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Topic: 8 - Headache

Abstract — WCN 2013
No: 3149
Topic: 8 — Headache
Intracranial hypotension is a rare cause of orthostatic headache: A review of the etiology, treatment and prognosis of 13 cases

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The aim of this investigation is to examine the causes, clinical picture, treatment, and prognosis of spontaneous intracranial hypotension, a rare cause of orthostatic headache, among the cases presenting in our clinic.
Thirteen cases (5 males and 8 females), diagnosed with spontaneous intracranial hypotension in our clinic between January 1st, 2009 and October 30th, 2011, were included in this study.
The presenting symptoms, treatment, findings on cranial magnetic resonance imaging, cerebrospinal fluid pressure measured at lumbar puncture (in available patients), and healing period of the patients were recorded. Five patients with orthostatic headache and accompanying symptoms were treated with bed rest, increase in oral fluid intake, intravenous hydration, and caffeine, and experienced a complete recovery. Complete recovery was observed in two patients (15.3%) within 10 days, in another two (15.3%) within 15 days and in one patient (7.6%) within 21 days. Headaches and other clinical symptoms significantly regressed within 30 days in four patients (37.6%) who received similar treatment, but a mild headache persisted intermittently during follow-up in these individuals. As the headache had not resolved after 30 days, an epidural blood patch was applied in these four cases (37.6%) and the clinical picture completely improved within 10 to 15 days.
Spontaneous intracranial hypotension should primarily be suspected in cases complaining about postural headache and contrast-enhanced cranial imaging should be performed. The presence of cranial nerve paralysis and pyramidal tract signs should be considered. Conservative treatments should be considered initially, however if conservative treatments fail, epidural blood patches must be applied.

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Abstract — WCN 2013
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Topic: 8 — Headache
Association of cholecystokinin receptor 1 gene polymorphism and migraine

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Background: Cholecystokinin (CCK) is one of the most abundant neurotransmitter peptides in the brain. CCK coexists with dopamine in dopaminergic neurons, and modulates the release of dopamine in the nucleus accumbens. The CCK system is believed to be involved in pain processing. The aim of the study was to investigate the prevalence of -81A/G (rs1799723), -128G/T (rs1800908) and 984T/C (rs1800857) polymorphisms of the CCK-AR gene in migraine patients and controls.
Method: 144 migraine patients (ICHD III), mean age = 41.6 ± 12.5 y.o. and 197 healthy controls living in Moscow and the Moscow Region were included. SNPs were genotyped by a PCR-RLFP technique: PCR with "GenPakTM PCR Core" (Isogene Lab., Ltd.) and restriction with HinfI for rs1799723 and rs1800908 and with PstI for rs1800857 (ferments by SibEnzyme Ltd.).
Results: C-allele frequency in 984C/T was significantly higher in migraine patients, 0.479 ± 0.030 compared with controls, 0.154 ± 0.026 ($\chi 2 = 85.44$, $p < 10–10$; OR = 5.0, 95% CI = 3.50–7.13). The -81A/G and -128G/T minor allele's frequencies didn't differ between groups: -81G = 0.049 ± 0.018 in the migraine group and 0,045 ± 0,015 in the controls; -128T = 0.045 ± 0.017 in the migraine group and 0.025 ± 0.011 in the controls.
Conclusion: This study is the first to report a more positive association of the C-allele of the CCK-AR gene 984T/C polymorphism in patients with migraine than in control subjects.

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Abstract — WCN 2013
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Can vision influence trigeminal nociception? A study of the effect of visual cortex activation on the nociceptive blink reflex

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Background: In migraine, the link between cortical phenomena and trigeminovascular activation is not clear and thus, headache as well.
Objective: To search in humans for a possible functional connection between the visual cortex and the trigeminal nociceptive system by studying the effect on the nociceptive blink reflex (nBR) of repetitive transcranial magnetic stimulation (rTMS) applied over the visual cortex, and to compare healthy volunteers (HV) and migraine without aura patients (MO).
Methods: Fifteen bilateral nBR responses were recorded by stimulating the right supraorbital nerve in 22 HS and 13 MO before and after 1 Hz (15 min train) or 10 Hz (20 trains with a 15 s intertrain interval) rTMS. For comparison, we also performed the same study in HV after an 8 Hz visual flash stimulation.

0022-510X/$ – see front matter

Objective: To ascertain the effect of perioperative BP on the development of PDPH in the patients who received surgery under spinal anesthesia.
Patients and methods: We evaluated the presence of PDPH in all consecutive 199 patients (122 males, 77 females, age: 15–76 years) who received elective knee surgery under spinal anesthesia between September 2012 and February 2013. The spinal anesthesia was performed by the same anesthesiologist with 25-G Quincke needle. Data regarding previous history of headache, pre- and post-operative BP, highest and lowest BP during operation as well as demographic features were analysed.
Results: The overall incidence of PDPH was 9.0%. It was higher in female than in male (15.6% vs 4.9%, $p = 0.02$). Age, history of hypertension or recurrent headache was not different between patients with and without PDPH. The duration of operation or spinal anesthesia was not different between the two groups. BP variables were expressed as pre- and post-operative mean arterial pressure (MAP), the highest and the lowest MAP during operation, and their differences were not different either.
Conclusion: PDPH after knee surgery under spinal anesthesia occurred more frequently in female patients, and was not influenced by their perioperative BP states.

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Abstract — WCN 2013
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Memory improvement after spreading depression by NMDA blocker as memory destructor

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Spreading depression (SD) is transient neural hyperexitablity followed by depolarization wave, which propagates through the brain and modulate electrical gradient and synaptic activity. Data have shown that SD wave distributes coincidence between neural activity and behavioral activity. Neural activity and electrical potential effect on memory retrieval have been demonstrated. Inhibitory effect of NMDA receptors in SD procedure can control memory impairment caused by SD. However, the negative effect of NMDA receptor blockage on memory has been proven in previous studies. In the present study the effect of NMDA receptors blockage (MK801) used to evaluate its efficiency in subsiding of SD negative influence on memory. Wistar rats (60–80 g) were randomly chosen in 6 groups and (NMDA blocker0.63–1 mg/kg) were administrated after 3 mol/L KCl injection for induction of repetitive SD in rat. The groups were evaluated by T-maze test and SD groups were compared with control groups, including (NMDA blocker 1–0.63 mg/kg controls) and sham group. T-maze data have showed that repeated SD could significantly alter memory retrieval performance. However, in the second week memory enhancement was induced by SD induction. Repeated SD induction during other weeks indicated impairment in memory. Application of NMDA blocker showed significantly enhanced memory retrieval and could potentially control memory impairment after SD. The studies indicated that NMDA blocker may decrease memory performance, on the other hand the effect of MK801 on inhibition of SD propagation may somehow weaken memory improvement due to its memory destruction effects.

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Abstract — WCN 2013
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Prevalence of migraine among medical studets in Kuwait University

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Background: Prevalence of migraine among medical students is of particular interest as they are subjected to lots of tests and stresses that may precipitate migraine attacks.
Objectives: To determine the prevalence of migraine among medical students in Kuwait University.
Methods: This cross-sectional and descriptive study, which included students registered to Medical Faculty at Kuwait University in the academic year of 2012–2013. Out of 808 registrants, 621 students accepted to participate in the study. Participants who had two or more headaches in the last 3 months were subjected to two preliminary questions and participants with at least one positive response were asked to perform the validated ID-Migraine™ test. The frequency of headache per month and severity of headache by Numeric Rating Scale (NRS) were reported.
Results: Migraine was detected in 173 subjects (27.9%) based on the ID-Migraine™ test. The mean age of the migraine students was 20.17 ± 2.29 (16–25 years). Thirty-seven were male (21.4%) and 136 were female (78.6%). Migraine was significantly more frequent in the last 2 grades (35.5% and 44%, $p < 0.000$). The frequency and the severity of headache were significantly increased during the last 2 grades (5.55 ± 1.34 and 7.23 ± 1.27, $p < 0.000$) (6.00 ± 0.76 and 6.68 ± 1.25, $p < 0.000$) respectively. Stress 43 (24.9%), irregular sleep 36 (20.8%), and much reading 32 (18.5%) were the most common triggering factors.
Conclusion: There is a high prevalence of migraine among medical students in Kuwait University. The frequency and severity of headache increase with years of educations.

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Abstract — WCN 2013
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Topic: 8 — Headache
A randomized doubled blinded trial of treatment with diamino-oxidase (DAO) in patients with migraine and deficit of enzyme's activity

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Background: Histamine has been considerate as a chemical mediator of migraine. The degradation is done in two different pathways. One of the enzymes that allow this process is the diamino-oxidase (DAO).
Objective: The aim of this study is to identify the prevalence of the deficit in the activity of DAO in patients with migraine, and test the supplementation of this enzyme in a randomized controlled double-blind trial.
Material and methods: This was a randomized parallel-group controlled study. After a 1-month run-in, patients with migraine attacks/month between 4 and 14 were randomized 1:1 to placebo or DAO three times at day during one month. Primary outcome measures were diminution of hours of pain, and the use of antimigraine drugs.
Results: We studied 137 patients with migraine, and find the deficit of DAO activity (<80 HDU/ml) in 119 (87%).

One hundred patients were randomized and included in the intention-to-treat analysis. Between run-in and first month of treatment, the mean number of hours of pain decreases in both groups but with significant difference in the final control in the group treated with DAO compared with placebo (6,3 vs 5,1: $p < 0.03$).
The use of the acute antimigraine drug was significantly reduced in the DAO but not in placebo group ($p > 0.022$).
There were no adverse events in either group.
Conclusions: Deficit in the activity of DAO is very prevalent in population with migraine.
The supplementation with the enzyme is effective and safe as a preventive therapy for migraine.

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Abstract — WCN 2013
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Subdural haematoma as a late complication of spontaneous cerebrospinal fluid hypovolemia (SCH) syndrome: Two case reports

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Background: SCH syndrome is relatively common, and a CSF leakage can be occasionally demonstrated. Subdural haematoma (SDH) has been reported in patients with SCH, mainly in older men, or these displaying longer time to diagnosis of SCH.
Objectives: We report two cases that developed SDH after apparent resolution of SCH.
Material and methods: A 41 year old man developed severe orthostatic headache and neck stiffness after repeated sneezing. Lumbar puncture showed an opening pressure of 0 mm H_2O. Cisternography demonstrated cervicothoracic CSF leak. A 43 year old man presented sudden headache after sport activity, highly suggestive of SCH, developing unilateral abducens palsy after several days. Cranial tomography (CT) was normal in both cases, with resolution of symptoms after 3 months of conservative therapy.
Results: Three months after the onset, when patients were almost asymptomatic, a control MRI showed subacute bilateral SDH. In both, resolution of the haematomas was verified after some weeks without need of drainage.
Conclusion: SCH is characterized by orthostatic headache, low CSF pressure, and sometimes typical MRI image. The development of SDH, although rare, has been reported. In our cases the late development of SDH is remarkable, perhaps related to the persistance of SCH for a long time. We emphasize the importance of monitoring patients with SCH, and consider conservative measures only in cases with a brief course. Epidural patching or surgical repair may prevent potentially serious complications such as SDH. Moreover, SCH should be excluded as a cause of SDH in young patients without risk factors.

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Abstract — WCN 2013
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Analysis of MAP0004 subjects with menstrually related migraine vs. non-menstrually related migraine

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Background: Menstrually related migraine (MRM), as defined by The International Classification of Headache Disorders, 2nd edition, occurs from days −2 to +3 of menstruation in $^{3}2$ of 3 menstrual cycles and at other times of the cycle. MRM generally lasts longer and is more severe and difficult to treat than non-MRM. MAP0004 is an investigational product that delivers dihydroergotamine through the lungs via a breath-synchronized metered-dose inhaler.
Objective: This post hoc analysis of phase 3 data evaluated the efficacy and tolerability of MAP0004 in MRM vs non-MRM.
Patients and methods: This analysis included 149 women from a modified intent-to-treat population who treated MRM ($n = 45$) and non-MRM ($n = 104$) with MAP0004. The study used the following clinical end points: pain relief and pain free at 2 h and sustained pain relief and sustained pain free at 2–24 h and 2–48 h.
Results: The efficacy of MAP0004 did not differ significantly in MRM vs non-MRM at 2 h (pain relief 62% vs 64%; pain free 36% vs 29%), at 2–24 h (pain relief 53% vs 49%; pain free 31% vs 23%), and at 2–48 h (pain relief 38% vs 38%; pain free 24% vs 15%). No significant differences were found in frequency of adverse events, and no drug-related serious adverse events were reported.
Conclusion: In this post hoc analysis of phase 3 data, MAP0004 was similarly effective and well tolerated in treating both MRM and non-MRM.
Study supported by MAP Pharmaceuticals, Inc., a wholly owned subsidiary of Allergan, Inc.

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Abstract — WCN 2013
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Analysis of the development of allodynia: Correlation between migraine duration and severity

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Background: Allodynia, the perception of pain from non-nociceptive stimuli, is a clinical presentation of central sensitization. Allodynia is reportedly common during migraine attacks. Although factors leading to development of allodynia are not well understood, duration and severity of migraine have been implicated.
Objective: This retrospective analysis evaluated the relationship between allodynia and the duration and severity of migraine to better understand the mechanisms related to migraine-induced central sensitization.
Patients and methods: This analysis included 792 patients from the double-blind period of a phase 3, placebo-controlled, randomized clinical trial of an investigational acute treatment for migraine (MAP0004). Baseline pain levels were recorded by patients using an electronic diary, and baseline allodynia data were obtained using a standard questionnaire. Correlations between percentage of patients reporting allodynia, severity of migraine, and duration of migraine were analyzed by Fisher's exact test or Chi-square test, as indicated.
Results: At baseline, 53% of patients reported allodynia. The presence of allodynia did not change in relation to the duration of the migraine (Chi-square $P = 0.2182$), regardless of migraine severity (moderate pain, Chi-square $P = 0.1807$; severe pain, Chi-square $P = 0.5830$). Patients reporting severe pain experienced significantly more allodynia (58.4%) than patients with moderate pain (48.2%; Fisher's exact test $P = 0.0053$).

A RANDOMIZED, DOUBLE-BLIND TRIAL OF DIAMINE-OXIDASE (DAO) TO TREAT PATIENTS WITH EPISODIC MIGRAINE AND DAO DEFICIENCY.

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ABSTRACT

Objective: This study sought to first assess diamine-oxidase (DAO) activity levels in patients with episodic migraine. We then carried out a parallel double-blind, randomized trial to compare DAO supplementation to placebo in migraine patients with confirmed DAO deficiency.

Methods: DAO activity was measured in 61 matched healthy subjects without migraine history and in 137 patients with episodic migraine. 100 patients with confirmed episodic migraine and DAO deficiency were randomized to receive either 4.2 mg of DAO supplementation every 8 hours or placebo. Duration (hours of pain), number and intensity of attacks, and need for analgesia (triptans) were recorded.

Results: DAO deficiency in the healthy subjects was 44% vs. 87% ($p<0.0001$) in patients with migraine. DAO supplementation reduced pain duration in migraine patients (DAO vs placebo; 2 vs 0.2 hours; $p=0.03$). Additionally, a trend towards fewer attacks was observed in the treatment group. The use of triptans in the DAO group decreased during the one-month follow up period ($p<0.022$). No adverse effects were observed.

Conclusions: DAO deficiency is significantly more common in patients with migraine than in an asymptomatic population. Supplementation with the DAO enzyme in patients with an activity deficiency is an effective and safe method for the preventive treatment of episodic migraine.

Perspective: We present two important novel findings: 1) DAO deficiency is significantly more common in patients with migraine than in an asymptomatic sample and 2) Supplementation with the DAO enzyme in migraine patients with DAO deficiency appears to be a safe and effective treatment as prevention for episodic migraine.

***Keywords**:* diamine-oxidase, histamine, migraine, episodic migraine, diamine-oxidase deficience, headache.

***Abbreviations**:* DAO (diamine-oxidase); IHS (International Headache Society); CGPR (Calcitonin Gene-Related Peptide); HDU/ml (histamine degradation units/ml); NPRS (Numeric Pain Rating Scale); C1 (consultation 1); C2 (consultation 2)

INTRODUCTION

Migraine is the most common neurological disorder, affecting approximately 8% of men and 17% of women. The incidence rate in the young population is notable (approximately 12%), and the high levels of pain associated with this disorder can negatively impact both family and work activities.[1, 2] The International Headache Society (IHS) defines episodic migraine as < 15 days of pain per month.[3]

Migraine is associated with neurogenic inflammation and various mediators—including substance P, calcitonin gene-related peptide (CGRP), nitric oxide, adiponectin and histamine—have been postulated to explain the genesis of this inflammation.[4, 5] The role of histamine is believed to be especially important because its presence in afferent neurons stimulates the adjacent sensitive nerve terminals,[6, 7, 8] which then influence hypothalamic activity involved in pain generation pathways.[9]

Histamine is a biogenic amine that is highly abundant in foods and present in multiple physiological functions in the body. Histamine degradation occurs principally in the digestive tract, where it is broken down by diamine-oxidase (DAO), and in the liver, where hydroxymethyltransferase acts on it.[10]

Excess histamine can cause a varied group of symptoms, including migraine but also skin, digestive, and respiratory system disorders. DAO activity deficiency may facilitate the accumulation of plasma histamine, thus increasing the potential risk of a migraine attacks.[11]

It has been suggested that DAO deficiency is more prevalent in migraine patients than in the general population, although precise figures are not available. Recently it has been published that DAO genotypes and allelic variants are associated with the risk for migraine in Caucasian Spanish people, especially in women. [12] Theoretically, DAO supplementation could compensate for reduced enzyme levels in migraine patients with DAO deficiency. However, no studies have previously been conducted to assess the benefits of this approach in migraine treatment.

Given the knowledge gap described above, we carried out the two-part study presented here. First, we assessed the prevalence of DAO deficiency in a healthy subjects -based sample and in patients with confirmed migraine diagnosis. Then, we performed a double-blind, randomized trial to compare the effects of DAO enzyme supplementation to placebo in migraine patients with confirmed DAO deficiency.

SUBJECTS AND METHODS

Patients and inclusion criteria

137 adults (122 females [89%] and 15 males [11%]) attending our headache unit who had been diagnosed by us as having episodic migraine according to current International Headache Society (IHS) criteria were consecutively included in this study. For the control group, we included 61 matched healthy volunteers who were recruited at Hospital General de Catalunya, Sant Cugat del Vallés, Barcelona, Spain (34 females [56%] and 27 males [44%]) without clinical criteria for migraine. The mean age of the healthy volunteers was 42.46 +/- 14.4 years vs. 41.95 +/- 11.3 in patients with migraine.

Blood samples were collected from all subjects by venipuncture with an EDTA tube after an 8-hour fasting period and the samples were analyzed with ELISA to determine DAO enzyme activity. Values above 80 HDU/ml (Histamine Degradation Units/ml) were considered normal while values < 80 HDU/ml were considered deficient, in accordance with a validation process carried out in 2006 and again in 2012 to correlate symptom scores with enzyme activity.[13, 14]

Then we performed a double-blind randomized study in 100 migraine patients whose DAO activity levels were below the predetermined cut-off point. Additional inclusion criteria were as follows: age between 18 and 65 years; 4 to 14 migraine episodes/month for a minimum of six months prior to study initiation. Exclusion criteria included beginning of migraine over 50 years, other kind of headache diagnosed in the same patient, the possibility of pregnancy and preventive treatment for episodic migraine during three month prior to the study.

The study was approved by the Ethics Committee of the *Hospital General de Catalunya*. All participants signed an informed consent form.

Product under study:

DAO enzyme, 4.2 mg (DR Healthcare, Barcelona, Spain), administered 20 minutes before breakfast, lunch, and dinner. The DAO enzyme is a food supplement with special medical uses[15, 16]

Procedures

Figure 1 provides details of the study procedures. Patients with migraine and DAO levels of < 80 HDU/ml underwent an initial baseline consultation and were given a “patient diary” to record relevant study data for one month prior to treatment initiation. Patients were asked to record the following: duration of migraine attacks (in hours), number of attacks, pain intensity, and analgesia used to control the attacks.

Pain intensity was assessed by the Numeric Pain Rating Scale (NPRS), a 10-point grading scale in which 0 represents absence of pain and 10 is the worst possible pain.

After one month, all patients were scheduled for the first consultation (C1) at which time they submitted the first patient diary. Patients were then randomized using the RANUNI procedure (SAS, v. 6.12, SAS Institute, Cary, NC, USA) into blocks of four patients to receive either DAO enzyme supplementation or placebo. Randomization was double-blind in both groups (1:1), and age and sex were considered in the process to assure similarity in baseline characteristics. The patients then received a package containing the study medication or placebo. The physical presentation of both active and placebo treatments was the same: capsules for oral administration. At the end of this consultation, patients were given a second diary to record relevant data during the treatment month, which they submitted at consultation 2 (C2). Treatment compliance was verified post-treatment by counting the remaining medication for each patient.

This trial was overseen by a independent data safety monitoring board.

Outcome measures:

The main outcome measure was as follows: 1) number of hours of pain between C1 and C2

Secondary measures included: 1) number of migraine attacks between C1 and C2. 2) Triptans use. 3) Perception of pain (NPRS) and 4) Adverse effects during treatment.[17]

Statistical analysis

The statistical analysis took into account the 12% prevalence rate (17% and 8%, respectively, in females and males) of episodic migraine in the Spanish population. We selected the main study variable—duration of migraine attacks—based on a literature review. Based on an assumed 5% type 1 error rate and a desired statistical power of 80%, we calculated that a total of 82 subjects (41 in each group) would be needed. Based on an expected 15% dropout rate, we included a total of 100 patients (50 per group) to assure that at least 82 subjects would complete the full study.

ANOVA was used to evaluate differences in migraine attack duration (hours), number of attacks, and pain scales. The Mann-Whitney test was used to evaluate the use of analgesics.

Statistical analysis was performed using a SPSS for Windows, version 15 (Chicago, IL).

RESULTS

The prevalence of DAO deficiency among the 61 healthy controls was 44% (27/61 subjects) compared to 87% (119/137 patients) in the group with episodic migraine. Consequently, DAO deficiency was significantly greater (87% vs 44%, respectively; p: <0.0001) in patients with migraine vs. the control group (Figure 2).

A total of 100 patients fulfilling episodic migraine criteria with DAO deficiency were consecutively randomized to receive placebo or DAO supplementation. One patient withdrew from the study at C2. Table 1 shows the characteristics of these patients. At baseline, there were no significant differences between the groups in terms of sex, age, and DAO activity levels.

As Figure 3 shows, there were no significant differences between the groups at C1 in mean duration (SD) of migraine attacks: 6.5 (2.8) vs. 7.1 (9.9) hours in the placebo and DAO groups, respectively (p= 0.374). However, after one-month of DAO supplementation, the differences were significant, with patients in the placebo group reporting a mean attack duration of 6.3 (3.3) hrs. vs 5.1 (3.5) hrs in the DAO group (p=0.03). Consequently, the mean duration of migraine attacks decrease by 2 hours in the DAO group vs. only 0.2 hours in the placebo group.

No differences were observed in the number of pre-treatment (C1) and post-treatment (C2) migraine attacks, although the treatment group showed a trend towards fewer episodes compared to the placebo group. (Figure 4)

No differences in pain intensity (NPRS) were observed between the two groups. Figure 5, shows the analgesic needs (mainly triptans) in both groups after one month of treatment. As Fig. 5 clearly shows, patients in the active treatment group required significantly fewer migraine-specific analgesics than patients in the placebo group (p<0.022).

The only adverse effect observed was one case of gastrointestinal intolerance in a patient in the placebo group. That patient subsequently abandoned the study at appointment C2.

DISCUSSION

This study found a significant difference in the prevalence of DAO enzyme deficiency in patients with migraine versus matched healthy subjects. In addition, we found that DAO supplementation significantly reduced pain duration in migraine patients. These findings suggest that enzyme supplementation in such patients may be an option in the preventive treatment of this disorder. To our knowledge, this is the first randomized study to assess the benefits of DAO supplementation in migraine patients.

The potential physiopathologic mechanisms that support DAO supplementation are complex. Under normal conditions, histamine— a biogenic amine derived from histidine and present in many foods[18,19]—mediates the allergic response, controls smooth muscle, and functions as a neurotransmitter. [20] In the nervous system, certain neurons synthesize histamine at the level of the posterior-basal hypothalamic nuclei, an area recently postulated as the locus of diverse primary headaches due to increased activity in this area detected during the prodromal phases of migraine attacks[9]. This mechanism is also associated with the thalamic nuclei that receive trigeminal outputs.[8, 21 , 22] Although it was first thought that histamine did not cross the blood-brain barrier, it now appears that it may stimulate hypothalamic activity through the circumventricular organs, which lack this barrier[9]. For this reason, an increase of blood histamine could make an increase of their concentration in hypothalamus.

Neurogenic inflammation involves the release of histamine, which, in turn, promotes the release of substance P and the CGRP peptide, both of which are closely linked to the pain process in patients with migraine.[6] The CGRP peptide is also associated with—and postulated as a marker in—chronic migraine processes.[23, 24]

Histamine degradation is carried out mainly in the digestive apparatus and liver, and DAO is one of the enzymes present in both systems. A reduction in DAO activity can be due to an increase in histamine intake (intoxication),[25, 26] alteration in enzyme synthesis (inflammatory bowel disease or drug interactions) or due to a congenital activity deficit.[27, 28] An increase in the plasma concentration of histamine due to lack of degradation can precipitate initiation of the physiopathologic mechanism that leads to a migraine attack.

Recently, it has been shown that this increased concentration is associated with allergic processes in the airways, such as rhinitis, and in gastrointestinal disorders, both in adults and children.[29] Involvement of the digestive system damages the intestinal villi—one of the most important locations for DAO synthesis—and this may lead to DAO deficiency, with all its attendant effects.[30, 31, 32]

In the present study, patients with DAO deficiency were given supplements to prevent intestinal absorption of histamine. This enzyme supplement does not penetrate the intestinal mucosa and cannot, therefore, reach the blood stream. To enable passage of the enzyme through the gastrointestinal tract, the enzyme has a protective coating, which allows it to the small intestine intact where it can act on histamine. DAO supplementation prevents the absorption of histamine obtained through the diet, and thus limits increases in histamine plasma concentration due to exogenous factors (e.g., food ingestion), thereby preventing pain genesis.

This study has shown a clear difference in the incidence rate of DAO deficiency in patients with migraine versus the healthy subjects. As discussed above, given that DAO deficiency may affect other systems in the body, we believe that some of the volunteers in the healthy control group who were found to have an enzyme deficiency without a diagnosis of migraine may have dysfunction in other unrelated systems. If so, this could have favored the appearance of false negatives, thus suggesting that the prevalence of DAO deficiency in the healthy population may actually be lower than the levels in the study sample.

We found that DAO supplementation significantly reduced the mean duration of attacks—which lasted only 12 minutes in the active treatment group vs. 2 hours in the placebo group—after only one month of treatment. In contrast, although the number of migraine attacks also decreased after DAO supplementation, the difference vs. placebo did not reach significance. Nevertheless, the trend was towards a greater reduction in the DAO group between C1 and C2.

Although DAO is a food supplement with special medical uses, we decided follow the majority of recommendations to design a controlled trial of drugs in episodic migraine. This decision was to make more comparable our result with other medical treatments in this pathology.

We choose the duration of attacks as a primary endpoint. As other authors, we hypothesize that the total duration of the attacks, rather than just the number of episodes, may be a more efficacious measure to assess the clinical and quality of life impact of DAO supplementation in patients with migraine.[33, 34, 35]

One possible explanation why DAO supplementation failed to significantly reduce the number of migraine attacks could have been the relatively short treatment period (one month). This period of time is shorter than that used in previous migraine studies, which also used dose escalation and need more time to reach levels of efficacy. If we extended the treatment period, as in other studies, it seems likely that the non-significant trend towards fewer attacks that we observed in our patients after just one month could become significant with a longer treatment period.

Pain intensity was assessed through the NPRS, with both groups showing similar scores (5.3 and 5.7). However, the value of measuring pain intensity in patients with long-term pain has been questioned given that, in such cases, scores tend to range from 4 to 6, an area of the scale known as the “golden section”.[36] To find a more objective measure of the possible effect of DAO supplementation on pain intensity during migraine attacks, we evaluated the analgesic needs of the patients, primarily the need to use triptans for intense pain. A clear decrease in the use of this family of drugs was observed in the DAO supplementation group. Consequently, it seems possible that DAO supplementation could help reduce the risk of chronification and also reduce the side effects associated with the overuse of this class of drugs.

It is worth highlighting that in this study no dietary recommendations (such as to reduce consumption of histamine-rich foods) were given to either group. This raises the possibility that complementing enzyme supplementation with dietary restrictions of histamine-rich foods could strengthen the results obtained here by reducing the exogenous contribution of this amine.

Another potential benefit of DAO supplementation is the lack of side effects observed in the active treatment group. Only one patient (placebo group) withdrew from the study due to gastrointestinal intolerance. Considering that Brandes et al. reported a drop-out rate of 30% in patients treated with 100mg/day of Topiramate due to side effects, this suggests that supplementation with DAO enzyme is a safe option that will increase compliance.[37]

We believe that the data reported here could be relevant for the study of the physiopathologic mechanisms for the origin of pain in patients with migraine. We obtained significant results in a short treatment period with a substance that is not typically included among the group of conventional drugs used in migraine patients. This finding seems to open a new line of research in the management of episodic migraine. Moreover, this may also present an opportunity to explore other disorders in which a DAO deficiency could be present.

Given the high prevalence of DAO deficiency in migraine patients, it may be possible to use DAO activity levels as a biological marker of migraine. Moreover, because this deficiency can be detected with a simple blood test, it may help to facilitate diagnosis and, consequently, treatment. DAO supplementation appears to offer a new line of treatment for episodic migraine without important side effects.

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FIGURE LEGENDS

Figure 1: Flow chart of the study procedures.

Figure 2: Percentage DAO activity deficiency in healthy volunteers and migraneous patients.

Figure 3: Duration of migraine attacks in placebo and treatment groups at baseline and after one – month of treatment.

Figure 4: Number of migraine attacks in placebo and treatment groups at baseline and after one – month of treatment.

Figure 5: Percentage increase or decrease in use of Triptans for analgesic purposes after 1-month of treatment.