Cerebral venous hemodynamic abnormalities in episodic and chronic migraine

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Summary

Alterations of cerebral venous drainage have been demonstrated in chronic migraine (CM), suggesting that cerebral venous hemodynamic abnormalities (CVHAs) play a role in this condition. The aim of the present study was to look for a correlation between CM and CVHAs.
We recruited 33 subjects suffering from CM with or without analgesic overuse, 29 episodic migraine (EM) patients with or without aura, and 21 healthy subjects as controls (HCs). CVHAs were evaluated by transcranial and extracranial echo-color Doppler evaluation of five venous hemodynamic parameters.
CVHAs were significantly more frequent in the CM and EM patients than in the HCs. In the migraine patients, CVHAs were not correlated with clinical features.
The significantly greater frequency of CVHAs observed in the migraineurs may reflect a possible relationship between migraine and these abnormalities. Prospective longitudinal studies are needed to investigate whether CVHAs have a role in the processes of migraine chronification.

KEY WORDS: cerebral venous hemodynamic abnormalities, chronic cerebrospinal venous insufficiency, chronic migraine, migraine

Introduction

Chronic migraine (CM) is one of the most disabling primary headache forms (Lipton, 2009), whose underlying processes are not yet fully elucidated. It has been speculated that the development of CM involves pain facilitation processes (mediated by central sensitization mechanisms) that depend on the frequent repetition of the attacks (Schwedt, 2014).
A high frequency of headache attacks and a long history of migraine have each been correlated with the accumulation of iron in the periaqueductal gray as well as in the red nucleus, putamen and globus pallidus (Welch et al., 2001; Kruit et al., 2009, 2010). In view of the high iron content of these structures, it has been hypothesized that repeated hyperoxia could cause free radical cellular damage that might be identified by measuring cumulative iron sequestration in brain tissue (Welch, 2003; Nagesh et al., 2000).
This 'iron hypothesis' might represent a mechanism able to explain the transition of the clinical phenotype from episodic migraine (EM) to CM (Welch, 2009). High levels of iron in brain tissue have also been found in other neurodegenerative and autoimmune diseases (Zamboni et al., 2007; Singh and Zamboni, 2009). In particular, in multiple sclerosis (MS) the deposition of iron has been correlated with the presence of venous insufficiency and with cerebral congestion (Zamboni et al., 2007; Singh and Zamboni, 2009).
Taking into account that cerebral venous abnormalities have been recently described in CM (Fofi et al., 2012; De Simone et al., 2011), we hypothesize that the occurrence of sterile inflammation due to frequent migraine attacks, associated with abnormal venous circulation, might facilitate the deposition of iron in target brain structures and then favor the processes of migraine chronification. For this reason, we speculate

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that cerebral venous hemodynamic abnormalities (CVHAs) could be more frequent in chronic than episodic migraineurs.

Materials and methods

We consecutively recruited patients attending our headache clinic and suffering from CM with or without analgesic overuse (codes 8.2 and 1.5.1 in the International Classification of Headache Disorders, 2nd Edition, ICHD-II) and EM with or without aura (ICHD-II codes 1.2 and 1.1). A group of age- and sex-matched healthy subjects with no personal or family history of headache and no vascular risk factors were also enrolled as controls (HCs). The study was approved by the local ethics committee and all the subjects participating in the study (cases and controls) provided their written informed consent, in accordance with the Declaration of Helsinki.

The inclusion criteria were age between 18 and 65 years, and the absence of a history of vascular risk factors such as hypertension, diabetes mellitus, obesity, thrombophilia, autoimmune diseases, cardiocerebrovascular disease, alcohol abuse and drug abuse. Migraine patients who were under prophylactic migraine therapy or had suspended it less than two months previously were also excluded.

All the subjects underwent standard clinical and neurological examinations. In the migraine patients, data on the following clinical characteristics of headache attacks were collected: type, location, intensity of pain (assessed by visual analog scale), frequency of attacks (days/month), duration of attacks (in hours), presence of aura, drug intake (number of pills per month), and disease duration (in years). To assess the impact of migraine on quality of life, we used two questionnaires: the Headache Impact Test (HIT-6), in which a score >50 indicates severe impact, and the Migraine Disability Assessment Scale (MIDAS), in which a score >20 indicates severe disability. All the patients underwent brain magnetic resonance imaging (MRI), including arterial and venous MR angiography.

CVHAs were assessed, according to strict operational criteria, by a single expert ultrasonographer (FP), who was blind to the identity of the sample examined. The subjects were evaluated by transcranial and extracranial echo-color Doppler (ECD) examination (Zaniewski et al., 2013). The apparatus used was a Siemens Acuson Sequoia 4v1c transducer with a 2 MHz probe for the study of the deep cerebral veins (DCVs) and a 9I4 9 MHz probe for studying the extracranial venous circulation. The patient was placed on a tilt bed so that the extracranial ECD, serving to investigate the internal jugular veins (IJVs) and vertebral veins (VVs), could be combined with the intracranial ECD, performed to study the DCVs. The procedure started with the patient in supine position, while the subsequent phase of the examination was conducted in a sitting position after an adaptation time. Episodic migraineurs underwent the examination during the interictal phase (at least 72 hours after the last attack). In patients with CM, the recordings were made regardless of the attack stage.

The five intracranial and extracranial venous hemodynamic parameters of the Venous Hemodynamic Insufficiency Severity Score (VHISS) (Zamboni et al., 2007) were evaluated:

VH1) Reflux/bidirectional flow in the IJVs and/or in the VVs, in sitting and in supine positions, defined as flow directed towards the brain for a duration of >0.88 seconds;

VH2) Reflux/bidirectional flow in the DCVs, defined as reverse flow for a duration of 0.5 seconds in one of the intracranial veins;

VH3) B-mode abnormalities indicating stenosis in IJVs. IJV stenosis is defined as an IJV cross-sectional area (CSA) ≤0.3 cm^2;

VH4) Flow that is not Doppler-detectable in the IJVs and/or VVs despite multiple deep breaths;

VH5) Reverted postural control of the main cerebral venous outflow pathway verified by measuring the difference between the IJV CSA in the supine and upright positions.

Positivity of any one of the five parameters described above was taken as an indication of the presence of CVHAs. In addition, the data were also analyzed according to the criteria proposed by Zamboni et al. (2007) to define the presence of chronic cerebrospinal venous insufficiency (CCSVI). According to these criteria, CCSVI is present when at least two of the five venous hemodynamic parameters listed above are altered.

Outcome measures and statistical analysis

Clinical migraine data and the presence of CVHAs were the main outcome measures in the three groups (CM, EM, HCs). Within the CM and EM groups, we analyzed patients separately according to the duration of their migraine history (more than 10 years versus less than 10 years) in order to explore the hypothesis that the effect of CVHAs might be greater in those with a longer disease history.

All the parameters were checked for normal distribution using the Wilks-Shapiro test. As the variables in the three groups did not all fit a normal distribution, the between-group comparisons were tested with non-parametric tests. The Mann-Whitney test was used for continuous variables and Fisher's exact test for discrete variables. Statistical significance was set at <0.05 after Bonferroni correction.

To study whether the presence of CHVAs might influence the clinical burden in CM and EM patients, a multivariate analysis of variance (MANOVA) was carried out to predict the severity of migraine disease. We used all the migraine parameters (frequency, intensity, attack duration in hours, etc.) as dependent factors in a pooled analysis, while group (episodic vs chronic), disease duration in years and presence of CCSVI were used as independent factors. Age and gender were used as covariants in the analysis.

Given the lack of epidemiological data on both CCSVI and CHVAs in healthy subjects and migraine patients, we performed a post-hoc power analysis to detect the B power of our study with a significance level of 0.05. The results of this analysis are described in the following section. All statistical analyses were performed using SPSS, version 17.

Results

We recruited 33 patients with CM, with or without analgesic overuse, 29 patients with EM, with or without aura, and 21 HCs. The patient groups did not differ significantly in demographic characteristics (Table I).
Compared with the EM patients, the CM group had significantly higher values for attack frequency and duration, and intake of pills; they also had significantly higher MIDAS and HIT-6 scores. The intensity of pain and the presence of aura did not differ between the CM and EM groups.
Table II summarizes the distribution of the parameters indicating the presence of CVHAs.

Compared with the controls, the CM and EM patients showed a higher frequency of positive VH1, VH3 and VH4 parameters (in the case of VH3, only the comparison with the EM patients was significant) (Table III). Furthermore, comparison of the venous hemodynamic parameters between the CM and EM patients revealed a significantly higher presence of VH4 in the CM group. After Bonferroni correction, only the differences in VH4 remained significant between the three groups (Table III).
CCSVI was present in 30.3% (n = 10) of the CM and 24% (n = 7) of the EM patients, whereas it was not observed in the HCs (Table III). The presence of CCSVI was significantly higher in the CM vs EM (p=0.04) and EM vs HC groups (p=0.04), after Bonferroni correction. There was no difference between the CM group and the HCs.
We observed that neither the presence of a positive VH4 criterion nor the presence of CCSVI affected the characteristics of the headache in the EM and CM groups. In fact, there were no differences in features such as attack frequency, duration of attacks, intensity of pain, and number of pills per month, or in HIT-6 and MIDAS scores. These results were also confirmed

Table I - Demographic, clinical and neuroradiological characteristics.

	CM (n=33)	EM (n=29)	HCs (n=21)
Sex (female)	82%	72.4%	71.4%
Age (years)	40.5 ± 12.3	34.4 ± 10.4	33.2 ± 4.3
MOH	75.5%	-	-
Number of analgesics/month	19.3* ± 9.6	4.4 ± 2.9	-
Attack frequency (days/month)	22.7* ± 6.5	4.5 ± 3.2	-
Attack duration (hours/attack)	38.5* ± 21.5	29.4 ± 22.9	-
Intensity of pain (VAS)	8.8 ± 1	8 ± 1.4	-
Aura	24%	24%	-
Years of migraine	20.5 ± 10.7	17.2 ± 9.7	-
Years with CM	6.7 ± 8.5	-	-
HIT-6 score	63.6*± 9	57.8 ± 8.5	-
MIDAS score	71* ± 50	13.2 ± 13.4	-
MRI	5/33 gliotic foci 2/33 hypoplasia of the transverse venous sinuses	3/29 gliotic foci 1/29 hypoplasia of the transverse and sigmoid venous sinuses	-

Abbreviations: CM=chronic migraine; EM=episodic migraine; HCs=healthy controls; MOH=medication overuse headache; VAS=visual analog scale; HIT-6=Headache Impact Test; MIDAS=Migraine Disability Assessment Scale; MRI=magnetic resonance imaging; *significant value (p<0.05)

Table II - Distribution of neurosonological venous hemodynamic criteria (VH1-VH5) in the sample populations.

	VH1	VH2	VH3	VH4	VH5
CM (n=33)	30.3%	-	63.6%	27.2%	-
EM (n=29)	20.6%	-	75.8%	6.8%	-
HCs (n=21)	-	-	31%	-	-

Abbreviations: CM=chronic migraine; EM=episodic migraine; HCs=healthy controls

by the application of the MANOVA model, which showed that neither a longer disease duration nor the presence of CCSVI was significantly associated with a worse clinical outcome (Wilks lambda, Pillai-Bartlett trace and Lawley-Hotelling trace: p>0.05; Roy's greatest root: p<0.05).
Finally, in the patients with a longer-than-10-year migraine disease history, we observed that both the EM and the CM patients had a positive VH4 parameter.
With regard to migraine disease duration, the presence of CCSVI was more frequent in CM patients with a long as opposed to a short disease duration (53% vs 6%). On the contrary, CCSVI was less frequent in EM patients with a long disease duration than in those with a short one (12% vs 29%) (Table IV).
The post-hoc power analysis for the Chi-square test showed a B-power of 0.81, with alpha=0.05, degree of freedom=5, number of patients=83 (CM+EM+HCs), effect size=0.4 (post-hoc).

Discussion

The processes underlying CM are still debated. However, a mechanism of central sensitization to painful stimuli (a multi-step mechanism, probably involving sterile neuroinflammation, impairment of endogenous analgesia and persistent cortical hyperexcitability) seems to play a main role in the transition from the episodic to the chronic form. Welch (2003) suggested that iron deposition in selective subcortical structures, observed in migraineurs, might be a consequence of sterile neuroinflammation and a possible marker of a proinflammatory state.
From this perspective, it has been claimed that cerebral venous reflux could act as a proinflammatory stimulus and promote iron deposition in chronic inflammatory diseases (such as MS) and other neurodegenerative diseases (Zamboni, 2006; Zamboni et al., 2007; Singh and Zamboni, 2009; Adams,1988; Zivadinov et al., 2011).
The origin of CVHAs has not yet been determined. It has been suggested that they may be physiological (Doepp et al., 2008; Baracchini et al., 2011), aging-dependent (Chung et al., 2010, 2011), congenital (Lee et al., 2010), or pathological.
Taking into account that cerebral venous abnormalities have recently been described in CM (Fofi et al., 2012; De Simone et al., 2011), we hypothesized that the occurrence of sterile inflammation due to frequent migraine attacks, associated with abnormal venous circulation, might facilitate the deposition of iron in target brain structures and then favor the processes of migraine chronification. We therefore investigated CVHAs in both chronic and episodic migraineurs.

CHVAs and migraine

We found that CVHAs were significantly more frequent both in chronic and in episodic migraineurs compared with HCs. In particular, the presence of a positive VH4 parameter was found to be significantly more frequent in the migraineurs overall than in the controls, and also in the chronic compared with the episodic form of migraine. Classifying CVHAs according to the criteria of Zamboni et al. (2007), we observed a significant occurrence of CCSVI in both the EM (24%) and the CM (30.3%) patients, whereas it was not found in any of the HCs.
Data on the prevalence of CCSVI in MS are inconclusive and widely varying, ranging from 0 to 100%, and some concerns have been raised about the reproducibility of the VHISS criteria (Baracchini et al., 2012). However our data seem quite consistent with the findings of a recent large Italian multicenter study in MS patients and controls (the CoSMo study), which demonstrated the presence of CCSVI in about 2% of

Table III - Between-group comparisons of single neurosonological venous hemodynamic criteria (VH1-VH5) and presence of CCSVI.

	VH1	VH3	VH4	CCSVI
CM vs EM	30.3% vs 20.6%; p=0.56	63.6% vs 75.8%; p=0.8	27.2% vs 6.8%; p=0.003*	30.3%; p=0.04*
EM vs HCs	20.6% vs 0%; p=0.06	75.8% vs 31%; p=0.05	6.8% vs 0%; p=0.024*	24%; p=0.04*
CM vs HCs	30.3% vs 0%; p=0.08	63.6% vs 31%; p=0.32	27.2% vs 0%; p=0.003*	-

Abbreviations: CM=chronic migraine; EM=episodic migraine; HCs=healthy controls; CCSVI=chronic cerebrospinal venous insufficiency; *significant after Bonferroni correction

Table IV - CCSVI and disease duration in chronic migraine and episodic migraine groups (Fisher's exact test 0.034).

Patients with CCSVI (n=17)	<10 years	>10 years
CM (n=10)	6% (n=1)	53% (n=9)
EM (n=7)	29% (n=5)	12% (n=2)

Abbreviations: CM=chronic migraine; EM=episodic migraine; CCSVI=chronic cerebrospinal venous insufficiency

HCs (Comi et al., 2013). These data are also similar to results obtained with catheter venography (still the gold standard for the diagnosis of venous flow disorders) in a healthy population (Traboulsee et al., 2014).
One possible explanation for the consistency, with literature data, of our results on CVHAs in controls is that our subjects were evaluated by a single trained expert, thus reducing inter-operator variability.
In addition, in our patients, MRI examination did not reveal major morphological abnormalities of the cerebral venous circulation. This suggests that the significant increase in CVHAs observed in the migraineurs may reflect a possible relationship between migraine and abnormalities in cerebral venous hemodynamics.

CVHAs and migraine chronification

Hemodynamic abnormalities in the brain that affect both the arterial and the venous system have already been demonstrated in migraineurs (Fofi et al., 2012; De Simone et al., 2010). Abnormalities of venous drainage, both morphological and/or functional, could result in a modification of the cerebral venous pressure. It has been hypothesized that mild but persistent central venous hypertension could facilitate pain hypersensitivity and induce central sensitization. Central venous hypertension might, due to congestion, cause a relative dilatation of the large vessels, which might promote inappropriate continuous nociceptive firing. This, in turn, would lead to a progressive increase in the frequency of migraine attacks, thus facilitating the progression towards migraine chronicity (De Simone et al., 2010).
The relationship between cerebral venous abnormalities and migraine clinical features is still under investigation. In our study, no differences in clinical parameters, clinical scales or the presence of CVHAs or CCSVI were found between the EM and CM groups. Similarly, the multivariate model performed to calculate the burden of migraine disease showed a significant value only in the Roy's greatest root, with the other three multivariate measures giving non-significant values. Since the Roy's greatest root represents only the upper boundary of the F distribution, it has a higher probability of Type I error, leading to the rejection of a true null hypothesis. Thus it is generally disregarded when the other tests are not significant.
Garaci et al. (2012) confirmed that there is no significant clinical relationship between MS and CCSVI, nevertheless the presence of CCSVI in MS patients as well as in healthy subjects was found to be correlated with decreased cerebral blood flow and cerebral blood volume.
This discrepancy could be explained, in part, by a new report on the presence of a lymphatic system in the brain. Louveau et al. (2015) recently discovered functional lymphatic vessels lining the dural sinuses, and suggested that a malfunction of this system could have a role in a variety of neuroinflammatory and neurodegenerative diseases.

Our initial hypothesis was that CVHAs could facilitate cerebral inflammatory processes, and, by supporting the phenomena of central sensitization, lead to the chronification of migraine. Unexpectedly, we did not find differences in the prevalence of CVHAs between the EM and CM groups. Therefore, our data suggest that CVHAs could play a role in the pathophysiology of migraine in the broad sense. In this regard, it should be said that migraine is a multifactorial disease and therefore it cannot be excluded that the presence of CVHAs may play a specific role in at least a subgroup of patients with migraine.

CVHAs and migraine disease duration

In an interesting study in patients with MS, Yamout et al. (2010) observed that the presence of extracranial venous abnormalities was significantly higher in patients with a long disease duration (over 10 years). They speculated that these abnormalities were a late phenomenon linked, precisely, to the long duration of the disease. The authors stated that, in MS in particular, chronic perivenous inflammation could hypothetically lead to the release of several inflammatory mediators; this would provoke venous endothelium alterations or vein valvulitis, which in turn can lead to venous stenosis.
In our study, we observed a higher prevalence of CVHAs in patients with CM and a more-than-10-year history of migraine disease. In patients with EM, the pattern was reversed: CVHAs were more frequent in cases with a migraine disease duration shorter than 10 years. This finding suggests that the presence of CVHAs in migraine patients may be a predisposing factor for migraine chronification. In patients with an EM history longer than 10 years, it is reasonable to find a lower occurrence of CVHAs.

Conclusion

In conclusion, our data showed a higher prevalence of CVHAs in migraineurs without any correlation with the clinical characteristics or type of migraine (i.e. episodic or chronic). Longitudinal studies in patients with EM could be useful to clarify whether CVHAs can play a role in facilitating the processes of migraine chronification.

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