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ORIGINAL ARTICLE

Low serum diamine oxidase (DAO) activity levels in patients with migraine

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Abstract Histamine intolerance is a disorder in the homeostasis of histamine due to a reduced intestinal degradation of this amine, mainly caused by a deficiency in the enzyme diamine oxidase (DAO). Among the several multi-faced symptoms associated with histamine intolerance, headache is one of the most recognized and disabling consequences. The aim of this study was to determine the prevalence of DAO deficiency in patients with a confirmed migraine diagnosis according to the current International Headache Society (IHS) and in non-migraine subjects. DAO activity was assessed in a total of 198 volunteers recruited at the Headache Unit of the Hospital General de Catalunya, 137 in the migraine group and 61 as a control group. DAO enzyme activity in blood samples was determined by ELISA test. Values below 80 HDU/ml (Histamine Degrading Unit/ml) were considered as DAO deficient. Mean value of DAO activity from migraine population (64.5 ± 33.5 HDU/ml) was significantly lower ($p < 0.0001$) than that obtained from healthy volunteers (91.9 ± 44.3 HDU/ml). DAO deficiency was more prevalent in migraine patients than in the control group. A high incidence rate of DAO deficiency (87%) was observed in the group of patients with migraine. On the other hand, 44% of non-migranous subjects had levels of DAO activity lower than 80 HDU/ml. Despite the multifactorial aetiology of migraine, these results seem to indicate that this enzymatic deficit could be related to the onset of migraine.

Keywords Headache · Migraine · Histamine · Diamine oxidase (DAO) · Histamine intolerance

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Introduction

Diamine oxidase (DAO), also called histaminase, is one of the main enzymes in the metabolism of histamine, playing an important role in the degradation of this amine in the intestinal epithelium, regulating its passage into the systemic circulation. A reduced DAO activity could be one of the causes of histamine intolerance, a disorder in the homeostasis of histamine, which provokes the accumulation of this amine in plasma and the appearance of multi-faced allergy-like clinical symptoms. DAO deficiency may be the result of a genetic mutation [1, 7] or related to certain diseases that limit the secretion of this enzyme, especially inflammatory or degenerative intestinal disorders [9, 15]. Finally, certain medications can also cause a specific and reversible inhibition of DAO activity [14, 17].

Unlike the well-known histamine intoxication, appearing after consumption of products with high histamine contents, histamine intolerance symptoms may appear even after the intake of low amounts of this amine [5]. Consequently, the dietary management is the main clinical tool to prevent the symptomatology related to histamine intolerance, based on the follow up of histamine-free diets [3, 24, 29, 30]. Apart from histamine, the presence of other bioactive amines, such

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as putrescine, could be co-responsible of the triggering of adverse health effects by competing for the same metabolic pathway [4, 14]. In addition, although there is lack of evidence about the mechanism, certain foods have been associated with an endogenous ability to release histamine, such as egg white, citrus, chocolate and crustaceans [27]. More recently, the supplementation with exogenous DAO enzyme has been postulated as a complementary preventive treatment for histamine intolerance, improving the quality of life of patients undergoing those dietary restrictions [13, 14].

Symptoms associated with the accumulation of histamine in plasma may occur due to the actions of histamine in multiple organs according to the expression of histamine receptors, including gastrointestinal tract, lung, skin, cardiovascular system and brain. Therefore, the main symptoms described for histamine intolerance are headache, flatulence, diarrhoea, abdominal pain, sneezing, rhinorrhea, hypotonia, arrhythmias, idiopathic urticaria and pruritus [14, 17]. Although there is no general consensus on histamine intolerance diagnosis, the most commonly used diagnostic algorithm includes the presentation of at least two of these symptoms and the clinical improvement after following a histamine-free diet. Negative results for food allergen-specific IgE are also required [14, 17].

Headache is one of the most recognized and disabling consequences of histamine intolerance [25, 31]. Migraine is a chronic neurovascular disorder that may be caused by several triggers (physiological, hormonal, behavioural, environmental and nutritional) as has been recently reported by Kokavec [12]. In patients diagnosed with migraine, increased plasmatic levels of histamine were reported during and among attacks [14]. According to Maintz and Novak [17], the association between headache and DAO deficit could be explained because the enzymatic deficiency would provoke an increase of plasmatic histamine that would be responsible for the appearance of headaches by releasing nitric oxide upon stimulation of H1R receptors found in intracranial arteries. In addition, a high DAO production by the placenta could potentially explain the improvement of migraine that some women experience during pregnancy [18].

Clinical studies have shown an association between a reduced DAO activity and some of the above-mentioned symptoms related to histamine intolerance. Mušič et al. [22] reported that 80% of 316 patients with suspected histamine intolerance showed a reduced serum DAO activity. Moreover, mean DAO activity levels of these patients were significantly lower than in healthy controls. Likewise, the study carried out by Manzotti et al. [19] evaluated DAO activity in 14 patients with a potential diagnosis for histamine intolerance, with the most reported symptoms being functional bloating, abdominal pain, tachycardia, diarrhoea, headache, pruritus, flushing, rhinorrhea or nausea. In this case, it was found that 71% of patients had serum DAO activity under the threshold considered as cut-off for histamine intolerance with a mean DAO activity value significantly lower than healthy controls. Apart from these studies dealing with patients with coexisting histamine intolerance symptoms, other clinical studies have correlated DAO deficiency with some specific pathologies, mainly gastrointestinal and dermatological complaints [6, 8, 9, 16, 21, 23, 25, 26]. However, according to our knowledge, there is little information available about serum DAO levels in patients clinically diagnosed with migraine. The aim of this study was to determine the prevalence of DAO deficiency in patients with a confirmed episodic migraine diagnosis according to the current International Headache Society (IHS) and in non-migraine subjects.

Material and methods

Subjects of the study

The study was performed in the Headache Unit of the Hospital General de Catalunya (Sant Cugat del Vallès, Barcelona, Spain) with a total of 198 adult volunteers aged between 18 and 65 years. Episodic migraine, as established by the IHS in the International Classification of Headache Disorders, is mainly characterized by the presence of 0 to 14 headache days per month. Two different groups were considered: a migraine group including 137 patients (122 females [89%] and 15 males [11%]) diagnosed according to current IHS criteria [10] and a control group of 61 volunteers (34 females [56%] and 27 males [44%]) without clinical criteria for migraine. For the migraine group, individuals with the onset of migraine over 50 years old, the diagnosis of other kind of headache, the possibility of pregnancy and the following of a preventive treatment for episodic migraine during 3 months prior to the study were excluded. The mean age of patients with migraine was 41.95 years (±11.3) and for control volunteers, it was 42.46 years (±14.4) (Table 1).

The Ethics Committee of the Hospital General de Catalunya approved the study, and all participants signed an informed consent form. This study is listed on the ISRCTN registry with trial ID ISRCTN10091019.

Table 1 Information about study subjects including migraine and control groups

Characteristic	Migraine group	Control group
N	137	61
Age (mean)	41.95	42.46
Gender (%)		
Female	89	56
Male	11	44

DAO activity analysis

Blood samples were collected from all subjects by venipuncture in an EDTA tube after an 8-h fasting period, and samples were analysed with ELISA to determine DAO enzyme activity in accordance with the manufacturer instructions (D-HIT, Sciotec, Austria). This method was previously used for the same purpose by Mušič et al. [22]. Values above 80 HDU/ml (Histamine Degrading Unit/ml) were considered normal while values below 80 HDU/ml were considered DAO deficient. One HDU corresponds to the DAO activity that degrades 1 pmol/ml of histamine.

Statistical analysis

Data distribution and statistical analysis was performed using SPSS for Windows, version 22 (Chicago, IL). Data distribution was obtained using the Kolmogorv-Smirnov test. As data were not normally distributed, Mann-Whitney test was used to compare DAO activity between both groups. Probability values of $p < 0.05$ were accepted as significant.

Results

The prevalence of DAO deficiency (<80 HDU/ml) assessed in migraine patients and individuals without clinical criteria for migraine as control group is shown in Fig. 1a. A high prevalence of DAO deficiency was observed in the migraine group with 87% of subjects with this enzymatic deficiency in comparison to 44% in the control group. Within the migraine group, the percentage of individuals that showed normal DAO activity levels was 13%. Figure 1b shows the proportion of DAO deficiency in the migraine group by gender. Although the number of women included in the study was higher than men, DAO deficiency was similar in both cases (86 and 90%).

Figure 2 shows the mean DAO activity (±SD) obtained for both study groups. Mean DAO activity in migraine population was 64.5 ± 33.5 HDU/ml, being significantly lower (Mann-Whitney U value = 2090.5, Wilcoxon W value = 11,001.5, $p < 0.0001$) than that obtained from control volunteers (91.9 ± 44.3 HDU/ml). Additionally, Fig. 3 graphically shows the distribution of DAO activity values in both groups. It seems important to highlight that the variability of DAO activity values observed in migraine patients is low, with 50% of cases comprised from 49.5 to 67.1 HDU/ml (percentile 25 and percentile 75, respectively). However, in this group, some extremely high values, statistically considered as outliers, were recorded, reaching DAO activity values close to 250 HDU/ml. On the other hand, greater variability was found in DAO activity values from control individuals. For this group, the interquartile range, calculated as the difference between percentile 75 (118.5 HDU/ml) and percentile 25

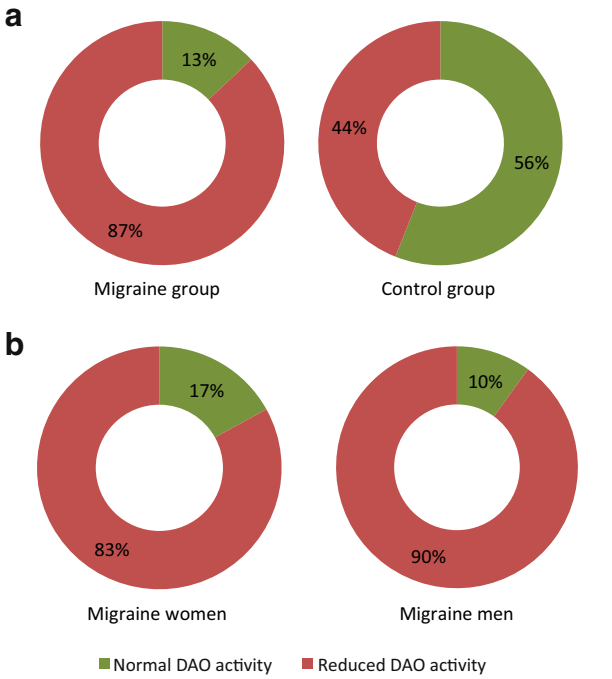

Fig. 1 Percentage of individuals with deficiency (<80 HDU/ml, *red*) and normal (>80 HDU/ml, *green*) DAO activity in both study groups (**a**) and depending on the gender in the migraine group (**b**)

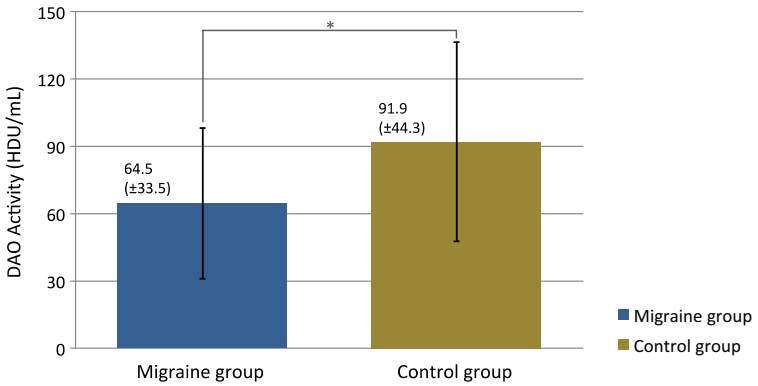

Fig. 2 DAO activity (mean ± SD) in migraine patients and individuals without clinical criteria for migraine as control group. A Mann-Whitney test was applied to compare DAO activity in both groups, *$p < 0.0001$

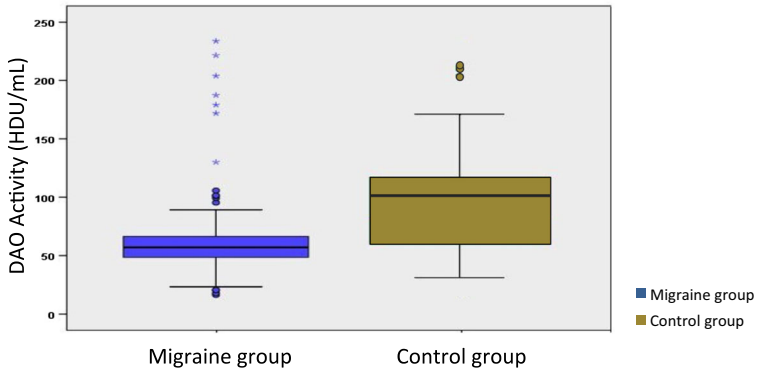

Fig. 3 Distribution of DAO activity in migraine patients and individuals without clinical criteria for migraine as control group. The *bottom* and *top* of the box (interquartile range) are the percentile 25 and the percentile 75, respectively. *Central line* represents the median. *Lines* extending vertically from the boxes (*whiskers*) indicate variability outside the interquartile range. Values statistically considered as outliers are plotted as *circles* (atypical value) or *asterisks* (extremely atypical value)

(59.80 HDU/ml), was 58.7 HDU/ml, threefold higher than the interquartile range obtained for migraine group (17.6 HDU/ml). Similarly to the migraine group, some atypically high DAO activity values were found, with maximum levels up to 211 HDU/ml.

Discussion

Headache has been reported as one of the most prevalent and disabling disturbances associated with an excess of histamine based on a deficit of DAO [17]. Back in 1993, Wantke et al. [29] described that headaches of 33 out of 45 patients decreased in frequency, duration and intensity after 4 weeks of avoiding histamine-rich foods, such as fish, cheese, hard cured sausages, pickled cabbage and alcoholic beverages. These authors hypothesised that a diminished histamine degradation based on a deficiency of DAO could be the cause of this food intolerance. Recently, a relationship between functional SNPs in the DAO gene and the risk for migraine has been proposed. García-Martín et al. [7] studied the frequency of four different genotypes and allelic variants in 197 patients with migraine and 245 healthy controls from Spain. The DAO SNP rs10156191, associated with decreased DAO enzyme activity, seemed to be more frequent in the migraine population. In the same vein, another study performed by Meza-Velázquez et al. [20] also found that a mutant DAO SNP was significantly more frequent in a group of women with migraine than in the control group. Despite that published studies seem to indicate that DAO deficit could be one of the triggers for headaches, data about serum DAO activity levels in affected populations would be important to support this association.

In this work, serum DAO activity was studied in patients diagnosed with migraine in comparison with a non-migranous population. The prevalence of DAO deficiency within migraine patients was elevated, finding that 87% of these individuals had serum DAO levels below the cut-off value of 80 HDU/ml (Fig. 1a). DAO deficiency was not found to be higher in women (Fig. 1b) despite that several authors have associated DAO levels with some female sex hormonal changes [11, 14]. Moreover, the mean value of DAO activity in the migraine group was significantly lower than that obtained in the control group (Fig. 2). These results point out that this enzymatic deficit could be related to the onset of migraine. On the other hand, the fact that 13% of migraine patients showed normal DAO activity levels evidenced that this enzymatic deficiency could be one of the triggers of migraine but not the single trigger responsible for this pathology with multifactorial aetiology.

In the control group, 44% of volunteers showed DAO enzyme deficiency but absence of migraine. As was previously mentioned, impaired intestinal histamine degradation by a deficit of DAO leads to the appearance of multi-faced clinical symptoms, which can coexist in histamine intolerants. In fact, headache is just one of the many symptoms associated with this intolerance. Unfortunately, no other symptoms were recorded in this study and therefore, it cannot be concluded that those individuals were actually asymptomatic for histamine intolerance.

It also has to be stated that DAO activity values found in the control group were more variable than those reported by migraine patients. This wide variability was also observed in the study performed by Manzotti et al. [19], which reported a larger range of DAO activity values for the cohort of healthy controls than in individuals suffering from histamine intolerance.

As in the present work, other clinical studies have been focused in the evaluation of serum DAO activity in specific pathologies (Table 2). In a previous study also focusing on neurological symptomatology, Steinbrecher and Jarisch [25] described that 23 out of 27 potential histamine-intolerant patients suffering from headache (85%) had decreased DAO levels. Furthermore, after 4 weeks of histamine-free diet, a

Table 2 Summary of the studies that measured serum DAO activity levels in patients with generic symptoms potentially related to histamine intolerance or other specific pathologies

Reference	Pathology	Study subjects	% of DAO deficiency	DAO activity[a]
[22]	Generic symptoms of histamine intolerance	316 patients with clinically suspected histamine intolerance	80	–
		55 healthy controls	22	–
[19]	Generic symptoms of histamine intolerance	14 patients with clinically suspected histamine intolerance	71	7.04
		34 healthy controls	–	39.5
[25]	Headache	35 histamine intolerant patients with headache	85	–
[16]	Atopic eczema	162 patients with atopic eczema	19	–
		124 patients with symptoms of histamine intolerance but without atopic eczema	20	–
		85 healthy controls	0	–
[28]	Chronic spontaneous urticaria	55 patients suffering for chronic urticaria and gastrointestinal disturbances	14	17.8
[30]	Atopic dermatitis	58 patients with atopic dermatitis	–	10
		19 healthy controls	–	14
[2]	Chronic idiopathic urticaria	75 patients with chronic idiopathic urticaria	57	–
		25 healthy controls	40	–
		55 patients with Crohn's disease	–	8.5
		43 patients with ulcerative colitis	–	8.9
[9]	Inflammatory bowel diseases	17 healthy controls	–	10.3
[6]	Lactose malabsorption	121 patients with lactose malabsorption	36	13.6
[26]	Damage of intestinal mucosa	21 patients with anorexia nervosa restricting type	–	8.2
		15 patients with anorexia nervosa binge-eating/purging type	–	12.3
		20 healthy controls	–	12.1
[21]	Damage of intestinal mucosa	20 patients with unresectable metastatic gastric cancer	–	2.4
[8]	Chronic abdominal pain	16 paediatric patients diagnosed with two of more digestive complaints	88	–
		394 paediatric patients	8	4.5

[a] Reduced DAO activity <10 U/mL

significant rise in DAO activity was noted and the majority of patients reported a complete remission or improvement in headache frequency.

Considering dermatological symptoms, Maintz et al. [16] evaluated serum DAO activity in patients with atopic eczema in comparison with histamine-intolerant patients without atopic eczema and also with healthy volunteers. No individuals with this enzymatic deficiency were found in the healthy control group. On the contrary, the percentage of patients with DAO deficiency was 19% in atopic eczema group and 20% in histamine intolerants without this dermatological affectation. Thus, both a significantly lower mean DAO activity and a higher total number of individuals with a reduced DAO activity was found in atopic eczema patients and histamine intolerants without atopic eczema in comparison with healthy controls. In another study that considered patients with chronic spontaneous urticaria accompanied by gastrointestinal disturbances, a prevalence of DAO deficiency of 44% was observed [28]. Conversely, other studies involving patients with atopic dermatitis and urticaria did not find statistically significant association between a reduced DAO activity and high plasma histamine levels in patients suffering from these skin diseases [2, 30].

In the field of gastrointestinal disorders, Honzawa et al. [9] evaluated the clinical significance of serum DAO activity in 98 patients with inflammatory bowel disease. This study demonstrated that DAO activity was significantly lower in patients with Crohn's disease or ulcerative colitis than in healthy controls, indicating a relationship between DAO levels and intestinal permeability. Furthermore, Enko et al. [6] measured serum DAO levels in 121 patients with lactose malabsorption, finding that 36.4% of this cohort showed a deficiency in this enzyme. Additionally, it was observed that individuals with lactose malabsorption and deficit of DAO tended to report more gastrointestinal symptoms during the lactose hydrogen breast test than those with normal DAO activity. Other authors concluded that low serum DAO activity levels could act as indicator of intestinal mucosal disturbances in patients with anorexia nervosa [26] or under chemotherapy treatment [21].

In clinical studies dealing with paediatric populations, an observational retrospective study performed by Rosell-Camps et al. [23] that involved 16 children with abdominal pain, chronic diarrhoea and vomiting found a direct relation between reduced serum DAO levels and these digestive complaints. Concretely, 88% of these paediatric patients showed DAO deficiency. More recently, in an observational study performed by Hoffmann et al. [8] in 394 children with chronic abdominal pain, only 8% showed DAO activity levels under the normal threshold.

The high prevalence of DAO deficiency in migraine patients found in the current study (87%) coincides with that described by Steinbrecher and Jarisch [25] in patients with headache (85%) and by Rosell-Camps et al. [23] in paediatric patients with digestive complaints (88%). Moreover, these percentages are in good agreement with those described by Mušič et al. [22] and Manzotti et al. [19], which considered patients clinically suspected as histamine intolerants with diverse coexisting symptoms (Table 2). However, other studies addressing different specific pathologies, such as atopic eczema, chronic urticaria, lactose malabsorption and chronic abdominal pain, reported lower percentages of DAO deficit, with values ranging between 8 and 57% [2, 6, 8, 16, 28].

In view of the results of this study, it can be concluded that DAO deficiency is more prevalent in migraine patients than in non-migranous individuals. More studies are needed to better establish the cut off value of DAO activity to allow not only a more accurate diagnosis of histamine intolerance but also to potentially become an additional diagnosis criterion for migraine. Likewise, further research is necessary to reasonably explain the variability found in serum DAO activity levels.

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Compliance with ethical standards

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

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