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Unlike the Stresa meetings from 1999 to 2013, which focused on specific aspects of headache conditions, I intend the present Headache Seminar to concentrate on current clinical research and treatment for primary and secondary headaches.

This will include social aspects of headache conditions, the pathophysiology of primary headaches – with emphasis on the latest neurophysiological and neurochemical findings – and recent theories on the chronicization of migraine.

Recent functional neuroimaging findings, as they pertain to adult migraine, adolescent migraine, and cluster headache, will be also be presented. This discipline continues to provide new data clarifying relations between cortical circuits and the trigemino-vascular system.

Other lectures will explore the classification of chronic headaches, the diagnosis and treatment of adolescent migraine, relations between migraine with aura and acute cerebrovascular conditions, the significance of patent foramen ovale in migraine with aura, and headache in women. Other speakers will discuss headaches related to autoimmune conditions, benign idiopathic hypertension without papilledema, and visual disturbances.

As part of the session on Clinical Aspects of Headaches there will be a lecture on headache in demyelinating autoimmune conditions, with particular reference to migraine headache in multiple sclerosis.

There will be Symposium presenting new data on the use of botulinum toxin in the prophylaxis of migraine without aura and chronic migraine.

There will also be the Symposium of the Italian Headache Foundation (FICEF), during which the definitive results of two clinical studies will be presented: the role of pharmacists in migraine management, and influence of lifestyle and adolescent headache.

An important session will be concerned with novelties in the pharmacological treatment of primary headaches, and also with long-term results of cutaneous and deep brain neurostimulation in patients with primary chronic drugresistant headaches. There will be a poster session and a brief communications session.

The Seminar is distinguished by the high quality of its speakers and the topicality of the themes treated. I hope that, like previous meetings, it will prove an important updating opportunity for all participants.

I thank all who contributed, particularly Eva Communication for their unflagging organizational effort.

Gennaro Bussone

The Editor in Chief authorizes the publication of the Proceedings of the STRESA HEADACHE SEMINAR 2015. 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.

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Burden of migraine: what should we say more?

Matilde Leonardi

Abstract Several international campaigns to increase awareness on the high burden of migraine stimulated population-based studies in the last few years that provided broader data on prevalence, correlates, and impact of migraine. The last version of the Global Burden of Disease 2010 posed migraine with a twofold increase with respect to the previous version as one of the first disabling diseases. Migraine, and in general headache disorders are among the top ten causes of disability because they are common and disabling: that is now clear. It is also clear that the descriptive epidemiology of migraine has reached its maturity. The prevalence rates and sociodemographic correlates have been stable across 50 years. Last but not least, despite international efforts an illness that can be relieved does not, and the heavy burden that it poses at individual and societal levels, persists when it could be mitigated. Describing and accounting the burden of migraine worldwide is not enough anymore, we need to change our paradigm again and move towards new pathways. The opportunity is provided by the biopsychosocial approach that enables to act on the environment once the most adequate medical therapy has been provided. To reduce the burden, international efforts should focus certainly on development of new drugs but mainly on improving health care systems' response to millions of migraine and headache sufferers.

Keywords Migraine · Disability evaluation · Biopsychosocial approach · Burden

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Background

Headache disorders are prevalent: most adults have suffered from one or more types during the last year and the global burden of headache is large [1]. The most common types, tension-type headache (TTH), migraine and medication-overuse headache (MOH) are associated to different disease costs [2]. The Global Burden of Disease Study 2010 confirmed that headache disorders are among the top ten causes of disability worldwide [3], a finding that was also described by Stovner and colleagues [4] earlier. It is, paradoxically, still a widely ignored burden, as stated by the World Health Organization (WHO) in the Atlas of Headache Disorders and Resources in the World 2011 [5]. Migraine is one of the most common diseases, with lifetime prevalence ranging between 14 and 16 % [2, 4]: it is commonly associated to high cost, in particular with regard to indirect costs, i.e. those associated to reduced productivity [6]. Although of relevance, this view is partial as it does not really capture the reduction in health due to migraine suffered by patients.

Although the work to prepare GBD 2000 had the credit to introduce migraine in the WHO issues of public health relevance, it considerably underreported the disability that migraine imposed on people throughout the world, and gave a poor account of headache disorders collectively. The evidence was not there. For more than half the world's population, estimates for migraine were based on very little data of acceptable quality that were not in existence for China, India and most other countries in South East Asia, most of Africa, all of the Eastern Mediterranean and all of Eastern Europe [4]. Headache disorders other than migraine were not considered in the GBD 2000 as for these disorders, at that time, evidence was lacking everywhere.

Filling this evidence gap has been a priority of the Global Campaign in its first years [7]: as a result, GBD

2010 has been much better informed and built on much sounder foundations than its predecessor. As Tim Steiner says "GBD 2010 was not a simple update of GBD 2000, but a complete rerun: an entirely new world survey. Working with many partners, the Global Campaign against Headache being one, it took from the world literature all the epidemiological evidence pertaining to burdensome diseases, assessed it for quality and derived from it, for each of 21 world regions, best age-related estimates of prevalence. Thanks to this work in the new GBD 2010 provided clear evidence that headache disorders are among the top ten causes of disability because they are common and disabling. Headache is one of the most frequent medical complaints: almost everybody has experienced it, at least 10 % of adults everywhere are sometimes disabled by it, and up to 3 % live with it on more days than not" [8]. The most recent reports state that migraine alone is responsible of almost 3 % of disability attributable to a specific disease, also in consideration of its comorbidity. This places migraine as the eighth most burdensome diseases, the seventh among non-communicable diseases and the first among all the included neurological disorders [3, 9, 10].

The new GBD is clearly a step forward in the recognition of the burden associated to migraine and headache disorders in general and much of this advancement is probably due to the "Lifting the Burden" campaign [1]. However, I share the concern recently raised by Steiner and colleagues [8]: the exclusion of medication-overuse headache is critical, as it adds enormously to the burden associated to headache disorders. So, in our opinion, the criticism of GBD 2010 must be taken as an opportunity: studies must be undertaken that show the impact of headache disorders using reliable disability outcome measures that enable comparative analysis across different headache disorders [11], as well as in different chronic conditions [9].

The clear impact on world disability due to headache disorders is certainly due to the initiation of active campaigns to increase awareness of the high magnitude, burden, and impact of migraine and other headache disorders that have stimulated numerous studies of population-based data on the prevalence, correlates, and impact of migraine and is certainly also due to the introduction of the second edition of the International Classification of Headache Disorders (ICHD-II) that allowed more precise data collection internationally. Kathleen Merikangas [12] in a recent article made a comprehensive review of the literature on the prevalence of migraine subtypes and tension-type headache defined by ICHD-II criteria on 19 articles that demonstrated that the descriptive epidemiology of migraine has reached its maturity. The prevalence rates and sociodemographic correlates have been stable across 50 years. She affirms that these developments justify a shift in efforts to the application of the designs and methods of analytic epidemiology. Retrospective case–control studies followed by prospective cohort studies that test specific associations, she said, are likely to enhance our understanding of the predictors of incidence and progression of migraine, subtypes of migraine with differential patterns of onset and course, and specific environmental exposures that may have either causal or provocative influences on migraine aetiology. She also stated that despite increasing efforts to increase awareness of migraine, approximately 50 % of those with frequent and/or severe migraine do not receive professional treatment.

The burden issue: what should we say more?

Tim Steiner and colleagues [8] drew attention to the very large numbers of people suffering for the disability due to headache who do not receive effective health care. The barriers responsible for this might vary throughout the world, but poor awareness of headache in a context of limited resources generally—and in health care in particular—was constantly among them. The consequences are inevitable: illness that can be relieved is not, and heavy burdens, both individual and societal, persist when they can be mitigated. The findings of GBD 2010, of all recent articles and papers and of the epidemiological surveys, sadly reflect this.

Describing and accounting the burden of migraine worldwide is not enough anymore, we need to change our paradigm again and to move towards new pathways. We described a possible way 10 years ago [13]. Part of our proposal has been taken into account by the international scientific community and the global campaigns and GBD 2010 data are the results of it, but this was only part of our proposal, we need to go further. The opportunity is provided by the evaluation of migraine and headache disorders in light of the biopsychosocial approach define by the WHO International Classification of Functioning Disability and Health, ICF [14]. The ICF conceptualises a person's level of functioning as a dynamic interaction between her or his health conditions, environmental factors, and personal factors. It is a biopsychosocial model of disability, based on an integration of the social and medical models of disability. Disability is multidimensional and interactive. All components of disability are important and anyone may interact with another. Environmental factors must be taken into consideration as they affect everything and may need to be changed. Although personal factors are recognised in the interactive model they are not classified in the ICF at this time. Such factors influence how disability is experienced by the individual.

Several papers have been published on evaluation of migraine with ICF and ICF-related instruments [15–19], and what comes out clearly is that to respond to the complain of poor public health attention for a disease that now has clearly a stable epidemiology, clearly drugs that could reduce the burden, clearly known causal effects, what we need now is to fully adopt the biopsychosocial perspective and address the change of environmental factors from being barriers in becoming facilitators.

Several papers made the picture clear now. What is needed worldwide is a common effort that is able to have an impact on heath care organisations so that a disease such as migraine can benefit not only by research on new and potentially preventive drugs, but also of clear public health actions able to reduce the burden, such as prevention, diagnosis, proper care, but also to improve the quality of life of million sufferers.

Maybe what we need to say more is that changing the environmental barriers is possible and is an international duty that we should start doing together.

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

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Approaches to treatments of chronic migraine associated with medication overuse: a comparison between different intensity regimens

A. Raggi · S. Schiavolin · M. Leonardi · L. Grazzi · S. Usai · M. Curone · D. D'Amico

Abstract Treatment of chronic migraine with medication overuse requires withdrawal from acute medications. However, guidelines and clear indications for different intensity regimens, i.e., day hospital (DH) vs. inpatient treatment, are not available. Patients completed disability, quality of life (QoL) and depression questionnaires; headaches frequency and overused medications category were collected. Mann–Whitney *U* test and Chi square were used to assess differences between inpatients and DH patients; Bonferroni correction was applied. 194 patients aged 43.9 ± 12 (160 females) were enrolled (100 from DH, 94 inpatients). Inpatients were older, less educated and with lower employment rates. Inpatients had higher MIDAS scores ($P = 0.003$) and headache frequency ($P = 0.002$). They had lower QoL for restrictive ($P = 0.002$) and preventive components; no difference was found for disability, mood state and QoL emotional component. Patients treated during hospitalization had higher disease severity and lower quality of life, but similar disability and mood state than those treated in DH.

Keywords Chronic migraine · Medication overuse · Health-related quality of life · Disability evaluation · Withdrawal

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Introduction

Chronic migraine associated with medication overuse (CM-MO) is characterized by frequent headaches and overuse of acute medications [1]. Approximately, 2 % of general population suffers from CM-MO [2, 3], and 2.5 % of migraineurs progress to CM each year [4]. Although the process of chronification has not been completely understood yet, it seems that lifestyle, comorbid conditions, genetic and metabolic factors [5, 6], abnormal somatosensory cortex excitability [7] and MO itself [8, 9] have a role.

The interruption of MO is the primary treatment endpoint, despite the individual differences based on the kind of overused medication [10–13], as well as the possible comorbidities or other psychosocial factors that might contribute to chronification and MO [14–16]. A general consensus exists on the need for a structured withdrawal treatment aimed to detoxify patients, stops the chronic headaches and improves the responsiveness to preventive treatments [17]. This kind of treatment can be carried out both in a inpatient and in a day hospital (DH) setting. A DH-based withdrawal is cheaper and can be successful in motivated patients, while an inpatient-based withdrawal enables a close monitoring over medication intake and immediate treatment of withdrawal symptoms [17]. According to expert consensus or national guidelines [18, 19], inpatient treatment is to be preferred if patients overused opioids or barbiturates, have psychological problems, severe medical comorbidities and withdrawal symptoms, or previously failed with DH-based withdrawal. To our knowledge, only one study evaluated the differences between patients treated in DH or in inpatient setting [20]: it longitudinally compared the decrease in headaches frequency, number of medication taken and MIDAS score

(Migraine Disability Assessment Schedule) [21] for 146 inpatients and 114 patients treated in DH and is suggestive of some baseline differences: at 12 months, monthly headaches frequency decreased by 59–59.3 %, monthly medications intake decreased by 75.5 % in both groups, MIDAS decreased by 67.1–67.4 %.

The aim of this paper is to assess differences between CM-MO patients treated in DH and in a inpatient setting with regard to disability, health-related quality of life (HRQoL), mood state and type of overused drug. Our hypothesis is that inpatients have a worse clinical profile and HRQoL, higher disability, and higher likelihood of opioids and barbiturates overuse.

Methods

Patients and Setting

Adult patients with CM-MO according to Silberstein's criteria [1] were consecutively recruited at the Headache Centre of the Neurological Institute C. Besta of Milan between June 2011 and December 2012. Patients were enrolled both at admission for inpatient and DH withdrawal treatment. The study was approved by the institute's ethical committee and written consent was obtained by each patient.

Patients completed the MIDAS [21, 22] for the evaluation of disease activity. It assesses the number of days over the previous 3 months in which patient cut back or avoided paid and school work, household work, and leisure/family/social activities, and headaches frequency. The different types of MO were defined as follows: overuse of non-steroidal anti-inflammatory drugs—NSAIDs (NSAIDS used $\geq$15 days/month); overuse of triptans (triptans used $\geq$10 days/month); overuse of both NSAIDs and triptans (NSAIDs used $\geq$15 and triptans $\geq$10 days/month); overuse of ergotamine, caffeine, opioids/barbiturates (used $\geq$10 days/month).

Disability was measured with the World Health Organization Disability Assessment Schedule (WHODAS 2.0) [23], a 36-item assessment tool that takes into account six domains: understanding and communicating; getting around; self-care; getting along with people; life activities (divided into household and work); participation in society. Patients answer questions regarding how much difficulty, they experienced during the previous 30 days using a 5-point scale (no problems–complete problems/cannot do). Both total and subscale scores range from 0 to 100, with higher scores reflecting greater disability.

HRQoL was measured with the Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ) [24] that was recently validated in Italian in CM-MO patients [25]. It is composed of 14 items rated on a 6-point scale (none of the time–all of the time) that investigate how frequently headaches limited patients' HRQoL during the previous 4 weeks. Three subscales are available, each with a 0–100 score, with lower scores indicating poor HRQoL: role restriction (RR), how migraines limited social and work-related activities; role prevention (RP), how migraines prevented social and work-related activities; emotional function (EF), that assess the emotions associated with headaches.

Mood state was assessed with the Beck Depression Inventory-2 (BDI-2) [26]. It is composed of 21 items, each rated on a 0–3 scale, connected to a cognitive and to a somatic-affective component and a total score: total score range is 0–63, with higher scores reflecting higher depressive mood.

Data analysis

The Chi square test was used to assess if there are differences related to gender, employment status (employed/students vs. unemployed retired, homemaker) and type of overused medication between patients in DH and those in inpatient setting.

Mann–Whitney U test was used to assess differences for MIDAS score, headaches frequency, WHODAS 2.0, MSQ and BDI-2 scales. As seven bivariate comparisons were made, the Bonferroni correction was applied: significance was set with type I error level at $\alpha = 0.007$ and two-tailed testing. Data were analyzed with SPSS 18.0.

Results

A total of 194 patients were enrolled: 160 were females and mean age was 43.9 (SD 12); 100 underwent a DH-based withdrawal, 94 were inpatients. Table 1 reports sociodemographic and clinical data, as well as group differences.

The two groups of patients did not differ for age and gender composition, while differences were found for education and employment: inpatients had lower education level and lower employment rates. Inpatients had higher frequency of headaches (approximately 20 days per month in the previous 3 months) and higher MIDAS scores, while no significant differences were found for the type of overused medication. Inpatients had lower MSQ-RR and MSQ-RP scores, while no differences were found for MSQ-EF, WHODAS 2.0 and BDI-2.

Discussion

The results of this study show that some differences between patients with CM-MO treated in inpatients vs.

Table 1 Comparison of CM-MO patients treated in inpatients vs. DH setting

	Inpatients (no. 94)	DH (no. 100)	
Sociodemographic data			
Age	45.3 ± 12.5	42.6 ± 11.4	$P = 0.181$
Years of education	11.8 ± 4.3	13.8 ± 3.4	$P < 0.001$
Gender			$\chi^2 = 0.04$; $P = 0.843$
Male	17 (18.1 %)	17 (17 %)	
Female	77 (81.9 %)	83 (83 %)	
Employment status			$\chi^2 = 5.66$; $P = 0.017$
Employed or student	62 (66 %)	81 (81 %)	
Unemployed, retired or homemaker	32 (34 %)	19 (19 %)	
Clinical data and outcomes			
Overused medications			$\chi^2 = 7.48$; $P = 0.058$
NSAIDs	30 (31.9 %)	27 (27 %)	
Triptans	16 (17 %)	26 (26 %)	
NSAIDs + triptans	25 (26.6 %)	35 (35 %)	
Other drugs	23 (24.5 %)	12 (12 %)	
Headaches frequency	62.1 ± 23.8	51.5 ± 22.7	$P = 0.002$
MIDAS	93.1 ± 58.4	72.9 ± 59.8	$P = 0.003$
BDI-2	18.3 ± 10.4	16.3 ± 9.7	$P = 0.172$
WHODAS 2.0	33.2 ± 13.7	29.5 ± 13.7	$P = 0.057$
MSQ-RR	29.1 ± 17.8	36.1 ± 16.1	$P = 0.002$
MSQ-RP	42.4 ± 21.7	52.5 ± 21.3	$P = 0.002$
MSQ-EF	38.5 ± 25.2	45.8 ± 24.1	$P = 0.044$

The "other drugs" category includes overuse of ergotamine, caffeine, opioids/barbiturates. For categorical variables, frequencies and percentages were reported; for continuous variables, mean ± SD (standard deviations) were reported. Mann–Whitney U test significant at $P < 0.007$ level

outpatient setting exist: inpatients had higher headaches frequency and disease activity and lower HRQoL, specifically when restrictive and preventive HRQoL issues are taken into account. On the contrary, we failed in demonstrating differences related to the kind of overused drugs, although inpatients were slightly more frequently overusers of ergotamine, caffeine, opioids/barbiturates, while those in DH were slightly more frequently triptan overusers.

What previous literature showed is that, compared to those with episodic migraine, patients with CM have different clinical features, which include problematic lifestyle, MO, genetic, metabolic and physiologic characteristics [5–7]. However, once chronification process has developed, there might be different degrees of disease severity, in terms of headaches frequency and type of overused medications. What we herein showed is that some differences exist, and these differences justify a more intense withdrawal regimen. They include: having approximately 3 days/month more with migraine headache, MSQ and MIDAS scores approximately 20 % worse, compared to patients who were treated in DH. Practically, this means that patients needing a more intense treatment regimen had a condition that limited or prevented social and work-related activities to a wider extent. These data represent an extension of the baseline differences suggested by Grazzi and colleagues [20]: what we added here is a measure of these differences. Further data will be needed to address the superiority of one withdrawal setting on the other, thus confirming—or disconfirming—the results of the previous study [20].

In contrast to what hypothesized, we found no difference in the kind of overused drug, contrasting a recent study where we found that overusers of NSAIDs and of ergotamine, caffeine, opioids/barbiturates were more likely to have higher disease severity [27]. However, it has to be noticed that two-third of patients overusing ergotamine, caffeine or opioids/barbiturates underwent inpatients withdrawal, which partly supports our hypothesis. As there are evidence of a higher depression in patients with CM compared to those with episodic forms [28–30], one could expect that depression levels should be higher in patients with a higher frequency of headache. This is not what we found in our data: it is possible to presume that the low mood level is a common clinical aspect among patients with a severe form of CM, more than a characteristic feature of subgroups of patients. In fact, the average BDI-2 scores in both the two groups could be categorized in the "mild depression" group (i.e., scores in the range 14–19). This is further on confirmed by the absence of a significant difference in MSQ-EF score. Disability data, derived from the WHODAS 2.0, also do not show differences between the two groups of patients. Also in this case, this is in part contrasting with what was expected based on a previous

study comparing an age- and gender-matched population of chronic and episodic migraineurs where, however, WHO-DAS 2.0 score was lower (i.e. 26.6 ± 12.5) [30] compared to both the two groups included in the present study. It is therefore possible to conclude that the personal burden of CM-MO selected for withdrawal treatment is relevant and pervasive, and that it is likely to have a more evident effect on health-related quality of life in those patients who need a more intense treatment regimen.

The most relevant limitation is related to sample, entirely derived from a single specialty center, where the most severe cases of CM-MO are treated: thus caution should be paid before generalizing our results to CM patients in general. Second, the cross-sectional research design does not allow us to define strict causal relationships.

In conclusion, we showed that CM-MO patients treated in inpatient setting had higher disease severity and lower HRQoL, but not higher disability and worse mood, indicating a relevant and pervasive personal burden of CM-MO.

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

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Difficulties in work activities and the pervasive effect over disability in patients with episodic and chronic migraine

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Abstract Migraine is associated with reduced productivity in work-related activities. The degree to which problems with work are, in turn, associated to the level of migraine-related disability as well as to headache frequency has been poorly explored. The aim of the study was to assess if migraine patients with different degrees of work difficulties showed a different level of migraine-related disability. A consecutive sample of patients with episodic migraine (EM) or with chronic migraine (CM) with medication overuse (MO) attending the Headache Centre of the Neurological Institute C. Besta of Milan was studied. All patients completed the MIDAS and the WHODAS 2.0 questionnaires. The total scores of both questionnaires, frequency of headaches, average pain intensity, and the scores of each subscale of the WHODAS 2.0 were calculated separately for EM and CM patients. The score of WHODAS 2.0 "Work difficulties" subscale was used to divide the studied patients into two groups, i.e. those above and those below the median "Work difficulties" subscale score. Independent sample *t* test was used to compare these two groups as far as all the other studied variables. A total of 296 patients (102 with EM and 194 with CM-MO) were enrolled. Patients with higher work difficulties score also displayed higher scores in the other WHODAS 2.0 subscales; for those with CM-MO, the differences were significant. The results of this study indicate that having more and more severe workplace problems is associated to a higher disability level in migraineurs. Further studies are needed to better understand workplace disability in different migraine forms, particularly in a qualitative way.

Keywords Chronic migraine (CM) · Medication overuse (MO) · Episodic migraine (EM) · Disability · Work · WHODAS 2.0

Introduction

Migraine is a disabling condition which impacts on daily functioning as well as on health-related quality of life [1]. Available data show that these negative consequences are higher in patients suffering from chronic migraine (CM) than in those with episodic migraine (EM), particularly when medication overuse (MO) is present [2, 3]. The more severe impact of CM as compared to EM was confirmed by recent population data [4].

In this context, productivity in work-related activities is negatively affected both in episodic and in chronic migraine [5–8]. The negative effect on paid work gives the reason of the high indirect costs of this disorder. According to a large US survey, the estimated annual productivity loss cost for EM represents more than 50 % of the total annual cost per individual, and this proportion is higher for CM (70 % of total cost per individual per year represented by productivity loss) [9, 10]. These costs are partly due to absenteeism, i.e. the situation in which migraineurs avoid a full day of work due to headaches, and in part due to reduced productivity: this is the situation in which patients stay on the workplace, but work at a lower level due to headaches. However, the degree to which problems with work activities are, in turn, connected to the level of

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migraine-related disability as well as to headache frequency has been poorly explored yet.

Aim

To assess if patients suffering from migraine, in the episodic and chronic forms, with different degrees of work difficulties showed a different level of migraine-related disability.

Patients and methods

A consecutive sample of patients with EM or with CM attending the Headache Centre of the Neurological Institute C. Besta of Milan was studied. Diagnosis of EM forms was made according to the international classification of headache disorders (ICHD-II) [11]; diagnosis of CM was made according to Silberstein and Lipton criteria [12]. All CM patients presented also MO, and were studied at admission to our headache center to perform a withdrawal treatment.

All patients completed two validated disability questionnaires: the migraine-specific MIDAS [13], and the generic disability questionnaire WHODAS 2.0 [14]. Frequency of headaches and average pain intensity were evaluated in each patient, relying on the responses to question A and B of the MIDAS.

To assess the impact of different degrees of work difficulties, we divided patients—separately for EM and CM—in two groups: those reporting a score above vs. below the median at the "Work difficulties" subscale score of WHODAS 2.0. Those scoring above the median had higher work-related difficulties; those scoring below had lower difficulties.

Independent sample *t* test was used to compare patients from the two groups, separately for EM and CM, with respect to MIDAS score, headache frequency, pain intensity, and the other subscales of the WHODAS 2.0 as well as its total score.

Results

A total of 296 patients (102 with EM and 194 with CM-MO; mean age 47.7, SD 11.8; 83.4 % females and 74.3 % employed) were enrolled. Median score of WHODAS 2.0 "Work difficulties" subscale was 21.4 for EM and 35.7 for CM-MO patients. In both patients' groups, those with higher work difficulties score also displayed significantly higher scores in the other WHODAS 2.0 scales. In the CM group, those with higher workplace difficulties displayed significantly higher score also in MIDAS score, headache frequency and pain intensity (Table 1).

Discussion

Our study confirmed that migraine, both in the episodic and in the chronic form, has a pervasive effect on daily activities and also on workplace activities. Disability scores were higher in patients with chronic migraine than in those with episodic migraine. As far as the specific aim, our results indicate that those migraineurs reporting higher difficulties in work-related activities also had difficulties in all the WHODAS 2.0 scales.

Table 1 Differences between patients with higher and lower workplace difficulties

	Patients with EM (median "work difficulties" 21.4)			Patients with CM (median "work difficulties" 35.7)		
	Below median	Above median	*t* test (*P*)	Below median	Above median	*t* test (*P*)
Understanding and communicating	12.5 (9.3–15.7)	22.2 (15.4–29.0)	2.625 ($P = 0.011$)	25.8 (21.6–29.9)	38.7 (34.5–42.9)	4.331 ($P < 0.001$)
Getting around	5.6 (2.5–8.7)	27.1 (18.7–35.4)	4.861 ($P < 0.001$)	20.5 (15.6–25.5)	34.5 (29.3–39.7)	3.893 ($P < 0.001$)
Self-care	2.4 (0.9–3.9)	13.2 (6.5–20.0)	3.187 ($P = 0.003$)	7.3 (4.6–9.5)	15.0 (11.0–19.0)	3.208 ($P = 0.002$)
Getting along with people	9.2 (6.2–12.1)	20.1 (12.5–27.7)	2.714 ($P = 0.009$)	15.5 (12.2–18.8)	29.2 (24.0–34.3)	4.454 ($P < .001$)
Household activities	15.9 (10.7–21.2)	46.5 (37.9–55.1)	6.140 ($P < 0.001$)	32.4 (27.1–37.7)	55.3 (49.0–61.6)	5.593 ($P < 0.001$)
Participation to social situation	16.0 (13.1–18.9)	30.5 (26.5–34.6)	5.952 ($P < 0.001$)	32.5 (29.2–35.9)	42.5 (38.7–46.3)	3.917 ($P < .001$)
WHODAS 2.0 overall score	11.2 (9.3–13.2)	29.2 (24.5–33.9)	7.189 ($P < 0.001$)	23.4 (20.9–26.0)	40.1 (37.3–42.8)	8.790 ($P < 0.001$)
MIDAS score	21.3 (14.2–28.5)	30.1 (23.1–37.2)	1.776 ($P = 0.081$)	63.6 (51.6–75.6)	106.3 (91.7–121.0)	4.533 ($P < 0.001$)
Headache frequency	15.5 (12.2–18.8)	16.5 (13.9–19.2)	0.474 ($P = 0.637$)	52.2 (46.7–57.7)	53.9 (48.9–59.0)	0.464 ($P = 0.011$)
Average pain intensity	6.5 (6.0–7.0)	6.8 (6.2–7.3)	0.758 ($P = 0.450$)	7.6 (7.3–7.9)	7.8 (7.5–8.2)	0.898 ($P = 0.011$)

Parallel to this, our results did not support the presence of more frequent and painful headaches and higher functional disability (as measured by the MIDAS) in patients with higher work-related difficulties; in fact this differences were significant only among patients with CM-MO, and not among those with EM. This may suggest that the impact on paid work may not only depend on the limitations imposed by the individual headaches but also by the negative effects experienced by migraine sufferers in performing different tasks and roles, also outside the headache episodes, i.e. by the so-called "interictal burden".

Research on the impact of migraine on work activities is relevant to expand knowledge on this disorder in its different clinical forms, and also to improve our perception of the costs on the individual and on society as a whole. Published research generally limited to the impact of migraine on work activities in terms of reduced productivity and most studies focused on absenteeism more than on presenteeism (reduced productivity while staying at work during migraine attacks) [9, 15]. A strength of our study is that we evaluated work difficulties as assessed by a specific subscale of a validated tool based on the International Classification of Functioning (ICF), the WHODAS2.0 [14, 16]. The questionnaire includes specific questions which investigate different aspects of the disability experienced by the subject in the workplace: these are intended as problems in executing an activity, due to the presence of a disease, and conceptualized as increased effort, pain or discomfort, slowness or difference in the way the person carries out the activity.

The most relevant limitation of the study is that patients were from a single specialty center, and therefore our sample is likely to represent the most severe spectrum of M and CM. This is also suggested by the fact that all CM patients had also MO. Thus caution should be paid before generalizing our results to migraine sufferers in general.

Conclusions

Further studies are needed to develop specific tools meant to evaluate the negative effects of migraine on work not only on a quantitative basis (the degree of absenteeism and of productivity loss), but also in a quantitative way, i.e. investigating difficulties and impairments in specific activities and domains, to have a deeper insight on the impact of the disease. Such an instrument should be based on patient-derived data to collect information on headache-related problems in work activities, and will be useful for epidemiological evaluations and for clinical use, particularly to assess the effect of treatment intervention on work difficulties.

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Physiopathology of cephalic pain: where are we?

Alberto E. Panerai

Abstract Cephalic pain and psychiatric disease physiopathology is one of the most elusive issues in medical research, and the cause might be common. Going through the possible reasons of the failure in understanding the physiopathology of these diseases might be helpful to project new studies that might overcome the difficulties encountered and thus open a window on cephalic pain and psychiatric disease. New approaches to psychiatric disease might be applied to cephalic pain.

Keywords Cephalic pain · Psychiatry

Cephalic pain and psychiatric disease share common features

We do not know the physiopathology of psychiatric disease, since we do not have biochemical, genetic markers or experimental models. Even the classification of single pathologies is shaky, since they often overlap, affecting treatment specificity and efficacy. This again is confusing, since drug effects in patients or experimental models can be useful in understanding the physiopathology of diseases.

The same picture applies to cephalic pain: many pathologies under the same umbrella, a difficult classification, many treatments, inconsistent effect of drugs in patients and experimental models [1].

Why are psychiatric disease and cephalic pain so similar? Both are multifactorial diseases, each characterized by a constellation of signs and symptoms that contribute to the final pathological picture. We can try to analyze some of the factors that led to such a difficult situation.

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Clinical studies

Within cephalic pain clinicians distinguish several diseases. All are different, but symptoms and signs may overlap, not always are all present or in the same sequence; treatments are not consistent. The attack progression differs between patients. Clinical observation should drive experimental research, but what can it offer? It can offer aura, allodynia, pulsating pain, nausea, lacrimation, few other signs and symptoms. None is specific; none has a unique cause or can be explained. Pulsating pain suggests vasodilation as a cause; allodynia drives our attention to sensitization; nausea and lacrimation point to dopamine and the autonomous nervous system. But then what? Vasodilation is not necessary: nitroglycerine (GNT) starts an attack in some subjects independently from vasodilation, and vasoconstriction not always works. Aura is present only in a sub-type of migraine and cortical spreading depression (CSD) is a possible cause, not always demonstrated and whose cause is largely unknown. Allodynia has several causes not fully understood. Nausea could be due to an increased dopaminergic activity, but also to other, less specific mechanisms. In conclusion, there is no clear message that should prompt models for basic research. Moreover, models are set up on feeble connections with cephalic pain. In general, a single factor is altered and reconstituted, i.e., the result, whose relevance to cephalic pain remains cloudy, is known from the beginning. This is tautology that does not offer any new insight.

In psychiatric disease, signs and symptoms are highly variable and changeable and often overlap between

pathologies. Again clinical observation offers almost no hints to experimental research. Again models are tautological: reserpine induces depression in humans or animals (rat or mouse) depleting amines and their reconstitution leads to recovery. Similarly, a drug that reverses reserpine effects is a putative antidepressant, yielding copy drugs with the old, known mechanism of action.

Another critical point in cephalic pain clinical research, as in many other diseases from neuropathic pain to inflammation or arthritis, is that scientists and clinicians neglect the natural history of the disease. Cephalic pain, i.e., migraine, has a beginning, a progression and a spontaneous resolution. Studies and therapies head to understand what starts the symptoms, and how to block them. It is known that in several diseases, spontaneous resolution is driven by endogenous factors that restore the initial condition or aim to that. Knowing the mechanisms involved in recovery is very important for two reasons. First, we could understand which factor would be important to stimulate or block to enhance the endogenous response, getting new hints for therapy. Second, it was shown, e.g., in inflammation, that often therapies used to dump symptoms, do also slow or block the endogenous drive toward resolution, thus delaying recovery [2].

Finally, classifications of psychiatric disease or cephalic pain were proposed and changed several times, but the clinical practice clearly shows how they are not fully representative of the real diseases.

Neurophysiology

In cephalic pain, the most important result of neurophysiological research has been CSD discovery. Neurophysiology connects CSD to aura, but still neurophysiology is only a measure and does not offer any hint on the causes of what it shows.

CSD can be induced, slowed and blocked. However, we just observe it after stimuli that are effective in some people or animals, but not in others. We antagonize those stimuli and block CSD: does this observation mean that the stimulus is the *pathologic* one and that cephalic pain is a peripheral or central disease? The answer is no.

Both in clinical and experimental research, neurophysiology can help to see, but not to understand much, and the message we get is partial and limited.

Biochemistry

New neurotransmitter, new peptide, new explanation of psychiatric disease: all rotating around the new discovery. Unfortunately, this has been and is a rule in psychiatry. It is comprehensible: psychiatrists need a light somewhere, since there is no real knowledge, but it is an approach that is not correct, partial and shortsighted.

In cephalic pain, we have witnessed the rise of peptides such as calcitonin gene-related peptide (CGRP), substance P (SP), orexins, mainly dopamine and serotonin. Sometimes, a relation to cephalic pain was directly (CGRP increase) or indirectly (drugs) demonstrated; this connection was not shown for others (SP), but any effect shown is not overall consistent. Concentrations and effects are not consistent, in relation not only to the type of the disease, but within the same disease, depending on patient, time of sampling, time of drug administration in relation to the progression of the attack, environmental interference, the parameters evaluated and measurement performed. In any paper that attempts to summarize or update knowledge on the physiopathology of cephalic pain [1, 3–7], we see very complicated and comprehensive figures. The alteration of any single factor illustrated in these figures is supposed to intervene or possibly intervene in initiating or maintaining cephalic pain. The putative demonstration comes from the observation that repairing the single error leads to recovery of the system. This approach not only is again a tautology, but also is not correct, since the real system is certainly highly interrelated and alternative pathways may be present and activated.

Imaging

Functional MR (fMR) [8] was of great help to better understand some phenomena or prove some hypotheses, e.g., CSD existence in human, but, at present, can find little space in a fluid system such as cephalic pain. fMR is a photograph in that brain, at that time, in that condition. An fMR image tells us that one area is up or is down, but not why. Does an *up* originate where we see it or is it due to an external input? Does an *up* move? In which direction? New techniques are approaching these issues; however, they remain images without content. PET gives more information on what is happening, what is acting, but its use is too much dangerous and difficult vs. the knowledge it yields.

Therapy/drugs

Pharmacologists always say that drugs are specific in their mechanism of action and, therefore, can dissect a physiological or pathological system leading to its understanding, but this does not really work so well. Drugs are not so specific and if not properly used lead to the tautology mentioned above. Drugs can sometime suggest hypotheses, e.g., schizophrenia—dopamine, pain—serotonin. Unfortunately, this is not the case for cephalic pain: drugs may

exert opposite effects in different pathologies, or moments of the pathology; drugs can act with mechanisms unknown (GNT); drugs can target a factor that has ambiguous effects (CGRP); the drug can be ambiguous reaching different receptors ($5HT_{1f}$ vs. $5HT_{1a}$). Drugs can also be unpredictable and this could be a clue to new knowledge in the physiopathology of the disease, but lack of clinical or experimental attention or the bias for expected results leads to the dismissal of these effects as wrong. Let us remember how important it is to urge the publication of negative data. Moreover, drugs might exert effects that are against the resolution of pain and this may be at least partially the case in medication overuse migraine.

Experimental models

Both psychiatric disease and cephalic pain are diseases of the human in that they have symptoms and signs that only humans can reliably refer or show. Rats or mice do not speak, do not sweat, do not have tears, do not have facial expression. Reliable experimental models of cephalic pain and psychiatric disease do not exist.

Scientists have been looking for in vitro and in vivo models. For psychiatric disease basic research focused on behavioral models as surrogates of human behavior; however, the approach has great limits and is far away from representing the disease.

The situation is worse for cephalic pain, where behavioral models do not exist [3, 7]. The measurable behaviors in cephalic pain models are not specific. After stimulation/sensitization of the trigeminovascular system, allodynia is present also in posterior limbs. Aversive behavior, grooming, decreased spontaneous activity, anorexia (a surrogate of nausea?) are nonspecific. Moreover, several models rely on stimulations that are not at all proven to represent the real pathology, e.g., inflammatory soup, while sterile inflammation is considered a consequence more than the cause of cephalic pain or the stimuli that might induce it. Freund adjuvant injection is a fair model for arthritic pain, but totally away from any cephalic pain, unless we believe that arthritis and headache share something. Biochemical changes observed in experimental models are probably nonspecific to cephalic pain.

Environmental factors

Sex and stress are important factors in human cephalic pain, especially for migraine. None of the two is taken into account in experimental studies in the animal, little in humans. All studies are conducted in male animals [3, 7], when it is well known that migraine prevails in females. The XX or XY weight in cells used in vitro in not considered, while cells with different chromosomal sets behave differently [9, 10]. This does not mean that only female animals should be used, but both males and females, and data evaluated both separately and together. The sex difference is not only relevant for the physiopathology of cephalic pain and its therapy, but also surprisingly for devices when applied to males or females [11]. What is almost incredible, is that the same one-sex experiment is performed also in humans [12]!

Stress is important in cephalic pain, and stress can modify basal conditions, responses to stimuli and drugs, but again, stress induces also different responses in males and females, even at the cellular level, e.g., on dendritic spines, elements strictly related to neurotransmission [13].

Where are we?

Both in cephalic pain and psychiatric disease, we are at an *almost* complete stop. Research does not offer any clue to the understanding of the physiopathology of these diseases. Pharmacology does not offer any new/innovative drug and the pharmaceutical industry is decreasing investment both in cephalic pain and in psychiatric disease.

I wrote *almost* since we are probably not at a complete stop and something is moving in psychiatric disease and pharmacology, of which cephalic pain could benefit.

What is going on in psychiatric disease?

In 2013, the DSM-5 was at last released and the doubts on the principles that had been underlying throughout all its preparation came to clear evidence. DSM-5, although it recognizes the limits of categorical classification of psychiatric disease, continues the approach of previous DSMs offering a classification of psychiatric disease that identifies wider categories, but still categories. Already during DSM-5 preparation, this view was claimed to be unrealistic, since psychiatric disease cannot be categorized, as it is shown by clinical practice and therapies. Recently, two papers were published [14, 15] introducing the concept of "Research Domain Criteria" (RDoC) aiming to suggest new research criteria in psychiatric disease. It can be summarized that RDoC suggest to use neurobiological dimensions (biochemical, genetic, behavioral, cognitive approaches) that cut through heterogeneous categories, since their clinical and therapeutic aspects often overlap in a full range of variations from normal to pathologic. Some features of the disease are common to different "categories". One can study the physiopathology and therapy of the single feature and apply the results to all diseases which

show that specific feature. The assumption is that one feature is transversely identic. In this view, all diseases can be de-constructed and re-constructed in a variable sum of signs and symptoms. The point is to figure out which should be the primary features to address and in which sets of diseases. Another important point is the idea of considering the disease state as disruption of the normal functioning of the system. The fact that certain stimuli become effective at a certain point in life, or not in all patients is a derangement from normality.

The characteristics of the RDoC approach suggest that it could be positively applied also to the study of cephalic pain. It is a relevant change, but it might be worthwhile. The big problem, promptly identified in psychiatry, is that the transition needs time to yield result and it will be long: the old and new approach faces a long period of "cohabitation".

What is going on in pharmacology?

A recent paper [16] looked into the difficulties that pharmacology has been facing in the last decades in offering new, innovative drugs. In the nineteenth century, pharmacology demonstrated that compound effects were dose-dependent leading to the receptor concept that remains the key to understanding disease causality and drug action. In the twentieth century through biochemical, molecular and genomic eras, understanding functions at the molecular level provided important insights, but leads to a strong reductionism. This resulted in the generation of data lacking physiological context that ignore dose–effect dependency and separated from the whole organism level. Under the trend of systems biology, pharmacological research went into a bioinformatics-based experimental replication that often had a limited link to reality.

The suggestion is that pharmacological research should work on testable hypotheses rather than technology. The possibility must be accepted, as it was in the past, to recognize the effect of a treatment and thereafter get into the search for its mechanism. This might lead to novel, unexpected knowledge and new therapeutics.

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

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Biochemistry of primary headaches: role of tyrosine and tryptophan metabolism

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Abstract The pathogenesis of migraine as well as cluster headache (CH) is yet a debated question. In this review, we discuss the possible role of the of tyrosine and tryptophan metabolism in the pathogenesis of these primary headaches. These include the abnormalities in the synthesis of neurotransmitters: high level of DA, low level of NE and very elevated levels of octopamine and synephrine (neuromodulators) in plasma of episodic migraine without aura and CH patients. We hypothesize that the imbalance between the levels of neurotransmitters and elusive amines synthesis is due to a metabolic shift directing tyrosine toward an increased decarboxylase and reduced hydroxylase enzyme activities. The metabolic shift of the tyrosine is favored by a state of neuronal hyperexcitability and a reduced mitochondrial activity present in migraine. In addition we present biochemical studies performed in chronic migraine and chronic tension-type headache patients to verify if the same anomalies of the tyrosine and tryptophan metabolism are present in these primary headaches and, if so, their possible role in the chronicity process of CM and CTTH. The results show that important abnormalities of tyrosine metabolism are present only in CM patients (very high plasma levels of DA, NE and tryptamine). Tryptamine plasma levels were found significantly lower in both CM and CTTH patients. In view of this, we propose that migraine and, possibly, CH attacks derive from neurotransmitter and neuromodulator metabolic abnormalities in a hyperexcitable and hypoenergetic brain that spread from the frontal lobe, downstream, resulting in abnormally activated nuclei of the pain matrix. The low tryptamine plasma levels found in CM and CTTH patients suggest that these two primary chronic headaches are characterized by a common insufficient serotoninergic control of the pain threshold.

Keywords Migraine · Cluster headache · Tyramine · Octopamine · Tryptamine

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Introduction

Primary headaches include migraine with and without aura and cluster headache (CH). Both pathological conditions are characterized by the episodic and chronic forms. In episodic migraine, the painful attacks occur in less than 15 days/month. In the chronic forms, they occur almost every day [1]. The pathogenesis of migraine is still not completely understood. We hypothesized that genetic mutations and/or polymorphism, yet be determined, regulating the brain energy, neurotransmitters metabolisms in the central nervous system, may determine a biochemical phenotype characterized by biochemical anomalies in the synaptic function of antinociceptive system (ANS) and sympathetic system (SS) [2, 3].

The excitatory and inhibitory functions of glutamic acid and GABA constitute the frame in which the other circuitries regulate the functions of the human brain [4, 5]. It has been hypothesized that anomalies of the metabolism of glutamate, GABA, together with those that govern the pain and vegetative functions such as serotonin (5HT), dopamine (DA) and noradrenalin (NE) constitute the phenotypical biochemical cause of the migraine [6]. Recent

studies have also shown that the elusive amines such as tyramine, octopamine and tryptamine play a role in migraine pathogenesis [7]. These amines, together with DA, NE and 5-HT are products of two different metabolic pathways of tyrosine and tryptophan. Tyrosine hydroxylase generates DOPA, DA and NE; the last two compounds by the DOPA decarboxylase and dopamine β-hydroxylase (Dβ-H), respectively. The alternative pathway, tyrosine decarboxylase, synthesizes tyramine, octopamine and synephrine; octopamine and synephrine by Dβ-H and PMNT enzyme activities [8]. Tryptophan (T) is the amino acid parent of 5-HT and tryptamine products of the T hydroxylase and decarboxylase enzymes activity, respectively.

We, here, in this review, will briefly summarize the evidences that support the role of the biochemical anomalies of these neurotransmitters and neuromodulators in the pathophysiology of migraine and CH and in the process of chronicity of migraine. Based on these evidences, we propose that future research efforts aiming to comprehend the pathophysiological relevance of neuromodulators such as trace amines in the CNS have the potential to provide new, more effective treatment options for migraine.

Glutamate and aura

Transitory visual and/or neurological phenomena constitute the clinical phenotype of migraine with aura [1]. We have hypothesized that a neuronal hyperexcitability constitutes the functional prerequisite of the occurrence of the aura [9–11]. An array of biochemical, neurophysiological, and pharmacological data in humans support this hypothesis. Glutamate released from neurons and glia, is the main excitatory neurotransmitter of the CNS [12]. Brain metabolism studies, using 1H-MRSand pNMR methodologies, have shown that, in comparison of control subjects, levels of N-acetylaspartylglutamate, a precursor of glutamate, glutamine and glutamate are higher in cingulate, insula and occipital cortex of migraine patients [13, 14].

Occurrence of CNS hyperexcitability in migraine is also supported by neurophysiological studies employing transcranial magnetic stimulation (TMS) of occipital lobe [15] and measuring the resting motor threshold and silent period [16]. Further evidence of the hyperexcitability of brain in migraineurs is supported by ^{31}pNMR studies and pharmacological evidences employing lamotrigine. In comparison to control subjects, the levels of magnesium (Mg), measured with ^{31}pNMR were found significantly lower in the brain of migraine patients, particularly during migraine attacks [17]. Mg is the unique compound known to block glutamate-dependent SD [18]. Lamotrigine is an antiepileptic drug acting by blocking voltage-sensitive channels leading to an inhibition of glutamate release [19]. A number of studies have confirmed the efficacy of lamotrigine in the prevention of the auras [20–24].

Tyrosine metabolism, premonitory symptoms and migraine attack

The first step of the pathophysiological events that characterize migraine attack may occur in the frontal lobe and, downstream, to pain matrix-connected areas of the CNS. Premonitory symptoms such as hyperosmia, yawning, mood changes, anxiety, food craving, sexual excitement, fatigue and emotional lability often preceded the painful attack [25–28]. These symptoms are considered markers of activation of the areas belonging to pain matrix; therefore, it is logical to attribute to these CNS abnormalities the first phase of the migraine attacks [29]. This hypothesis is also supported by the evidences that in such areas of CNS TAARs, g-protein receptors activated by elusive amines, and dopamine receptors are abundantly distributed. Their activation may be related to the high levels of DA, octopamine and synephrine found in plasma and platelets of migraine without aura sufferers during headache-free periods [30, 31].

We support the hypothesis that the activation of trigeminal system depends on abnormal pain process initiating in the frontal lobe and, thereafter, progressing downstream to the connected pain centers [32]. Functional fRMN and PET studies have demonstrated that a reduced function of the frontal lobe occurs in chronic migraine when the pain subsides [33]. Other evidence from fMRI and PET studies has demonstrated that nuclei behind the aqueduct of the brain stem are activated before and during migraine attacks [34, 35].

Abnormal levels of elusive amines and DA and NE may play an important role in the pathophysiology of migraine attacks. Indeed, as mentioned before, TAARs are located in the many subcortical centers of CNS. These areas are important parts of the pain matrix that modulate the pain threshold [36]. The physiological functions of the pain matrix neurons are regulated mainly by synapses that utilize DA and NE as neurotransmitters [37]. Octopamine acts, in the same synaptic clefts, as neuromodulator. Thus, one of the possible physiologic roles of octopamine is the regulation, together with the DA and NE, of the synapse clefts of the pain matrix [38]. We hypothesized that, in same steps of the migraine pathophysiological process, an abnormality of tyrosine metabolism occurs with a shift toward an elevated decarboxylase enzyme activity with an increase of synthesis of elusive amines, and a decrease of NE. In favor of this hypothesis, biochemical studies have shown that plasma and platelets levels of octopamine and synephrine together with

platelet DA levels are elevated in MwoA patients [31, 39]; a polymorphism of the gene that code for DβH may be the cause of a reduction of this enzyme activity [40] and of the high levels of DA [41, 42] since DβH transforms DA in NE. In agreement with this, the plasma levels of NE were found significantly low in migraine patients [43–45]. If the same biochemical anomalies shown in plasma and platelet are present in the CNS, an abnormal ratio between the amounts of neuromodulators and neurotransmitters may be present in the synaptic clefts innervating the pain matrix. The pathological consequence would be a possible abnormal function of hypothalamus [46], ANS nuclei with a downstream activation of trigeminal nucleus, release of CGRP in the cephalic circulation and head pain.

Biochemical tryptophan anomalies and painful attack

The main product of tryptophan hydroxylase is serotonin (5-HT), whereas tryptamine is the neuromodulator that derives from the decarboxylase enzyme activity [47]. Numerous studies have been done, in the last decades, to explore possible anomalies of this in indole in migraine patients with very few compelling results. One study has found that in migraine female patients, the levels of platelet 5-HT fluctuate differently to those of healthy woman, in the different phases of the menses and, more important, the levels of the indole decrease significantly in luteal phase in menstrual migraine before the painful attacks [47, 48]. The reason why the levels of 5-HT drop before the attack is not known; however, it is possible to conceive that the reduction of 5-HT may due to a shift of T metabolism toward an increase of decarboxylase enzyme activities activity during this phase of the menstrual cycle of migraine sufferers.

GABA and migraine

GABA plays an important inhibitory role in the modulation of the pain threshold. Drugs GABA agonist such as valproate and topiramate are very effective in the preventing the migraine without aura attacks [49]. However, direct evidence of GABA-related abnormalities in migraine is poor [50]. One study has shown that plasma levels of GABA increase at the end of migraine attack. It is possible that the activation of GABA metabolism is necessary for the conclusion of migraine attack [51].

Mitochondrial energy, metabolic shifts, and migraine

The synthesis of neurotransmitters is energy dependent [52, 53]. The abnormal levels of elusive amines and the possible tyrosine enzyme derangement, found in migraine patients, may be the consequence of a decreased mitochondrial function. In support of this hypothesis, there is a study of elusive amine levels in CSF of the early post-mortem subjects. In the first hours after death, the levels of tyramine, octopamine and synephrine increase dramatically suggesting that when the brain energy fails, the tyrosine decarboxylase enzyme is activated [54]. Deposition of free radicals may contribute to mitochondrial energy decline in these patients. In fact it is known that the iron ions accumulated in brain stem centers is proportional to frequency of migraine attacks [55]. Abnormal levels of this ion, on the surface of mitochondria, reduce the availability of neuron energy substrates [56].

Elusive amines and CH

Cluster headache is a primary headache characterized by excruciating painful attacks, that lasts between 15 and 180 min, localized in the first trigeminal branch area and strictly lateralized [1]. The crisis is accompanied by tearing, conjunctival injection, ptosis, nasal stiffness and rinorrea. All these autonomic signs are expression of a reduced sympathetic and increased parasympathetic activity. In this CH, the active period, in which the painful attacks occur in a variable frequency, is followed by a silent period. Studies with PET and MRI demonstrated that the posterior area of hypothalamus is characterized by an increased synaptic activity [57] and anatomical abnormality (a bigger volume of gray matter) [58]. In addition, the stereotactic stimulation of the posterior hypothalamus is very effective to cure intractable chronic CH patients [59]. All these evidences strongly support the hypothesis that functional, and possibly anatomical, anomalies of hypothalamus play an important role in the pathogenesis of CH.

Taking in mind that hypothalamus contains the maximal concentration of trace amines and their receptors, we measured plasma levels of tyramine, octopamine, synephrine and dopamine in CH patients in remission and active periods. All patients, in the two phases of the disease, showed very high levels of trace amines and DA in plasma and platelets [30, 60]. All these results suggest that also in CH patients is present an anomaly of tyrosine metabolism.

Tyrosine metabolism and chronic migraine

Chronic migraine (CM) is a form of headache in which the frequency of attacks progressively increases to daily or near-daily headache attacks. The pathogenesis of CM is largely unknown. The natural history raises the possibility

that CM constitutes a complication and/or transformation of episodic migraine when the frequency of the attacks increases over time [61, 62]. It is reasonable to hypothesize that the aspects of the pathogenesis of migraine without aura (MwwA) play an important role in the transformation of MwwA into CM.

It is unknown if anomalies of tyrosine metabolism in MwwA are also present in CM patients, and if these alterations affect the evolution of episodic MwwA to CM or the occurrence of CM per se. To explore this hypothesis, we measured the levels of DA, NE, tyramine and octopamine in plasma of healthy controls, CM and chronic tension-type headache (CTTH) patients. The plasma levels of DA and NE and tyramine were severalfold higher in CM patients compared with control subjects and these levels progressively increased with the duration of the CM. The catecholamine and elusive amine levels of CTTH patients were found in the same range of control subjects suggesting that tyramine metabolism is normal in this chronic primary headache. The pathophysiology and the treatment of CTTH remain unknown [63].

Tryptophan metabolism and CM and CTTH

Tryptophan (TRP) is the aminoacid precursor of indoles as 5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA) and tryptamine. tryptamine together with tyramine, octopamine and synephrine have, for a long time, been nominated elusive amines. The enzymes that govern the synthesis of 5-HT, 5-HIAA and tryptamine are TRP hydroxylase and TRP decarboxylase, respectively [47].

Tryptamine is a biogenic amine structurally related to 5-HT. The specific functions of this biogenic amine were unknown until a few years ago when it was discovered that tryptamine is an agonist of 5-HT1A, 5-HT2A and TAARs receptors [64]. 5-HT1A and receptors are present in large amount in many of the cortical and subcortical areas of CNS. 5-HT1A is the major somatodendritic autoreceptor on 5-HT neurons where it acts in an inhibitory manner. These neurons together with TAARs receptors, project widely throughout the brain regulating many functions, including that of the pain threshold [65]. As a consequence, anomalies of 5-HT1A, 5-HT2A and TAAR receptor functions have been hypothesized to play a role in the pathogenesis of migraine and tension-type headache; however, direct evidence in support of this hypothesis is still lacking. To verify this hypothesis, plasma levels of 5-HT, 5-HIAA and tryptamine were measured along with those of 5-HT in platelets of CM and CTTH sufferers versus control subjects. The main result of this study was that the tryptamine levels are significantly lower in plasma of both groups of headache patients, whereas 5-HT and 5-HIAA levels were in the same range to those of controls. Together these results raise the possibility that the tryptophan decarboxylase enzymatic activity is, unlike that of tryptophan hydroxylase, reduced in the CM and CTTH sufferers [66].

If the same low amine plasma levels are present in the CNS of headache patients, the finding that circulating tryptamine levels are low in CM patients is suggestive of a dysfunction of the serotonergic system [67]. It is possible that the low levels of tryptamine, found in CM patients, result in an increase in GABA release and, consequently, inhibition of the functionality of PAG system that modulates the nociceptive transmission at the level of the spinal cord. Moreover, low levels of tryptamine may further increase this inhibition because of a reduced activation of 5-HT2A receptors with a reduced synthesis and release of 5-HT in raphe magnum that, in turn, modulates serotonergic neurons of the orbitofrontal cortex [68–70]. These abnormalities may play a role in the chronicity of the migraine and CTTTH.

Conclusions

All the data shown above provide a possible functional framework in how anomalies in different biochemical pathways play a role in the pathogenesis of migraine and CH. Indeed, are necessary further studies on the physiology and pathology of elusive amines and their relationship with TAAR function in CNS to clarify their role in migraine. Equally important will be to explore the possible genetic and epigenetic anomalies related to the tyrosine and tryptophan metabolism in general and in these primary headaches in particular. Also important is to test functions of mitochondria, in adequately stressed animal models, to evaluate the decarboxylase and hydroxylase enzyme activities that require different amount of energy to work. These studies may shed light on the physiological and pathological significance of decarboxylase activity that are ancient enzymes, of evolutionary importance, in humans. Until few years ago, octopamine was considered only as the main noradrenergic neurotransmitters of the lowest species of the evolutionary scale, as firefly, cockroach and octopus [8]. In conclusion we suggest that the pathological combination of energy failure and the metabolic shift of tyrosine metabolism such as an increase neuromodulators and an unphysiological amount of neurotransmitters in platelet and plasma, as shown to be present in headache patients, may mirror the same biochemical anomalies in the synaptic clefts of pain matrix and constitute the pathological biochemical background in which migraine and cluster headache attack occur.

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

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The role of intracranial hypertension in the chronification of migraine

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Abstract Besides a similar clinical presentation, idiopathic intracranial hypertension (IIH) and chronic migraine (CM) also share relevant risk factors, show a higher prevalence of allodynic symptoms and both respond to topiramate. Moreover, sinus stenosis, a radiological marker of IIH, in CM patients is much more prevalent than expected. As a consequence of these striking similarities, IIH without papilledema (IIHWOP) may be easily misdiagnosed as CM. Actually, IIHWOP has been found in up to 14 % of CM clinical series. Considering that, on one hand, an asymptomatic sinus stenosis-associated raised intracranial pressure (ICP) may be highly prevalent in the general population, and on the other, that IIH clinical presentation with chronic headache may require a migraine predisposition, we have proposed that an overlooked IIHWOP could represent a risk factor for migraine progression. This hypothesis prompted us to investigate the prevalence of IIHWOP and its possible role in the process of migraine chronification in a consecutive series of CM patients selected for unresponsiveness to medical treatment and evidence of significant sinus stenosis. The main finding of our study is that the large majority of such patients actually suffer from a chronic headache secondary to IIHWOP. This implies that an IIHWOP mimicking CM is much more prevalent than believed, is commonly misdiagnosed as CM on the basis of ICHD criteria and is strictly predicted by refractoriness to preventive treatments. However, our data fully comply with the alternative hypothesis that an overlooked IIHWOP, although highly prevalent amongst healthy individuals, in migraine-prone subjects is a powerful (and modifiable) risk factor for the progression and the refractoriness of pain. The normalization of ICP by even a single LP with CSF withdrawal may be effective in a significant proportion of patients with a long history of refractory chronic headache, who represent about one-fifth of the patients screened in our study. We suggest that IIHWOP should be considered in all patients with almost daily migraine pain, with evidence of sinus stenosis and unresponsive to medical treatment, referred to specialized headache clinics.

Keywords Idiopathic intracranial hypertension · Chronic migraine · Risk factor · Sinus venous stenosis

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Background

Chronic migraine (CM), a condition with an estimated prevalence of about 2–3 % [1, 2], is characterized by 15 or more headache days per month, 8 of which with migraine features [3]. CM results from the progressive worsening of attacks frequency, up to a daily or near-daily pain, that may develop, more or less progressively, in a part of episodic migraine sufferers. The annual rate of progression from episodic to chronic migraine is about 2.5 % [4, 5]. However, recent epidemiological data highlight that CM is neither a fixed nor an irreversible condition. In fact, there is an annual rate of remission from chronic to episodic pattern of 14 % [4]. Thus, migraine progression is a dynamic and a *reversible* event. As a consequence, the identification of the risk factors associated to both, migraine progression and

remission, is of crucial relevance in headache research and management.

Risk factors for migraine chronification have been extensively studied in recent years [5–9]. Besides non-modifiable risk factors such as female gender, age, low socioeconomic status and history of head injury, the main modifiable risk factors for migraine progression are medication overuse, the high frequency of attacks at baseline, obesity, sleep disturbances, psychiatric comorbidity and stressful life events. Additionally, idiopathic intracranial hypertension without papilledema (IIHWOP), a recently identified [10–14] variant of the form with papilledema (IIH), is emerging as a new potential risk factor for the progression and the refractoriness of migraine pain [15, 16].

Idiopathic intracranial hypertension

Intracranial hypertension clinical presentation includes headache, often on a daily basis, papilledema, visual disturbances, diplopia, vertigo and tinnitus. According to a comparative study, headache features in IIH with or without papilledema are very similar [17] but the reported intracranial pressure (ICP) values, in IIHWOP, are lower or fluctuating [16, 17] suggesting that papilledema may not develop in cases with mild or intermittent ICP increase. With an estimated incidence ranging from 1 to 19/100,000 per year [18–21], IIH is definitely an infrequent disease. Instead, IIHWOP prevalence on general population is not known.

Which is the prevalence of IIHWOP?

Generally considered as an infrequent variant of IIH, a quite rare condition, in clinical series of chronic/transformed migraine patients IIHWOP is not so uncommon, as it can be found in up to 14 % of such cases [14, 22, 23]. Of note, chronic headache is not an obligatory symptom in IIH as it may lack in subjects without history of migraine or in the presence of a migraine protective factor as pregnancy [24]. These observations suggest that IIH clinical presentation with chronic headache may require a primary headache predisposition and imply that IIHWOP could run almost asymptomatically in non-primary headache-prone individuals. Interestingly, in a large community study [25] an asymptomatic increase of intracranial pressure has been identified in about one-half of subjects with bilateral dural sinus stenosis, which represented about a quarter (23 %) of the population studied, and in none of the subject with normal dural sinus anatomy [25]. Actually, an asymptomatic form of raised intracranial pressure associated with sinus stenosis could be extraordinarily prevalent amongst healthy individuals.

According to the above considerations we recently proposed [26] that a clinical and epidemiologic *continuum* might exist amongst (a) IIH with papilledema, possibly representing only the visible part of a hidden and much larger phenomenon; (b) *symptomatic* IIHWOP, presumably largely overlooked at present mostly because of frequent CM misdiagnosis, and (c) *asymptomatic* IIHWOP a completely hidden condition possibly with high prevalence amongst healthy subjects.

The role of sinus stenosis in IIH pathogenesis

Intracranial hypertension results from an increased resistance to the CSF outflow into the cerebral venous blood collectors, promoted by a raised cerebral venous pressure of various aetiologies [27]. Although the pathogenetic role of sinus stenosis is debated [28–30], it represents a specific (93 %) and sensitive (93 %) marker of IIH [31] and has been recently included amongst the radiological signs suggestive of IIHWOP [32]. Long considered a consequence of the raised ICP without pathogenetic relevance, there is evidence of a significant pressure gradient across the stenosis [33]. Moreover, the stenting of sinus stenosis is consistently followed by the remission of IIH symptoms [34–36]. These findings suggest a causal involvement of sinus stenosis in IIH mechanisms.

We have recently proposed [37] that in patients with evidence of cerebral venous outflow disturbances at magnetic resonance venography (MRV), a *self-limiting* venous collapse (SVC) feedback loop may lead to a *self-sustained* coupled increase of venous blood and CSF pressures up to a relatively stable new balance at higher pressure. The SVC mechanism is *reversible* provided an adequate perturbation is carried at either side of the loop, such as sinus stenting on one hand [34–36], and CSF shunting [38, 39] or even a single lumbar puncture with CSF withdrawal [16, 40–42], on the other. The SVC model may explain the longstanding remissions not infrequently observed in IIH patients after a single diagnostic LP.

Is IIHWOP a risk factor for migraine progression?

IIH without papilledema may present with a mild continuous headache, thus resembling a chronic tension-type headache [43]. However, most of the patients show superimposed recurrences of severe migrainous pain, up to a clinical picture indistinguishable from CM [14]. Wang et al. [13] compared the clinical features of 25 patients with IIHWOP with those exhibiting chronic daily headache (CDH) but with normal CSF pressure, and no difference in headache profile was found. Besides clinical presentation, IIH and CM also share some relevant risk factors such as

female gender, obesity and sleep disturbances [44–46] and both show a higher prevalence of allodynic symptoms [47–50]. Topiramate, a drug with documented efficacy in CM [51, 52] that shares with acetazolamide the inhibition of carbonic anhydrase isoenzyme [53], has been found as effective as acetazolamide in IIH treatment [54], suggesting that the topiramate efficacy in CM could be mediated, at least partially, by an acetazolamide-like CSF pressure lowering effect. Finally, significant dural sinus stenosis, a marker of IIH, has recently been found highly prevalent also in CM [55–57].

On the basis of the above-outlined clinical similarities and considering that, on one hand, an asymptomatic sinus stenosis-associated raised intracranial pressure may be highly prevalent in general population [25], and on the other, that IIH clinical presentation with chronic headache may require a migrainous background [15], we have proposed that a sinus stenosis-associated IIHWOP, albeit highly prevalent amongst healthy individuals, in migraine predisposed subjects could represent a powerful and modifiable risk factor for migraine progression [15, 26].

The findings of a recent well-conducted study support the above hypothesis. In a consecutive series of 98 chronic headache patients, an MRV and LP with 1 h ICP monitoring were performed [55]. Sinus stenosis was present in 48.9 % of the sample. Based on 1-h ICP monitoring, an overall IIHWOP prevalence of 44.8 % was found. This group represented the 91.6 % of sinus stenosis carriers. Conversely, CSF pressure resulted within normal limits in all chronic headache patients showing a normal MRV. Intriguingly, the authors noticed that a transitory (2–4 weeks) improvement of headache after the LP was reported by the majority of patients with raised ICP. These observations confirm the high prevalence of IIHWOP in chronic headache sufferers and its strict association with sinus stenosis. However, the lack of venous outflow disturbances and of raised ICP in more than half of patients with chronic headache [55] and the high prevalence of sinus stenosis-associated raised ICP found in subjects without chronic headache [25] indicate that IIHWOP is neither a necessary nor a sufficient condition for chronic headache development but has to be considered a risk factor for progression and refractoriness of pain in primary headache-prone individuals.

Intracranial hypertension and progression of migraine

To assess the intracranial pressure in unresponsive CM sufferers and to test the possible involvement of IIHWOP in the progression and refractoriness of migraine, we performed a clinical prospective study in which the opening pressure (OP) and the clinical outcome of a single CSF withdrawal by LP have been evaluated in a series of consecutive CM/TM patients, carefully selected for unresponsiveness to medical treatments [16].

Out of 278 consecutive patients diagnosed with CM/TM with or without medication overuse, 56 (20.1 %) failed to respond to two consecutive medical treatments at therapeutic doses. The prevalence of sinus stenosis in these patients, defined as bilateral sinus stenosis/hypoplasia or at least unilateral segmental flow gap/aplasia at uncontrasted MRV, was even higher (52/56; 92.8 %) than reported in unselected chronic headache patients [55, 57] and close to the prevalence found in IIH patients (93.0 %) [31]. Of these patients, 44 accepted to perform a lumbar puncture (LP) and 38 of them (86.4 %) had an OP >200 mmH_2O, with 19/44 patients (43.2 %) showing an OP >250 mmH_2O. Normalization of ICP by a single 20–30 ml of CSF withdrawal by LP was followed by the immediate amelioration of pain in 77.3 % of the sample, and by the return to an episodic pattern of headache that lasted at least 2 months in more than half of the patients (24/44; 54.6 %) and at least 4 months in more than one-third of the patients (17/44; 38.6 %). The benefit persisted even longer in 7 patients (15.9 %), being still episodic after a median follow-up of 25 months (range 12–60 months). After relapse, LP repetition leads to a new longstanding remission of the chronic headache pattern in most responders. Based on ICHD-2 criteria [58], 70.4 % of our patients could be diagnosed with "Headache attributed to IIH" despite the absence of papilledema.

The most striking finding of our study is that the large majority of patients diagnosed with proven unresponsive CM in specialized centres actually suffer from chronic headache secondary to IIHWOP. This implies that an IIHWOP *mimicking* CM is much more prevalent than believed, is commonly misdiagnosed as CM on the basis of ICHD criteria [3] and is strictly predicted by refractoriness to preventive treatments. Moreover, we showed that normalization of ICP by LP may be effective in patients with a long history of refractory chronic headache, who represent about one-fifth of the patients screened in this study. However, our data fully comply with the alternative hypothesis [15, 26] that an overlooked IIHWOP, although highly prevalent amongst healthy individuals, in migraine-prone subjects is a powerful (and modifiable) risk factor for the progression and the refractoriness of pain.

Putative mechanisms

According to the SVC model [37], in subjects harbouring one ore more collapsible segments of central veins, any promoting factor leading to a sufficient increase of either CSF pressure or cerebral venous pressure, could trigger a positive feedback loop between the CSF pressure, that

compresses the sinus, and the consequent venous pressure rise, that increases the CSF pressure. The cerebral venous congestion induced by the recumbent position may aggravate a running migraine pain [59, 60]. We speculate that the opposite increased pressures acting on both, the blood and the CSF side of the venous wall, might promote the activation of dural sinus trigeminovascular nociceptors, leading to central sensitization of pain pathways [37]. Allodynia, a clinical marker of central sensitization, usually develops in the course of primary headache attacks [61–65] but is bilaterally detected during the intercritical phase in over 70 % of chronic headache subjects [49]. Amongst migraine sufferers, allodynia has been associated with female sex, frequent headache, increased BMI and depression [66, 67]. It may represent the final pathway on which the actions of most risk factors for migraine progression validated by the recent literature converge [68]. Interestingly, Ekizoglu et al. [50] recently found allodynia in about one-half of an IIH patient series and it was associated with a chronic migraine-like headache profile.

On the basis of the above considerations and findings we recently proposed [26] that the mechanism linking raised ICP to migraine pain progression may rely on the central sensitization of pain pathways, induced by a continuous trigeminovascular firing at the congested sinus stenosis level.

Conclusions

Intracranial hypertension without papilledema shares with CM a number of clinical features and it can be documented in chronic headache series much more frequently than expected. However, the lack of venous outflow disturbances and of raised ICP in more than half of patients with chronic headache [55], on one hand, and the high prevalence of sinus stenosis-associated raised ICP found in subjects without chronic headache [25], on the other, indicate that IIHWOP is neither a necessary nor a sufficient condition for chronic headache development but has to be considered a powerful and modifiable risk factor for chronification of migraine. Our recent finding highlights that most refractory CM/TM patients referring to specialized headache clinics actually harbour a comorbid cerebral sinus venous stenosis-associated IIHWOP causatively involved in both the progression and the refractoriness of pain. We speculate that a central sensitization induced by a continuous trigeminovascular firing at the congested sinus stenosis level may be the mechanism linking the raised ICP and migraine pain progression in such patients. We suggest that IIHWOP should be considered in all patients with almost daily migraine pain, with evidence of sinus stenosis and unresponsive to medical treatment referred to specialized headache clinics.

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

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Rationale for use of onabotulinum toxin A (BOTOX) in chronic migraine

P. Barbanti · G. Egeo · L. Fofi · C. Aurilia · S. Piroso

Abstract Chronic migraine is a severely disabling headache evolving from episodic migraine as a result of different transforming factors and characterized by atypical pain modulation and peripheral and central sensitization. Discovered by serendipity, onabotulinum toxin A (BoNT-A) represents the only drug specifically approved for CM prophylaxis. According to the dominant opinion, BoNT-A acts peripherally, impairing the exocytosis of neuropeptide and neurotransmitter and the delivery of receptors and ion channels on the cell surface of peripheral trigeminal endings, thereby indirectly reducing central sensitization. However, it is not excluded that BoNT-A has also a central antinociceptive action, probably associated with an enhanced opioidergic and GABA-ergic transmission. This review discusses the rationale for use of BoNT-A in CM including its mechanisms of action and molecular targets and provides suggestions for a more tailored BoNT-A prophylaxis in patients with CM.

Keywords Chronic migraine · Onabotulinum toxin A · Treatment · Migraine · Disability

Introduction

Chronic migraine (CM) is a severely disabling headache affecting from 2 to 3 % of general population. Typically, CM evolves from episodic migraine as a result of different transforming factors encompassing female sex, low socio-economic status, stressful life events, psychiatric comorbidities, medications overuse, excessive caffeine intake, snoring, head or neck trauma, obesity, cutaneous allodynia, and concomitant pain conditions [1]. Transformation of episodic migraine into CM occurs over months to years and involves atypical pain modulation and central sensitization triggered by repetitive inputs from sensitized peripheral sensory neurons [1]. The overactivation of the trigeminovascular system could result from the nociceptors activation by cortical spreading depression, mast cell degranulation, neurogenic inflammation, hydrogen ions, and ATP release, or from the up-regulation of different sensory receptors or ion channels including transient receptor potential channels TRPV1, TRPA1, and TRPM8, ATP-gated P2X3 receptors, dopaminergic D1 and D2 receptors, serotoninergic 5-$HT_{1B/1D}$ receptors, calcitonin gene related peptide (CGRP) receptors, tumor necrosis factor α (TNF-α), and acid-sensing ion channel 3 (ASIC-3) [2].

The management of CM is challenging and sometimes frustrating, and requires a multimodal-multidisciplinary approach including education, behavioral therapy, and pharmacological prophylaxis [3]. The patient should be encouraged to lose weight, increase physical activity, reduce caffeine, alcohol, and analgesic intake, and reduce stress, get regular sleep, and meals; medical or psychiatric comorbidities should be carefully recognized and treated. Different pharmacological preventive treatments, in most cases with limited supporting evidence, have been considered for CM, ranging from anticonvulsants (topiramate, sodium valproate, gabapentin, pregabalin, and zonisamide) to antidepressants (amitriptyline, fluoxetine), beta-blockers (atenolol), myorelaxants (tizanidine), and memantine [3]. At present, onabotulinum toxin A (BoNT-A) is the only drug approved for CM prophylaxis by the American Food

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and Drug Administration and the European Medicines Agency [4].

The discovery of BoNT-A efficacy in migraine

Onabotulinum toxin A is a neurotoxin ("sausage poison") derived from Clostridium Botulinum, a Gram-positive anaerobic spore-forming bacterium, which can contaminate canned or fermented foods being responsible for botulism [5]. BoNT-A represents one of the most potent toxins known. Of the seven immunologically distinct toxins (A-G), the serotype A has been used in human therapy since 1980 when Scott proposed BoNT-A injection into extraocular muscles as an alternative to strabismus surgery [6]. Nowadays, BoNT-A has therapeutic indications for cervical dystonia, blepharospasm, strabismus, upper limb spasticity, primary axillary hyperhidrosis, overactive bladder, and chronic migraine [7].

The usefulness of BoNT-A in migraine prevention was discovered by serendipity in the 1990s by a plastic surgeon who noted an unexpected correlation between pericranial BoNT-A injection and migraine improvement in patients treated for hyperfunctional upper facial lines, reporting that "several patients who suffered from either migraine or chronic headache pain had relief of their symptom after the administration of botulinum toxin to the forehead, temporal and/or glabella regions" [8]. Since then, a number of exploratory studies with BoNT-A using heterogeneous doses and injection paradigms has been carried out in miscellaneous headaches including chronic daily headache, migraine, and tension-type headache: results were inconclusive for episodic migraine and tension-type headache but the post hoc analysis of the phase 2 chronic daily headache study suggested that BoNT-A treatment might be more effective in patients with frequent migraine headaches, pointing the way for a phase 3 pharmacological trial in CM prophylaxis [4, 9].

Mechanism of action of BoNT-A

Successful delivery of neurotransmitters, ion channels and receptors from synaptic vesicles at nerve terminal depends on the interaction between vesicle-associated membrane-protein (VAMP)/synaptobrevin with 25 kDa synaptosomal-associated protein (SNAP-25) and syntaxin which constitute the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) complex [10].

BoNT-A is a 900 kDa protein complex: its active portion consists of a heavy chain (100 kDa, involved in membrane translocation) linked to a light chain (50 kDa, responsible for intracellular catalytic activity) by a disulfide bridge [11]. After tissue injection, BoNT-A anchors to the outer side of plasma membrane, the heavy chain binds to synaptic vesicle glycoprotein 2, ganglioside receptor and fibroblast growth factor receptor 3 and is internalized into the cell. BoNT-A endocytosis into the acidic compartment of small synaptic vesicles (a dynamin-dependent phenomenon) is increased by neuronal activity, which favors synaptic vesicle recycling. Then, the light chain undergoes a conformational change and cleaves the SNAP-25, whose integrity is required for the full fusion of synaptic vesicle membrane with plasma membrane [11]. In this way, BoNT-A compromises the delivering of neurotransmitters into the synaptic cleft and the expression of protein channels or receptors on the cell surface, inducing a chemical denervation in motor, autonomic, and sensory fibers [7, 11]. BoNT-A inhibits the release of glutamate, serotonin, noradrenaline, dopamine, gamma aminobutyric acid (GABA), enkephalin, glycine, substance P, ATP, and CGRP [12–18]. BoNT-A blocks the vesicular release not only from neurons but also from pancreatic beta cells (insulin), chromaffin cells (acetylcholine), astrocytes (glutamate), and Schwann cells (acetylcholine) [19–22]. BoNT-A effects are long lasting, due to the stability of the light chain in the cytosol, but reversible and nerves restore their normal synaptic activity over time [11].

BoNT-A in chronic migraine: putative mechanisms

The exact mechanism of action of BoNT-A in chronic migraine is still a matter of speculation. The dominant hypothesis is that the toxin exerts its antinociceptive action via peripheral mechanisms [23]. It is believed that BoNT-A directly inhibits peripheral sensitization by attenuating neuropeptide and neurotransmitter exocytosis from peripheral sensory neurons, thereby indirectly reducing central sensitization, the hallmark of chronic migraine [23].

BoNT-A lowers hyperalgesic or allodynic responses in acute inflammatory or chronic pain, but does not alter normal nociceptive thresholds or acute nociceptive pain in both humans and animals [24]. Experimental studies in rat demonstrated that BoNT-A given subcutaneously blocks the release of neurotransmitters (glutamate, substance P, CGRP) from peripheral sensory neurons, neurogenic inflammation, Fos-like immunoreactivity in the dorsal horn and wide dynamic range neuron evoked-activity in the spinal cord [24]. BoNT-A inhibits mechanical nociception to suprathreshold stimuli in peripheral trigeminal neurons acting on C but not on Aδ meningeal nociceptors, disrupting protein kinase C-mediated membrane normal cycling of TRPV1, TRPA1, and ATP-gated P2X3 receptors from inside the axon to the axon membrane surface [2]. In human models of capsaicin-induced pain, BoNT-A given

intramuscularly exerts antinociceptive and anti-inflammatory effects, reduces muscle glutamate concentration, decreases mechanical sensitivity of nociceptors in muscles and periosteum (dependent on glutamate concentration), and inhibits neurogenic vasodilation [25, 26].

However, a pure peripheral mechanism of action of the toxin has been recently questioned as some evidence suggests that BoNT-A antinociceptive effect is centrally mediated (being probably associated with an enhanced opioidergic and GABA-ergic transmission) and axonal transport-dependent [24, 27–29]. In an animal model of formalin-induced pain, the analgesic effects of peripheral BoNT-A administration were completely abolished by colchicine injection into the trigeminal ganglion, confirming the hypothesis that toxin axonal transport occurs via trigeminal sensory neurons [29]. Furthermore, immunohistochemical studies revealed the occurrence of truncated SNAP-25 in trigeminal nucleus caudalis, in keeping with the assumption that axonally transported BoNT-A can affect central sensory nociceptive nuclei (presynaptically, by SNAP-25 cleavage in central terminals of primary afferent neurons, or following transcytosis) [29].

BoNT-A in CM treatment: which patient may benefit more?

The efficacy and safety of BoNT-A in CM prophylaxis has been demonstrated in 2 large (1384 patients) multicenter randomized clinical trials—Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and 2 [30–32]. Each study included a 24-week randomized, double-blind phase followed by a 32-week open-label phase. CM patients were randomized (1:1) to BoNT-A (155/195U) or placebo injections every 12 weeks for five cycles. The studies revealed significant improvements in headache and migraine day frequencies, moderate/severe headache days and cumulative headache hours on headache days as well as in patients' functioning, vitality, psychological distress, and overall health-related quality of life [30–32]. Despite some debatable aspects, such as a relatively small treatment effect compared to placebo and the possibility of an inadequate blinding [9], the PREEMPT study represents one of the largest pharmacological trial ever carried out in migraine.

Interestingly, several evidence suggests that some migraineurs respond better to BoNT-A than others. Pericranial allodynia, unilaterality of migraine pain and pericranial muscle tenderness may predict BoNT-A responsiveness in chronic daily headache [33]. Two studies suggested that migraineurs with unilateral pain in the area supplied by the ophthalmic branch of the trigeminal nerve respond better than others to BoNT-A: Jakubowski et al. [34] reported a 100 % responder rate in episodic and chronic migraine sufferers with ocular head pain using BoNT-A at the dose of 100 U and, similarly, Grogan [35] described that episodic and chronic migraine patients with ocular-directed headaches "are most likely to be sustained >75 %-responders" to rimabotulinumtoxin B. More recently, Cernuda-Morollón et al. [36] stated that elevated interictal blood levels of CGRP, marker for peripheral trigeminal activation, and to a lesser degree of vasoactive intestinal peptide (VIP), marker for cranial parasympathetic activation, identify responders to BoNT-A. The aforementioned data suggest that the pharmacological response to BoNT-A might be better when the migraine headache is "trigeminal" in pain location and trigeminal-autonomic reflex activation [37], as applies for triptans in acute migraine treatment [38]. As a consequence, future pharmacological trials with BoNT-A (as well as with other trigeminal-targeted treatments) should identify migraineurs who overactivate peripheral trigeminal endings during the attack by means of easily obtainable patient-reported clinical findings, such as pain location and the presence of cranial autonomic symptoms [37–39].

Conclusions

Discovered by serendipity, BoNT-A is an effective, well-tolerated, and safe preventive treatment for CM, a disease characterized by peripheral and central sensitization. BoNT-A acts on C but not on Aδ meningeal nociceptors inhibiting mechanical nociception to suprathreshold stimuli in peripheral trigeminal neurons. Its mechanism of action in CM includes not only the impairment of neuropeptide and neurotransmitter release from sensitized trigeminal endings but also the disruption of normal cycling of TRPV1, TRPA1, and ATP-gated P2X3 receptors from inside the axon to the axon membrane surface. Besides these peripheral mechanisms of action, behavioral and immunohistochemical data indicate that BoNT-A exerts also a central antinociceptive action probably associated with an enhanced opioidergic and GABA-ergic transmission.

Finally, emerging evidence suggests that identifying migraineurs who overactivate peripheral trigeminal endings during the attack by means of easily obtainable clinical features (unilateral pain location, the presence of cranial autonomic symptoms) may be of help for a more tailored BoNT-A therapy in patients with CM.

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

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Onabotulinum toxin A (Botox) for chronic migraine treatment: an Italian experience

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Abstract Chronic migraine is a common and debilitating headache syndrome. Botulinum neurotoxin, a potent toxin produced by the anaerobic bacterium clostridium botulinum, used largely for treatment of disorders associated with increased muscle tone and hyperhidrosis, is used for patients suffering from chronic migraine. In this study, a group of patients suffering from chronic migraine with medication overuse was treated with onabotulinum toxin A (Botox) to verify its efficacy for chronic migraine. The results confirmed the efficacy of onabotulinum toxin A (Botox) when used at the dosage of 155 UI according to the PREEMPT protocol. Although these results are preliminary, they led to intense efforts to evaluate the analgesic properties of onabotulinum toxin A (Botox) and to assess its use in clinical practice, in particular in migraine field.

Keywords Onabotulinum toxin A (Botox) · Chronic migraine (CM) with medication overuse (MO) · PREEMPT study

Introduction

Chronic migraine (CM) is a disabling syndrome which involves 2/3 % of the general population [1] with >15 or more days per month for >3 months, and often associated with medication overuse (MO). This category of patients is problematic and difficult to treat and only partial benefit is obtained from oral preventive medications.

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Nowadays, onabotulinum toxin A (Botox) is considered an effective alternative to manage this condition as already evidenced by the PREEMPT study and other clinical experiences [2–4].

The rationale of the potent analgesic effect of the toxin is based on the results from animal and human studies indicating that Botox inhibits the release of nociceptive mediators as CGRP, glutamate and substance P. Blocking the release of these neurotransmitters 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 [5–7].

The PREEMPT study confirmed the efficacy of Botox [2, 3] to reduce significantly days of headache per month and medication intake per month after 1 year of treatment. Moreover, HIT-6 values decreased too [2–4].

Concerning tolerability and safety of the treatment, the study confirmed low incidence of adverse events during the course of treatment and a good tolerability [2–4].

A shift from overuse to non overuse was observed after treatment in a significant proportion of patients [8].

The use of Botox for chronic migraine in Italy was indicated 2 years ago (January 2013) with the possibility of reimbursement for adults patients with a specific diagnosis of CM according to IHS criteria [9], and patients intolerant or unresponsive to pharmacological treatments.

Encouraged by preceding clinical experiences, Botox has been used to treat patients referring to our headache center, suffering from CM with MO, according to the PREEMPT study protocol schedule.

Aim of this study was to evaluate a group of patients treated with 155 UI of Botox to verify its efficacy for chronic migraine treatment.

Methods

A group of 75 adults patients suffering from CM with MO (diagnosis made according to the IHS criteria) [9] was studied.

Patients were treated by a withdrawal protocol in a day hospital regimen for 5 days to stop the overuse of symptomatic medications. After that, patients were treated by Botox injections, in multiple sites, according to the protocol of the PREEMPT study, at the dosage of 155 UI for 31 sites. Every session of local injection (155 UI per 31 sites; 5 UI per each site) was repeated every 3 months for a period of 1 year. Totally five injections of Botox were performed.

Clinical indexes as number of medication intake per month and days of headache per month, were recorded using an headache daily diary.

Questionnaires for disability and quality of life (MIDAS; HIT-6) were also performed at every session of treatment.

Forty-six patients achieved the 3rd session of treatment and 20 patients completed the period of treatment of 1 year with the five injections schedule.

Results

Data concerning the group of 46 patients who completed the 3rd session of treatment evidenced that days of headache/month decreased significantly during the period of treatment from the first to the third session of therapy, (pre 21.7 ± 6.8 post 15.6 ± 8.7 $p < 0.005$). Also medication intake decreased significantly (pre 20.3 ± 67.5 post 14.3 ± 8.4 $p < 0.0005$). The group of 20 patients who completed the treatment showed a significant decrease of number of migraine days per month and a decrease, although not significant, of medication intake per month (22.4 ± 6.5 vs 13.8 ± 7.4; 20.7 ± 7.2 vs 16.4 ± 18.6, respectively). MIDAS total score decreased significantly after treatment (63.1 ± 50.1 vs 31.4 ± 34.1); HIT-6 values decreased, but not significantly (65.4 ± 7.5 vs 59.9 ± 9.3).

Discussion

CM is a serious clinical condition for patients, very disabled and at risk of medication overuse; the partial response to treatment is so common for this category of patients, that the possibility to use new therapeutic options is crucial.

In the past decade, data from different studies were not conclusive about efficacy of Botox for CM, 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.

The selection of patients is the key to the successful use of Botox in chronic migraine management [10].

Our results are preliminary, but they led to intense efforts to evaluate analgesic properties of Botox and to assess its clinical applicability and efficacy in a limited, but homogeneous group of patients.

The pharmacological profile of Botox 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.

Although we did not assess it specifically, patients did not report any adverse event and the treatment was well tolerated. Patients did not miss any appointment and they did not ask for any supplemental visit between the sessions.

The problem concerning the cost of this innovative treatment was not evaluated specifically, even if a lower medication intake and a lower number of neurological visits in emergency departments were observed: these can be indexes of a decrease in medical costs as reported by Rothrock et al. [11] in a recent study.

In conclusion, data from recent studies show encouraging results: Botox seems to be effective for patients with CM, 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 Botox can be also indicated in the early stage of the disease and this may result in better treatment outcome [2, 3].

Future studies will be aimed to identify possible predictors of response for this innovative treatment and also to determine the best strategy to manage patients after 1 year of treatment: if more than one treatment can be performed and which could be the best interval of time for patients who need supplemental treatments; in fact it seems that supplemental treatments can enforce the efficacy of this approach by increasing the benefit obtained at the first cycle of treatment [12, 13].

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

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NEUROIMAGING OF HEADACHES

Vestibular migraine pathophysiology: insights from structural and functional neuroimaging

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Abstract Vestibular migraine (VM) has been increasingly recognized as a frequent cause of episodic vertigo, affecting up to 1 % of the general population, with female preponderance. Recently, both the Bárány Society and the Migraine Classification Subcommittee of the International Headache Society have proposed original diagnostic criteria for VM, which have been included in the recent edition of the ICHD-3 beta version. VM diagnosis implies that vestibular symptoms are present during a migraine attack, with or without headache, in the absence of objectively demonstrated interictal vestibulopathy. Nevertheless, despite a growing body of literature, there is still an ongoing debate regarding whether VM origin is principally central or peripheral. However, during the past few years, the extensive application of advanced MRI techniques has contributed to significantly improve the understanding VM pathophysiology. Functional and structural abnormalities have been detected in brain areas involved in multisensory vestibular control and central vestibular processing in patients with VM. In this brief review, we will focus on these recent neuroimaging findings.

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Introduction

Vestibular migraine (VM) is a disabling neurological disorder characterized by vestibular symptoms, such as vertigo, dizziness, or imbalance in at least 50 % of migraine episodes in patients with migraine without aura (MwoA) or with aura (MwA) [1]. This condition has been increasingly recognized as a frequent cause of episodic vertigo, affecting up to 1 % of the general population, with female preponderance. Nevertheless, up to the second edition of the International Classification of Headache Disorders (ICHD-2) [2], vestibular symptoms were not considered in the "migraine chapter" except in the context of basilar-type migraine in adults and benign paroxysmal vertigo of childhood. Recently, both the Bárány Society and the Migraine Classification Subcommittee of the International Headache Society have proposed original diagnostic criteria for VM [3] which have been included in the recent edition of the ICHD-3 (beta version) [1]. According to VM diagnostic criteria, vestibular symptoms should be present during migraine attacks (with or without headache) in the absence of objectively demonstrated vestibulopathy.

Despite well-defined diagnostic criteria, the pathophysiology of VM remains largely unknown, although it is thought that genetic, epigenetic, and environmental factors probably contribute to its development [4]. Nevertheless, in the last few years, imaging studies have elucidated the central mechanisms related to both pain and vestibular processing in patients with VM. The aim of this brief review is to examine these imaging findings and their contribution to the understanding of VM pathophysiology.

Discussion

The relationship between migraine and vertigo may be explained in different ways. It may be, for example, the result of the chance co-occurrence of two frequent pathologies such as migraine and central or peripheral vestibular disorders. However, a more than accidental association between migraine and vertigo has been epidemiologically observed [5]. In this context, VM has been convincingly advocated as a term that underlines the vestibular manifestation of migraine to avoid the confounding coexistence of vestibular symptoms not strictly associated with migraine pathophysiology [6]. Indeed, several studies have considered VM as a variant of migraine in which a large convergence and overlap between migraine and vestibular pathways have been suggested [3, 4].

According to this hypothesis, cortical spreading depression (CSD), the neurophysiological correlate of migraine aura, could play a critical role. Indeed, an evident (with aura) or silent (without aura) wave of cellular depolarization may produce vestibular symptoms when it reaches the multisensory vestibular cortex, through the activation of cerebral areas generally involved in migraine aura propagation [3, 7].

Furthermore, biochemical overlap between vestibular and migraine mechanisms is present as well. Some neurotransmitters, such as calcitonin gene-related peptide, serotonin, noradrenaline, and dopamine, that are crucial in migraine pathogenesis, are also involved in neuronal activity modulation of the central and peripheral vestibular processing, likely contributing to the vestibular migraine pathogenesis [3]. Moreover, although no specific genetic defects have been identified in VM, mutations in genes encoding voltage-gated calcium channel may be candidate mechanisms for VM. Indeed, voltage-gated calcium channel defects have been founded in families affected from hemiplegic migraine and episodic ataxia type 2, two paroxysmal disorders exhibiting as prominent features both migraine and vestibular-like symptoms [3].

Unfortunately, VM does not appear to be characterized by a consistent electrophysiological pattern with clear-cut discriminating characteristics. Video-oculography observations [8], as well as visual evoked myogenic potentials experiments [9] and vestibulo-cochlear evaluations [10] do not seem to be helpful for the differentiation of VM from other vestibular conditions and have not provided conclusive pathophysiological insights today.

In the last decades, in order to improve the knowledge of the underlying mechanisms of migraine, brain functional MRI (fMRI) approach has been employed. By means of fMRI studies, atypical brain responses to visual, olfactory, and painful cutaneous stimulation, and atypical functional connectivity of sensory processing regions have been consistently demonstrated. Moreover, correlations between brain functional abnormalities and clinical parameters of migraine severity have suggested that migraine could produce a cumulative effect on brain function or, alternatively, preexistent functional abnormalities could be related with migraine generation and severity. In the wake of these studies, during the past few years, patients with VM (recognized as a "new" migraine subtype) have been investigated by means of metabolism, structural, and functional techniques to better elucidate underlying VM pathophysiological mechanisms.

Specifically, positron emission tomography (PET) and blood oxygenation level dependent (BOLD)-fMRI studies have addressed important VM issues, improving our understanding of the circuitry that may be involved in the generation, maintenance, and recurrence of both pain and vestibular symptoms in VM.

Recently, an ^{18}F-fluorodeoxy glucose-PET study [11] has been conducted in two patients who underwent a detailed neurotological evaluation, during and between VM attacks. This work, although with the very small sample limitation, first analyzed regional brain metabolism of patients with VM, according to Lempert's criteria [3], in comparison with that of age-matched healthy controls (HC) in each patient.

During VM attacks, both patients showed an increased metabolism in frontal and temporal cortices, bilateral cerebellum, dorsal pons, and midbrain and a reduced metabolism of the bilateral posterior parietal and occipitotemporal areas. However, the most interesting finding is the PET images comparison between interictal and ictal metabolism showing an involvement of vestibulo-thalamo-cortical pathway (such as bilateral cerebellum, frontal and temporal cortices, posterior insula, and thalami). According to previous observations, [12], cerebellar hyper-metabolism during and between VM attacks may represent an adaptive cerebellar mechanisms to suppress the vestibular system hyperactivity in these patients. Contrariwise, thalamic hypermetabolism may be related to the activation of vestibular nuclei and vestibule-cortical projections via the posterolateral thalamus. Furthermore, the comparison between interictal and ictal metabolism revealed also an occipital cortex hypo-metabolism in both patients. These findings, showing a divergent metabolism of vestibular and visual systems, could represent the reciprocal inhibition between the two systems in patients with VM. Similarly, previous studies have demonstrated an occipitotemporal-reduced metabolism both in patients with visual aura [13] and in patients with vestibular neuritis [14], which further underlines the reciprocal inhibition between brain pathways involved in visual and vestibular processing.

These findings are partially consistent with a recent BOLD-fMRI study [15], conducted by our group, in patients with VM (according to ICHD-III beta version) [1] during interictal period. In this experiment, the functional response of vestibular neural pathways during caloric vestibular stimulation in patients with VM and HC has been explored. To evaluate the specificity of any observed differences between patients and HC, a group of age and sex-matched patients with MwoA has been further examined. In these subjects, electronystagmography evaluation was performed to exclude vestibular disorders and to verify that caloric stimulus induced vestibular nystagmus. In all subjects, caloric vestibular stimulation elicited a statistically significant activation in bilateral insular cortex, thalamus, cerebellum, and brainstem. Interestingly, a discrete periaqueductal gray activation has been observed, suggesting a peculiar relationship between vestibular stimulation and activation of a brain area which plays a key role in pain processing [16]. This finding could suggest that reciprocal connections between brainstem vestibular nuclei and structures involved in modulation of trigeminal nociceptive inputs may have some role in VM pathophysiology [17]. Furthermore, the analysis of difference between groups showed a significant divergent response in mediodorsal thalamus in patients with VM relative to both patients with MwoA and HC. It is noteworthy that the thalamus represents a key structure in transmitting sensory input from the brainstem to the cortex, exerting a pivotal function in pain processing and cortical excitability control. This observation could shed a light on the VM pathophysiological mechanism, suggesting a dys-modulation in the multimodal sensory integration and processing of both vestibular and nociceptive information, resulting in a vestibulo-thalamo-cortical dysfunction. Furthermore, thalamic functional abnormalities exhibited a positive correlation with the frequency of VM attacks. Nevertheless, it is not possible to establish whether thalamic findings are a primary phenomenon due to the hereditary liability resulting in VM attacks or a secondary phenomenon as a result of repetitive VM attacks.

In the past years, in addition to functional changes in patients with migraine, structural abnormalities have been demonstrated in brain areas involved in processing of pain perception and its cognitive-affective contents [18–21]. However, despite advances in neuroimaging techniques, it is not yet clear if migraine is associated with gray matter (GM) changes [22]. However, structural brain changes have been recently explored also in patients with VM [23], and to our knowledge, there is only one study in which voxel-based morphometry (VBM) approach has been used in these patients. After a video-nystagmographic assessment to avoid any possible interference related to unilateral or bilateral vestibulopathies, seventeen patients with VM, according to the ICHD-III beta version criteria, were compared with 17 HC. Imaging findings, using first a whole-brain and then a region-of-interest (ROI)-based approach, revealed a GM volume decrease bilaterally in the inferior temporal gyrus, the cingulate cortex, and the posterior insula. GM reduction was also detected in the superior, middle temporal gyri, supramarginal and inferior occipital gyri, superior parietal lobules, and dorsolateral prefrontal cortex. Although independent replications of these findings are warranted, they are very interesting for several reasons. First of all, the authors found GM reduction in regions that are generally associated with higher level multisensory vestibular function, underlying the overlap of migraine-related central circuits with central vestibular pathway. Secondly, the GM reduction into the pain and vestibular processing pathways exhibited a negative correlation with disease duration in some specific brain areas and a negative correlation with headache intensity in others. Therefore, VBM findings suggest that repeated VM attacks over time could determine morphological alterations in cerebral structures involved in pain and vestibular processing, likely reflecting mechanisms of cortical plasticity adaptation.

In conclusion, although supported by few imaging studies, we can draw some suggestions about VM pathophysiology. Taken together, functional and structural alterations identified in patients experiencing VM resemble those previously described for migraine. Furthermore, brain areas involved in multisensory vestibular control and central vestibular compensation showed abnormalities in both structure and function in these patients. In other terms, VM may probably represent the pathophysiological paradigm of migraine and vestibular pathways connection.

However, future investigations are needed to better elucidate the complexity of VM pathophysiology. Specifically, it will be useful to further investigate neuronal interactions between nociceptive and vestibular processing also in different phases of migraine cycle, and the role of internal reciprocal trigger mechanisms between migraine disorder and vestibular phenomena [24].

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

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NEUROIMAGING OF HEADACHES

Resting-state fMRI functional connectivity: a new perspective to evaluate pain modulation in migraine?

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Abstract Resting-state (RS) functional magnetic resonance imaging (fMRI) is a relatively novel tool which explores connectivity between functionally linked, but anatomically separated, brain regions. The use of this technique has allowed the identification, at rest, of the main brain functional networks without requiring subjects to perform specific active tasks. Methodologically, several approaches can be applied for the analysis of RS fMRI, including seed-based, independent component analysis-based and/or cluster-based methods. The most consistently described RS network is the so-called "default mode network". Using RS fMRI, several studies have identified functional connectivity abnormalities in migraine patients, mainly located at the level of the pain-processing network. RS functional connectivity is generally increased in pain-processing network, whereas is decreased in pain modulatory circuits. Significant abnormalities of RS functional connectivity occur also in affective networks, the default mode network and the executive control network. These results provide a strong characterization of migraine as a brain dysfunction affecting intrinsic connectivity of brain networks, possibly reflecting the impact of long lasting pain on brain function.

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Keywords Migraine · Resting-state functional MRI · Pain · Functional connectivity

Introduction

If we consider network as a representation of a complex system made of finite number of nodes (the basic network element) and links (the connection between nodes), we can state that the brain should be defined as the most complex, unique and efficient network system. Neurons are the basic elements of this structural network: this anatomical substrate (approximately 86 billion neurons in the human brain) is able to create a coherent physiological activity, information processing and mental representations. In particular, brain network is composed of different brain regions with specific function, but that are continuously sharing information. In this way, they form a complex integrative network in which a stimulus is analyzed and transported in a continuous stream between structurally and functionally linked brain areas. A neural network is made of structurally and functionally interconnected areas at many levels (microscopic synapses, mesoscale circuitry and macroscale anatomical sites and fiber tracts). Connections can be either anatomical (a structural, physical connections between nodes appearing as fiber tracts) or functional (synchronous neuronal oscillations, considering that physical connection is not mandatory for a functional connection between nodes). The basic brain network connectivity, according to the graph theory of network analysis, has a short mean path length (related to high global efficiency and information transfer), high clustering (associated to robustness to random error), a distribution in agreement with the presence of hubs (nodes with high degree or high centrality) and a modular community

structure (each module contains several densely interconnected nodes, with few connections between nodes in different modules) [1, 2]. Functional connectivity (FC) can be defined as the temporal dependency between spatially remote neurophysiological events [3, 4], and the study of this connectivity is made possible by functional magnetic resonance imaging (fMRI). This technique allows describing the relationship between the neuronal activation patterns of anatomically separated brain areas, reflecting the quality of functional intercommunications between regions.

Functional magnetic resonance imaging: the beginning of a new era in brain research

fMRI studies are based on the modification of blood oxygenation level-dependent (BOLD) signal derived from the neural response to an externally controlled task or stimulus. For this reason, BOLD signal is used as a non-invasive and indirect measure of changes in neuronal activity. fMRI is a technique able to detect large-scale neural networks at different spatial and temporal resolutions. During active fMRI tasks, the signal derived in the "on" period (the stimulus) is contrasted with that of a control condition, thus measuring a relative signal change caused by the ongoing process. For example, modifications of visual cortex fMRI BOLD signal can be detected during visual stimulations. In the past few years, more attention has been focused on the analysis of the baseline state of the brain by measuring FC between brain areas as the level of co-activation of spontaneous fMRI time series recorded during rest ("resting-state experiments"). In the resting-state (RS) studies, subjects are placed into the scanner and instructed to relax (with eyes closed or with a fixation point) and not to think of something without falling asleep, while their level of spontaneous brain activity is measured. RS fMRI has certain properties that make it particularly advantageous for the study of neurological diseases: the limited behavioral demands of the acquisition procedures (the task is to rest quietly) and the simplicity of the data acquisition. First results of its application demonstrate that during rest, the right and left hemispheric areas of the motor network are not silent, showing a direct correlation with fMRI BOLD time series, confirming ongoing information processing and coherent FC between these areas [5]. These results opened a new era in brain research. Because it was considered as a "noise signal" in task-response studies, this spontaneous aspect of the BOLD signal was until that moment minimized. In fact, noise is the modulation in a measured signal that is not related to the activity of interest. For this reason, minimization of noise through averaging is a simple method to amplify the effect in study. Nevertheless, there are some motivations to emphasize the interest on this noise signal. First, spontaneous BOLD activity is not random noise, but it is well organized. In particular, the spontaneous low-frequency fluctuations (0.01–0.1 Hz) observed in the BOLD signal have been interpreted to display spatial structure linked to task-related activation [6]. Cardiac and respiratory oscillations have been detected with a complete different frequency pattern (>0.3 Hz). Is still debated if these fluctuations in BOLD signal are due to changes in the brain physiology independent of neuronal function or reflect neuronal baseline activity of the brain when external input or task-directed neuronal activity is not present [7, 8]. The assumption that coherencies in resting fluctuations are the representation of functional RS networks linked to underlying neuronal modulation is consistent with the replication of these coherencies in specific functional brain gray matter areas (i.e., motor network, brain regions involved in language, auditory and visual processing) [9, 10]. The large body of results in this field underlies that during rest the brain network is not idle, but rather shows a large amount of spontaneous activity that is strictly correlated between multiple specific brain areas [11]. Therefore, RS BOLD fluctuations of cortical and subcortical regions reflect spontaneous neuronal activity. The related observed temporal correlation between fMRI time series and specific anatomically separated brain areas is the reflex of a level of ongoing FC between brain regions during rest. One important and validated way to study the functional connections of a particular brain area is to correlate the RS series of such an area of interest (a priori choice, investigator-driven region of interest-based approach) against the time series of other regions [12]. The final result is a FC map defining the functional connections of predefined brain region (the so-called seed), which provides robust information about the functional links between the seed and other brain regions. Alternatively, to examine whole-brain connectivity patterns, model-free methods have been developed (without the need of defining an a priori seed region) [13], including principal components analysis (PCA), independent component analysis (ICA) and normalized cut clustering. ICA-based methods (data-driven methods) show a very good level of consistency and can be applied to whole-brain voxel-wise data. It is important to state that ICA, clustering and seed methods show a high level of overlap. The ICA approach enables identification of several networks consisting of spatially independent and temporally correlated areas.

Group RS analysis (although using different methods and different acquisition protocols) has consistently identified specific functionally linked sub-networks in resting conditions, the so-called RS networks. They consist of functionally linked brain regions, although anatomically

separated, showing a high level of ongoing FC at rest and include the primary sensorimotor network, the primary visual and extra-striate visual network, right and left lateralized networks consisting of superior parietal and superior frontal regions, the "salience network" which is an anterior cingulated/frontoinsular system with links to limbic and subcortical autonomic control areas, and the so-called "default mode network" consisting of posterior cingulated cortex-precuneus/medial temporal/lateral temporoparietal/medial frontal network that is often deactivated during cognitively demanding tasks [14–16]. The default mode network is thought to mediate processes that are important for the RS, and its response to cognitive tasks is indeed unique. Most of these RS networks tend to represent specific functional networks, overlapping brain areas that are known to share a common function (primary motor areas, primary visual regions and parietal–frontal networks involved in attention processing) [17]. RS networks may also show an internal specific topology that is strictly organized to their sub-functions [18]. It is conceivable that FC may give help to stabilize functional systems in an active state, improving performance and their reaction time. In the absence of an active and specific task, these networks show evidence of a tight spatial correspondence with the functioning circuits during sensorimotor, emotional and cognitive tasks [19]. The connectivity strength within these networks at rest has been demonstrated to correlate with emotional and cognitive situations, supporting the possibility to assess particular conditions in a disease state [20]. Recent investigations have demonstrated that almost all functionally linked regions of the RS networks are interconnected in a structural way (white matter tracts) [21]. This is in agreement with the concept of a general structural group of RS networks, linking structural and functional connectivity on a whole-brain scale.

Resting-state functional connectivity in neurological disorders

Analyses of RS time series have described a very efficient organization of functional communication in brain networks, showing that brain is not made of random networks, but is specialized in a complex system with a high level of local and global efficiency. One application of network theory is to provide a possible measure to quantify differences between controls and patient groups in parameters of brain networks derived from fMRI (comparison of correlation patterns between groups). Disturbances in the correlation structure of spontaneous activity have been reported in a large number of neurological and psychiatric conditions. Recent studies have suggested a direct link between RS FC patterns and human cognition, and several works have detected possible functional disconnectivity effects in many neurological and psychiatric disorders, including Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis [22–24] and schizophrenia [25]. Most of these studies have been focused on the default mode network, although more recent works have examined the overall organization of functional brain networks. The results of these studies underline the decreased integrity of interconnected brain networks, rather than single brain areas: there is convergent evidence that abnormal topological organization of structural and functional brain networks could be hypothesized as the basic abnormality in degenerative neuropsychiatric pathologies [26].

Resting-state functional MRI connectivity in migraine

As non-invasive way to measure intrinsic fluctuations in BOLD signals, RS fMRI has attracted considerable attention in migraine patients, to examine potential alterations of baseline intrinsic brain activity caused by long-term migraine attacks. In previous studies focused on patients suffering from chronic pain disturbances (e.g., chronic pain and fibromyalgia), default mode network (DMN) FC resulted disrupted, confirming that pain has a significant impact on brain activity and function, possibly affecting first dynamics of pain perception [27, 28]. In migraine patients, several studies were focused on potential alterations of baseline intrinsic brain activity caused by repetitive attacks.

One RS FC study in migraine patients during the pain-free state demonstrated alterations of baseline functional interaction within the periaqueductal gray matter (PAG) network, a key region involved in nociceptive processing [29]. This dysfunction could be attributable to the impairment of the descending pain modulatory circuits. In another study (analyzing the temporal homogeneity of regional fMRI BOLD signals) a focal functional alteration, significantly related to longer disease duration, was detected in pain-processing areas such as in rostral anterior cingulated cortex, prefrontal cortex and orbitofrontal cortex [30].

Another study of migraine without aura patients investigated whether brain regions with abnormal regional RS properties show dysfunctional connectivity. The results showed that these patients had altered RS spontaneous neuronal activity in pain-processing areas, including the left rostral anterior cingulated cortex, bilateral prefrontal cortex and right thalamus [32].

An investigation of migraine without aura patients found an aberrant RS FC within the salience and executive networks, as well as increased connectivity between the default mode network and the executive network and the insula (a critical region involved in pain processing). The

correlation found between increased RS FC within the insula and the duration of migraine suggested that these abnormalities may be the consequence of a persistent central neural system dysfunction [31]. In a more recent study of migraine without aura patients, the prefrontal and temporal areas of the DMN, showed reduced RS FC [33]. Interestingly, these functional abnormalities were unrelated to detectable structural abnormalities or clinical and neuropsychological features of migraineurs. Since these regions are implicated in sensory-discriminative, integrative and cognitive pain functions in the well-known neurolimbic pain network, these findings open questions about a possible link with maladaptive brain response to repeated stress, specific functional damage and migraine. RS FC analysis has been combined with morphometric analysis to characterize central nervous system abnormalities in medication-overuse headache patients. This particular group of patients showed an altered RS FC in the DMN as well as an increased connectivity between the precuneus and hippocampal temporal areas, which did not have corresponding structural abnormalities. The authors stated that alterations in pain-processing networks might be due to long-lasting pain processes, whereas alterations in DMN could be related to addiction processes [34]. The impaired FC might precede alteration in brain areas morphology. Another recent paper investigated brain RS FC in the interictal phase of migraine with aura and found no difference between patients and controls [35]. To define how early network abnormalities occur in migraine patients, a very recent study explored RS FC and functional interaction among networks in pediatric patients with migraine, as well as their correlation with patients' clinical characteristics [36]. RS fMRI is particularly advantageous for the study of pediatric patients due to the limited behavioral demands of the acquisition procedure (young participants may in fact have difficulty performing a task paradigm in task-based fMRI studies). Compared to pediatric controls, pediatric migraine patients had an increased RS FC of the precuneus of the DMN and the dorsolateral prefrontal cortex of the right working memory network. They also experienced a decreased RS FC of the anterior cingulum of the salience network and the temporo-parietal junction of the left working memory network. Functional network connectivity analysis detected a decreased communication between the visual and the fronto-parietal network in pediatric migraine patients compared to controls. No significant correlation was found between intra- and inter-network RS FC abnormalities and patients' clinical characteristics. These data showed that RS FC abnormalities occur in pain-processing networks of pediatric migraine patients. Brain regions involved in cognition were selectively involved, suggesting that abnormalities of cognitive modulation of pain in migraine patients occur from an early stage of the disease. Moreover, the increased connectivity between the visual networks and the fronto-parietal attention network supports an enhanced attention to visual stimuli in these patients.

Conclusions

All these body of scientific data has to be interpreted with caution because of small sample sizes, patients' clinical heterogeneity and sometimes lack of consistent methodological approach. Admittedly, over-interpretation of these results is a risk when subject's motion is present. Recent studies demonstrated that even small amounts of in-scanner subject motion systematically biases measured FC, with motion strongly related to age. Advances in MRI acquisition and post-processing techniques have been shown to mitigate motion artifact adequately [37, 38].

The unsolved question is whether functional changes are the cause or the consequence of a long-term migraine condition. The study of functional network dysfunction in migraine is in its infancy. The effort to harmonize imaging acquisition parameters and clinical phenotyping/genotyping strategies will provide an opportunity for integrating genomic data to understand how genetic spectrum may be associated with abnormalities in functional brain networks that lead to symptoms of migraine. Spontaneous activity in brain function, as observed through fluctuations in the fMRI BOLD signal, could provide new insights to disentangle the knots about the interpretation of pain in migraine. Longitudinal studies are necessary to evaluate the specific timing of selective network involvement. Future topics to improve the knowledge of network organization will depend on the understanding of how brain structure influences brain function and vice versa. The integration of structural and functional connectivity into a common framework may lead to a more complete definition of the overall altered brain organization in migraine patients.

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

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NEUROIMAGING OF HEADACHES

Resting state fMRI in cluster headache: which role?

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Abstract The pathophysiology of cluster headache (CH) is not well-known. For several years, the most widely accepted theory was that CH was triggered by hypothalamus with secondary activation of the trigeminal-autonomic reflex. However, it was recently suggested that the posterior hypothalamus might be an actor of the pain modulating network more involved in terminating rather than triggering attacks. To investigate this hypothesis, resting state fMRI could provide valuable information on functional connectivity between brainstem and hypothalamus, as well as other brain structures that could be involved in CH pathophysiology. In this framework, here we review recent studies investigating functional connectivity by means of resting state fMRI. Despite the important findings of these studies, we suggest that important steps in the comprehension of CH pathophysiology will be done when the scientific community will use the new methodological approaches recently suggested to study functional connectivity in the brainstem.

Keywords Cluster headache · Resting state fMRI · Brainstem

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Introduction

In cluster headache (CH), activation of the trigeminal nerve is thought to mediate pain, while parasympathetic activation running with facial nerve produces the local autonomic features [1, 2]. The pain is strictly unilateral, mainly around the orbital and temporal regions and is typically characterized by a striking circannual and circadian pattern. CH onset usually occurs between the third and fifth decade with a clear male preponderance [3]. The pathophysiology mechanisms of CH are not well-known.

For several years, the most widely accepted theory was that primary CH was triggered by hypothalamus with secondary activation of the trigeminal-autonomic reflex [4]. Indeed, the converging evidence of the neuroendocrinological studies, the clinical observations of the clockwork regularity of attacks and the seminal results of a positron emission tomography (PET) study [5], led to identify the ipsilateral posterior hypothalamic area as attack generator.

On the basis of this theory, deep brain stimulations (DBS) targeting the region of posterior inferior hypothalamic area ipsilateral to the attack, were introduced as treatment with a long-lasting improvement occurred up to about 70 % [6, 7] and with complete control of attacks recorded in about 30–50 % [8, 9].

However, the latency of chronic stimulation and inefficacy of acute stimulation suggest that, in the complex pathophysiology of CH, the posterior hypothalamus might be an actor of the pain modulating network more involved in terminating rather than triggering attacks, as a relay in the dynamic connections between the cortical and subcortical areas [2].

In this new framework, several neuroimaging studies conducted with voxel-based morphometry (VBM) [10],

diffusion tensor imaging (DTI) [11] and PET [5, 12–14], have demonstrated, during and outside CH attacks, structural and functional changes in many cerebral areas belonging to the "pain matrix" [10]. Indeed these studies, consistently identified abnormalities in anterior and posterior cingulate cortices, in insula cortex, in frontal cortex, in primary sensorimotor areas and in thalamic nuclei.

Resting state fMRI studies

Functional abnormalities of the pain matrix have also been confirmed by very recent functional magnetic resonance imaging studies conducted in resting state condition (RS-fMRI), a cognitively unbiased approach to explore functional brain connectivity. RS-fMRI focuses on spontaneous low-frequency fluctuations (<0.1 Hz) in the blood oxygenation level-dependent (BOLD) signal and allows characterization of the spatio-temporal distribution of spontaneous coherent fluctuations of BOLD signals between temporally correlated brain regions. These functionally connected regions are defined resting state (RS) networks and have been reliably and reproducibly detected using fMRI [15, 16] and PET [17].

Among them, the most consistently reported RS network is the default-mode network (DMN), which is highly relevant for cognitive processes [18] and its alterations have been associated with patients' clinical status and cognitive impairment [19, 20] Other relevant networks include the executive control, the primary visual, the lateralized fronto-parietal, the temporo-parietal, the auditory, and the sensorimotor components [21].

On the basis of studies suggesting widespread alterations of the central nervous system [22] using RS-fMRI, the authors investigated whole-brain functional connectivity in 13 episodic CH patients outside the attack. By means of independent component analyses (ICA), they were able to show alterations of functional connectivity between resting state fluctuations in the sensorimotor and primary visual networks. Moreover, by means of seed-correlation analyses, they showed dysfunctions in the pain matrix: CH patients presented an increased functional connectivity between resting state fluctuations of hypothalamus and the anterior cingulate cortex, bilateral secondary somatosensory cortex, V1, right middle occipital gyrus, right thalamus and right insula; moreover the authors showed that patients presented an increased functional connectivity between the thalamus and primary sensorimotor cortex, supplementary motor area and anterior cingulate cortex. The results of their study indicated widespread alterations of brain functional connectivity involving, not only, as expected, the antinociceptive network, but also the sensorimotor and primary visual networks, suggesting a distribute abnormal information processing. Interestingly, they found a correlation between these abnormalities and the disease duration, suggesting the possibility that these alterations are a consequence of the disease, with a probable rewiring of cerebral areas [22].

Due to the supposed pivotal role of the hypothalamus in CH pathophysiology, two recent RS-fMRI [23, 24] studies focused completely on the functional connectivity between this structure and other brain regions.

Qiu et al. [23] investigated the role of the hypothalamus using RS-fMRI during and outside attacks in 12 episodic CH patients. Using seed-based correlation analyses, they showed increased functional connectivity between RS fluctuations of the hypothalamus, ipsilateral to the pain attack, with regions devoted to the somatosensory, cognitive and emotional processing of pain (pain matrix), such as the anterior cingulate cortex, the parietal cortex, insula and amygdala. The authors of this study observed that functional and structural changes of the pain matrix are often observed during pain condition, therefore opening the perspective that the alterations they have found are not specific of CH pathophysiology. Interestingly, confirming the findings of Rocca et al. [22], the authors found that, outside the attacks, resting state abnormalities were also present between RS fluctuations of the hypothalamus and occipital cortex.

Yang et al. [24] studied, by means of seed-based correlation approach, the functional connectivity of RS fluctuations of the hypothalamus in a sample of 18 CH patients during in-bout and out-bout periods. CH patients, in comparison to healthy participants, showed hypothalamic functional connectivity dysfunctions with frontal regions and cuneus. The comparison of 'out of bout' scans with the 'in-bout' scans showed decreased hypothalamic functional connectivity with frontal areas, precuneus and cerebellum. Interestingly, a significant correlation was observed between the hypothalamic functional connectivity and the cerebellum areas.

From the studies reported above, it is clear that functional connectivity is impaired in cortical regions beyond the pain matrix in CH patients in and outside attacks. Very interestingly, from these studies emerged as important replication an abnormal RS functional connectivity within primary visual network [22] and between the visual areas and the hypothalamus [23, 24].

A different methodological approach (general lineal model) was used to study spontaneous attacks by Morelli et al. [25]. Using for the first time fMRI to investigate CH, they confirmed the presence of significant hypothalamic activation during spontaneous attacks in four episodic CH patients. As already showed by May et al. [26] in their PET study during induced attacks, the authors found that the hypothalamic activation was ipsilateral to the side of the attack.

The same group, some years later [27], showed, during a spontaneous CH attack in one patient, increased activity in bilateral red nucleus, ventral pons, trigeminal root entry zone and hypothalamus ipsilateral to the pain side during the attack.

Although the authors argued that the activity in the red nucleus was linked to pain avoidance and represented a defense reaction, it is interesting that they pointed to a possible involvement of brainstem nuclei in CH attack.

Despite the very probable pivotal role of the brainstem in descending pain modulatory system [28] with the involvement of periaqueductal gray (PAG), nucleus cuneiformis, and rostral ventromedial medulla, to our knowledge, this important structure was never investigated in a deep way with functional connectivity neuroimaging techniques. In this direction, Teepker et al. [11] reported, by means of DTI, anatomical abnormalities in the white matter microstructures of the brainstem in seven episodic CH patients in headache-free state.

Methodological reasons and limits can explain why RS-fMRI was never applied to investigate the brainstem in CH.

Brainstem RS-FMRI

Despite the importance of brainstem nuclei regions in the regulation of vital function and arousal, the functional relationships between various brainstem nuclei, their projection targets, and afferent regulatory areas remain poorly characterized. The combination of two negative factors led to suboptimal performance of standard neuroimaging methods in brainstem nuclei regions in particular for RS-fMRI.

One of the limitations is linked to the elevated level of physiological noise. It is related to pulsatile motion of respiratory fluctuations and of large arteries in the direct vicinity as well as flow of cerebro-spinal fluid (CSF). Moreover, the frequencies of physiological noise, cardiac rate variation and respiratory signal, share the same low-frequency range (0.01–0.08 Hz) of the RS-fMRI BOLD fluctuations within functional networks [29, 30]. Therefore, the standard application of a low-pass filter (e.g., retaining frequencies <0.1 Hz) as a preprocessing step, is aimed at removal of higher frequencies and it is not enough to limit these effects.

The second factor is related to the reduction of the signal-to-noise ratio of echo-planar imaging of these areas compared to the cortical region. These sources of noise and artifacts may have a global effect across the brain and inflate estimated correlations between subcortical regions.

In these last years, there is a growing interest in the optimization of RS-fMRI acquisitions and analyses to investigate functional connectivity [31] also in these deep regions. Different strategies have been proposed to correct these effects during the acquisition and the post-processing of images. During the acquisition, it was proposed the use of cardiac signal (e.g., pulse oximeter) to trigger acquisition, so that structures of interest are always imaged at the same relative position in the cardiac cycle [32]. Unfortunately, due to heart rate variability, this implies a non-constant time repetition (TR) across dynamic volumes, making the data analyses more challenging.

In the post-processing, two different approaches were introduced: one in the temporal domain and one in the spatial domain. The former noise-suppression method is based on motion and physiological noise regression. These signals (cardiac and respiratory) might be simultaneously recorded during image acquisition [29] or derived from the original data using the average signal in ventricles and white matter [33, 34], areas containing a relatively high proportion of physiological noise. The latter approach tries to eliminate the physiological noise spatially, combining ICA with an inclusive anatomical mask of the brainstem regions [35].

While strategies have been proposed to remove these artefactual contributions, it is not clear how correction for these effects would affect the quality of RS-fMRI measurements. Future studies assessing reproducibility and specificity of connectivity maps also in these regions are necessary to define quality of RS-fMRI measures.

The assessment of the reliability and reproducibility of these approaches could improve the functional and effective connectivity measures of brainstem nuclei in humans using standard fMRI sequences.

Conclusion

Although all the RS-fMRI studies investigating CH focused on functional connectivity of cortical regions and hypothalamus, gave important contribution in the comprehension of some aspects of CH, we believe that it is time to move on the investigation of the functional connectivity of the brainstem.

Despite RS-fMRI in the investigation of the brainstem is still at its infancy, we believe that this technique, when extensively applied, would have a tremendous impact on the comprehension of the mechanisms of CH pathophysiology in and outside attacks.

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

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CLINICAL ASPECTS OF HEADACHES

Chronic headaches: a clinician's experience of ICHD-3 beta

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Abstract The International Classification of Headache Disorders, 3rd edition (beta version) has significantly improved the categorization of chronic headaches. From a clinical standpoint, however, it still has a few limitations, both general and specific. Among the former is the fact that international headache classifications are aimed less at defining the disease than at characterizing the features of attacks, meaning that their structure is ill suited to dealing with chronic headaches where the patient must be the focus of the discussion. Among the latter is the fact that the diagnostic criteria for chronic migraine do not distinguish between cases differing widely in severity and that the issue of whether medication overuse headache can be considered an autonomous entity is still unsolved. We propose that changes be made in the systematizations of chronic migraine and medication overuse headache to make them more consistent with clinical practice.

Keywords Chronic migraine · Chronic headache · Chronic daily headache · Medication overuse headache · International classification of headache disorders

Introduction

The third edition of the international classification of headache disorders (ICHD-3) [1] has introduced some changes over the two previous editions concerning the different forms of chronic headache, especially chronic migraine. In 2013 it was published as a beta version ahead of the final version, to synchronize it with the World Health Organization's next revision (11th edition) of the International Classification of Disease (ICD-11) due out in 1–2 years. Hopefully, in the meantime, researchers and clinicians could field-test ICHD-3 beta and propose any amendments that they deem fit.

Based on our clinical experience from the observation of a large series of patients with chronic headache followed over a long period of time at the University of Parma Headache Centre, we have been able to review ICHD-3 beta and see that there are a number of strictly clinical considerations that might merit further examination.

Some of these considerations are general, because they concern the two previous classifications—the International Headache Society (IHS) classification of 1988 [2] and the International Classification of Headache Disorders, 2nd edition (ICHD-2) of 2004 [3]—as much as ICHD-3. The guiding principles that their compilers adhered to are the same and also the classification structure has remained unchanged.

Other considerations are more specific of ICHD-3 beta, because they arise from a few novelties and changes that have been included in this edition over the previous ones.

General considerations

In the preface to ICHD-3 beta [1], the authors correctly say that "Clinicians and researchers should start using the criteria of ICHD-3 beta", but in the next section *How to use this classification* they admonish that "This extensive document is not intended to be learnt by heart. Even members of the Classification Committee are unable to remember all of it. It is a document that should be consulted time and time again",

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which may be an appropriate statement for a document that is 180 pages long. In the same section *How to use this classification*, they point not only to the different role the classification has in research as opposed to clinical practice, but also to the need of using it in two different ways. Thus, based on their indications, clinicians will use this classification when a patient's diagnosis is uncertain, while researchers will adhere strictly to its diagnostic criteria whenever they recruit patients for drug trials or for pathophysiology or biochemistry studies.

Well, are we really sure that the first IHS classification [2], ICHD-2 [3] and ICHD-3 beta [1] are tools whose design and structure are entirely suitable to use in clinical practice and research?

Like the previous editions, ICHD-3 beta is a classification of attacks, not of disease. The diagnostic criteria for individual headache types—especially primary headaches and the chronic headaches considered here in particular—provide a very clear and accurate description of the clinical features of attacks, but they tell us nothing about the patient. We do not even have the entire description of an attack, just a snapshot of a single moment in a single attack. This is not meant to be a critique of the classification, but rather the recognition of how it has been designed and what we should reasonably expect of it. However, helpful the classification may be from a clinical standpoint, it needs to be supplemented by a number of data from the patient's past medical history to get to a reliable diagnosis. The question is even more complex for researchers. The use of this classification poses no problems in drug trials to evaluate the efficacy of symptomatic treatments. By contrast, big problems may arise in drug trials to evaluate the efficacy of prophylactic treatments, or in epidemiological studies on the prevalence or disability rates of certain headache types, or in genetic or pathogenetic studies. Precisely because they provide a snapshot of a single moment in a single attack and do not give any clues to the disease, the diagnostic criteria of the IHS classifications may be misleading when used alone. If you apply them at the start of an attack, you might get first a diagnosis of tension-type headache and then, as the attack progresses, a diagnosis of migraine without aura.

If we are well aware that IHS classifications classify attacks, not patients, then we will easily understand why—from the first edition of 1988 to the latest of 2013—the major controversies concerned the inclusion and characterization of chronic headaches. While in episodic forms the greatest focus is on the attack, in chronic forms it is the patient in his/her entirety and complexity that takes centre stage.

Considerations specific of ICHD-3

Today, the term "chronic headache" is used to describe four types of primary headache: chronic migraine (CM), chronic tension-type headache (CTTH), hemicrania continua (HC), and new daily persistent headache (NDPH).

Of these, only CTTH was included in the IHS classification of 1988 [2], while all four appear in ICHD-2 [3] and in ICHD-3 beta [1].

In ICHD-3 beta, however, only CTTH maintains the same coding and the same diagnostic criteria that it was given in ICHD-2.

HC has been moved, and correctly so, from Group 4 *Other primary headache disorders* to Group 3 *Trigeminal autonomic cephalalgias (TACs)*, with only minor changes in diagnostic criteria.

NDPH presents no significant coding changes—it still appears in Group 4 *Other primary headache disorders*, where it is now coded to 4.10 instead of 4.8, but only because ICHD-2 listed eight headache types, not 10 as does ICHD-3 beta. By contrast, its diagnostic criteria are significantly changed. In ICHD-2 they were entirely comparable to those for CTTH: the two headache types were considered having the same clinical features, the only difference being NDPH's chronic, continuous character from the start. In light of recent literature findings [4] indicating the possibility that NDPH may also have migraine-like features, ICHD-3 beta refrains from any categorization of its clinical features.

CM is the chronic headache type with the most changes from ICHD-2 to ICHD-3 beta. First of all, it is still in Group 1 *Migraine*, but instead of being listed among the complications of migraine (code 1.5.1 of ICHD-2), it is coded at a two-digit level as 1.3, i.e. at the same diagnostic level as migraine without aura and migraine with aura, which precede it as 1.1 and 1.2, respectively. The diagnostic criteria of CM are significantly changed as well. Those proposed by ICHD-2 in 2004 had appeared inadequate and scarcely consistent with clinical practice from the start. CM was characterized as: (a) headache always fulfilling the criteria of migraine without aura on 15 or more days per month for more than 3 months; and (b) absence of medication overuse.

Those who are concerned with headaches primarily from a clinical point of view know that only a minority of patients with CM fulfill those criteria. Thus, as early as 2006, the diagnostic criteria for CM were changed, with the addition of the possibility that it might also have tension-type features; absence of medication overuse was retained [5]. Now, ICHD-3 removes this constraining criterion, suggesting that CM patients with medication overuse should be given two diagnoses: one of CM (code 1.3) and one of medication overuse headache (MOH) (code 8.2). Only after evaluating the effects of drug withdrawal on the headache course it will be possible to confirm either diagnosis. In addition, ICHD-3 beta agrees with what had already been formally indicated in 2006, i.e. that headache may not always have the same features of migraine without aura. What is surprising here is

that also migraine with aura is mentioned (Table 1), although clinicians know very well that the evolution of migraine with aura into CM is extremely rare.

"Clinical" remarks on how CM is classified and defined in ICHD-3 beta

From the point of view of clinical practice, ICHD-3 beta certainly includes significant improvements over ICHD-2 for CM, but it still has two major limitations:

(a) The diagnostic criteria for CM do not distinguish between patients with very different degrees of severity;
(b) The link between CM and MOH is not yet clear.

The first limitation is clearly apparent from the short description of two patients (Table 2) seen at our Headache Centre. These patients represent two very different clinical cases in terms of severity and prognosis of the disease, but based on the diagnostic criteria in ICHD-3 they would receive an identical diagnosis: CM and MOH.

Table 1 Diagnostic criteria for chronic migraine of the international classification of headache disorders, 3rd edition (beta version)

A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. On ≥8 days per month for >3 months, fulfilling any of the following:
   1. criteria C and D for 1.1 *Migraine without aura*
   2. criteria B and C for 1.2 *Migraine with aura*
   3. believed by the patient to be migraine at onset and relived by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

Table 2 Patients meeting ICHD-3 criteria for 1.3 Chronic migraine and for 8.2 Medication-overuse headache

Case 1
A 45-year-old woman, married, working as an employee. Family history of migraine (mother). Non-smoker. Regular menstrual cycle. Nothing significant in her past medical history
Since age 18, attacks of migraine without aura
In the first 4–5 years after onset, the attacks varied in frequency between 1 and 3 times a month and lasted 1–2 days, responding well to NSAIDs. As soon as she started to work after her graduation, the frequency of attacks increased (about once a week, more often in her off days). The attacks ceased almost completely during her only full-time pregnancy at age 29, but reappeared after childbirth, especially when she stopped breastfeeding at about 6 months. Then, they resumed with a frequency not exceeding once a week and continued to respond well to NSAIDS
The patient sought treatment at our Headache Centre because in the past year she went through a stressful time due to family problems (she had to serve as a caregiver for her diseased mother) and her migraine attacks increased progressively in frequency recurring up to 5–6 times a month in the last 6 months
The attacks still had the same clinical features of migraine without aura, but now were more severe and no longer responded to the usual NSAIDs (ibuprofen 600 mg orally and/or ketoprofen 100 mg rectally or parenterally), lasting for 3 days on end. When the patient was first seen at our Centre, she had never been on preventive treatment and had never used triptans as symptomatic medication
Case 2
A 52-year-old woman, married, working as a self-employed artisan. Family history of migraine (mother and maternal female ancestor). Non-smoker. Two full-term pregnancies. Menopause at age 50
In her past medical history, she reported hypothyroidism since age 35 (Eutirox 75, 5 days/week), arterial hypertension since age 47 (now well-controlled with bisoprolol 2.5 mg and ramipril 5 mg). Since age 40, she had also suffered from depression and insomnia, for which she was currently on treatment with citalopram 20 mg and lorazepam 2.5 mg in the evening before going to bed
The patient began to suffer from migraine without aura, especially perimenstrually around age 22–23. Until age 37–38—except during the two pregnancies, when her migraine improved even though it did not cease completely—she continued to have 1–2 attacks a week, each lasting 1–2 days and responding very well to Difmetre suppositories (indomethacin + prochlorperazine + caffeine)
After age 38, the frequency of attacks progressively increased and their clinical features changed gradually: the headache was no longer located anteriorly but posteriorly, was no longer consistently unilateral, was on average less severe and no longer associated with vomiting. However, Difmetre was less effective, despite an increased intake. Since about age 40, the headache occurred every day, with only few hours of reprieve after the single Difmetre doses
The patient sought treatment at our Headache Centre because she did not benefit from various preventive treatments received (flunarizine, pizotifen, amitriptyline, topiramate). She tried triptans as symptomatic medication, to no avail. Currently, she is no longer able to live a normal family and working life, despite having taken 4–5 Difmetre suppositories every day for a couple of years now

As to the second limitation, we should bear in mind that MOH, included both in ICHD-2 and in ICHD-3 beta among secondary headaches, always affects patients who have been suffering from migraine without aura for many years and eventually overuse their medication. Despite the large numbers of reports published in the literature on this subject, however, we still do not have solid evidence either on the actual role that symptomatic drugs may have on the evolution of migraine (can they cause or worsen migraine?), or on the type of drugs that could potentially trigger a process of "chronicization" of migraine, or for how long or how often they have to be used to induce MOH. Inspite of all these uncertainties, ICHD-3 beta confirms that MOH is an autonomous clinical entity and that the specified numbers of days of medication use considered to constitute overuse are 10–15 or more per month for more than 3 months, as in ICHD-2. Although there is still no supporting evidence from clinical practice or the literature, ICHD-3 now includes also paracetamol- and aspirin overuse, as well as overuse of multiple drug classes not individually overused, as possible causes of MOH.

Clinically, such limitations could be overcome by differentiating migraine without aura into low-, medium- or high-frequency (or chronic) forms, down to transformed migraine, which should be considered a true complication of migraine (Table 3). High-frequency (or chronic) migraine and transformed migraine should be coded to a four-digit level, depending on whether or not medication overuse is also present (Table 3). Classifying the presence of medication overuse in this way would simply be tantamount to recognizing its existence without having to be more explicit about its possible role in the evolution of migraine.

Table 3 Proposed revision of migraine classification, and proposed diagnostic criteria for the three migraine without-aura subtypes, and for transformed migraine

1.1 Migraine without aura
- 1.1.1 Infrequent migraine without aura
- 1.1.2 Frequent migraine without aura
- 1.1.3 Very frequent migraine without aura
  - 1.1.3.1 With medication overuse
  - 1.1.3.2 Without medication overuse

1.5 Complications of migraine
- 1.5.1 Transformed migraine
  - 1.5.1.1 With medication overuse
  - 1.5.1.2 Without medication overuse

1.1.1 Infrequent migraine without aura
Diagnostic criteria:
A. Headache fulfilling criteria C and D for 1.1 *Migraine without aura* on ≤ 3 days/month for ≥ 3 months
B. Not attributed to another disorder

1.1.2 Frequent migraine without aura
Diagnostic criteria:
A. Headache fulfilling criteria C and D for 1.1 *Migraine without aura* on > 3 but < 10 days/month for ≥ 3 months
B. Not attributed to another disorder

1.1.3 Very frequent migraine without aura
Diagnostic criteria:
A. Headache fulfilling criteria C and D for 1.1 *Migraine without aura* on ≥ 10 but ≤ 20 days/month for ≥ 3 months
B. Not attributed to another disorder

1.5.1 Transformed migraine
Diagnostic criteria:
a. Headache (tension-type and/or migraine) on > 20 days/month for ≥ 1 year and never with more than 5 consecutive headache-free days
b. Occurring in a patient who has had at least five attacks fulfilling criteria for 1.1 *Migraine without aura*
c. On ≥ 10 days/month for ≥ 1 year, headache has fulfilled criteria for pain and associated symptoms of migraine without aura or patient has been successfully treated with an ergot or triptan
D. Not attributed to another disorder

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

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CLINICAL ASPECTS OF HEADACHES

Migraine with aura: which patients are most at risk of stroke?

F. A. de Falco · A. de Falco

Abstract The complex association between migraine (M) and ischemic stroke (IS) is discussed. Epidemiological studies and meta-analyses show that M with aura (MA) and not M without aura, doubles the risk of IS. The risk is higher for female gender, young age and higher headache attacks frequency. Smoking habit and oral contraceptives, especially if associated, increase stroke risk. The underlying pathogenetic mechanisms are not completely understood, but it is hypothesized that a particular brain susceptibility to cortical spread depression could explain the association between MA and IS. The absolute risk of IS in migraineurs is relatively low and an antithrombotic primary prevention is not indicated, but it is mandatory to investigate and treat associated risk factors for IS and, in young MA women, consider only progestinic oral contraceptives, if needed, and smoking cessation.

Keywords Migraine · Migraine with aura · Stroke · Risk · Association

Introduction

Association between migraine (M) and ischemic stroke (IS), is a complex and still debated question and particularly migraine with aura (MA) has been proven to be a risk factor for IS mainly in women. M and IS are both "neurovascular disorders" but they strongly differ for age of onset, sex and population prevalence, familiarity, episode frequency and treatment. M is primarily a neuronal event accompanied by vascular changes. IS is primarily a vascular disease with a well-known pathophysiology even in different subtypes.

Neurological syndromes in which M and stroke coexist as CADASIL and mitochondrial diseases (MELAS) are also known. In patent foramen ovale (PFO) MA and IS are also associated, but the pathophysiological interpretation is still debated. Migrainous infarction is another rare association between MA and IS and MA has been also considered a risk factor for cervical artery dissection. It is also known that white matter abnormalities and silent ischemic-like lesions are more frequent in M patients. Understanding which M patients are more at risk is critical for stroke prevention.

Epidemiological data

Migraine prevalence in the population is about 18.5 % and for MA is 4.4 %, both are higher compared to stroke [1]. Epidemiological studies showed a higher incidence of S in patients with MA and three large meta-analyses confirmed these findings [2–4]. Relative risk (RR) for IS in MA patients was significantly higher (more than doubled) compared to subjects without M (RR 2.27 [2]; RR 2.16 [3]; RR 2.25 [4]). Conversely RR for IS in patients with migraine without aura (MO) was not significantly higher compared to controls (Table 1).

Meta-analyses also showed that in MA patients non-modifiable factors, such as female gender and age, and modifiable factors, such as attack frequency, oral contraceptives (OC) use and smoke habit, all increase the risk [2, 3]. In the Guidelines for the prevention of stroke in women, MA was considered a specific risk factor for IS in women [5]. MA patients aged under 45 years have an higher stroke

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Table 1 Meta-analyses of epidemiological study (modified from Kurth et al. [10])

	Etminan et al. [2]	Schurks et al. [3]	Spector et al. [4]
Overall migraine			
All studies	2.16 (1.89–2.48)	1.73 (1.31–2.29)	2.04 (1.72–2.43)
Case–control studies	2.18 (1.86–2.56)	1.96 (1.39–2.76)	–
Cohort studies	2.10 (1.61–2.75)	1.47 (0.95–2.27)	–
Women	–	2.08 (1.13–3.84)	–
Men	–	1.37 (0.89–2.11)	–
Women and men < 45 years	2.36 (1.92–2.90)	2.65 (1.41–4.97)	–
Women < 45 years	2.76 (2.17–3.52)	3.65 (2.21–6.04)	–
Oral contraceptive use	8.72 (5.05–15.05)	7.02 (1.51–32.68)	–
Smoking	–	9.03 (4.22–19.34)	–
Migraine with aura	2.27 (1.61–3.19)	2.16 (1.53–3.03)	2.25 (1.53–3.33)
Smoking	–	1.5 (1.1–2.3)[a]	–
Women currently using oral contraceptives and smoking	–	10.0 (1.4–73.7)[a]	–
Migraine without aura	1.83 (1.06–3.15)	1.23 (0.90–1.69)	1.24 (0.86–1.79)

Summary of the relative risk (95 % CI) between migraine and ischaemic stroke in three meta-analyses of observational studies

– Not reported

[a] Estimate provided by only one study

risk [3, 6] and in women of childbearing age with more than 12–13 headache attacks per year there was a significant increase of risk [7, 8]. This finding was confirmed in the Women Health Study with a RR 4.25 in women with almost one headache attack per week [9]. OC use [2, 3] and smoking habit [3] increase the risk and, if associated, the RR increases up to 7–10 [3, 8].

Migraine seems to be a risk factor also for hemorrhagic stroke (HS). Although the results of individual studies were conflicting, a recent meta-analysis showed that migraine is associated with a 1.48-fold increase in the risk of hemorrhagic stroke, including subarachnoid hemorrhage. RR was not significant higher for MA group, but only for women and for age <45 years, regardless of M subtype [11]. In another study, MA has been associated with HS, and risk was stronger in the subset of women with fatal HS and <55 years of age [12].

The absolute risk of IS or HS in migraineurs is relatively low, but MA is significantly associated with a higher IS risk in women whereas MO is not. The two primary migraine subtypes show clear different clinical characteristics, well-defined by the International Headache Society (IHS) [13], but the possible difference in their pathophysiology is debated. Clinical overlapping is frequent and MA occurs in about a third of people with migraine, and in those with MA up to 33 % have both types of attack [14]. In a population-based study, 40 % of migraineurs reported at least one attack accompanied by aura [15]. It remains unknown whether MA has a different pathophysiological basis compared to MO. In the intensive debate whether they should be considered distinct subtypes or part of the same disease spectrum [16–18], the epidemiological strong evidence of enhanced IS risk in MA but not in MO supports the hypothesis of two distinct disorders and suggests that the cortical spread depression (CSD) could be the link between MA and IS.

Epidemiological studies showed some critical issues concerning definition of stroke subtype. IS subtypes have different underlying pathogenesis and this is relevant in understanding the pathophysiology of the association. MA has also been associated with transient ischemic attack (TIA) with a RR 1.56 and with IS with good functional outcomes as measured with Rankin scale (mRS scores 0–1; RR 2.33) [19]. The association with TIA raises the question of differential diagnosis with migrainous aura and may be challenging particularly in older age. The good outcome together with the reported evidence of high prevalence of silent infarct-like MR lesions (ILLs) in patients with migraine with aura [20], indicate that the small vessel disease could be the IS subtype associated with MA. In a large meta-analysis, structural brain changes, including white matter abnormalities (WMAs), silent ILLs, and volumetric changes in GM and WM regions, were reported to be more common in migraineurs than in control groups with stronger evidence for MA. The meta-analysis of WMAs prevalence showed an association with MA (OR 1.68; $p = 0.03$) but not with MO (OR 1.34; $p = 0.08$). The association with ILLs was greater for MA (OR 1.44; $p = 0.04$) than for MO, but no association was found for MA ($p = 0.52$) and MO ($p = 0.08$) compared to controls [21].

M has been associated with other vascular disorders. A recent meta-analysis [22] showed an association with cervical artery dissection (CAD) with a OR 2.06 (1.33–3.19) and could be a predisposing condition. In another study, a higher association for MA patients (OR 2.41; 1.53–3.80) and female gender was reported [23]. In PFO, a possible cardioembolic source in juvenile cryptogenic stroke, MA and IS are strongly associated. PFO is twice as frequent in patients with MA and MA is twice as frequent in patients with PFO than in controls. The relation is complex and debated and is probably due to a genetic predisposition to both disorders [24–26]. A double-blind, randomized clinical trial of PFO closure [27] showed no benefit on migraine attacks. Moreover, the association between ILLs and MA was confirmed in young patients with cryptogenic IS but no evidence for a mediating effect of PFO was found [28].

Pathophysiological hypotheses

The possible role of a higher prevalence of common vascular risk factors (RF) in migraine patients has been extensively discussed in a recent paper [29]. In conclusions, in young age the prevalence of common vascular RF is lower and MA appears directly associated with IS, while in older migraineurs they seem to increase IS risk [30, 31]. Among genetic RF, the MTHFR 677C > T or the ACE D/I polymorphisms seem to increase IS risk in people with MA [32].

The complex pathophysiology of migrainous aura is not completely understood, but the CSD is presumably the underlying mechanism. There is an initial slow-moving wave of cortical depolarization, accompanied by short-lasting increased blood flow, followed by persistent oligemia during a prolonged phase of cortical suppression [33]. The evidence of significant association of IS and MA suggests a role of CSD as a mechanism underlying the migraine-stroke association. Cortical hyperexcitability has been postulated as a mutual mechanism of migraine pathogenesis and increased vulnerability to cerebral ischemia in migraine-susceptible brains [34]. Dalkara et al. hypothesized that migraine and stroke might both be triggered by hypoperfusion and could, therefore, exist on a continuum of vascular complications in a subset of patients who have hereditary or acquired comorbid vascular conditions. This mechanism could be also explained the rare occurrence of the migrainous infarction as defined in HIS [13]. The pathogenetic link could be mediated by multiple different factors such as platelets hyperactivity, coagulation disorders, endothelial dysfunction, inflammation [35, 36]. At present, a conclusive explanation of the complex relationship between migraine and stroke cannot be given, but certainly many different factors, to varying degrees, contribute to determine it.

Which migraine patients are at risk and what we have to do

The absolute risk of stroke across the overall migraine population is relatively low [5], but the epidemiological data show a clear profile of the migraine patient at risk. The risk is well-defined in MA and female gender, age under 45 years, high headache attacks frequency, OC drugs and smoking habit, all increase the risk. It is presumably relevant to the association with common vascular RF particularly in older and with thrombophilic factors as MTHFR and ACE polymorphisms. What we have to do (or not to do) in a young woman with MA? First of all, we must act on modifiable factors, recommending smoking cessation and carefully evaluating treatment with OC. If needed, give preference to low-estrogen or progestin-only contraception preparations [37]. In MA women on OC, smoke must be prohibited and the possible coexistence of hypertension and hyperhomocysteinemia should be investigated. Treatments to reduce migraine frequency might be reasonable, although evidence is lacking that this reduces the risk of first stroke [5]. In older women, all the traditional RF should be investigated and opportunely treated. At present, no drugs are recommended for the vascular prevention in migraineurs patients without other vascular risk factors, given the low absolute risk of stroke and the side-effects of antithrombotics agents. When an IS occurs in young patients with MA, the presence of PFO should be investigated. Whatever the age, the secondary prevention after IS in migraineurs does not differ with respect to non-migraineurs, but there is a contraindication to use of triptans and ergot derivatives for the acute attack [38].

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

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CLINICAL ASPECTS OF HEADACHES

Migraine with aura and patent foramen ovale: myth or reality?

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Abstract Several observational studies report that subjects with migraine with aura have a higher prevalence of right-to left shunt, commonly due to patent foramen ovale, and that patent foramen ovale is more prevalent in subjects with migraine with aura. Although migraine without aura has been less extensively studied, it does not seem to be associated with an increased prevalence of right-to left shunt. The mechanism that underlies the possible relationship between patent foramen ovale and migraine with aura remains speculative. The proposed mechanisms are migraine-triggering vasoactive chemicals bypassing the pulmonary filter and reaching the cerebral circulation and paradoxical microembolization. However, it is unclear, at this time, if there is a causal or comorbid association between the two conditions. In some families atrial shunts show a dominant inheritance that seems to be linked to inheritance of migraine with aura. Migraine with aura is an independent risk factor for ischemic stroke, and patent foramen ovale is present more frequently in patients with cryptogenic stroke than in controls. At this moment, there is no convincing evidence that excess stroke risk of migraine is simply mediated by patent foramen ovale through paradoxical embolism. Several non-controlled studies suggest that closure of the foramen ovale significantly reduces attack frequency in migraine patient, but the only prospective placebo-controlled trial does not support these results. Patent foramen ovale closure, at present, is not indicated as a treatment for migraine in clinical practice.

Keywords Migraine · Migraine with aura · Patent foramen ovale · Right-to-left shunt

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Introduction

The foramen ovale is a connection between the right and left atrium of the heart, which is normally present during fetal development. At birth, the pulmonary pressure decreases and the left atrial pressure exceeds that of the right. This forces the septum primum against the septum secundum, functionally closing the foramen ovale. In approximately 20–25 % of the general population, a complete closure does not occur (patent foramen ovale) causing a persistent connection that may allow the passage of blood from the right to the left atrium either permanently or only when further increases in right atrial pressure occur, such as during a Valsalva maneuver. Patent foramen ovale (PFO) is the most common right-to left shunt (RLS), representing about 95 % of all RLS [1].

PFO is asymptomatic in the great majority of subjects, but it is considered a potential cause of cryptogenic ischemic stroke, mainly via paradoxical embolism, in some situations [2].

An association between patent foramen ovale and migraine with aura (MA) was for the first time described in 1998 by our group [3] and confirmed by another Italian group in 1999 [4].

This association raised many, partially unresolved, questions, such as the kind of relationship that links the two conditions, the likelihood that PFO may be a trigger for migraine attacks and the mechanism by which PFO may

induce a migraine attack, the role of PFO in enhancing risk for ischemic stroke in migraine patients and finally if a closure of PFO is advisable in migraine patients. The present paper will review the state of the art on this topic.

Prevalence of PFO in migraine subjects

The presence of PFO may be revealed by three different methods: transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) or transcranial Doppler, after the injection of saline agitated with air (cTCD). Valsalva maneuver is performed to temporarily increase right atrial pressure and open the flap valve in patients with latent PFO. The RLS may be present at rest or only during Valsalva, and the RLS size is usually classified on the basis of number of microbubbles detected. TEE is considered the gold standard technique in the diagnosis of PFO [5]. However, cTCD is a non-invasive method with excellent sensibility and specificity [6]. These technical aspects are to be taken into account, when evaluating the results of studies concerning PFO detection.

PFO has been shown to be more common in migraineurs with aura than in the general population by several studies.

In 1998 [3], we compared 44 patients suffering from MA with 73 subjects younger than 50 years with focal cerebral ischemia and 50 matched controls, without a history of migraine or cerebrovascular disease. RLS presence was explored by means of bilateral cTCD. Eighteen out of 44 migraine patients (41 %) showed RLS, as opposed to 8 of 50 controls (16 %) ($P < 0.005$). Furthermore RLS was present in 26 out of 73 patients with cerebral ischemia (35 %). We concluded that the prevalence of RLS in patients with MA is significantly higher than in normal controls and that it is almost similar to that observed in young patients with stroke.

In the following years, this finding was confirmed by several studies. In 2008 Schwedt et al. [7], in a quantitative systemic review of the literature, estimated the strength of association between migraine in general and PFO, reflected by summary odds ratios, 2.54 (95 % CI 2.01–3.08). In 2013, Schwerzmann et al. [8] reviewed nine studies on the relationship between migraine and PFO. A composite evaluation of the results showed that about 57 % of patients with MA had PFO compared with 19 % of control subjects, while the prevalence of PFO in patients with migraine without aura (MO) did not differ from the general population.

Although MO has been studied less extensively, it does not seem to be associated with an increase in the prevalence of PFO since the first studies [4].

A recent systematic review [9] summarized the prevalence of PFO in migraineurs from 12 case series and found that it ranged from 46.3 to 88.0 % in MA, from 16.2 to 34.9 % in MO and was 27.3 % in the general population.

One study [10] revealed that migraineurs with atypical aura have a greater prevalence of PFO (79.2 %) when compared with those with typical aura (46.3 %).

The relationship between MA and PFO seems to be bidirectional. People who have PFO are more likely to have MA with an OR 5.13 (95 % CI 4.67–5.59) [7] and a prevalence ranging from 9.13 to 51.7 % [9]. The size of PFO seems to influence the probability of having migraine. Wilmshurst et al. [11, 12], in two different papers, evaluated migraine frequency in a group of scuba divers affected by decompression illness, who were found to have PFO. They found that PFO was more common in subjects with MA, but not in subjects with MO and that having a large shunt increased the risk of being affected by MA. This finding was confirmed by other studies, using different techniques of PFO detection. Schwerzmann et al. [13] evaluated the presence and size of PFO in subjects with MA by means of TTE and found that the prevalence of small shunts was similar in migraineurs and controls, while larger shunts were more prevalent in patients with MA. Anzola et al. [14] analyzed shunt size by means of cTCD in patients with migraine, history of stroke or non-migraineur controls. They found that large RLS occurred twice as often in migraineurs compared with non-migraineurs. This association was strengthened by the presence of stroke: patients with both migraine and stroke had larger shunts than patients with migraine without stroke, non-migraineur subjects with stroke and control subjects.

Some studies do not confirm the association between PFO and migraine. The only population-based study available on this topic [15] did not find a difference in the prevalence of PFO between subjects who had migraine (26/178, or 14.6 %) and those who did not (138/923, or 15.0 %; $P = 0.9$). This study has several important limitations: the presence of PFO was assessed by TTE, which is considered a less reliable method, and the diagnosis of migraine was self-reported. The prevalence of self-reported migraine in the cohort was 16 % (178), of which 13 % (140) were migraine with aura, with a ratio between MO and MA that is not plausible. In 2010, Garg et al. [16] published a large case-controlled study reporting that the prevalence of PFO in MA subjects was not different from controls. The presence of PFO was determined by TTE and cTCD with or without Valsalva maneuver. PFO, however, was considered present if both studies were positive. So, the poor sensitivity of TTE in PFO detection conditioned the final results.

Finally, one study [17] examined the association between PFO and migraine in children, revealing that children with MA have a higher prevalence of PFO than patients with MO and age-matched controls (50 vs. 25 %;

$P = 0.0004$); these results reproduced, in fact, those of the adult population.

In summary, the data available in literature strongly suggest that there is a higher prevalence of PFO in patients with MA and vice versa.

The proposed mechanisms of association between MA and PFO

The mechanism that underlies the possible relationship between PFO and migraine remains speculative. It is unclear, at this time, if there is a causal or comorbid association between the two conditions.

The finding of co-existence of inheritance of large PFOs and MA in some families [18] supports a non-causal relationship. When the proband has MA and atrial shunt, the first-degree relatives with a significant RLS have 70 % likelihood to also have MA. The authors conclude that in some families there is a dominant inheritance of atrial shunts that is linked to the inheritance of MA. We can suppose that a genetically determined common endothelial-endocardial dysfunction might determine the co-occurrence of atrial septal abnormalities and migraine.

However, these data do not exclude the possibility of a causative association as other observations suggest. As we have seen, large shunts more often than small ones are associated with MA [11–14] suggesting a kind of dose–effect relationship. Some cases of MA induced by paradoxical gas embolism across atrial shunts have been reported and the severity of the episode of MA appears to correlate to the numbers of bubbles crossing the defect [11, 19]. In one case of MA precipitated by cTCD [19], MR images, including DWI and ADC, performed during aura, did not show any signal abnormality, a finding that is consistent with a "non-ischemic" mechanism. Another factor which supports a causative relationship between PFO and MA is the improvement of MA in some patients [20, 21] after closure of atrial shunts, but also new onset of MA after transcatheter closure of atrial septal defect [22].

Regarding the mechanisms, we can speculate that RLS may allow vasoactive substances that are usually present in the venous circulation and are able to trigger a migraine attack, to bypass the pulmonary filter and reach the cerebral circulation. Migraine subjects with large PFO frequently recognize, among triggers of their migraine attacks, exertional activities, which increase the amount of the shunt [23].

Serotonin, which has been demonstrated to be a vasoactive prothrombotic substance inducing cardiac oxidative stress, has been implicated in migraine attack [24]. Usually, lung monoamine oxidase takes part in serotonin metabolism, but if some blood is shunted, thereby bypassing the pulmonary circulation, the arterial level of serotonin may increase and could trigger MA attack directly or by means of a serotonin-mediated platelet activation and aggregation. It has been found that serotonin decreases after percutaneous closure of PFO.

Paradoxical cerebral embolism is the other mechanism that may be involved in inducing the aura phenomenon. Paradoxical microembolization of platelet aggregates might trigger a focal transient ischemia, which in turn might induce a cortical spreading depression (CSD) that is believed to be the electrophysiological substrate of aura. Paradoxical embolism appears to be more frequent in the posterior circulation, in the areas involved in hypoperfusion during the visual aura. In a mouse model, microemboli are able to induce CSD often without causing a permanent ischemic lesion [25]. In the mouse model, air microinjection was found to be the most reliable CSD trigger. The same phenomenon might explicate the cases of microbubble-induced attacks of MA in humans described in literature [19]. Air microembolism through large PFOs is able to cause cerebral bioelectrical disturbance, evaluated by spectral electroencephalography, in MA patients; this finding may reflect an increased reactivity of migrainous brain to transient subclinical hypoxia–ischemia [26]. MA represents a mild risk factor for ischemic stroke [27] and MA patients also have an increased risk for silent brain lesions and silent infarcts in the posterior circulation [28, 29]. Furthermore, PFO has been linked to some degree of arterial blood oxygen desaturation; hypoxia may directly induce CSD, but also increase the expression of plasminogen activator-1, which is able to suppress fibrinolysis, increasing the likelihood of a paradoxical microembolism development [30]. In spite of these data, a spontaneous source of air microembolization does not exist in humans, and it is difficult to speculate that a frequent microembolization of platelet clots or fibrin-rich, soft, red-type venous clots may occur with an almost always benign clinical course, as seen in MA.

A small double-blind crossover study demonstrates that aspirin, an anti-platelet drug that is able to reduce the formation of platelet–fibrin aggregates, has a statistically significant prophylactic effect on migraine [31]. The effect of aspirin in the subset of MA subjects with PFO has not been systematically studied. Clopidogrel has been found to reduce MA frequency after transcatheter closure of PFO and atrial septal defects [32]. Anti-platelet drugs might prevent microemboli development, but also reduce the release of serotonin from aggregating platelets. Platelet activation and aggregation are increased in patients with migraine [33] and this may be further enhanced in MA subjects with PFO.

A recent paper [34] found that RLS is associated with impairment of dynamic cerebral autoregulation and

proposed that this mechanism may play a role in migraine attack induction.

PFO and enhanced risk for ischemic stroke in migraine subjects

Migraine with aura has been associated with an increased risk, both of ischemic and hemorrhagic stroke [35, 36]. In particular, MA is an independent risk factor of ischemic stroke, especially in patients under the age of 45 years whose risk is increased by six- to eightfold. In general, meta-analysis report an at least twofold increase in risk of stroke for all ages in MA [27]. MA is also a risk factor for subclinical brain lesions and silent infarct in the posterior circulation [28, 29].

In patients with cryptogenic stroke, PFO is present more frequently than in controls, in particular when the subjects are young. In these cases, a paradoxical embolism with a passage of venous emboli toward the arterial circulation through the PFO is thought to be the mechanism underlying the ischemic stroke [2].

It is not known if the increased risk for ischemic stroke observed in MA subjects might be attributed to episodes of paradoxical embolism due to PFO. Prospective studies comparing the incidence of ischemic stroke in migraine subjects with or without PFO do not exist.

The association of PFO, ischemic stroke and migraine has been assessed by Lamy et al. [37], who evaluated possible differences in stroke risk factors in 581 young cryptogenic stroke patients with and without PFO. The presence of PFO and atrial septal aneurysm was evaluated by TEE. Two hundred and sixty-seven stroke patients (45.9 %) had PFO. The prevalence of migraine was higher in patients with PFO (27.3 %) than in those without (14.0 %). The presence of PFO was significantly and independently associated with migraine (OD 1.75, 95 % CI 1.08–2.82). This association was reinforced by the presence of PFO and atrial septal aneurysm (OD 2.71, 95 % CI 1.36–5.41).

Large PFOs are considered to carry a greater risk for paradoxical embolism; patients with MA have overall larger shunts than non-migraineurs and this is particularly true if they have had a stroke [14].

Migraine is also a risk factor for subclinical brain lesions and silent infarct in the posterior circulation [28, 29], but there is no evidence suggesting a causative effect of PFO on this association. We studied migraine characteristics and cerebrovascular risk factors in 87 subjects consecutively seen for MA. All subjects underwent cTCD to evaluate RLS presence and MRI with T2-weighted and diffusion-weighted imaging (DWI) to evaluate the presence, number and volume of white matter lesions (WMLs). The presence, number and total volume of WMLs increased with subjects' age and did not differ between subjects with and without RLS. We concluded that RLS does not increase the risk of WMLs in migraineurs with aura [38]. Our findings have been confirmed by other studies [39, 40].

In conclusion, there is no convincing evidence that excess stroke risk of migraine is simply mediated by PFO through paradoxical embolism. On the other hand, there is increasing evidence that MA is not only a risk factor for ischemic stroke, but also for myocardial infarction and other ischemic vascular events. This makes it evident that the relationship between migraine and vascular diseases is much more complex.

PFO closure in migraine

The causative nature of association between PFO and migraine remains controversial; nevertheless, several studies have been carried out to determine whether closure of PFO defect is able to affect migraine frequency.

In the first study, Wilmshurst et al. [41] found that the closure of cardiac RLS, done to prevent recurrence of decompression illness or stroke, significantly reduces attack frequency in migraine patients. In the following years, some non-randomized studies confirmed these results. In a quantitative systematic review, Schwedt et al. [7] reported that PFO closure, in a total of 194 migraine patients with and without aura, was followed by resolution of headaches in 10.4–80.0 % and improvement of headaches in an additional 14.0–83 %.

Similarly, Butera et al. [20], in a quantitative synthesis of previous studies, reported that resolution of migraine was observed in 46 % (95 % CI 25–67 %) and significant improvement in 83 % (95 % CI 78–88 %) of the cases.

These studies have several limitations. Most of them were retrospective, migraine frequency and intensity were evaluated using subjective recall, different devices were utilized and residual shunting was not analyzed in all studies. All the studies were not blind and were non-controlled; therefore the possibility of "placebo effect" must to be taken into account. Almost all subjects received clopidogrel and/or aspirin for 3–6 months after closure, drugs that, as we have seen, may reduce migraine frequency [31, 32].

To overtake these limitations, a prospective, randomized, double-blind and sham-controlled trial to study the effects of PFO closure in migraine subjects was carried out [Migraine Intervention with STARflex Technology (MIST) trial] and published in 2008 [42]. This study included subjects with refractory migraine (defined as non-responding to two types of preventive medications), with 5–23 migraine days per month and without history of

cerebrovascular events. The trial did not achieve both the primary and secondary end points, defined respectively as complete resolution of migraine and more than 50 % reduction of headache days. Several reasons can explain the difference of results between MIST and previous retrospective reports. MIST population was quite different. None of the non-randomized studies was focused on patients with a high-frequency refractory migraine, and most of the patients had a low frequency of attacks (1 or 2 migraine attacks per month). The residual shunt rate in MIST was quite high and this may have negatively influenced the results.

In the following years, some other randomized trials about effect of closure of PFO in migraine subjects have been started. MIST II and ESCAPE have prematurely stopped because of financial reasons. Two other trials [European Percutaneous Closure of PFO In Migraine with Aura (PRIMA) trial, Northern American Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer® PFO Occluder Compared to Medical Management (PREMIUM) trial] are still ongoing.

Khessali et al. [43] focused their attention on the relationship between PFO and visual aura, with a non-randomized prospective controlled study. They found the prevalence of RLS to be 96 % in patients who had visual aura with migraine, 72 % in patients who had visual aura unrelated in time to migraine and 67 % in patients with visual aura without migraine. One year after closure, aura resolved in 52, 75 and 80 % of patients, respectively. These results seem to underline the relationship between PFO and visual aura rather than headache. However, the prevalence reported is much higher than in all previous studies.

In conclusion, considering that the pathophysiological relevance of PFO closure in migraine is uncertain and that its efficacy has not been demonstrated, this procedure is not recommended to prevent migraine.

Moreover, percutaneous PFO closure is not a completely risk-free procedure [44]. Up to 8 % of surgical procedures cause complications that require further intervention. The most serious complications reported are formation of thrombus on the implant device, thromboembolism related to the implant device, cardiac perforation, infective endocarditis or cardiac arrhythmias.

Conclusions

Several observational studies report that patients with MA have a higher incidence of PFO and that PFO is more prevalent in patients with MA. Although MO has been less extensively studied, it does not seem to be associated with an increase in the prevalence of PFO.

The mechanism that underlies the possible relationship between PFO and MA remains speculative. The proposed mechanisms are migraine-triggering, vasoactive chemicals bypassing the pulmonary filter and reaching the cerebral circulation or paradoxical microembolization. However, it is unclear, at this time, if there is a causal or comorbid association between the two conditions.

MA is an independent risk factor for ischemic stroke. In patients with cryptogenic stroke, PFO is present more frequently than in controls. At this moment, there is no convincing evidence that excess stroke risk of migraine is simply mediated by PFO through paradoxical embolism. In asymptomatic PFO, primary prevention with anti-platelet drugs is not indicated. There is no evidence that this lack of indication must be influenced by the presence of migraine.

Several non-controlled studies suggest that the closure of cardiac right-to-left shunts significantly reduces attack frequency in migraine patients, but the only prospective placebo-controlled trial does not support these results. Migraine is a complex neurological disorder with many possible exogenous and endogenous triggers, so any simple "definitive" treatment, such as PFO closure, is unlikely to exist. Therefore, PFO closure is not indicated as a treatment of migraine in clinical practice.

Taking in account the previous considerations, at this time, migraine should not be considered an indication for PFO screening.

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

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CLINICAL ASPECTS OF HEADACHES

Headache in subarachnoid hemorrhage and headache attributed to intracranial endovascular procedures

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Abstract Headache is a critical problem in the emergency setting. In this paper we briefly review the epidemiological data regarding headache in Subarachnoid Hemorrhage (SAH), considering the role of headache as a warning symptom and the other clinical manifestation of SAH. We have also introduced a recent clinical entity, represented by headache associated to intracranial endovascular procedures (IEPs).

Keywords Headache · Subarachnoid hemorrhage · Intracranial endovascular procedures

Introduction

SAH is a significant cause of morbidity and mortality throughout the world. Although the incidence of SAH varies widely among populations, mortality rate is 40–50 % and half of survivors are left disabled.

Increasing data suggest that new mini-invasive techniques of aneurysm repair, combined with aggressive management of SAH complications will lead to improved outcomes in terms of morbidity and mortality.

Moreover, considering the rapid improvement in endovascular treatment of cerebrovascular diseases (brain arteriovenous malformation, aneurysms, ischemic stroke…), incidence of headache related to IEPs will soon increase.

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Headache in subarachnoid hemorrhage

Epidemiology of SAH

A considerable variation in the annual incidence of SAH exists in different regions of the world.

A World Health Organization study found, in European and Asian countries, a tenfold variation in the age adjusted annual incidence that ranges from 2.0 cases per 100,000 population in China to 22.5 cases per 100,000 in Finland [1]. In a more recent systematic review of population based studies, the incidence of SAH ranged from 2 to 16 per 100,000 [2]. Because death resulting from SAH often occurs before hospital admission (10–20 % of cases) [3, 4] the true incidence of SAH could be even higher. Although a number of population based studies have indicated that the incidence of SAH remained relatively stable over the last four decades [2, 5, 6], a recent review, with data adjusted for age and sex, suggested a slight decrease in incidence between 1950 and 2005 for regions except Japan, South and Central America and Finland [1, 7, 8]. These data are consistent with studies that show that the incidence of SAH increases with age, with a typical average age of onset in adults ≥50-years-old [1, 7, 8].

SAH is relatively uncommon in children [9]. The majority of studies also indicate a higher incidence of SAH in women than in men [10, 11]. Evidences of a sex-age effect on SAH incidence has emerged from pooled study data, with a higher incidence reported in younger men (25–45 years of age), in women between 55 and 85 years of age, and in men >85 years [12]. Differences in incidence of SAH by race and ethnicity appear to exist. Blacks and Hispanics have a higher incidence of SAH than white Americans [13–15].

Risk factors for SAH

Risk factors for SAH include hypertension, smoking, alcohol abuse, and the use of drugs as cocaine. The risk of SAH is increased by the presence of ruptured cerebral aneurysm, a history of familiar aneurysm, a family history of SAH and some genetic syndromes as autosomic dominant polycystic kidney disease and type IV Ehlers–Danlos syndrome [16, 17].

Clinical manifestation and diagnosis

Anamnestic data and clinical examination are fundamental for the diagnosis.

The IHS classification [18] includes the diagnostic criteria:

A. Any new headache fulfilling criterion C
B. Subarachnoid haemorrhage (SAH) in the absence of head trauma has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
    1. headache has developed in close temporal relation to other symptoms and/or clinical signs of SAH, or has led to the diagnosis of SAH
    2. headache has significantly improved in parallel with stabilization or improvement of other symptoms or clinical or radiological signs of SAH
    3. headache has sudden or thunderclap onset
D. Not better accounted for by another ICHD-3 diagnosis

The hallmark of SAH in a patient who is awake is the complaint "the worst headache of my life", referred by 90 % of patients who can give a history [19]. This headache is usually of sudden onset, excruciating and immediately reaching maximal intensity (thunderclap headache). It may arise during daily rest or in relation to a physical strain. A warning or sentinel headache that precedes the SAH is reported by 10–43 % of patients. This sentinel headache increases the odds of early re-bleeding tenfold [20–22]. The onset of headache may be associated with additional signs. Increased intracranial pressure is the cause of many associated symptoms like photofobia, nausea, vomiting and loss of consciousness. Meningism and focal neurological signs may be present. Focal neurological deficits occur when an aneurysm compresses a cranial nerve or bleeds into the brain parenchyma, or from focal intracranial due to acute vasoconstriction after aneurysm rupture. Neck stiffness is important but not essential for the diagnosis of SAH and appears 24–48 h after the hemorrhage event. Ocular hemorrhage may be found in 20–40 % of cases, usually in association with aneurysm of the anterior circulation. Despite the classic presentation of SAH, individual findings occur inconsistently, and because the type of headache from SAH is sufficiently variable, misdiagnosis of SAH occurred in as many as 64 % of cases, with more recent data suggesting a misdiagnosis rate of 12 % [23, 24]. Misdiagnosis is associated with a nearly fourfold higher likelihood of death or disability at 1 year in patients with minimal or no neurological deficit at the initial visit [23]. The most common diagnostic error is failure to obtain a noncontrast CT scan [23–25]. Noncontrast head CT remains the cornerstone of diagnosis of SAH. The sensitivity of CT in the first 3 days after SAH remains very high (close to 100 %), after which it decrease moderately during the next few days. After 5–7 days, the rate of negative CT increases sharply, and lumbar puncture is after required to show xanthochromia. However, Magnetic Resonance particularly the use of fluid, attenuated inversion recovery, proton density, diffusion weighted imaging, and gradient-echo sequences, can often allow the diagnosis of SAH to be made when a head CT scan is negative and there is clinical suspicion of SAH. The computed tomographic angiography (CTA) may be considered in the workup of SAH. If an aneurysm is detected by CTA this study may help guide to decision for type of aneurysm repair, but if CTA is inconclusive digital subtraction angiography (DSA) is still recommended.

Conclusions

The crucial points in the management of SAH are: (1) In the diagnostic workup of SAH are very crucial the anamnestic data about headache characteristics in the emergency department (ED). The "headache diagnostic alarms" guide the neurologist throughout the pathway of the differential diagnosis and the choice of the best diagnostic workup. (2) Hospital characteristics and systems of care. Low volume hospitals should consider early transfer of patients with SAH to high volume centres with experienced cerebrovascular surgeons, endovascular specialists and multidisciplinary neuro-intensive care services.

Headache attributed to intracranial endovascular procedures

Nowadays cerebral IEPs 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.

The International Headache Society classification of headache disorders (ICDH-III) [18] includes headache attributed to intracranial endovascular procedures (6.7.1).

Diagnostic criteria:

A. Any new headache fulfilling criterion C
B. Intracranial angioplasty or embolization has been performed
C. Evidence of causation demonstrated by all of the following:
    1. headache has developed within seconds of the procedure
    2. headache has resolved within 24 h after the end of the procedure
    3. headache is severe, unilateral and ipsilateral to the procedure
D. Not better accounted for by another ICHD-3 diagnosis, and arterial dissection has been excluded by appropriate investigations.

The bibliography related to these criteria is scarce. Only four articles are reported [26–29], which focused on headache characteristics and pathophysiology.

Headache during endovascular procedures (HdEVP) occurs among 19.1–55.6 % [29, 32] of patients undergoing endovascular procedures - either therapeutic embolizations or diagnostic angiography. HdEVP is described as a stabbing or pressure-like mild unilateral short-lasting pain, always occurring in consequence of a specific manoeuvre, which was ipsilateral to the pain location in all but one case.

The type of headache described is quite stereotyped [28]. It is of sudden onset, intense, focal and short lasting. It is never described as throbbing as one would expect of a purely vascular pain. This headache is similar to ones described at the very onset of cerebral embolism and to warning headaches of aneurysmal subarachnoid hemorrhage. These are also two examples of sudden vascular wall damage. It differs from headache associated with ischemic stroke by its short duration and its localization, which suggests that in the latter, other factors (associated vasodilation, edema, ischemia) contribute to the persistence of pain.

The variation of pain site suggests that different branches of the ophthalmic division of the trigeminal nerve innervate different vessels. Besides, it shows that innervation accompanies small cortical and penetrating branches and pain is not exclusive of the larger vessels. This topography also corroborates the importance of the trigeminovascular system in the pathogenesis of vascular head pain.

Another study [30] described three cases of migraine (two with aura) immediately after an IEPs (embolization of a dural arteriovenous fistula; cerebral angiography; embolization of the arteriovenous malformation-AVM). The duration of headache in IEPs can be longer than 24 h as indicated in ICDH-III Classifation and can last from 3 days to 3 months [31, 32].

Some studies focused on risk factors for headache in IEPs.

Factors associated with occurrence of HdEVP were female sex, therapeutic procedures and previous headache frequency more than four attacks per month [29].

The results suggested that HdEVP might be a direct consequence of local mechanical arterial distension (either from embolization or contrast injection) and tends to occur more frequently in predisposed individuals, such as female patients with frequent previous headache attacks (>4/month).

Two studies [31, 32] exclude the role of a history of hypertension as a risk factor for headache associated with IEPs.

The physiopathological mechanism was investigated [28, 29, 33]. Theories about the genesis of pain associated with IEPs include 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 from trigeminal C fiber stimulation; local toxicity or chemical reaction (dye, glue), or inflammatory changes, caused by embolic or contrast materials injected intra-arterially; hemodynamic changes (vasodilation) in collateral vessels or vascular spasm; parenchymal ischemia; immunologic or idiosyncratic reaction; vasogenic edema; cortical irritation; acute pressor changes; thrombosis and hemorrhage within the aneurysmal vessel wall; and physical and psychological stress from pain or fear.

Conclusions

The neurovasolar interventional center of Niguarda Hospital performs about 300 IEPs per year (aneurysm embolization, mechanical thrombectomy, treatment of dural fistula and AVM). Most of treated patients referred headache after IEPs. The severity, disability and duration of headache often leads to the need of further neuroradiological investigations and clinical monitoring, increasing the duration of hospital stay.

The lack of clinical indicators about headache in IEPs corroborate the need to include headache evaluation in future studies on complications of IEPs and the need to consider the duration range of headache in IEPs.

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

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CLINICAL ASPECTS OF HEADACHES

Confusional state as first symptom of HaNDL syndrome

Fabio Frediani · Gennaro Bussone

Abstract HaNDL (transient headache and neurological deficits with cerebrospinal fluid lymphocytosis) syndrome is an infrequent condition included at group 7 "headache attributed to non-vascular intracranial disorder" in the recent International Classification of Headache Disorders (ICHD-3), code 7.3.5. The description states "migraine-like headache episodes (typically 1–12) accompanied by neurological deficits including hemiparaesthesia, hemiparesis and/or dysphasia, but positive visual symptoms only uncommonly, lasting several hours. There is lymphocytic pleocytosis. The disorder resolves spontaneously within 3 months". In this description confusional state is not considered as a main symptom, even if in the literature this aspect is frequently reported. Here, we report the cases of two young boys presenting with confusional state as the main complaint. The possible pathogenesis of the different clinical presentation is discussed.

Keywords Headache · Pseudomigraine · Confusion · Neurologic deficit · Lymphocytosis · HaNDL

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Introduction

Bartleson and Colleagues in 1981 [1] described seven patients who experienced 3–12 episodes of headache accompanied by neurologic deficits and CSF lymphocytosis. The condition was self-limited in all patients, with headaches accompanied by neurologic deficits occurring over 1–12 weeks. Headache and neurological symptoms typically occurred together. Headache persisted after the neurological symptoms disappeared.

In 1995, Berg and Williams [2] described seven more patients and reviewed all the published cases resembling this condition, that they termed "headache with neurologic deficits and CSF lymphocytosis" (HaNDL). They found 40 cases, 56 % female and 44 % male; mean age of onset was 27 and in about one-third of the patients viral illness symptoms preceded the onset of the neurological symptoms. Fever was present in a third of the patients at the onset of the syndrome and, globally, viral illness symptoms and fever were present in about 50 % of the patients. A personal history of migraine was present in 24 % and a family history of migraine in 42 %. The main neurological complaints were hemiparesis, hemisensory changes, and aphasia when left hemisphere was involved. They stated "some patients had confusional episodes diagnosed as basilar artery migraine". 27 % of patients had a single episode, 30 % had repeated episodes with the same presentation, and 43 % had several episodes involving different brain regions. All the patients had a cerebrospinal fluid lymphocytosis, ranging from 16 to 350 cell per mm^3, with a mean of 136 cells per mm^3. Most patients had elevated CSF protein; the maximum total protein ranged 35–247 mg/dL. All CT-scans performed (30 pts) were normal and two out of five patients that performed MRI had "several nonspecific, small high signal areas on T2-

weighted images". "Several" patients underwent cerebral angiography, all normal, and one patient after the procedure developed a confusional state. Headache was reported as 'severe' in almost all of the patients and only one described the pain as "usual migraine". Most of the patients described the pain in the site of the cerebral region involved in neurological deficit. The headache had typical characteristic of migraine, with unilateral location, pulsating quality, severe intensity and accompanying symptoms like nausea and photophobia.

Similar characteristics were found in the 50 new patients reported from the Spanish group coordinated by Julio Pascual 2 years later [3]. They found similar mean age (28 years) but different gender distribution (68 % male vs. 32 % female); each patient experienced a mean of three episodes and all the episodes subset in a maximum of 49 days. The mean duration of the single episode was 5 h (range 5 min to 3 days) and 22 % of the patients had only 1 episode. 26 % of patients had a prior history of migraine. CSF pleocytosis ranged 10–760 cell/mm^3 and lymphocytic cells were >90 % in most samples.

Following these reports, in the second edition of the International Classification of Headache Disorders (ICHD-II), this disease was defined and classified as "syndrome of transient headache and neurological deficits with CSF lymphocytosis (HaNDL)" in group 7, code 7.8 [4]. Confusional state was not considered as a clinical symptom characteristic of the disease. In more recent years, several reports considered confusion as a clinical hallmark of the syndrome [5–11], but still the Committee of the International Headache Society does not consider this aspect among the clinical spectrum of neurologic deficits. Despite the different reports, the comment of ICHD-3 about the point 7.3.5 (syndrome of HaNDL) says "The neurological manifestations include sensory symptoms in about three-quarters of cases, aphasia in two-thirds and motor deficits in a little over half. Migraine-aura-like visual symptoms are relatively uncommon (fewer than 20 % of cases). The syndrome resolves within 3 months. In addition to CSF lymphocytosis (up to 760 cells/ml), there are elevations of CSF total protein (up to 250 mg/dL) in >90 % of cases and of CSF pressure (up to 400 mm/Hg) in more than 50 % of cases. The presence of a viral prodrome in at least one-quarter of cases has raised the possibility of an autoimmune pathogenesis." [12].

Here, we report the case of two young men that presented a confusional state as the first and main complaint of HaNDL syndrome.

Case 1

A 18-year-old male with a history of sporadic (5–6/years) headache episodes since he was 13, came to our attention. The pain was localized in the occipital region, lasted 20–30 min and presented with nausea and vomiting, photo- and phonophobia. Common analgesics were effective. In the past, at age of 2, he had one episode of febrile convulsions that did not require medical treatment.

Three years before the visit, he presented one episode with sudden onset of confusion, fever, headache and vomiting. The patient was hospitalized and underwent lumbar puncture that showed 22 cells/mm^3, most lymphocytes, normal glucose levels, and a minimal increase in protein concentration. PCR and antibodies for viral infections were negative or absent. CT scan and MRI study were normal, and EEG showed slow waves on posterior left regions. Patient was treated with antibiotic and antiviral therapy and then discharged in normal condition with the diagnosis of "Encephalitis".

Two months before our consulting, during school time, the patient presented confusion, headache, slurred speech, vomiting, and distal paresthesia at the arms. Fever was present at the onset of the symptoms but disappeared after 24 h. Neurological examination did not reveal focal deficits or signs of meningeal irritation. Examination of the cerebrospinal fluid (CSF) was impossible to obtain. Basal and enhanced gadolinium MRI was normal. EEG showed non-epileptic left anterior fronto-temporal theta-delta waves. Confusional state lasted for 4–5 h and headache subsided after 3 days. Patient was well at discharge.

Between the two confusional episodes, the patient presented some occasional headache attack, as the usual ones, but 'major' episodes were not reported.

Case 2

This previously healthy 22-year-old man presented with a 10-day history of fluctuating holocranial dull headache, lasting few hours. He had some headache-free days and 3 days before admission presented one episode of nausea and vomiting. The day of hospitalization he presented acute onset of a confusional state, psychomotor agitation, fluctuating level of consciousness between a hypervigilant state with occasional bursts of agitation and a drowsy state. He complained of diffuse and moderate headache without nausea or vomiting and photo- or phonophobia. He was afebrile. On neurological examination, he had no meningeal irritation signs, was clearly confused with poor attention and judgment, disoriented in time and place; no focal signs for neurological deficits were found. Fundoscopy was normal.

Lumbar puncture performed at admission was normal. Persisting the confusional state, spinal tap was repeated 6 days later and the examination disclosed lymphocytic pleocytosis (50/mm^3) with normal protein and glucose.

CSF bacterial, fungal, and viral cultures and PCR studies also proved negative on both the examination. Blood count, serum electrolytes, blood glucose, urea, and an extensive biochemical workup including liver, kidney, thyroid function tests as well as coagulation studies and serological tests for collagen, rheumatic, venereal, infectious, and parasitic disease were either negative or within normal range. Chest X-ray and head CT-scan were normal. MRI studies showed, on the DP-T2 and FLAIR sequences, one little aspecific hyperintensity alteration in the white matter of the left posterior periventricular region, without contrast-enhancement. EEG registration detected slow non-epileptic waves on the right temporal region.

The patient was given acyclovir (10 mg/kg 3 times a day) and ceftriaxone (2 g b.i.d.) intravenously since the first day of hospitalization. After the second lumbar puncture, he gradually improved and recovered completely in 2 weeks. Therapy was discontinued after 8 days of treatment, upon reception of the negative PCR results of the second CSF examination.

At the out-patient control 2 months later he was well and neurological examination was normal.

Discussion

Since 1995, when Berg and Williams described the first 40 cases (7 own patients and 33 from the published reports) and named the syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis "HaNDL syndrome", neurological deficits were identified as motor, sensory or language problems. In their description, confusional episodes reported by "some patients" were diagnosed as basilar artery migraine [2]. The migrainous nature of head pain was not so clear. Very few patients had an analytic description of their headache, and it was generally defined as "severe". Moreover, most patients did not have a history of migraine, and the prevalence of migraine in patients and their relatives was not different from general population.

In the 50 cases of Gomez-Aranda, headache characteristics were better specified [3]. Pain was moderate to severe in all the patients, throbbing in 81 %, bilateral in 59 %, and lateralized in 37 %. Duration ranged from 1 h to 7 days. Nausea isolated was registered in 6 % and nausea plus vomiting in 54 %. Photophobia and phonophobia were present in 16 % of all the patients. These aspects of the attacks seem quite far from migraine. No mention was reported about the presence of basilar artery migraine, and confusional symptoms did not appear in any patients. More evidences on the non-migrainous status of these patients come from other reports that describe acute episodes with mild or no headache [13–15]. In this view, the term "pseudomigraine" seems more appropriate than "migrainous" or "migraine like".

After the first description, many other papers reported confusional state as a clinical characteristic of HaNDL syndrome. In the cases described by Toth [16], confusion is the symptom of clinical presentation in half of the patients. Following these first reports, several other authors described confusional state as a clinical manifestation of HaNDL syndrome [5–7, 17–20], and more recently confusion was recognized as possible presentation symptom either in adults or in pediatric patients. It can be the result of a "functional derangement" in troncoencephalic and/or limbic structure, however, representing a neurological deficit of the brain of the patient.

Despite the increasing number of cases in the literature, pathogenesis remains uncertain and debated.

An inflammatory mechanism is likely to be involved, because the preceding symptoms of viral infection, flu-disease or fever reported in about one-third/half of patients, for the presence of fever at the onset of acute symptoms in some patients, for the CSF cells, and for the benign self-limited course. Even the lack of a strong personal and family history of migraine seems to support the inflammatory rather than migrainous hypothesis.

The similitude with familial (or sporadic) hemiplegic migraine—FHM (SHM)—may suggest a possible genetic or metabolic (channelopathy?) mechanism. FHM and HaNDL share the presence of sensory and motor deficits, transitory and duration of the acute phase, sometimes the presence of visual aura, or the sensitivity to cerebral angiography [2, 21, 22]. On the other hand, they differ in consistency of lymphocytosis, only sporadically reported in FHM, in the features of headache attacks, in the self-limited course of HaNDL, and in genetics [23].

A third possibility is that HaNDL syndrome could be an autoimmune disease. The inflammatory mechanism could be sustained by the presence of auto-antibodies [24] or by an immune "over-reaction" to some antigenic presentation [25, 26].

In conclusion, HaNDL syndrome remains a diagnosis of exclusion, to be consider whenever a patient with the suspicion of meningo-encephalitis or with focal/systemic reversible neurological deficits, among which confusional state may represent one of the opening symptoms, comes to our attention.

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

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CLINICAL ASPECTS OF HEADACHES

Headache in multiple sclerosis and autoimmune disorders

L. La Mantia · V. Prone

Abstract The headache may be considered among the neuropathic pain syndromes of multiple sclerosis (MS). Several studies have showed that it is more frequent in MS patients than in controls or general population. Headache may occur at the pre-symptomatic phase, at clinical onset and during the course of the disease. Tension-type headache and migraine without aura are the most common primary headaches reported in MS patients. The disease-modifying therapies, such as interferons, may cause or exacerbate headache, although the new available treatments do not seem to increase the risk of pain. Pharmacological and not pharmacological approach may be considered in selected patients to prevent the risk of headache, ameliorate quality of life and increase the adherence to treatment.

Keywords Multiple sclerosis · Vasculitis · Headache · Therapy

Introduction

Headache has been reported in patients with autoimmune disorders and in patients with multiple sclerosis (MS). In autoimmune disorders such as central vasculitis it has been mainly described at the onset of the disease. In MS patients, many studies have underlined that headache occurs more frequently than in general population, in any stages of the disease. It has been considered among the painful MS syndromes, such as trigeminal and occipital neuralgia and Lhermitte's sign [1]. A recent systematic review found that the overall pain prevalence in MS patients was 63 %, the most frequent painful syndrome being headache (43 %) [2].

However, conflicting results have been reported on the prevalence of headache in MS patients in general as well as during the course of the disease. Attention has been drawn to the occurrence of headache during immunomodulating therapies [3] and to the correlation with demyelinating lesions [4].

The aim of this study is to review the recent published data on headache in MS, to clarify the clinical aspects and the influence of MS therapies on headache incidence.

Headache in multiple sclerosis

Clinico-epidemiological aspects

Since 1950 [5] several studies have investigated the association between MS and headache. Variable frequencies have been reported, ranging from 4 to 69 % (Table 1), probably due to differences on study design and included population. In general, the results have showed that its prevalence is higher in MS patients (more than 50 %) than in controls [3]. Tension-type headache (TTH) and migraine without aura [6] are commonly reported. Ophthalmoplegic migraine-like [7], complicated migraine [8], cluster headache-like [9], may also occur in single cases.

The possibility of a link between migraine and MS was suggested over a half-century ago [10]. Both migraine and MS are relapsing disorders with occasional chronic evolution, are more frequent in women, may be due to a combination of environmental and genetic causes and are

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Table 1 Prevalence of headache in multiple sclerosis patients

References	Number of patients with headache (%)
Adams et al. [5]	389 (2.1)[a]
Compston and McAlpine [10]	250 (2.0)[a]
Abb and Schaltebrand [26]	1420 (37.5)
Bonduelle and Albaranes [27]	145 (5.5)
Poser et al. [28]	111 (8.0)
Kurtzke et al. [12]	234 (26.1)[a]
Watkins and Espir [29]	100 (27)
Clifford and Trotter [30]	317 (5.0)
Freedman and Gray [16]	1113 (4.0)
Rolak and Brown [31]	104 (52)
Pollmann et al. [32]	157 (40)
D'Amico et al. [24]	116 (57.7)
Gee et al. [17]	277 (56.6)
Vacca et al. [33]	238 (51.3)
Villani et al. [34]	102 (61.8)
Yetimalar [13]	21 (28.5)[a]
Martinelli Boneschi et al. [11]	428 (35.5)
Nicoletti et al. [6]	151 (57.4)
Putzki et al. [35]	491 (56.2)
Kister et al. [36]	204 (46)
Martínez Sobrepera et al. [37]	50 (69)
Kister et al. [38]	375 (28)
Kister et al. [1]	131 (69)

[a] At onset of the disease

influenced by hormonal factors. Furthermore, predisposing factors may be fatigue, insomnia, other neuropathic pain, depression and stress [1].

A correlation between type of MS and type of headache has been showed, migraine being more frequent in relapsing–remitting, while TTH in progressive MS. Females have a higher risk of migraine, while TTH seems to be associated with male sex and older age [11].

Headache at onset, already considered by Kurtzke [12] as a "minor" symptom, has been reported with variable frequencies, ranging from 1.6 to 28.5 % [3]. Headache has been also described in "asymptomatic MS" [13], but with radiological findings suggestive of the disease, before clinical conversion [14], currently called radiologically isolated syndrome [15].

Neuroradiological aspects

Freedman and Gray [16] found that half of the patients with headache during an attack of MS had clinical signs of brain stem involvement. MS patients with a plaque within the periaqueductal gray matter area have an increase in migraine-like headaches when compared to patients without this lesion [17, 18].

Severe headache associated with diplopia or trigeminal neuralgia, or cluster-like attacks have been reported in single patients with isolated brain stem demyelinating lesions, usually responsive to steroid treatment [19]. In one study, spinal cord lesions were more common in TTH patients [20]. Acute trigeminal autonomic cephalalgia, occipital neuralgiform pain may be symptomatic of demyelinating lesions of the brain stem or of the upper spinal cord (C1–C2) area [21].

Pharmacological aspects

Interferon-beta (IFN) is commonly used for long-term treatment of MS [22]. A systematic review showed that headache is significantly more frequent in MS patients treated with IFN as compared to placebo [23]. IFN may aggravate a pre-existing migraine or TTH and may precipitate their attacks [11]. In one study, about half of the patients with the novo headache after starting on IFN have developed migraine and the other half TTH [24]. Glatiramer acetate seems to have a minor headache-inducing potential [3].

It may be of interest that the new MS treatments do not seem to increase the risk of headache, considering the incidence of this adverse event, reported in the placebo-controlled clinical trials (Table 2).

Preventive therapies should be evaluated in selected patients to ameliorate adherence to treatment and quality of life. To the best of our knowledge, studies focused on the most effective preventive therapies are still not available.

Headache in autoimmune disorders

Autoimmune diseases are heterogeneous inflammatory disorders characterized by systemic or localized inflammation, leading to ischemia and tissue destruction. The headache is more commonly described in some diseases (e.g., giant cell arteritis and primary central nervous system vasculitis) and is mainly reported at the onset of the disease; the characteristic is often not specific, raising important diagnostic problems [25].

Conclusions

The main conclusion is that migraine is common in patients with MS, affecting more than 50 % of cases. Recent

Table 2 New drugs in MS: prevalence of headache in treated versus placebo groups

References	Therapy	Actively treated patients (%)	Placebo-treated patients (%)
Miller et al. [39]	Natalizumab	40	38
Kappos et al. [40]	Fingolimod	25.2	23
Gold et al. [41]	BG-12	<1	0
Miller et al. [42]	Teriflunomide	13	13

evidences confirm that it may occur at onset of the disease, similarly to what reported in other autoimmune disorders. In this case, a careful differential diagnosis is needed.

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

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CLINICAL ASPECTS OF HEADACHES

Migraine in perimenopausal women

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Abstract Hormonal changes during the reproductive cycle are thought to account for the variation in migraine occurrence and intensity. Although the majority of women and the specialists treating them do not consider migraine as a component of the climacteric syndrome, many women, in fact, do experience migraine during perimenopause. If a woman already suffers from migraine, the attacks often worsen during menopausal transition. Initial onset of the condition during this period is relatively rare. Women with the premenstrual syndrome (PMS) prior to entering menopause are more likely to experience, during late menopausal transition, an increased prevalence of migraine attacks. Hormone replacement therapy (HRT) can be initiated during the late premenopausal phase and the first years of postmenopause to relieve climacteric symptoms. The effect of HRT on migraine, either as a secondary effect of the therapy or as a preventive measure against perimenopausal migraine, has been variously investigated. HRT preparations should be administered continuously, without intervals, to prevent sudden estrogen deprivation and the migraine attacks that will ensue. Wide varieties of formulations, both systemic and topical, are available. Treatment with transdermal patches and estradiol-based gels is preferable to oral formulations as they maintain constant blood hormone levels. Natural menopause is associated with a lower incidence of migraine as compared with surgical menopause; data on the role of hysterectomy alone or associated with ovariectomy in changing the occurrence of migraine are till now unclear.

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Keywords Hormone replacement therapy · Menopause · Migraine · Surgical menopause

Introduction

Adult women experience migraine attacks more commonly than men by a ratio of three to one. Hormonal changes during the reproductive cycle are thought to account for the variation in migraine occurrence and intensity. It is widely believed that migraine symptoms improve with menopause, and many women await this phase of their reproductive life in the hope that headache attacks will eventually subside. Statistically this may be true, but menopause proceeds through various stages, each of which can differently influence migraine. Other factors that can affect migraine expression are whether a woman enters menopause naturally or has undergone surgery or has begun hormone therapy to counteract the many different symptoms menopause can cause on her body and mind. Here we discuss several of the many factors that can influence the clinical expression of migraine during menopause.

Menopausal stages and clinical evolution of migraine

The stage of reproductive aging workshop *STRAW + 10 criteria* (Table 1) delineates the stages of menopausal transition and postmenopause according to the characteristics of the menstrual cycle and serum sex hormone levels [1]. Two phases of *menopausal transition* are distinguished: the *early phase* is characterized by variable cycle duration ($\geq$7 days) and the *late phase* by amenorrhea, which may last between 2 and 11 months. Similarly,

Table 1 Some of the STRAW + 10 criteria for staging reproductive aging in women

	Menarche					Last menstrual period				
Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	early	peak	late		early	late	early			late
					PERIMENOPAUSE					
Duration	variable				variable	1-3 years	2 years (1+1)		3-6 years	Remaining lifespan
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	regular		Subtle changes in flow/ length	Variable length Persistent ≥ 7 day Difference in length of consecutive cycles	Interval of amenorrhea of ≥ 60 days				

postmenopause is divided into two phases: the *early phase* lasts between 5 and 8 years, is characterized by amenorrhea for $\geq$1 year and low serum estrogen and high follicle stimulating hormone (FSH) levels; the *late phase* is characterized by stably low ovarian hormone levels and continues for the rest of a woman's life. Finally, the term *perimenopause* refers to a period of 2–8 years between the last menses (*menopausal transition*) and 1 year after the last menses (*postmenopause*).

Migraine incidence peaks about age 50, coinciding with fluctuations in reproductive hormone levels which produce typical symptoms (the so-called climacteric symptoms) such as hot flashes, night sweats, vaginal dryness, irritability, sleep disturbances, and headache [2]. If a woman already suffers from migraine, the attacks often worsen during menopausal transition. Initial onset of the condition during this period is relatively rare [3]. Usually, symptoms will improve when a woman enters postmenopause and hormone levels have stabilized. About two-thirds of women migraineurs report that migraine intensity and frequency diminish significantly during postmenopause [4].

Headache intensity, as rated on a pain scale from 0 to 3 (0 = no pain, 1 = mild, 2 = moderate, 3 = severe), correlates with the different phases of menopausal transition. The percentage of women reporting moderate-to-severe headache pain is higher during both the early and late phases of menopausal transition than during postmenopause (24 vs. 36 and 32 %, respectively) [2].

The theory that best explains the hormone-mediated mechanism that triggers migraine is based on cyclical fluctuations in estrogen levels: the transient decrease in estrogen around menses triggers headache attacks (menstrually related migraine, pure menstrual migraine) in over 50 % of women [5, 6]. Estrogen fluctuations can also trigger migraine when estrogen deprivation persists for weeks or months, as occurs during late menopausal transition and early postmenopause [7].

Women with the premenstrual syndrome (PMS) prior to entering menopause are more likely to experience, during late menopausal transition, an increased prevalence of migraine attacks, which then diminish during postmenopause. In their study on migraine prevalence during menopausal transition, Wang et al. [8] found that, as compared with the patients in late menopausal transition, migraine prevalence was higher among those in early menopausal transition with a history of PMS (31 vs. 21 %, respectively). A history of PMS is considered a predictor for the development of migraine during the menopausal transition as it may indicate a higher sensitivity to hormonal fluctuations and greater predisposition to developing moderate-to-severe climacteric symptoms [2]. Furthermore, the intensity and duration of climacteric symptoms (hot flashes, palpitations, night sweats, and mood swings) can contribute to exacerbation of migraine attacks [9]. Worsening of migraine may also be secondary to concomitant conditions such as depression, which raises the risk of the development of chronic pain and insomnia that could increase migraine frequency [10, 11].

Migraine and hormone replacement therapy

Hormone replacement therapy (HRT) can be initiated during the late premenopausal phase and the first years of postmenopause to relieve climacteric symptoms. Wide varieties of formulations, both systemic and topical, are available. Treatment with transdermal patches and estradiol-based gels is preferable to oral formulations as they maintain constant blood hormone levels [12, 13]. Although the majority of women and the specialists treating them do not consider migraine as a component of the climacteric syndrome, many women, in fact, do experience migraine during perimenopause. The effect of HRT on migraine, either as a secondary effect of the therapy or as a preventive measure against perimenopausal migraine, has been variously investigated. HRT preparations should be administered continuously, without intervals, to prevent sudden estrogen deprivation and the migraine attacks that will ensue. In her preliminary uncontrolled study, MacGregor et al. [14] reported that, as compared with oral formulations, transdermal estrogen replacement in premenopausal and postmenopausal women was associated with improvement in migraine. Moreover, in an earlier study she found that elevated doses can more easily induce new migraine with aura or exacerbate attack frequency and intensity, whereas the aura disappears with the administration of lower doses or switching from an oral to a topical formulation [15]. Similar results were obtained by Nappi et al. [13] who reported that migraine worsened in women receiving an HRT with oral estradiol plus medroxyprogesterone acetate but did not change in those receiving HRT with a transdermal patch plus medroxyprogesterone.

During perimenopause, women with intact uterus should be offered protection against the development of atypical endometrial hyperplasia and endometrial carcinoma. HRT strategies include the association of progestogen for 12–14 days in many cases. However, combined-continuous estrogen and progestin therapy is better tolerated than cyclical administration.

In their prospective longitudinal study, Facchinetti et al. reported that HRT increases migraine attack intensity and frequency in postmenopausal women. By comparing with other therapy regimens, combined-continuous HRT was found to be preferable in migraine as is it associated with shorter duration of attack and fewer days of migraine [16]. Nand et al. [17] studied whether progesterone dose had an effect on migraine. They tested three different doses of medroxyprogesterone acetate combined with estradiol in three different groups but found no differences between them. Aegidius et al. [19] evaluated a sample of 5507 patients receiving HRT and found a strong association between therapy, both oral and topical formulations, and migraine. In their study involving a sample of 10,107 menopausal women, Misakian et al. [18] found a significant correlation between HRT and migraine (OR 1.42, 95 % CI 1.24–1.62). It is also possible, however, that women with migraine more often receive exogenous hormone therapy to prevent exacerbation of the condition [20, 21].

Contrary to guidelines on the use of estroprogestinic contraceptives, according to which migraine with aura is an absolute contraindication to take these drugs, migraine with aura is not an absolute contraindication to HRT when the route of administration is topical with low dose natural estrogens as they involve a minor risk of thromboembolism. If new migraine with aura occurs during HRT, a transient ischemic attack or other vasomotor events need to be excluded. If the aura recurs or worsens, HRT should be discontinued [22].

Migraine with aura is associated with a two-fold higher risk of ischemic stroke [23, 24]. In their meta-analysis, Spector et al. found an association between migraine and stroke, with an overall pooled effect estimate of 2.04 (95 %

CI 1.72–2.43). Subgroup analysis showed a difference between migraine with and without aura (OR 2.25, 95 % CI 1.53–3.33 vs. OR 1.24, 95 % CI 0.66–1.79). Despite the difference, the confidence intervals for the pooled adjusted ORs overlap, so that it cannot be considered statistically significant [24]. These data were consistent with another meta-analysis which reported a relative risk (RR) of 1.73 (95 % CI 1.31–2.29) for any type of migraine and ischemic stroke. Subanalysis of women aged >45 years showed a RR of 1.22 (95 % CI 0.88–1.68), not statistically significant. The RR rose to 10.0 (95 % CI 1.4–73.3) in women with migraine with aura who take estroprogestinic contraceptives and smoke. In women with migraine with aura, the risk of stroke was 2.08 (95 % CI 1.3–3.31), while the association with migraine without aura was not statistically significant. The risk of death due to cardiovascular causes in women with migraine was 1.60 (95 % CI 1.06–2.42) [23]. The limitations of these two studies were that they included data from men and women, without distinguishing between the sexes in some cases, and that no subanalysis of postmenopausal women was carried out.

In their prospective randomized study, Nappi et al. compared the effect of tibolone vs. continuous combined HRT on migraine in women requiring exogenous hormone replacement. Although tibolone did not reduce the number of days with migraine without aura, after 3 months of therapy it did significantly reduce the number of hours during which pain impeded activities of daily living and the amount of pain killer taken [25].

Migraine and surgical menopause

Natural menopause is associated with a lower incidence of migraine as compared with surgical menopause [4, 26, 27]. The difference was present also when these two groups of women were compared, considering only those with PMS [8]. In their study involving a large sample of postmenopausal women, Neri et al. reported an improvement in migraine as compared with the premenopausal period in two-thirds of cases, while tension-type headache improved less. In the women who had undergone ovariectomy, however, the course of migraine was worse than in those who had entered menopause naturally ($p = 0.003$). Among the women who had received surgery, 67 % reported worsening of migraine and 33 % improved. Among those who entered menopause naturally, 67 % reported improvement, 24 % no change, and 9 % worsening of their condition [4].

In a cross-sectional survey involving 986 hysterectomized women with one or both ovaries preserved and 5636 non-hysterectomized women with both ovaries, far fewer of the non-hysterectomized reported worsening of migraine compared to the hysterectomized group (8.8 vs. 15.1 %, respectively) [26]. This finding contrasts with previous observations and appears to emphasize only the importance of the presence or absence of the uterus.

In their study on migraine prevalence, Wang et al. also examined whether it was related to type of surgery: hysterectomized women with bilateral annexectomy were found to experience improvement as compared with hysterectomized women with unilateral annexectomy or only hysterectomized. The difference was not statistically significant, however [8].

Moreover, a study on compliance with HRT showed that migraine occurs more often in women with intact uterus who receive sequential HRT than in hysterectomized women receiving continuous oral estrogens [28].

Martin et al. reported that pharmacological ovariectomy with gonadotropin-releasing hormone (GnRH) analogs plus systemic estradiol appears to reduce pain severity but not episode frequency. The study included 21 women with migraine (age range 21–45 years) randomized to two treatment groups: one group received goserelin (a GnRH analog) then 1 month later a patch containing 100 mcg of 17 beta estradiol. The other group received a placebo patch. At 2 months into therapy, the group that had received the 17 beta estradiol patch reported improvement in pain intensity, disability, and severity but not in episode frequency [29].

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

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CLINICAL ASPECTS OF HEADACHES

Headaches attributed to visual disturbances

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Abstract Ocular pain due to ophthalmological diseases is most commonly associated with redness and inflammation of the ocular surface and surrounding tissues. Pain in a quiet eye can be referred as headache and can be the first sign of a number of ocular or orbital conditions. Painful symptoms may be considered non-specific if signs of targeted diseases are not identified. Collection of appropriate history of pain around the eye and associated symptoms or signs should be considered to recognize when ophthalmological examination is needed. Some painful diseases such as intermittent angle closure glaucoma, uveitis or optic neuritis, can lead to severe and permanent visual loss and require a prompt diagnosis and treatment.

Keywords Eye pain · Dry eye · Glaucoma · Uveitis · Refractive error · Optic neuritis

Introduction

Periocular pain may be a commonly referred symptom from many different diseases that can involve orbital and ocular structures and can be described as migraine when localized unilaterally, radiated to the temporal region or associated with photophobia, nausea and sensitivity to light.

Ophthalmologic evaluation is mandatory in cases that present with conjunctival injection and photophobia suspecting an ocular inflammation but also in case of a quite eye to look for visual loss, intraocular hypertension, ocular motility impairment, ptosis or eyelid retraction, proptosis or enophthalmos. The presence of a relative afferent pupillary defect (RAPD) strongly suggests unilateral optic neuritis [1, 2].

A careful history is necessary to specify onset and frequency of symptoms as well as the duration and severity of headache and their relationship with visual loss. It is also very important to detect some risk factors for ocular-related headache such as long lasting PC use or reading, unrevealed refractive errors or pain in some eye positions [3]. Instrumental tests would include standardized computerized visual field analysis, OCT, ultrasound and pattern-VEP; neuroimaging may be required to reveal orbital or sinus inflammation [4].

Asthenopia, refractive errors and strabismus

Asthenopia refers to a set of symptoms that include chronic frontal or peribulbar headache, eye fatigue or burning and blurred vision. This condition can be caused by uncorrected or residual refractive errors (hypermetropia or astigmatism), latent strabismus, impairment of accommodation or convergence. In cases of uncorrected hyperopic defects, headache can be the only symptom and may be present almost daily, during or after prolonged reading. Uncorrected refractive error can be compensated by accommodative effort associated to intraocular muscular spasm, resulting in ocular pain and convergent strabismus. Ophthalmological examination including refraction with cycloplegia is necessary. Proper correction of the refractive error leads to immediate alleviation or disappearance of symptoms including headache.

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Manifest or intermittent strabismus is non-associated with headache because, thanks to suppression, binocular diplopia, which would require muscular effort to merge the images, is not present. Asthenopic symptoms may also arise in cases of reduced muscular fusion capability as occurs with neuromuscular junction disease or myopathy. The occlusion of one eye leads painful symptoms to disappear.

Convergence deficiency causes difficulties in prolonged reading with latent or manifest strabismus (exophoria) that can be demonstrated by cover/uncover test. Convergence capability, that can be less than the closely age-related accommodation, may be improved by exercise in childhood. In cases of accommodative defect or whin altered convergence/accommodative convergence ratio (C/AC), it has to be distinguished between uncorrected hyperopia or presbyopia, presence of emotional or psychological factors, parasympathetic postganglionic palsy in Adie syndrome, third cranial nerve paralysis or iatrogenic cycloplegia.

Ocular surface disease

Bilateral chronic pain of the eye or retrobulbar region that typically worsens during the day after prolonged reading or PC use may indicate an ocular surface disease (dry eye syndrome). Symptoms can also be described as "ocular discomfort" or "sand in the eyes"; increased tearing, photophobia and mild conjunctival hyperemia, associated with secretion deposits at the base of the eyelashes, are usually noticed on awakening in cases associated with blepharitis.

Dry eye may be due to "quantitative tear deficit" related to sub-atrophy of the lacrimal glands due to age or to endocrinological (thyroid disease or menopause) or immune-mediated diseases (Sjogren), iatrogenic insufficient tearing (psychiatric drugs, anti-histamine drugs, NSAID) or tumors of the lacrimal gland. Another mechanism is "increased evaporation" related to lagophthalmos, ectropion, proptosis or low ambient moisture.

Dry eye treatment includes chronic use of artificial tears eventually associated with mechanical eyelid closure during sleeping [5].

Chronic tears insufficiency leads to blepharitis with involvement of the Meibomian glands, lipid layer changes and secondary increase of tears evaporation.

Tear disfunction can be diagnosed with biomicroscopic evaluation of the quality of tear film through measurements of the break-up time (BUT) and with the Schirmer test to assess the tear secretion. Blepharitis is diagnosed by evaluating the patency of Meibomian glands orifices, eyelid margin regularity and normal closure of the eyelids.

Corneal diseases

The cornea has a high concentration of free nerve endings; therefore, even a mild keratitis can trigger a sharp pain collected from fibers of the first branch of the trigeminal nerve. Keratitis is usually associated with severe and readily identifiable pain; it is headquartered in unilateral departure from the eyeball, involves the orbital region and it is partially reduced by closing the eyelids. In severe cases nausea may be present. Keratitis causes intense photophobia, tearing, foreign body sensation, conjunctival hyperemia, blurred vision and colored halos perception around light sources. The most frequent causes of keratitis are direct trauma due to foreign bodies or contact lenses, infections (especially herpes virus or acanthamoeba), sterile immune-mediated inflammation (e.g., staphylococcal hypersensitivity), exposure to lagophthalmos or post eyelid surgery, UV light, epithelial toxicity from chronic local therapy with preservatives (e.g., eye drops used for glaucoma treatment).

Slit-lamp biomicroscopy reveals loss of transparency of corneal layers and damage of corneal epithelial surface assessed through fluorescein staining. It is also important to evaluate the adequacy of eyelid closure, the absence of foreign body or pathological grow of eyelashes towards to the eye (trichiasis). According to etiologies, treatment may require lubricating agents, antibiotics, antiviral eye drops or ointment.

Scleritis and uveitis

Inflammatory diseases involving the sclera or the uvea are typically associated with ocular pain that may extend to the head [6]. Episcleritis, anterior scleritis and anterior uveitis are characterized by intense conjunctival hyperemia that accompanies severe pain especially during eye movements, photophobia, tearing, foreign body sensation and, in more severe cases, impairment of visual function. In posterior scleritis or posterior uveitis conjunctival hyperemia is usually very mild, while visual loss is often present with intense photophobia and ipsilateral pain that may be confused with migraine or trigeminal neuralgia. Reduced pupillary activity secondary to adhesions between the iris and the lens (posterior synechiae) may be present.

Scleritis and uveitis may represent clinical manifestations of immune-mediated (LES, Behcet disease, rheumatoid arthritis, sarcoidosis) or infectious diseases (tuberculosis, syphilis, toxoplasmosis, cat scratch disease, candidiasis, HSV, HZV, CMV). Complications of uveitis are intraocular hypertension, macular edema and retinal exudation or detachment. Full ophthalmological evaluation is required to search inflammatory cells or proteic material in the aqueous

humor (Tyndall phenomenon), presence of posterior synechia and to measure the intraocular pressure. Indirect ophthalmoscopy can reveal signs of vitreitis, retinal vascular changes, optic disc or macular edema. OCT analysis is useful to diagnose and monitoring posterior uveitis since it can provide thickness and reflectivity of the outer retinal and the choriocapillaris layers as well as measurements of peripapillary nerve fibers layer thickness. Ultrasound can be used to exclude deep scleral inflammation or serous retinal detachment. Treatment requires, when possible, etiological diagnosis since it should consider topical or systemic NSAID, glucocorticoids or immunosuppressive agents and, in specific cases, antibacterial, antiviral or antimycotic drugs.

Intermittent angle closure glaucoma

A very intense unilateral acute eye pain, sometimes accompanied by nausea and vomiting, is one of the prominent symptoms of acute glaucoma attack. This condition is due to a sudden blocking of the aqueous humor outflow from the anterior chamber through the trabecular meshwork into the conjunctival and scleral veins, which determines an abrupt increase in intraocular pressure [7]. Pain is associated with photophobia, tearing and colorful halos around lights correlated with corneal edema. Intermittent angle closure glaucoma may be misdiagnosed as migraine with aura especially when episodes fully recover in phases of quiescence. Reduction of the anterior chamber depth, worsened by evolved cataract or mydriasis, may lead to reduced aqueous humor outflow. High intraocular pressure causes pain, corneal edema, optic nerve dysfunction, impairment of retinal arteriolar flow and, therefore, visual function changes. The conjunctiva can be hyperemic and the pupil can be slow reacting or fixed mydriatic.

Gonioscopy, analysis of the optic disc and neuroretinal rim, UBM ultrasound, pachymetry and monitoring of the intraocular pressure in different hours during the day can be used to complete the diagnostic process. Evaluation must also include standardized automated perimetry and OCT analysis with quantitative evaluation of parameters of the optic disc. Treatment may include laser iridotomy or selective trabeculoplasty; surgical trabeculoplasty or trabeculectomy associated with local hypotonic therapy to reduce production of the aqueous humor or to facilitate its outflow.

Myositis and orbital inflammations

Trochleitis

Severe periocular pain radiating to the ipsilateral head, often in young women, variably accompanied by photophobia and nausea, which worsens during eye movements especially in down gaze and during reading, may be attributable to an inflammation of the trochlea [8]. The trochlea is a cartilaginous ring-shaped structure surrounded by a synovial membrane, localized in the superomedial orbit, which contains the superior oblique muscle tendon. It is innervated by trigeminal nerve and its inflammation is typically associated with localized pain that can be exacerbated by finger pressure. Trochleitis is often idiopathic and only rarely secondary to arthritis, systemic inflammatory diseases, immune-mediated systemic connectivitis [9]. Classification of primary trochlear headache can be difficult since this disease affects most commonly female and autonomic features of other headache syndromes can be present. Orbit CT scan with coronal acquisitions allows to diagnose calcifications, inflammatory trochlear thickening, while MRI with contrast shows its volumetric increase and inflammatory enhancement. Treatment may require local injections of lidocaine and dexamethasone.

Myositis and inflammatory orbital disease

Orbital myositis is a subgroup of primary or secondary inflammation, involving the extraocular muscles, typically affecting young women with recurrent episodes. The idiopathic form (orbital pseudotumor) is the second most common cause of extraocular muscle enlargement after thyroid-associated ophthalmopathy [10]. Patients with myositis, report pain during eye movements and binocular diplopia. Muscle involvement associated with autoimmune thyroid disease is typically characterized by limitation of upgaze or abduction, respectively, due to inferior rectus or medial rectus enlargement (restrictive myopathy). Other signs are: edema and hyperemia of eyelids and periorbital soft tissue; inflammation of the conjunctiva and caruncles; mild increase of the intraocular pressure, especially in upward positions. The pathognomonic sign of restrictive myopathy is retraction of the upper eyelid in primary position that does not follow the eyeball during downgaze (Von Graefe's sign); proptosis is often present, because of the increased muscular and adipose tissues volume due to inflammatory infiltration or fibrosis. Orbital MRI scan, performed with fat suppression and targeted sequences, can be used for differential diagnosis and to distinguish the active inflammatory from the inactive fibrotic phase of muscular involvement [11, 12].

With orbital cellulitis, pain is often referred to hemifacial area particularly when arising from infective sinus diseases. In these cases significant eyelid edema and hyperemia are present and are associated with ptosis, ocular motility impairment and eventually optic neuropathy;

malaise and fever may also occur. Differential diagnosis includes Wegener's granulomatosis and sarcoidosis as well as metastatic tumors (breast cancer is typically associated with enophthalmos due to infiltration of orbital fat tissues and muscles) [13]. Myositis must be treated with oral or intravenous corticosteroids; immunosuppressive agents when it is associated with immune-mediated disease [14]. Infective orbital cellulitis needs to be promptly treated with intravenous antibiotics.

Optic neuritis

Optic neuritis is due to inflammation with different etiologic mechanisms, the most common of which is represented by multiple sclerosis (MS). Spontaneous ocular pain exacerbated by eye movements is a typical symptom [15] that has been reported in 92 % of cases included in the Optic Neuritis Treatment Trial [16, 17]. Pain usually precedes by 2 or 3 days of central visual loss characterized by impaired visual acuity, color vision and central scotoma or generalized depression on automated visual field testing. The presence of an afferent pupillary defect (RAPD) characterizes unilateral optic neuritis. In about one-third of cases, the ocular fundus examination reveals edema of the optic disc (anterior optic neuritis or papillitis) which, in most cases, appears normal when the site of inflammation is distal (posterior optic neuritis). Optic disc pallor, focal or diffuse, is the sign of chronic phases and it can be detected about 4 weeks after the onset of symptoms. Pain, more frequently present in posterior optic neuritis, is related to sensory stimulation of meningeal sheath that are stretched and to inflammation of tissues around the optic nerve. It can be radiated to the ipsilateral face or head following the territories of sensory innervation which refer to the first two branches of the trigeminal nerve. The characteristic worsening of pain during eye movements is related to the insertion of the rectus muscles at the level of the meningeal coating of the optic nerve at the orbital apex [18].

Other than multiple sclerosis, optic neuritis can be associated with neuromyelitis optica (NMO), immune-mediated diseases (Behcet, LES, sarcoidosis), retinitis (neuroretinitis) or infectious diseases (cat scratch disease, syphilis, TBC, Lyme disease, viral etiology) possibly also involving other regions of the CNS (neurobrucellosis, meningoencephalitis, chlamydia) [19, 20]. Treatment requires intravenous corticosteroids in acute phase followed by immunosuppressive or immunomodulating therapy according to the underlying diseases. Specific treatment must be addressed for infective optic neuritis.

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

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CLINICAL ASPECTS OF HEADACHES

Adolescent migraine: diagnostic and therapeutic approaches

Roberto Sangermani · Agata Boncimino

Abstract Migraine prevalence increases from infancy to adolescence thus suggesting the important role of adolescent somatic and emotional maturation in supporting the disease. New family and society relationship and scholastic experiences represent more or less stress moments, producing risk factors for adolescent migraine. There are few studies adequately assessing migraine treatment efficacy in adolescent attack and prevention. Adolescent migraine's treatment with pharmacological and nonpharmacological therapies needs an individualized approach considering adolescent development degree, risk factors and trigger circumstances, psychological correlates and even psychiatric or other comorbidities.

Keywords Migraine · Adolescent · Psychosocial factors · Abortive therapy · Prophylactic treatment

Introduction

"Adolescent's definition has undefined features, without a clean break … it must be situated in the entire development's process of a person … it begins when the person shows to need less protection and attention from his family, when physiological and hormonal development begins to approach to the adult age, when he begins to take charge of his responsibilities, those responsibilities that will mark his life as an independent and autosufficient adult" [1].

An adolescent is neither a child nor an adult. He is an adolescent and as such he needs to be considered. The beginning and the end of the adolescence could differ basing on individual experiences.

In the last decades the migraine incidence is dramatically increasing [2].

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Epidemiology

According to Abu-Araef 10.6 % of children and adolescents aged 5–15 years suffers from migraine and migraine prevalence increases from 3.4 % at 5 years to 19.1 % after 12 years. Migraine occurs more frequently in male up to the age of 12 years, after which it becomes more common in girls with a ratio of 2:1 [3]. Occurrence of menarche increases the risk of headache and headache frequency. The prevalence of headache is higher in girls with menarche at 12 years or before than in those with menarche after 12 years and it has been well documented that the prevalence of migraine decreases with the increasing menarche age [4].

The increasing prevalence of migraine from infancy to adolescence suggests the important role of the complex somatic and emotional maturation of this age in supporting the disease in the adolescents.

Migraine has a negative impact on adolescents quality of life. In adolescent with migraine disability degree grows as much as the frequency and the intensity of migraine's symptoms increase. Whenever it happens, there is a shorter free time from episodic to chronic headache.

Frequent migraine can significantly impair an adolescent quality of life in about 60 % of affected patients, with an involvement similar to cancer or rheumatic arthritis [5].

Despite the high disability degree, major than adults, adolescents use less drugs and specific therapies than adults.

According to a big population study (12–19 years old patients), more than 80 % adolescents with chronic migraine did not consult their doctor in the year before the interview and 13 % of them did not use pain drugs during the last month. Not taking care of this significant disease, expose to the risk of chronic migraine and of adult discomfort. Midas questionnaire modified for children and adolescents (PedMidas), measures the migraine interference of scholastic, social and family activities and allows to objectively evaluate the real weight of migraine disease and the response to therapy [5–7].

Risk's factors for adolescent migraine

New family and society relationship and scholastic experience represent more or less stress moments for the adolescents, thus producing risk's factor for migraine. It has been well documented that chances of a successful treatment increase when intervening on specific factors of risk and on any comorbidity. Many studies have reported a close association between psychosocial factors, pain symptoms and headache [6].

The main risk's factors for adolescent migraine are dysfunctional, cognitive and emotional factors, social and environmental factors and behavioral ones. These risk's factors are usually expressed in adolescents with primary headache, but are more frequent in adolescents with migraine [6].

Cognitive and emotional factors are the most related with migraine risk and the symptoms are mainly anxiety, depression, low self-esteem. Stress possibly related to school is significantly related to migraine [7]. The association is even major when there is a comorbidity with specific learning disabilities or with ADHD. Others risk's factors for migraine have been widely reported such as experience of emotional, physical or sexual abuse, having a negative impact on affectivity.

Some adolescent situations, habits and behaviors have been reported as risk's factors for migraine [8].

Lifestyles well known as risk's factors for migraine are: regular use of nicotine (12–18 years, odd ratio (OR) 2.7), regular alcohol ingestion (13–19 years, OR 3.4), habitual coffee consumption (13–19 years, OR 2.4), being overweight (12–18 years, OR 1.4), low levels of physical activity (12–19 years, OR 2.2). Use of video games and digital media does not seem to be significantly related to headache.

Adolescent behaviors associated with migraine risk are: not much free time (8–15 years, OR 2.12), loss of satisfaction (12–13 years, OR 1.85), negative personal experiences (12–13 years, OR 1.85), bullying even rare or frequent (11–15 years, OR 1.40 and 1.86), feel badly treated by teachers (11–15 years, OR 1.24), little time to dedicate to pleasant activities.

Risk's factors related to familiar life are: high family expectations (12–13 years, OR 1.4), family conflicts (8–15 years, male OR 1.78, female OR 1.25), parental separation (13–15 years, OR 5.8) [8].

In diagnostic and therapeutic workup is important to speak with the adolescent about his family, social and scholar experiences, considering the presence of physical and psychiatric comorbidity, quantifying the related disability degrees, focusing on the possible negative impact on schooling [9].

The bases of treatment are to discuss about the possibility to face the stress causes in school, society and family and, if possible, to modify the risk factors. It is also important to suggest a regular sleep, a regular physical activity, drink and eat well, take part to scholastic and family activities.

Management

We should keep in mind that the adolescent migraines treatment must consider that adolescents have different characteristics due to their cognitive development. If for a young adolescent parents presence is important especially at the beginning of the visit order not to lose significant information for the diagnosis, for a more mature adolescent a direct access to the doctor and the therapies could be more essential [9].

Despite the high prevalence of adolescent migraine, the indications for pharmacological treatment in acute attacks and in prevention are poorly documented [5, 9, 11]. Proven efficacy elements in adult therapy are not often confirmed in adolescents, due to the positive placebo response in adolescents. In a meta analysis comparing drug/placebo in children and adolescents, the pharmacological treatment was not more efficient than placebo in decreasing pain in 50 % of trials and in resolving migraine in 47 % of trials [10]. The pathophysiology of migraine in youngster stems directly from what we have learned in adults. The reasons for a different response to placebo in adolescent migraine versus adult migraine are unknown, but it is possible to suppose that, almost in part, the physiopathology of adolescent migraine is different and more heterogenic than the adult one. This phenotypic difference could be due to the peculiar concentration of stress conditions, typical of adolescent experiences. In this context, the efficacy of medical intervention could be influenced even by a major placebo effect [10].

Acute treatments

Due to the fewer number of controlled studies on efficacy and safety of migraine therapies in adolescents, the chosen treatment mostly depends on doctor's personal preferences, sometimes using off label drugs. Abortive therapy is the mainstay of treatment when a child has a moderate-severe migraine. The symptomatic therapies for migraine attacks are: paracetamol, ibuprofen, ketoprofen, diclofenac, naproxen sodium, acetylsalicylic acid, indomethacin, prochlorperazine, ketorolac, triptans.

Paracetamol and ibuprofen have been specifically evaluated in infants and adolescents studies to asses efficacy and safety. Paracetamol efficacy is major than placebo after 1 h and equal after 2 h in decreasing pain but, in any case, minor than ibuprofen. Ibuprofen is more effective in decreasing pain than placebo after 1 and 2 h. In clinical practice, considering their high tolerance, paracetamol and ibuprofen should be considered as first chosen drugs [5, 10]. Adolescent drug-resistant migraine could be treated with triptans. Triptans pharmacokinetics is almost the same in adults and adolescents and even the efficacy results in treating the migraine attack are similar, but the adolescent high response to placebo could influence the statistical significance of triptans efficacy. There are no significant differences on maximum serum concentration and on peak time in triptans pharmacokinetics (almotriptan, sumatriptan nasal spray, zolmitriptan, eletriptan, rizatriptan) between adolescents and adults [11]. Triptans approved for adolescent migraine therapy (12–17 years old) are: nasal sumatriptan (off label in USA), nasal zolmitriptan (off label in USA), rizatriptan (off label in Europe) and almotriptan (off label in Europe). Oral sumatriptan, oral zolmitriptan, eletriptan, naratriptan, frovatriptan and sumatriptan–naproxen are prescribed as off label drugs.

Oral sumatriptan (50–100 mg) efficacy is not established in adolescent (8–16 years old) migraine treatment [10]. Nasal sumatriptan (20 mg) is more efficacious than placebo in decreasing pain after 2 h in ¾ studies and his ability in complete regression of the acute attack was major than placebo in ¼ studies. Giving 10 mg of intranasal sumatriptan in adolescent less than 40 kg weight has the same efficacy [10]. Nasal sumatriptan 20 mg safety and efficacy has been well documented for the adolescent migraine [10]. A crossover study showed the major efficacy of oral zolmitriptan (2.5 mg) in adolescents (6–18 years old) versus placebo, while the efficacy was equal to ibuprofen [10].

Assessment of oral zolmitriptan (2.5, 5 and 10 mg) efficacy in 12–17 years old adolescents was not confirmed in a bigger study, due to the high response to placebo. Effects of nasal zolmitriptan (5 mg) in 12.17 years old patients are higher in a controlled study when eliminating the rapid placebo responses [10].

Rizatriptan use in adolescent is also safe, being the efficacy assessment conditioned by the high response to placebo. Even in this case, studies eliminating the rapid response to placebo in 6–17 years old patients demonstrated the rizatriptan efficacy, dosing the therapy for weight (5 mg in patients less than 40, 10 mg in adolescents more than 40 kg) [10]. Almotriptan given to 12–17 years old adolescents shows a major efficacy than placebo at the 25 mg dose but only in decreasing pain in 2 h and not in removing pain [10]. Sumatriptan–naproxen in 12–17 years old adolescents is better than placebo and could be useful in treatment of patient refractory to triptan therapy alone [10, 11].

The adverse affects, similar among all molecules, are rare and include mainly asthenia, vertigo and xerostomia.

Pharmacological prophylaxis

Even if migraine is a common and disabling disease, often starting in adolescent period, only 1/3 of affected adolescents eligible to prophylaxis, receives indication on it [5, 12]. Moreover indications on migraine preventions are varied and there are not evidences based guidelines on migraine prevention in adolescents. Prophylaxis with daily drugs is recommended in frequent and severe migraine or in prolonged attacks with significant disability or even if treatment of the single attack is not well tolerated or is contraindicated or overused [5, 10, 12].

In prescribing drugs, the doctors could evaluate the presence of a comorbidity, to use the therapy as a better. For example, amitriptilin should be used if there are sleep problems, topiramate in case of overweight, gabapentin or pregabalin in fibromyalgic patients, valproate if migraine is associated with epilepsy. Propanolol should not be prescribed in depressed ad asthmatic patients or athlete; antidepressive and antihistaminic could increase the weight [9]. In 2014 FDA approved Topiramate use in migraine treatment for pediatric patients. Topiramate 100 mg is an effective and well-tolerated prophylactic therapy for adolescent migraine patient (12–17 years old). Monthly migraine attack and monthly migraine days are significantly decreased. At the dose of 100 mg adverse effect (paresthesias, abdominal pain, anorexia and upper respiratory tract infection) are few and well tolerated [13].

Amitriptilin and valproate efficacy has been well documented in open studies in adolescent, but not confirmed in controls studies with placebo [11, 12].

Valproate is as efficacious as propanolol and topiramate [12]. Propanolol has been used in comparative studies, with controversial results in efficacy, being his use limited by collateral effects with fall in pressure, depression and physical exercise asthma [12]. Flunarizin is more efficacy

than placebo in a double blinded study [11, 12]. Botulinum A toxin (11–17 years old patients) decreases the frequency and severity of migraine and improves the quality of life in two little retrospective studies [9].

Alternative therapies

Nutraceutical prophylaxis has been proposed and used as alternative to the traditional drug therapy and it is well accepted by adolescents and their families. Association of magnesium, riboflavin, Q complex with feverfew, ginkobiloba and butterbur extract is used for adolescent migraine; currently there are few studies on their efficacy [9].

Alternative measures as behavioral therapies (i.e. autohypnosis, biofeedback, relaxation techniques, agopuncture) have been proposed for migraine prophylaxis [9].

A recent review Cochrane evidenced the efficacy of nonpharmacological treatments (i.e. cognitive-behavioural therapy (CBT), biofeedback or combined therapies (CBT + biofeedback)) in 90 % of studies evaluating adolescents migraine [14]. Nonpharmacological interventions have a prolonged efficacy in decreasing pain and disability in chronic headache. Even is not possible to distinguish the efficacy in migraine versus others headache, psychological treatment could be considered in migraine treatment, with or without associated pharmacological measures [14].

Conclusions

Migraine could lead to important disability degree in adolescents, sometimes not well recognized.

Although the large use of different drugs for the adolescent migraine's prevention, there are still few controlled studies of efficacy, defining clearly the guidelines of the issue.

The evaluation of drugs efficacy with controlled studies is complicated by the minor duration of adolescents migraine attacks and by the elevate response to placebo.

Adolescent migraine needs to be treated with an individualized approach, thinking about the level of the development, the psychological and emotional factors and the possible presence of psychiatric co -morbidity.

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

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FICEF SYMPOSIUM

Migraine attacks in the pharmacy: a gender subanalysis on treatment preferences

P. Brusa · G. Allais · S. Rolando · F. Baratta · M. Giaccone · G. Bussone · R. Allais · C. Benedetto

Abstract 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. Epidemiological studies on migraine have consistently shown that migraine is far more common among women than men. This gender difference is also reflected in the higher percentage of women visiting a pharmacy to obtain treatment or advice for headache attacks. In this study, we further explored gender differences in healthcare-seeking behavior and use of migraine medications. The aim of the study was to determine whether women made better selective use of migraine medications and whether visiting a headache center for consultation and treatment reflected awareness of how best to manage their condition. Among the drugs usually taken for relieving head pain, there was no statistically significant difference between men and women in the routine use of NSAIDs (55.6 vs. 51.6 %) or ergot derivatives (8.7 vs. 9.3 %). Statistically significant differences emerged between men and women (27.9 vs. 35.4 %) in the use of triptans ($p = 0.003$; OR 1.41, 95 % CI 1.12–1.78) and in the use of combined medications (8.5 vs. 12.2 %) ($p = 0.029$; OR 1.49, 95 % CI 1.04–2.14) but not in the use of simple OTC non-NSAIDs. Less men than women sought professional medical care for managing migraine (65.7 vs. 72.4 %) ($p = 0.003$; OR 0.71, 95 % CI 0.57–0.89); more women than men sought treatment at a headache center (21.7 vs. 17.4 %) ($p = 0.044$; OR 1.31, 95 % CI 1.07–1.72).

Keywords Adequacy of care · Community pharmacy · Migraine · Triptans

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Introduction

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 [1]. The survey was supported by the Italian Headache Foundation (FICEF), 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 [2, 3] 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" [1, 4].

Epidemiological studies on migraine have consistently shown that the condition is far more common among

women than men. This gender difference in the prevalence of migraine is also reflected in the higher percentage of women visiting a pharmacy to resolve questions about medicines or obtain treatment or advice for headache attacks. Building on evidence from previous studies and our recent survey, we further explored gender differences in healthcare-seeking behavior and use of migraine medications. The aim of the study was to determine whether women made better selective use of migraine medications and whether visiting a headache center for consultation and treatment reflected awareness of how best to manage their condition.

Patients and methods

Between December 2012 and March 2013, a total of 9100 questionnaires were distributed to community pharmacies throughout Piedmont; 3065 correctly completed questionnaires were returned and the responses were entered into an electronic database for analysis. In all, 2154/3065 (70.3 %) of responders were women and 911/3065 (29.7 %) were men. The mean age was 44.1 ± 13.5 years.

The present study examined only the data for responders ($n = 2011$) who had an ID Migraine Screener test score that categorized them as having definite migraine ($n = 1042$) or probable migraine ($n = 969$). The ID Migraine Screener test consists of three questions [2–5]: nausea or vomiting (Yes, No), photosensitivity (Yes, No), limited daily activities during headache (Yes, No) and can be used to classify subjects into definite migraine (3/3 positive answers) or probable migraine (2/3 positive answers).

Women accounted for 77.2 % of responders with definite migraine (81.6 %) or probable migraine (72.4 %).

We then explored gender differences in the use of common medications for relieving acute pain according to five drug classes: nonsteroidal anti-inflammatory drugs (NSAIDs), ergot derivatives, triptans, combination drugs, and simple over-the-counter (OTC) non-NSAID pain relievers (e.g., acetaminophen). We also wanted to determine whether gender influenced the choice of the healthcare professional consulted for assistance and whether there was a gender difference in access to headache center services.

Statistical analysis

Data analysis was performed by calculating descriptive statistics presented as count and percentages. In order to verify the existence of significant associations between the different groups of respondent, identified by the ID Migraine Screener Test, a Chi-square test was performed for two rows by two columns contingency tables. Moreover, in order to quantify how strongly behavioral differences are associated with gender, odds ratios and their 95 % confidence intervals were calculated. All analyses were carried out using the Software IBM-SPSS Statistics Analysis System package (version 21).

Results

Among the drugs usually taken by the patients, there was no statistically significant difference between men and women in the routine use of NSAIDs (55.6 vs. 51.6 %) or ergot derivatives (8.7 vs. 9.3 %) for relieving acute headache pain. Statistically significant differences emerged between men and women (27.9 vs. 35.4 %) in the use of triptans [Chi-square test; $p = 0.003$; odds ratio (OR) 1.41, 95 % confidence interval (CI) 1.12–1.78] and in the use of combined medications (8.5 vs. 12.2 %) ($p = 0.029$; OR 1.49, 95 % CI 1.04–2.14) but not in the use of OTC non-NSAIDs. Less men than women sought professional medical care for managing migraine (65.7 vs. 72.4 %) ($p = 0.003$; OR 0.71, 95 % CI 0.57–0.89); far more women than men were more likely to talk with their general practitioner about their condition (40.5 vs. 35.9 %) ($p = 0.082$; OR 1.211, 95 % CI 0.976–1.503), though the difference was only nearly significant, and to seek treatment at a headache center (21.7 vs. 17.4 %) ($p = 0.044$; OR 1.31, 95 % CI 1.07–1.72).

Discussion

Pharmacists are often the first healthcare professional patients turn to for assistance in treating acute, prolonged headache. Recognizing pharmacists' key role in pain management, we conducted this questionnaire survey in Piedmont pharmacies to obtain data on migraine sufferers seeking help from their pharmacist. We focused our analysis on persons with migraine because of the greater disability associated with the condition than with tension-type headache, for example, and because of the increased risk of medication abuse and development of chronic pain in migraine sufferers who self-medicate. The primary area of focus in this subanalysis was gender differences in the use (or not) of appropriate medications for migraine attacks (particularly triptans, which are the drugs of choice in the treatment of acute migraine) and in access to specialist headache care.

Our data show that significantly more women than men use triptans (35 vs. 27.9 %) to relieve headache pain. Although studies on gender difference in the use of triptans are scarce, our data are consistent with those reported in a study on migraine prevalence (11,388 migraine episodes)

published in 2011 which found that women were significantly more likely to use triptans for episodic migraine attacks (OR 1.89, 95 % CI 1.64–2.16). Similarly, though on a far smaller scale, the percentage of women in our sample who took combined drugs for treating migraine was higher than that recorded for men. This difference is corroborated by the analysis of drug-dispensing data for triptans based on National Health Service prescriptions presented at community pharmacies throughout Piedmont during the study period. Data from the Regional Federation of Pharmacies (Federfarma Piemonte) show that 77.52 % (83,410/107,599) of the medicines dispensed were prescribed for women ranging in age from 40 to 59 years, in 60.49 % of cases (40–49 years in 33.32 % and 50–59 years in 27.16 %). Of note, however, is that the disproportionate use of triptans between men and women reflects mainly the fact that migraine prevalence is higher among women and only partially that women are better educated about the appropriate use of their migraine medications. Moreover, women are more likely to talk with their general practitioner about their condition and to visit a specialized headache center.

Given the gender differences in the self-treatment of migraine headache, with either medications or specialist consultation or both, community pharmacists can play a key role in assisting migraine sufferers manage their condition. Using their understanding of which type of headache can be safely self-treated and which should be referred to a physician for specialist care, pharmacists can provide counseling to both men and women to improve therapy adherence, particularly with triptan therapy or other prescription drugs for migraine headache.

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

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FICEF SYMPOSIUM

Migraine and lifestyle in childhood

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Abstract Migraine is one of the most frequently reported somatic complaints in childhood, with a negative impact on health-related quality of life. The incidence of migraine in childhood has substantially increased over the past 30 years, probably due to both increased awareness of the disease and lifestyle changes in this age group. Indeed, several conditions have been identified as risk factors for migraine in childhood. Amongst these, dysfunctional family situation, the regular consumption of alcohol, caffeine ingestion, low level of physical activity, physical or emotional abuse, bullying by peers, unfair treatment in school and insufficient leisure time seem to play a critical role. Nevertheless, there are only few studies about the association between migraine and lifestyle in childhood, due to previous observations specifically focused on "headache" in children. In this brief review, we will concentrate upon recent studies aimed to explore migraine and lifestyle risk factors in childhood.

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Keywords Migraine · Childhood · Children lifestyle · Trigger factors

Introduction

Migraine-related symptoms in childhood are a group of heterogeneous periodic and paroxysmal neurologic disorders [1]. Amongst these, cyclic vomiting, abdominal migraine and benign paroxysmal vertigo have been already defined by previous International Headache Society criteria as childhood periodic syndromes which are usually precursors** of migraine [2, 3]. Recently, the International Classification of Headache Disorders (ICHD-3 beta Version) [4] has replaced the "periodic symptoms" terminology with "episodic symptoms which are associated with migraine" and that will no longer be limited just to childhood. Similarly, headaches are not strictly related to adulthood but are very frequent during childhood, becoming more common during adolescence. Generally, headaches in childhood are subtended by primary headache syndromes with a significant negative impact on the quality of life and a high risk of developing in chronic and persistent form in adulthood [5]. Previous studies have emphasized the role of different risk factors for headache. Amongst these dysfunctional family situation, the regular consumption of alcohol, caffeine ingestion, smoking, low level of physical activity, physical or emotional abuse, bullying by peers, unfair treatment in school and insufficient leisure time seem to be strictly related to migraine. Risk factors identification can be very important in the therapeutic approach, because a multimodal program including lifestyle modification and psychotherapeutic intervention, are necessary in children who experience migraine attacks. Nevertheless, previous observations have

been focused on general "headaches" rather than on a specific migraine condition in childhood. For this reason, there are only few studies about association between migraine and lifestyle in children, to date. In this brief review, we will concentrate upon recent studies aimed to explore migraine and lifestyle-related risk factors in childhood.

Epidemiology

Migraine is the most important cause of headache leading to a substantial impact on physical and mental health as well as on school performance and quality of life in children [6]. The estimated overall mean prevalence of headache was 54.4 % and the overall mean prevalence of migraine was 9.1 % [7]. Totally, 10.4 % of the children, predominantly the girls, received the diagnosis of migraine when they grew older [8]. Indeed, it is well known that children frequently change their headache prevalence and characteristics, and even the type of headache shows important changes in the course of the adolescence and adulthood, independently from the use of either pharmacological or behavioural treatment or both. Specifically, age influences the expression of some of the accompanying symptoms in the migraine. For example, headache exacerbation by physical activity and occurrence of aura phenomenon were more common in females with migraine. Otherwise, vomiting and phonophobia are referred more frequently in males with migraine [9, 10]. However, some authors support that migraine and tension-type headache should not be considered two different clinical conditions in childhood, but two aspects of the same spectrum of headache [11]. Moreover, both migraine and tension-type headache phenotypes during childhood equally predict migraine in puberty with significant changes in accompanying symptoms and pain quality and localization [12]. It is noteworthy that migraine predisposition in children population may be related to genetic factors. Indeed, the most important explaining factor for the migraine manifestations in 10-year-old children seems to be a positive family history of headache attacks [13]. This finding was to be expected, because genetic predisposition has been shown in migraine but not in non-migrainous headache [14, 15]. However, the incidence of childhood migraine has significantly increased over the last decades. The causes of the increase in migraine prevalence are not completely understood or known at this time.

Migraine risk factors

However, they probably involve multiple factors. For example, an increased awareness of migraine in childhood could be related to lifestyle changes in this age group. *Lifestyle factors* such as overweight, physical activity and smoking are associated with headache in adults, but studies about the importance of risk factors amongst children are scarce and only few studies have so far investigated the impact of the combination of these lifestyle factors in relation to migraine amongst children [16]. Nevertheless, the *environmental* and *psychological factors* may play an important role in migraine with onset in preschool age, and diagnostic–therapeutic approaches must take these factors into account [17]. In this context, a very interesting study [18] assessed the evolution of idiopathic headache with early onset and investigated the influence of early *somatic disorders* and "*life events*" on the onset and the course of headache. The authors found a significant association between early somatic disorders and persistence of headache and also between the presence of *psychiatric disorders* at the end of follow-up and the persistence of headache. "Life events", on one hand, whilst not showing a significant association with the headache progression, may nevertheless influence the headache course in some children. According to the importance of "life events" in the genesis of migraine, *childhood maltreatment* has been associated with an earlier age of migraine onset and could shed a light on the role of stress responses in migraine pathophysiology [19, 20]. Similarly, a recent review [21] has shown that children with low socioeconomic status experience more frequently headache attacks. On the other hand, childhood maltreatment and low *socioeconomic status* may be indirectly associated with migraine. Indeed, above-mentioned impacting life events cast the children into situations of extreme questioning of their lives and contribute to several others risk factors for migraine such as depression, anxiety and substance abuse in the course of patients' life. Amongst *lifestyle-related risk factors* for migraine, a wide range of sleep disorders have been demonstrated in children [22]. Indeed, a correlation and comorbidity between migraine *sleep disorders* (such as insomnia, sleep apnoea, sleep bruxism and restless legs syndrome) exist due to common anatomical structures and neurochemical processes. Therefore, comorbid sleep conditions should be always considered in children experiencing migraine to improve management and to choose the most appropriate treatment [23]. Furthermore, migraine is associated with a number of *comorbidities* such as asthma, allergies and *obesity* [24, 25]. The latter is another chronic disorder that is very frequent in paediatric population. Previous studies, exploring the prevalence of obesity within a paediatric headache population, concluded that obesity seems to occur at greater frequency in children with migraine compared with the general population, showing a significant correlation between obesity and headache frequency and disability [26, 27]. Data from 2003 to 2006 demonstrated

that 16.3 % of children and adolescent fulfilled criteria for overweight [28]. Children with overweight/obesity have a greater prevalence of headache compared with non-overweight children [29]. Moreover, obesity (and often body mass index of the patients) seems to be related to both the high frequency and degree of migraine attacks and the prevalence of the migraine [30]. Interestingly, a higher body mass index (BMI) score in girls with headache than those without headache has been observed [31]. Similarly, a more recent study [16] found a higher overweight prevalence in adolescent with headache than in those without headache. Although a clear comorbidity between migraine and obesity exists, the real link between them is still matter of debate and the basic nature of this association is still under debate. Migraine and obesity can probably have some common pathophysiologic pathways and share different mechanisms (e.g., inflammatory mediators). It follows that, for children who are overweight or at risk for overweight, educational intervention may be necessary to improve weight control and subsequent migraine treatment outcomes. For some children, behavioural weight management may be mandatory to facilitate appropriate lifestyle changes (increasing exercise and improving adherence to dietary guidelines) for effective weight control and optimal migraine management [30].

Moreover, the paediatric obesity could be associated with several other comorbidities such as type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, hyperandrogenemia and hyperinsulinism, high blood pressure, proteinuria, nonalcoholic fatty liver disease, gallstones, orthopaedic pathologies, pseudotumor cerebri, and finally above-mentioned both psychosocial problems and sleep disorders [32]. Related to both obesity and overweight in childhood, diet has been shown to be a major risk factor in precipitation of headache in children with migraine [33]. *Dietary triggers* influence migraine attacks by means of the release of serotonin and norepinephrine, causing vasoconstriction or vasodilatation, or by direct stimulation of trigeminal ganglia, brainstem, and cortical neuronal pathways. The list of foods, beverages, and additives that trigger migraine includes cheese, chocolate, citrus fruits, hot dogs, monosodium glutamate, aspartame, fatty foods, ice cream, caffeine withdrawal, and alcoholic drinks, especially red wine and beer. Moreover, tyramine, phenylethylamine, histamine, nitrites and sulphites are involved in the mechanism of food intolerance headache. It is important to underline that underage drinking is a significant potential cause of recurrent migraine attacks in children, whereas immunoglobulin E-mediated food allergy is an infrequent and underrecognized but serious cause of migraine in children [34]. Finally, a recent study has demonstrated that an underreported but very important headache precipitant in children is the excessive gum-chewing [35]. Diet-related triggers should be investigated in the management of children with recurrent headaches.

Conclusions

Altogether, these observations emphasize the impact of several lifestyle-related risk factors for migraine in children. Physician and patient's awareness of lifestyle could have a significant impact on the quality of life of children with migraine. Indeed, the management of children with migraine should consist primarily of lifestyle triggers identification and avoidance [36]. Therefore, comorbid conditions should be always screened in children with migraine to improve patient management and to choose the most appropriate treatment.

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KEY LECTURE

The lesson of chronic migraine

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Abstract The hypothesis that central sensitization/allodynia is the common final mechanism responsible for the progression of migraine pain is supported by the possibility of tracing back to allodynic mechanisms the action of the main risk factors for chronic migraine validated by the recent literature. The comorbidity between migraine and idiopathic intracranial hypertension without papilledema is emerging as a new, commonly overlooked risk factor for migraine progression whose putative mechanism might also converge on the sensitization of central pain pathways. If headache progression always occurs at the end of a pathogenetic sequence typical of an individual susceptibility to allodynia, then the primary character of chronic migraine might be debated. Allodynia is not specific to migraine but is implied in the progressive amplification of pain after repeated stimuli, a universal adaptive phenomenon. Being largely conditioned by the individual comorbidity profile, allodynia may only in part be defined as primary in itself. Many migraine comorbid conditions, including a hidden idiopathic intracranial hypertension without papilledema, may emphasize susceptibility to allodynia and promote chronic migraine. These factors and comorbid conditions require to be individually assessed and adequately treated to optimize the therapeutic response.

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Introduction

There is a first issue we would make clear introducing the lesson of chronic migraine. Chronicity is a status from the beginning or a status achieved through a gradual conversion of an acute or recurrent pathological event to chronicity. This process will be defined as chronification. The relevance of such a statement is not only semantic but also substantial, since it takes into account the causative and/or the pathogenetic implications of the semantic distinction.

A pathological process may start as chronic or chronic progressive, and if so, causative factors and/or pathogenetic events are involved all over the time in the natural history of the developing illness. A radical difference concerns a process starting as acute or episodic (whose causative event or condition may be known or not) and shifting to chronicity; if so, the causative factor and/or the pathogenetic sequence towards chronicity have to be investigated "ex novo", in a broad perspective of single or multiple causative events. Such an investigation may or may not discriminate aetiology and/or pathogenesis of the initial illness and of the process of chronification.

The study of the comorbidity becomes crucial. Six years ago, we wrote [1] "Once epidemiologically established through population or community surveys, the study of the comorbidity direction and of the chronological patterns of associated clinical entities may offer relevant information from both a clinical and scientific point of view".

Comorbidity profiles of migraine offer a paradigmatic example to praise and highlight headache patient clinical

complexity, allowing the conversion of diagnosis from a validated cluster of symptoms to a person-centred clinical diagnosis. Herewith, the point is not only to emphasize comorbidity in the light of clinical complexity but also to look at comorbidity as a condition potentially involved as causative and distinguish between direct and indirect causative effects. While we suggest to read again our paper [1] mentioned above, we think that a few findings need to be pointed out to introduce the present topic: (1) comorbidity may be unidirectional or bidirectional; (2) a unidirectional comorbidity link (a disease increases the risk of the other, but not vice versa) may suggest that a condition is involved in the pathogenetic mechanisms of the other, while bidirectional comorbidity (each condition is a risk factor for the development of the other) suggests the presence of a shared physiopathological step (genetically determined or acquired) between the two conditions; (3) a strict chronological association between onset and/or remissions of comorbid conditions reduces the possibility of a coincidental association and (4) the identification of a related comorbid condition requires an acute awareness both in scientific research and clinical practice.

Let us talk now of chronic migraine (CM) to get the lesson we promised in the title of the lecture, but keeping in mind that when a disease shifts towards chronicity at a certain stage, this progression itself requires new etiopathogenetic investigation. This should be primarily addressed to the spectrum of the indexed disease comorbidities [1] and focused upon the reciprocal interplay of epidemiological, clinical and pathogenetic factors that arise by the coexistence of two distinct disorders in the same individual.

Table 1 Migraine: main comorbidity areas (from Bonavita and De Simone 2008)

Community-based evidence	Clinical series-based evidence
Psychiatric disturbances	Arterial hypertension
Stroke	PFO
Epilepsy	Sydenham's chorea
	Tourette syndrome
	Essential tremor
	Helicobacter pylori
	Lupus
	Raynaud's phenomenon
	Allergy
	Coeliac disease
	Obesity
	Vertigo
	Transient global amnesia
	Marfan syndrome

Table 1 gives a list of migraine main comorbidity areas. In the table, which is taken from the 2008 paper [1] we have cited more than once, there is no mention of the role of intracranial hypertension, to which we have deserved increasing effort in our research on chronic migraine.

Chronic migraine

Chronic migraine, a condition whose taxonomic collocation is still debated [2–6], represents a perfect example of the problems that arise when a headache is defined as primary. Still coded as a "migraine complication" in the 2004 revision of the International classification of headache disorders (ICHD) [7], CM has been recognized as a distinct migraine subtype in ICHD-III and is considered a primary condition, to the point that when it is associated with excessive analgesic intake, it has to be distinguished from medication overuse headache (MOH)—a condition classified among the secondary forms that is nosographically separate, although clinically indistinguishable [8]. The recently revised ICHD-III [6] has removed the need for an unsuccessful 2 months medication withdrawal to confirm CM diagnosis, and this will probably result in a less problematic recruitment of patients for clinical trials. Still, when excessive analgesics intake is present, it is recommended to diagnose both conditions; in case of favourable response to overuse withdrawal, the CM diagnosis will be subsequently discharged and vice versa. Therefore, also the recently revised ICHD-III distinguishes a progression "secondary" to medication overuse from a "primary" one, unequivocally excluding any other possibility [1].

Chronic migraine and analgesic overuse

It is interesting to note that a pre-existing episodic migraine is a necessary condition for developing chronic pain in the presence of medication overuse [9], although not sufficient, as it is only observed in a minority of migraine sufferers who take NSAIDs daily due to rheumatologic problems [10]. Drug overuse is noticed very often in the outpatient's department, although data reported on population studies indicate that 1/3 [11] to 2/3 [12] of subjects with chronic migraine do not abuse analgesics. After an isolated suspension of overuse, a return to an episodic pattern only occurs in 45 % of patients with probable MOH [13]. Taken all together, these observations suggest that overuse is neither necessary nor sufficient to determine the progression of pain. Consequently, it should be considered as a relevant risk factor for CM, becoming causative only in a part of migraine sufferers, furtherly sharing an unknown predisposition.

Which hypotheses may be formulated on the nature of this predisposition? From a biochemical viewpoint, there is evidence of a downregulation of the trigeminal serotoninergic receptors [14] and of a reduced serotonin synthesis at the level of the dorsal raphe nucleus [15], associated with analgesic overuse. A recent PET study in MOH patients has found an orbitofrontal hypometabolism persisting after analgesic overuse withdrawal [16]. This finding may indicate that a primitive hypofunction of the orbitofrontal cortex affects the development of MOH in a number of migraineurs. Alternatively, orbitofrontal hypometabolism could represent a long-term, or even permanent, effect of alterations in the pain pathways, produced by a long-standing overuse [16]. In a recent fMRI study on MOH patients, the right supramarginal gyrus and the right inferior and superior parietal cortex were hypoactive in course of medication overuse, but activity recovered to almost normal 6 months after withdrawal of the drug overuse. Findings of these studies indicate that there exists a modification of the pain network in MOH, and suggest that these changes are the consequence of a prolonged exposition to analgesics [17].

Which are the physiopathological correlates of such brain changes in subjects overusing analgesics? An important neurophysiologic study conducted on subjects with MOH shed some light on this issue. Through the simultaneous evaluation of the nociceptive blink reflex (nBR) and of the pattern reversal-evoked potential (PREP) before and after overuse suspension, it was possible to prove that (1) central sensitization is the causative mechanism involved in MOH; (2) it is reversible upon suspension and (3) it is not limited to the second order trigeminal nuclei neurons, but mainly affects the thalamocortical ones [18].

Hence, the mechanism through which medication overuse induces the progression of migraine could ultimately be reconducted to a facilitation of the central sensitization of pain pathways, a mechanism believed to be at the basis of allodynia.

Medication overuse, allodynia and migraine chronification

In contrast with episodic migraine, in which allodynia occurs only during the attack [19–21], chronic migraine is associated with allodynia also intercritically, suggesting that the neurons of the trigeminal nuclear complex are chronically sensitized in these patients [22]. A recent study indicates that allodynic phenomena are bilaterally detected during the intercritical phase in over 70 % of subjects suffering from chronic headache [23]. The frequency of the crises is related to central sensitization [24, 25], and there is evidence that an increased sensitivity to pain in migraineurs is a consequence of repeated pain attacks [26]. Allodynia has been recently included among the "putative" risk factors for migraine progression [27], and the findings reported herein confirm that the central sensitization of the pain pathways plays a causative role in mechanisms of migraine pain progression.

The question is how should we look at allodynia? As the specific mechanism leading to pain chronification in MOH or as a common final pathway in migraine chronification? The analysis of hypothesized mechanisms of action of the most important recognized risk factors for CM may help to clarify the role of allodynia in migraine pain progression.

Risk factors for migraine progression

Risk factors for migraine progression have been extensively studied in recent years. Besides analgesic overuse and central sensitization, the main recognized risk factors for migraine progression are elevated headache frequency at baseline, psychiatric comorbidity, obesity and female gender [28, 29]. Although it is not included in recent authoritative reviews on the topic, a comorbidity with an idiopathic intracranial hypertension without papilledema (IIHWOP) has been documented [30, 31], and it seems to be involved involved in progression of migraine [32] with a causative effect.

Could it be possible to bring back the heterogeneous risk factors to a common mechanism involving central pain pathway sensitization? What are the evidences available to sustain such a hypothesis?

High headache frequency at baseline

The high frequency of headache at baseline appears to be among the most predictive risk factors for migraine progression in prospective trials [28, 29]. This epidemiological finding is largely expected. In contrast with the fast adaptation of mechanoreceptors, the progressive lowering of nociceptors threshold that follows repetitive stimuli up to development of allodynia is, in fact, a universal characteristic of the pain perception, modulated by the complex central pain network and responsible for the unique defensive role of nociception. Actually, the facilitation of nociceptive pathways after repetitive stimuli that underlie allodynia might be regarded as an evolutionarily modelled process with a crucial adaptive value [33].

Obesity

Obesity is associated with a higher frequency and intensity of migraine recurrences [34] and increases up to five times its risk of chronification [35]. Obesity increases many

mediators involved in migraine pathophysiology, including interleukins and calcitonin gene-related peptide (CGRP). These mediators may increase the frequency, severity and duration of migraine attacks leading to central sensitization [36]. An association between obesity and allodynia has been recently found in CM patients [25], suggesting that obesity may directly modulate the individual susceptibility to allodynia.

Anxiety and depressive disorders

Migraine and psychiatric disorders are linked by a bidirectional comorbidity [37–39], each condition representing a risk factor for the development of the other [40]. This suggests a pathogenetic link between migraine and psychiatric disturbances [39]. Depressive and anxiety symptoms are more prevalent among frequent headache sufferers [41] and may anticipate a MOH [42]. Life stressful events [43, 44] and chronic exposure to stress [45] may promote migraine chronification. Recently, depression has been found independently associated with high scores on the cutaneous allodynia scales [24], suggesting again that the central sensitization of pain networks represents the shared pathogenetic mechanism underlying the epidemiological comorbidity linking migraine and psychiatric disorders.

The female gender

Women pay the higher tribute to both episodic and chronic migraine. The role of sexual hormones fluctuations in promoting migraine attack and the protective effects of pregnancy are well established. Allodynic cutaneous area after capsaicin injection is larger in women than in men, with a peak in the menstrual period and a minimum during the luteal phase. This strongly suggests that female sexual hormones and their physiologic fluctuations may have a role in the modulation of women susceptibility to allodynia [46]. This might account for many of the gender related epidemiological and clinical differences that characterize migraine.

Idiopathic intracranial hypertension without papilledema and chronic migraine

Idiopathic intracranial hypertension without papilledema (IIHWOP) is emerging as a new risk factor for migraine chronification [32, 47]. IIHWOP is considered an infrequent variant of the form with papilledema (IIH). However, it has recently been found that an asymptomatic variant of this condition, generally milder and with large intraday fluctuations, can be observed in most individuals with bilateral sinus stenosis, that represent about a quarter (23 %) of general population [48]. Conversely, all patients with normal sinus anatomy showed an intracranial pressure within normal limits. Accordingly, we have proposed [49] that a clinical and epidemiologic "continuum" may exist among (a) IIH with papilledema, an infrequently observed condition probably representing only the visible little part of a hidden and much larger phenomenon; (b) symptomatic IIHWOP, presumably largely misdiagnosed and/or underdiagnosed at present and (c) asymptomatic venous stenosis–associated intracranial hypertension, a completely hidden condition possibly highly prevalent among "healthy" individuals.

Indeed, that sinus stenosis is a reliable marker of idiopathic intracranial hypertension with a 93 % sensitivity and specificity has been shown since 2003 [50], but its pathogenetic role is still debated [51]. We have recently proposed a model of sinus stenosis-associated IIH pathogenesis, whereby a self-limiting venous collapse (SVC) feedback-loop leads to a self-sustained coupled increase of venous blood and cerebrospinal fluid (CSF) pressures [52]. The new, high pressure balance is reversible provided an adequate perturbation is carried at either side of the loop, such as sinus stenting [53] on one hand and CSF shunting or even a single lumbar puncture with CSF withdrawal [32] on the other. The SVC model may explain the long-standing remissions not infrequently observed in IIH patients after a single diagnostic LP.

IIHWOP and CM are often clinically indistinguishable [30–32]: they share a similar risk factor profile, have a higher prevalence of allodynic symptoms [54] and both respond to topiramate [55]. Moreover, they share a sinus stenosis prevalence much higher than expected [56, 57]. IIHWOP has been found in 10 to 14 % of CM patients in two clinical series [30, 31]. On the basis of such striking similarities and according to other robust available evidences [48, 56], we have proposed [47] that an overlooked sinus stenosis-associated IIHWOP, although highly prevalent among healthy subjects, in migraine prone individuals could represent a powerful and modifiable risk factor for migraine progression.

This hypothesis prompted us to investigate the opening pressure and the efficacy of a CSF pressure normalization by lumbar puncture (LP) in a consecutive series of 44 chronic migraine patients [32] with a history of progressive transformation of an episodic migraine into a chronic form, and proven unresponsiveness to medical treatments. The large majority (92.8 %) of our series of had significant sinus stenosis at MRV and all but 6 had an OP> of 200 mm H20 at LP. An immediate amelioration of pain, soon after the LP (or at the resolution of post-lumbar puncture headache), has been observed in 77.3 % of the sample. The benefit after a single LP with 20 to 30 mL CSF withdrawal—as predicted by the SVC pathogenetic model—

was maintained in more than half (54.6 %) of the cases at 2 months and in more than one-third (38.6 %) of the series at 4 months.

Our findings indicate that a sinus stenosis-associated IIHWOP mimicking a CM is a very common finding and that a raised intracranial pressure is involved in progression and refractoriness of migraine pain. However, our data furtherly support the alternative hypothesis [47, 49] that an overlooked IIHWOP, although with high prevalence among healthy individuals, in migraine prone subjects is a powerful and modifiable risk factor for the progression and the refractoriness of pain.

Which is the putative mechanism linking raised intracranial pressure and progression of migraine pain? As known, dural sinus veins have a dense trigeminovascular nociceptive innervation, and there is evidence that the cerebral venous congestion induced by the recumbent position may aggravate a running migraine pain [58, 59]. We speculate that the SVC induced simultaneous increase of fluids pressures at each side of the dural sinus wall might be sufficient to promote a continuous nociceptive trigeminovascular firing, at least in migraine prone individuals, responsible of the central sensitization of pain networks and of the development of allodynic symptoms and pain progression. Actually, allodynic symptoms have been found to be very prevalent in IIH patients [54]. Again, allodynia appears to be the key mechanism linking the raised intracranial pressure to the chronification of migraine.

Comments

Taken together, the above observations support the hypothesis that allodynia is involved not only in the physiopathology [60] and in the evolution and response to treatments of the migraine attack [20], but might also represent the final mechanism leading to the progression and refractoriness of the migraine pain, whichever be the putative promoting factor. Notably, allodynia is not specific to migraine but is involved in the spontaneous tendency to progression described in many different chronic pain conditions [61], such as neuropathic pain, fibromyalgia, chronic tension-type headache, low back pain, trigeminal neuralgia presenting with continuous interictal pain and complex regional pain syndrome.

The possibility of tracing back to allodynic facilitation, the mechanisms of action of the main CM risk factors and of its known promoting comorbid conditions, implies that allodynia should be regarded as the primary event leading to migraine chronification in the presence of a number of different predisposing or promoting factors. This model gives reason of the overlapping clinical presentation of CM, MOH and IIHWOP, three completely different forms of chronic headache converging on allodynia as the common final pathophysiologic mechanism.

Chronic migraine remains a perfect example of clinical complexity for which a diagnostic approach should include the meticulous research of any comorbid condition or factor with a known, or suspected, promoting role. The treatment of comorbid conditions is often mandatory. Analogously to MOH, also the hidden comorbid IIHWOP, we have found in almost all our CM cases was associated with a definite unresponsiveness to medical treatment that promptly remitted after intracranial pressure normalization by LP. Finally, there is evidence that the treatment of obesity [62] or of comorbid psychiatric disturbances [63] may improve the clinical outcome of CM patients carrying such comorbidities.

Conclusions

Chronic migraine may be included among those conditions the primary character of which might be debated: migraine progression should be seen as the event occurring at the end of a pathogenetic sequence typical of a peculiar individual susceptibility to allodynia. The latter is not specific to migraine but is implied in the progressive amplification of pain that always occurs after repeated nociceptive stimuli, a phenomenon with high evolutionary value. Being largely conditioned by the individual comorbidity profile, allodynia may only in part be defined as primary in itself. Many known comorbid conditions, including a hidden IIHWOP, may emphasize susceptibility to allodynia, particularly in migraineous individuals. These factors require to be individually assessed and adequately treated to optimize the therapeutic response.

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

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Emerging treatments for the primary headache disorders

Nathaniel M. Schuster · Sarah Vollbracht · Alan M. Rapoport

Abstract Migraine and cluster headache are common, episodic, often chronic and disabling disorders of the brain. Although there are many standard treatment techniques, none are ideal. This article reviews various novel pharmacologic and device-related treatments for migraine and cluster headache. Emphasis is given to recent advances in the development of monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) and its receptor, including promising results from phase 2 trials studying the safety and efficacy of LY2951742, ALD403 and TEV-48125, three anti-CGRP mAbs. Other new pharmacologic treatments discussed include the 5-HT1F receptor agonist lasmiditan and glial cell modulator ibudilast. Also reviewed is neuromodulation for migraine and cluster headache, including promising recent results of randomized controlled trials studying sphenopalatine ganglion stimulation, trigeminal nerve stimulation, transcutaneous vagus nerve stimulation, and transcranial magnetic stimulation. Finally, we discuss patch, inhaled, and intranasal methods of triptan and dihydroergotamine delivery.

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Keywords Headache treatment · Migraine · Cluster headache · Calcitonin gene-related peptide · Neuromodulation

Introduction

The primary headache disorders are common, episodic, often chronic and disabling neurovascular disorders of the brain. Although there are many standard treatment techniques, none are ideal. We will review various novel pharmacologic and device-related treatments for migraine and cluster headache (CH), such as monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) and its receptor, neuromodulation for migraine and CH, and newer, improved delivery methods for older acute migraine treatment medications.

Calcitonin gene-related peptide (CGRP)-targeted therapies

CGRP is a 37-amino acid neuropeptide that plays an important role in migraine pathophysiology [1]. Small-molecule CGRP receptor antagonists showed promise as migraine treatments in several acute care trials as well as in one preventive trial. However, these results were overshadowed by hepatotoxicity concerns beginning with the first preventive trial [2]. No small-molecule CGRP receptor antagonists are being developed at this time.

Three monoclonal antibodies (mAbs) targeting CGRP and one targeting the CGRP receptor are currently in clinical trials. The first 3 to announce results from phase 2 studies were LY2951742, ALD403, and TEV-48125.

LY2951742 (Lilly & Co.) is a fully humanized anti-CGRP mAb with a half-life of 28 days. In a phase 2 trial, 218 patients with 4–14 migraine headache days per 28 days (MHD/28d) were randomized to LY2951742 150 mg or placebo administered subcutaneously (SC) every 2 weeks for 12 weeks. The primary outcome was change in MHD/28d from baseline to weeks 9–12. Patients in the LY2951742 group experienced a reduction of 4.2 MHD/28d (62.5 % decrease) compared to 3.0 MHD/28d (42.3 % decrease) in the placebo group ($p = .003$). The LY2951742 vs. placebo responder rates were as follows: 50 % responder rates were 70 % of verum-treated patients vs. 45 % for the placebo, the 75 % responder rates were 49 vs. 27 %, and the complete response rates (no migraines in the 3-month trial) were 32 vs. 17 %. The most common adverse event (AE) was upper respiratory tract infections (17 % in experimental group and 9 % in placebo group). Injection-site reactions occurred in 20 % of the experimental group and 6 % of the placebo group. The serious AEs in the trial were deemed unrelated to the study drug and there were no concerning changes on serum laboratory testing, electrocardiography, or vital signs. Neutralizing antibodies were detected in 8 patients at screening and 20 patients at the end of the study [3].

ALD403 (Alder BioPharmaceuticals) is a genetically engineered, desialylated, humanized anti-CGRP IgG1 antibody with a 31-day half-life. In a phase 2 trial, 163 patients with 5–14 MHD/28d were randomized to receive either a single dose of 1000 mg ALD403 or placebo administered intravenously (IV). The primary efficacy endpoint was change in MHD/28d from baseline to weeks 5–8. The mean reduction in MHD/28d was 5.6 in the ALD403 group and 4.6 in the placebo group, with a significant intergroup difference favoring the experimental group ($p = .0306$). A post hoc analysis revealed that 16 % of the patients in the experimental group had zero migraines during the 12 weeks of follow-up, while none of the patients in the placebo group had a complete response. There were no significant differences between the 2 groups in treatment-related AEs, no infusion reactions and serum laboratory testing and vital signs revealed no concerning changes [4]. Limitations of this study include that only a single dose was administered to patients and that the study was designed for 5 % one-sided significance. Results of phase 2b studies using IV ALD403 for chronic migraine (CM) and SC ALD403 for frequent episodic migraine (EM) are expected in 2015.

TEV-48125 (formerly known as LBR-101, Teva Pharmaceuticals, Ltd.), is a fully humanized anti-CGRP mAb with a half-life of 40–48 days depending on the dose. In February 2015, Teva announced that TEV-48125, administered SC monthly for 3 months, met its primary and secondary efficacy endpoints in a phase 2b trial for treatment of CM ($\geq$15 headache days and $\geq$8 migraine days/month), with numerical results forthcoming. This would represent the first evidence of anti-CGRP mAb efficacy in CM. There is also an ongoing phase 2 trial involving TEV-48125 for high-frequency EM (8–14 headache days/month), with results expected in 2nd quarter of 2015.

The only anti-CGRP receptor mAb currently being studied is AMG-334 (Amgen), with 2 phase 2 trials currently ongoing, 1 enrolling patients with 4–14 migraine days/month, and the other enrolling patients with CM.

Given that CGRP is a potent vasodilator, it is worth noting that no animal or human trials on antibodies to CGRP or its receptor have revealed cardiovascular or cerebrovascular AEs thus far. Further studies monitoring for these critical concerns are needed.

Other novel pharmaceuticals for treatment of migraine

Serotonin receptor agonists

The 5-HT_{1F} receptor is located throughout the peripheral and central trigeminovascular system. Unlike 5-$HT_{1B/1D}$ agonists ("triptans"), 5-HT_{1F} receptor agonists ("ditans") do not appear to cause vasoconstriction in in vitro experiments. The first 5-HT_{1F} receptor agonist, LY334370, showed efficacy in a phase 2 study, but development was discontinued due to liver toxicity in dogs [5]. Lasmiditan (CoLucid Pharmaceuticals, Inc.) has been studied for acute migraine treatment in 2 phase 2b studies. In the oral lasmiditan phase 2b study, the 2-h headache response rates at four studied doses of lasmiditan ranged from 34 to 52 %, all of which were superior to the 21 % 2-h response rate in the placebo group ($p \leq .025$). These studies have shown no evidence of drug-related cardiovascular adverse effects or chest symptoms, and the drug does not seem to constrict blood vessels. However, some patients have developed dose-dependent side effects such as paresthesia, dizziness, fatigue, and nausea. Notably, dizziness was experienced by 26 % of subjects receiving the 100 mg dose vs. 0 % of patients receiving placebo [6]. A phase 3 trial studying lasmiditan for acute migraine treatment is planned. This study will include patients with cardiovascular risk factors, which is significant given that cardiovascular disease is listed as a contraindication in the manufacturer's package inserts for all 7 available triptans.

Glial cell modulators

Satellite glial cells in the trigeminal ganglion may play a vital role in peripheral sensitization during migraine. Ibudilast (MediciNova, Inc.) is a non-specific

phosphodiesterase (PDE) inhibitor, most potent at PDE-3 and PDE-4, which suppresses glial cell activation. It has been used in Japan for treatment of post-stroke dizziness and asthma. Two phase 2 trials studying oral ibudilast are ongoing; the first is enrolling patients with CM, and the second is enrolling patients with medication overuse headache and chronic daily headache. These studies will include monitoring of proposed biomarkers serum glutamate, CGRP, glial fibrillary acidic protein and S100β. Ibudilast is also being studied for use in progressive multiple sclerosis, amyotrophic lateral sclerosis, and drug dependence.

Innovative neuromodulation devices

Sphenopalatine ganglion stimulator

The sphenopalatine ganglion (SPG) is a collection of neuronal cell bodies located in the pterygopalatine fossa containing synapsing parasympathetic nerves and post-synaptic sympathetic fibers that pass through it to their end organs. It appears to be involved in the pathogenesis of CH and likely also contributes to the autonomic dysfunction seen in migraine. The Pulsante SPG Neurostimulator (Autonomic Technologies, Inc.) is an on-demand, remote-controlled SPG stimulator that is placed over the SPG using a minimally invasive, trans-oral approach under general anesthesia. During a recently completed European study on chronic cluster headache (CCH), 566 cluster attacks were treated randomly with either full, sub-perception, or sham stimulation. Among the 28 patients who completed the experimental course, 68 % experienced either ≥50 % decrease in pain within 15 min during attacks, ≥50 % decrease in attack frequency, or both. Pain relief was achieved in 67 % of attacks treated with full stimulation, vs. 7 % of attacks treated with sham stimulation and 7 % of attacks treated with sub-perception stimulation. The study was well tolerated, with transient sensory disturbances and pain being the most common AEs [7]. An 18-month, long-term follow-up study has been reported and a larger, randomized, controlled trial (RCT) is currently enrolling up to 120 patients in the US. A CM study is ongoing in Europe.

Trigeminal (supraorbital nerve) stimulator

Transcutaneous electrical stimulation of the supraorbital branches of the trigeminal nerve using the Cefaly device (STX-Med) demonstrated efficacy in a multicenter, sham-controlled RCT enrolling 67 patients with at least 2 migraine attacks per month. Stimulation was applied bilaterally to the supraorbital and supratrochlear nerves. The treatment group outperformed the sham group significantly in reduction of headache days, migraine attacks, and use of abortive medications [8]. However, early consensus in clinical practice is that this treatment is less promising for migraine prevention than the results of the trial suggest; paresthesias produced are quite uncomfortable according to some patients who have tried the stimulator outside of the trial.

Transcutaneous vagal nerve stimulator

The gammaCore device (electroCore LLC) is a non-invasive vagal nerve stimulator (nVNS) which transcutaneously stimulates the cervical branch of the vagus nerve. It has shown promise for the treatment of CCH. In a RCT with 93 evaluable patients, nVNS plus standard of care (SoC) outperformed SoC alone in the acute and preventive treatment of CCH. Patients in the experimental group self-administered 3, 90-s stimulations twice daily for preventive treatment, as well as optional acute treatments for cluster attacks. A sham control was not used. The experimental group experienced a reduction of 7.6 cluster attacks/week vs. reduction of 2.0 attacks/week in the SoC group ($p = .002$). Patients used fewer sumatriptan injections and less oxygen therapy in the arm of the study that included nVNS [9]. The device is currently approved for use in the EU, UK, and Canada, with approval in the US anticipated this year.

The gammaCore device is also being studied for treatment of migraine. In an open-label, single-arm, multiple-attack pilot study, 27 patients with EM treated 80 migraine attacks acutely with 2, 90-s nVNS treatments [10]. In double-blind, sham-controlled pilot RCT using nVNS to prevent CM, 59 patients received 2, 90-s stimulations 3 times a day for 2 months, followed by a 6-month open-label phase [11]. These pilot studies suggested that nVNS was safe and well tolerated for acute and preventive treatment for migraine. Further studies are warranted.

Occipital nerve stimulator

Occipital nerve stimulation (ONS) has demonstrated promising preliminary results in CCH. Fifty-nine patients across 6 open-label studies have experienced a decrease in attack frequency >50 % in 75 % of patients, and 63 % of patients would recommend the procedure [12]. ONS has also been studied for intractable CM, with promising open-label studies leading to the ONSTIM trial (Medtronic). This multicenter, blinded, feasibility RCT missed its primary endpoint by achieving a 3-month 50 % responder rate of 39 %, although greater than half of the participants achieved a ≥30 % reduction in headache severity or frequency with ONS [13]. The OPTIMISE trial, testing the Boston Scientific Corporation Precision System in the management of intractable CM, is ongoing.

Transcranial magnetic stimulator

Transcranial magnetic stimulation (TMS) creates fluctuating magnetic fields applied externally to the scalp to induce a current in the underlying cerebral cortex. Single-pulse TMS (sTMS) has been studied as an abortive treatment for migraine with aura, while repetitive TMS (rTMS) is being studied for preventive treatment of migraine.

A portable sTMS device, SpringTMS (eNeura Inc.), was approved by the FDA in December 2013 for patient-administered acute treatment of migraine with aura. In a phase 3 trial, 267 participants were randomized to administer 2 pulses about 30 s apart of either sTMS or sham stimulation to the occiput within 1 h of aura onset. The pain-free response at 2 h after treatment was 39 % in the sTMS group and 22 % in the sham group ($p \leq .02$) [14]. A new model that will be marketed in the US is being developed.

New delivery methods for old migraine acute care medications

In an attempt to outrace cutaneous allodynia, to bypass migraine-induced nausea, vomiting, and gastroparesis, or to extend duration of delivery in patients prone to recurrence of migraine, reformulations of existing migraine acute care treatments have been developed. Examples that are already commercially available include diclofenac potassium powder for solution that dissolves in water (Cambia in the US, Voltfast in Europe) and intranasal formulations of sumatriptan, zolmitriptan and dihydroergotamine (DHE).

The Zecuity battery-powered, transdermal sumatriptan patch (Teva Pharmaceuticals, Ltd.) uses an electrical current to deliver sumatriptan across the skin into the SC space, bypassing the gastrointestinal system. It maintains therapeutic drug levels twice as long as a 50 mg tablet of sumatriptan and four times as long as the 6 mg injection, but is slower to become effective. It outperformed placebo for the primary endpoint of 2-h headache freedom (18 vs. 9 %, $p = .0092$); this superiority was maintained at all time points up to 12 h post-patch administration (all $p = \leq .01$) [15]. As of February 2015, Teva is advertising that the Zecuity patch will be available soon.

The Semprana Tempo inhaler (Allergan), an orally inhaled DHE formulation, was superior to placebo in its 4 co-primary endpoints including 2-h pain relief (58.7 vs. 34.5 %, $p \leq .0001$) and it demonstrated equal efficacy in patients with and without allodynia in its phase 3 trial [16]. However, FDA approval has been delayed by technical obstacles in manufacturing and filling the canisters.

The OptiNose (AVP-825) breath-powered intranasal delivery system (Avanir Pharmaceuticals) improves the nasal absorption compared to liquid nasal sprays. Blowing against resistance elevates the soft palate, preventing the powder from entering the nasopharynx. This technique coats a large surface area of mucous membranes in both nostrils leading to rapid absorption. A phase 3 trial studied 11 mg sumatriptan powder delivered via the OptiNose device. The 2-h pain relief primary endpoint was superior to placebo (67.7 vs. 45.2 %, $p = .02$) and to historical rates of response to oral sumatriptan. Its rate of onset appeared to be faster than oral sumatriptan's but less quick than that of SC sumatriptan. It also demonstrated a lower rate of side effects than the oral and SC formulations, which is probably attributable to the lower peak serum concentration [17]. In November 2014, the FDA requested that Avanir perform a new human factors validation study, delaying release of the product until later in 2015.

Conclusion

Results from recent clinical trials create optimism that new pharmaceutical and device-assisted neuromodulation treatments will expand our armamentarium of effective, well-tolerated treatments for patients with migraine and CH.

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Conflict of interest N.M. Schuster and S. Vollbracht have no actual or potential conflicts of interest in relation to this article. A. Rapoport serves on the speaker's bureau of Depomed and serves on the advisory board of Depomed, Doctor Reddy's, Impax, Merck, Teva and Winston Laboratories Inc. He is an editor of CNS Drugs, Headache, and Neurology Reviews.

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Electromyography data in chronic migraine patients by using neurostimulation with the Cefaly® device

H. A. Didier · P. Di Fiore · C. Marchetti · V. Tullo · F. Frediani · M. Arlotti · A. B. Giannì · G. Bussone

Abstract The objective of this observational study is to report clinical and instrumental results obtained in 23 chronic migraine sufferers treated with transcutaneous neurostimulation with the Cefaly® device. The electromyography (EMG) parameters of the patients monitored before and during neurostimulation with the Cefaly® device showed a significant increase in the EMG amplitude and frequency values in the frontalis, anterior temporalis, auricularis posterior and middle trapezius muscles. The Cefaly® device could act on the inhibitory circuit in the spinal cord thus causing a neuromuscular facilitation and may help reduce contraction of frontalis muscles.

Keywords EMG (electromyography, K7 electromyograph) · TNS (neurostimulation) · Supraorbital nerve · TA (anterior temporalis muscle) · FR (frontalis muscle) · TP (auricularis posterior) · TR (middle trapezius)

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Introduction

The objective of this study is to examine the potential role that surface EMG can play in detecting myoelectrical signals with a transcutaneous neurostimulator called Cefaly® placed on the supraorbital nerve and recording frontalis, anterior temporalis, auricularis posterior and middle trapezius muscles.

Patients and methods

The study included 23 patients, 18 women and 5 men (whose mean age was 44 years, ranging from 20 to 76). All 23 patients were chronic migraine sufferers who met ICDH-3 beta 2013 criteria [1]. 14 out of the 23 subjects were overusing medications.

Migraine days were on average 20 a month. All patients signed the written informed consent.

The results of clinical and neurological examinations were normal for all patients. None of them had serious health problems or psychiatric disorders. All subjects were treated with prophylactic antimigraine drugs.

All 23 patients underwent a neurological examination and surface EMG of frontalis, anterior temporalis, auricularis posterior and middle trapezius muscles at rest

before using the Cefaly® device and during the neurostimulation.

The test was carried out using a K7 electromyograph and Au-C1 Duotrode bipolar electrodes (by Myotronics-Noromed Inc., Seattle, WA).

The parameters observed were: amplitude (μV), mean frequency (Hz) and median frequency (Hz) of the myoelectrical signal.

With regard to the neurostimulator (the Cefaly® device), programmes 1 and 2 were used, respectively, recommended for 'crisis treatment' and 'prevention'. The stimulation parameters were as follows: Programme 1 is 250 μs long–16 mA max intensity–100 Hz frequency; Programme 2 is 300 μs–16 mA max intensity–60 Hz frequency.

All patients experienced symptoms of paresthesia and tingling on the area of neurostimulation (frontalis muscle) and the impulse intensity was just below the pain perception threshold.

All subjects underwent surface EMG evaluation of their frontalis, anterior temporalis, auricularis posterior and right and left trapezius muscles, using Scan 18 in compliance with current guidelines set by Jankelson [2].

Bipolar, skin, adhesive and disposable electrodes (duotrodes) were placed over the muscles to be examined, specifically the anterior temporalis, the frontalis at the level of the motor point located along the vertical axis of the eye pupil, the auricularis posterior just above the mastoid process, the trapezius at the level of its intermediate region, using as landmarks four fingers laterally from the VII cervical vertebra.

The evaluation of the myoelectrical signal was conducted at rest and during the neurostimulation with the patient seated and resting their elbows on their knees, inviting them to be as relaxed as possible. The objective is to assess possible differences between the myoelectrical signal at rest and electrically elicited in the above mentioned muscles. The evaluation regarded the myoelectrical activity at rest 2′ from EMG start and at the 14th minute, choosing two time windows pre-stimulation and during the stimulation which lasted 1.44′ as showed in Figs. 1, 2 and 3. Each patient gave a pre-stimulation value for the right muscles and one for the left ones and as many during the stimulation for a total of 16 values.

Statistical analysis

Electrophysiological data were analyzed with the two-tailed Student's t test. The requested statistical significance level is $p < 0.01$.

Results

Our study on temporalis, auricularis posterior and trapezius muscles has indicated a significant difference in frequency domain parameters between values recorded at rest and

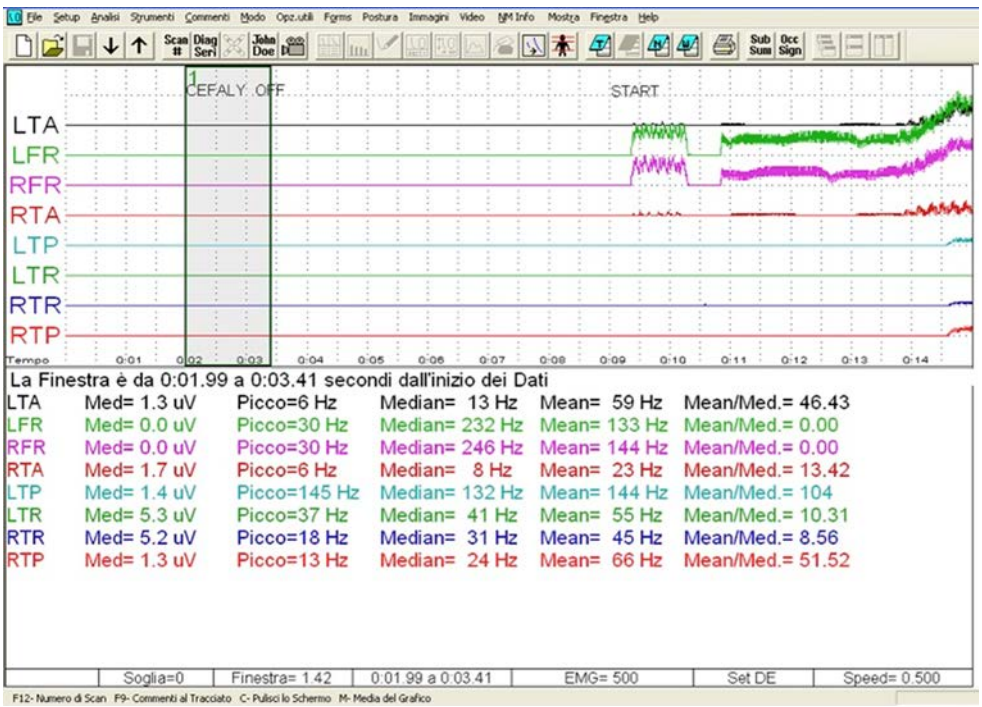

Fig. 1 With Cefaly® off and at the response of the eight muscles (auricularis posterior and trapezius muscles respond approximately 5 s after frontalis and temporalis)

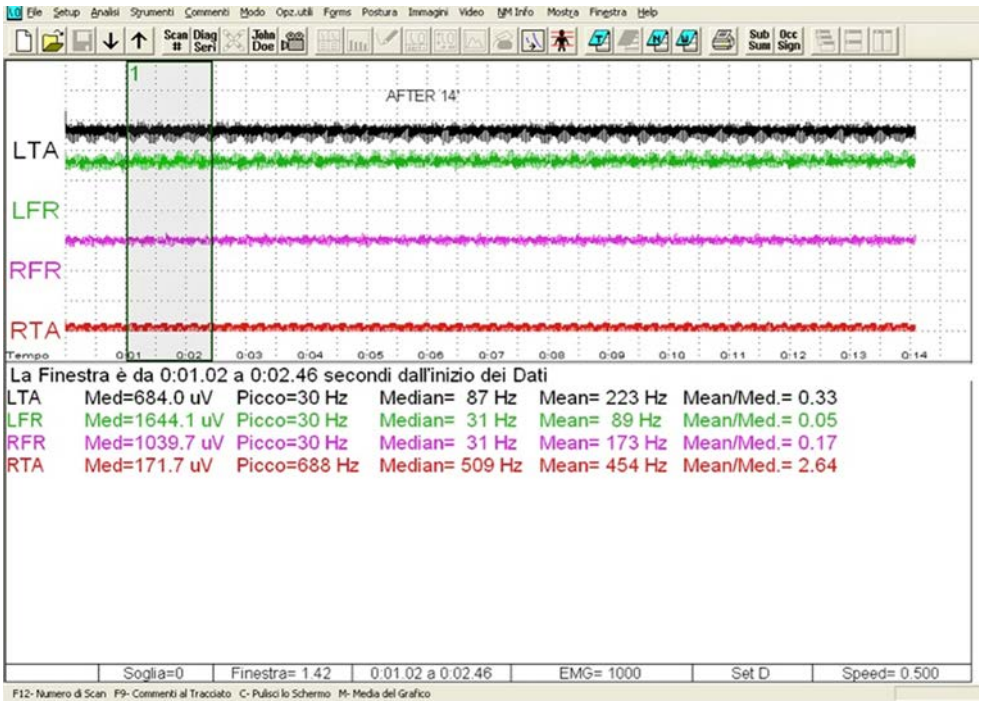

Fig. 2 With Cefaly® on, 14 min later, monitoring frontalis and temporalis muscles

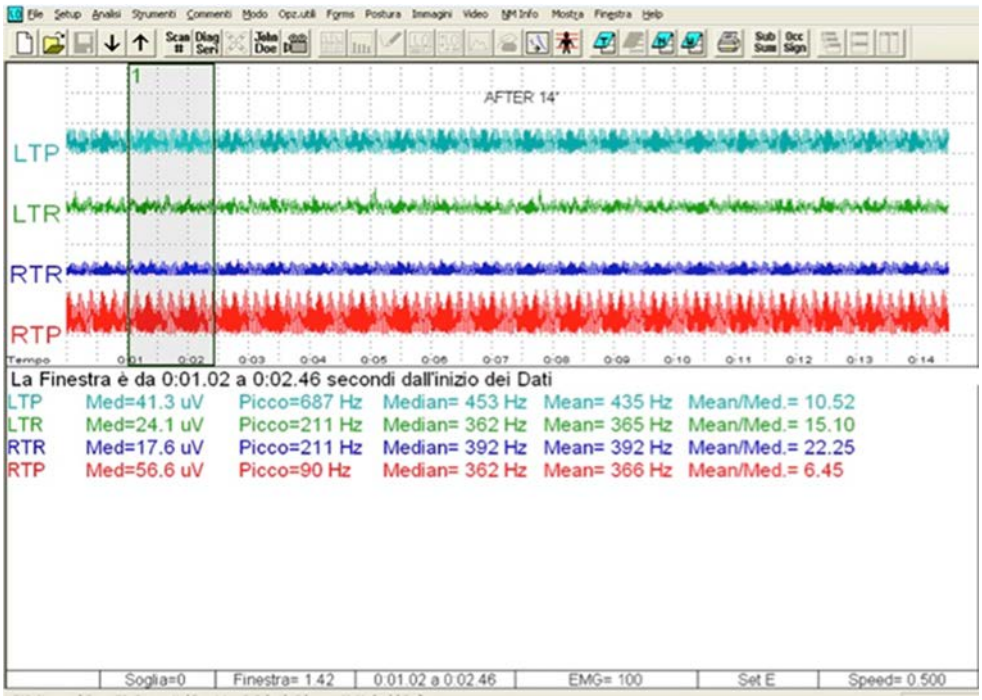

Fig. 3 With Cefaly® on, 14 min later, monitoring auricularis posterior (TP) and trapezius (TR) muscles

during neurostimulation ($p < 0.0001$). On the frontalis muscle, the difference is significant in amplitude parameters ($p < 0.0001$) between values recorded at rest and those during neurostimulation. The median frequency values do not show a p value which can be statistically significant (p 0.248 for the left frontalis muscle and p 0.083 for the right frontalis), however, the sample of patients has shown a reduction in the median frequency, although not significantly, between before and during neurostimulation from 184.4 Hz pre-stimulation to 147.5 Hz during stimulation as to the left frontalis muscle and from 168.0 to 111.4 Hz for the right frontalis muscle.

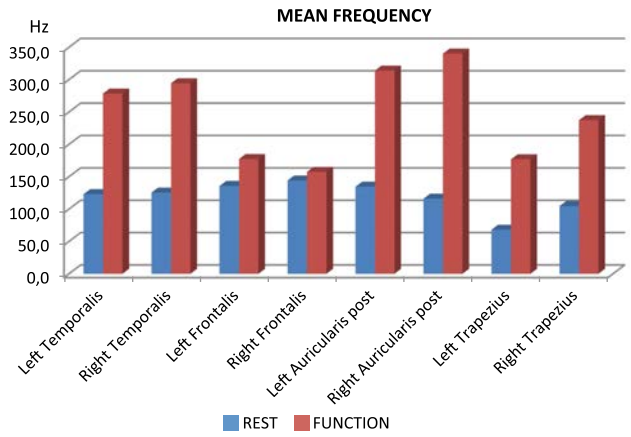

Fig. 4 Temporalis, auricularis post and trapezius muscles has indicated a significant difference in domain parameters between values recorded at rest and during neurostimulation (Function)

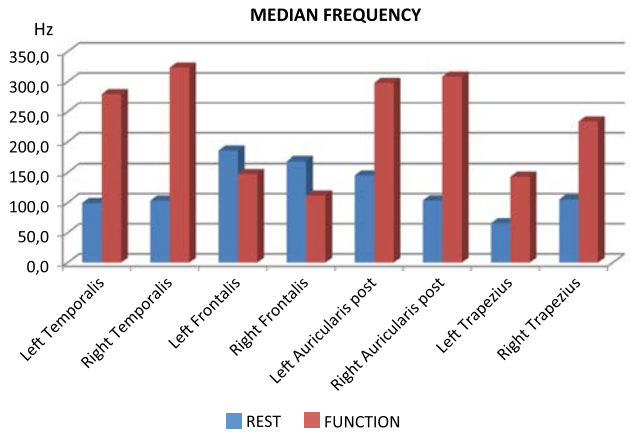

Fig. 5 The median frequency values do not show a p value statistically significant, however, has shown a reduction in the median frequency during neurostimulation (Function)

The hypothesis is that, the different neuromuscular response of the frontalis muscle is caused by the direct action of neurostimulation on the frontalis muscle that elicits the intramuscular nerve endings of the facial nerve which, being very small, become exhausted quickly (Figs. 4, 5). This decrease in median frequency could indicate premature fatigue of the frontalis muscle during neurostimulation [3].

With regard to the possible myorelaxant effect of neurostimulation on the frontalis muscle with the Cefaly® device, no significant contraction was measured by EMG on these muscles at rest.

20 out of the 23 patients, before and during neurostimulation, had EMG results within a normal range, one patient during a migraine attack had an increase in the EMG activity after 20 min of neurostimulation and two patients, experiencing as well increasing EMG activity at rest, reached normalization after 20 min of neurostimulation with the Cefaly® device.

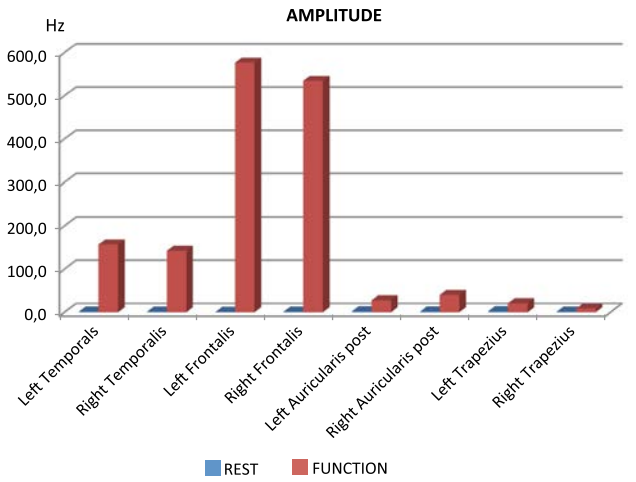

Fig. 6 Significant difference in amplitude parameters between values at rest and during neurostimulation (Function)

It is necessary to increase the sample size to interpret the role played by surface neurostimulation in relaxing the frontalis muscle.

Discussion

The sensory trigemino cervical complex is an area in the upper cervical spinal cord where nerve fibers in the descending tract of the trigeminal nerve (spinal trigeminal nucleus caudalis) interact with the spinal root of the spinal accessory nerve (CN XI) which originates from the anterior horn of the first five segments of the cervical cord.

This functional intersection between motor and sensory fibers of the spinal root of CN XI and the descending tract of the trigeminal nerve [4] is thought to provide a functional connection of somatosensory, proprioceptive and nociceptive information between cervical muscles, i.e. sternocleidomastoid and trapezius muscles, and the trigemino cervical nucleus [5].

The physiological communication between the first cervical spinal nerve roots and the spinal trigeminal tract, involving the ophthalmic branch of the trigeminal nerve, could trigger migraine attacks with pain radiating behind the corresponding eye [6–9]. Transcutaneous neurostimulation (TNS) applied to the supraorbital nerve is supposed to use this nerve pathway to spread the impulse from the frontalis muscle to peripheral muscles thus being recorded in other muscles far from the application area of stimulation.

The Cefaly® device could act therapeutically on the inhibitory circuit in the spinal cord causing a neuromuscular facilitation. The increase in the amplitude values recorded on all muscles under examination may support this theory.

The data collected prove a significant increase in the electrical activity in an area where signals of certain muscles converge, such as: frontalis, temporalis, trapezius, sternocleidomastoid and auricularis posterior muscles. Such increase could explain the therapeutical effect of the Cefaly® device (Fig. 6).

Conclusions

The results of this preliminary study, although a further research on a larger sample size is necessary, show that the decrease in the median frequency in the frontalis muscle is probably due to the direct neurostimulation.

The median frequency can be a particularly interesting parameter, whose decrease indicates the premature fatigue of a muscle. The study confirmed the fact under examination i.e. that neurostimulation of the first branch of the trigeminal nerve can also activate peripherical muscles that are far from the area of the electrical stimulation and recordable using a non-invasive technology such as surface electromyography.

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

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Role of neurostimulation in migraine

L. Grazzi · A. Padovan · P. Barbanti

Abstract Chronic forms of headache characterized by daily or almost daily headache, affect almost 3 % of general population. They represent the most disabling forms of headache inducing high degree of disability, poor quality of life for patients. During the last decades, several neuromodulatory surgical techniques have been developed for the management of headaches that are unresponsive to medical treatment. Invasive and non invasive central and/or peripheral neurostimulation techniques have been developed by different research groups with encouraging results for different type of headaches. In this report, the acute effect of non invasive vagus nerve stimulation (nVNS) (gammacore) was evaluated to treat migraine attacks in a population of patients affected by high-frequency episodic migraine or chronic migraine. The aim of this study was to verify the efficacy of nVNS to treat migraine attacks in this specific category of patients.

Keywords Neurostimulation · Vagus nerve stimulation · Acute treatment · Migraine without aura

Introduction

Chronic forms of headache characterized by daily or almost daily headache, affect almost 3 % of general population. They represent the most disabling forms of headache responsible for high patients' disability and poor quality of life. The most part of pharmacological treatments effective for primary headaches are not helpful for patients suffering from frequent attacks, so patients may develop medication overuse (MO) headache by using frequently symptomatic medications to manage their pain episodes [1]. Chronic migraine (CM) is the most common from among chronic headaches; it is mentioned in the new classification of IHS [2] and frequently associated with MO, a complication of the pathological condition as patients are difficult to treat and refractory to common prophylaxis [2].

Alternatively to pharmacological treatments, during the last decades, several neuromodulatory surgical techniques have been developed for the management of headaches unresponsive to medical treatment [3]. Invasive central and peripheral neurostimulation targeting the hypothalamus, sphenopalatin ganglion, and occipital, supraorbital or auriculotemporal nerves in chronic headache refractory to conventional treatment, has been performed by different research groups with encouraging results [3].

Clinical and quality evidence of the different approaches are highly variable but it is common opinion that they represent suitable alternatives for the most difficult and problematic conditions.

Deep brain stimulation (DBS) is one of the most invasive therapeutic methods developed to treat different chronic pain disorders: this approach has grown for the most intractable patients before the development of minimally invasive procedures or non invasive procedures as transcutaneous stimulation.

In particular, DBS applied for patients with chronic forms of cluster headache has given good results [4], but it is not used frequently nowadays for its invasivity. The

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rationale is based on hormonal abnormalities as well as structural and functional hypothalamus as a pivotal structure in the pathogenesis of cluster headache [4]. Differently, a minimally invasive technique of implantation is occipital nerve stimulation (ONS) used in various chronic primary headaches. This technique represents a peripheral neurostimulation, non destructive approach [3]. Different hypothesis have been advanced on its mechanism of action, but probably the analgesic effect is induced by an activation of afferent A beta fibers and gate control in the spinal cord and also to descending supraspinal control from the ventromedial medulla or the periacqueductal grey matter. Results are very different among the different studies depending from the population of patients. A possible lead migration or battery recharge needing are common problematic pitfalls. [3, 5, 6].

Among the newest approaches, the transcranial dermo cutaneous stimulation (t DCS) is a central neurostimulation technique, a non invasive and safe approach able to modulate the excitability of cerebral cortex [7]. Weak currents are used to modify the resting membrane potential, inducing a focal modulation of cortical excitability. It is a suitable technique helpful for different models of pain and recently used in headache field with encouraging results [7] also if the rationale is not completely clarified yet.

Vagus nerve stimulation (VNS) is a surgical procedure already approved for the treatment of medically refractory epilepsy and depression [8, 9], it has been used in selected intractable migraine cases, especially with comorbid depression, with promising results [10, 11].

VNS modulates neurostransmitters, influences cerebral metabolism [11] and blood flow [12] in the limbic system and in some pain matrix regions and exerts antinociceptive effects in acute or inflammatory pain models [12–15].

Recently a non invasive model of VNS has been tried to manage different disorders as epilepsy and depression. Results by Mauskop [11] evidenced good response to nVNS used as symptomatic in two of four patients with chronic migraine treated. Devices tested in headache patients to stimulate the vagus nerve transcutaneously have shown encouraging results when used for attack treatment. Non invasive transcutaneous neurostimulation techniques represent a promising opportunity in headache management [3, 5] with pote ntial use for the acute and preventive treatment of migraine, including episodic migraine. In animals, nVNS reduces glutamate in trigeminal nucleus caudalis and reverses the GTN-induced increase in Glu when administered 90 min after the GTN injection [16], nVNS would act on solitary tract nucleus leading to an increased release of serotonin, norepinephrine and GABA by brainstem nuclei, hence modulating excess Glu levels in the trigeminal nucleus caudalis [15].

More recently, the development of non-invasive vagus nerve stimulation (nVNS) devices contributed to an easier treatment of migraine attack. Hand-held patients controlled nVNS device (Gammacore) has been realized to treat migraine attack. In an open-label study of 30 episodic migraineurs, Goadsby et al. [17] reported that transcutaneous nVNS was effective in the acute treatment of migraine attacks, demonstrating a 2-h pain-free rate of 22 %. In our recent clinical experience, the acute effect of nVNS (gammacore) was evaluated in migraine attacks in a population of patients affected by high-frequency episodic migraine with more than eight attacks per month or chronic migraine. The aim of this study was to verify the efficacy of nVNS to treat migraine attacks in this specific category of patients.

Method

A population of 30 patients, aged 18–65, suffering from high frequency migraine without aura according with IHS criteria, (5–9 migraine days per month), were included in this open-label, single arm, multiple attack study. Patients, after a specific educational training, treated from 3 to 5 migraine episodes in 3 weeks by the portable VNS device. Treatment consisted of one, 90 s doses delivered to the right cervical branch of the vagus nerve. Subjects were asked to treat attack from moderate to severe and also to record on a visual analogue scale the level of pain in an interval of time from 30 min to 24 h after the device application.

Results

One hundred and twelve migraine attacks were treated globally by a single shot application: 44 attacks were resolved completely within 30 min (39.2 %); for 50 (44.6 %) attacks, the application did not show any benefit in the first 2 h so patients recurred to rescue medication; in 18 (16.2 %) attacks the result was uncertain: no resolution of attack, only a moderate pain relief, but patients did not recur to rescue medication. From results emerged that gammacore is a well-tolerated and safe technique associated with patients satisfaction (i.e. nearly half of patients said they were satisfied with device and were willing to try it again in the future) and therapeutic adherence.

Conclusion

Results from our report show good efficacy of gammacore to manage migraine attacks. Neurostimulation is a field of

growing interest for management of headache. Progress has been driven by technological advances and the relative absence of effective and well tolerated drugs for prevention of primary headaches. A significant population of patients has been treated by neurostimulation techniques with favourable results. Many studies are open trials and a placebo effect cannot be excluded, also a more specific selection of patients has to be conducted. Nowadays, the use of invasive neurostimulation has been reserved to particular difficult patients, and the experts in this field switched form use of invasive techniques to minimally invasive or non- invasive methods. The response rate for non-invasive neurostimulation technique is not superior to that of the most effective preventive drug treatment. Neurostimulation therapies, even if non invasive, have to be applied by trained experts in specific headache centers [18]. The most part of the devices are fairly expensive as they are products of high level technology. The challenge for the future to convince policy makers that they could be advantageous from a pharmacological and an economical perspective: a preceding report by Leone et al. [4] assessed these factors in posterior deep brain stimulation which was estimated to reduce directs costs in a population of patients suffering from chronic cluster headache in a drug resistance condition [4]. It will be necessary to define the mechanism of action of the different neurostimulation techniques, to determine adequate neurostimulation protocols, to determine also if the effectiveness can be for acute treatment or also for preventive therapy. Also as in all chronic diseases, patients are included to search for the last chance of treatment to resolve their condition and here comes the attraction for interventional therapy. Patients tend to believe that interventional procedures might be effective in migraine with only minor or no long-term adverse events and fail to apply the necessary lifestyle modifications [19].

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

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Advanced technologies and novel neurostimulation targets in trigeminal autonomic cephalalgias

Giorgio Lambru · Emmanouil Giakoumakis · Adnan Al-Kaisy

Abstract The trigeminal autonomic cephalalgias (TACs) are a group of rare but disabling primary headache disorders. Their management is challenging, since only few effective treatments are available and high doses may be required to control the headache, compromising patients' adherence to treatments. A significant minority of patients, who fail to respond to or tolerate established treatments, are left with enormous level of disability and disruption to their quality of life. A growing body of evidence demonstrates the efficacy of central and peripheral neuromodulation approaches for management of patients with refractory TACs. In view of the potential risks related to deep brain stimulation of the posterior hypothalamic region, occipital nerve stimulation is currently considered the first treatment option for refractory chronic TACs. However, in view of the presence of paraesthesia induced by the stimulator, no robust controlled trials have been possible so far. Additionally, the equipment used for occipital nerve stimulation is not designed specifically for peripheral nerve stimulation, thus a significant proportion of patients experience device-related complications that often require surgical revisions. To overcome these issues, new neurostimulation technologies using less invasive or non-invasive approaches and modulating different neuroanatomical targets have been recently studied.

Keywords Neurostimulation · Occipital nerve stimulation · Sphenopalatine ganglion stimulation · Vagus nerve stimulation · Trigeminal autonomic cephalalgias

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Introduction

The trigeminal autonomic cephalalgias (TACs) is a group of primary headache conditions which encompasses cluster headache (CH), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA), paroxysmal hemicrania (PH) and hemicrania continua (HC) [1]. The syndromes share common clinical features, namely the laterality of the pain and the accompanied cranial autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, eyelid or periorbital oedema, forehead and facial sweating, meiosis or ptosis, and a sense of restlessness or agitation. However, they differ in frequency and duration of attacks and response to medical treatments [2].

The majority of patients respond favourably to the established medical treatments. However, a significant minority of sufferers, especially those with the chronic form of TACs fail to tolerate or obtain sufficient relief from medications. This group of patients can experience an enormous level of disability [3]. In the relative absence of emerging prophylactic drugs, neuromodulation treatments targeting central and peripheral nerves have been offering attractive alternatives to medications for the management of refractory TACs [4].

The pioneering work by Leone and collaborators [5] using deep brain stimulation (DBS), targeting the posterior hypothalamic region, has opened the avenue of neurostimulation for the management of patients with refractory chronic CH. Occipital nerve stimulation (ONS) has subsequently emerged as a similarly effective, but less invasive surgical modality to DBS for the treatment of refractory TACs [4]. However, the traditional ONS carries

several flaws, including the scarcity of studies exploring the basis of its effect in primary headaches and the high rate of device-related adverse events, often requiring additional surgery [6]. Finally, the sensation of paraesthesia produced in the territory of the occipital nerves, has prevented the assessment of this treatment in robust randomised sham-control trials [7].

The stimulation of different neuronal targets, namely the sphenopalatine ganglion, the vagus nerve and the cervical spinal cord, using advanced technologies, has recently been tested in CH, whereas, very little evidence has hitherto been produced for the other TACs. Advantages of these new treatments include the availability of some initial preclinical and clinical data that have shed light on their potential mechanisms of action, thus supporting their use in clinical practice. Moreover, the non-invasive and minimally invasive modalities of some of these devices may overcome the issue of the high device-related complication rate of traditional ONS.

Sphenopalatine ganglion stimulation

The rationale for targeting the sphenopalatine ganglion (SPG) is based on the close relation between headache and autonomic activation in the TACs. The parasympathetic autonomic symptomatology of the TACs is mediated by crosstalk between trigeminal nociceptive afferents and cranial parasympathetic efferent fibres that arise from the superior salivary nucleus. The SPG receives preganglionic parasympathetic fibres from the superior salivatory nucleus in the brain stem via the greater petrosal nerve, which forms the vidian nerve. Postganglionic parasympathetic fibres innervate the lacrimal gland, the nasopharyngeal mucous membranes and meningeal vessels [8]. When activated, these fibres release neurotransmitters and vasodilators that activate sensory trigeminal fibres causing further activation of the trigeminal pain pathway which, in turn, causes further parasympathetic outflow, referred to as the trigeminal-autonomic reflex [9]. A non-destructive approach using acute percutaneous SPG stimulation with a removable electrode was examined in five patients with CH. This proof of concept study showed a complete pain relief in 11/18 (61.1 %) of the attacks, partial resolution (50 % VAS reduction) in 3/18 attacks (16.7 %) and minimal to no relief in 4/18 attacks (22.2 %). Stimulation also resolved the associated autonomic features of CH [10]. Based on these preliminary findings, a new implantable microstimulator was developed. This device is positioned in the pterygopalatine fossa (PPF), powered and controlled transcutaneously by radio frequency waves generated by an external remote controller (Autonomic Technologies Inc., Redwood City, CA, USA). A multicenter randomised double-blind and sham-controlled trial has been conducted to examine the efficacy of acute SPG stimulation in refractory CCH [11]. In this study, 32 CCH patients experiencing a minimum of four attacks per week were included. The design of the study consisted of a 4-week baseline period followed by a post-implant stabilisation and therapy titration period. The experimental period lasted until 30 CH attacks were treated or, if attack frequency was not high enough, for a maximum of 8 weeks. During this period, patients were instructed to use the stimulator to treat each attack for 15 min. The pain score was recorded using an electronic headache diary prior to each use and after the start of stimulation. One of three stimulation doses was randomly applied when the patient initiated the treatment to treat an attack: full stimulation, sub-perception stimulation and sham stimulation. The primary endpoint of pain relief after 15 min of stimulation was achieved in 67.1 % of full stimulation-treated attacks compared to 7.4 % of sham stimulation-treated attacks. Remarkably, 43 % of patients experienced an attack frequency reduction of >50 % from baseline. Given that paresthesia in the roof of the nose accompanies stimulation of the SPG, the blinding of participants may have been inaccurate. This may explain the very low response rate of the attacks treated with sham stimulation (7.4 %). Five device or procedure-related side effects occurred. Three were lead revision and two neurostimulators were explanted. Sensory disturbances occurred in 81 % of patients with complete resolution in the majority of patients. Two patients experienced infections, though in both cases they were resolved with antibiotic therapy.

SPG stimulation offers several major advantages as opposed to the traditional neurostimulation approaches. It has shown, for the first time in the headache neuromodulation field, the ability to provide abortive therapy. The device delivers an "on demand" treatment for the management of the acute attacks, as opposed to the continuous stimulation of the traditional ONS. This allows patients to apply it multiple times per day without any limitation due to cardiovascular risks, as are associated with the use of sumatriptan injections [12]. Moreover, preliminary findings have shed lights on the neurobiological basis for the therapeutic effect of SPG stimulation in CH. A double-blind randomised cross-over study investigated headache characteristics following 3 min "low frequency" (5 Hz) and higher frequency (80–120 Hz) SPG stimulation in six patients with CH that had been already enrolled in the Pathway CH-1 study. Four out of six patients (67 %) reported an ipsilateral CH-like attack after low-frequency stimulation. Application of higher frequency stimulation led to suppression or significant improvement of the attacks within 10 min. Interestingly, two patients reported the onset of CH attacks after high frequency stimulation. These attacks were aborted by

applying high frequency stimulation for 10 min. These findings have led to several speculations on the possible mechanisms of action of SPG stimulation in aborting CH attacks. The authors suggested that the therapeutic effect of high frequency stimulation might be caused by physiological block of parasympathetic activity as a result of depletion of stored neurotransmitters [13].

As far as the SPG stimulation device is concerned, the wireless stimulation avoids those hardware-related complications that are routinely reported by patients treated with ONS. Moreover, since the microstimulator is fixed with two or three bone screws to the zygomatic process of the maxillary bone, the chance of electrode migration or breakage is unlikely, as opposed to the significantly high lead migration rate that has been reported using traditional ONS [6].

The SPG stimulation using this advanced wireless on demand technology certainly constitutes a step forward in the management of refractory CH. Nonetheless, long-term data on SPG stimulation efficacy is required and better designed randomised controlled studies with more reliable sham stimulation should be performed to confirm the preliminary findings of the Pathway CH-1 study.

Vagus nerve stimulation (VNS)

Vagus nerve stimulation is a well-established treatment for intractable epilepsy and depression. Initial positive data on the efficacy of VNS in migraine was gathered from retrospective analysis of patients implanted for the treatment of epilepsy [14, 15]. In another study, two of four patients with refractory chronic migraine (CM) and depression improved significantly with VNS [16]. Similarly, a positive effect of VNS was reported in two CCH patients who also suffered from severe depression [17]. VNS consists of a subcutaneous pulse generator (Cyberonics) typically implanted in the left chest wall connected by a wire to the bipolar lead wrapped around the left cervical vagus nerve. The stimulation consisted of electrical pulses, 30 s in duration at intervals of 5 min [16].

The rationale of using non-invasive VNS for headache management derives from initial animal studies showing that VNS alleviates trigeminal allodynia and pain in rats after only 2 min of stimulation, without the need for an implantable device. Moreover, microdialysis experiments demonstrate that non-invasive VNS stimulation suppresses the increase in extracellular glutamate in allodynic rats after glycerin trinitrate (GTN) treatment. The suppression of the increased glutamate levels seems to take place in the trigeminal nucleus caudalis (TNC) which is a key structure involved in the pathophysiology of primary headaches [18].

A non-invasive, portable transcutaneous VNS device (GammaCore) has recently been tested in the acute and preventive treatment of primary headaches, including the TACs. Twenty-five patients with episodic or chronic CH have been treated over a 12-month period in an open label study. The study was an audit of outcome. The treatment was given acutely (three consecutive doses) to treat an attack or in a preventive fashion (two to three consecutive doses) twice daily. Patients were trained to deliver the stimulation on the side of the neck ipsilateral to the majority of the cluster attacks. The outcomes were collected from patients' subjective opinion. Nineteen out of 25 patients were included in the analysis. Fifteen out of 19 patients (79 %) reported a reduction of approximately 50 % in CH attack frequency during the treatment period. Four patients did not report any improvement. In addition to a prophylactic effect, some patients also obtained a favourable abortive effect in approximately 11 min. The treatment was generally well tolerated [19]. This initial experience justifies formal testing of this treatment in methodologically robust trials, which are underway.

Cervical spinal cord stimulation

Cervical spinal cord stimulation has been used for the last 30 years to alleviate refractory head and facial pain. The rationale for its use in primary headaches including TACs derives from its postulated multiple segmental spinal and supraspinal mechanisms of action. At the segmental level, as animal models indicate, SCS attenuates the hyperexcitable multimodal wide dynamic range cells (WDR neurons) in the dorsal horn [20], and increases γ-aminobutyric acid (GABA) release [21, 22] from inhibitory interneurons particularly by activation of the GABA-B receptor [23]. The stimulation of supraspinal pain modulating centers such as the trigeminocervical complex in the brainstem through cervical sensory input seems to be responsible for the modulation of the trigeminal traffic, which may also be one of the ONS mechanisms in primary headache [24].

Recently, low-frequency stimulation of the high cervical spinal cord (hcSCS) has shown positive results in a case series of seven refractory CCH patients implanted with a percutaneous cervical epidural lead and followed-up prospectively with the aid of headache diaries for a mean follow-up of 23 months (median 12 months, range 3–78 months). At baseline, mean frequency of attacks of the seven patients was 6.0 per day (range 1.7–10.0, SD 3.3, median 8.0), mean duration was 50 min (range 22–70 min, SD 16.9, median 60.0), and mean intensity was 7.4/10 on the VAS (range 4.3–10.0, SD 2.1, median 7.0). Postoperatively, mean attack frequency was reduced to 1.4 attacks/day (range 0–3.5, SD 1.2, median 1.3), mean duration

to 23 min (range 0–56 min, SD 17.4, median 21.4), and intensity to 4.5 on the VAS (range 0–7.6, SD 2.6, median 5.2). These differences were statistically significant for attack frequency, duration, and intensity ($p = 0.008$, $p = 0.006$, and $p = 0.013$, respectively). Pain medication was markedly reduced after the operation in all patients. Triptan use was stopped in five patients and reduced in two patients. Four patients could discontinue all prophylactic medication [25].

One of the advantages of this treatment seems the equal or larger effect size compared to the studies using ONS for CH. Additionally, hcSCS seems to exert an immediate and maximal effect after surgery, allowing a short stimulation trial to be considered a relatively meaningful predictor for long-term responders. However, the high rate of adverse effects, reported in that study, mostly lead revision, seems exceedingly high and needs to be considered when selecting the type of neurostimulation treatments.

Conclusions

A growing body of evidence has suggested a key role of central and peripheral neuromodulation modalities in the management of patients with refractory TACs. However, their clinical use is limited by the lack of adequately controlled data [4]. For this reason, the process of selection of suitable candidates for neurostimulation treatments should be dictated by shared guidelines. On this note, the members of the European Headache Federation has recently published a consensus statement on the definition of refractory CCH for clinical and research use. The diagnostic criteria require the presence of at least three severe CH attacks per week that impact patients' quality of life. Patients have to fail prophylactic trials with at least three established treatments such as verapamil, lithium, oral or intravenous steroids, greater occipital nerve infiltration, topiramate, methysergide, ergots, civamide and long acting triptans, at the maximum tolerated dose over a sufficient period of time. Secondary CH has to be ruled out by appropriate investigations [26].

A relatively broad arsenal of neurostimulation approaches seem to be potentially effective in the treatment of TACs in different quality studies. Based on published evidence, in refractory CCH, it would be advisable to use ONS and SPG stimulation as first line treatments, followed by the more invasive DBS of the posterior hypothalamus [27]. However, if the recent promising open label evidence in the use of transcutaneous VNS in CH is confirmed in controlled trials, it is arguable that application of a non-invasive device, which is relatively harmless and less costly than other procedures, may be tried before the more invasive neurostimulation modalities.

Ultimately, the success of any neuromodulatory device critically depends on well-orchestrated multidisciplinary teamwork involving a headache neurologist, a pain physician or neurosurgeon with expertise in neuromodulation, a psychologist with expertise in chronic pain and headache specialist nurses with expertise in neuromodulation. Such specialized team should be able to recommend the most suitable neuromodulation approach for the individual patient and takes responsibility for post-implant care, which are often the most demanding and time-consuming part of these groups of highly disabled patients.

Conflict of interest Giorgio Lambru received payment for training sessions and the development of educational presentations from Allergan, Electrocore and Nevro Corp. El has nothing to declare. AA travel sponsorship and speaker fees from Medtronic and Nevro Corp. and he is the principal investigation in separate studies sponsored by Medtronic and Nevro Corp.

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Surgery for treatment of refractory chronic cluster headache: toward standard procedures

Angelo Franzini · Giuseppe Messina

Abstract The degree of disability due to chronic cluster headache refractory to conservative treatments justifies surgical procedures as second-line treatments. Many studies and reports nowadays confirm the efficacy of the two mostly used surgical techniques in such cases. Both deep brain stimulation and occipital nerve stimulation are in fact currently utilized for this purpose but the surgical technique has not yet been standardized. We describe the surgical steps of both procedures.

Keywords Chronic cluster headache · Occipital nerve stimulation · Deep brain Stimulation · Hypothalamus · Surgical technique

Introduction

Chronic cluster headache (CCH) is a pathological entity leading to a severe degree of disability; it is characterized by pain attacks occurring daily or spaced out by remission periods of <1 month, contrarily to the episodic form, in which attacks occur during a period ("cluster period") of 6–12 weeks interrupted by remission periods lasting up to 12 months. When the condition results to be refractory to prophylactic treatments (verapamil, lithium, sodium valproate, methysergide, topiramate, gabapentin, indomethacin, and corticosteroids), when abortive therapy results unsatisfactory, and when such condition is present for at least 2 years [1, 2], surgical treatment is indicated [occipital nerve stimulation (ONS) and deep brain stimulation (DBS)].

Since 2001, refractory cluster headaches have been shown to benefit from neuromodulation procedures. The first series of patients submitted to DBS of the posterior hypothalamus in Milan has been operated in Milan between 1998 and 2001 [3]. The rationale for neuromodulation in such cases was derived from neuroimaging and particularly position emission tomography and voxel-based morphometric brain MRI which pointed to the posterior hypothalamus as hyperactive node of the neuronal network responsible for autonomic trigeminal neuralgia [4, 5].

In 2003, Bartsch [6] demonstrated experimentally the role of the trigeminocervical complex in the etiogenesis of autonomic cephalalgia. This concept led to the introduction of occipital nerve electrical stimulation to modulate this system in patients affected by refractory cluster headaches. Due to its less invasiveness, ONS is usually performed as first choice procedure and posterior hypothalamic (pHyp) DBS is reserved only to ONS refractory patients as a second choice procedure.

ONS

The procedure described here has also been described in a previous report [7]. The patient is placed on the operating table in a prone position with his/her head fixed in the Mayfield head holder system. Bony prominences, the chest wall and iliac crests must be adequately padded to prevent post-operative skin and peripheral nerve lesions. The head is slightly flexed and positioned in line with the chest to avoid skin creases and curvatures. We then position the three-pin Mayfield headholder in the parietal region bilaterally.

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It is possible to implant two quadripolar bilateral electrodes or one longer octopolar one to obtain complete coverage of the suboccipital region, due to the frequent contralateral irradiation of the pain and to the frequent anastomoses among the main suboccipital nervous trunks [8].

After shaving of the occipital hairline, a small vertical incision is made in the posterior cervical region in the midline from 1 cm above to 1 cm below the external occipital protuberance (EOP). The greater occipital nerve is usually present about 4 cm lateral to the midline turning in a slight medio-lateral direction before dividing into a medial and a lateral branch about 1 cm above the EOP [9]. Two symmetric vertical incisions are then made 4 cm lateral to the EOP on both sides.

A blunt dissection of subcutaneous tissue is then performed, thus exposing the cervical fascia located superficial to the trapezius and splenius capitis muscles.

Then, a Tuohy needle is inserted from each lateral incision to the midline incision in a lateral-to-medial direction, allowing the insertion of the electrode. The lead should be located at 4 cm lateral to the midline where the main trunk of the GON is located. Positioning the electrode tip too far laterally could prevent an optimal coverage of the electrical field (Fig. 1). The wires connected to the electrodes are then tunneled together in a caudal direction along the occipital and neck midline until about the middle dorsal level. At subcutaneous cervical level, we anchor both electrodes to the underlying fascia with non-resorbable stitches to prevent their caudal dislodgement, and relief loops are made at both this site and at more caudal sites along tunneling passages to prevent excessive tension, with possible discomfort to the patient, and fracture of the leads [10]. The age of the patient and his/her individual anatomy will determine the rostro-caudal level of the location of the lead connectors. We use 60- or 95-cm-length connection wires to prevent, again, any excessive strain on the whole system. It is important at this point to create a little subcutaneous pocket at this level to allow enough room for both of the connectors and to avoid skin erosions. Another incision is then made in the midline at the lumbar level. Both dorsal and lumbar incisions serve as guides for midline tunneling of both wires. The two connection wires may then diverge with one on each side if two single-channel IPGs (Soletra, Medtronic, Libra, St Jude) are used or may run on the same side if a dual-channel IPG is positioned on one side (Activa PC, Medtornic, Libra xp, St Jude) (Fig. 2).

We consider the possibility of converting ONS into hypothalamic deep brain stimulation, thus leaving intact the implanted IPGs and lead extensions.

Subcutaneous pockets for the pulse generators are made approximately 4 cm above the iliac crest at the level of the external oblique muscle, paying attention not to jeopardize the latter muscle to prevent excessive bleeding and postoperative pain.

DBS

The planning procedure is performed with the aid of a stereotactic head frame (Leksell, Micromar, Maranello, CRW has been used in our Institute) with the patient under local anesthesia. A pre-operative set of MR images (generally axial, volumetric, fast spin echo inversion-recovery T1-weighted with Gd and T2-weighted sets) is obtained to acquire high-definition images for precisely defining the location of anterior and posterior commissures (AC, PC) and midbrain structures below the commissural plane (mammillary bodies and red nucleus). Magnetic resonance images are then merged with computerized tomography (CT) scans obtained under stereotactic conditions after

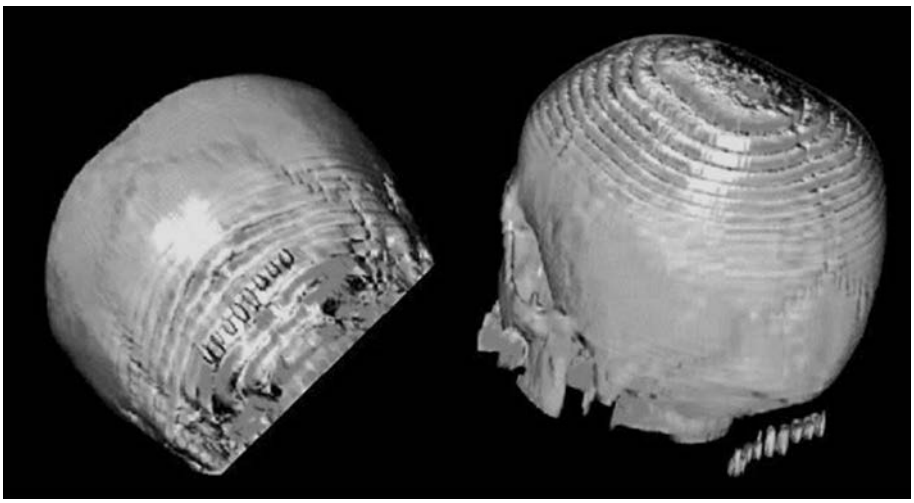

Fig. 1 3D CT reconstruction of correct suboccipital lead placement

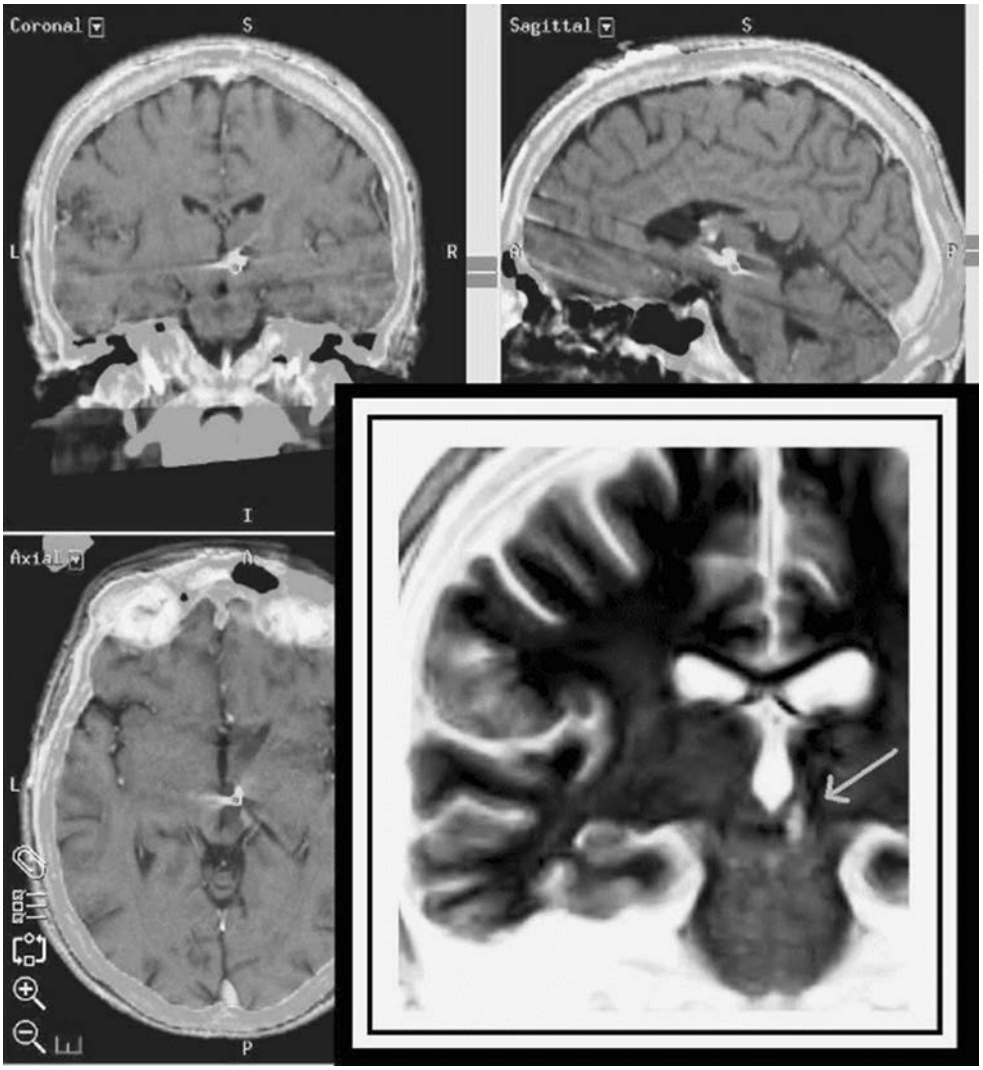

Fig. 2 Merging between pre-operative MRI and post-operative CT of a patient submitted to pHyp DBS in the three planes; *lower right* post-operative MRI showing the correct positioning of the DBS electrode (*arrow*)

positioning the head frame. The fusion of the 2 imaging sets is performed using an automated technique based on a mutual-information algorithm (Frame-link 5.0, Sofamor Danek Stealthstation, Medtronic). The merged images as well as every single slice of the imaging set are coregistered with the dedicated digital stereotactic atlas (available on internet at http://www.angelofranzini.com). Anyway midcommissural (MCP) point-related coordinates of the target are 2 mm lateral to MCP, 3 mm lateral and 5 mm inferior to it. It has to be remarked that targeting procedures based exclusively on the MCP or AC–PC plane may lead to slight electrode misplacement, due to the anatomical variability of the angle between the brainstem's major axis and the intercommissural plane. To overcome this problem, we took into account a new anatomical landmark that was incorporated into the final targeting procedure; we named this landmark the interpeduncular point (IPP). It is localized in the apex of the interpeduncular cistern 8 mm below the AC–PC plane at the level of the maximum diameter of the mammillary bodies. With this correction point, target coordinates are individualized for every single patient. Under local anesthesia, two small incisions are made about 2 cm anterior to the coronal suture and 3 cm lateral to the midline. Trough two small hand-driven burr holes, dura mater is coagulated and two blunted cannulas containing recording microelectrodes are inserted at about 5 mm above the target. Microrecordings within the pHyp are performed only in proximity to the target (starting at about 5 mm above it).

At the target, we record single-unit activity with the patients fully awake and in a pain-free state. All data sampled obtained by us in patients with TACs describe a low-frequency, tonic, and non-oscillatory discharge pattern. Anyway mean firing rates at the target differ among

different authors: Cordella et al. [11] described a mean discharge rate of 24 Hz in 3 patients; Bartsch et al. [12] a mean firing rate of 17 Hz and Sani et al. [13] a mean firing rate of 13 Hz. In our experience, the firing discharge did not change after tactile, motor, autonomic, and emotional tests performed during the surgical session.

Anyway Brittain [14] was able to record neural activity during a cluster headache attack: the pain attack was associated with an increase in the relative LFP power and specifically a distinct 16- to 22-Hz peak in neural activity. The presence of a specific neural rhythm was the first direct evidence of pHyp involvement during the cluster pain as indirectly described in neuroimaging studies. After this intraoperative evaluation, the definitive electrode (Medtronic, St Jude) is positioned at the target. Intraoperative macrostimulation with such electrodes is then performed, and the threshold for ipsilateral ocular deviation should be established at values higher than 3 Volts (130 Hz, 60 μsec). If ocular movements are evoked by lower amplitude stimulation, the electrode should be positioned more laterally and the microrecording procedure should be repeated along the new trajectory.

Finally, to confirm the correct positioning of the electrode within the pHyp, we perform a second stimulation session increasing the amplitude over the threshold for ocular movements and we should evoke fear and unpleasant sensations lasting just few seconds. At the end of this intraoperative evaluation, the definitive electrode is secured to the burr hole by biological glue and by a titanium miniplate.

Then bilateral single IPGs (Medtronic Activa SC, St Jude Libra) or dual-channel monolateral IPGs (Medtronic Activa PC, St Jude Libra xp) are positioned into subclavicular subcutaneous pockets and connected to brain electrodes by tunneling connecting cables for chronic electrical stimulation. Post-operative brain CT or MR imaging constitutes a useful tool both for assessing the accuracy of electrode placement and correlating the extent of the clinical benefit or adverse effects. The two sets of images can be merged, taking advantage of the lower degree of image distortion with CT and the more precise defined gray–white matter boundaries provided by MR imaging [15].

Discussion and conclusions

Even if patients affected by refractory CCH are relatively few (<1 %) [16, 17], in our opinion, hypothalamic DBS and ONS should be available in neurosurgical units to treat these cases. Really these procedures have been utilized worldwide by different surgeons and their efficacy has been confirmed by multicentric studies [18] and large series by single qualified authors [19–21].

The rate of complications is the same of all neuromodulation procedures with implantable devices. The success rate of these procedures ranges between 50 and 80 % and should be considered highly significant in a pool of patients refractory to any other treatment. Due to neuromodulation, the limit of treatability of TACs has been overpassed in the last 10 years. The aim of this report was to describe the surgical steps of DBS and ONS to suggest neurosurgeons a standard procedure.

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

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BRIEF COMMUNICATION

Headache attributed to intracranial pressure alterations: applicability of the International Classification of Headache Disorders ICHD-3 beta version versus ICHD-2

M. Curone · C. Peccarisi · G. Bussone

Abstract The association between headache and changes in intracranial pressure is strong in clinical practice. Syndromes associated with abnormalities of cerebrospinal fluid (CSF) pressure include spontaneous intracranial hypotension (SIH) and idiopathic intracranial hypertension (IIH). In 2013, the Headache Classification Committee of the International Headache Society (IHS) published the third International Classification of Headache Disorders (ICHD-3 beta version). The aim of this study was to investigate applicability of the new ICHD-3 versus ICHD-2 criteria in a clinical sample of patients with intracranial pressure (ICP) alterations. Patients admitted at our Headache Center for headache evaluation in whom a diagnosis of ICP alterations was performed were reviewed. 71 consecutive patients were studied. 40 patients (Group A) were diagnosed as IIH, 22 (Group B) as SIH, 7 (Group C) and 2 (Group D), respectively, as symptomatic intracranial hypertension and symptomatic intracranial hypotension. Main headache features were: in Group A, daily or nearly-daily headache (100 %) with diffuse/non-pulsating pain (73 %), aggravated by coughing/straining (54 %) and migrainous-associated symptoms (43 %). In Group B, an orthostatic headache (100 %) with nausea (29 %), vomiting (24 %), hearing disturbance (33 %), neck pain (48 %), hypacusia (24 %), photophobia (22 %) was reported. In Group C, a diffuse non-pulsating headache was present in 95 % with vomiting (25 %), sixth nerve palsy (14 %) and tinnitus (29 %). In Group D, an orthostatic headache with neck stiffness was reported by 100 %. Regarding applicability of ICHD-2 criteria in Group A, 73 % of the patients fitted criterion A; 100 %, criterion B; 100 %, criterion C; and 75 %, criterion D; while applying ICHD-3 beta version criteria, 100 % fitted criterion A; 97.5 %, criterion B; 100 %, criterion C; and 100 %, criterion D. In Group B, application of ICHD-2 showed 91 % patients fitting criterion A; 100 %, criterion B; 100 %, criterion C; and 68 %, criterion D; while applying ICHD-3 beta version all patients, 100 % fitted criterion A, B, C, D. 73 % patients of Group A fitted all ICHD-2 criteria and 97.5 % all ICHD-3 beta version criteria for headache attributed to IIH. 68 % patients of Group B fitted all ICHD-2 criteria and 100 % all ICHD-3 beta version criteria for headache attributed to SIH. In Group C and Group D, although patients fitted some clinical criteria, the underlying disorder caused exclusion of both ICHD-2 and ICHD-3 beta version applicability for headache attributed to IIH and SIH; they were coded in criteria for the secondary headaches. In summary, ICHD-3 beta version seems to have better applicability but worse reliability in defining headache features in CSF alterations.

Keywords Idiopathic intracranial hypertension · Spontaneous intracranial hypotension · Intracranial pressure alterations · ICHD-3 beta version

Introduction

Headache can be the leading symptom of intracranial pressure (ICP) alterations. Clinical syndromes associated with abnormalities of cerebrospinal fluid (CSF) pressure include spontaneous intracranial hypotension (SIH) and idiopathic intracranial hypertension (IIH). Diagnostic criteria for "Headache attributed to IIH" and "Headache attributed to spontaneous (or idiopathic) low CFS pressure"

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Table 1 Headache attributed to IIH and SIH (ICHD-2 2004)

Headache attributed to IIH
(A) Progressive headache with at least one of the following characteristics and fulfilling criteria C and D:
1. Daily occurrence
2. Diffuse and/or constant (non-pulsating) pain
3. Aggravated by coughing or straining
(B) Intracranial hypertension fulfilling the following criteria:
1. Alert patient with neurological examination that either is normal or demonstrates any of the following abnormalities:
(a) Papilloedema
(b) Enlarged blind spot
(c) Visual field defect (progressive if untreated)
(d) Sixth nerve palsy
2. Increased CSF pressure (200 mm H_2O in the non-obese, 250 mm H_2O in the obese) measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring
3. Normal CSF chemistry (low CSF protein is acceptable) and cellularity
4. Intracranial diseases (including venous sinus thrombosis) ruled out by appropriate investigations
5. No metabolic, toxic or hormonal cause of intracranial hypertension
(C) Headache develops in close temporal relation to increased intracranial pressure
(D) Headache improves after withdrawal of CSF to reduce pressure to 120–170 mm H_2O and resolves within 72 h of persistent normalization of intracranial pressure
Headache attributed to SIH
(A) Diffuse and/or dull headache that worsens within 15 min after sitting or standing, with at least one of the following and fulfilling criterion D: neck stiffness, tinnitus, hypacusia, photophobia, nausea
(B) At least one of the following: evidence of low CSF pressure on MRI (e.g., pachymeningeal enhancement), evidence of CSF leakage on conventional myelography, CT myelography or cisternography, CSF opening pressure <60 mm H_2O in sitting position
(C) No history of dural puncture or other cause of CSF fistula
(D) Headache resolves within 72 h after epidural blood patching

were previously given in the International Classification of Headache Disorders, ICHD-2 [1]. On July 2013, the Headache Classification Committee of the International Headache Society (IHS) published the ICHD-3 beta version [2]. The World Health Organization (WHO) wants field-testing for a couple of years this third classification parallel with the new WHO version of International Classification of Diseases which process is underway, in order to make it much more useful in clinical practice [3].

Objective

The aim of this study was to investigate the applicability of the new ICHD-3 beta criteria versus ICHD-2 criteria in a clinical sample of patients with headache attributed to intracranial pressure alterations.

Patients and methods

Charts of patients admitted at our Headache Center from 2010 to 2013 for headache evaluation with a final diagnosis of ICP alterations were reviewed. Diagnosis of ICP alteration (IIH or SIH) was performed according to ICHD-2 headache attributed to IIH and headache attributed to SIH criterion B (Table 1); then ICHD-3 beta version criteria for headache attributed to IIH and headache attributed to SIH (Table 2) were applied.

Results

71 consecutive patients (45 F, 25 M, mean age 41.8 years) were studied. 40 patients (Group A), 31 F and 9 M, were diagnosed as IIH; 22 patients (Group B), 14 M and 8 F, as SIH; 7 patients (Group C), 2 M and 5 F, as symptomatic intracranial hypertension; and 2 patients (Group D), 1 M and 1 F, had symptomatic intracranial hypotension. In all patients, headache was the onset symptom. In Group A a daily or nearly-daily headache was present in 100 % with diffuse/non-pulsating pain in 73 % and pulsating in 27 %. Moreover, in 57 % of patients of Group A headache was aggravated by coughing or straining, in 20 % headache had unilateral distribution while in 43 % migrainous associated symptoms were reported. In Group B, the headache was orthostatic in 100 % with nausea (29 %), vomiting (24 %), hearing disturbance (33 %), neck pain (48 %), hypacusia

Table 2 Headache attributed to IIH and SIH (ICHD-3 beta version 2013)

Headache attributed to IIH
(A) Any headache fulfilling criterion C
(B) Idiopathic intracranial hypertension (IIH) has been diagnosed, with CSF pressure >250 mm CSF (measured by lumbar puncture performed in the lateral decubitus position, without sedative medications, or by epidural or intraventricular monitoring)
(C) Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in temporal relation to IIH, or led to its discovery
2. Headache is relieved by reducing intracranial hypertension
3. Headache is aggravated in temporal relation to increase in intracranial pressure
(D) Not better accounted for by another ICHD-3 diagnosis
Headache attributed to SIH
(A) Any headache fulfilling criterion C
(B) Low CSF pressure (<60 mm CSF) and/or evidence of CSF leakage on imaging
(C) Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or has led to its discovery
(D) Not better accounted for by another ICHD-3 diagnosis

(24 %), photophobia (22 %). In 91 %, headache resolved on recumbency within minutes or hours. In Group C, a diffuse non-pulsating headache was present in 95 % with vomiting (25 %), sixth nerve palsy (14 %) and tinnitus (29 %). In Group D, an orthostatic headache with neck stiffness was reported by 100 %. Regarding applicability of ICHD-2 criteria, in Group A, 29/40 (73 %) patients fitted criterion A; 40/40 (100 %), criterion B; 40/40 (100 %), criterion C; and 30/40 (75 %), criterion D; while applying ICHD-3 beta version criteria, 40/40 (100 %) fitted criterion A; 39/40 (97.5 %), criterion B; 40/40 (100 %), criterion C; and 40/40 (100 %), criterion D. In Group B, application of ICHD-2 showed 20/22 (91 %) patients fitting criterion A; 22/22 (100 %), criterion B; 22/22 (100 %), criterion C; and 15/22 (68 %), criterion D; while applying ICHD-3 beta version all patients (22/22, 100 %) fitted criterion A, B, C, D. 29/40 (73 %) patients of Group A fitted all ICHD-2 criteria and 39/40 (97.5 %) all ICHD-3 beta version criteria for headache attributed to IIH. 15/22 (68 %) patients of Group B fitted all ICHD-2 criteria and 22/22 (100 %) all ICHD-3 beta version criteria for headache attributed to SIH. In Group C and Group D, although patients fitted some clinical criteria, the underlying disorder causes exclusion of both ICHD-2 and ICHD-3 beta version applicability for headache attributed to IIH and SIH but they were completely coded in criteria for the secondary headaches.

Discussion

The association between headache and changes in intracranial pressure is strong and headache aspects in CSF dynamic alterations can be quite important in clinical practice. As we compared the two classifications, ICHD-3 beta version seems to have better applicability but at the same time worse reliability in defining headache features in CSF alterations because it does not specify any additional or descriptive characteristic of headache. Moreover, the new criteria for headache attributed to IIH and SIH do not highlight headache as a symptom, removing the headache description of the 2004 classification. These results seem to suggest the validity of ICHD-2 versus ICHD-3 in better defining headache because in fact ICHD-3 beta version underrates headache as a symptom in these syndromes. Those characteristics which were included in the ICHD-2 for headache attributed to IIH and SIH were reported by a remarkable proportion of the studied patients. On the other hand, some headache features usually attributed to migraine forms, and which are not among the required criteria for headache attributed to IIH of the ICHD-2 were present in some patients (i.e., pulsating quality and unilateral distribution of pain and migrainous-associated symptoms). Since the relation of headache to intracranial pressure is remarkable, our survey may contribute to better define headache aspects in these forms but further and larger studies are needed, especially in the light of the new ICHD-3 criteria as a tool for diagnosis.

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

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BRIEF COMMUNICATION

Familial cluster headache in an Italian case series

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Abstract To investigate the familial occurrence of cluster headache (CH) in a series of Italian patients, we focused on possible differences in the mean age of onset between familial and non-familial CH cases. We considered all consecutive patients referred to the Parma Headache Centre between 1975 and 2013 affected by CH; we subsequently reviewed these cases applying the ICHD3-beta criteria (785 probands, 569 men and 216 women). We identified those cases who reported at least a first-degree relative with a diagnosis of CH, which was confirmed by the clinical documentation they provided. Each one of the "familial cases" was matched by sex and age (±2 years) at the first visit to three consecutive CH patients who did not report any first-degree relative affected by CH. A positive family history of CH was found in 40 probands (5.1 %), 28 men (4.9 %), and 12 women (5.6 %). The male:female ratio was 2.3:1 among the 40 CH familial cases, while it was 2.7:1 among all the CH non-familial cases (745 patients). The mean age of onset was significantly ($p < 0.01$) lower in women with familial CH (28.5 years, SD 17.7 years, range 10–63 years) than in women with non-familial CH (46.7 years, SD 13.7 years, range 11–74 years); we did not find a significant age difference among men (the mean age of onset for the familial cases was 29.6 years, SD 13.6 years, range 6–63 years; while for the non-familial cases, it was 29.3 years, SD 13.2 years, range 13–59 years). Our study suggests that genetic factors may play a role in the female gender causing an earlier age of onset and a lower male-to-female sex ratio in familial cases.

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Keywords Headache · Cluster headache · Familial cluster headache · Age of onset

Introduction

Cluster headache (CH) has been considered to be a sporadic disorder, but several epidemiological surveys since the 1990s have suggested that this condition could be, at least in part, of genetic origin. Compared with the general population, the first-degree relatives had a 5 to 18 times higher risk of having CH [1–3]. Among the few surveys referred to the Italian epidemiological context [4–6], Leone et al. [4] indicated that first-degree relatives are 39 times more likely to have CH than the general population.

The aim of the present study was to investigate the familial occurrence of CH in an Italian case series focusing on possible differences in the mean age of onset between familial and non-familial CH cases.

Materials and methods

We considered all consecutive patients referred to the Parma Headache Centre between 1975 and 2013 affected by CH, diagnosed by our team of trained neurologists; the CH cases were subsequently reviewed applying the ICHD3-beta criteria [7]. In this way, our initial study sample consisted of 785 probands, 569 men and 216 women.

Among the probands, we identified those cases who reported at least a first-degree relative (i.e., parents, siblings and offspring) with a diagnosis of CH in their family histories. We asked these subjects to collect clinical documentation (office visits, hospital discharge letter,

neurological consultations), which they provided us during a further clinical interview, regarding their relatives' CH diagnosis. We critically analysed the documentation applying the ICHD3-beta criteria to confirm the diagnosis of CH.

Each one of the "familial cases" was matched by sex and age (±2 years) at the first visit to three consecutive CH patients who did not report any first-degree relative affected by CH.

Informed consent was obtained from all subjects who participated in our study.

The collected data were analysed using SPSS, version 20.0 for Windows. Statistical analysis was done using Mann–Whitney test; we calculated two-tailed p values and set statistical significance at $p < 0.05$.

Results

A positive family history of CH was found in 40 probands, corresponding to 5.1 % of the initial sample: 28 men (4.9 %) and 12 women (5.6 %). We found 42 first-degree relatives with a CH diagnosis, 28 men (11 fathers, 13 brothers and four sons) and 14 women (eight mothers, five sisters and one daughter).

The male:female ratio was 2.3:1 among the CH familial cases, it was 2.0:1 among their first-degree affected relatives, while it was 2.7:1 among all the CH non-familial cases (745 cases).

Twenty-six probands had a male affected relative (M: F ratio 2.3:1), 12 probands had a female affected relative (M:F ratio 2:1), while two probands had multiple first-degree relatives with a diagnosis of CH.

Among the 40 familial cases, overall mean age of CH onset was 29.3 years (SD 14.7 years, range 6–63): 29.6 years (SD 13.6 years, range 6–63 years) in men and 28.5 years (SD 17.7 years, range 10–63 years) in women. Among the 120 non-familial matched cases, we found that the overall mean age of onset was 34.5 years (SD 15.5, range 11–74): 29.3 years (SD 13.2 years, range 13–59 years) in men and 46.7 years (SD 13.7 years, range 11–74 years) in women.

When comparing the two groups of CH cases, we found that the mean age of onset was significantly ($p = 0.003$) lower in women with familial CH than in women with non-familial; we did not find a significant age difference among men and among all CH cases, even if the latter was at the upper limits of the statistical significance ($p = 0.053$).

Discussion

In our study, familial CH was found in 5.1 % of the 785 index patients. This percentage of familial CH cases is similar to those previously reported in literature. Kudrow et al. and Russell et al. [1, 2] reported a positive familial history of CH in, respectively, 11.3 and 7 % of CH patients; in a series of French CH sufferers, 10.75 % of cases were found to be familial [3].

The few studies conducted in the Italian epidemiological context [4–6] found a percentage which ranges between 2.2 [6] and 20 % [4].

In our survey, we observed that women with familial CH had a significant lower age of onset than did women with non-familial CH. This result agrees with our previous survey in an Italian case series of 691 patients [5]. Russell and Andersson [8] in their study found that mean age of onset was lower in the patients' children than in their parents; the authors concluded that the presence of possible genetic components may anticipate CH onset.

Considering CH in general, the age of headache onset in clinical studies ranges from 3 to 83 years with preponderance of onset between 20 and 60 years [9]. Our data are comparable to those observed in literature.

In our study the male:female ratio in familial CH cases and among their first-degree affected relatives was lower than the ratio reported in literature on CH in general [10]. Similar conclusions were made by El Amrani et al. [3] in their French case series.

Our results suggests that there could be a different expression of possible genetic alterations in the two sexes, causing an earlier age of onset and a lower male-to-female sex ratio in female familial cases. Mechanisms associated with sex hormone regulation could be suggested.

The methodological strengths of our study are (1) use of a clinical interview carried out by neurologists expert in headache diagnosis; (2) revision of CH diagnosis according to the recent ICHD-3beta criteria.

Some limitations of our study need to be addressed: (1) it was not possible a confirmation of CH diagnosis by a direct interview with the possibly affected relatives; this limit was at least partly balanced by critical analysis of the complete clinical documentation we specifically asked the probands, which they subsequently provided us. (2) Non-familial cases were not checked to exclude the presence of CH sufferers among their first-degree relatives. It must be mentioned that we survey the presence of familiarity for headache, in all patients referring to our Headache Centre, in the same way we collect other anamnestic and clinical information.

In conclusion, our data referred to an extensive series of 785 Italian patients suggest the existence of a heritable component in some CH cases; genetic factors seem to affect the age of onset of familial CH in the female gender.

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

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BRIEF COMMUNICATION

Osmophobia in allodynic migraineurs: cause or consequence of central sensitization?

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Abstract Migraine is a primary headache characterized by recurrent attacks of head pain associated with nausea or vomit, photophobia, phonophobia and osmophobia. The presence of osmophobia during migraine attacks seems to be a very specific complaint. Cutaneous allodynia (CA) is very common in migraineurs, and it is the most evident clinical manifestation of central sensitization, a mechanism involved in migraine chronification. This study was aimed at identifying the possible correlation between osmophobia and CA in migraineurs. 673 migraineurs were studied (492 episodic, 181 chronic). The prevalence of both CA and osmophobia was higher in chronic than in episodic migraineurs. The association between these two symptoms was significant in chronic migraineurs at Chi square test. The highlighted relationship between CA and osmophobia may be interpreted in different ways: central sensitization induced by recurrent pain stimulation may in parallel induce a distortion of both cutaneous sensitivity (CA) and olfaction (osmophobia); alternatively, the recurrent olfactory stimulation in subjects with a hypersensitivity to olfactory stimuli may co-work with repetitive pain stimulation to induce the central sensitization process.

Keywords Migraine · Chronic migraine · Osmophobia · Cutaneous allodynia

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Background

Migraine is a primary headache characterized by recurrent attacks of head pain associated with nausea or vomit, and with hypersensitivity to external stimuli. This cohort of symptoms is the expression of a hyperactive and hypometabolic brain [1] that, episodically, needs to restore a normal energetic level by resting and avoidance of stimulations. Osmophobia seems to be a very specific complaint, although not included in the diagnostic criteria of migraine [2]. Moreover, neuroimaging studies found evidences that olfactory stimulation during a migraine attack increases activity in the rostral part of the pons, a region thought to play a central role in migraine pain [3]. Migraine-associated cutaneous allodynia (CA) is the most evident clinical manifestation of central sensitization that in turn is a process of transformation of the nuclei of the pain matrix, principally induced by recurrent painful stimulations, at least among predisposed subjects [4]. In fact, central sensitization-induced CA may be found in most but not all chronic migraineurs and, on the contrary, it can be observed also in patients with a very low frequency of attacks [5].

Aim of the study

The aim of the study was to identify the possible relationship between osmophobia and CA in migraineurs.

Materials and methods

Population

The study included 673 migraineurs consecutively evaluated at the Headache Center of the L. Sacco Hospital

of Milan during the year 2013. The cohort comprised 101 males and 572 females (mean age 38.4 ± 13.7 years).

Diagnostic criteria

Diagnosis of episodic migraine was made according to the ICHD-II criteria [6]; the diagnosis of chronic migraine was made according to the criteria proposed by Silberstein and Lipton [7].

The presence of CA was assessed by asking the patients a set of standardized questions, already used in previous studies of our group [8]. The patient was asked to give yes/no responses to written questions as follows: (1) Have you experienced abnormal scalp sensitivity or discomfort during headache attacks? (2) If yes, does this abnormal sensitivity or discomfort arise from (a) touching head skin; (b) touching hair; (c) combing hair; (d) brushing hair; (e) wearing glasses; (f) using a hair-band, curlers or ponytail; (g) lying with head resting on the pain side? Patients replying yes to the first question and at least to one of the following options (a–g) were considered to have CA.

Presence of osmophobia was evaluated by asking patients if smells or intense perfumes were avoided during headache attacks and/or were able to induce intense discomfort.

Statistical analysis

The prevalence of osmophobia and of CA was calculated. Chi square test with Bonferroni correction was used to assess the correlation between these two symptoms.

Results

Prevalence of CA

About half of the included patients complained CA during migraine attacks. CA was more prevalent among chronic versus episodic migraineurs (60.8 vs 49.2 % $p = 0.009$ at Chi square test).

Prevalence of osmophobia

Migraine-associated osmophobia was complained by 24.1 % patients from the total sample, with a slightly higher prevalence among chronic versus episodic migraineurs, not significant at Chi square test.

Relationship osmophobia: CA

Among the 161 osmophobic subjects, prevalence of CA was 57.8 %, while among the 508 subjects without osmophobia, 50.6 % were allodynic, without significant differences ($p = 0.10$).

In the sub-group of chronic migraineurs, the prevalence of CA was higher among osmophobic with respect to non-osmophobic patients (73.9 vs 56.7 %, $p = 0.03$).

No difference was found in terms of prevalence of CA between osmophobic and non-osmophobic patients (51.3 vs 48.4 %, $p = 0.52$) in the episodic migraine sub-group.

The prevalence of CA among all the osmophobic patients was higher in chronic rather than in episodic migraineurs (73.9 vs 51.3 %, respectively, $p = 0.01$). On the other hand, among the 508 non-osmophobic migraineurs, no difference in prevalence of CA was found according to the different diagnostic groups (chronic vs episodic: 56.7 vs 48.4 %, $p = 0.10$) (Table 1).

Duration of migraine history

Duration and mean attack frequency were higher in allodynic patients with respect to non-allodynic ones: 19.5 vs 15.1 years ($p < 0.001$), and 11.2 vs 9.3 days/month, ($p = 0.002$), respectively.

Comparing osmophobic and non-osmophobic migraineurs, history of migraine was longer in osmophobic subjects: 21.1 vs 16.3 years ($p < 0.001$). Mean frequency of attacks was similar in the two groups, without significant differences (10.8 vs 10.1 days/month, $p =$ NS).

Conclusions

We found that osmophobia was associated with a longer history of migraine in a clinical sample with different migraine forms, and that it was related to the presence of CA. These findings suggest that, similar to CA, osmophobia needs time and a history of repeated headache attacks to develop a pattern which suggests a process of hypersensitization.

A previous work on this field seems to support this hypothesis [2]: ictal osmophobia during migraine attacks was found to be related to a broader sensorial hypersensitivity.

On the other hand, the observation that osmophobia, exactly as CA, may also be reported at the onset of a migraine history, and that also people with episodic migraine often report being osmophobic, both during and between acute migraine attacks, may suggest another possible explanation of the observed relationship between osmophobia and allodynia. By this viewpoint, osmophobia may be seen as the expression of a particular hypersensitivity to olfactory stimuli. Among these hypersensitive patients, olfactory stimulations might sensitize pain matrix nuclei, like

Table 1 Correlation of CA and osmophobia in episodic and chronic migraineurs

Osmophobic patients ($N = 161$)	Chronic migraine ($N = 46$)	Allodynic	34	73.9 %	$p = 0.01$
		Non-allodynic	12	26.1 %	
	Episodic migraine ($N = 115$)	Allodynic	59	51.3 %	
		Non-allodynic	56	48.7 %	
Non-osmophobic patients ($N = 508$)	Chronic migraine ($N = 134$)	Allodynic	76	56.7 %	$p = 0.10$ (NS)
		Non-allodynic	58	43.3 %	
	Episodic migraine ($N = 374$)	Allodynic	181	48.4 %	
		Non-allodynic	193	51.6 %	

repetitive painful stimulations. Other works, focused on photophobia, put in evidence the possibility that multiple different stimulations, such as the optic one, may converge the neuronal firing on nuclei of the pain pathway reinforcing the sensitisation process [8]: likewise, olfactory stimulation may act in the same way in hypersensitive subjects. The presence of ictal osmophobia also in patients with episodic forms of migraine in which CA is not present seems to reinforce this second physiological explanation. On the contrary, a recent work on episodic migraineurs [9] did not found differences between patients and controls in term of "olfactory identification ability", apparently in contrast with the hypothesis that the hypersensibility to olfactory stimulation may contribute to the sensitization process. In fact, this statement is not entirely true: the study was limited to episodic migraineurs and it did not separate osmophobic migraineurs from non-osmophobic neither clinically hyperosmic from non-hyperosmic. It may be possible that these subgroups have a different olfactory identification ability, and consequently a different intensity in the neuronal firing from olfactory structures toward pain matrix nuclei. Furthermore, the same olfactory identification ability may lead to different effects on head pain nuclei of controls, as they do not have a "migraine brain".

In conclusion, we found a relationship between CA and osmophobia, particularly in patients with chronic migraine. This finding may contribute to the insight in the neuronal abnormalities of the "migraine brain", and in the mechanisms leading to migraine chronification. The correlation between these peculiar symptoms of migraine may be interpreted in different ways: is osmophobia a cause or consequence of central sensitization in allodynic migraineurs? The above-discussed hypotheses should be tested in further studies, possibly comparing prospectively the frequency of osmophobia, hyperosmia, and CA, since the onset of a migraine history.

Conflict of interest There is no actual or potential conflict of interest in relation to this article.

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BRIEF COMMUNICATION

Headache in cerebral venous thrombosis associated with extracranial tumors: a clinical series

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Abstract Cerebral venous thrombosis (CVT) may represent the clinical onset of malignancies or complicate their course, also in phase of quiescence. In literature, there are several case reports on the association between CVT and tumors, but there are few articles on its clinical characteristics in cancer patients (Pts). Our aim was to analyze the clinical characteristics of CVT associated with extracranial tumors. We identified nine cases of CVT in adults affected by extracranial tumors in 6 years from six hospitals. The median age was 40 years; eight Pts were female. Associated tumors were: lymphoma (4/9); breast (2/9), rhinopharynges (1/9) and gastric (1/9) carcinomas. One patient presented a kidney tumor and a melanoma at the same time. Multiple sinuses were affected in seven Pts. MRI showed parenchymal lesions in most cases (7/9). Clinical manifestations were: focal deficits (7/9), headache (6/9), early seizures (4/9) and consciousness disorders (3/9). Headache was the onset symptom in six Pts. In four of these Pts, headache preceded the onset of the focal deficit and/or seizures than 2–15 days. The characteristics of the headache were variable in intensity, location and type but all the Pts agreed in saying that it was an unusual headache, unresponsive to common pain medications. Five of the six Pts complaining of headache in the course of CVT presented focal deficits and parenchymal lesions at admission to the emergency room. All nine Pts were anticoagulated without further haemorrhagic complications. At discharge, the Pts presented a complete recovery in four cases, mild sequelae in four and moderate sequelae in one. In conclusion, we would like to underline the importance of particular care to cancer Pts complaining of headache, since the early diagnosis and the appropriate anticoagulant treatment could prevent the appearance of parenchymal lesions and the consequent neurological deficits. Also in the cases of normal brain CT, a brain MRI/MR venography should be performed in emergency setting if CVT is suspected.

Keywords Cancer · Cerebral venous thrombosis · Headache

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Introduction

Cerebral venous thrombosis (CVT) may represent the clinical onset of tumors or they may complicate their course, also in phase of quiescence [1]. Raizer [2] identified a CVT's prevalence of 0.3 % in a population of cancer patients (Pts). In a multicenter study, cancer represented a risk factor in 7.4 % of the cases [3]. In literature, there are several case reports on the association between CVT and tumors, but there are few articles on its clinical characteristics in cancer Pts [2]. Moreover, there are few articles

on the feature of headache in this particular population of CVT [4].

Our aim was to analyze the clinical characteristics of CVT associated with extracranial tumors, with particular attention to the characteristics of the headache.

Materials and methods

We identified nine cases of CVT in adults affected by extracranial tumors, in the period January 2004–December 2009 from six of the General or Universitary Lombardia hospitals (Table 1).

Results

The median age was 40 years; eight Pts were female. The diagnosis of CVT was established by MRI/MR venography in eight Pts and by intra-arterial angiography in one. Malignancies were active in eight cases. The clinical manifestations were: focal deficits (7/9), headache (6/9), seizures (4/9) and consciousness disorders (3/9). Headache was the onset symptom in six Pts. In four of these, headache preceded the onset of other clinical manifestations than 2–15 days. The characteristics of the pain were variable in intensity, location and type but all Pts agreed in saying that it was an unusual headache, unresponsive to common analgesies (Table 1). In most cases, headache was associated with nausea and vomiting. Five Pts complaining of headache presented focal deficits and parenchymal lesions at admission to the emergency room (ER). MRI showed parenchymal lesions in seven Pts, satellite hemorrhages in four. All Pts were anticoagulated without further haemorrhagic complications. At discharge four Pts presented a complete recovery (mRS 0), four Pts mild sequelae (mRS 1–2) and one moderate sequelae (mRS 3). At 6-month follow-up, two Pts died because of the tumor progression, one had arterial stroke and one developed partial seizures.

Discussion

Headache was the principal onset symptom of CVT but unfortunately 84 % of these Pts presented to the ER when focal deficits were already appeared. It is important to underline the correlation between an early CVT diagnosis and a favorable outcome [3]. Thus, headache should not be underestimated in oncologic Pts, also in the cases of normal brain CT scan (as it happens in 30 % of confirmed CVT) [5]. The medical management of these Pts is extrapolated and it is similar to the treatment of CVT from all

Table 1 Demographic and clinical data of our patients

Patients	Age	Tumor	Other risk factors	Onset of TVC	Clinical manifestations	Headache characteristics	Involved sinuses/veins	Parenchymal lesions	Tp	Outcome at discharge
ET, F	75	Breast	CTX	A	FD, CD	–	SS, DVS	Yes	LMWH	mRS 2
LF, F	59	Gastric	Steroid therapy	Occasional remark	None	–	LS, jugular vein	No	LMWH	mRS 0
BS, F	32	NHL	None	A	FD, seizures	–	SSS, LS	Yes	LMWH	mRS 0
SC, F	29	HL	CTX	A	HA, FD, seizures	SA, frontal bilateral, S, RtD[a]	SSS	Yes	LMWH	mRS 0
RV, F	40	Breast	OT, HHC	SA	HA, FD	SA, right hemicranius, MO/S, N/V, RtD[b]	SS, DVS, LS	Yes	UH	mRS 2
FP, F	24	NHL	CTX, factor V Leiden mutation	A	HA, FD, seizures	A, generalized, MO/S, RtD[b]	SSS	Yes	LMWH	mRS 1
BE, F	31	NHL	CTX, OC	SA	HA, FD, CD, seizures	SA, generalized, MO, N/V, RtD[b]	SSS, LS	Yes	UH	mRS 0
PAM, F	59	Kidney and melanoma	HHC	SA	HA, FD	SA, frontal bilateral, MO, N/V, RtD[a]	SSS, SS, LS	Yes	LMWH	mRS 1
GC, M	61	Rhinopharynges	None	SA	HA, CD, ocular movement deficits	SA, frontal bilateral, MO/S, N/V, RtD[a]	Cavernous sinus	No	LMWH	mRS 3

F female, *M* male, *CA* carcinoma, *HD* Hodgkin's lymphoma, *NHL* non-Hodgkin's lymphoma, *CTX* chemotherapy, *OC* oral contraceptive, *HHC* hyperhomocysteinemia, *A* acute, *SA* subacute, *HA* headache, *FD* focal deficit, *CD* consciousness disorder, *MO* moderate, *S* severe, *NV* nausea/vomiting, *RtD* response to drugs, [a] absent or [b] partial, *SSS* superior sagittal sinus, *SS* straight sinus, *LS* lateral sinus, *DVS* deep venous system, *UH* unfractionated heparin, *LMWH* lower molecular weight heparin, *mRS* modified Rankin Scale

causes [1]. Anticoagulant therapy is widely used also in presence of intraparenchymal hemorrhage [3, 6]. Our experience seems to confirm the usefulness and safety of the anticoagulant therapy, also in the subgroup of oncologic Pts.

Conclusions

We would like to underline the importance of particular care to cancer Pts complaining of headache since the early diagnosis and the appropriate anticoagulant treatment could prevent the appearance of parenchymal lesions and the consequent neurological deficits. Also in the cases of a normal brain CT, an MRI/MR venography should be performed in emergency setting, if CVT is suspected.

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

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BRIEF COMMUNICATION

Persistent orthostatic headache without intracranial hypotension: which treatment?

M. Curone · A. Proietti Cecchini · L. Chiapparini · D. D'Amico

Abstract Orthostatic headache can be the leading symptom of intracranial hypotension, however, not all orthostatic headaches are due to cerebrospinal fluid leaks and these forms can be a clinical problem, especially for treatment. Aim of this study was to review patients with persistent orthostatic headache in whom a detailed head and spinal MRI follow-up did not reveal any sign of intracranial hypotension and to evaluate which treatment can be considered the first choice. Patients admitted to our headache center for evaluation of persistent orthostatic headache and followed after first admission with clinical and neuroradiological controls were systematically reviewed. 11 patients (7 M, 4 F) followed in a period lasted from 10 months up to 2 years were studied. Six patients (54, 5 %) reported a MRI performed previously elsewhere with a suspect diagnosis of intracranial hypotension which was not confirmed at MRI at our hospital such as during the radiological follow-up. Three patients (27.2 %) had developed orthostatic headache short after a neck or head trauma with no evidence of neuroradiological pathological signs and two patients (18 %) had a previous history of psychiatric disorder. We administrated antidepressants in five patients, atypical neuroleptic in three patients, association of antidepressant and antipsychotic in one patient and muscle relaxants in two cases. All patients showed a certain improvement of headache in the weeks after introduction of the pharmacological treatment; six (54, 5 %) had pain relief during the follow-up and five (45, 5 %) were pain free at the last clinical control. We found out that patients with the best outcome were the ones treated with antidepressants. Persistent orthostatic headache without any neuroradiological sign of intracranial hypotension is a challenging problem for clinicians. Although the International Classification of Headache Disorders (ICHD-3 beta version) criteria suggests the possibility of epidural blood patch in orthostatic headache without causes, we believe that a pharmacological treatment tailored on each patient should be always considered and antidepressants can be the first choice.

Keywords Intracranial hypotension · Orthostatic headache · Antidepressants

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Introduction

Orthostatic headache can be the leading symptom of intracranial hypotension, however, not all headaches caused by cerebrospinal fluid (CSF) leaks are orthostatic and not all orthostatic headaches are due to CSF leaks. Moreover, orthostatic headaches can occur without head and spinal MRI evidence of intracranial hypotension [1]. This headache forms, when persistent and with no response to acute therapies, can be a clinical problem particularly as far as treatment.

Objective

Aim of this study was to review patients with persistent orthostatic headache and normal head and spine MRI to evaluate which treatment can be considered the first choice.

Patients and methods

We reviewed the charts of patients admitted to our Headache Center for persistent orthostatic headache followed with several clinical and neuroradiological controls after first admission in whom a detailed head and spine MRI study did not reveal signs of intracranial hypotension or any other causes of secondary headache.

Results

11 patients (7 M, 4 F) mean age 37.4 years (range 18–58 years) followed in a period lasted from 10 months up to 2 years were studied. All patients complained at admission a moderate to severe daily/near daily non pulsating diffuse headache with a dull pressure occipital and/or frontal, the longer they were upright with improving in a variable time frame of 5 min to 3 h after lying down. Past medical history was positive for chronic migraine in 2 on 11 (18 %). All patients considered this headache disabling. In six patients (54.5 %) headache was partially relieved by analgesics while in five (45.4 %) was acute-drugs resistant. Two patients (18 %) reported constriction in the neck area without worsening after sitting or standing. No nausea, fullness, dizziness or vomiting was described by patients. Six patients (54, 5 %) showed a brain MRI performed previously elsewhere with a suspect diagnosis of intracranial hypotension which was not confirmed at brain and spine MRI performed at our Hospital such as during the radiological follow-up. Three patients (27.2 %) had developed orthostatic headache short after a neck or head trauma with no evidence of neuroradiological pathological signs and two patients (18 %) had a previous history of psychiatric disorder. All these 11 patients received medical treatment with different drugs for at least 4 months to 1 year. We administrated antidepressants in five patients, atypical neuroleptic in three patients, association of antidepressant and antipsychotic in one patient and muscle relaxants in two cases. Two patients were treated with amitriptyline 25 mg/day and one with association of amitriptyline and chlordiazepoxide, respectively, at daily dose of 25 and 10 mg. One patient was treated with escitalopram 10 mg per day, and one with duloxetine up to 60 mg/day. Three patients were treated with tiapride administrated orally 100 mg three times a day and one patient with association of escitalopram 10 mg/day and olanzapine 5 mg/day. Two patients were treated with an increasing dosage of cyclobenzaprine (from 10 mg/day up to 30 mg/day). All patients showed a certain improvement of headache in the weeks after introduction of the pharmacological treatment; six (54, 5 %) had pain relief during the follow-up (at 4, 8, 12 and 24 months) and five (45, 5 %) were pain free at the last clinical control. We found out that patients with the best outcome were the ones treated with antidepressants.

Table 1 Headache attributed to spontaneous intracranial hypotension: diagnostic criteria of the International Headache Society (ICHD-III beta version) and comments

Diagnostic criteria
A. Any headache fulfilling criterion C
B. Low CSF pressure (<60 mm CSF) and/or evidence of CSF leakage on imaging
C. Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or has led to its discovery
D. Not better accounted for by another ICHD-3 diagnosis
Comments
In patients with typical orthostatic headache and no apparent cause, after exclusion of postural orthostatic tachycardia syndrome (POTS) it is reasonable in clinical practice to provide autologous lumbar EBP. It is not clear that all patients have an active CSF leak, despite a compelling history or brain imaging signs compatible with CSF leakage. Cisternography is an outdated test, now infrequently used; it is significantly less sensitive than other imaging modalities (MRI, CT or digital subtraction myelography). Dural puncture to measure CSF pressure directly is not necessary in patients with positive MRI signs such as dural enhancement with contrast

Discussion

Persistent orthostatic headache without neuroradiological signs of intracranial hypotension is a challenging problem for clinicians. The International Classification of Headache Disorders (ICHD-3 beta version) criteria for "headache attributed to spontaneous intracranial hypotension" [2] (Table 1) specify in comments that in patients with typical orthostatic headache and no apparent cause, it is reasonable in clinical practice to provide autologous lumbar epidural blood patch (EBP) but the choice of an invasive surgical treatment without specific indication raises some ethical issues. Moreover, a psychiatric evaluation should be performed to exclude a comorbid psychiatric condition underlying headache [3]. We believe that a pharmacological treatment tailored on each patient should be always taken into account in these cases. Considering their efficacy in several headache forms [4, 5] antidepressants may be the first choice.

Conflict of interest The authors declare no conflict of interest.

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BRIEF COMMUNICATION

Triptan use among hospital workers affected by migraine

G. Viticchi · L. Falsetti · L. Buratti · A. Plutino · L. Provinciali · M. Silvestrini · M. Bartolini

Abstract Triptans represent the most specific and effective treatment for migraine attacks. Nevertheless, in clinical practice, they are often underused. Hospital workers, in particular physicians, are expected to be more aware of the correct use of specific drugs, especially for a very common disease such as migraine. Aim of this study was to evaluate whether different hospital workers affected by migraine are able to correctly manage the most suitable therapy for their migraine attacks. During a 1-year period, we submitted hospital employees to a structured interview with a questionnaire to investigate the presence of headache and its characteristics. In particular, in the subpopulation of subjects affected by migraine, we took information regarding their usual treatment for the control of attacks. The type of drug and the category of the working activity were synthesized as two different ordinal variables. Difference in the distribution of the different drug categories was evaluated with Chi squared test. Statistics was performed with SPSS 13.0 for Windows systems. We enrolled 1250 consecutive subjects: 20.3 % of the population (254 patients) was affected by migraine. Triptans use was significantly lower than that of non-steroidal anti-inflammatory drugs. The distribution of the use of the drugs was significantly different ($p < 0.0001$) at Chi squared test. Among migraineur physicians, only 10.7 % used triptans. Even in this subgroup, we observed a significant difference ($p < 0.0001$) in the distribution of the use of the drugs at Chi squared test. Our findings show a reduced use of triptans among hospital workers. These data reflect the unsatisfactory dissemination of knowledge regarding the correct management of migraine attacks and the advantages of treatment with triptans. An incorrect therapeutic approach to migraine contributes to the risk of the most important complications, such as drugs abuse or illness chronicization. These findings suggest that an insufficient awareness of migraine-related therapeutic options also involves hospital workers, including physicians.

Keywords Migraine · Hospital workers · Triptans · Therapy

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Introduction

Migraine is one of the most common medical conditions, affecting millions of subjects worldwide; moreover, it remains, for a large part of affected people, a sub-diagnosed illness [1, 2]. In several cases, patients do not receive a correct diagnosis and consequently they do not obtain a specific treatment [1–3].

Triptans represent the most specific and effective treatment for migraine attacks [4]. Nevertheless, in clinical practice the use of these drugs is less widespread than that of other, less specific drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs). Several studies showed that among recognized migraineurs few subjects are submitted to specific treatment [5]. In a recent investigation, only from 0.7 to 1.0 % of the analyzed population on migraine subjects used triptans [6], while in other studies the percentage varied between 3.0 and 19 % [7, 8].

Hospital workers, in particular physicians, are expected to be more aware of the correct use of specific drugs, especially for a very common disease such as migraine. Aim of this study was to verify whether hospital workers affected by migraine are actually able to handle the most suitable treatment for their migraine attacks.

Methods

Over a 1-year period, during visits for the verification of the ability to work, we submitted each hospital workers of the University Hospital of Ancona to a structured interview with a specific questionnaire. The enrolled hospital employees were representative of all different working roles (physicians, nurses, technicians, sanitary workers and administrative staff members). The survey included several questions concerning the presence of headache and its characteristics; particularly, among subjects affected by migraine, we took information regarding the treatment for the control of their attacks and the typology of employed drugs. We adopted the ID-migraine test, a validated three-question test to formulate a migraine diagnosis in primary care settings [9].

Sex, the presence of headache and the diagnosis of migraine were collected in different dichotomous variable. Age was considered as a continuous variable. The type of drug used for the attack and the category of the worker were synthesized as two different ordinal variables. Difference of distribution of the different drug categories was evaluated with Chi squared test. Statistics was performed with SPSS 13.0 for Windows systems.

Results

We enrolled 1250 consecutive subjects, with a mean age of 40.9 (±11.63) years. Males represented 36.5 % of the sample; 20.3 % of this population (254 patients) was affected by migraine. 160 (62.9 %) migraine patients did not take any drug, 9 (3.74 %) used paracetamol, 22 (8.5 %) triptans, 42 (16.7 %) NSAIDS, 4 (1.7 %) steroids, while 1 (0.34 %) used ergotamines; the remaining part of this patients took undefined analgesics (16 subjects, 6.29 %). Triptans use was significantly lower than NSAIDs. The distribution of the use of the drugs was significantly different ($p < 0.0001$) at Chi squared test. Among migraineur physicians (28 subjects, 8.9 %), the results were particularly unexpected. During acute attacks, 19 (67.9 %) did not use any drug, 1 (3.57 %) took paracetamol, 3 (10.7 %) NSAIDS, 1 (3.57) % unspecified analgesic drugs and 1 (3.57 %) still used ergotamines. Only 3 (10.7) % of them used triptans. Even in this subgroup, we observed a significant difference ($p < 0.0001$) in the distribution of the use of the drugs at Chi squared test.

Discussion

Our findings show a reduced habit in the use of triptans among hospital workers. This observation was common in all the categories considered in this investigation. Our results largely overlap literature data concerning larger populations, reflecting a low rate of utilization and a high percentage of treatment discontinuation [10]. Triptans represent, according to international guidelines [4], the most specific and effective therapy for acute migraine attacks. However, their use remains limited among migraineurs. According to our results, the use of NSAIDs or paracetamol is widely preferred.

This incorrect therapeutic approach involves all the in-hospital workers categories, including physicians. Our data highlight the unsatisfactory dissemination of knowledge about the correct management of migraine attacks among hospital workers, theoretically more sensitized about health problems and, in particular, about the advantages of using the most specific and effective treatments for a well-known and diffuse illness like migraine. Moreover, according to our data, clinicians seem to be scarcely aware about the possible complications of a wrong treatment for migraine attacks, such as drugs abuse or illness chronicization.

Spreading the knowledge of the current guidelines and increasing triptans use must be considered a target for a correct management of migraine, particularly among hospital workers.

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

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BRIEF COMMUNICATION

Early (≤1-h) vs. late (>1-h) administration of frovatriptan plus dexketoprofen combination vs. frovatriptan monotherapy in the acute treatment of migraine attacks with or without aura: a post hoc analysis of a double-blind, randomized, parallel group study

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Abstract The early use of triptan in combination with a nonsteroidal anti-inflammatory drug after headache onset may improve the efficacy of acute migraine treatment. In this retrospective analysis of a randomized, double-blind, parallel group study, we assessed the efficacy of early or late intake of frovatriptan 2.5 mg + dexketoprofen 25 or 37.5 mg (FroDex 25 and FroDex 37.5) vs. frovatriptan 2.5 mg alone (Frova) in the acute treatment of migraine attacks. In this double-blind, randomized parallel group study 314 subjects with acute migraine with or without aura were randomly assigned to Frova, FroDex 25, or FroDex 37.5. Pain free (PF) at 2-h (primary endpoint), PF at 4-h and pain relief (PR) at 2 and 4-h, speed of onset at 60, 90, 120 and 240-min, and sustained pain free (SPF) at 24-h were compared across study groups according to early (≤1-h; $n = 220$) or late (>1-h; $n = 59$) intake. PF rates at 2 and 4-h were significantly larger with FroDex 37.5 vs. Frova (early intake, $n = 71$ FroDex 37.5 and $n = 75$ Frova: 49 vs. 32 % and 68 vs. 52 %, $p < 0.05$; late intake, $n = 20$ Frodex 37.5, and $n = 18$ Frova: 55 vs. 17 %, $p < 0.05$ and 85 vs. 28 %, $p < 0.01$). Also with FroDex 25, in the early intake group ($n = 74$) PF episodes were significantly higher than Frova. PR at 2 and 4-h was significantly better under FroDex 37.5 than Frova (95 % vs. 50 %, $p < 0.001$, 100 % vs. 72 %, $p < 0.05$) in the late intake group ($n = 21$). SPF episodes at 24-h after early dosing were 25 % (Frova), 45 % (FroDex 25) and 41 % (FroDex 37.5, $p < 0.05$ combinations vs. monotherapy), whereas they were not significantly

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different with late intake. All treatments were equally well tolerated. FroDex was similarly effective regardless of intake timing from headache onset.

Keywords Migraine · Frovatriptan · Dexketoprofen · Early use · Late use

Introduction

Available monotherapies against migraine attacks include triptans, nonsteroidal anti-inflammatory drugs (NSAID), ergot derivatives, and antiemetic [1–3]. Triptans are selective 5-HT1B/1D agonists especially effective at treating moderate-to-severe acute migraine attacks. Frovatriptan is one of the newest compounds, designed to potentiate the long-term duration of analgesic properties, and to limit side effects and drug interactions [4]. The half-life of frovatriptan is five times longer than other triptans, and the maximum concentration is similar, when given orally [5, 6]. NSAIDs are indicated for acute management of mild-to-moderate migraine attacks [1]. Dexketoprofen is a cyclooxygenase inhibitor that reaches the maximum plasma concentration after 30-min since its oral administration and has short half-life [7]. According to a recent survey, among 8440 oral triptan users, 27 % reported the use of triptan and NSAID combination therapy to treat the last attack [8]. The practice of combining multiple drugs reflects the fact that not all patients obtain consistent and complete relief of headache and related symptoms with a single agent [2, 9]. However, there is also a rationale for frovatriptan and dexketoprofen combination based on the pharmacological properties of the two compounds. In principle, dexketoprofen would provide good early pain relief of migraine pain, while the longer half-life of frovatriptan would reduce the recurrence within 48-h [2]. A randomized double-blind parallel group study evaluated the combination of frovatriptan and dexketoprofen (25 or 37.5 mg) over frovatriptan alone in the acute treatment of migraine. Both the combinations had an improved pain free activity at 2-h and ameliorated sustained pain free at 24-h compared to frovatriptan monotherapy [10]. The early use of triptan after headache onset is particularly recommended for patients with rapid pain onset and worsening, high frequency of recurrence and severe associated symptoms [11]. Therefore, a retrospective analysis from the aforementioned randomized study was performed to analyze whether drug use within 30-min from headache pain onset may affect combination efficacy. The timing of drug intake relative to the onset of headache did not seem to influence clinical benefits of frovatriptan plus dexketoprofen [12]. The combination was confirmed as similarly effective at treating acute migraine attacks either with early or late administration.

Since, early treatment was never univocally defined in the various studies of triptans' efficacy, with most common time points set at 30 or 60 min of pain onset [13–16] and since the post hoc analysis on early intake of frovatriptan plus dexketoprofen at 30 min was already published, we decided to further investigate whether frovatriptan plus dexketoprofen or frovatriptan alone could have shown different efficacy when taken within or after 1-h from headache onset.

Methods

Study population and design

As detailed in the main publication [10], the study enrolled 18–65 years old male and non-pregnant and non-breast feeding female subjects, suffering from migraine with or without aura [17] with at least one, but no more than six migraine attacks per month for 6 months prior to entering the study. In this post hoc analysis, we separately selected subjects who treated headache pain within 1-h of its earliest onset, or when headache pain was established (late use, >1-h).

This was a multicenter, randomized, double-blind, active-controlled, three parallel group study, conducted in 25 different Italian Headache Centers. Following a screening visit, eligible patients were randomized to frovatriptan 2.5 mg (Frova), or to extemporaneous combinations of frovatriptan 2.5 mg + dexketoprofen 25 mg (FroDex 25) or frovatriptan 2.5 mg + dexketoprofen 37.5 mg (FroDex 37.5). To ensure blinding the study drugs were over encapsulated. At the end of the randomization visit a headache diary was dispensed to the patient in order to document the characteristics of the headache pain and associated symptoms. The intensity of headache and the associated symptoms were graded according to a four-point rating scale, as recommended by the International Headache Society [17]. Each subject received the study medication and was instructed to self-administer the drug at home and complete the diary, for the first migraine attack occurring during the study period (i.e., within 1 month from randomization). Further details on the study protocol and methodology may be found in the original study publication [10].

Data analysis

The full analysis set of the original study was used for this retrospective analysis and included all subjects randomized

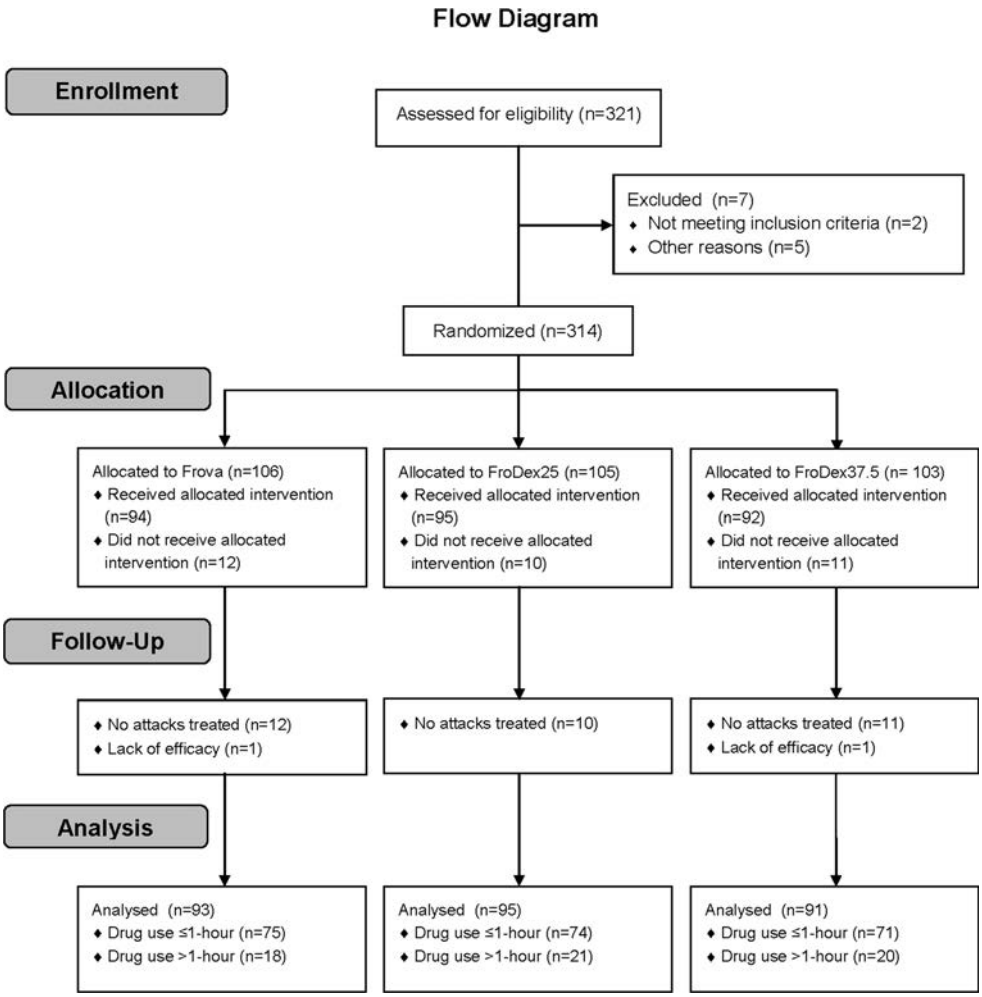

Fig. 1 Flow diagram of the patients throughout the study

and treated, for whom at least one post-dose headache attack was recorded. The analysis was separately performed in the subgroup of patients reporting early (within 1-h) or late (after 1-h) study drug use.

The following efficacy endpoints were evaluated for each of the subgroups: (a) proportion of pain-free subjects at 2-h before any rescue medication (primary study endpoint, estimated according to International Headache Society Guidelines) [17]; (b) proportion of pain-free subjects at 4-h before any rescue medication [17]; (c) proportion of patients with pain relief at 2 and 4-h, defined as the percentage of subjects with a decrease in headache from severe or moderate to mild or none within 2 or 4-h [17]; (d) speed of onset, defined as the proportion of subjects with a decrease of at least one point in pain intensity at 60, 90, 120 or 240-min; (e) sustained pain free within 24-h (pain free episode at 2-h with no use of rescue medication or recurrence within 24-h); (f) time to meaningful relief, defined as a reduction of at least two points on the four-point scale (i.e., from pain score of 3 at baseline to mild or no pain of score 1/0); (g) proportion of subjects taking rescue medication; and, (h) subjects' preference for treatment.

Continuous variables were summarized by computing mean values and standard deviations (SD), and categorical variables by computing the absolute value and the frequency (as percentage). The primary study endpoint was assessed by the Fisher-Freeman-Halton exact test statistics using either a 3×2 contingency table for testing association or a 2×2 contingency table for comparisons between treatments. The Fisher exact test based on 2×2 contingency tables was applied to secondary variables to check difference between pairs of treatments. A t test of Student was used to evaluate differences between continuous variables. All tests were two-sided and the level of statistical significance was set at 0.05 for all analyses.

Results

Figure 1 shows the flow diagram of patients through the study. 220 out of 279 subjects of the full analysis set took

Table 1 Demographic and clinical characteristics of the 279 patients of the full analysis set at the time of randomization

	Early drug use (≤1-h)				Late drug use (>1-h)			
	Frova ($n = 75$)	FroDex 25 ($n = 74$)	FroDex 37.5 ($n = 71$)	All ($n = 220$)	Frova ($n = 18$)	FroDex 25 ($n = 21$)	FroDex 37.5 ($n = 20$)	All ($n = 59$)
Age (years, mean ± SD)	38.3 ± 9.1	38.0 ± 10.5	40.7 ± 9.8	39.0 ± 9.8	41.0 ± 8.2	41.6 ± 9.3	40.5 ± 10.1	41.0 ± 9.1
Females (*n*, %)	70 (93.3)	64 (86.5)	58 (81.7)	192 (87.3)	18 (100.0)	20 (95.2)	16 (80.0)	54 (91.5)
Height (cm, mean ± SD)	165.0 ± 5.7	166.8 ± 7.6	166.9 ± 7.4	166.2 ± 7.0	161.7 ± 5.3*	162.6 ± 6.6*	164.5 ± 8.9	162.9 ± 7.1**
Weight (kg, mean ± SD)	61.9 ± 8.6	61.6 ± 9.8	64.6 ± 12.7	62.7 ± 10.5	57.6 ± 8.9	60.7 ± 10.7	59.6 ± 9.8	59.4 ± 9.8*
MIDAS score (mean ± SD)	24.0 ± 16.9	24.8 ± 29.2	24.0 ± 18.0	24.3 ± 22.0	19.0 ± 17.4	28.4 ± 30.7	19.1 ± 9.8	22.4 ± 21.6
Presence of aura (*n*, %)	7 (9.3)	2 (2.7)	2 (2.8)	11 (5.0)	2 (11.1)	–	3 (15.0)	5 (8.5)
Intensity of attack (*n*, %)								
Mild	8 (10.7)	6 (8.1)	3 (4.2)	17 (7.7)	–	–	–	–
Moderate	44 (58.7)	45 (60.8)	41 (57.7)	130 (59.1)	14 (77.8)*	17 (81.0)**	16 (80.0)	47 (79.7)**
Severe	23 (30.7)	23 (31.1)	27 (38.0)	73 (33.2)	4 (22.2)*	4 (19.0)**	4 (20.0)	12 (20.3)**
Presence of nausea (*n*, %)	37 (49.3)	35 (47.3)	33 (46.5)	105 (47.7)	8 (44.4)	12 (57.1)	9 (45.0)	29 (49.2)
Presence of photophobia (*n*, %)	51 (68.0)	48 (64.9)	50 (70.4)	149 (67.7)	13 (72.2)	13 (61.9)	13 (65.0)	39 (66.1)
Presence of phonophobia (*n*, %)	49 (65.3)	48 (64.9)	42 (59.2)	139 (63.2)	9 (50.0)	14 (66.7)	9 (45.0)*	34 (57.6)
Preventive therapy (*n*, %)								
Antidepressant	4 (5.3)	5 (6.8)	9 (12.7)	18 (8.2)	5 (27.8)	3 (14.3)	1 (5.0)	9 (15.3)
Antiepileptics	6 (8.0)	5 (6.8)	9 (12.7)	20 (9.1)	1 (5.6)	1 (4.8)	1 (5.0)	3 (5.1)
Beta-blocking agents	3 (4.0)	2 (2.7)	6 (8.5)	11 (5.0)	1 (5.6)	1 (4.8)	3 (15.0)	5 (8.5)
Triptan users (*n*, %)	17 (22.7)	14 (18.9)	16 (22.5)	47 (21.4)	6 (33.3)	10 (47.6)*	8 (40.0)	24 (40.7)**
NSAIDs users (*n*, %)	20 (26.7)	10 (13.5)	10 (14.1)	40 (18.2)	5 (27.8)	5 (23.8)	5 (45.0)	15 (25.4)

Data are separately shown for the early (≤1-h) and late (>1-h) drug use and by type of treatment, and are summarized as mean (± SD), or absolute (*n*) and relative frequency (%)

Frova frovatriptan, *ForDex* frovatriptan + dexketoprofen, *MIDAS* migraine disability assessment, *NSAID* nonsteroidal anti-inflammatory drugs

Asterisks refer to the statistical significance of the difference between the early vs. late subgroup (* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$)

the drug within 1 h (75 Frova, 74 FroDex 25 and 71 FroDex 37.5) and 59 more than 1 h after headache onset (18 Frova, 21 FroDex 25 and 20 FroDex 37.5). The main demographic and clinical characteristics of patients at randomization, stratified in respect to the time of first drug use and allocated treatment, are summarized in Table 1.

Subjects in the early drug use subgroup had a significantly ($p < 0.01$) higher proportion of migraine attacks of severe intensity (33.2 vs. 20.3 % late drug administration), while those in the late drug intake group reported a higher proportion of moderate intensity attacks (79.7 vs. 59.1 % early drug intake). Additionally, phonophobia was reported more frequently ($p < 0.05$) in subjects in the early drug use group treated with FroDex 37.5 (45.0 vs. 59.2 %). Subjects with early drug use also reported a significantly ($p < 0.01$) lesser use of triptans prior to enrollment into the study (21.4 vs. 40.7 % late drug use). No differences were observed among the different treatment groups within each subgroup of the study (early or late drug intake).

Primary study endpoint

As shown in Fig. 2, the proportion pain free at 2-h was significantly larger for the combination therapy vs.

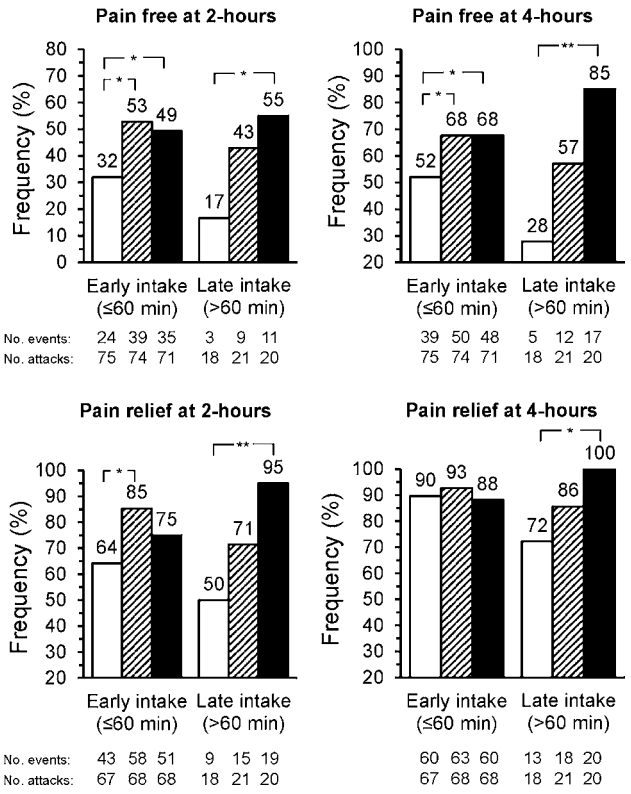

Fig. 2 Proportion (%) of pain free at 2 and 4-h, and of pain relief at 2 and 4-h, after administration of frovatriptan 2.5 mg (*open bars*), frovatriptan 2.5 mg + dexketoprofen 25 mg (*striped bars*) and frovatriptan 2.5 mg + dexketoprofen 37.5 mg (*full bars*), separately shown for the patients reporting early or a late drug use. *Asterisks* indicate a statistically significant difference ($*p < 0.05$ and $**p < 0.01$) between the combination treatment and the monotherapy

monotherapy for both the late and early drug use subgroup ($p < 0.05$). When pairs of treatments were compared, a statistically significant difference was observed between FroDex 25 and Frova for the early dosing subgroup [20.7 % (95 % confidence interval: 5.2, 36.2); $p < 0.05$] and between FroDex 37.5 and Frova for both the early [17.3 % (1.6, 33.0); $p < 0.05$] and late drug use [38.3 % (10.6, 66.1); $p < 0.05$] subgroup.

No statistically significant difference was observed between early and late drug users, in terms of efficacy of combination treatment on pain free at 2-h.

Secondary study endpoints

In both study subgroups, the proportion pain free at 4-h was larger in the combination than in the monotherapy group, with differences achieving statistical significance for FroDex 25 in the early drug use ($p < 0.05$) and for FroDex 37.5 in the early ($p < 0.05$) and late ($p < 0.01$) drug use subgroup (Fig. 2).

Pain relief at 2 and 4-h was significantly larger under FroDex 37.5 than under Frova alone in the late drug use group, whereas in patients with early drug intake pain relief was not significantly different between the combination and the monotherapy, except for pain relief at 2-h under FroDex 25 vs. Frova alone (Fig. 2).

The proportion of sustained pain free over the 24-h was significantly ($p < 0.05$) larger under FroDex 25 (33/74, 44.6 %) and FroDex 37.5 (29/71, 40.9 %) than under monotherapy (19/75, 25.3 %) in case of early drug dosing, whereas no differences were observed across treatment groups in case of late drug intake (Frova: 3/18, 16.7 %; Frodex 25: 8/21, 38.1 %; FroDex 37.5: 9/20, 45.0 %).

The speed of onset of analgesic effect was quicker in case of early than late drug intake. In all time points, the combination therapy was better than monotherapy, with differences reaching a statistically significant difference at 60 and 90 mins in case of early intake, and at 120 and 240 mins in case of late intake (Fig. 3).

Time to meaningful relief in the early drug dosing subgroup was 14.1 ± 16.2 min for Frova, 9.6 ± 13.6 min for FroDex 25, and 11.4 ± 14.3 min for FroDex 37.5, with no statistically significant difference across the randomization groups ($p = 0.300$). On the contrary, in the late drug use group, the time to meaningful relief was significantly ($p < 0.05$) less in the FroDex 37.5 (5.6 ± 2.0 min) and in the FroDex 25 (10.5 ± 13.3 min) than in the monotherapy group (20.6 ± 15.2 min).

Use of rescue medication was not significantly different among the three treatment groups for patients with early drug intake (Frova: 30/75 patients, 40.0 %, FroDex 25: 19/74, 25.7 % and FroDex 37.5: 20/71, 28.2 %), while among those with late drug intake it was significantly ($p < 0.05$) lower with FroDex 37.5 (6/20, 30.0 vs. 12/18, 66.7 % Frova and 12/21, 57.1 % FroDex 25).

Treatment was judged good or excellent by significantly more patients treated with the combination drug than with the monotherapy in the early (FroDex 25: 45/74 patients, 60.8 % and FroDex 37.5: 43/70, 61.4 % vs. Frova: 36/75, 48.0 %, $p < 0.01$ for both) as well in the late dosing group (FroDex 25: 12/21 patients, 57.1 % and FroDex 37.5: 15/20, 75.0 % vs. Frova: 5/18, 27.8 %, $p < 0.05$ and $p < 0.01$, respectively) (Fig. 3).

Non statistically significant differences were reported in the occurrence of total and drug-related adverse events (data not shown).

Discussion

This post hoc analysis of a previous randomized, double-blind, dose comparison study [10] specifically evaluated the efficacy of frovatriptan plus dexketoprofen compared to frovatriptan alone, when administered within or after 1-h from headache onset.

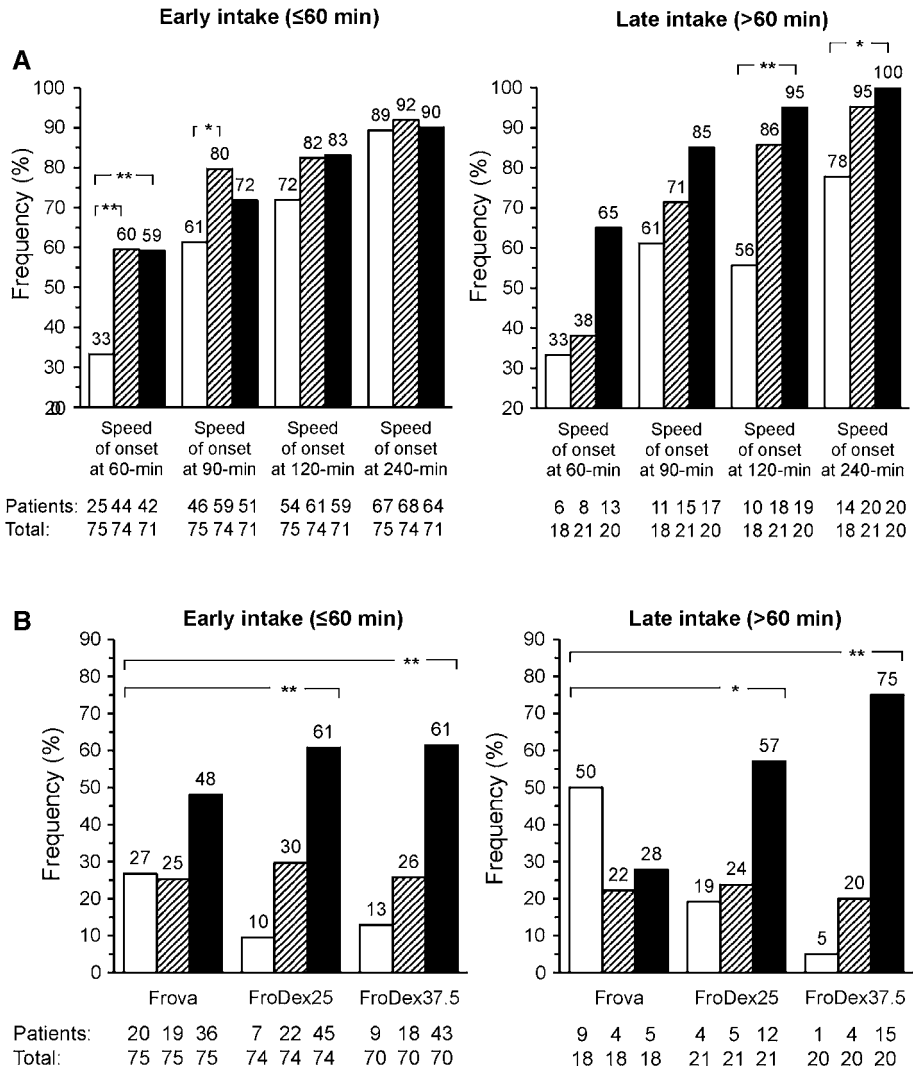

Fig. 3 Proportion (%) of patients with a decrease of one point in pain intensity (speed of onset) 60, 90, 120 and 240-min after drug intake, treated with frovatriptan 2.5 mg (*open bars*), frovatriptan 2.5 mg + dexketoprofen 25 mg (*striped bars*), and frovatriptan 2.5 mg + dexketoprofen 37.5 mg (*full bars*) (**a**) and of patients judging treatment poor or very poor (*open bars*), reasonable (*striped bars*) or good or excellent (*full bars*) (**b**). Data are separately shown for the subgroup of patients reporting early drug dosing and for those with late drug dosing, and for the three different treatments (*Frova* frovatriptan 2.5 mg, *FroDex 25* frovatriptan 2.5 mg + dexketoprofen 25 mg, *FroDex 37.5* frovatriptan 2.5 mg + dexketoprofen 37.5 mg). *Asterisks* indicate a statistically significant difference (*$p < 0.05$ and **$p < 0.01$) between the combination treatment and the monotherapy

The combination was more effective than monotherapy on pain free at 2-h regardless of timing and dosing, confirming evidence from the main study [10] and from a previous post hoc analysis assessing the efficacy of the drug taken 30-min before or after pain onset [12]. The early intake of FroDex 25 mg increased pain-free activity at 2 and 4-h compared to Frova. The FroDex 37.5 mg late intake significantly improved pain-free activity at 4-h and pain relief at 2 and 4-h compared to Frova. Late intake and high dose dexketoprofen reduced the time to achieve meaningful relief and the use of rescue medications. Both early and late intake of FroDex significantly improved the speed of onset as compared to Frova. The combination was judged good or excellent in a larger proportion of patients than frovatriptan alone. Therefore, these results confirm that, when dexketoprofen is used in combination with frovatriptan, early or late intake does not affect response to treatment.

In our previous post hoc analysis in which we defined as "early" the intake within 30-min from headache onset, we observed a significant improvement on pain free at 2-h activity in the late intake group (FroDex 25 51 % vs. Frova 22 %, $p < 0.005$, FroDex 37.5 50 % vs. Frova 22 %, $p < 0.005$), while in the early intake group the difference in favor of the combination did not achieve the statistical significance [12]. Here, even the early intake resulted significantly more efficient than monotherapy at promoting pain-free activity at 2 and 4-h. FroDex intake after 30-min but within 1-h from headache onset may have major and longer benefits than triptan monotherapy on pain control, even with lower NSAID dosing. Current evidence suggests the administration of triptan monotherapy as early as possible from headache onset to ensure the best effect [3, 18, 19], but the early use of triptan for all migraine attacks is still controversial [16, 20, 21]. This study showed that the addition of dexketoprofen seems to contribute to high pain-

free response also for patients in the early use subgroup who reported high severity of migraine attacks with frequent episodes of phonophobia.

The decrease of one point in pain intensity was more frequent, and thus the speed of onset faster, in the combination subgroups. Noteworthy, with the early intake even FroDex 25 mg was able to significantly improve pain intensity, while the late intake necessitated FroDex 37.5 mg to increase the speed of onset, but the effect lasted longer. Therefore, the late intake of frovatriptan plus high dose dexketoprofen resulted efficient at managing the most severe and difficult attacks.

FroDex late intake decreased the use of rescue medications in respect of monotherapy, thus confirming our previous results with late intake after 30-min [12]. Thus, the combination of triptan plus NSAIDs could reduce the risk of medication-overuse headaches and related adverse drug effects [11, 16]. In this regard, a two-drug combination, as that between frovatriptan and dexketoprofen, ensuring both quick and sustained pain-free activity, should be regarded as a useful treatment option for migraineurs [22, 23].

The main limitations of this study are the post hoc nature and the small number of subjects included in the late use study arm; thus, we suggest further prospective randomized trials to evaluate the proper timing of drug use to magnify analgesic properties of triptan plus NSAIDs combination.

In conclusion, the frovatriptan plus dexketoprofen combination was similarly efficient at treating acute migraine attack irrespective of the time of the drug intake. In particular, this triptan plus NSAID combination showed a longer effect in relieving pain.

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Conflict of interest All authors have occasionally served as scientific consultants for manufacturers of frovatriptan.

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BRIEF COMMUNICATION

Proposal of a model for multidisciplinary treatment program of chronic migraine with medication overuse: preliminary study

L. Grazzi · A. Prunesti · G. Bussone

Abstract The treatment of patients with chronic migraine associated with medication overuse is challenging in clinical practice; different strategies of treatment have been recently developed, multidisciplinary treatment approaches have been developed in academic headache centers. Education and support of patients are necessary to improve patients' adherence to pharmacological treatments as well as to non-pharmacological therapies. This study reports a clinical experience conducted at our Headache center with a group of female patients, suffering from chronic migraine complicated by medication overuse, treated by a multidisciplinary approach and followed for a period of 1 year after withdrawal. Results confirm the efficacy of a multifaceted treatment to manage this problematic category of patients.

Keywords Chronic migraine · Medication overuse · Multidisciplinary treatment · Mindfulness

Introduction

The problem concerning treatment of patients with chronic migraine (CM) associated to medication overuse (MO) is challenging in clinical practice and often a single modality of treatment, pharmacological prophylaxis in the most part of cases, can be insufficient for this problematic category of patients. Different strategies of treatment have been recently developed, as new options of pharmacological therapies, new devices for neurostimulation methods and non-pharmacological approaches [1–3].

Up to now, clinical experiences indicate, when chronic migraine is complicated by medication overuse, withdrawal as the most adequate procedure to help these patients to stop the vicious circle between medication and pain; this procedure is helpful to educate patients how to manage their pain without using medications, also this prospectively helps patients to avoid relapses in overuse by increasing their sense of self-confidence to manage the pain episodes [3, 4].

Nevertheless, after withdrawal, usually patients are not adequately followed: they are treated by pharmacological prophylaxis for migraine according to their characteristics and their migraine history, they are seen with periodic appointments for checking their medical condition at fixed follow-up, but they are not supported to continue the process of detoxication. In particular during the first phase after withdrawal, it has been observed that migraine attacks can be intense: for patients it can be difficult to face up with these new attacks without using medications and, if not well supported and encouraged, the risk of relapse in overuse is high in this critical phase [5].

In the last decades, multidisciplinary treatment approaches have been developed in academic headache centers [5–7]. Education and support of patients are necessary to improve patients' adherence to pharmacological treatments as well as to non-pharmacological therapies.

Aim of this study

This study reports a clinical experience conducted at our Headache center with a group of female patients, suffering from chronic migraine complicated by medication overuse

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(diagnosis according to IHS 2013-beta criteria [8]); they were submitted to a withdrawal in a day hospital setting; after that, they followed a multidisciplinary treatment program to learn how to manage their migraine after withdrawal and we verified the clinical improvement at long follow-up.

Methods

Nineteen female patients (mean age 44.2 ± 6.8) suffering from chronic migraine complicated by medication overuse (diagnosis according to IHS 2013-beta criteria; [8]) were submitted to a withdrawal in a day hospital setting; after that they were followed with pharmacological treatment for prophylaxis; moreover, a physical activity schedule (twice per week, 45 min of aerobic exercise) and cognitive behavioral approach (6 sessions of relaxation training combined with mindfulness practice, twice per month, with CD for home practice) were provided for all patients. Lifestyle modifications were suggested to patients according to their habits and their job and family necessities. Patients were submitted to psychological tests to evaluate disability, quality of life, anxiety, by MIDAS questionnaire, HIT-6 test, Spielberger test in the two forms (STAI X1–X2 for state and trait anxiety). A daily headache diary was given to record pain attacks and their intensity and medication intake every day. Follow-up were fixed at 3, 6 and 12 months after the end of the program to determine the clinical improvement by the analysis of the diary and to repeat the psychological tests.

Results

Patients improved from the clinical point of view: days of migraine per month decreased significantly (23.4 ± 6.6 vs. 11.7 ± 8.3, $p < 0.0003$) and medication intake decreased significantly too (18.1 ± 4.4 vs. 8.8 ± 4.33, $p < 0.005$). MIDAS total score decreased significantly (82.3 ± 75.4 vs. 43 ± 55.21, $p < 0.03$). Anxiety levels and HIT-6 test score did not change significantly. After 1 year we did not record relapses in medication overuse. Although we did not record it specifically, all patients completed regularly the clinical program and they did not report any adverse event.

Conclusions

Although the study lack of a control group or a comparison condition, data obtained suggest that a multidisciplinary strategy seems to be a good option to manage patients with CM and MO instead of pharmacological treatment only.

Other studies in the literature evidenced the effectiveness of multidisciplinary treatment program for patients with chronic migraine. Harpole [9] included in a specific treatment program headache specialists, psychologists, and human care physicians. He found a significant reduction in MIDAS and headache days after 6 months. Gaul [10] in his report too evidenced significant clinical improvement for patients who followed a multidisciplinary treatment program with behavioral intervention, lifestyle modifications, aerobic exercise. In our report, although we did not record it specifically and the sample size was limited, all patients followed the therapeutic program carefully without missing any appointment; in particular, patients were able to follow the sessions for mindfulness practice and they reported increased of self-confidence in managing pain attack during and after the period of training and increased ability to manage stress situations. As we know [4], stress is considered a trigger for headaches and migraine; consequently, a mind–body intervention including mindfulness practice, lifestyle modifications, readjustment of diet and sleep rhythm can be considered very effective to support patients through their therapeutic program. This kind of multifaceted intervention, including mindfulness and meditation practice, has already shown significant advantages for patients, as emerged from preceding studies [11], and even if our report is a pilot study with a limited population of patients and without a comparison condition, the clinical improvement is significant and maintained until 12 months after the end of the program without relapses in overuse. These results may indicate the efficacy of a multidisciplinary intervention and also larger studies with longer follow-up will be necessary to confirm these preliminary data.

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

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POSTERS

Predictor factors influencing the response to botulinum toxin type a bonta) in chronic migraine: a new therapeutic strategy

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Background: Some patients with chronic migraine (CM) are unresponsive to treatment with botulinum toxin type A (BoNTA) through PREEMPT paradigm. Whether there are factors influencing the response to BoNTA treatment in patients with CM is poorly understood.
Aim: To evaluate whether cutaneous allodynia (CA), location and methods of injection influence the efficacy of BoNTA treatment.
Methods: sixty four consecutive patients with CM unresponsive to BoNTA treatment were evaluated for detecting both the location of the pain and the severity of CA, then they underwent either trigeminal or occipital/cervical subcutaneous/intramuscular injections of BoNTA. During the follow up patients were evaluated at 30 and 60 days. Primary end-point was change >50 % in number of monthly headache-free days. Moreover, the same patients were treated with false injections in the area of verum treatment.
Results: According to location of the pain and severity of CA, patients were categorized in 2 groups: Group 1, allodynic patients with trigeminal location of pain, performed subcutaneous BoNTA injections in the trigeminal area; Group 2, non-allodynic patients with occipital location of pain, performed subcutaneous/intramuscular injections in occipital/cervical area. The treatments decreased significantly the number of monthly headache-free days in 56 % of patients in Group 1, and 43 % of patients in Group 2. The efficacy lasted about 60 days. While, few patients had a temporary response to false treatment.
Conclusions: The severity of CA, the location and the methods of injection are factors influencing the efficacy of BoNTA in unresponsive patients with CM.
Reference
Burstein R. 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

Worsening/improving of headache is related to positional changes in CSF pressure in headache arising from high/low csf pressure

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Background: The postural headaches are characterized by position-related worsening/improving of pain, but there is no evidence base that this clinical feature is related to positional changes in CSF pressure.
Aim: To test if worsening/improving of postural headache is related to positional changes in CSF pressure.
Methods: We prospectively performed lumbar puncture in order to measure lumbar CSF opening pressures and to monitor, for 1 h through a lumbar needle, the CSF pressure in 37 consecutive headache sufferers with postural headache. During continuous monitoring of CSF pressure, patients were placed before in lateral decubitus for 15 min and then in Trendelenburg positioning (TP) for the next 15 min in order to record CSF pressure changes.
Results: Of the 37 headaches sufferers with postural headache 18 patients had an elevated CSF opening pressure (>250 mmH_2O) and 10 had a low CSF opening pressure (<60 mmH_2O). Nine patients had a normal CSF opening pressure. TP induced an increase of CSF pressure (mean ± DS 86.2 ± 15.2 mmH_2O) and a worsening of headache in patients with elevated CSF pressure, while a less change in CSF pressure associated with improving of pain were observed in patients with low CSF pressure (mean ± DS, 28 ± 7.1 mmH_2O). There was no significant change in CSF pressure during TP in patients with normal CSF pressure.
Conclusions: Changes in CSF pressure are associated with the worsening/improving of the postural headache, suggesting that TP may be useful in diagnostic strategy of headache arising from high/low CSF pressure.

Increased shear stress as a possible link between stroke and migraine

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Background: Migraine has been associated with an increased risk for ischemic stroke occurring remote from the migraine attack. The mechanisms explaining this association remain poorly understood. A recent study proposes that the enhanced prevalence of ischemic stroke in migraine patients is caused by platelet aggregates, that are, among others, induced by elevated shear stress.
Aim: The aim is to verify the presence of an increased shear stress in the cerebral arterial network in migraine with (MA+) and without aura (MA−).

Methods: We measured the time-delay in milliseconds (ms) between the R-wave of an electrocardiogram and the arterial pulse wave of cerebral microcirculation (R-APWCMtd) on the frontal cortex detected by near-infrared spectroscopy (NIRS) in 10 patients with MA+ (age 39.5 ± 12.2 years), in 10 with MA− (age 40.3 ± 10.2 years), according to ICHD-3 criteria 2013, during the interictal period of migraine, and in 15 age-, sex- and height-matched healthy control subjects. The cases and controls were free from overt cardiovascular events, diabetes, major cardiovascular risk factors and migraine prophylactic medications.
Results: The patients with migraine had a significantly longer R-APWCMtd than the control subjects $F = 13.4$, $p < 0.001$: MA+:+38.3 ms; MA−:+34.7 ms indicating an increased distensibility of the wall of cerebral arterial network. In multiple regression analysis, R-APWCMtd was significantly associated with migraine ($R2 = 0.50$, $p < 0.0001$) but not with age, gender, height, migraine attack frequency and disease duration.
Conclusions: In our migraine patients, a longer R-APWCMtd is independently associated with migraine and indicates an increased distensibility of the wall of cerebral arterial network. The increased distensibility leads to an increased flow pulsatility into the cerebral arterial network that may lead to an increased shear stress. This condition may represent one possible mechanism underlying the increased ischemic stroke risk especially in patients with MA+.

Work-related difficulties in patients with episodic and chronic migraine: a study protocol to define relevant themes

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From literature emerges that migraine has a considerable impact on work activities. This leads to labour and social security problems, as well as increased disease's costs. However, data on the specific type of work activities mainly affected in migraine sufferers are basically not available and this makes difficult to evaluate the real effectiveness of migraine preventive therapies and the cost-benefit of available treatments.

We present here the study design of an observational, cross-sectional study aimed to obtain, from patients with episodic or chronic migraine, relevant information on which work activities are particularly limited, and on the secondary effects of therapies they are taking.

The study is based on a qualitative technique which will employ focus groups, conducted with persons with migraine of working age (6–8 persons for each group, balanced for gender, age and diagnosis). The topics proposed and debated in the focus groups will derive from a previous study that enabled to define some relevant areas for understanding disability in migraineurs, including activities specifically connected to work. Focus groups will be audio-recorded and their content transcribed and analysed through specific software, in order to identify the most relevant themes.

Information collected from focus groups of patients followed by C. Besta Neurological Institute Foundation, will be presented. Descriptive analysis of socio-demographic features of the sample, collected through a questionnaire, will be illustrated too. The main problematic themes emerged from this preliminary study will be used to develop a scale for the evaluation of work-related difficulties in migraine patients, that will be validated in a future national survey.

Panic-agoraphobic spectrum in migraineuses patients

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Background: The correlation between migraine and the panic attack disorder has been the object of numerous speculations in both clinical and pharmaceutical field.
Aim: In our study a sample of migraineuses was given a clinical interview structured for the panic agoraphobic spectrum (SCI-PAS) proposed to evaluate the agoraphobic panic and is articulated on VIII domains, aiming at detecting and quantifying its presence in those patients.
Methods: A sample studied is formed by 188 patients (136 women) of an average age of 41.4 years (SD 11.5) suffering from migraine without aura (ICDH'04 criteria) during the previous 4 years. At that time they weren't on a treatment with drugs of prevention and they had never been before: they didn't suffer from any know psychiatric pathology.
Results: In 118 patients (62.8 %) were satisfied the domain I (sensitivity to separation); in 139 (73.9 %) the domain II (the symptoms of panic); in 16 (8.5 %) the domain III (sensitivity to stress); in 44 (23.4 %) the domain IV (sensitivity to drugs and other substances); in 81 (43.1 %) the domain V (anxious expectation); in 98 (52.1 %) the domain VI (agoraphobia); in 2 (1.1 %) the domain VII (phobia of diseases and hypochondria); in 58 (30.1 %) the domain VIII (sensitivity of the reassurance).
Conclusions: These data are particularly interesting as they show the notable percentage of patients with migraine with a beginning of agoraphobic panic which can be spotted. In our opinion, this needs to be considered at the moment of the therapeutic approach.

Post traumatic headache and therapeutic approach with paroxetine

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Objective: The aim of our study has been verify the efficacy and safety of the therapy with paroxetine in patients affected by chronic post traumatic headache (PTH).
Materials and methods: 200 patients (96 females) (39.8 years age mean, SD 15.8) affected by PTH (ICHD'04 criteria) (post-minor cranial trauma) have been studied by a complete battery of neuroradiological (TC, NMR), neurophysiological (multi evoked evoked potentials) and psychometric tests (Zung, MHQ). All patients have negativity of all strumental examinations and absence of headache and psychiatric disorders history. Therapy with paroxetina (20 mg/die) was suggested.
Results: 34 (17 %) patients deserted the study (side effects and poor compliance); 136 (68 %) patients have showed a significant reduction of the index migraine ($p < 0.05$) at basal vs follow-up (1, 3 and

6 months) and a significant reduction ($p < 0.05$) of the items for anxiety and depression at the psychometric test (basal vs. follow-up); 30 (15 %) patients did not show a significant reduction ($p > 0.05$) in scores for the values neither index migraine nor scales for anxiety and depression (basal vs. follow-up).
Conclusions: Recently, a chain of biochemical events have been associated to a minor cranial trauma and migraineuse patients (in particular is noted a unstable serotoninergic neurotransmission). Our data show the utility of the paroxetine (a SSRI drugs more potent and selective) in the theraphy of PTH and, generally, in the post-traumatic syndrome and its encourage controlled studies and case histories more wide.

The valsalva maneuver during delivery effort does notcause a recurrence of orthostatic headache from spontaneous intracranial hypotension

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Objective: To describe the outcome after vaginal delivery in a woman with history of orthostatic headache from spontaneous intracranial hypotension (SIH).
Introduction: SIH is characterized by low CSF pressure, orthostatic headache, and characteristic abnormalities on MRI. The exact cause of spontaneous CSF leaks often remains undetermined. Neverthless, significant minority of patients shows clinical or neuroradiological features suggestive of the presence of connective tissue matrix disorder. The evidence for a preexisting dural sac weakness has been increasingly recognized. Many patients have joint hypermobility or have ectatic dural sacs, multiple meningeal diverticula, or dilated nerve root sleeves. A trivial previous trauma caused by the Valsalva maneuver such as in coughing, sneezing, vomiting, pulling, pushing, and lifting is sometimes reported in a minority of these patients. Delivery effort has been rarely reported as a causal factor of SIH, as well.
Materials and methods: 291 patients with SIH according to the criteria of the ICHD 2004 were observed from 1992 to 2014. Out of these 189 patients underwent lumbar epidural blood patch (EBP) with autologous blood. In this case series were included 4 women mean age 30 years (range 25–38 years) who started pregnancy after the SIH. One woman was treated with conservative therapy (bed rest plus overhydration), and another, suffering from joint hypermobility was treated with two EBP, as SIH relapsed 7 days after the first EBP. The other two women were treated with one EBP. Post-labor follow-up mean was 67 months (range 6–156 months).
Results: In women treated with conservative therapy orthostatic headache disappeared after about a month, while in the remaining three women orthostatic headache disappeared immediately after treatment with EBP. These women delivered at a mean of 33.5 months (range 6–72 months) after SIH episode. All the women were recommended to perform vaginal delivery. No woman was treated with epidural analgesia during labor. All infants were healthy. None of the women showed recurrence of SIH by Valsalva maneuver during delivery effort.
Discussion and conclusions: Although the literature has described a few cases of SIH caused by delivery effort, our observation shows that the Valsalva maneuver during delivery effort does not cause a recurrence of orthostatic headache from SIH. On the other hand we believe that perform vaginal delivery rather than Caesarean surgery should be preferable, as surgery is not risk free. Moreover, even though a recurrence of SIH can occour, this would be easily treatable with EBP that is less invasive of cesarean section.
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Early pain relief from orthostatic headache and hearing changes in spontaneous intracranial hypotension after epidural blood patch in trendelenburg position: a prospective study

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Background: Spontaneous intracranial hypotension (SIH) is characterized by orthostatic headache (OH), diffuse pachymeningeal enhancement on brain MRI and low CSF pressure. Hearing change (HC) is a frequent finding. Epidural blood patch (EBP) is now the most recommended available treatment. Our study aimed at investigating the EBP efficacy on OH and HC by asking patients to rate their OH and HC at different time intervals.
Methods: 28 consecutive patients with SIH were treated with EBP. Two Psychologists asked them to rate on a visual analogue scale (VAS) the intensity of their OH and HC before, 24 h after, and 2 months after treatment.
Results: 24/48 h after EBP, a significant improvement in OH and HC was found ($p < 0.001$). When followed-up, all patients showed complete relief from OH. 4 patients out of 16 reported very mild HC.
Discussion and conclusions: To the best of our knowledge, this is the first time a specific pain assessment with VAS was conducted before and after EBP, showing a fast improvement of OH and HC in a large group of SIH patients. Importantly, patients have been followed up about 2 and 13–25 months after discharge, which confirmed the effect to be complete and long-lasting. In a future work, it may be worth monitoring patients' changes over time with multiple follow-ups, also involving larger patients sample in a multicentric study.

Osteopathic manipulative treatment of headache in a polytrauma patient: case report

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Background: The International Headache Society classification through the ICHD-II ranks among the secondary headaches those

arising as a result of a head injury and/or neck. To the authors' knowledge, there are no prior reports in the literature that describe an osteopathic manipulative treatment (OMT) approach for patients with chronic post-traumatic headache.
Case description: A woman 50 years, automobile accident in 1994 with the mild head trauma (GlasgowComaScale = 13), signs and symptoms of concessive syndrome; distraction of the cervical spine; fractures of acetabulum, pelvis, femural neck, knee, ulna and radius; dislocated shoulder was hospitalized for surgery. During hospitalization began to suffer from headaches. Performed neurological examination and neuro-radiological investigations without relief of abnormality, she was then diagnosed with post-traumatic headache. From 1995 to 2005 surgeries for removal of fixation and prosthetic hips with rehabilitation. In this period permanent recurrent headache: two/three attacks per month for a period of two/three days, not always tolerable and placated with taking ibuprofen. In 2012 tamponade, with a verticalization of the cervical spine. She was prescribed collar Shanz, drug therapy and physiotherapy. Despite therapy, continued to have about three episodes of headache per month. In 2013, with diagnosis of chronic post-traumatic headache attributed to mild head injury (ICHD-II codes: 5.2.2-ICD-10: G44.31) asked our consultation. In the previous fortnight had continuous headache.
Description of treatment: The OMT was applied individually and different techniques were used Depending on the Somatic Dysfunctions (SD) That was found. Were performed five treatments. The first 3 to 2 weeks apart, the fourth after 3 weeks and the fifth distance of 1 month.
Results: Were used as the outcome scale HIT-6 to the first ($t0$), the last treatment ($t1$) and then at a distance of 1 month after the last treatment ($t2$) and a scale of quantitative evaluation of pain NSR before each treatment ($t0$–1–2–3–4). For the HIT-6 were detected the following results: $t0 = 63$; $t1$ and $t2 = 38$. For the NRS, the results were: $t0 = 8$, $t1 = 0$, $t2 = 2$, $t3$ and $t4 = 0$.
Conclusions: From the results it was found as the OMT did change the impact of headache on the life of the patient, to important at minimum or no impact. One year after the last treatment, the patient says she has only had two episodes of headache but mild, lasting only 1 day and no longer needed to take medication.

Osteopathic treatment of migraine without aura: outcome research

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Background: Migraine without aura is the most known and widespread primary headache (IHS:1.1-ICD10:G43.0), suffers more than one person out of 10, in 1/3 of the cases from childhood. Leads to a marked decrease in quality of life and health status of the patient. The management of the patient with migraine is complex and cannot be separated from a pharmacological approach, considering that alternative and complementary therapies are increasingly present in patient management. This study aims to verify the efficacy of osteopathic manipulative treatment (OMT) in patients with migraine without aura undergo drug treatment as needed.
Methods: Twenty-two patients from Headache Surgery of San Giovanni Battista Hospital in Rome, of whom three males and nineteen females, were included in a single treatment group. Five treatments were carried out in a period of 8 weeks. All patients completed the headache diary for a total period of 6 months and the MIDAS questionnaire before the first treatment (t_0) and 1 month after the last treatment (t_1). Patients need to take the medication recommended by your doctor. The MIDAS questionnaire and headache diary were used to assess the frequency and intensity of the attacks and the frequency of intake of drug therapy. Data on the frequency, intensity and drug therapy were evaluated by comparing the average of the diary data for 3 months before and 3 months after t_0 and the values of the scale MIDAS at t_0 and t_1. The OMT was applied to each subject individually and different techniques were used depending on the dysfunction that was found.
Results: The outcomes observed in the study, analysed (t test) at 3 months, showed a general improvement after OMT: the average of the frequency of migraine attacks was reduced by 5.36 days ($p = 0.018$), the average rate in the taking drugs and is reduced by 6.14 days ($p = 0.001$), the average intensity of the pain and reduced by 1.41 points ($p = 0.0005$).
Conclusions: This study suggests that osteopathic manipulative treatment has a positive effect on migraine without aura, so it can be inserted in the patient's migraine management. Future studies with a control group and with a follow-up in the long term could make even more evident the effectiveness of osteopathy in the treatment of patients suffering from migraine without aura.
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Osteopathic manipulative treatment and chronic tension-type headache

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Introduction: The purpose of this study was to verify OMT's effectiveness in those patients suffering from chronic tension-type headache (HIS:2.3-ICD10:G44.2) as a therapeutic support cooperating with pharmacological treatments.
Methods: Thirty-three patients were found and fourteen of them with chronic tension-type headache, of both sexes and aged between 28 and 64 years old, were enrolled for our outcome research. The HIT-6 scale was analysed as primary outcome and was analysed the prevalence of somatic dysfunctions (SD). The study provided five osteopathic treatment sessions. During the first session ($t0$) and the last one ($t1$), and within 1 month after the last treatment ($t2$), the patients filled up the HIT-6. The OMT was applied to each subject individually and different techniques were used depending on the SD that was found.
Results: The analysis of the prevalence of SD showed that the SD of C1 (++left rotation) had a prevalence of 85.7 % in subjects enrolled. The HIT-6, analysed by comparing measurements of $t0$ and $t1$, and then of $t0$ to $t2$, showed in the first case an average reduction of the HIT-6 scores so we obtained a statistically significant result ($p = 0.002$); the reduction observed comparing $t0$ and $t2$ showed a very significant result with $p = 0.001$.
Conclusions: The prevalence of SD on C1 would show that this vertebra could be involved in the mechanical aetiology of chronic tension-type headache. We consider the most credible hypothesis that C1 dysfunction adapting the tone of rectus posterior capitis minor muscle. Some studies (Hack 1995; Alix 1999; Kahkeshani 2012) show the anatomical relationship between the rectus posterior capitis minor muscle and the dura (myodural bridge) and show how a mechanical disturbance of this link can develop a tension headache. In our study we could confirm that this link may be involved in chronic tension-type headache. The study showed a good statistical

significance concerning the primary outcome analysed (Hit-6); we can therefore state that the improvement resulted from the osteopathic treatment rather than from the chance. The results we obtained let us state that OMT can be an efficacious aid for those patients with chronic tension-type headache.

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Quantum molecular resonance (QMR) for treatment of chronic tension type headache according with I.A.R.A. model: observational study

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Introduction: QMR has been proved to promote cell regeneration process through direct cell stimulation which is able to decrease local inflammatory reaction and consequently pain level. Chronic-tension-type-headache (CTTH) is a clinical entity where high muscle tension level, in particular in trapezium area, may induce a pain sensation in the same area. The QMR treatment has been already tested in different muscular pathological conditions. This study reports a clinical experience of QMR treatment for tension type headache, associated to I.A.R.A. approach, which increases consciousness of patients who can participate actively to QMR therapy.

Methods: Twenty-six patients (3 males/23 female), suffering from CTTH, diagnosis according to International Headache Society (IHS) criteria, were undergone to an 8 sessions QMR treatment protocol, 120 min each. Two patients withdrawn from the study protocol at the third session leaving 24 patients included in the program. Thirteen patients were using prophylaxis for tension type headache (antidepressants and/or muscle relaxants) and for associated Migraine without aura. A daily headache diary was given to record headache episodes and medication intake per month. Follow up meetings were fixed 1, 3, 6 months after the end of the program.

Results: Up to now patients achieved the 1-month follow up. Days of headache/month decreased significantly (23 ± 7.3 vs. 8 ± 9 $p < 0.00005$). Patients did not report any side effect.

Conclusions: QMR seems to be effective for patients with CTTH and results are confirmed until the 1-month-follow-up. Treatment is well tolerated and safe for patients. Further studies and longer follow-up will be necessary to confirm the efficacy of this innovative approach.

Use of botulinum toxin type A in the management of patients with drug-resistant chronic migraine with and without medication overuse at the parma headache centre

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Introduction: Chronic migraine affects about 2–3 % of the general population, leading to severe disability and reduced quality of life. The efficacy and safety of botulinum toxin type A (BOTOX®) in adult subjects with chronic migraine has been demonstrated in the PREEMPT study. It therefore represents a viable therapeutic solution for chronic migraine patients who did not respond to common prophylactic treatments. Few data exist in the literature about its use in clinical practice.

Methods: Thirty-six adults with drug-resistant chronic migraine with ($n = 31$) or without ($n = 5$) medication overuse were treated with Botox according to the PREEMPT protocol between February 2014 and January 2015 at the Parma Headache Centre. The data about frequency and other clinical parameters of the headache, before and after treatment, were collected using a headache diary.

Results: Twenty-four patients out of 36—21 women and three men—received at least two Botox treatments and 13 of them (54.1 %)—10 women (76.9 %) and three men (23.1 %)—received at least three Botox treatments. Only three patients out of 36 received four treatments. For patients who received two treatments ($n = 24$), we saw an improvement in the number of days with headache, which decreased from a median of 29 [interquartile range (IQR) 20–30] at baseline to a median of 25 (IQR 11–28) ($p = 0.002$). Considering only the patients with at least 6 months of follow-up ($n = 13$), the median decreased from 24 (IQR 15–30) at baseline to 22 (IQR 11–26) at 3 months to 15 (IQR 11–27) at 6 months ($p = 0.02$).

Fifteen patients out of 36 (41.6 %) reported adverse effects: neck pain (19.4 %), eyebrow lifting (11.1 %), dropped head (8.3 %) and sweating (2.8 %). Fourteen patients discontinued treatment due to ineffectiveness (7/36), adverse effects (4/36) or poor compliance (3/36).

Conclusions: Our results are in agreement with the recent data from a UK study [1] and confirm that botulinum toxin type A can be an effective, well-tolerated treatment in patients with drug-resistant chronic migraine with or without medication overuse.

Reference

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Employment difficulties in persons with headache: a systematic literature review

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Aims: Headache (HA) is a common health problem leading to significant levels of disability and burden. Predominantly affecting persons of working age, persons with HA often experience employment-related difficulties. The current study aimed to systematically assess the literature on HA and employment difficulties in order to (1) determine the impact of HA on employment and (2) identify factors that are related to employment difficulties in persons with HA.

Methods: A literature search was performed in PubMed for studies published between January 1993 and October 2013. Studies were preliminarily selected if they reported quantitative data on any kind of work-related difficulties, or factors associated to these difficulties as primary or secondary outcome measures. The final decision on study selection was taken by full-text reading.

Results: The search resulted in 604 potentially relevant studies, of which 44 studies were ultimately included, reporting data on 69,682 individuals (71 % female, mean age 42). Results indicated that persons

with HA had higher unemployment rates, a lower number of workdays per week, higher numbers of missed workdays, days with reduced productivity, lost workday equivalents, and days worked with headache than persons without HA. Moreover, these negative employment outcomes were higher in persons with migraine in comparison to persons with other types of HA. In terms of related factors, which were only reported in a minority of studies, female gender, non-white race, younger age, lower educational level, lower income level, higher HA frequency, higher pain intensity, higher disability, and the presence of depressive symptoms were associated with worse employment outcomes, whereas triptan use and participation to educational HA programs were associated with better outcomes.
Conclusions: Results of this systematic review highlight once again the negative impact that persons with HA experience with regards to their working life and also show that there is still a lack of knowledge regarding associated factors. There is a pressing need for future studies to pay more attention to these factors, especially those that are susceptible to change and/or those that have a protective effect, in order to find ways to decrease the negative employment outcomes experienced by persons with HA.

Normal rnfl and gcc thickness in migraine with and without aura

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Background: Alteration of optic nerve head perfusion or retinal layers microcirculation occurring in migraine attacks may potentially lead to thinning of the peripapillary retinal nerve fiber layer (RNFL) and the macular ganglion cell complex (GCC) measured by means of Optical Coherence Tomography (OCT).The aim of this study was to evaluate Spectral Domain OCT (SD-OCT) measurements of peripapillary RNFL and macular GCC thickness in patients with migraine with and without aura.
Methods: 25 patients with migraine with aura (group 1), 18 patients with migraine without aura (group 2) and 24 healthy subjects (group 3) were included in the study. SD-OCT (Optovue, RTVue 100) was used to measure the RNFL and GCC average (Avg) thickness in 134 eyes. Statistical comparisons were made by means of the *t* students test for data of one eye for each patient randomly selected.
Results: The mean age was 36.92 years ± 9.7 (range 20–64) in group 1 (6 M; 19 F), 33.2 years ± 12.69 (range 18–63) in group 2 (3 M–15 F) and 35.04 years ± 7.8 (range 22–51) in group 3 (5 M; 19 F). Avg-RNFL and Avg-GCC were respectively 107.56 ± 10.68 and 97.22 ± 6 in group 1; 109.50 ± 12.4 and 95.3 ± 6.8 in Group 2; 108.17 ± 5.4 and 97.54 ± 2.92 in Group 3. Not statistically significant differences were found for Avg-RNFL and Avg-GCC thickness between all migraine patients (group 1 and 2) and controls (group 3). Data were neither significantly different for comparisons within migraine groups.
Conclusions: SD-OCT measurements did not demonstrated evidence of peripapillary RNLF and macular GCC degeneration in patients with migraine, with or without aura. These results do not confirm those previously reported in other studies that are still controversial, when only sectorial RNFL thinning has been showed by some, and that cannot be however compared since obtained with different OCT devices.

Metilprednisolone ev in medication overuse headache

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Background: Medication overuse headache (MOH) is a secondary chronic headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication (10–15 or more days per month) for more than 3 months. It usually, but not invariably, resolves after the overuse is stopped. Benefit of acute withdrawal of the overused medication has been shown in some studies, nevertheless there is no international consensus about which suspension strategy is the most effective. Some centers prefer to perform a transitional therapy ("bridge therapy") during the days of withdrawal, in order to ensure symptomatic relief from rebound headache and to avoid withdrawal symptoms. One of the most chosen approach involves the use of corticosteroids: most of the studies in literature focused on the use of prednisone per os. Less data are available for the use of methylprednisolone ev, but it seems to have a protective role from headache episodes occurring during wash-out treatment. Our retrospective study aims to evaluate the effectiveness of detoxification protocol used by our department for patients with medication overuse headache. Reduction of monthly days of headache is the parameter adopted.
Methods: Our protocol was based the endovenous administration of methylprednisolone 125 mg plus diazepam 10 mg and esomeprazole 40 mg for 5 consecutive days; in some patients, prophylactic therapy for chronic headache is modified or started at the end of the wash-out. 27 patients (for a total of 32 treatments) were treated from August 2010 to December 2014. For all patients a one-month follow up control is available; at the moment for 18 patients (for a total of 21 treatments) is available also a 3-month follow-up control. We evaluated the reduction of monthly days of headache, comparing the total before (T0) and after pharmacologic wash-out (T1: 1 month; T2: 3 months).
Results: At T0, in 32 treatments, patients presented with a mean of day per month of headache of 22.4 (95 % confidence interval: 3.09); at T1, monthly days of headache decreased to a mean of 10.0 (55 % of reduction from T0; 95 % confidence interval: 3.29); in 21 treatments with 3-months follow up, at T3 mean of days of headache per month was 10.9 (51 % of reduction from T0; 95 % confidence interval: 3.21). Paired *t*-test for repeated measures showed that this decrease is significant (T0–T1: paired t-test $= 0.3 \times 10^{-7}$; T0–T3: paired t-test $= 0.9 \times 10^{-5}$).
Conclusions: Our results showed that the performed protocol was effective and well tolerated for the reduction of headache days per month in patients with medication overuse headache.

MRI findings in idiopathic intracranial hypertension (IIH): results in 60 Italian patients

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Background: Different diagnostic criteria for idiopathic in intracranial hypertension (IIH) are available [1, 2]. Although different findings have been described showing high sensitivity and specificity

[3] in IIH patients, the role of neuroimaging has not been established as a major diagnostic criterion. The presence of at least 3 neuroimaging abnormalities among empty sella, flattening of the posterior aspect of the globe, distention of the perioptic subarachnoid space with or without a tortuous optic nerve and transverse venous sinus stenosis has been included among the diagnostic criteria only in patients without papilledema [2].

Objective: The aim the study was to evaluate the presence and the frequency of MRI and MRV abnormalities in an Italian clinical sample.

Methods: We enrolled all patients with a diagnosis of IIH according to the diagnostic criteria of ICHD 2004 [1] admitted to our Neurology Unit from January 2012 to December 2013. All patients underwent brain MRI and MRV and the images were reviewed by two expert neuroradiologists.

Results: 60 patients were studied. Brain MRI findings were as follows: different degree of empty sella in 45/60 (75 %); different degree of perioptic subarachnoid space distension in 46/60 (77 %); optic nerve tortuosity in 24/60 (40 %); flattening of the posterior aspect of the globe 34/60 (57 %); protrusion of the optic nerve papillae into the vitreous cavity 16/60 (27 %). MRV findings were as follows: bilateral and unilateral narrowing of the middle of the transverse sinuses in 37/60 (62 %), unilateral in 11 cases and bilateral in 26; normal aspect, mild asymmetry and dural sinuses malformations in 23/60 (38 %). The combination of MRI and MRV abnormalities was present in 37/60 (62 %).

Conclusions: Our results are in line with recent literature reports indicating a high prevalence of several imaging findings, particularly of empty sella, perioptic subarachnoid space distension and transverse sinuses abnormalities. These data indicate that the diagnostic role of neuroimaging findings should be re-evaluated. Further studies investigating differences in neuroimaging findings according to different subgroups of IIH patients (e.g. according to presence/absence of papilledema, presence/absence of headache, different intracranial opening pressure values) are warranted.

Supraorbital transcutaneous neurostimulation in "de novo" patients with migraine without aura: the first Italian experience

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Background: Cephalic transcutaneous neurostimulation (TNS) has been recently proposed for the treatment of migraine. Supraorbital TNS has been found superior to sham stimulation for episodic migraine prevention in randomized trials. We evaluated both the safety and efficacy of a brief period of supraorbital TNS, in a group of patients with migraine without aura (MwoA).

Methods: We enrolled 20 consecutive patients with MwoA experiencing a low frequency of attacks ($\leq$ 5 attacks/month), which had never taken migraine preventive drugs in the course of their life. Patients performed a supraorbital high frequency TNS daily for 20 minutes for two months (frequency: 60 Hz; pulse width: 250 μs; intensity: 16 mA). Primary outcome measures were significant change in monthly migraine attacks and days ($p < 0.05$). Secondary outcome measures were significant reduced average of pain intensity during migraine attacks (by means of visual analogic scale) and HIT-6 (Headache Impact Test) rating as well as in monthly intake of rescue medication ($p < 0.05$). Finally, compliance to TNS treatment and potential adverse effects have been evaluated.

Results: Between run-in and second month of TNS treatment, primary and secondary endpoints were both met. Indeed, we observed a statistically significant decrease in the frequency of migraine attacks ($p < 0.001$) and days ($p < 0.001$) as well as a reduction in average of pain intensity during migraine attacks ($p < 0.001$) and HIT-6 rating ($p = 0.002$) and intake of rescue medication ($p < 0.001$). All patients showed good compliance levels and no relevant adverse events or side effects occurred during the TNS period.

Conclusion: In patients with MwoA experiencing a low frequency of attacks, significant improvements in multiple migraine severity parameters have been observed following a brief period (two months) of supraorbital high frequency TNS. Furthermore, supraorbital TNS is well accepted and tolerated as migraine preventive treatment in these patients. Additional studies are needed to better define the duration of anti-migraine effect and the potential benefit of combination between supraorbital TNS and pharmacological preventive therapies.

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Author Index