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Original article

Usefulness of the histamine intolerance assessment questionnaire for diagnosis

Utilité du questionnaire d'évaluation de l'intolérance à l'histamine pour le diagnostic

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ABSTRACT

Background. – Histamine intolerance results from an imbalance of the ingested histamine and the individual capacity for its degradation. There are numerous tests not validated for the diagnosis of histamine intolerance that are usually found directly by customers, being able to generate a false perception of intolerance when there could be other possible explanations for their symptoms. One of these is the histamine intolerance questionnaire.

Objective. – To analyse the diagnostic capacity of this questionnaire compared with an objective test of enzymatic activity of the diamine oxidase.

Methods. – Descriptive and analytical observational study in volunteer adults, who attended for a reason other than suspected histamine intolerance, recruited consecutively from the outpatient departments of a tertiary hospital. Sociodemographic variables, histamine intolerance questionnaire (0–7 points) and DAO activity test were collected. Analysis of ROC curve was performed using the diamine oxidase deficient (<80 HDU/mL) as a condition and the value of the histamine intolerance questionnaire as a contrast variable to evaluate which could be the most appropriate cut-off point in clinical practice.

Results. – A total of 166 Caucasian patients were recruited. ROC curve that contrasts the questionnaire value, quantifying the area under the curve (0.537, $P=0.415$) with a 95% CI (0.448–0.625), not finding statistically significant differences for an appropriate cut.

Conclusions. – The results of this work do not support the reliability of this questionnaire as a screening method for patients with suspected histamine intolerance. Research should continue in order to clarify, standardize and improve the detection methods of these pathologies.

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R É S U M É

But de l'étude. – L'intolérance à l'histamine résulte d'un déséquilibre de l'histamine ingérée et de la capacité individuelle à sa dégradation. Il y a de nombreux tests non validés ciblés pour la détection de l'intolérance à l'histamine et, d'habitude, ce sont ces méthodes d'examen que les patients trouvent plus facilement, en créant ainsi la fausse sensation d'intolérance même quand leurs symptômes pourraient être expliqués

Mots clés :

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par d'autres maladies. L'un de ce test, c'est le « questionnaire d'intolérance à l'histamine ». Le but de cette étude est d'analyser la capacité du questionnaire pour diagnostiquer cette maladie en comparaison avec le test objectif de détermination de l'activité diamine oxydase dans le sérum.

Matériels et méthodes. – Il s'agit d'une étude analytique et observationnelle réalisée chez des patients adultes consultant pour d'autres symptômes que ceux associés à l'intolérance à l'histamine dans un hôpital de soins tertiaires. Les données suivantes ont été collectées : des variables sociodémographiques, le questionnaire d'intolérance à l'histamine (0–7 points) et le test de détermination de l'activité DAO. Pour l'analyse des courbes ROC, l'on a utilisé le déficit de DAO (< 80 HDU/mL) comme condition et le résultat du questionnaire d'intolérance à l'histamine comme variable de contraste pour évaluer la valeur limite la plus appropriée pour utiliser en pratique clinique.

Résultats. – Un total de 166 patients caucasiens ont été recrutés. En quantifiant l'aire sous la courbe ROC qui fait le contraste de la valeur du questionnaire (0,537, $p = 0,415$) avec un intervalle de confiance à 95 % (0,448–0,625), l'on n'a pas trouvé de différences significatives pour une valeur limite adéquate.

Conclusion. – Les résultats de ce rapport ne supportent pas la fiabilité de ce questionnaire comme méthode de dépistage pour ceux des patients soupçonnés d'avoir de l'intolérance à l'histamine. Il faudra continuer à investiguer pour standardiser ce test ainsi comme pour améliorer les méthodes diagnostiques de ces maladies.

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1. Introduction

The prevalence of food intolerances is estimated to be 15–20% and in recent decades has been gaining relevance and prominence in routine clinical practice [1,2]. In those affected by food intolerances, it is believed that there is a significant number of people who, without being diagnosed, have a compatible clinical situation that makes them think that their ailments may be due to any of these pathologies.

Histamine intolerance (HIT) belongs to the group of non IgE-mediated hypersensitivity reactions and is a pharmacological food intolerance. It results from an imbalance of the ingested histamine and the capacity for its degradation. The main cause is a deficit in its degradation, caused by a genetic or acquired error in the enzymatic function of the diamine oxidase (DAO), one of the main enzymes in the metabolism of histamine (Fig. 1) [3–5]. Under normal circumstances, there is an enzymatic barrier formed by DAO in cells of intestinal epithelium in healthy individuals, which sufficiently protects from resorption of histamine from ingested food into the blood stream. HIT provokes an increased histamine concentration in blood, in such cases, symptoms occur even in ingestion of small amount of histamine in food, which is usually well tolerated in healthy individuals [3,4]. Eating histamine-rich food (products with microbial fermentation such as cheese, processed meat, tomato, spinach, blue fish, etc.), alcohol, or drugs that release histamine or block DAO in these patients, can cause symptoms in various organs. Some clinical studies have established a relation between DAO deficiency and specific pathologies, mainly gastrointestinal, respiratory, dermatological diseases and migraine (Fig. 1) [5–16], depending on the expression of histamine receptors (H1–H4) on them. Due to this variability of symptoms, the existence of HIT is frequently underestimated [3,4].

Currently, the detection and diagnosis of HIT is a complex process and, according to the recommendations based on scientific evidence, should be based on a detailed anamnesis made by experts in the field and be supported by complementary tests if necessary [1,2,17]. Although there are no quality scientific studies to support the use of these techniques, there are numerous not validated questionnaires for the diagnosis of HIT that are usually found in pharmacies, health insurers, private health centres, alternative medicine centres, health websites, private laboratories, gyms and even hairdressers, which can be purchased directly by customers [17].

The false results of these unproven intolerance tests can give rise to misleading advice that leads patients to undergo major dietary restrictions, which can cause damage to growth and even malnutrition, particularly in the most vulnerable groups such as children [1,2,17]. One of these tests proposed by numerous groups with scientific endorsement is for screening through the Histamine Intolerance Questionnaire (HIQ), which is accessible in numerous internet sites, does not require an interview with an expert doctor, is done in about 1 min, and inquiries about the existence or not of possible symptoms related to HIT (Table 1) [18,19]. A patient with 3 or more affirmative answers in this questionnaire is directly recommended to perform a blood determination of DAO enzymatic activity.

This could generate a false perception of intolerance when is it possible that other possible explanations for their symptoms and even a protective halo is created with respect to real intolerances, considering that it is other foods that are causing the damage. The objective of this study is to analyse the diagnostic capacity of the HIQ compared with an objective test of enzymatic activity of the DAO, as well as to look for the best cut-off point if possible.

2. Methods

2.1. Study design and data collection

A descriptive and analytical observational study in volunteer adults, who attended for a reason other than suspected histamine intolerance, recruited consecutively from the outpatient departments of a tertiary hospital. This research involved human participants and was approved by the Hospital's Ethics Committee (Code: 2016/106). Informed consent was obtained from all individual participants included in the study.

Selection criteria of the volunteer participants were not being treated for the past 2 weeks with the DAO enzyme or any medication that could not be suspended and causes acquired decrease (antihistamines, systemic glucocorticosteroids, aminophylline, cefuroxime, clavulanic acid, metoclopramide, verapamil, etc.) or increase (heparin) in DAO activity [3–5]. Additionally, patients with a 2-week intake history of foods containing histamine such as fermented foods, beverages, processed meat and seafood, or patients with any other medical disorders (hepatic, gastrointestinal or renal disease, deficiency of vitamin B6, vitamin C, copper or

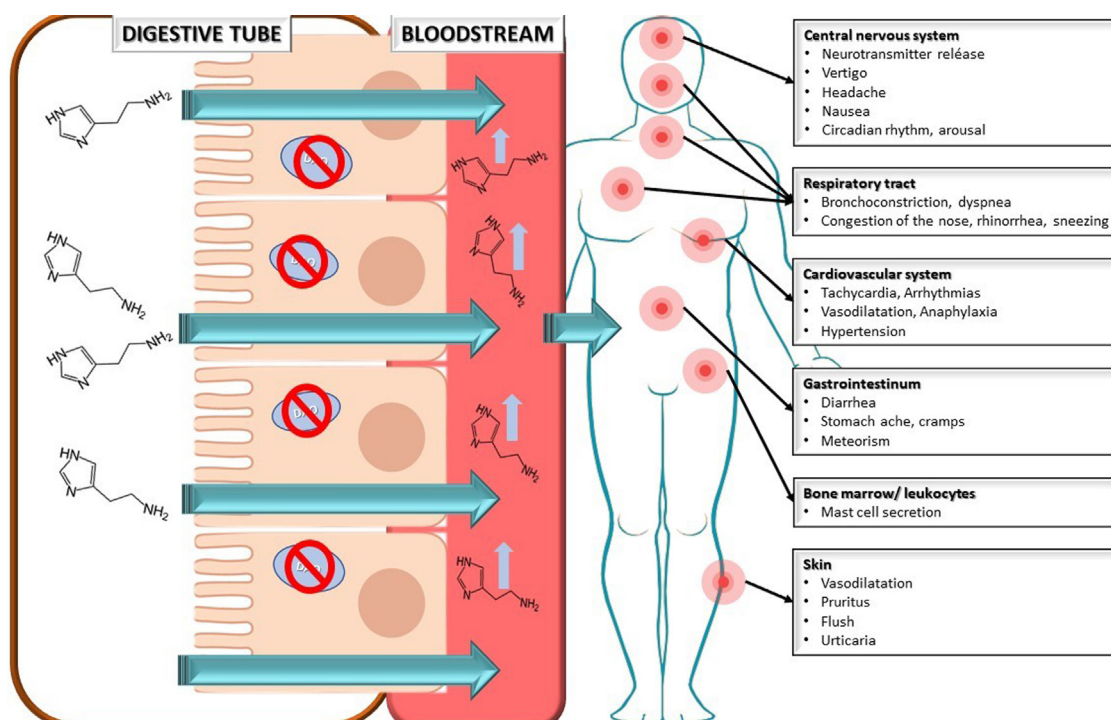


Fig. 1. Pathways of histamine absorption and degradation, and its mediated symptoms. DAO: diamine oxidase.

Table 1
Histamine Intolerance Questionnaire (0–7 points) with affirmative responses in each item.

	Affirmative answers	
	n	%
1. Do I have seizures or migraine attacks at least twice a month?	40	24.1
2. Do I have constipation and / or do I have diarrhea at times without knowing why?	72	43.37
3. Do I have a feeling of swelling of the abdomen? Do I have flatulence, discomfort or pain, or heavy digestion after meals, even without eating too much? (Feeling bloated)	90	54.22
4. Does my back hurt or do I have muscle and / or joint pain or contractures?	126	75.9
5. Do I have dry skin, redness on certain occasions, or do I often get redness, pimples or rashes, or have you ever told me that I have atopic skin?	96	57.83
6. Am I always very tired and I do not know why?	90	54.22
7. Have I ever been suggested, implied or diagnosed that I have fibromyalgia?	14	8.43

n: number.

zinc, etc.) or pregnant were excluded from this study. Sociodemographic variables, histamine intolerance questionnaire (0–7 points) and DAO activity test were collected.

2.2. Histamine Intolerance Questionnaire

This questionnaire consists of 7 items with a possible dichotomous (Yes/No) answer (Table 1). The questions refer to the presence or absence of any of the symptoms, previously described (Fig. 1), which have been related in some clinical study to the HIT [3–5].

Each affirmative answer supposes 1 point and each negative answer 0 point; therefore, the total score would oscillate between 0 and 7 points. According to its current use, a result ≥ 3 would suggest the possible existence of a histamine intolerance and the recommendation to perform complementary tests [18].

2.3. DAO activity analysis

Blood samples were collected from all subjects by venepuncture 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, Sciotech, Austria).

This method was previously used for the same purpose by Mušič et al. [20]. 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.

2.4. Statistical analysis

Analysis were made with the statistical package IBM SPSS® Statistics 26. Statistical tests were two tailed with a 95% confidence interval. Quantitative variables were expressed as mean $\pm$ standard deviation (SD) and median as appropriate. Qualitative variables were expressed as frequency and percentage. The Chi² homogeneity test was used. For the comparison of means between groups, parametric tests (Student's *t*-test and ANOVA) were applied for variables that verified the hypothesis of normality (Shapiro–Wilk test) and for the comparison of variances the Levene test. In cases where non-normality was significant, non-parametric methods were applied (Wilcoxon test and Kruskal–Wallis test).

An analysis of ROC curve was performed using the DAO deficient as a condition and the value of the histamine intolerance questionnaire as a contrast variable to evaluate, which could be the most

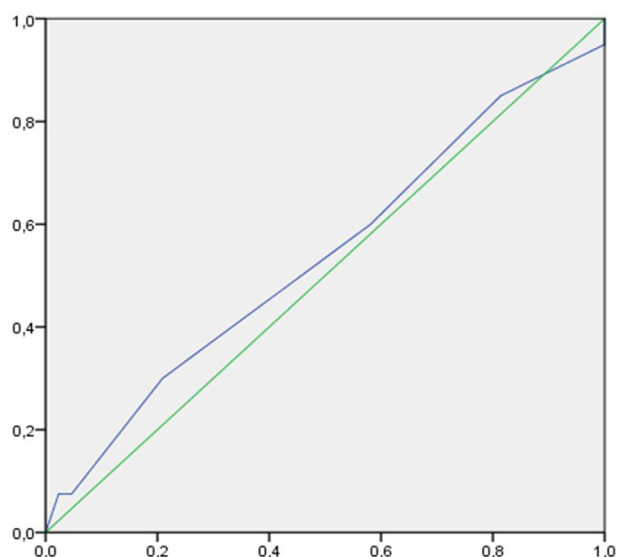


Fig. 2. ROC-curve using the DAO deficient as a condition and the value of the histamine intolerance questionnaire as a contrast variable. “y” axis representing the sensitivity and the “x” axis representing 1-specificity.

appropriate cut-off point in clinical practice. The effectiveness of the histamine intolerance questionnaire in predicting DAO deficient was estimated by its sensitivity and specificity and Youden's J statistic.

3. Results

A total of 166 Caucasian patients were recruited. Of these, 46 were men (27.71%) and 120 (72.29%) women. The mean age of the group was 37.26 ± 13.68 years, 34.48 ± 12.74 years for men and 38.33 ± 13.92 years for women ($P=0.044$).

According to the ELISA test, 86 (51.8%) patients had a normal enzyme activity versus 80 (48.2%) with decreased activity. According to sex, in the group with normal activity 28 (32.6%) were men and 58 (67.4%) women. And in the group with enzymatic deficit 18 (22.5%) were men and 62 (77.5%) were women ($P=0.148$). The mean blood determination of the DAO enzyme activity was 97.42 ± 50.75 HDU/mL, being 94.26 ± 39.12 HDU/mL in men and 98.63 ± 54.65 HDU/mL in women ($P=0.656$). The mean activity was 132.49 ± 47.93 HDU/mL in the group with normal function compared to 59.71 ± 11.31 HDU/mL in the group with enzyme deficit ($P<0.000$).

Frequency distribution of the number of affirmative responses of the HIQ are summarized in Table 1, with the result of 2 affirmative responses being the most repeated (24.1%) and item 4 the most frequently answered affirmatively (75.9%).

Fig. 2 shows the ROC curve that contrasts the HIQ value, quantifying the area under the curve (0.537, $P=0.415$) with a 95% CI (0.448–0.625), not finding statistically significant differences for an

appropriate cut. The sensitivity, specificity results and the Youden's statistic can be found in Table 2.

4. Discussion

Despite the fact that several tests have been proposed, there is no agreement on which is the ideal method for the diagnosis of DAO activity deficit [1,17]. The current consensus is that a detailed medical history, supported by an histamine degradation test, is the method of choice for the diagnosis of HIT [1,2,20] in order to standardized this anamnesis, a series of questionnaires without scientific validation for the screening or diagnosis of this pathology have appeared in recent years [17–19]. The objective of this study was to analyse the diagnostic capacity of HIQ compared with an objective test of enzymatic activity of DAO.

The ideal would be to find a non-invasive, rapid and economic test that could well diagnose or screen patients with a deficit of DAO activity. The questionnaire studied was born from this idea, so its study against an objective test was mandatory. The results found in this study did not support the use of HIQ as a diagnostic method of HIT due to the inability to discriminate patients with different enzymatic activities.

Caution should be exercised when studying the histamine given the risk of causing confusion or misinterpretation due to the complexity of the metabolic function of it [2]. A falsely positive or negative test can delay access to diagnostic techniques and more effective treatments, with the consequent loss of productivity due to inadequately controlled diseases [2,17]. Patients with allergies or intolerances treated incorrectly cause most of the high healthcare costs related to this issue. Also, several studies show that, throughout life, patients with food allergy have a worse quality of life than those with diseases that are sometimes considered more serious, such as diabetes. That is why an early and reliable diagnosis is fundamental [2,17].

It seems logical to think that, for the diagnosis of DAO activity deficit, it is recommendable to carry out an anamnesis along with an in vitro analysis of the functional activity of the DAO enzyme in order to have an objective diagnosis [20]. It is important to highlight that the in vitro diagnostic tests that only measure “the concentration” of the DAO enzyme do not offer diagnostic utility, since the concentration or amount of enzyme does not guarantee that the enzyme has activity, that is to say, has degrading capacity of histamine [13,20–22]. Currently, what could provide some validity for the purpose of an objective diagnostic, is the in vitro measurement of the “functional activity” of the DAO enzyme, expressed in HDU/mL [20,23–25]. This parameter has been frequently used in clinical studies because it supposes a measurable and reproducible quantitative result [20,24], in order to be able to compare results between different works. Despite this, there is some controversy about the role of analytical studies and they still do not represent the gold standard in normal practice [1,26,27], where the clinical history is the main diagnostic method. Likewise, other diagnostic methods based on complementary tests like the histamine 50-skin-

Table 2

Frequency distribution of the affirmative items and translation of these results into sensitivity and specificity of the test.

n of affirmative Items	n patients	%	Sensitivity	1-Specificity	Youden's J statistic
0	4	2.4			
1	24	14.5	0.950	1.000	−0.050
2	40	24.1	0.850	0.814	0.036
3	28	16.9	0.600	0.581	0.019
4	28	16.9	0.450	0.395	0.055
5	32	19.3	0.300	0.209	0.091
6	2	1.2	0.075	0.047	0.028
7	8	4.8	0.075	0.023	0.052

n: number.

prick test [26], the measurement of intestinal enzyme activity, [28] the measurement of histamine in stool samples [29], the methylhistamine in urine or the oral provocation with histamine [10,30,31], have emerged as support for clinical diagnosis [17].

5. Conclusion

On one hand, given that the symptoms presented by people suffering from a deficiency of the DAO are diverse and complex, they should be assessed by a specialist with a detailed history and could be supported by additional tests if necessary [1,17]. On the other hand, more well-designed clinical trials before exposing patients to screening tests, like the one presented in this work, that offer little evidence of effectiveness are necessary, [1,2,17,32] with the objective of supporting the physician in his daily practice. Therefore, research should continue in order to clarify, standardize and improve the detection methods of these pathologies.

Disclosure of interest

The authors declare that they have no competing interest.

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