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PhD Thesis

THE ROLE OF RAISED INTRACRANIAL PRESSURE IN THE PROGRESSION AND REFRACTORINESS OF MIGRAINE. A PILOT STUDY.

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The role of raised intracranial pressure in the progression and refractoriness of migraine. A pilot study.

Abstract

To assess the prevalence and possible pathogenetic involvement of raised intracranial pressure in patients presenting with unresponsive chronic migraine (CM), the intracranial opening pressure (OP) and the clinical outcome of a single cerebrospinal fluid withdrawal by lumbar puncture (LP) has been evaluated in 44 consecutive patients, diagnosed with unresponsive CM and evidence of sinus stenosis at magnetic resonance venography. The large majority of patients complained of daily or near-daily headache. Thirty-eight (86.4%) had an OP >200 mmH2O. Normalization of intracranial pressure by LP resulted in prompt remission of chronic pain in 34/44 patients (77.3%) and an episodic pattern of headache was maintained for 2, 3 and 4 months in 24 (54.6%), 20 (45.4%) and 17 (38.6%) patients, respectively. The medians of overall headache days/month and of disabling headache days/month significantly decreased ($p<0.0001$) at each follow-up versus baseline. Despite the absence of papilledema, 31/44 (70.5%) patients fulfilled diagnostic criteria for "Headache attributed to Intracranial Hypertension". Our findings indicate that most patients diagnosed with unresponsive CM in specialized headache clinics may present an increased

intracranial pressure involved in the progression and refractoriness of pain. Moreover, a single LP with cerebrospinal fluid withdrawal results in sustained remission of chronic pain in many cases. Prospective controlled studies are needed before this procedure can be translated into clinical practice.

Clinical relevance summary

- In episodic migraine patients an usually overlooked comorbid sinus stenosis-associated intracranial hypertension without papilledema may represent the pathogenetic key, leading to a central sensitization–related progression and refractoriness of pain.

- Treatment of the comorbid raised intracranial hypertension, even by a single LP with CSF withdrawal, may result in a longstanding restoration of the previous episodic pattern of headache attacks.

BACKGROUND

Chronic Migraine

Migraine is a common disorder affecting more than 10% of adult population. Its lifetime prevalence in women and men has been reported to be 15% to 25%, and 6 to 9% respectively [1]. World Health Organisation (WHO) reported migraine as one of the world's top 20 most disabling diseases [2] and recently, it has been ranked seventh highest among specific causes of disability [3]. Migraine which used to be seen as a purely episodic disorder is now tended to be accepted as a chronic disorder with episodic manifestations. Some migraine sufferers may have attacks of increasing frequency over time leading to chronic migraine (CM) which, is termed as clinical progression of migraine. CM, a condition with an estimated prevalence of about 2%-3% [4-5] is characterized by 15 or more headache days per month, 8 of which with migraine features [6]. CM results from the progressive worsening of attacks frequency, up to a daily o 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% [7-8]. 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% [7]. 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 progression have been extensively studied in recent years [8-12]. 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 [13-17] variant of the typical form with papilledema (IIH), is emerging as a new potential risk factor for the progression and the refractoriness of migraine pain [18-20].

Idiopathic intracranial hypertension

IIH 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 but the reported intracranial pressure (ICP) values, in IIHWOP, are lower or fluctuating [21], suggesting that papilledema may not develop in cases with mild or intermittent ICP increase. With an esteemed incidence ranging from 1 to 19/100.000 per year [22-25], IIH is definitely an infrequent disease that occurs mostly in women in the childbearing years

[23] and has been associated to obesity and to sleep disorders [26-28]. Instead, IIHWOP prevalence on general population is not known.

Which is IIHWOP prevalence?

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 [17, 29-30]. Of note, chronic headache is not an obligatory symptom in IIH as it may lack in subjects without history of migraine or in presence of a migraine protective factor as pregnancy [31]. 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 [32] an asymptomatic increase of ICP has been identified in about one half of subjects with bilateral dural sinus stenosis, that represented about a quarter (23%) of the population studied, and in none of the subject with normal dural sinus anatomy [32]. Actually, an asymptomatic form of raised intracranial pressure associated with sinus stenosis could be extraordinarily prevalent among healthy individuals.

According to the above considerations we recently proposed [20] that a clinical and epidemiologic continuum might exist among: 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 among healthy subjects.

The role of sinus stenosis in IIH pathogenesis

IIH 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 [33]. Although the pathogenetic role of sinus stenosis is debated [34-36], it represents a specific (93%) and sensitive (93%) marker of IIH [37], and has been recently included among the radiological signs suggestive of IIHWOP [38]. Long considered a consequence of the raised ICP without pathogenetic relevance, there is evidence of a significant pressure gradient across the stenosis [39]. Moreover, the stenting of sinus stenosis is consistently followed by the remission of IIH symptoms [40-42]. These findings suggest a causal involvement of sinus stenosis in IIH mechanisms.

We have recently proposed [43] 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 [40-42], and CSF shunting [44-45] or even a single lumbar puncture with CSF withdrawal [46-48], 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?

IIHWOP may present with a mild continuous headache, thus resembling a chronic tension-type headache [49]. However, most of the patients show superimposed recurrences of severe migraine pain, up to a clinical picture indistinguishable from CM [17]. Wang et al. [16] 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 [50-51] and both show a higher prevalence of allodynic symptoms [52-55]. Topiramate, a drug with documented efficacy in CM [56-57] that shares with acetazolamide the inhibition of carbonic anhydrase isoenzyme [58], has been found as effective as acetazolamide in IIH treatment [59], 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 [60-62].

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 [32] and, on the other, that IIH clinical presentation with chronic headache may require a migrainous background [19] we have proposed that a sinus stenosis associated IIHWOP, albeit highly prevalent among healthy individuals, in migraine predisposed subjects could represent a powerful and modifiable risk factor for migraine progression [20].

The findings of a recent well conducted study support the above hypothesis. In a consecutive series of 98 chronic headache patients, a MRV and LP with 1 hour ICP monitoring were performed [60]. Sinus stenosis was present in 48.9% of the sample. Based on 1 hour 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 [60] and the high prevalence of sinus stenosis-associated raised ICP found in subjects without chronic headache [32] 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.

AIM OF THE STUDY

Intracranial hypertension and progression of migraine

Although reported, the rate of responders and the duration of the clinical benefit after a single CSF withdrawal by LP in IIH/IIHWOP patients is unknown. 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 and with evidence of cerebral venous outflow disturbances at MRV.

PATIENTS AND METHODS

Study population

The study sample consisted of consecutive CM outpatients enrolled at Headache Centre of Department of Neurosciences of University of Naples "Federico II", who agreed to undergo CSF withdrawal via LP and who fulfilled the following criteria:

Inclusion criteria

(i) diagnosis of transformed migraine (TM) with or without medication overuse according to the Chronic Daily Headache criteria established by Silberstein and Lipton [63] up to 2006, and subsequently a diagnosis of chronic migraine (CM) according to the ICHD-II R2 criteria [64];

(ii) directly assessed unresponsiveness (failure to return to an episodic pattern of attacks) to withdrawal of medication overuse (when applicable) and to at least 2 consecutive migraine preventive treatments at standard doses lasting at least 2 months each. Drugs were chosen on the basis of the patient's co-morbidity profile among 7 drugs effective in migraine prevention (namely, amytriptiline, propranolol, flunarizine, pizotifen, valproic acid, zonisamide and topiramate);

(iii) normal brain magnetic resonance imaging, and availability of a brain MRV;

(iv) cerebral venous outflow disturbances defined as bilateral transverse sinus (TS) stenosis/hypoplasia or at least unilateral segmental TS flow gap/aplasia at uncontrasted MRV;

(v) availability of complete headache diary-based clinical data starting at least 1 month before LP (baseline) to at least 4 months after LP, or collection of possible missing headache diary data by direct visit or phone interview.

Exclusion criteria:

(i) evidence of a secondary cause of intracranial hypertension, including venography evidence of cerebral venous thrombosis and abnormal CSF chemistry and/or cell counts;

(ii) presence of papilledema;

(iii) age < 18 years.

Study protocol

Outpatients fulfilling the above-mentioned criteria were admitted to hospital. They underwent a complete neurological and physical examination including height and weight measurements. The absence of papilledema was confirmed by an ophthalmologic consultation with funduscopic examination.

According to institutional policy, patients underwent brain magnetic resonance and MRV in external radiologic services linked to the public health system. Consequently, there was a lack of homogeneity in the MRV techniques used. All MRVs were re-evaluated by an expert neuroradiologist. Some patients had spontaneously interrupted prophylactic treatment at least 1 month before LP. To avoid confounders of clinical outcome, all patients were asked to maintain their the current regimen up to 4 months after LP. Headache diary data referring to 30 days before LP were collected at admission and served as baseline. All patients were recommended to continue recording all headache activity also during the 4 months after LP.

Cerebral spinal fluid pressure was measured with a standard spinal manometer calibrated in mm Hg ("Lumbal" Riester, Germany) connected to the spinal needle via a three-way stopcock, with the patient in the lateral recumbent position with legs extended. All pressure values were multiplied by 13.56 (i.e., the specific weight of mercury) to convert values into mmH20. The spinal needle was inserted with the bevel orientation parallel to the long axis of the spine, the stilet was reinserted before the needle was extracted, and the patient was invited to rest in bed for at least two hours after LP. In patients with an OP $\leq$ 200 mmH20 the procedure was stopped after withdrawal of 6 mL of CSF required for routine analysis. In subjects with an OP >200 mmH2O, ICP was measured after each withdrawal of 2 mL CSF, up to its normalization (at about 100 mmH2O) or up to the

withdrawal of about 30 mL of CSF. We used a 20 G spinal needle because the rate of spontaneous CSF drip with thinner needles (22 G or smaller) is very low (up to less than 1 mL/min) when the patient is in a recumbent position, and it may take more than 1 minute to allow the correct transduction of CSF pressure onto a standard spinal manometer [65]. This would have prolonged unacceptably the CSF withdrawal procedure, and consequently increased the patient's discomfort and the risk of infectious complications. Lumbar punctures were performed by 2 operators using the same technique and instruments.

The upper limit of normal ICP is debated [32,38, 66-70]. We used the value of 200 mmH2O because IIHWOP patients may have lower ICP values than IIH patients [21]. Moreover, in a large sample of individuals without signs or symptoms of raised ICP [32], OP values above 200 mmH2O were closely associated with sinus stenosis.

All patients signed an informed consent declaration before enrollment in the study. The study was approved by the local Ethics Committee.

Clinical evaluation and data collection

All the patients' clinical data were collected using the AIDA Cefalee, a validated software [71] for headache management based on ICHD-II criteria [66]. All patients were prospectively evaluated for headache frequency and intensity in two structured follow-up visits scheduled 2 and 4 months after

LP. At the first visit, data were collected regarding months 1 and 2 after LP, and at the second visit data were collected regarding months 3 and 4 after LP. A few patients who missed the follow-up visits were given a new appointment or communicated their headache diary data by telephone. Therefore, complete data were obtained for all the patients. The median number of overall headache days (of any intensity) and of disabling headache days (i.e. with moderate or severe pain) in the 30 days before LP served as baseline data and were compared with the corresponding medians calculated at each follow-up. Clinical data collected one month after LP are reported but are not included in the statistical evaluation because of the confounding effect of post-LP headache (PLPH), which is highly prevalent in chronic headache sufferers [72-73]. Subsequent follow-ups were planned on clinical basis. Data on responder rate after LP , subsequent to 4th month follow-up, and the outcome after LP repetition, performed in some of our patients, are briefly reported.

Control groups

We compared the OP values of our series (Group A) with those of 2 control groups: Group B, which derives from a previous study of 217 neurologic patients without chronic headache or other symptoms or signs of raised intracranial pressure [32], and Group C, which is a retrospective series of 13

patients diagnosed at our clinic affected by IIH with papilledema in which OP was measured with the same LP procedure used for Group A.

End points

The primary end points of the study were:

(i) the prevalence of OP >200 mmH2O;

(ii) the percentage of "responders" (i.e. return to fewer than 15 headache days per month) during the 2nd, 3rd and 4th month after CSF withdrawal by LP;

(iii) the reduction of the median values of overall headache days per month and of disabling headache days per month during the 2nd, 3rd and 4th month after LP versus baseline.

The secondary endpoints were:

(i) difference in the baseline and primary endpoints between the subgroup undergoing preventive treatment at the time of LP and the subgroup not undergoing preventive treatment;

(ii) existence of factors predictive of a long-term response (a return to an episodic pattern of attacks during the 2nd month after LP), namely, body mass index (BMI), OP, CSF volume withdrawn or ongoing prophylactic treatment;

(iii) comparison of OP distribution in our series (Group A) versus Group B (no signs or symptoms of IIH) and Group C (definite IIH with papilledema).

Statistical analysis

Normality of data distribution was determined with the Anderson-Darling test. When normality was not assumed, non-parametric tests were used to assess differences in medians, namely, the Mann-Whitney-Wilcoxon and Friedman's tests for repeated measures with post-hoc test. Otherwise equality of variances was tested by the Fisher-Snedecor F-test using Sidak's correction for multiple comparisons. Differences in means were tested with Student's t-test (with Satterthwaite's correction when variances differed) with Sidak's correction for multiple comparisons. Values of $p < 0.05$ were considered statistically significant. A bias-reduced logistic regression model was performed to determine if some of the parameters measured at the time of LP (BMI, OP, amount of CSF withdrawn and presence/absence of ongoing preventive treatment) could be predictors of a long-term response (defined as a return to an episodic pattern of migraine attacks 2 months after LP). A statistics software freely available on the web was used for the logistic regression analysis [74].

RESULTS

Population description

Of the 278 consecutive patients diagnosed with TM/CM who completed the diagnostic and therapeutic workup, 56/278 (20.1%) were labeled "unresponsive" after failure of analgesic withdrawal (if applicable) or of at least two different preventive treatments lasting at least 2 months each. All patients had suffered from episodic migraine that had worsened up to an almost continuous daily migraine pain of variable intensity. Bilateral dural sinus narrowing, unilateral flow gap or aplasia at MRV were present in 52/56 (92.8 %) of unresponsive patients. Of the 52 subjects with cerebral venous outflow abnormalities, 44 (84.6%) agreed to LP and constitute our study sample.

The demographic features of our patients are listed in Table 1. Twenty-six of the 44 patients (59.1%) were found to overuse symptomatic medication defined according to ICHD-II [66] at first observation but failed to respond to analgesic withdrawal. Seven were found to overuse symptomatic mediation also at the time of LP. Twelve patients (27.3%) had spontaneously interrupted treatment at least one month before LP because of inefficacy and/or reduced tolerance. In the remaining 32 patients (72.7%) with ongoing therapy, the actual exposure to the last treatment was 12.2 weeks (range 8.3-23.8). Physical and neurological examinations were

unremarkable in all patients. No patient complained of diplopia or showed papilledema.

Time-of-flight MRV was used in 17 patients (38.6%) and three-dimensional phase contrast MRV in the remaining 27 (61.4%) patients. The main sinus stenosis patterns found at MRV in our series are illustrated in Figure 1. Bilateral TS stenosis/flow-gaps were identified in 15/44 cases (34.1%). An isolated unilateral TS gap was identified in 17/44 (38.6%) patients; a combined unilateral TS stenosis associated with a gap at the posterior segment of the superior sagittal sinus was observed in 2/44 patients (4.5%), and a unilateral TS stenosis/flow gap associated with the separation of superficial and deep venous circulation at torcular level was found in the remaining 10/44 (22.7%) cases.

Baseline

During the 30 days before LP, most patients had daily or near-daily pain. The median of overall headache days per month was 29.5 (95% C.I. 27-30; range 20-30); the median of disabling headache days per month was 12 (95% C.I. 9-17; range 5-25).

Opening pressure

The median OP was 244 mmH2O (95% C.I. 224-265; range: 81-403). An OP >200 mmH2O was found in 38/44 patients (86.4%) of whom 19 (43.2%) had an OP >250 mmH2O. The distribution of OP is reported in Figure 2.

Outcome one month after lumbar puncture

Within a few hours to 3 days after LP, 30 (68.2%) patients developed an orthostatic headache that fulfilled the ICHD-II criteria for PLPH [66]. Median PLPH duration was 7.5 days (range 1-30). PLPH was treated conservatively in all patients (hydration, non-steroidal anti-inflammatory drugs and bed rest). Headache diary data of the 1st month after LP could not be unequivocally attributed to previous pain or to PLPH, and therefore were not included in the statistical analysis. However, of the 14 patients without PLPH, 11 (78.5%) experienced a sudden decrease of pain soon after LP or, in some cases even during LP. Twenty-three of 30 (76.6%) patients with PLPH reported the disappearance of daily pain soon after PLPH resolution or in the late PLPH stage, provided a recumbent position was maintained. Overall, 34/44 (77.3%) patients experienced a dramatic decrease of pain at least for a few days or weeks after LP or at PLPH resolution. Based on this finding, 31 of these cases (70.4% of the whole sample) fulfilled the ICHD-II criteria for “Headache attributed to IIH” [66] despite the absence of

papilledema. The criteria were not fulfilled in 2 patients with OP <200 mmH2O or in 1 obese patient with OP <250 mmH2O.

Primary end-points

The primary endpoint results are summarized in Table 2. Twenty-four subjects (54.6%) experienced a return to an episodic pattern of headache during the 2nd month after LP; this was maintained in 20 patients (45.4%) at the 3rd month, and in 17 (38.6%) at the 4th month after LP. Two of 6 patients with an OP <200 mmH2O were classified as "responders" 2 months after LP. One of them still had episodic headache 4 months after LP. The median overall headache days per month decreased significantly ($p<0.0001$) from 29.5 days at baseline to 12 in the 2nd month, 19 days in the 3rd month and 26 days in the 4th month. No differences were found between the data obtained 2, 3 and 4 months after LP. The median number of disabling headache days per month decreased significantly ($p<0.0001$) from 12 at baseline to 5.5 in the 2nd month, 5 in the 3rd month and 6.5 in the 4th month. There were no differences between the data obtained at the 2nd and 3rd months after LP, whereas the number of disabling headache days per month was significantly higher at the 4th month than at the 2nd and 3rd months.

Secondary end points

We evaluated differences between patients with (n=32; 72.7%) and without (n=12; 27.3%) prophylactic therapy at the time of LP. At baseline, the median of disabling headache days, but not the overall number of headache days, was significantly lower in patients with ongoing treatment versus patients without [9.5; 95% C.I: 7-15 vs. 16.0; 95% C.I. 8-20 (p=0.02)]. The two groups did not differ significantly in terms of median OP or in the rate of responders at each follow-up. Neither did they differ in terms of the medians of overall headache days per month and of disabling headache days per month at each follow-up. The bias-reduced logistic regression model showed that none of the parameters measured at the time of LP (BMI, OP, amount of CSF withdrawn and presence/absence of ongoing preventive treatment) independently contributed to the long-term response (OR= 1.23, 95% CI 0.14-11.09; OR= 1.01, 95% CI 0.14-7.24; OR= 0.92, 95% CI 0.12-7.37; OR= 1.85, 95% CI 0.03-114.21, respectively for BMI, OP, mL of CSF withdrawn, presence/absence of ongoing preventive treatment).

Table 3 shows OP distribution of our series (Group A), and of the two control groups (Group B without signs and symptoms of raised ICP; Group C with definite IIH with papilledema). The OP distributions in the three groups were Gaussian. Analysis of variance showed that the variance of Group B differed from the variances of the two groups with raised ICP

(Group A and Group C), but the variances of the latter two were equal. Finally, the means of OP differed among the three groups.

Additional follow-up data

Of the 17 patients still suffering from episodic headache 4 months after LP, 13 (29.5%) and 9 (20.5 %) remained "episodic" 6 and 12 months, respectively after LP. Seven patients (15.9%) still had an episodic pattern of migraine attacks after a median observation period of 25 months (range 12-60 months).

Repetition of the lumbar puncture

Cerebral spinal fluid withdrawal via LP was carried out 16 times in 13 patients: 9 classified as responders at the 2nd month who relapsed and 4 non responders who had a clear-cut but short-lasting remission of CM after LP. An OP > 200 mmH2O was found in all procedures but 3. An extended benefit was observed in 7 cases (all belonging to the responder group after the first LP).

Relapses after LP were usually reported as abrupt in onset and were announced by the reappearance of a mild to moderate continuous pain at awakening associated with concomitant increase of disabling headache days frequency. LP with CSF subtraction were repeated in 13 patients: 9

responders at 2nd month who relapsed overtime and 4 non responders at 2nd month who had shown a clear-cut but short-lasting remission of CM after the first LP.

After the second LP we observed no change of the ongoing pain in 2 cases (1 responder and 1 non responder after the first LP), a short-lasting (1 to 2 weeks) benefit in 4 (1 responder and 3 non responder after the first LP) and the replication of an extended benefit in 7 cases (all responders after the first LP). Of these, 5 patients relapsed again after a median interval of 5 months (range 1,5-12) whereas 2 were still episodic after a follow-up of 2 and 42 month respectively.

LP has been repeated a third time in 3 cases. Two patients who relapsed 7 and 12 months after the 2nd LP replicated an extended benefit after the 3rd LP and were still episodic at the end of the study. (after 2 and 3 months respectively). An additional patient, classified as responder after the 1st LP but showing an early relapse after the second LP, unsuccessfully underwent the 3rd LP.

The median OP of the 16 repeated LP was 222.5 mmH2O (95% C.I. 213-244; range 135-325). An OP > 200 mmH2O was found in all procedures but 3.

DISCUSSION

In our series of selected unresponsive CM/TM patients, pain mostly occurred on a daily or almost daily basis. The prevalence of sinus venous stenosis was even higher (52/56; 92.8%) than reported in unselected chronic headache patients [60,62] and close to the prevalence found in IIH patients (93.0%) [37]. The vast majority of our patients (38/44; 86.4%) had an OP >200 mmH20, and a mean OP significantly higher than asymptomatic patients (Group B) but, as expected [21], significantly lower than patients with a definite diagnosis of IIH (Group C). Based on ICHD-2 criteria [66], 70.4% of our patients could be diagnosed with "Headache attributed to IIH" despite the absence of papilledema. These findings indicate that proven unresponsiveness to medical treatment strongly predicts the presence of sinus stenosis and of a raised ICP in clinical series of chronic migraine patients.

Normalization of ICP consequent to a single CSF withdrawal by LP was followed by the return to an episodic pattern of headache that lasted at least 2 months in more than half the patients (24/44; 54.6%), and at least 4 months in more than one-third of patients (17/44; 38.6%). Both overall and disabling headache days per month were significantly fewer at each follow-up visit compared with baseline values. The benefit persisted even longer in 7 patients (15.9%), i.e., after a median follow-up of 25 months (range 12-60

months). Overall, 77.3% of patients experienced a clear cut amelioration of pain soon after LP or at PLPH remission, which was maintained in 54.6% of them at the 2nd month. Finally, most responders at the first LP who relapsed, responded also to a subsequent LP. These findings strongly support the existence of a causal link between CSF withdrawal via LP and clinical outcome.

Two of the 6 patients with a normal OP also responded to the withdrawal of 6 mL CSF, which was required for routine analysis. It is conceivable that these patients were affected by intermittent IIHWOP [60, 75-76], but ICP monitoring, which is required to identify such cases, was not performed in this study.

The clinical outcome measures of this study did not differ between subgroups with and without ongoing treatment during follow-up. As expected, only the number of disabling headache days at baseline was significantly lower in patients with ongoing medical treatment. Therefore, ongoing preventive treatment did not seem to affect the clinical outcome of our patients. Similarly, baseline BMI, OP and the amount of CSF withdrawn did not seem to predict the long-term benefit of the procedure.

In our sample, 30/44 (68.2%) patients developed a post lumbar puncture headache (PLPH) after the first therapeutic lumbar puncture (LP). Although extraordinarily elevated, this finding is in agreement with previous observations in chronic headache sufferers undergoing even a diagnostic LP

(i.e. with only a few ml of CSF collection) [72-73; 77-78]. Using 22 G needles, a 85,7% prevalence of PLPH has been recently reported in the subgroup with chronic headache of a prospective series of neurologic patients undergoing diagnostic LP (cases requiring LP for therapeutic CSF drainage were excluded from the series) [78]. Conversely, using 20 G needles to perform diagnostic LP in a large unselected neurologic patients series, a previous history of chronic headache was found in 50 out of the 88 cases (56,7%) who developed PLPH [73]. While the reasons for such an high prevalence of PLPH in chronic headache sufferers remains to be clarified, the above considerations suggest that neither the use of 20 G needles nor the subtraction of large amounts of CSF played a relevant role in high PLPH prevalence observed in this series.

The most striking finding of our study is that the large majority of patients diagnosed with proven unresponsive CM in specialized centers might be suffering from chronic headache secondary to IIHWOP. This implies that IIHWOP mimicking CM is: a) a condition much more prevalent than hitherto believed; b) commonly misdiagnosed as CM if the diagnosis is based on ICHD-2R criteria; and c) strictly predicted by refractoriness to preventive treatments. Moreover, we show 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.

All our patients had a history of episodic migraine that had worsened over time. A raised ICP associated to sinus stenosis was reported to occur almost asymptomatically in up to 11% of individuals of a community series, which indicates that it is not a sufficient cause of chronic headache [32]. Conversely, in unselected CM patients, about half the cases were not associated with significant sinus stenosis nor with a raised ICP, which indicates that a raised ICP is not necessary for chronic headache development [60]. Moreover, there is evidence that chronic headache presentation of IIH may require a migrainous background [31].

According to the SVC model [43], 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 [79-80]. 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 [43]. Allodynia, a clinical marker of central sensitization, usually develops in the course of primary headache attacks [81-83] but is bilaterally detected during the intercritical phase in over 70% of chronic headache

subjects [54]. Among migraine sufferers, allodynia has been associated with female sex, frequent headache, increased BMI and depression [84-85]. It may represent the final pathway on which converge the actions of most risk factors for migraine progression validated by the recent literature [86]. Interestingly, Ekizoglu et al. [55] recently found allodynia in about one half of a IIH patients series and it was associated with a chronic migraine-like headache profile.

On the basis of the above considerations and findings we recently proposed [20] 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.

This series of considerations support the alternative hypothesis that a frequently overlooked comorbid sinus stenosis-associated increased ICP, although very common in otherwise healthy subjects, is, in migraine-prone individuals, a powerful modifiable risk factor for pain progression, and is causatively involved in its refractoriness [19]. A prospective controlled study is needed before withdrawal of CSF by LP could be translated into routine clinical practice. Studies are also required to determine if patients with chronic pain and raised ICP should be diagnosed with IIHWOP mimicking CM or if they should be considered primary migraine subjects with a comorbid IIHWOP-dependent progression and unresponsiveness of pain. Whatever the case, our findings suggest that intracranial hypertension

without papilledema should be considered in all patients referring to specialized headache clinics for an almost daily migrainous pain unresponsive to medical treatments and with evidence of dural sinus abnormalities at MRV.

Study limits

The main limitation of this study is the lack of a control group for the clinical outcome of LP. However, even given the susceptibility of migraine patients to the placebo effect, the lack of a control group may be partially counteracted by the very high prevalence of intracranial hypertension in our series (86.4%), the immediate improvement observed after LP (or soon after PLPH resolution) in patients selected for longstanding and refractory chronic headache syndromes and, lastly, the reproducibility of the sustained benefit at LP repetitions in 7 out of 9 responders after relapse.

At time of LP a significant proportion of patients (19/44, 43.2%) were treated with topiramate (100 to 200 mg per day), a drug that can lower ICP [59]. However, this potential bias would have only resulted in an underestimation of OP values, without affecting the strength of data. The inhomogeneity of the MRV technique is an unavoidable consequence of the naturalistic scenario of this study. However, it precludes the possibility of establishing a reliable statistical correlation between the degree of stenosis and the baseline data or clinical outcome. Studies designed to establish a

more precise definition of this radiologic finding and to identify the most suitable MRV technique to use in IIH patients are urgently needed.

CONCLUSIONS

IIHWOP shares with CM a number of clinical features and it can be documented in chronic headache series much more frequently than expected [17, 29-30]. However, the lack of venous outflow disturbances and of raised ICP in more than half of patients with chronic headache [60], on one hand, and the high prevalence of sinus stenosis-associated raised ICP found in subjects without chronic headache [32] 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 findings show that the vast majority of patients diagnosed with unresponsive CM in specialized headache clinics may present increased intracranial pressure that is involved in the progression and refractoriness of pain. A single CSF withdrawal via LP may result in a sustained remission of chronic pain in a relevant proportion of cases. 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.

Prospective controlled studies are needed before this procedure can be translated into routine clinical practice. Nonetheless, we suggest that intracranial hypertension without papilledema should be considered in all patients suffering from an almost daily migrainous pain with evidence of unresponsiveness to medical treatments and cerebral venous outflow abnormalities at MRV.

TABLES AND FIGURES

Table 1. Demographic and clinical data

Subjects, No. (%)	44 (100%)
Women, No. (%)	39 (88.63%)
Men, No. (%)	5 (11.36%)
Age, median value (95% CI)	37,5 (33-40)
BMI, median value (95% CI)	26,17 (24,46-28,69)
- Normal weight (BMI 20-25), No. (%)	19 (43,2%)
- Overweight (BMI 25-30), No. (%)	14 (31,8%)
- Obese (BMI>30), No. (%)	11 (25,0%)
Medication overuse at first observation, No. (%)	26 (59,1%)
Medication overuse at time of LP, No. (%)	7 (15,9%)

Table 2. Clinical outcome after CSF withdrawal

	Baseline	Follow-up 1	Follow-up 2	
		2nd month	3rd month	4th month
Responders (episodic headache pattern) n. (%)	-	24 (54.5%)	20 (45.4%)	17 (38.6%)
Overall headache days/month Median (95% C.I.; range)	29.5 (27-30; 20-30)	12 [a, b] (6-28; 2-30)	19 [a, b] (6-29; 1-30)	26 [a, b] (7-28; 3-30)
Disabling headaches days/month Median (95% C.I.; range)	12 (9-17; 5-25)	5.5 [a] (4-8; 0-25)	5 [a] (3-11; 0-23)	6.5 [a,c] (5-12; 1-25)
[a] $p<0.0001$ compared to baseline				
[b] not significant compared with the other time point follow-up values				
[c] $p<0.01$ compared to the 2nd and 3rd month follow-up				

Table 3 Comparison of opening pressure distribution in study series vs. control groups

	Group A Study series	Group B* Patients without signs or symptoms of IIH	Group C Patients with definite IIH	p
Patients n.	44	217	13	
OP, mmH2O mean (S.D.)	245.5 (62.8)	149.3 (47.5)	310.4 (76.7)	a,b,c

* data derived from Reference 32.

[a] Anderson-Darling test for normality distribution: $p > 0.05$ for each group (data normally distributed)

[b] Fisher F-test for equality of variances:
- Group A vs. Group B: $p = 0.01$
- Group A vs. Group C: $p = 0.32$ (n.s)
- Group B vs. Group C: $p = 0.005$

[c] Student t-test for equality of means:
- Group A vs. Group B: $p < 0.01$
- Group A vs. Group C: $p < 0.01$
- Group B vs. Group C: $p < 0.01$

OP, opening pressure; IIH, idiopathic intracranial hypertension

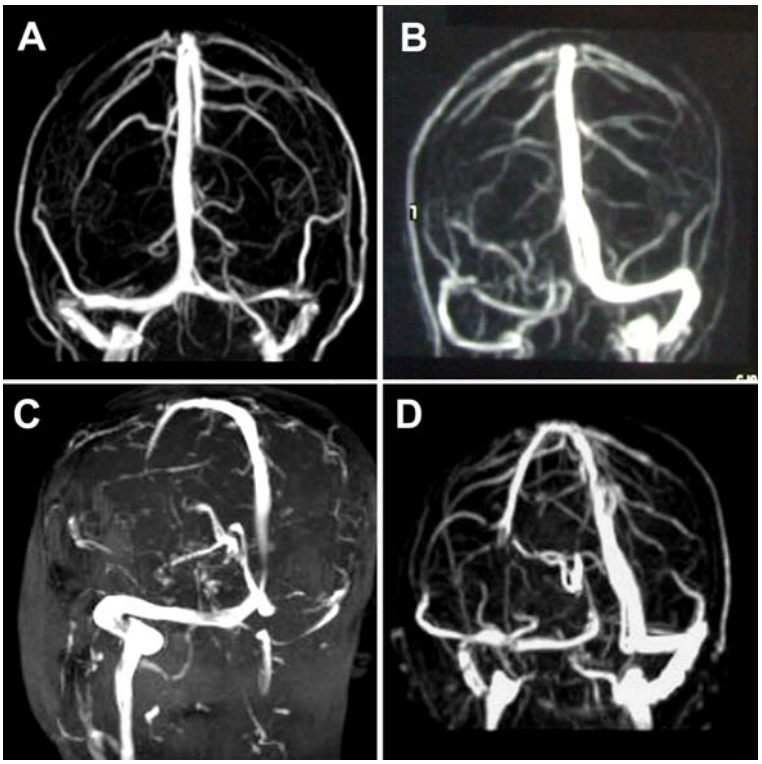

Fig. 1 Examples of the main sinus stenosis patterns found at MRV. (A) Bilateral TS stenosis; (B) Isolated unilateral TS stenosis; (C) Unilateral TS stenosis associated with posterior SSS stenosis; (D) Unilateral TS stenosis combined with separation of superficial and deep venous system at torcular level.

MRV: Magnetic Resonance Venography; TS: Transverse sinus; SSS: Superior sagittal sinus.

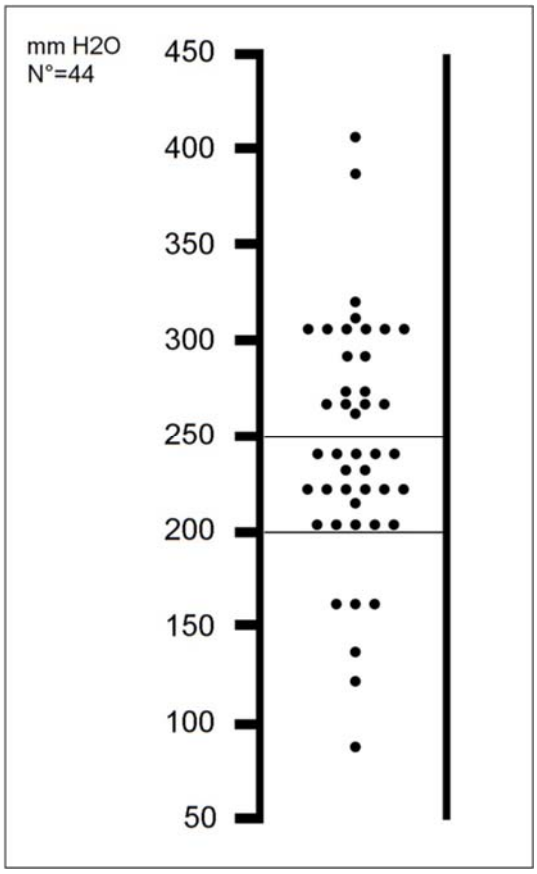

Fig. 2 Distribution of the opening pressure in the whole sample.

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