Evaluation of DAO-deficiency in patients with migraine. *(MigraDAO trial)*

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Abstract

Objective: To determine the proportion of patients diagnosed with migraine that present DAO-deficiency regarding the observed deficit in non-migrainous population.

Hypothesis: Migrainous patients present lower DAO concentrations than healthy subjects. Therefore, this deficiency may be the cause of histamine intolerance and represents a physiopathological factor of the studied neurological entity. That being the case, an etiologic treatment approach could be hypothesized based on the administration of DAO in patients with this deficiency.

Design of the trial: A descriptive observational cross-sectional prospective study with a control group without masking or randomisation.

Sample population: The target population are volunteer subjects suffering migraine, members of the Spanish Association of Patients with Headache that meet the diagnostic criteria accepted by the International Headache Society (IHS). The healthy controls are chosen among volunteers of their microsocial environment.

Key words: Histamine, diamine Oxidase (DAO), migraine, food histaminosis.

Introduction

Migraine is a complex neurological disease, recurrent and incapacitating. It is suspected a genetic origin, but its etiopathogeny remains unknown.

Several clinical, histochemical, electrophysiological, molecular and genetic approaches constitute a setting of findings that slowly shed light on the etiopathogeny.

Headache is often unilateral, pulsating and associated with photo- and phonophobia, nausea and vomiting. Headache is the major and most important clinical sign of migraine.

Most of the therapeutic approaches for the acute treatment of migraine include medicines interfacing with the vascular recipients. In the past, it was the agonists of alpha-adrenergic recipients (ergotamine, dihydroergotamine, etc.). In the last 20 years, the advent of agonist recipients 5-HT(IB/ID) has occurred in parallel with Sumatriptan and the successive generations of triptans.

The prophylaxis of migraine contemplates frequently with these agonists, calcium channel blockers and beta-adrenoceptor antagonists. Despite this progress, and due to its complex etiopathogeny, the disease remains underdiagnosed and sometimes undertreated. The last studies about the treatment focus the need to find new approaches that insist on the biochemical mediators of the disease.

One of the most significant is histamine. This substance has a selective affinity to H3 recipient and may have an inhibitory effect of the neurological response involved in the pathophysiology of migraine.

This biogenic amine is in different concentrations of many food of the daily diet. In healthy people, histamine is rapidly degraded by amine oxidases, but certain people presenting a lower activity of these

oxidases may have a higher risk of histaminic toxicity. Histamine intolerance, involved in multiple process of immune-allergic and inflammatory nature, including migraine, is the result of an imbalance between accumulation and degradation.

Histamine is essentially metabolized by two ways, methylation and desamination. In the last way, acts the enzyme diamine oxidase (DAO) or the histaminase, followed by a conjugation of ribose to form the riboside of the imidazole acid. DAO is the enzyme with higher involvement in the metabolization of the ingested histamine. It is accepted therefore that a decrease in the histamine degradation related to a decrease in DAO activity may be the cause of an excess of histamine that would increase the risk of suffering different clinical pictures that mimic an allergic-type reaction: diarrhea, conjunctivitis, rhinitis, asthma, low blood pressure, arrhythmia, hives, *flushing,* itching and headache among others.

The intake of alcohol or food rich in histamine that increases the histamine concentration or the blockage of DAO activity could trigger the above mentioned reaction.

This symptomatology may occur when decreasing the intake of alcohol or food rich in histamine or by favouring the action of oxidases.

Probably, its existence could be underestimated due to the heterogeneous nature of a symptommatology associated with histamine intolerance. Despite the fact that existing evidences in the literature are not conclusive, experts recommend to develop experimental studies to determine the presence of histamine intolerance in patients with this clinical picture.

In recent times, unverified information suggests a genetic role, not in the genesis of migraine, but in the deficiency of oxidases. In such a way that what could be transmitted was the histamine intolerance condition linked to the deficiency of oxidases.

Objective: To determine the proportion of patients diagnosed with migraine that present DAO-deficiency regarding the observed deficit in non-migrainous population.

Hypothesis: Migrainous patients present lower DAO concentrations than healthy subjects. Therefore, this deficiency could be the cause of histamine intolerance and represents a physiopathological factor of the studied neurological entity. That being the case, an etiologic treatment approach could be hypothesized based on the administration of DAO in patients with this deficiency.

Design of the study: A descriptive observational cross-sectional prospective study with a control group without masking or randomisation.

Material and methods:

1.- Target population. The target population are volunteer subjects suffering migraine, members of the Spanish Association of Patients with Headache that meet the diagnostic criteria accepted by the International Headache Society (IHS). The healthy controls are chosen among volunteers of their microsocial environment.

2.- Sample volume. Among an unknown proportion of migrainous subjects presenting histamine intolerance due to DAO-deficiency, it was chosen the most unfavourable proportion p=0,05. For a unilateral hypothesis with an alpha error of 0,05, a power of the trial of 0,9 and with the aim of detecting intergroup differences of 10%, volunteer patients were recluted during a month, until the sample of 164 patients was completed.

3.- Sampling technique. The patients fulfilling the inclusion criteria defined in the trial, were selected by a simple non-random sampling among those volunteer subjects that apply for participating in the trial through the recruitment page of the Spanish Association of Patients with Headache. Likewise, non-migrainous patients in the control group, were selected among those subjects that, voluntarily, wanted to be included in the control group and were members of the microsocial environment of the patients.

Both contingents were assigned by the research team without randomization or masking to the previously defined groups.

4.- Sample size: The total sample size was 164 patients distributed in two groups, of 82 patients each; group 1 (migrainous) and group 2 (non-migrainous) , without stratification by age, sex, or severity of the migrainous picture.

5.- Recruitment period. Patients were recruited between the 8th and 26th of February, until the defined sample size was completed.

6.- Description: The trial expected to determine the level of DAO activity in the subjects composing the groups through analytical determination with validated ELISA procedure and the use of a test with acceptable predictive value and a defined cut-off point. The trial was developed by properly trained personnel and using accurately calibrated devices in Sabater-Tabella Análisis S.A. laboratory, that owns the appropriate accreditation to carry out the trial. Both groups of patients underwent a blood extraction of 5 ml of venous blood.

7.- Materials:
1.- Patient information sheet.
2.- Informed consent form.
3.- A number of 164 analytical tests to determine the DAO concentration.
4.- Data Collection Logbook (DCL) .
5.- Documentation to inform about the inclusion of patients in the database of subjects participating in the trial to the Spanish Data Protection Agency.

8.- Trial duration: The fieldwork for the trial took place during February 2010. The analytical part of the trial was finished in 2 months after the end of the field stage.

Rule values and evaluation criteria

Very low DAO activity
DAO < 40 HDU/ml
Reduced DAO activity
DAO 40 - 80 HDU/ml
Normal DAO activity
DAO > 80 HDU/ml

RESULTS

It has been developed a descriptive analysis of the characteristics of the population being studied regarding the global independent variables.

1.- The average age for patients with migraine is 37,98 years with a standard deviation of +/- 12,46 years. The mode is established between 32 and 46 years. The age range varies between 17 and 92 years.

2.- The 65% of the studied patients present a diagnostic time of 10 years or more. The 85% of the patients have an accurate diagnosis made over 5 years ago.

3.- The average intensity perceived by the patients, measured with a validated visual analogue scale, was 7,7 (minimum value 0, maximum value 10) with a standard deviation of +/- 1,58. The mode was 8. The 38.8% of the patients presented this value. It should be emphasised that 12 (15%) of them suffered a pain described as unbearable (maximum store of 10) during the crisis.

4.- The average obtained for the value of DAO activity in migrainous patients was 45,87 with a standard deviation of +/-20,31.

The obtained range varies between 20,9 and 155.

The 48,8% of patients present values compatible with a much reduced DAO activity, the 47% values compatible with reduced DAO activity and the 5,2% present normal values.

5.- The 50% of patients presented an average of 2 or 5 crisis in a month.

6.- The 95% of migrainous patients underwent symptoms related to non-migrainous pathology compatible with histamine intolerance when eating certain food or after drinking alcohol.

The 41,3% of patients underwent 3 or 4 of these associated symptoms.

The proportion contrast and the comparison of averages carried out in the migrainous group regarding the control group, show the next results:

a. Despite the average value of DAO activity for both groups is situated in the category of reduced activity, the comparison of the said average value, is lower in the intervention group (45,88) than in

the control group (56,37), with a difference between averages of -10,49 (IC 95% 3,58:-17,41). The difference observed is statistically significant (p=0.003).

b. Bringing together the categories of reduced DAO activity (very low and low) the average value obtained for DAO activity is lower among the migrainous group (41,73) than in the control group (48,73), with an observed difference between averages of -6,99 (IC 95% -2,988:-11,008). The difference observed is statistically significant (p=0.001).

c.- Among those with a reduced DAO activity, there is in the migrainous group, a higher proportion of patients (52%) with a very low DAO activity (<40), regarding the controls (29%). This is, therefore, a significant difference (p=0.004).

If this proportion is observed by bringing together the categories of reduced activity (>40 y <80) and normal activity (>80) regarding a very low activity (<40), the difference gains even more statistical significance (p=0.001), because the relative "weight" of very low activity, has a higher decease among non-migrainous patients.

d. The odds (excess of risk ratio) that a patient with a much reduced indicative value of DAO activity presents migraine are 2,85 regarding those presenting compatible values with reduced or normal activity. The odds are 1,62 when comparing patients with values compatible with reduced activity regarding the patients presenting normal values.

e. The trial found no association in the migrainous group with regard to the value of DAO activity for any of its categories regarding the age, the diagnostic time, the number of crisis and their severity or the existence of comorbidity of non-migrainous nature.

Conclusions

The stratified analyses for the variable DAO concentration show a lower DAO activity concentration in the migrainous group regarding the controls.

Moreover, the proportion of subjects with much reduced activity values is higher in the migrainous group.
The differences observed are statistically significant.

The results answered affirmatively to the question targeted in the research, **so it can be stated that DAO activity is significantly lower in migrainous patients regarding the controls.**

It should be noted, that this difference could be undervalued, being the control subjects members of the microsocial environment of the cases or having kinship relationships. If it is assumed a genetic etiology of the studied enzyme deficiency, controls could present this deficiency in higher proportion than general population despite not appearing as neurological pictures.

There is a higher risk of suffering migraine in subjects that have a much reduced DAO activity (<40) or reduced (>40 y <80) regarding those subjects with a normal activity (>80). The excess of risk is all the higher the smaller the DAO activity is.

Bibliography

- Amon, U., Bangha, E., Raster, T., Menne, A., Vollrath, IB.,Gibbs BF. (1999). Enteral histaminosis: Clinical implication.Inflammation Research 48: 291-295
- Anderson, KE (2010). Effects of specific foods and dietarycomponents on drug metabolism. Chapter 9 en Boulatta JI.,ArmentiVT (Eds). Handobook of Drug-nutrient Interactions.Second edition. Human Press, , New York, USA
- Diel, E , Bayas, N., Stibbe, A., Muller, S., Bott, A., Schrimpf D.,Diel, F. (1997). Histamine containing food: Establishment of a German Food Intolerance Databank (NFID). Inflammation Research 46, Supplement 1: S87--S88
- Fogel, WA., Lewinski, A., Jochem, J. (2007). Histamine in food: is there anything to worry about?. Biochemical Society Transaction 35: 349-352
- Garcia-Martin, E. y col (2008) Histamine-N-Methyl Transferase Polymorphism and Risk for Migraine.Headache,48:1343-1348
- Gordon, J., Millichap, MD., Michelle, MY. (2003). The diet factor in pediatric and adolescent. Migraine Pediatric Neurology 28: 9-15
- Jarisch, R , Wantke, F. (1996). Wine and headache. International Archives of Immunology 110: 7-12

- Klocker J. Y col (2005) Synthesis, metabolism and release of histamine Expression of histamine degrading enzymes in porcine tissues. Inflammation Research, 54, (Supp 1): :854-857
- Maintz, L., Bieber, T., Novak, N. (2006). Histamine intolerante in clinical practice. Dtsch Arztebl 103: 3477-3483
- Maintz, L., Novak, N. (2007). Histamine and histamine intolerante. American Journal of Clinical Nutrition 85 (5): 1185-1196.
- Maintz, L., Schwarzer, V., Bieber, T., van der Ven, K., Novak,N. (2008). Effects of histamine and diamine oxidase activities on pregnancy: a critical review. Human Reproduction Update pp. 1-11
- Mailer, I., Missbichler, A., Wantke, F., Focke, M., Reichl, H.,Winter, M., Jarisch, R (2005). Optimized radiextraction assay for quantitative determination of diamine oxidase (DAO) activity in human serum and blood. Allergologie 28 (1): 1-8
- McGrath, AP., Namer, KM., Collyer, CA., Shepard, EM., Elmore, BO., Brown, DE., Dooley, DM., Guss, JM. (2009). Structure and inhibition of human diamine oxidase. Biochemistry 48, 9810 - 9822
- Raithel, M., Kofner, M., Ulrich, P., Hahn, EG. (1999). The involvement of the histamine degradation pathway by diamine oxidase in manifest gastrointestinal allergies. Inflammation Research, 48, suplemmet 1: S75-S76
- Battler, J., Hesterberg, R , Lorenz, W., Schmidt, U., Crombach, M., Stahlknecht, CD. (1985). Inhibition of human and canine diamine oxidase by drugs used in an intensive care unit: relevance for clinical side effects?. Agents Actions 16: 91-4
- Battler, J., Lorenz, W. (1999). Intestinal diamine oxidases and enteral-induced histaminosis: estudies on three prognostic variable in an epidemiological model. Journal of Neural Transmission Supplements 32: 291-314
- Sun-Edelstein, C., Mauskop, A. (2009). Foods and supplements in the management of migraine headaches. Clinical Journal of Pain 25:446-452
- Veciana-Nogués, MT., Vidal-Carou, MC. (2008). Dieta Baja en histamina. Capitulo 45 en Salas-Salvador (Ed) Nutrici6n y Diet6tica Clinica. 2a Edici6n. pp 443-448
- Vidal-Carou, MC., Veciana-Nogues, MT., Latorre-Moratalla, ML., Boyer-Cid, S. (2007). Biogenic amines: Risk and control. Chapter 3 en Toldra F. (Ed). Handbook of fermented meta and poultry. Blackwell Publishing, Ames, US, pp 455-468
- Wantke, F., G6tz, M., Jarisch, R (1993). Histamine-free diet: treatment of choice for histamine induced food intolerance and supporting treatment for chronical headaches. Clinical and Experimental Allergy 23: 982-985
- Zimatkin, SM., Anichtchik, OV. (1999). Alcohol-histamine interactions. Alcohol & Alcoholism 34 (2): 141-147

