved efficacy of current available therapies, with respect to Horton's time period dated more than 50 years ago. Nonetheless, violent behavior and self-inflicted injuries are far more common in CH patients [6]. Several studies have tried to investigate psychopathological aspects in CH patients. The prevalence of these studies focused on *Axis I* disorders of DSM–IV [7] that included mood, anxiety and the somatoform disorders (e.g. Conversion Disorder, Pain Disorder). Correlation between CH and depression [8, 9] or anxiety disorders [10, 11] were found.

Several Minnesota Multiphasic Personality Inventory-MMPI studies failed to show any abnormal incidence of psychopathology in CH populations, although patients with the chronic form resulted more prone to develop psychological disturbances [12, 13]. Conversion disorders with typical "V" profile (high scores for the hypochondria and hysteria scales with low scores for depression) were found by some but further studies were not consistent, leading to discordant results. Particularly, "V" profile was reported by Steinhilber [14] and Harrison [15] in their CH patients groups, meanwhile conversely, Blanchard [16] and Andrasik [17] found no difference between controls and CH patients. Further, Rogado [18] described significantly higher scores for the psychasthenia (obsessive–compulsive) scale in CH patients with respect to normal control subjects.

Personality is seen as a complex pattern of deeply embedded psychological characteristics that are expressed automatically in almost every area of psychological functioning. That is, personality is viewed as the pattern of characteristics across the entire matrix of the person. Individuals with personality disorders tend to exhibit lack of resilience, under conditions of stress and are adaptively inflexible [19]. Millon and Davis [20] argued that the personality constitution among other things will influence the ability to cope with substantial stressors like chronic pain.

The aim of present study is to analyze the personality profile of CH patients using the MCMI-III [21] a validated questionnaire based on DSM-IV particularly focused on Axis II disorders (i.e. Personality Disorders).

Methods

We recruited consecutive in-ward patients between January 2014 and December 2016 at the Headache Center of the Foundation IRCCS Neurological Institute Carlo Besta in Milan. We included all patients with CH defined according to the ICHD-3, beta. The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and latest revisions (the latest in 2013). Patient informed consent to be included in the study has been obtained.

Personality traits were evaluated using the MCMI-III, a validated self-administered inventory assessing 14 PDs Scales (coordinate with DSM-IV Axis II disorders) and 10 Clinical Syndrome Scales (coordinate with DSM-IV Axis I disorders). The inventory MCMI-III is composed of 175 true–false questions that reportedly take 25–30 min to complete. The personality and clinical syndrome scales were scored using Base Rate (BR) scores. A BR score of 75–84 is assumed to indicate a significant personality trait or mental health concern and a BR score of 85 and higher indicate a persistent, significant clinical concern or PDs.

Presence and frequencies of psychopathological aspects and correlation between personality patterns and clinical syndromes was analyzed (IBM SPSS—Statistical Package for the Social Science 24.0 Inc., Chicago, IL, USA).

Results

We recruited 26 in-patients with CH (5 female, 21 male). Mean age at inclusion was 43.2 $\pm$ 10.2; mean age at CH onset was 35 $\pm$ 12.7. Mean educational level was 10.6 $\pm$ 3.1. At the time of assessment 2 patients (7.7%) had episodic headache, and 24 patients (92.3%) had chronic CH.

Personality disorders were observed in 92% (BR score $\geq$85) of patients; features of PDs (BR score $\geq$75) in the remaining 8%. The most frequent *personality disorders* according to DSM-IV Axis II were: obsessive–compulsive (30.8%), histrionic (26.9%), narcissistic (11.5%), paranoid (11.5%) and avoidant (11.5%) (for details see Table 1). The most frequent *personality traits* were the histrionic traits (26.9%) followed by narcissistic, obsessive–compulsive and passive–aggressive (19.2% per trait).

In addition to those personality traits, Axis I of DSM-IV disorders appeared among more than half of the patients.

Table 1 MCMI-III personality patterns and clinical syndromes for CH patients ($n = 26$)

	BR score ≥75 % (*n*)	BR score ≥85 % (*n*)
Personality patterns		
Schizoid	–	3.8% (1)
Avoidant	–	**11.5% (3)**
Depressive	3.8% (1)	–
Dependent	–	7.7% (2)
Histrionic	**26.9% (7)**	**26.9% (7)**
Narcissistic	**19.2% (5)**	**11.5% (3)**
Antisocial	7.7% (2)	–
Aggressive	–	–
Compulsive	**19.2% (5)**	**30.8% (8)**
Passive–aggressive	**19.2% (5)**	3.8% (1)
Self-defeating	–	–
Schizotypal	3.8% (1)	–
Borderline	3.8% (1)	7.7% (2)
Paranoid	–	**11.5% (3)**
Clinical syndromes		
Anxiety	**19.2% (5)**	**34.6% (9)**
Somatoform	**15.4% (4)**	**15.4% (4)**
Bipolar: manic	3.8% (1)	3.8% (1)
Dysthymia	**30.8% (8)**	7.7% (2)
Alcohol dependence	3.8% (1)	–
Drug dependence	3.8% (1)	3.8% (1)
Posttraumatic stress disorder	11.5% (3)	–
Thought disorder	3.8% (1)	–
Major depression	**15.4% (4)**	**26.9% (7)**
Delusional disorder	3.8% (1)	–

Bold indicates more frequent personality patterns and syndromes

The results showed significant clinical symptoms for anxiety (34.6%), major depression (26.9%) and somatoform disorder (15.4%).

Discussion

In the present study PDs were observed in the vast majority (92%) of CH patients. These results are unexpected if compared with prevalence of PDs in European Population estimated about 4.4% [22]. A selection bias cannot be excluded as the main cause of our findings. Notwithstanding this observation, the surprisingly high frequency of PDs among our CH patients needs to be discussed.

The most frequent PDs observed in our study were obsessive–compulsive (30.8%) and histrionic (26.9%) disorders.

A recent study by Muñoz [23] on personality traits examined with the *Salamanca* screening test in a group of 80 CH patients—mostly episodic CH—reported a trait prevalence of anancastic (52.5%), anxious (47.5%), histrionic (45%), schizoid (42.5%), impulsive (32.5) and paranoid (30%).

The relationship between PDs and chronic pain has been already well described in the literature. In Fishbain et al. [24] study 59% of 283 consecutive patients admitted to pain unit who experienced chronic (longer than 2 years) regional pain syndromes (such as headache) fulfilled criteria for a diagnosis of PDs (62% of men and 55% of women). The most frequent diagnoses were dependent (17%), passive aggressive (15%) and histrionic (12%) PDs. Men were significantly more prone to have paranoid and narcissistic disorders while significantly more females were diagnosed as histrionic PDs. The most frequently identified personality types in these patients were compulsive (24.5%) and dependent (10.6%), with no gender differences.

For as it concerns Clinical Syndromes (Axis I) we found a prevalence of anxiety (34.6%), major depression (26.9%) and somatoform symptoms (15.4%). These data are not surprising: in fact, as substantial comorbidity occurs between PDs and common mental disorders in the spectrum of anxiety [25], depression [26] and somatoform symptoms [27–29].

In agreement with Millon's Personality Theory histrionic and obsessive personality disorders the observed PDs in the present study can both exhibit somatic symptoms (as pain), even with different characteristics.

Histrionic patients can use somatoform symptoms to draw attention, comfort, and nurturance from others. Whenever the histrionic feels empty, isolated, or bored, the secondary gains become more tempting, so the disorder seems to be exacerbated. For obsessive–compulsives, bodily symptoms may be used as a means of rationalizing failures and inadequacies or a means of "saving face" by ascribing shortcomings to causes obviously beyond their control. Moreover, sickness allows them to escape the condemnation of a sadistic superego that is always ready with blame. The manifestation of physical symptoms can also be seen as an expression of accumulated tension and anxiety turned inward toward the body. For some, there is nowhere else anxiety can be expressed, for its presence destroys their façade of competency [30]. The relationship between pain and psychopathological characteristics can bring important changes to the subject's "pain" experience [31].

Larger studies are needed to confirm whether and how personality traits are directly related to CH and pain. Several major limitations are in this survey study, the main one being that we do not have a matched healthy control population and a gender bias is present. More focused studies will be necessary to solve these limitations and to

confirm whether and how personality traits are relevant to CH manifestations.

In conclusion, in our sample of CH patients, PDs as assessed by Millon questionnaire tend to be highly comorbid and this should deserve much more research as it might influence both clinical course and the successful outcome. The very high prevalence of PDs in our patients suggests that CH could also be considered among the spectrum of somatoform and pain syndromes in patients with PDs.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Headache Classification Subcommittee of the International Headache Society (2013) The international classification of headache disorders: 3rd edition (beta version). Cephalalgia 33:629–808
2. Fischera M, Marziniak M, Gralow I, Evers S (2008) The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. Cephalalgia 28:614–618
3. Waldenlind E (1999) Biological rhythm in cluster headache. In: Olesen J, Goadsby PJ (eds) Cluster headache and related conditions. Oxford University Press, London, pp 171–178
4. Horton BT (1952) Histamine cephalgia. Lancet 72:92–98
5. Markley HG, Buse DC (2006) Cluster headache: myths and the evidence. Curr Pain Headache Rep 10(2):137–141
6. Kudrow L (1980) Cluster headache: mechanisms and management. Oxford University Press, London
7. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorder: DSM-IV, 4th edn. APA, Washington, DC
8. Donnet A, Lanteri-Minet M, Guegan-Massardier E et al (2007) Chronic cluster headache: a French clinical descriptive study. J Neurol Neurosurg Psychiatry 78:1354–1358
9. Seifert CL, Valet M, Pfaffenrath V et al (2011) Neurometabolic correlates of depression and disability in episodic cluster headache. J Neurol 258:123–131
10. Robbins MS, Bronheim R, Lipton RB et al (2012) Depression and anxiety in episodic and chronic cluster headache: a pilot study. Headache 52:600–611
11. Jorge RE, Leston JE, Arndt S, Robinson RG (1999) Cluster headaches: association with anxiety disorders and memory deficits. Neurology 53:543–547
12. Andrasik F, Blanchard EB, Arena JG, Teders SJ, Rodichok LD (1982) Cross-validation of the Kudrow–Sutkus MMPI classification system for diagnosing headache type. Headache 22(1):2–5
13. Cuypers J, Altenkirch H, Bunge S (1981) Personality profiles in cluster headache and migraine. Headache 21(1):21–24
14. Steinhilber RM, Pearson JS, Rushton JG (1960) Some psychological considerations of histaminic cephalalgia. Mayo Clin Proc 35:691–699
15. Harrison RH (1975) Psychological testing in headache: a review. Headache 14:177–185
16. Blanchard EB, Andrasik F, Evans DD, Neff DF, Appelbaum KA (1985) Behavioral treatment of 250 chronic headache patients: a clinical replication series. Behav Ther 16(3):308–327
17. Andrasik F, Blanchard EB, Arena JG, Teders SJ, Teevan RC, Rodichok LD (1982) Psychological functioning in headache sufferers. Psychosom Med 44(2):171–182
18. Rogado AZ, Harrison RH, Graham JR (1974) Personality profiles in cluster headache, migraine and normal controls. Arch Neurobiol 37:227–241
19. Millon T, Millon CM, Meagher SE, Grossman SD, Ramnath R (2004) Personality disorders in modern life, 2nd edn. Wiley, Hoboken
20. Millon T, Davis R (1996) Disorders of personality: DSM-IV and beyond. Wiley, New York
21. Millon Th, Davis R, Millon C (1997) MCMI-III. Millon Clinical Multiaxial Inventory-III. Adattamento italiano a cura di Zennaro A, Ferracuti S, Lang M, Sanavio E. (tr. it. 2008). Una rivoluzione nell'assessment clinico della personalità. Firenze: Giunti O.S. Organizzazioni Speciali
22. Coid J, Yang M, Tyrer P, Roberts A, Ullrich S (2006) Prevalence and correlates of personality disorder among adults aged 16 to 74 in Great Britain. Br J Psychiatry 188:423–431
23. Muñoz I, Hernández MS, Santos S, Jurado C, Ruiz EL, Toribio DE, Sotelo EM, Guerrero AL, Molina V, Uribe F, Cuadrado ML (2016) Personality traits in patients with cluster headache: a comparison with migraine patients. J Headache Pain 17:25
24. Fishbain DA, Goldberg M, Meagher BR et al (1986) Male and female chronic pain patients categorized by DSM-III psychiatric diagnostic criteria. Pain 26:181–197
25. Welander-Vatn A, Ystrom E, Tambs K, Neale MC, Kendler KS, Reichborn-Kjennerud T, Knudsen GP (2016) The relationship between anxiety disorders and dimensional representations of DSM-IV personality disorders: a co-twin control study. J Affect Disord 190:349–356
26. Reichborn-Kjennerud T, Czajkowski IN, Roysambu E et al (2010) Major depression and dimensional representations of DSM-IV personality disorders: a population-based twin study. Psychol Med 40(9):1475–1484
27. Goodwin RD, Brook JS, Cohen P (2005) Panic attacks and the risk of personality disorder. Psychol Med 35:227–235
28. Johnson JG, Cohen P, Kasen S, Brook JS (2005) Personality disorder traits associated with risk for unipolar depression during middle adulthood. Psychiatry Res 136:113–121
29. Loranger AW (1990) The impact of DSM-III on diagnostic practice in a university hospital. A comparison of DSM-II and DSM-III in 10,914 patients. Arch Gen Psychiatry 47:672–675
30. Mattheisen M, Samuels JF, Wang Y, Greenberg BD, Fyer AJ, McCracken JT, Geller DA, Murphy DL, Knowles JA, Grados MA, Riddle MA, Rasmussen SA, McLaughlin NC, Nurmi EL, Askland KD, Qin HD, Cullen BA, Piacentini J, Pauls DL, Bienvenu OJ, Stewart SE, Liang KY, Goes FS, Maher B, Pulver AE, Shugart YY, Valle D, Lange C, Nestadt G (2015) Genome-wide association study in obsessive–compulsive disorder: results from the OCGAS. Mol Psychiatry 20:337–344
31. Bertolotti G, Vidotto G, Sanavio E, Frediani F (2003) Psychological and emotional aspects and pain. Neurol Sci 24:S71–S75

Neurol Sci (2017) 38 (Suppl 1):S185–S187
DOI 10.1007/s10072-017-2943-4

BRIEF COMMUNICATION

Pediatric migraine with aura in an Italian case series

Arens Taga[1] · Marco Russo[1] · Antonio Genovese[1] · Maria Vittoria Paglia[1] · Gian Camillo Manzoni[1] · Paola Torelli[1]

Abstract The aim of the present study was to describe the characteristics of migraine with aura (MwA) in a case series of patients with headache onset before 12 years of age. We considered all consecutive patients referred to the Parma Headache Centre between 1975 and 2015 affected by MwA, diagnosed by our team of trained neurologists; the cases were subsequently reviewed applying the ICHD3-beta criteria. We then identified those cases with headache age-of-onset <12 years (i.e., "pediatric" cases), which were compared to all remaining cases. We identified 283 cases with pediatric onset (87 males and 196 females). The male-to-female ratio was 1:2.3 in both "pediatric" and "non-pediatric" cases. The time lag between MwA onset and our first evaluation was significantly higher among the pediatric cases (18.7 ± 13.3 vs 10.4 ± 10.4 years). In both groups of patients, visual aura was the most common type of aura, followed by sensory and speech disturbances; however, these two latter aura symptoms were significantly more common among pediatric cases. In this group of patients, aura without headache was significantly less frequent (1.8 vs 5.3%); furthermore, headache had migraine characteristics in a higher proportion of cases (90.1 vs 82.6%). A family history of MwA was significantly more frequent among cases with pediatric onset (31.1 vs 16.9%). Males but not females with pediatric MwA had more frequently a comorbid migraine without aura (27.6 vs 16.8%). Among cases with pediatric onset, we did not find any significant differences between males and females. In conclusion, in our very large case series of MwA, patients with headache onset before 12 years of age seem to have a specific clinical phenotype, without significant gender differences.

Keywords Migraine · Aura · Children · Age-of-onset

Introduction

Migraine is a relatively common complaint among children seeking medical advice [1]; its prevalence [2] increases from 3% in the preschool years to 4–11% by the elementary school years. Puberty is a turning point in migraine prevalence, being headache more frequent among males before puberty, in contrast to the higher female prevalence after puberty [3, 4].

The diagnosis of headache is challenging in pediatric population, because of the difficulties of patients in describing their symptoms. Moreover, neurologists and neuropsychiatrists are often not comfortable diagnosing headache syndromes in the pediatric population.

Most studies on headache with pediatric onset have dealt with migraine without aura (MwoA), and there are only few literature data on migraine with aura (MwA) [5–7].

The aim of the present study was to describe the characteristics of MwA in a case series of patients with headache onset before 12 years of age.

Methods

We performed a cross-sectional study in all consecutive patients referred to the Parma Headache Centre between 1975 and 2015 affected by MwA, diagnosed by our team of trained neurologists.

The cases were subsequently reviewed applying the current ICHD3-beta criteria [8]. We then identified those cases with

✉ Arens Taga
arens.taga@gmail.com

[1] Headache Centre, Department of Medicine and Surgery, University of Parma, via Gramsci 14, 43100 Parma, Italy

headache age-of-onset <12 years (i.e., "pediatric" cases), which were compared to all remaining cases (i.e., "non-pediatric" cases). We chose this cut-off because it corresponded to the median age of menarche in our female patients (12.3 ± 1.2 years).

All patients authorized the use of personal data in clinical studies. Informed consent was obtained by parents of underage patients.

The collected data were analyzed using SPSS, version 20.0 for Windows. Statistical analysis was done using *t* test and chi-square test; we calculated two-tailed *p* values and set statistical significance at $p < 0.05$.

Results

Our initial study sample consisted of 2114 patients, 646 males and 1468 females. We identified 283 cases with pediatric onset (87 males and 196 females) and 1831 non-pediatric cases (559 males and 1272 females). The male-to-female ratio was 1:2.3 in both pediatric and non-pediatric cases.

Age of onset of pediatric cases ranged between 5 and 11 years for males and 3 and 11 years for females.

The time lag between MwA onset and our first evaluation was significantly higher among the pediatric cases (18.7 ± 13.3 vs 10.4 ± 10.4 years, $p < 0.0001$).

In both groups of patients, visual aura was the most common type of aura, followed by sensory and speech disturbances; however, these two latter aura symptoms were significantly more common among pediatric cases ($p = 0.046$, $p = 0.007$). In this group of patients, aura without headache was significantly less frequent (1.8 vs 5.3%, $p = 0.01$); furthermore, headache had migrainous characteristics in a higher proportion of cases (90.1 vs 82.6%, $p < 0.0001$).

A family history of MwA was significantly more frequent among cases with pediatric onset (31.1 vs 16.9%, $p < 0.0001$). Males but not females with pediatric MwA had more frequently a comorbid MwoA (27.6 vs 16.8%, $p = 0.016$).

Other clinical features such as aura duration and frequency, comorbidity with MwoA, tension-type headache, and anxiety disorder were similarly distributed in the two groups of patients.

Among cases with pediatric onset, we did not find any significant difference regarding MwA features when males were compared to females.

Discussion

We report a very large cohort of MwA patients with headache onset before 12 years of age.

The high time lag between headache onset and our first evaluation highlights the difficulties in diagnosing headache in pediatric population [9].

We did not find previous literature studies focusing specifically on the influence of age of onset on MwA phenotype; furthermore, there are only few reports on MwA with headache onset before puberty [5–7, 10].

Mavromichalis et al. [7] described a cohort of 99 MwA cases with age of onset between 3 and 14 years. When compared to our study, they found a similar proportion of visual auras (87%), but a lower frequency of sensory auras (12%) and no aphasic aura. Pain features and associated symptoms were similar in children with and without aura; this finding suggests that among children with MwA, headache following aura commonly has "migrainous" features.

We observed a lower proportion of males than females with headache onset before 12 years of age, which is in contrast with existing evidence that MwoA peaks earlier in males than females, but it is in accordance with previous reports [5] on pediatric MwA occurring more often in females than in males.

First-degree relatives of patients suffering from MwA had a fourfold increased risk of MwA [10], which suggests a possible genetic susceptibility. In our study, we found a high proportion of MwA with a family history (i.e., first-degree relatives) of MwA, which was significantly more frequent among cases with pediatric onset. Genizi et al. [5] found no difference in family history of migraine between younger (≤12 years) and older (>12 years) children with MwA; however, they considered a family history of both migraine with and without aura.

The strengths of our study are the following: (i) the case series that we report is very large and includes patients with MwA diagnosis according to the ICHD-3 beta criteria; (ii) the diagnosis was made by face-to-face examination, and secondary causes were excluded; and (iii) all reported cases were personally seen by one of the authors (GCM). Some limitations of our study need to be addressed: (i) our study is retrospective so that a recall bias is possible and (ii) our study population is not representative of the general population due to the clinic-based design.

In conclusion, MwA patients with headache onset before 12 years seem to have a specific clinical phenotype, without significant gender differences; furthermore, they are more likely to have a family history of MwA, suggesting a possible genetic susceptibility.

Compliance with ethical standards All patients authorized the use of personal data in clinical studies. Informed consent was obtained by parents of underage patients.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Genizi J, Srugo I, Kerem NC (2013) The cross-ethnic variations in the prevalence of headache and other somatic complaints among adolescents in northern Israel. J Headache Pain 14:21–27
2. Al-Twaijri WA, Shevell MI (2002) Pediatric migraine equivalents: occurrence and clinical features in practice. Pediatr Neurol 26:365–368
3. Deubner DC (1977) An epidemiologic study of migraine and headache in 10-20 year olds. Headache 17:173–180
4. Victor TW, Hu X, Campbell JC et al (2010) Migraine prevalence by age and sex in the United States: a life-span study. Cephalalgia 30: 1065–1072
5. Genizi J, Khourieh MA, Zelnik N et al (2016) Frequency of pediatric migraine with aura in a clinic-based sample. Headache 56(1): 113–117
6. Mortimer MJ, Kay J, Jaron A (1992) Childhood migraine in general practice: clinical features and characteristics. Cephalalgia 12:238–243
7. Mavromichalis I, Anagnostopoulos D, Metaxas N et al (1999) Prevalence of migraine in schoolchildren and some clinical comparisons between migraine with and without aura. Headache 39: 728–736
8. Headache Classification Comittee of the International Headache Society (2013) The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 33:629–808
9. Lee LH, Olness KN (1997) Clinical and demographic characteristics of migraine in urban children. Headache 37:269–276
10. Russell MB, Iselius L, Olesen J (1996) Migraine without aura and migraine with aura are inherited disorders. Cephalalgia 16:305–309

Neurol Sci (2017) 38 (Suppl 1):S189–S191
DOI 10.1007/s10072-017-2873-1

BRIEF COMMUNICATION

Stroke-like attack: first episode of sporadic hemiplegic migraine

Enrico Ferrante[1] · Valentina Prone[2] · Marco Longoni[2] · Elio Clemente Agostoni[2]

Abstract Hemiplegic migraine (HM) is a rare migraine with aura; it can be familiar or sporadic. A 46-years-old man presented left migraine followed by right hemiparesis with bilateral plantar flexion of cutaneous plantar reflex (CPR). Brain CT and CT-angiography were normal. The next day patient got worse. The EEG showed left fronto-temporal cuspidate delta waves and brain MRI showed a minimal hyperintensity at T2-sequences in the left frontal cortex with a minor representation of the cortical veins at susceptibility weighted imaging sequences. After 3 days, he had a progressive neurological improvement. After 2 weeks, EEG and brain MRI were normal. He was discharged with diagnosis of probably first attack of sporadic HM and after 8 months he was asymptomatic. The normal CPR on the hemiplegic side might be a clinical marker of functional hemiplegia. For the international classification of headache disorder (ICHD-3) two attacks are necessary for HM diagnosis. We propose for the first attack of HM to make diagnosis of "probable" HM as expected to the same ICHD-3 for migraine. Further studies are necessary to support our hypotheses.

Keywords Headache · Hemiplegic migraine · Stroke-like attack · Cutaneous plantar reflex

✉ Enrico Ferrante
enricoferrante@libero.it

[1] Headache Centre, Neurosciences Department, Niguarda Ca' Granda Hospital, Milan, Italy

[2] Neurosciences Department, Niguarda Ca' Granda Hospital, Milan, Italy

Introduction

Hemiplegic migraine (HM) is a rare subtype of migraine with aura that includes motor weakness [1, 2]. The attacks of sporadic HM (SHM) have identical clinical characteristics as the familial type, but patients have negative family history of first- or second-degree relatives. The sporadic and familial forms occur rarely with an equal prevalence of 0.01% [1]. The familial type is caused by mutations in membrane channels (CACNA1A, ATP1A2 or SCN1A) [2]. The average age of onset is 12–17 years (range 1–51 years) [3, 4]. Like other form of migraine, women have a higher prevalence of HM, with female to male ratios ranging from 2.5:1 to 4.3:1 [4, 5]. The aura associated with HM attacks is characterized by motor weakness, but is often associated with sensory, visual or language disturbances. In rare cases, patients may present cerebellar ataxia, encephalopathy or coma [2]. The first attack of SHM needs an accurate clinical evaluation of the other potential causes of acute onset of neurological deficits and headache (mainly ischaemic stroke). It is a diagnosis of exclusion [1].

Case report

On 7 June 2016 at 8.00 p.m., a 46-years-old man, diabetic, with episodic tension type headache since one year, suddenly presented a confusional state, unknowing the road to home. After few minutes the patient had dysphasia, paresthesia from right hand dating back to the elbow and moderate left button migraine with nausea and vomiting. At midnight in emergency room he presented right hemiparesis. Neurological exam showed dysphasia, slight right hemiparesis, lower right facial nerve paresis and bilateral plantar flexion of cutaneous plantar reflex (CPR). Brain CT and CT-angiography were

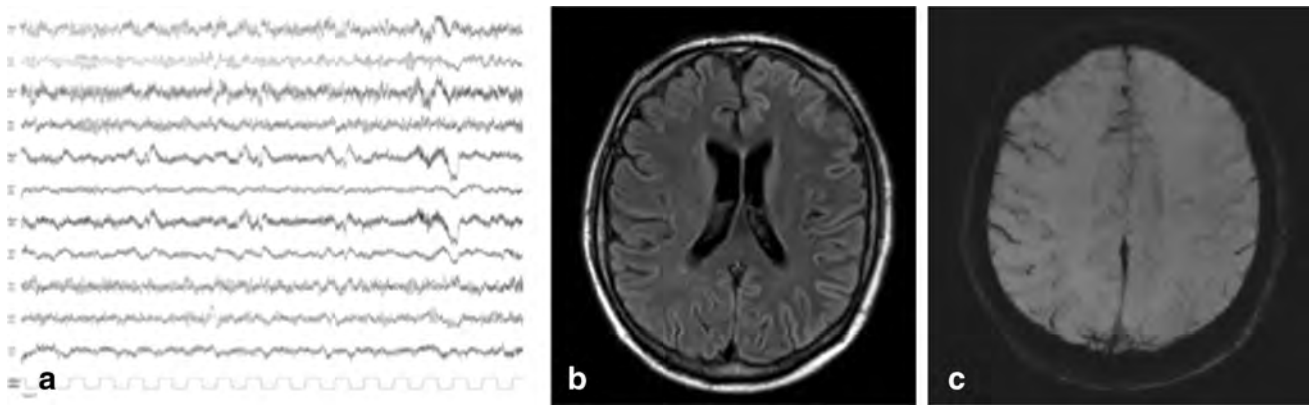

Fig. 1 During the attack, EEG showed left fronto-temporal cuspidate delta waves with slow pseudo-periodic trend (**a**). After 2 days Gadolinium MRI showed a minimal diffuse signal alteration at T2 sequences in the left frontal cortex (**b**) and a minor representation of the cortical veins in the same zone at susceptibility weighted imaging (SWI) sequences (**c**)

normal. On 8 June at 11.00 a.m. neurological examination showed stupor, aphasia, right flaccid hemiplegia and bilateral plantar flexion of CPR. The EEG showed left fronto-temporal cuspidate delta waves with slow pseudo-periodic trend (Fig. 1a); the control brain CT was normal. For a slight fever a lumbar puncture was performed with a protein increased (103.1 mg/dl). On 9 June the gadolinium brain MRI showed a minimal diffuse hyperintensity at T2 sequences in the left frontal cortex (Fig. 1b) and a minor representation of the cortical veins in the same zone at susceptibility weighted imaging (SWI) sequences (Fig. 1c), with negative DWI for acute ischaemic lesions. After 3 days he had a progressive neurological improvement with complete recovery in 5 days. After 2 weeks EEG and brain MRI were normal. The patient was discharged with diagnosis of probably first attack of SHM. Genetic test for familiar HM was negative. After 8 months the patient was asymptomatic.

Discussion

Patients with SHM can arrive at the emergency room mimicking an acute ischaemic stroke [2]. The absence of acute ischaemic lesions at brain CT and DWI-MRI and normal CPR on the hemiparetic side exclude the ischaemic etiology and the consequent procedure of intravenous thrombolysis. In our cases the encephalitic etiology was excluded too for the normalization of the EEG. The CSF protein increase was probably due to the alteration of the encephalic blood barrier secondary to the cortical spreading depression (CSD) associated with the migraine attack. The CSD cause a reversible cerebral cortical dysfunction characterized by a neuronal excitation followed by a prolonged inhibition of neurological activity. Increased excitatory glutamate release caused a higher oxygen extraction fraction and veins alterations on SWI sequences [1]. Brain MRI SWI sequences provide information about any tissue with magnetic susceptibility that differs from neighboring structures [6]. Iron and calcium-rich tissues increase magnetic susceptibility. SWI generates a source of contrast from the relative differences in tissue-iron content and generally shows asymmetrical prominence of the cerebral veins during SHM aura [1]. In our case, MRI was made 2 days after the attack and SWI sequences show a minor representation of the cortical veins likely caused by CSD. The CPR is in plantar flexion on the hemiplegic side probably for the reversible neuronal dysfunction during CSD. The diagnosis of first attack of SHM remains a diagnosis of exclusion.

Conclusion

Brain MRI SWI sequences might have diagnostic value for the hemiplegic aura. For the International Classification of Headache Disorder (ICHD-3) two attacks are necessary for HM diagnosis. We propose for the first attack of HM to make diagnosis of "probable" HM as expected to the same ICHD-3 for migraine. Furthermore, considering that in emergency room neuroradiological exams are generally normal, the possibility to have a clinical marker like normal CPR on the hemiplegic side can be helpful in differential diagnosis between ischaemic stroke and stroke mimics (e.g. SHM) and to avoid intravenous thrombolysis with consequent bleeding risk. Further studies are necessary to support our hypothesis.

Compliance with ethical standards

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

Ethical standards The studies have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and latest revisions (the latest in 2013). Patient informed consent to be included in the study has been obtained"

References

1. Fedak EM, Zumberge NA, Heyer GL (2013) The diagnostic role for susceptibility-weighted MRI during sporadic hemiplegic migraine. Cephalalgia 33(15):1258–1263
2. Bosemani T, Burton VJ, Felling RJ, Leigh R, Oakley C, Poretti A, Huisman TAGM (2014) Pediatric hemiplegic migraine: role of multiple MRI techniques in evaluation of reversible hypoperfusion. Cephalalgia 34(4):311–315
3. Ducros A, Denier C, Joutel A et al (2001) The clinical spectrum of familial hemiplegic migraine associated with mutation in a neuronal calcium channel. N Engl J Med 345:17
4. Thomsen LL, Eriksen MK, Roemer SF et al (2002) A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. Brain 125:1379
5. Thomsen LL, Ostergaard E, Olesen J, Russell MB (2003) Evidence for a separate type of migraine with aura: sporadic hemiplegic migraine. Neurology 60:595
6. Haacke EM, Mittal S, Wu Z et al (2009) Susceptibility-weighted imaging: technical aspects and clinical applications, part 1. Am J Neuroradiol 30:19–30

Neurol Sci (2017) 38 (Suppl 1):S193–S196
DOI 10.1007/s10072-017-2895-8

BRIEF COMMUNICATION

Endolymphatic hydrops in idiopathic intracranial hypertension: prevalence and clinical outcome after lumbar puncture. Preliminary data

Angelo Ranieri[1,2] · Michele Cavaliere[3] · Stefania Sicignano[3] · Pietro Falco[2] · Federico Cautiero[2] · Roberto De Simone[2]

Abstract Idiopathic intracranial hypertension is characterized by raised intracranial pressure (ICP) without any underlying pathology, presenting with (IIH) or without papilledema (IIHWOP). Headache, often on daily basis, is the most frequent symptom. Among audiovestibular symptoms, tinnitus and dizziness are commonly reported, while vertigo and hearing impairment are infrequent reports. Endolymphatic hydrops (ELH) is the typical histopathologic feature of Ménière disease, a condition featured by episodes of vertigo, dizziness, fluctuating hearing loss, tinnitus, and aural fullness. Evidences suggest that ICP is transmitted to inner ear. The aim of this study is to investigate the prevalence of ELH symptoms in IIH/IIHWOP and the relationship between the raised ICP and ELH. The prevalence of chronic headache and of ELH symptoms was investigated in a consecutive series of IIH/IIHWOP patients, and a standard audiometry with hearing threshold measurement (pure-tone average—PTA) was performed. Differences in chronic headache and ELH symptoms prevalence and changes of PTA threshold were calculated after ICP normalization by lumbar puncture (LP). Thirty-one patients (17 with IIH and 14 with IIHWOP) were included. Before LP, chronic headache was present in 93.5%. The percentages of patients reporting tinnitus, dizziness, vertigo, and aural fullness were 67.7, 77.4, 22.6, and 61.3%, respectively. Headache frequency as well as ELH symptoms and PTA significantly improved after LP. The improvement of PTA and of ELH symptoms observed after LP in this series of IIH/IIHWOP patients indicates that a raised ICP, a condition known to be involved in the progression and refractoriness of migraine pain, has also a role in ELH. We propose that intracranial hypertension may represent the shared pathogenetic step explaining the large epidemiological comorbidity between migraine and vestibular symptoms, at present conceptualized as "vestibular migraine."

Keywords Raised intracranial pressure · Idiopathic intracranial hypertension · Endolymphatic hydrops · Vestibular migraine · Ménière disease

Introduction

Idiopathic intracranial hypertension (IIH) is characterized by raised intracranial pressure (ICP) without any underlying pathology. Headache, mainly on a daily basis, is the most frequent symptom. The typical sign of papilledema may be absent (IIHWOP), complicating the diagnostic work-up as the clinical presentation of IIHWOP may be indistinguishable from primary forms of chronic headache [1–3].

In addition to headache, patients with IIH/IIHWOP may be affected by visual symptoms, back and/or radicular pain and audiovestibular symptoms. Among the latter, tinnitus and dizziness are reported by up to half of the patients [4]; vertigo and hearing impairment, mainly on low frequencies, are uncommon complaints [5].

The pathophysiology of audiovestibular symptoms in IIH remains poorly understood. Tinnitus may be provoked

✉ Roberto De Simone
rodesimo@unina.it

[1] IDC Hermitage Capodimonte, Naples, Italy

[2] Department of Neurosciences, Reproductive Sciences and Odontostomatology, Headache Centre, University of Naples "Federico II", Via Pansini, 5, 80131 Naples, Italy

[3] Department of Otolaryngology, University of Naples "Federico II", Naples, Italy

by flow turbulence across sinus stenosis, a common finding in IIH patients with pathogenetic relevance [6, 7], which improves after ICP normalization [5, 8]. Little is known about hearing loss in IIH patients. A reversible hearing threshold elevation has been documented in raised ICP attributed to brain tumors or hydrocephalus [9]. Transmission of ICP changes to the inner ear fluids has been demonstrated in both humans [10, 11] and animal models [12, 13]. Preclinical evidence showed that the inner ear fluid pressure (both in the endolymph and perilymph) increases proportionally to the ICP increase, inducing the alteration of cochlear auditory system [13].

Endolymphatic hydrops (ELH) is the anatomopathologic correlate of inner ear pressure increase and may result from several conditions [14]. Ménière disease (MD) is considered the "idiopathic syndrome of ELH" [15] and its typical presentation includes vertigo, dizziness, tinnitus, hearing fluctuation and aural fullness.

Aim of the study

To further elucidate the relationship between the raised ICP and ELH, we evaluated the prevalence of typical ELH symptoms in patients affected by IIH/IIHWOP before and after ICP normalization by lumbar puncture (LP).

Patients and methods

Consecutive patients diagnosed with IIH/IIHWOP according to recent diagnostic criteria [16] were included in this study. All the patients signed an informed consent. The study has been performed in accordance with the Declaration of Helsinki and latest revisions.

All patients underwent an uncontrasted magnetic resonance (MR) of the brain with venography (MRV) and an ophthalmological evaluation to assess the presence/absence of papilledema. Data regarding the characteristics and frequencies of headache and of possible ELH-related audiovestibular symptoms occurring during the month preceding LP were collected. Each ELH symptom was considered as "present" if it was reported at least once. Each patient performed a standard audiometry within the week before LP, and a second test was performed after LP (within 1 week or at the resolution of post LP headache). A pure-tone average (PTA) threshold at each of the 0.125, 0.25, 0.5, 1, 2, 3. 4, 6, and 8 kHz was calculated for each ear separately, and the PTA values of both ears of each patient were used for subsequent analyses. We used the PTA in dB as a continuous variable. Low-frequency PTA (125, 250, and 500 Hz) and high-frequency PTA (2, 3, 4, 6, and 8 kHz) were also calculated. LP was performed in the recumbent lateral position; ICP was measured as opening pressure (OP) and every 2 ml of cerebrospinal fluid (CSF) withdrawal up to about 100 mm H_2O.

At a follow-up visit one month after LP, chronic headache and each ELH symptom (tinnitus, dizziness, aural fullness, and vertigo) were considered "improved" if their frequency was reduced at least by 50%. Changes in symptoms frequency was evaluated as percentage change: (new percentage − old percentage)/old percentage. Differences in symptoms frequency were evaluated by McNemar test on paired proportions. Significance level was set at 0.05. The differences in PTA between pooled ears before and after LP were assessed using the Wilcoxon test with significance level at 0.05. Analyses were performed using the software SPSS version 22.

Results

Thirty-one patients (29 women and 2 men; mean age 35.2 ± 11.0) were included (17 with IIH and 14 with IIHWOP). Chronic headache with migraine feature was present in 29 out of 31 patients (93.5%). Significant sinus stenosis was found in 30 patients (96.7%). This was unilateral in 21 (67.7%) and bilateral in 9 (29%). The percentage of patients referring tinnitus was 67.7%, dizziness was present in 77.4%, aural fullness was referred by 61.3% of the patients, and episodes of vertigo observed in 22.6% of the cases.

Mean OP was 287 ± 47.4 mmH_2O (302 ± 55.9 mmH_2O in IIH and 267 ± 22.9 mmH_2O in IIHWOP). A mean of 27.0 ml of CSF was subtracted (range 16–36).

At 1 month after LP, a chronic pattern of headache (>15 days per month) was encountered in only 6 out 31 patients (19.4%) with a percentage reduction of 79.2% compared with baseline ($p < 0.01$). The prevalence of each ELH symptom after LP significantly reduced ($p < 0.05$): [tinnitus 16.1% (76.2% reduction); dizziness 12.9% (83.3% reduction); aural fullness 9.7% (84.2% reduction); and vertigo 0% (100% reduction)].

The median of PTA at baseline was 16.9 dB (interquartile range 10.6) and it significantly reduced to 14.1 (interquartile range 11.7) after ICP normalization ($p < 0.05$). A difference in low-frequency PTA ($p < 0.05$) was found after LP, while no difference in high-frequency PTA was observed.

Discussion

As expected, almost all the patients of this series carried significant intracranial sinus stenosis, confirming its role as a neuroradiological marker of raised ICP [16, 17]. We

found a high prevalence of vestibular symptoms in our series of IIH/IIHWOP patients. Besides tinnitus, dizziness and vertigo, which have already been associated to the condition [4, 5], aural fullness also is commonly complained by these patients. To the best of our knowledge, this association has not been previously reported. Thus, the cluster of vestibular symptoms occurring in IIH/IIHWOP fully overlap with typical ELH clinical presentation [15]. This observation may be of relevance in IIHWOP diagnosis, a neglected condition often overlooked or misdiagnosed as a primary chronic headache [1–3]. We documented a dramatic reduction of both chronic headache and ELH symptoms soon after the LP as well as the improvement of PTA. These findings strongly support a role for the raised ICP in ELH mechanisms, possibly mediated by direct pressure transmission to the inner ear fluids [13].

Vertigo, dizziness, and migraine are commonly comorbid conditions. The identification of migraine-associated vertigo or dizziness led in the past decades to the definition of Vestibular Migraine (VM) [18], experimental diagnostic criteria of which have been included in the appendix of the ICHD 3beta version [19]. Mechanisms underlying this association still need to be clarified. A recent study revealed the presence of ELH in VM patients by locally enhanced inner ear MR [20], suggesting that vestibular symptoms in VM are caused by a derangement of inner fluids pressures.

Sinus stenosis is a very common finding in chronic headache patients [1, 21, 22], and a raised ICP may be causatively involved in pain mechanisms in these patients [1]. Our findings suggest the causative role of raised ICP also in ELH, allowing us to hypothesize that an overlooked IIH/IIHWOP may represent the shared pathogenetic step explaining the large epidemiological comorbidity between migraine and vestibular symptoms, at present conceptualized as "vestibular migraine."

Conclusions

Vestibular symptoms in IIH/IIHWOP also include aural fullness, therefore mimicking the typical ELH syndrome, and revert after ICP normalization. This finding supports the hypothesis that an overlooked IIHWOP may represent the shared pathogenetic step explaining the association between migraine and vestibular symptoms in VM. Further studies assessing the prevalence of sinus stenosis and of other neuroradiological signs of intracranial hypertension in VM patients are needed.

Compliance with ethical standards

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. De Simone R, Ranieri A, Montella S et al (2014) Intracranial pressure in unresponsive chronic migraine. J Neurol 261(7):1365–1373
2. Mathew NT, Ravishankar K et al (1996) Coexistence of migraine and idiopathic intracranial hypertension without papilledema. Neurology 46:1226–1230
3. Vieira DS, Masruha MR et al (2008) Idiopathic intracranial hypertension with and without papilloedema in a consecutive series of patients with chronic migraine. Cephalalgia 28:609–613
4. Wall M, Kupersmith MJ, Kieburtz KD (2014) The idiopathic intracranial hypertension treatment trial: clinical profile at baseline. JAMA Neurol 71(6):693–701
5. Sismanis A (1988) Pulsatile tinnitus. A 15-years experience. Am J Otol 19:472–477
6. De Simone R, Ranieri A, Montella S et al (2014) The role of dural sinus stenosis in idiopathic intracranial hypertension pathogenesis: the self-limiting venous collapse feedback-loop model. Panminerva Med 56(3):201–209
7. De Simone R, Ranieri A, Bonavita V (2017) Starling resistors, autoregulation of cerebral perfusion and the pathogenesis of idiopathic intracranial hypertension. Panminerva Med 59(1):76–89
8. Chiarella G, Bono F, Cassandro C et al (2012) Bilateral transverse sinus stenosis in patients with tinnitus. Acta Otorhinolaryngol Ital 32:238–243
9. Saxena RK, Tandon PN, Sinha A et al (1969) Auditory functions in raised intracranial pressure. Acta Otolaryngol 68(5):402–410
10. Macrae JH (1972) Effects of body position on the auditory system. J Speech Hear Res 15:330–339
11. Voss SE, Horton NJ, Tabucchi TH et al (2006) Posture-induced changes in distortion-product otoacoustic emissions and the potential for noninvasive monitoring of changes in intracranial pressure. Neurocrit Care 4(3):251–257
12. Carlborg B, Farmer JC (1983) Transmission of cerebrospinal fluid pressure via the cochlear aqueduct and endolymphatic sac. Am J Otolaryngol 4:273–282
13. Yoshida M, Uemura T (1991) Transmission of cerebrospinal fluid pressure changes to the inner ear and its effect on cochlear microphonics. Eur Arch Otorhinolaryngol 248(3):139–143
14. Semaan MT, Megerian CA (2010) Contemporary perspectives on the pathophysiology of Meniere's disease: implications for treatment. Curr Opin Otolaryngol Head Neck Surg 18(5):392–398
15. Lopez-Escamez JA, Carey J, Chung WH et al (2015) Diagnostic criteria for Menière's disease. J Vestib Res 25(1):1–7
16. Friedman DI, Liu GT, Digre KB (2013) Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology 81(13):1159–1165
17. Farb RI, Vanek I, Scott JN et al (2003) Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. Neurology 60:1418–1424
18. Neuhauser H, Leopold M, von Brevern M et al (2001) The interrelations of migraine, vertigo, and migrainous vertigo. Neurology 56:436–441

19. International Headache Society Classification Subcommittee (2013) The International Classification of Headache disorders, 3rd edn (beta version). Cephalalgia 33:629–808
20. Gürkov R, Kantner C, Strupp M et al (2014) Endolymphatic hydrops in patients with vestibular migraine and auditory symptoms. Eur Arch Otorhinolaryngol 271(10):2661–2667
21. Fofi L, Giugni E, Vadala R et al (2012) Cerebral transverse sinus morphology as detected by MR venography in patients with chronic migraine. Headache 52(8):1254–1261
22. Bono F, Salvino D, Tallarico T et al (2010) Abnormal pressure waves in headache sufferers with bilateral transverse sinus stenosis. Cephalalgia 30(12):1419–1425

Neurol Sci (2017) 38 (Suppl 1):S197–S199
DOI 10.1007/s10072-017-2942-5

BRIEF COMMUNICATION

Non-invasive vagus nerve stimulation (nVNS) as symptomatic treatment of migraine in young patients: a preliminary safety study

Licia Grazzi[1,2] · Gabriella Egeo[3] · Eric Liebler[4] · Anna Maria Padovan[5] · Piero Barbanti[3]

Abstract Recent clinical experiences and clinical trials have demonstrated the safety, tolerability, and efficacy of non-invasive vagus nerve stimulation (nVNS; gammaCore®) for the acute and prophylactic treatment of migraine. nVNS has a favorable adverse event profile, making it an attractive option for sensitive patient populations. We explored the safety, tolerability, and efficacy of nVNS as acute migraine treatment in adolescents. A group of adolescent patients suffering from migraine without aura were trained to use gammaCore to manage their migraine attacks. 46.8% of the treated migraine attacks (22/47) were considered successfully treated and did not require any rescue medication. No device-related adverse events were recorded. This preliminary study suggests that nVNS may represent a safe, well-tolerated, and effective for acute migraine treatment in adolescents.

Keywords Young age · Migraine without aura · Symptomatic treatment · nVNS approach · gammaCore device

✉ Licia Grazzi
licia.grazzi@istituto-besta.it

[1] Headache Center, Carlo Besta Neurological Institute and Foundation, Milan, Italy

[2] Headache Unit, "C. Besta" Neurological Institute and Foundation, Via Celoria, 11, 20133 Milan, Italy

[3] Headache and Pain Unit, Department of Neurological Motor and Sensorial Science, Istituto di Ricovero e Cura a Carattere Scientifico, San Raffaele Pisana, Rome, Italy

[4] ElectroCore, LLC, Basking Ridge, NJ, USA

[5] Kiara Association, Torino, Italy

Background

Migraine, a highly disabling neurological disorder, is characterized by recurrent moderate to severe episodes associated with vegetative symptoms [1]. Migraine is also a well-recognized entity in adolescents, an important factor epidemiologically [2]. Pharmacological treatments generally used in adults, are often applied to young patients even if associated with problematic side effects or contraindications. Clinicians and researchers are interested in novel and non-invasive approaches to treating young migraine patients [3].

During the last decade, neuromodulatory approaches have been developed to manage headaches that do not respond adequately to traditional therapy [4].

Several neuromodulatory approaches, beginning with invasive devices have been tried with encouraging results [4].

Subsequent to the use of implanted vagus nerve stimulation (iVNS), as a treatment for epilepsy, depression, and more recently for intractable headache [5–8], a non-invasive VNS device (nVNS gammaCore) has been developed and is CE-marked [9] for acute and prophylactic treatment of all forms of primary headache disorders including migraine, cluster headache, and in menstrual-related migraine [10–15]. In these clinical reports, the technique has been used for acute and preventive treatment without any significant device-related side effects. It appears convenient to use and is well tolerated by patients [15, 16].

It is a favorable adverse event profile, makes it a particularly interesting option for sensitive patient populations.

We explored the safety, tolerability, and effectiveness of nVNS as an acute migraine treatment in a population of adolescents suffering from migraine without aura.

Methods

In this open-label, single-arm study, 9 adolescents (3 males; 6 females), 13 to 18 years old, suffering from migraine without aura were included in this study; diagnosis was made according to *International Classification of Headache Disorders, 3rd edition (beta version)* criteria [1]; migraine frequency ranged from 4 to 8 migraine days per month.

Patients were consecutively enrolled at the headache center of the Neurological Institute C. Besta in Milan; patients and their parents provided written informed consent before recruitment. The study population excluded patients with a history of seizure, heart arrhythmias, and syncope.

A monthly educational meeting with the neurologist and a nurse-counselor, involving patients and their parents with groups of 3–5 patients was performed.

Patients and their parents were instructed, during a one-hour training session, on the use of the nVNS device for the self-treatment migraine attacks over a 4-week period (4 to 8 episodes) [15].

For each attack, patients delivered one 120-s of electrical stimulation on the right side of the neck; a second stimulation was allowed within 1 h of the first stimulation, as needed, if the patient was not pain free. Patients recorded pain intensity at several pre-specified time points between 30 min and 24 h after treatment. Rescue medication was allowed after 2 h from device use if they perceived no meaningful reduction in pain.

At the end of the study, patients and parents completed a questionnaire: which asked for a score on a scale from 0 to 5 concerning effectiveness, safety, and feasibility of the technique (where 0 was the lowest score and 5 the highest score).

Results

Forty-seven migraine attacks were treated. Twenty-two out of 47 (46.8%) did not require rescue medication: in particular, pain freedom in 1 h occurred in 19 attacks (40.4%) and pain relief at 2 h was reported in an additional 3 attacks (6.3%) with one stimulation. No device-related adverse events were recorded. Twenty-five attacks required rescue medication, these patients feared progression to a more intense migraine and chose to take the medication less than 1 h after treatment with VNS.

All Patients and parents completed the questionnaire: all of them considered the sage and east to use (score 5); regarding overall effectiveness, 5 patients provided the highest satisfaction (score 5), while 4 of them were not at all satisfied.

Conclusions

This preliminary study suggests that the use of nVNS in adolescents is safe and well tolerated and practical for the treatment of migraine without aura.

Acute treatment was effective in almost a half of the migraine attacks (46.8%): none of them required rescue medications.

As previously reported [15, 16], initiation of nVNS treatment when pain is milder in intensity is more likely to result in a pain-free outcome at 1 h. This is particularly relevant given the rapid onset and short duration of attacks that occur in adolescents [15].

Results of this pilot study are comparable to open-label data from other sensitive patient populations [15, 16] and provide a rationale for larger studies on nVNS as a potential acute treatment option for adolescents with migraine.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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. Wober-Bingol C (2013) Epidemiology of migraine and headache in children an adolescents. Curr Pain Headache Rep 17(6):341
3. Hershey AD (2010) Current approaches to the diagnosis and management of paediatric migraine. Lancet Neurol 9(2):190–2014
4. Magis D, Schoenen J (2012) Advances and challenges in neurostimulation for headaches. Lancet Neurol 11(8):708–719. doi:10.1016/S1474-4422(12)70139-
5. Connor DE Jr, Nixon M, Nanda A, Guthikonda B (2012) Vagal nerve stimulation for the treatment of medically refractory epilepsy: a review of the current literature. Neurosurg Focus 32(3):E12. doi: 10.3171/2011.12.FOCUS11328
6. Grimm S, Bajbouj M (2010) Efficacy of vagus nerve stimulation in the treatment of depression. Expert Rev Neurother 10(1):87–92. doi:10.1586/ern.09.138
7. Mauskop A (2005) Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. Cephalalgia 25(2):82–86. doi: 10.1111/j.1468-2982.2005.00611.x
8. Multon S, Schoenen J (2005) Pain control by vagus nerve stimulation: from animal to man...And back. Acta Neurol Belg 105(2):62–67
9. ElectroCore® receives FDA approval for chronic migraine study. http://www.electrocoremedical.com/electrocore-receives-fda-approval-for-chronic-migraine-study. Published June 14, 2012. Accessed April 17, 2015
10. Jürgens TP, Leone M (2013) Pearls and pitfalls: neurostimulation in headache. Cephalalgia 33(8):512–525. doi:10.1177/0333102413483933
11. Goadsby PJ, Grosberg B, Mauskop A, Cady R, Simmons KA (2014) Effect of noninvasive vagus nerve stimulation on acute

migraine: an open-label pilot study. Cephalalgia 34(12):986–993. doi:10.1177/0333102414524494

12. Nesbitt AD, Marin JC, Tompkins E, Ruttledge MH, Goadsby PJ (2015) Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. Neurology 84(12):1249–1253. doi:10.1212/WNL.0000000000001394
13. Silberstein SD, Da Silva AN, Calhoun AH et al. (2014) Non-invasive vagus nerve stimulation for chronic migraine prevention in a prospective, randomized, sham-controlled pilot study (the EVENT Study): report from the double-blind phase. Late-breaking poster presented at: 56th Annual Scientific Meeting of the American Headache Society; Los Angeles, California; June 26–29, 2014. LBP19
14. Gaul C, Diener HC, Solbach K et al (2014) gammaCore® use for prevention and acute treatment of chronic cluster headache: findings from the randomized phase of the PREVA study. Ann Neurol 76(suppl 8):S15
15. Barbanti P, Grazzi L, Egeo G, Padovan AM, Liebler E, Bussone G (2015) Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: an open-label study. The Journal of Headache and Pain 16:61
16. Grazzi L, Egeo G, Calhoun AH, McClure CK, Liebler E, Barbanti P (2016) Non-invasive vagus nerve stimulation (nVNS) as mini-prophylaxis for menstrual/menstrually related migraine: an open-label study. J Headache and Pain 17(1):91

Neurol Sci (2017) 38 (Suppl 1):S201–S206
DOI 10.1007/s10072-017-2916-7

BRIEF COMMUNICATION

Transcutaneous supraorbital neurostimulation for the prevention of chronic migraine: a prospective, open-label preliminary trial

Paola Di Fiore[1] · Gennaro Bussone[2] · Alberto Galli[1] · Henri Didier[3] · Cesare Peccarisi[4] · Domenico D'Amico[5] · Fabio Frediani[1]

Abstract Since chronic migraine is difficult to treat and often associated with medication overuse, non-invasive neurostimulation approaches are worth investigating. Transcutaneous supraorbital neurostimulation using the Cefaly® device is promising as a non-invasive preventive treatment for episodic migraine, but no data are available for chronic migraine. Our aim was to perform a preliminary evaluation of the efficacy of the Cefaly® device for the prophylaxis of chronic migraine with or without medication overuse. Primary endpoints were 50% reduction in monthly migraine days and 50% reduction in monthly medication use over 4 months. In an open-label study, twenty-three consecutive headache center patients with chronic migraine, diagnosed according to International Headache Society criteria, were recruited prospectively. After informed consent, patients were trained to use Cefaly® and instructed to use it for 20 min daily over 4 months. All patients received active neurostimulation. Thirty-five percent of the patients enrolled in the study achieved the study endpoints. Over half the patients had a greater than 50% reduction in acute medication consumption.

Keywords Chronic migraine · Migraine prophylaxis · Medication overuse · Transcutaneous supraorbital neurostimulation

✉ Paola Di Fiore
paola.difiore@libero.it

[1] Neurological and Stroke Unit Department, Headache Center, ASST Santi Paolo e Carlo, San Carlo Borromeo Hospital, Via Pio II, 3, 20153 Milan, Italy

[2] C. Besta Neurological Institute IRCCS Foundation and Igea Healthcare Institute, Milan, Italy

[3] Maxillo-Facial and Dental Unit, Dental and Oral Surgery, Headache and Facial Pain Center, IRCCS Foundation Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

[4] LIMPE-DISMOV Academy, University La Sapienza, Rome, Italy

[5] Headache Center, Carlo Besta Neurological Institute and Foundation, Milan, Italy

Introduction

Chronic migraine (CM) is estimated to affect 2–4% of the population, while the prevalence of CM with medication overuse (MO) is estimated at 0.7–1.7% [1, 2]. Although various acute and prophylactic treatments are effective against episodic migraine, pain remains an unsolved problem in CM patients, who by definition have frequent, disabling headaches that are difficult to treat [3, 4]. Furthermore, because CM patients frequently develop MO, it may be useful to find effective non-pharmaceutical treatment modalities. Invasive neurostimulation procedures (deep brain stimulation, greater occipital nerve stimulation, sphenopalatine ganglion stimulation, vagus nerve stimulation, supraorbital nerve stimulation) have been shown that can be effective in primary headache. However, non-invasive neurostimulation would be preferable to invasive neurostimulation, and several non-invasive methods have been developed over the last decade to prevent headache attacks in patients with migraine without aura. In particular, transcranial magnetic stimulation, repetitive transcranial magnetic stimulation, and transcutaneous supraorbital neurostimulation (TSNS) have proven effective and safe as treatments for episodic migraine without aura [5–8].

TSNS with the Cefaly® device (Cefaly Technology, Liège, Belgium) has been used for preventive treatment in

episodic migraine. The multicentre PREMICE trial conducted by Schoenen and collaborators showed that treatment with the Cefaly supraorbital transcutaneous stimulator was safe and effective as preventive therapy for migraine [9]. However, this treatment has not been used in CM patients. The aim of the present study was to perform a preliminary evaluation of the efficacy and safety of the Cefaly device in CM prophylaxis.

Patients and methods

Twenty-three consecutive patients with a diagnosis of CM with or without MO according to the International Classification of Headache Disorders (ICHD-3) criteria [10] were recruited from among those attending three Italian Headache Centers over the period April to December 2014. Patients were recruited six at a time as only six Cefaly® devices were available for the study. Inclusion criteria were: (a) 18 years old or more (b) CM for at least 1 year, (c) no participation in withdrawal program to stop MO over the previous year, (d) normal neurological examination, (e) normal neuroimaging findings, (f) absence of major neurological, systemic or psychiatric illness, and (g) not pregnant. The absence of major disease and pregnancy was reported by patients at the baseline (T0) visit during which diaries reporting headache days and analgesic consumption over the preceding three months were inspected by the treating neurologist. All patients gave written informed consents to participate. Preexisting preventive and acute treatments for CM were not changed.

All recruited patients were prescribed active treatment with Cefaly® device's Programme 2, designed to prevent migraine. They first received training with the device. Each patient was given a device to take home and use for the duration of the study (4 months). Instructions were to use it for 20 min each day over the 4-month study period. Patients were also asked to continue with their headache diaries, recording days with headache and every time they took acute medication for their headache.

Patients were followed up monthly at the outpatient department of San Carlo Borromeo Hospital, Milan. They brought with them their Cefaly® devices which were checked for correct use (particularly frequency of use) by means of dedicated software. Headache diaries were checked, and patients were questioned about device tolerability.

The primary endpoints were 50% or more reduction in headache days per month, and 50% or more reduction in consumption of acute headache relief medications per month.

The Cefaly® device is provided with a self-adhesive bipolar electrode (30 × 94 mm) which is affixed to the center of forehead and extends bilaterally to the supraorbital nerves. When used for headache prophylaxis, the device generates biphasic rectangular impulses of 250 μs pulse width, 60 Hz frequency, and 16 mA current intensity for a fixed period of 20 min.

Tests of descriptive statistics were used to describe the categorial data.

Results

Eighteen (78.3%) of the 23 patients were female, 14 (60.9%) had MO. Mean age was 43.7 ± 13.6 years; mean duration of headache condition was 26.4 ± 12.8 years, and mean duration of the chronic phase was 10.7 ± 8.7 years. At baseline, patients were experiencing a mean of 20.7 ± 5.7 migraine days per month, and were taking acute headache relief medications a mean of 20.2 ± 12.4 times per month.

All patients were also taking prophylactic medication (tricyclic antidepressants, calcium channel blockers, beta blockers, anti-epilepsy drugs) and had been doing so for at least the previous year.

Four (17.4%) patients dropped out: one a few days after recruitment when another comorbidity (keratoconjunctivitis) occurred. The other three dropped out within one month after enrollment (T1) for inability to tolerate TSNS: one reported headache worsening and two reported development of neck tension.

The remaining 19 patients completed the four-month follow-up. Headache days per month and monthly drug consumption are shown in Tables 1 and 2, respectively. For the 19 patients, the mean overall decrease in migraine days per month was 31.0%, and mean overall decrease in acute medication consumption was 49.6%. Twelve patients reduced acute medication consumption by at least 50%: actual reduction was 65.5% (19.6/month at T0, 6.8/month at T4).

Eight (34.8%) patients achieved both endpoints and were, therefore, considered responders: mean reduction in headache days per month was 57.9% (18.1 at T0, 7.6 at T4, Fig. 1); mean reduction in acute medication consumption was 68.8% (20/month at T0, 6.3/month at T4, Fig. 2). As is evident from Figs. 1 and 2, these improvements in responders were achieved gradually.

Among the 11 patients (47.8% of 23) who completed the study and did not achieve both primary endpoints, migraine days/month reduced by 15.3%, and monthly acute medication reduced by 35.9%. If we consider significant a reduction of at least 50%, neither of these reductions can be considered clinically significant.

Thirteen (68.4%) of the 19 patients who completed the study had medication overuse, including 6 (75%) of the 8

Table 1 Migraine days per month at baseline (T0) and monthly (T1–T4) over the 4-month study period in 23 chronic migraine patients prescribed active supraorbital stimulation with the Cefaly® device

Patients	T0	T1	T2	T3	T4
1	30	30	30	30	30
2	20	20	14	20	15
3	15	14	15	12	12
4	20	9	7	8	21
5	15	12	3	10	16
6	28	16	15	18	7[a]
7	30	30	30	30	30
8	28	22	24	20	18
9	15	15	10	11	13
10	20	14	16	14	9[a]
11	16	8	8	7	8[a]
12	15	14	8	9	7[a]
13	15	14	9	11	7[a]
14	20	7	10	13	10[a]
15	21	20	16	14	19
16	15	5	5	4	5[a]
17	17	10	8	6	8[a]
18	28	29	20	20	18
19	26	24	26	25	18
Tot (mean)	394 (20.7)	313 (16.5)	274 (14.4)	282 (14.8)	271 (14.3)
20	15	n.a.		Drop-out	
21	30	n.a.			
22	20	n.a.			
23	15	n.a.			
Tot (mean)	474 (20.6)				

[a] Decrease ≥50%

responders. These data suggest that MO had no influence on whether or not TSNS was effective.

The monthly tests conducted on the Cefaly® devices using the dedicated software showed that all patients who completed the study used the device (Programme 2 setting) everyday for 20 min. As noted, three patients reported side effects at T1 and withdrew from the study. None of the other patients reported side effects and at any of the monthly follow-ups.

Discussion

Our study, even if there are some limitations, can stimulate several considerations. It is an open-label trial and the number of patients is limited. But to date, there are no available data on supraorbital neurostimulation in chronic migraine. Eight (34.8%) of our recruited patients achieved both endpoints, with a mean reduction in headache days of 57.9% and a mean reduction in medication consumption of 68.8%. Three (13.0%) patients withdrew for inability to tolerate the Cefaly® device. These results are encouraging: they support that Cefaly® is safe and generally well tolerable for CM treatment.

The fact that about 35% of patients achieved benefit over four months is particularly encouraging because headache center CM patients are difficult to treat [11–14], and our patients in particular had long chronic phase illness duration (mean 10.7 years, range 1–44) and most (60.9%) had MO.

If treatments do not produce reliable or significant pain relief, episodic migraine sufferers tend to overuse symptomatic drugs. MO is in fact a major risk factor for the transformation of episodic migraine into CM [15–18]. Thus, it is particularly noteworthy that medication intake reduced by at least 50% in 65% (12 patients about 19 of the group) of the patients who completed our study. Reduced drug consumption may reduce the risk of iatrogenic complications, and may also tend to restore the patient to 'normal' drug user status.

Previous prophylactic treatment had not been changed and this does not seem to modify the response to TSNS.

There is evidence that detoxification improves outcomes and the efficacy of subsequent prophylactic medication in

Table 2 Monthly acute medication consumption at baseline (T0) and over the 4-month study period (T1–T4) in 23 chronic migraine patients prescribed active supraorbital stimulation with the Cefaly® device

Patient	T0	T1	T2	T3	T4
1	60[a]	40	40	40	40
2	20[a]	14	7	11	10[b]
3	15[a]	5	5	6	3[b]
4	30[a]	18	14	5	14[b]
5	10	7	7	8	4[b]
6	20[a]	16	13	13	6[b]
7	5	5	7	6	7
8	8	7	7	6	5
9	20[a]	15	10	11	13
10	20[a]	20	19	17	10[b]
11	10	5	6	4	4[b]
12	22[a]	17	4	4	4[b]
13	28[a]	8	5	6	5[b]
14	25[a]	7	10	13	12[b]
15	21[a]	24	16	14	19
16	5	0	0	0	1[b]
17	30[a]	15	10	6	8[b]
18	12	7	6	8	8
19	22[a]	18	22	21	20
Tot (mean)	383 (20.2)	248 (13.1)	208 (10.9)	199 (10.5)	193 (10.2)
20	20[a]	n.a.		Drop-out	
21	8	n.a.			
22	20[a]	n.a.			
23	12	n.a.			
Tot (mean)	443 (19.3)				

[a] Abuser

[b] Decrease ≥50%

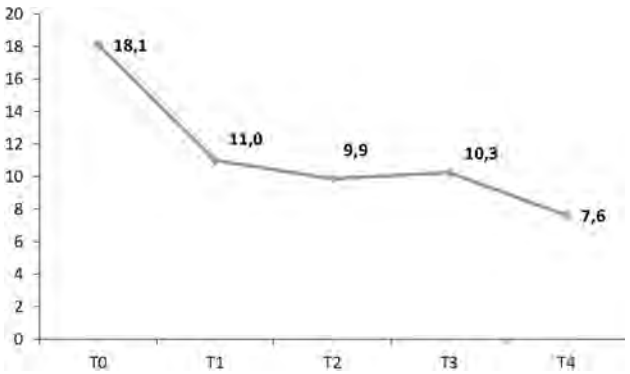

Fig. 1 Mean migraine days per month in responders: 4-month follow-up

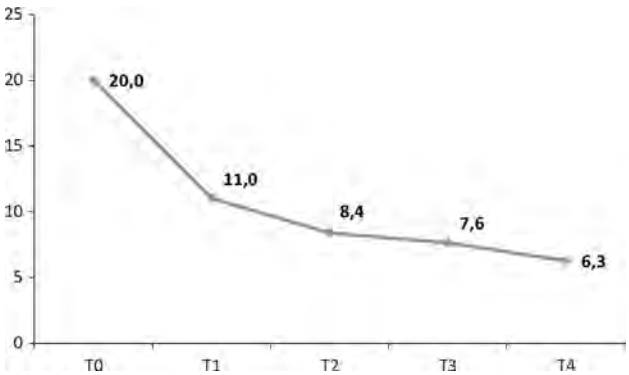

Fig. 2 Mean drugs per month in responders: 4-month follow-up

CM patients with MO [19–21]. Several studies have evaluated the efficacy of pharmaceutical prophylactics in CM. Double-blind placebo-controlled studies on tizanidine [22], gabapentin [23], and sodium valproate [24] showed significant improvements, in all cases without tolerance or safety problems. However, inadequacies in patient selection and study design do not allow firm conclusions about the efficacy of these agents. By contrast, topiramate appears an effective treatment for CM. Double-blind, randomized, placebo-controlled studies conducted for sufficient time show a >50% decrease in attack frequency in 22–77% of treated patients [25–28]. Topiramate with triptans may be able to revert CM with MO to episodic migraine [25]. Results of the PREEMPT double-blind,

randomized, placebo-controlled trials [29–32] indicate that onabotulinumtoxinA is also effective as a prophylactic agent in CM patients with MO.

However, prophylactic pharmaceuticals may be associated with side effects and intolerability, particularly on long-term use. About 15 years ago, central and peripheral neurostimulation techniques started being investigated as treatments for primary headaches, particularly for chronic drug-resistant headache forms [33]. However, while central neurostimulation has not been tested for CM, peripheral neurostimulation has been widely investigated as an alternative to pharmacological prophylaxis for this condition. Options have been proposed that act on occipital, supraorbital, or vagal nerves, the sphenopalatine ganglion peripheral, and that cerebral cortex. Efficacy findings are variable [6, 7, 34–39].

The first double-blind, randomized, sham-controlled trial of TSNS for the prevention of episodic migraine was conducted by Schoenen and colleagues on 67 patients [9]. They assessed the efficacy and safety of the Cefaly® device to stimulate the supraorbital region. They found, for the active stimulation group, that migraine days were reduced by 38.2%, and acute anti-migraine medication intake was reduced by 36.7%. The advantageous effect was achieved fairly early in the study and was maintained during follow-up. The mechanism by which supraorbital stimulation improves the condition of patients with migraine is unclear. It is known that trigeminovascular system is involved in migraine pathophysiology, so it has been suggested that transcutaneous stimulation of the supraorbital region may modulate pain transmission within this system [40, 41]. An alternative suggestion is that stimulation results in modulation of central pain matrix structures. This is supported by a fluorodeoxyglucose-positron emission tomography study on patients with refractory cluster headache. Following percutaneous occipital nerve stimulation, an increase in glucose metabolism was detected in perigenual anterior cingulate gyrus, possibly reflecting an alteration in top-down pain regulation [42].

Conclusions

This was a small, non-controlled study in which all participants received active TSNS with the Cefaly® device. It was in fact a preliminary study designed to indicate whether more rigorous studies are justified. The results are encouraging and suggest that this form of neurostimulation may have efficacy similar to that of established pharmacological prophylactics for CM [43]. It is particularly noteworthy that in over half the patients acute medication consumption was reduced by over 50%, suggesting that TSNS could be useful in reducing MO and medication-associated adverse events in CM patients. These findings justify use of the Cefaly® device in a randomized-controlled trial of real vs. sham neurostimulation in CM patients, including those with MO.

Compliance with ethical standards

Funding This study had no external funding source. Cefaly® devices were made available by the manufacturer (Cefaly Technology, Liège, Belgium) free of charge, for use in the study, Cefaly® Technology had no role in the design or conduct of the study

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Natoli J, Manack A, Dean B et al (2010) Global prevalence of chronic migraine: a systematic review. Cephalalgia 30:599–609
2. Evers S, Marziniak M (2010) Clinical features, pathophysiology, and treatment of medication-overuse headache. Lancet Neurol 9:391–401
3. D'Amico D, Grazzi L, Usai S et al (2011) Disability in chronic daily headache: state of the art and future directions. Neurol Sci 32:S71–S76
4. Manack AN, Buse DC, Lipton RB (2011) Chronic migraine: epidemiology and disease burden. Curr Pain Headache Rep 15:70–78
5. Jürgens TP, Leone M (2013) Pearls and pitfalls: neurostimulation in headache. Cephalalgia 33:512–525
6. Magis D, Schoenen J (2012) Advances and challenges in neurostimulation for headaches. Lancet Neurol 11:708–719
7. Magis D, Jensen R, Schoenen J (2012) Neurostimulation therapies for primary headache disorders: present and future. Curr Opin Neurol 25:269–276
8. Gallagher RM, Kunkel R (2003) Migraine medication attributes important for patient compliance: concerns about side effects may delay treatment. Headache 43:36–43
9. Schoenen J, Vandersmissen B, Jeangette S et al (2012) Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology 80:697–704
10. Headache Classification Committee of the International Headache Society (IHS) (2013) The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 33(9):629-808. doi:10.1177/0333102413485658
11. D'Amico D, Leone M, Grazzi L et al (2008) When should "chronic migraine" patients be considered "refractory" to pharmacological prophylaxis? Neurol Sci 29:S55–S58
12. Mathew NT (2009) Dynamic optimization of chronic migraine treatment: current and future options. Neurology 72:S14–S20
13. 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
14. Zwart JA, Dyb G, Hagen K et al (2003) Analgesic use: a predictor of chronic pain and medication overuse headache: the Head-HUNT study. Neurology 61:160–164
15. Katsarava Z, Schneeweiss S, Kurth T et al (2004) Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology 62:788–790
16. Bigal ME, Lipton RB (2009) What predicts the change from episodic to chronic migraine? Curr Opin Neurol 22:269–276

17. 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
18. Bigal ME, Serrano D, Buse D et al (2008) Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 48:1157–1168
19. 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
20. Freitag FG, Lake A 3rd, Lipton R, US Headache Guidelines Consortium, Section on Inpatient Treatment Chairpersons et al (2004) Inpatient treatment of headache: an evidence-based assessment. Headache 44:342–360
21. Zeeberg P, Olesen J, Jensen R (2006) Discontinuation of medication overuse in headache patients: recovery of therapeutic responsiveness. Cephalalgia 26:1192–1198
22. Saper JR, Lake AE 3rd, Cantrell DT et al (2002) Chronic daily headache prophylaxis with tizanidine: a doubleblind, placebo-controlled, multicenter outcome study. Headache 42:470–482
23. 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
24. Yurekli VA, Akhan G, Kutluhan S et al (2008) The effect of sodium valproate on chronic daily headache and its subgroups. J Headache Pain 9:37–41
25. Mei D, Ferraro D, Zelano G et al (2006) Topiramate and triptans revert chronic migraine with medication overuse to episodic migraine. Clin Neuropharmacol 29:269–275
26. Silvestrini M, Bartolini M, Coccia M et al (2003) Topiramate in the treatment of chronic migraine. Cephalalgia 23:820–824
27. Diener HC, Bussone G, Van Oene JC, TOPMAT-MIG-201(TOPCHROME) Study Group et al (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia 27:814–823
28. Silberstein S, Lipton RB, Dodick DW et al (2007) Efficacy and safety of topiramate in the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. Headache 47:170–180
29. Silberstein SD, Blumenfeld AM, Cady RK et al (2013) OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci 331:48–56
30. Dodick DW, Turkel CC, DeGryse RE, PREEMPT Chronic Migraine Study Group et al (2010) OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 50:921–936
31. Aurora SK, Dodick DW, Turkel CC, PREEMPT 1 Chronic Migraine Study Group et al (2010) OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 30:793–803
32. Diener HC, Dodick DW, Aurora SK, PREEMPT 2 Chronic Migraine Study Group et al (2010) OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 30:804–814
33. 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
34. Lambru G, Matharu MS (2014) Peripheral neurostimulation in primary headaches. Neurol Sci 35:77–81
35. Saper JR, Dodick DW, Silberstein SD et al (2011) Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia 31:271–285
36. Bartsch T, Paemeleire K, Goadsby PJ (2009) Neurostimulation approaches to primary headache disorders. Curr Opin Neurol 22:262–268
37. Popeney CA, Aló KM (2003) Peripheral neurostimulation for the treatment of chronic, disabling transformed migraine. Headache 43:369–375
38. Dodick DW, Silberstein SD, Reed KL et al (2015) Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: long-term results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia 35:344–358
39. Tepper SJ, Rezai A, Narouze S et al (2009) Acute treatment of intractable migraine with sphenopalatine ganglion electrical stimulation. Headache 49:983–989
40. Noseda R, Burstein R (2013) Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. Pain 154:S44–S53
41. Bartsch T, Goadsby PJ (2003) The trigeminocervical complex and migraine: current concepts and synthesis. Curr Pain Headache Rep 7:371–376
42. 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
43. D'Amico D (2010) Pharmacological prophylaxis of chronic migraine: a review of double-blind placebo-controlled trials. Neurol Sci 31:S23–S28 **(369–375)**

Neurol Sci (2017) 38 (Suppl 1):S207–S212
DOI 10.1007/s10072-017-2951-4

POSTERS

An unusual cluster headache

S. Magno[1], M. Secchi[2], D. Belvedere[2], C. Rosci[2], C. Casellato[2], C. Gambini[2], L. Campiglio[2], F. Bianchi[1], A. Priori[1,2]

[1]School of Neurology, University of Milan, Milan, Italy
[2]ASST Santi Paolo e Carlo, III Neurologic Clinic, Milan, Italy

We report a case of a 21-year-old man with a 5-year history of typical Cluster Headache who developed a progressive stabbing headache associated with dizziness and visual blurring. A brain MRI was performed showing a pituitary adenoma and white matter hyperintensities. The patient underwent further investigation: the spine MRI disclose a contrast enhanced cervical lesion; CSF studies showed oligoclonal band; infective and autoimmune screening comprehensive of HLAB51 were within normal limits. The patient was treated with Cabergoline and Amitriptiline with symptoms resolution. Subsequent brain and spine control MRI showed lesions dissemination in time and space leading to a diagnosis of Multiple Sclerosis. The patient was therefore started with Galatiramer Acetate. This case highlights the importance of careful follow up in order to promptly recognize novel pain characteristics without overlooking symptoms that could hide concomitant evolving diseases.

Headache in immigrants living in Italy: differences between various ethnic groups

F. De Marchi, G. Tondo, L. Magistrelli, L. Bolamperti, D. Mittino, R. Cantello

Università del Piemonte Orientale, Ospedale Maggiore della Carità di Novara, Novara, Italy

Introduction and aim: Nowadays an increasing number of foreign patients come at our Headache Unit. The aim of our study was to analyze the headache features in immigrant patients (IM) referred to our Center and search for possible clinical and phenotypic differences between various ethnic groups.
Patients and methods: We conducted a retrospective study (12 months, year 2016) of the first visits of the IM to the Headache Unit at the Maggiore della Carità Hospital in Novara, Italy. We analyzed the country of birth, the time parameters of the headache, the diagnoses according to the IHS criteria and the therapy used.
Results: The IM represent 21.9% (n = 64) of the total number of first visits because of headaches (n = 292). IM came mostly from East Europe (43.8%); 26.57% from Africa, 15.63% from South of America, 9.38% from Asia. The distribution of the headache diagnoses is similar in the different ethnic groups, with the exception of the Asian patients, where the incidence of migraine is very low (<10%). In our population only the 10.94% of the IM know triptans before the first visit (and they came only from East Europe) and only 12.5% received a preventive treatment before. Nobody used triptan or received therapy prior to immigration.
Conclusions: With the exception of Asian patients, the type of headache in the IM is very similar whatever the origin. Moreover the use of appropriate symptomatic and preventive drugs is extremely low in the IM.

Botulinum toxin type A in chronic migraine with medication overuse: the experience of the Headache Centre of "Spedali Civili Brescia"

C.R. Mancinelli, S. Caratozzolo, E. Pari, R. Rao, P. Liberini, A. Padovani

Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia Italy

Objectives: Botulinum toxin type A (BoNT-A) has shown to be effective in the treatment of chronic migraine (CM) with or without medication overuse (MO). The aim of this study was to examine its efficacy and tolerability in the real-life setting.
Material: We reported a post-marketing experience of patients with CM with MO, diagnosed according to the International Headache Society diagnostic criteria, which started treatment with BoNT-A at the Headache Centre of the Neurology Unit, "Spedali Civili Hospital", Brescia, between September 2014 and November 2016.
Methods: BoNT-A was injected following the PREEMPT protocol, at the dosage of 155 UI for 31 fixed-sites or using a "follow-the-pain" strategy. No withdrawal treatment was carried out before starting BoNT-A. Clinical assessment comprised headache frequency and analgesic consumption, which were collected from the patients' headache diaries during pre-treatment period and throughout the study. Disability was documented with the Migraine Disability Assessment Score Questionnaire (MIDAS).
Results: We enrolled 17 consecutive CM patients (88%females) with a mean age of 48.9 ± 11.9 years, mean disease duration of 9.8 ± 5.0 years and a median past migraine prophylaxis treatment of 4 (range 1–9). All subjects received at least 3 infusions during a follow-up of 9 months. The Botulinum Toxin intervention elicited statistically significant changes in days with headache over time ($F_{(2,24)}$ = 10.557, p < 0.001, partial η2 = 0.398); there was a significant decrease in days with headache from 21.82 ± 5.02 to 13.18 ± 7.83 (p = 0.002) from the first to the third session of therapy. BoNT-A treatment reduced medication intake over time ($F_{(2,24)}$ = 4.604, p = 0.015, partial η2 = 0.223) without a significant decrease in analgesics per month (p = 0.060). A significant improvement was observed in the MIDAS score (p = 0.032). When we consider the intensity of headache, we find a significant decrease in days with mild headache from 12.24 ± 9.09 to 4.82 ± 5.68 (p = 0.049) from the first to the third session of therapy.
Conclusions: Treatment with BoNT-A is effective and well-tolerated in patients with CM associated to MO. However, we don't observe a significant reduction in the intake of analgesics.

Headaches in the elderly population

S. Caratozzolo, E. Pari, E. Venturelli, F. Rinaldi, C. Mancinelli, P. Liberini, R. Rao, A. Padovani.

Department of Clinical and Experimental Science, University of Brescia, Brescia, Italy

Background: Headache in community-living adults aged more than 65-year-old is the 10th most common reported symptom in women and the

14th most common in men. Although the prevalence of headache declines with age, approximately 10% of women and 5% of men, 70 years old aged, experience severe recurrent or constant headaches. Much less is known about the evolving clinical profile of migraine over life span. Present study aimed to investigate different type of headaches in elderly people and was carried out on a group of patient over 60 years of age.
Methods: 2032 consecutive patients assessed at the Headache Center of the Neurological ward of the Spedali Civili, Brescia, Northern Italy, between September 2011 and December 2013 were enrolled. Variables such as gender, years of headache duration, history of aura, headache characteristics, associated symptoms, presence of allodynia, headache frequency, headache days, and disability were collected. Medical history of these patients was also recorded. Headache diagnosis were made according to ICHD-2 criteria. Patients were stratified by age into 2 groups: group I (under 60 years old), group II (more than 60 years old).
Results: The diagnoses founded in patients aged more than 60 years old were: without aura migraine ($n = 23$; 5,3%), with aura migraine ($n = 2$; 11%) chronic migraine ($n = 11$, 15.7%), tension-type headache ($n = 1$; 5.6%), chronic tension-type headache ($n = 4$.10%), other headache ($n = 6$, 35.3%). Without aura migraine is the most frequent form of headache in aging patients, while chronic migraine showed a stable incidence during age.
Discussion: Although the prevalence of headaches in elderly is relevant, few epidemiological studies have been conducted so far. In most epidemiological studies concerning the adult population, in fact, have been studied subjects with less than 60 years old. Studies of community-based headache population are warranted to define the influence of age on the full spectrum of migraine.

Use of non-invasive vagus nerve stimulation for acute migraine attack

C.R. Mancinelli[1], S. Caratozzolo[1], A.M. Padovan[2], E. Pari[1], P. Liberini[1], R. Rao[1], A. Padovani[1]

[1]Department of Clinical and Experimental Science, University of Brescia, Brescia, Italy
[2]Kiara Association, Turin, Italy

Objectives: Non-invasive vagus nerve stimulation (nVNS) has been studied in several primary headache disorders. We investigated the effects of nVNS for acute treatment of migraine attacks in patients with high-frequency episodic and chronic migraine (HFEM and CM), associated to medication overuse (MO).
Methods: 14 patients with HFEM ($n = 9$) and CM ($n = 5$), complicated by MO, were enrolled in this 2-month, prospective, two-phase study. All patients received training on the proper use of the device, through a practical demonstration and an instructional video. In the first phase (phase A), attacks that occurred during a 1-month period were treated with two 90-second trials of nVNS at 15-minute intervals, delivered to the right cervical branch of the vagus nerve. Patients were allowed to take a rescue medication if they perceived no reduction in pain 2 h after nVNS treatment. In the second phase (phase B), patients treated all attacks with medication, as they usually did, without using the nVNS. At the end of the two phases of the study headache frequency and analgesic consumption were collected from the patients' headache diaries and health- and migraine-related quality of life were documented with the Short Form Health Survey (SF-36) and the Headache Impact Test (HIT-6), respectively.
Results: During phase A, 177 attacks were reported and all were treated with nVNS. Only 24 (13.5%) attacks required medical treatment within 2 hoursh of the onset of migraine while 70 attacks (39.6%) did not require the use of a rescue medication. When all attacks ($n = 177$) were considered, the pain-free rate was 5% at 30 minutesmin and 18% at 2 h, whereas the sustai ned pain-free rate was 62.1% at 24 h. The device was very well tolerated with no relevant adverse events. At the end of the two phases, no significant differences were observed in the mean number of attacks, in HIT 6 score and in all SF-36 items. In phase B, 175 attacks were reported and all required medical treatment**.** We observed a non-significant increase in the mean number of medication intake during phase B (from 11.9 to 14.1, $p = 0.211$).
Discussion: Our study showed that nVNS reduced the number of attacks requiring medical treatment (39.6%), while in phase B all attacks required analgesics (100%).
Conclusions: nVNS might potentially provide an effective and well-tolerated solution for the treatment of acute migraine attacks. Its use is desirable in order to reduce medication overuse and medication-associated adverse events.

Working difficulties caused by migraine: results of an Italian survey

D. D'Amico, C. Scaratti, E. Guastafierro, M. Leonardi, A. Raggi, L. Grazzi, S. Usai, V. Covelli

Fondazione Istituto Neurologico C. Besta, Milan, Italy

Different studies underlined the effect of headaches in general and particularly of migraine (M) on work. Considering the high lifetime prevalence of M (18.5%; 13% among men and 25.6% among women), this disorder is likely to cause social security problems connected to decreased productivity. There are no data related to the kind of working activity which are mostly related to the negative impact of M on workplace.
The aim of the present research was to understand which were the main difficulties on work activities reported by patients suffering from different forms of M.
In this a cross-sectional, observational study consecutive patients suffering from episodic and chronic M, all adults with a paid job, were recruited. Patients answered to a series of questions investigating several working areas (also rating the difficulty degree in each area), and different factors limiting work activity.
Data on the firs 63 patients (81.4% females; mean age 42.4 yrs; 68.3% with episodic, and 31.7% with chronic M) showed that, during the 30 days before recruitment, they have been absent from work for an average 1.6 working days, and working with headache for 11 days. The main working areas with difficulties due to M were: "manage business stress" (which was rated as severe by >40% of the sample), "pay attention to working tasks", "use the PC", "read and write", "manage the business stress", "manage the business problem", "talk and connect with other people", which were all rated as medium difficulties by >40% of the sample. The factors linked to M ranked as severe by >40% were "feel stunned/confused", "working stress", "sounds" and "ambient brightness".
Our results provide preliminary indications about the main difficulties reported by patients with M in doing their job. Further analyses on a larger, multicenter sample will enhance our knowledge about the work difficulties experienced by migraineurs, and about the possible differences existing in different forms (M without or with aura, chronic M)—eventually leading to the development and validation of a specific standardized tool, the HeadWork questionnaire.
This study was partially funded by ALLERGAN.

Headache in immigrants: similarities and differences with Italian population

G. Tondo, F. De Marchi, L. Magistrelli, E. Virgilio, L. Bolamperti, D. Mittino, R. Cantello

Università del Piemonte Orientale, Ospedale Maggiore della Carità di Novara, Novara, Italy

Background: Headache is one of the most common neurological diseases. It's well known that there are differences in the perception and in the management of pain in various populations. Immigrants represent a growing portion between neurology outpatients. We analyzed the epidemiological characteristic of headache in immigrants (IM) come to our attention during 2016, in comparison with Italians (IT).
Methods: Retrospective study (12 months) on the first visits to the Headache Unit at the Maggiore della Carità Hospital of Novara, Italy. Data collected included age at immigration, age of onset of headache, headache's type (HIS criteria) and psychiatric comorbidities.
Results: The number of patients was 292 (M:70). IM represents 22% (n = 64, M:13) of the total. The two groups did not differ for age at headache onset and age at the first access. There were not substantial differences in the incidence of headache subtypes: migraine was the most frequent diagnosis in both groups (70% IT, 64% IM), followed by tension type headache (13% IT, 20% IM). The incidence of depression was similar (9% *vs* 8%), while anxiety was significantly less frequent in IM (3% *vs* 8%).
Conclusions: Studies on neurological diseases in immigrants are few. The data available seem to show no differences in the incidence, but rather in treatment. Our study confirms the evenness of two population, local and foreign, afferent in a Headache Unit, according to the single similar study (Vidal-Jordana 2011), except for anxiety, maybe related to language difficulties or cultural background.

A case of intracranial hypertension attributed to anabolic and polivitaminic abuse

T. Croese, M. Cascavilla, G. Truci, G. Comi, B. Colombo

San Raffaele Hospital, Milan, Italy

We describe a case of a man, 36-year-old bodybuilder that after a car crash starts to experience unusual continuous pulsatile occipital headache (VAS 7–8/10) with concomitant multiple intermittent episodes of blurred vision. No nausea neither neck stiffness nor retro bulbar pain were reported. He had never experienced such a painful headache and there was no prior history of persistent headache. He reported regular assumption of various anabolic drugs for at least 2 years (Testoviron, Nandrolone, Testovis i.m. 2–3 per week, Trembolone i.m. 2 per week, Gonase, GH i.m. 2.4 U die, Insulina s.c. 5 U per day) and Vit. A 20000 UI/die 400% D.V. A CT was performed and found to be normal. A dilated fundus examination using a direct ophthalmoscope showed bilateral disc swelling. At the next ophthalmic evaluation, visual field showed an enlarged blind spot in both eyes. Optical coherence tomography (OCT) indicated bilateral optic nerve fibre layer elevation. Fluorescein angiography showed in OO a delayed venous outflow. In our department, a lumbar puncture performed in sitting position showed an opening pressure of 33 mmHg with a normal concentration of glucose, 82 mg/dl of proteins (n.v. 12–60 mg/dl) and 2 cells/μl in the cerebrospinal fluid. Brain magnetic resonance imaging (MRI) of the patient show a slight thinning of the optic chiasm but did not show intracranial lesions nor ventricular enlargement. Angio-MR ruled out venous sinus thrombosis and Visual Evoked Potentials were reported as normal. A therapy with acetazolamide 250 mg two times a day was initiated and the patient discharged with indication to attend a neuro ophthalmological follow-up examination within one month. There are a few cases of paediatric intracranial hypertension due to the administration of Growth Hormone and some reports of pseudotumor cerebri associated with hypervitaminosis A. In this case, the only identified association was excess intake of both vitamin A and GH. Increased intracranial pressure may be idiopathic or secondary. Clinicians must take care to exclude secondary causes of raised ICP in all patients, particularly in men, children and women of high body mass index. This case highlights the importance of not underestimate headache nor slight visual impairment (specifically asking about dietary intake and supplements) when evaluating a patient with high-risk of dietary and parenteral supplements (vitamins and hormones) intake as bodybuilders. An accurate pharmacological anamnesis is essential to corroborate the clinical suspect.

Thunderclap headache PRES-related during puerperium in a patient with tension-type headache: a real case

F. De Angeli, M. Piatti, P. Santoro, L. Fumagalli, I. Appollonio, C. Ferrarese

Department of Neurology, San Gerardo Hospital and University of Milano-Bicocca, Monza, Italy

Introduction: Posterior reversible encephalopathy syndrome (PRES) is a clinical radiographic syndrome of heterogeneous etiologies grouped together because of similar findings on neuroimaging studies. It is an uncommon cause of secondary headache. Hypertension and endothelial dysfunction play a key role in the development of vasogenic white matter oedema. Common associated conditions are hypertension encephalopathy preeclampsia and other pregnancy related hypertension disorders and immunosuppressive therapy.
Case report: A 35-year-old woman was admitted for iper-acute onset of intense headache (NRS = 10) with pressing/tightening quality, bilateral location and nausea. No prodromic symptoms were related. Patient was puerpera (9 days post partum). Pregnancy was conducted without clinically relevant problems. Past medical history included infrequent episodic tension type headache associated with pericranial tenderness controlled with FANS on demand. No intracranial lesions were described at the CT scan. The new headache was different in quality if compared with typical TTH and was treated with FANS at ER. Recovery was not suggested. High blood pressure was treated with intravenous injection with clonidine and no neurological examination was required. Before discharge a new CT scan was done because of the onset of a generalized tonic clonic seizure, treated with intravenous midazolam. The CT showed small posterior parietal hyperdense lesion described as haemorrhage and the patient was hospitalized. Focal neurological deficit were not reported. At a new CT scan after 24 hours the haemorrhage was stable and new little hypodense diffused lesions were described. Neurological examination showed mild somnolence with the persisting of moderate headache treated with FANS without a real benefit. The MRI showed numerous punctate asymmetric areas of increased signal on T2 weighted images with hypo-isointense signal on DWI compatible with white matter oedema localized in frontal, posterior parietal regions and in the brainstem and in the posterior cerebellar hemispheres. These findings were compatible with posterior reversible encephalopathy syndrome. During recovery patient showed a progressive spontaneous reduction of headache ad an improvement of consciousness. Because of the breastfeeding and the spontaneous improvement of symptoms an AED therapy was not started. Obstetric evaluation concluded for a late postpartum preeclampsia without the requirement of specific therapy. An MRI after 15 days showed a complete resolution of radiological findings.
Discussion: Posterior reversible encephalopathy syndrome can occur in hypertensive encephalopathy, preeclampsia and other pregnancy related hypertension disorders, during immunosuppressive therapy and in others numerous diseases such as vasculitis, acute or chronic renal diseases, hemolitic and uremic syndrome, thrombotic thrombocytopenic purpura and comorbid medical conditions (sepsis, hyponatremia, fever). Clinical

manifestations can be very different and diagnosis could be not simple. Headache is the most frequent symptom. It is described as constant, not localized, moderate to severe, not responsive to analgesia. If the patient has a story of primary headache, the new one is described as different in quality and onset if compared with the typical headache. Other symptoms can be present such as altered consciousness (from mild somnolence to coma), visual disturbance (hemianopia, visual neglect, visual hallucinations) and seizures. In these case the only presence of headache in patient with a story of TTH complicated the diagnosis. However instrumental studies in association with history and clinical follow up allowed us to confirm the diagnosis of posterior reversible encephalopathy syndrome in late puerperium preeclampsia.

Suggested readings:

- Stott VL, Hurrell MA, Anderson TJ (2005) Reversible posterior leukoencephalopathy syndrome: a misnomer reviewed. Intern Med J 35:83
- Schwartz RB, Feske SK, Polak JF, et al. (2000) Preeclampsia-eclampsia: clinical and neuroradiographic correlates and insights into the pathogenesis of hypertensive encephalopathy. Radiology 217:371
- Dodick DW, Eross EJ, Drazkowski JF, Ingall TJ (2003) Thunderclap headache associated with reversible vasospasm and posterior leukoencephalopathy syndrome. Cephalalgia 23:994

Acute confusional migraine in CADASIL: role of EEG

E. Ferrante, E.P. Verrengia, A. Savino, E.C. Agostoni

Headache Centre, Neurosciences Department, Niguarda Hospital, Milan, Italy

Background: ACM (Acute Confusional Migraine) can represent a clinical manifestation of CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy). EEG (electroencephalogram) can represent a useful tool to evaluate this condition.
Case report: A 54-year-old woman with diagnosis of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) was admitted to our Hospital in February 2016. Patient history includes recurrent stroke, chronic headache since childhood classified as migraine with visual aura, typical neuroimaging findings. She has no family history of stroke and dementia. The assumption of no cognitive decline was based on her ability to perform business activity. The diagnosis was confirmed by mutation in Notch3 gene in 2006. In December 2015 she was hospitalized in London with a severe headache associated with visual impairment (migraine with aura), agitation, and speech disturbance. Patient confusion lasted four days. Brain computed tomography (TC) in acute phase was negative and EEG, performed five days after the clinical event, was normal. In absence of new ischemic lesions on DWI-MRI, she was treated with Levetiracetam 500 mg twice a day. In February 2016 she was evaluated in our Emergency Department with a similar episode compared to the one of London 2015. The patient presented a prolonged duration visual aura migraine since early morning. During this episode, she presented agitation associated with an inability to communicate and to comprehend spoken words. Agitation was treated with benzodiazepines with a resolution in 24 hrs, but she presented an alteration of cognitive/behavioral status for seven days. In acute phase, in absence of new lesions on TC scan, an EEG revealed a disorganized track with slow bilateral activity, non-reactivity to algic stimuli, no epileptiform figures. Her brain DWI-MRI revealed pre-existing infarcts, leukoencephalopathy, hemosiderin foci, but no recent ischemic lesions. Based on basal features and subsequent improvement of EEG, we decided to discontinue antiepileptic therapy. In January 2017 she was able to perform her work activities in absence of ACM events.
Discussion and conclusions: We describe two episodes of ACM in the same CADASIL patient, lasted four and seven days respectively. EEG shows a typical pattern in acute phase ACM and excludes seizure related to pre-existing cerebral infarcts. Further data are required to support the role of EEG to qualify this phenomenon.

A case of unilateral headache turning symptomatic

M. Riolo[1,2], G. Giussani[1], E. Botto[1], L. Stanzani[1], A. Lunghi[3], A. Salmaggi[1]

[1]Dipartimento di Neuroscienze, ASST Ospedale A. Manzoni, Lecco, Italy
[2]Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche, Università degli Studi, Palermo, Italy
3Dipartimento di Neuroradiologia, ASST Ospedale A. Manzoni, Lecco, Italy

Objectives: To describe a case of a patient with spontaneous bilateral carotid artery dissection, starting with unilateral migrainous headache and followed by irradiation to laterocervical region, Horner syndrome and hypoglossal nerve palsy.
Introduction: Headache and pain in the neck can be caused by a variety of diseases, from flu, muscle contractions to tumors and vascular diseases. Nevertheless, when they are associated or followed by focal deficits, they can be the warning symptoms of a cervical carotid and/or vertebral artery dissection. Here we describe a case of originally isolated headache followed by neck pain, Horner symptoms and lower nerves palsy due to cervical vessels dissection.
Case report: A 49-year-old woman with negative history for headache was referred to our department for onset of nuchal pulsatile headache, with irradiation to the left frontoparietal areas and. The symptoms mildly improved with non steroidal anti inflammatory drug. Previously, she had had an episode of flu. Due to the persistence of the symptomatology and to the onset of irradiation to the left part of neck in the following weeks, she also performed neck radiography and brain CT with iodine contrast, which did not show any lesions. Blood samples examination revealed only an increase in sedimentation rate velocity (39 mg/dl) and C reactive protein (6 mg/dl), with normal range of white blood cell count. Two weeks before hospital admission, she noticed a difficulty in chewing, especially in the left side of the mouth, and in performing rapid tongue movements. At the same time, she reported the presence of mild dysphagia and a "nasal" tone of her voice. At admission to the neurological ward, the neurological examination revealed dysarthria, ptosis in the left eye, with fluctuant left miosis, left paralysis of the soft palate, dysphagia and left tongue deviation on protrusion with atrophy in the left part; strength, sensitivity and coordination in limbs were normal, as tone and reflexes. Considering the presence, in a young female patient, of unilateral pulsatile headache associated with incomplete Horner syndrome (left ptosis and left miosis) and isolated lower nerves palsy, a primary diagnostic work-up was performed to rule out the presence of cervical artery dissection. Therefore, cervical vessels color-coded duplex sonography was performed and it showed a normal carotid bifurcation without atherosclerotic wall changes, with the presence, in the distal part of both internal carotid arteries, of a mild stenosis due to wall thickening, determining a significant increase in blood flow velocities. These findings were compatible with the suspect of bilateral carotid artery dissection. Because there was only the indirect finding of increase of outer vessel diameter, the presence of a subadventitial mural hematoma was hypothesised and a brain and

neck MRI was performed, with T1 fat sat suppression technique. This revealed the presence of a hyperintense crescent-shaped signal, representing mural hematoma in both internal carotids and diagnosis of bilateral carotid dissection was confirmed. In the suspect of a vasculitis, autoimmunity screening and TC-PET were performed and both were non significant with this hypothesis. So, considering the irregular vessels morphology and the evocative imaging at angio-CT, a probable diagnosis of muscular fibrodysplasia was performed, even in the absence of angiography. Patient was discharged home with antiaggregation and regular follow-up.

Discussion and conclusions: Headache with neck pain can be the only manifestation of cervical artery dissection and it is the inaugural symptom in 33–86% of cases [1]. Sometimes it is followed by brain ischemia, especially if the dissection involves the subintima [1, 2]. In our case, as it is described in other cases in the literature [3], the subadventitial involvement caused not only the head and neck pain, but also the compression of the hypoglossal nerve and the sympathetic fibres without central involvement. Our case satisfied current diagnostic criteria of HIS Classification ICHD-3 Beta (6.5.1). It is the example of how the presence of isolated migrainous headache, as it was supposed to be for the first two weeks of patient's symptoms, should not mislead clinicians to diagnose a migraine attack, but it should raise suspicion of symptomatic headache, especially if no previous headache history is present. Moreover, in these cases, the role of the physician and of clinical examination are crucial in identifying among the many people with headaches those who require extensive investigations [4].

References

1. Debette S, Leys D (2009) Cervical-artery dissections: predisposing factors, diagnosis, and outcome. Lancet Neurol 8:668–78
2. Silbert PL, Mokri B, Schievink WI (1995) Headache and neck pain in spontaneous internal carotid and vertebral artery dissections. Neurology 45(8):1517–22
3. Sturzenegger M, Huber P (1993) Cranial nerve palsies in spontaneous carotid artery dissection. Journal of Neurology, Neurosurgery, and Psychiatry 56:1191-1199
4. Mawet J, Debette S, Bousser M-G, Ducros A (2016) The Link Between Migraine, Reversible Cerebral Vasoconstriction Syndrome and Cervical Artery Dissection. Headache 56:645-656

Reversible cervical vasoconstriction syndrome presenting as recurrent thunderclap headache

M.R. Mazza[1], L. Rapisarda[1], A. Quattrone[1,2], F. Bono[1,2]

[1]Headache Group, Institute of Neurology, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy
[2]Neuroimaging Research Unit, Institute of Molecular Bioimaging and Physiology, National Research Council, Catanzaro, Italy

Introduction: Thunderclap headache (TCH) associated with reversible cerebral vasoconstriction syndrome (RCVS) is well recognized, while TCH associated with cervical reversible vasoconstriction syndrome (CRVS) has been rarely reported. We here describe two patients with recurrent TCH due to CRVS.

Case description: *Case 1.* A 25-year-old woman had a history of episodes of sudden and severe head pain, unilateral, peaking in less than 1 minute, lasted few hours. During headache she experienced elevated blood pressure. An important physical and emotional stress caused an acute myocardical infarction without thrombosis. Two years later the patient complained of recurrent episode of TCH associated with decrease in visual acuity in right eye and numbness in the right arm, these symptoms disappeared spontaneously after few hours. Brain MRI was normal; cervical MR angiography (MRA) with gadolinium revealed a right laterocervical mass with intense vascularization, compatible with paraganglioma, and the stenosis of ipsilateral carotid artery. These data allowed us to make a diagnosis of recurrent TCH associated with CRVS due to paraganglioma. The administration of nimodipine and then the surgical removal of paraganglioma led to resolution of headache. Repeated cervical MRA showed the resolution of radiological CRVS.

Case 2. A 36-year-old woman developed an acute, severe thunderclap headache, located primarily in the right frontal-parietal area, associated with numbness and weakness in the right arm and in the right leg. Headache and the other neurological symptoms resolved spontaneously in a few days. After a month she developed other two episodes of severe thunderclap headache, associated with unilateral or bilateral blurring vision lasted about one hour. Neurological examination revealed only the hypoesthesia in the right side of body. Brain MRI was normal; cervical MRA revealed a stenosis of both right vertebral artery and left carotid artery. The administration of nimodipine improved her neurological symptoms. During the follow up cervical MRA was normal.

Discussion and conclusions: The first case describes TCH due to CRVS associated with paraganglioma; the second one shows TCH associated with CRVS. These cases provide the evidence that recurrent TCH may also occur in patients with CRVS. We realized that CRVS is not uncommon and should be considered in patients presenting recurrent TCH and focal neurological signs in the absence of other etiologies.

Mobile phone headache: is there a relationship with altered CSF pressure?

L. Rapisarda[1], M.R. Mazza[1], A. Quattrone[1,2], F. Bono[1,2]

[1]Headache Group. Institute of Neurology, University Magna Graecia, Catanzaro, Italy
[2]Neuroimaging Research Unit, National Research Council, Catanzaro, Italy

Introduction: It has already been hypotesised the association between headache and use of mobile phone. Several studies focused on neurological disorders and electromagnetic fields, particularly on mobile phone use and headache. Nevertheless the results of these studies were inconclusive. We reported a case of a patient with headache triggered by mobile phone.

Case description: A 30-year-old man with one-year history of isolated headache triggered by prolonged use of mobile phone. Neurological examination was normal. A provocative test revealed that a 30 minutes phone call triggered muffling and bilateral headache lasting some hours (VAS 6); moreover the use of hearphones provoked just muffling and mild head pain (VAS 3); whereas the use of fixed phone did not triggered the headache. Functional tests such as audiometry and impedence meter test and electrophysiological tests such as auditory evoked potentials (AEP) were not altered. Brain MRI was normal, except for an empty sella. Moreover cerebral MR venography displayed a unilateral cerebral venous outflow disturbance. Lumbar CSF short-term monitoring showed opening and mean CSF pressure at the upper limit of the reference range (about 200 mmH_2O).

Discussion: This case provides evidence that headache is triggered by prolonged use of mobile phone. In essence, the provocative test demonstrated a causal relationship between headache and use of mobile phone, while the use of fixed phone did not triggered the symptoms. In addition the neuroimaging evidences of empty sella

and unilateral cerebral venous outflow disturbance, associated with CSF pressure at the upper limit of reference range, may lead to hypothesize a relationship between altered CSF pressure and mobile phone headache. These data agree with those studies which reported the effects of small electromagnetic fields as possible triggers for headache. By contrast other studies claim that there is not a significant association between them.

Conclusions: Our data confirm that isolated headache may be triggered by mobile phone. Further studies are needed to investigate the role of small magnetic fields as possible triggers of headache.

Author Index