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ORIGINAL ARTICLE

Diamine oxidase levels in different chronic urticaria phenotypes

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Abstract
Background: Diamine oxidase (DAO) is a polyamine-degrading enzyme also implicated in histamine metabolism. Chronic urticaria (CU) has a wide spectrum of clinical presentations and causes. *Anisakis* sensitisation associated chronic urticaria (CU+) has been characterised as a phenotype with different clinical and immunological characteristics and possibly associated with previous acute parasitism. We aimed to analyse serum DAO levels in different CU phenotypes. We further analysed the possible association of DAO with fish eating habits.
Methods: We studied 35 CU+ patients and 39 non-sensitised CU patients (CU−) as well as 19 controls. We analysed fish-eating frequency as well as fish intake associated exacerbation of CU (FIAE) or gastro-intestinal complaints (GI). DAO levels were further analysed with respect to lymphoproliferative responses, cytokine and specific IgE production.
Results: DAO levels were not different between CU and controls, but were significantly higher in CU+ than in CU−. CU+ patients with FIAE had lower DAO levels, but no differences were detected in patients with GI. DAO levels correlated positively with oily and canned fish consumption in CU−. In CU+, DAO levels correlated positively with specific *Anisakis* IgE, percentages of proliferation in *Anisakis* stimulated peripheral blood lymphocytes, serum IL-2 and IL-6, but correlated negatively with mitogen stimulated TGF-β in supernatants.
Conclusions: DAO levels in CU depend on fish-eating habits and in CU+ on the amount of specific IgE production. In the CU+ phenotype, lower levels of DAO predispose to urticaria exacerbation after fish intake, probably due to a relative insufficient enteric availability of this enzyme.

Abbreviations: CU, chronic urticaria; CU+*Anisakis*, sensitisation associated chronic urticaria; CU, chronic urticaria without sensitisation against *Anisakis*; FIAE, fish intake associated exacerbation of urticaria; GI, fish intake associated gastro-intestinal complaints.

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Introduction

Chronic urticaria (CU) is a disease without any well-defined cause, but the clinical appearance results from the convergence of multiple possible factors on mast cell activation and degranulation, which liberates a vast array of mediators. Histamine is one of the most potent mediators and is responsible for the appearance of wheals and pruritus. Therefore, biochemical pathways in the production as well as the degradation of histamine can provide clues to the pathophysiology of this disease.

Diamine oxidase (DAO) is responsible for scavenging extracellular histamine.[1] Initial studies of plasma DAO measurements were performed by displacing enteric DAO from the intestinal mucosa into the peripheral circulation by intravenous heparin administration,[2] but more sensitive commercially available ELISA kits made it later possible to assess serum or plasma levels directly.

Over the last few years, DAO has gained interest in different research fields. Within the different pathologies attended at allergy clinics, the focus has been on histamine intolerance as well as on chronic urticaria. In both cases, interest is therefore directed towards possible dietary advice or substitution therapy. In the scientific literature there is still controversy on possible dietary control in CU, even though in CU about 30–40% of patients attribute their symptoms to food intolerance.[3]

In histamine intolerance, increased availability of biogenic amines, together with an impaired histamine degradation can lead to generalised symptoms including urticarial rash.[4] Clinical parameters are the main factors leading to a suspected diagnosis, and in a high percentage of cases DAO serum levels are found to be lower than in controls.[5]

On the other hand, in chronic urticaria the possible implication or usefulness of DAO determination is not straightforward.[3,5,6] A role of DAO in modulating biologic effects of histamine is warranted,[7] but it is postulated that elevated histamine levels in CU result from secondary mediator release rather than a specific defect in the histamine metabolic pathway.[8]

Another feature of DAO is its possible association with intestinal gut dysfunction and is proposed as a marker of mucosal integrity.[9] Thus, several human and animal studies revealed that DAO activity is inversely associated with intestinal permeability of the small intestine.[10]

In the Mediterranean region, *Anisakis* sensitisation associated chronic urticaria (CU+) is a frequent phenotype of CU.[11–14] Sensitisation is due to a previous parasitic episode by *Anisakis* which is occasionally the eliciting factor for the chronic urticarial reaction. In CU+, patients often claim that exacerbation of urticaria is associated with fish intake. There are however reports on urticaria, but also isolated gastro-intestinal complaints after fish intake which can easily be misinterpreted as being due to an IgE-mediated response in *Anisakis*-sensitised patients with previous parasitism.[15] A true allergic IgE-mediated cause or de novo parasitism by the fish borne nematode can only rarely be accountable for symptom worsening.[16]

It is known that especially oily or canned fish is rich in histidine, which is transformed to biogenic amines, such as histamine[17] and thus a direct triggering of intestinal or cutaneous symptoms by fish intake could be a possible explanation, when enteric DAO is insufficiently produced. Therefore, the assessment of serum DAO could be useful in the assessment of this cause-effect relationship.

We hypothesised that in a region with high fish consumption, DAO serum levels would vary in different CU phenotypes as well as in those patients who present with adverse gastro-intestinal or urticaria symptoms after fish intake.

Methods

Study protocol

We included prospectively 74 patients with CU: 35 of whom were sensitised against *A. simplex* (CU+). Nineteen subjects without a history of urticaria, adverse reactions associated with fish intake or sensitisation against *A. simplex* served as controls. Two phenotypes of CU were differentiated: criteria to include patients in the *Anisakis* sensitisation associated chronic urticaria (CU+) were a positive Skin Prick Test (SPT) against *A. simplex* and detectable specific IgE against *Anisakis* larval antigen. CU− patients had neither a positive SPT nor serum specific IgE against *A. simplex*. Furthermore, patients were asked for exacerbation of urticaria or gastro-intestinal complaints after fish intake. Two subgroups were established:

As fish consumption is rather high in our region and in order to reduce possible bias, fish intake associated exacerbation (FIAE), was ascertained if patients claimed at least two episodes of worsening of urticaria within six hours after fish intake. Likewise, patients claiming gastro-intestinal complaints (GI) had at least two associated episodes. A further necessary inclusion criterion in CU+ was that the implicated fish-meal (canned, deep-frozen or well-cooked fish preparation) was not suspected to have induced a new parasitic episode by *Anisakis*. These groups were compared with those who did not claim any fish intake associated adverse reactions. Patients with only one episode of FIAU or GI or in those situations, where a new acute parasitic episode could not be ruled out, were not included in the analysis of FIAE or GI.

Chronic urticaria was defined as wheals recurring at least twice per week for at least the previous six weeks. Patients were not included in this study if physical stimuli were the only eliciting agents of urticaria. Other known factors associated with CU, such as positive hepatitis serology, antithyroid antibodies or autoimmune status as assessed by autologous serum skin test, were not an exclusion factor, and were not further analysed.

Patients were asked for the number of weekly fish portions (fresh/deep-frozen, oily/non-oily, canned) by a standardised questionnaire as previously described.[13]

Urticaria activity score (UAS) was assessed as previously described.[18] Shortly, severity of urticaria in CU patients was clinically assessed after withdrawing antihistamines for five days. The mean score of the last four days was calculated as the sum of the wheal number score (between 0 and 3: 0;