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A curious case of anaphilaxis

Gaia Mancuso[1]*; Yacoub MR[2]

[1]Service of Allergy and Clinical Immunology, Department of Internal Medicine, EOC, "La Carità" Hospital of Locarno, Switzerland.

[2]IRCSS San Raffaele Milano, Italy.

***Corresponding Author: Gaia Mancuso**
Service of Allergy and Clinical Immunology, Department of Internal Medicine, EOC, "La Carità" Hospital of Locarno, Switzerland.
Email: mancuso.gaia@hsr.it

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Abstract

Introduction: Anaphylaxis is a serious systemic reaction by immediate hypersensitivity, secondary to the release of mediators active on vascular and bronchial muscles such as histamine, prostaglandins, leukotrienes etc. Exposure to an allergen in a sensitized patient is the simplest method of triggering anaphylaxis. The diagnostic procedure in this context involves the collection of an accurate medical history, which takes into account the favoring factor and tests in vivo and in vitro, while the oral challenge is contraindicated for the severity of the reaction. The etiopathogenesis of forms of anaphylaxis not related to allergens is less known although the presence of primary alterations of the metabolism of bronchus / vasoactive substances responsible for anaphylaxis can be hypothesized. The Diamin oxidase (DAO) is the enzyme responsible for histamine metabolism and previous studies have correlated a DAO deficiency with the development of histamine-dependent manifestations such as hives or migraine. Fewer data are available about the role of DAO in anaphylaxis.

Methods: We describe the case of a 46-year-old woman who came to the allergology clinic for repeated episodes characterized by hives and post-prandial pressure drop. The last episode was treated at ED (Emergency Department) with adrenaline. She had identified fish, shellfish and mussels as possible food triggers. The patient underwent an allergological tests including: prick test with allergenic extracts (fish, shellfish, mussels, anisakis, latex) and with fresh foods (fish, shellfish and mussels), serum specific IgE dosage for suspect foods (extracts and recombinants molecules), Basophil Activation Test (BAT) with suspect foods and with sulphites. To complete the diagnostic procedure we performed tryptase and DAO dosage.

Results: Prick tests with extracts and fresh foods, specific IgE and BAT with suspect foods were negative. BAT with sulphites is also negative. The tryptase was normal (3.88 mcg/L, vn<10), making the hypothesis of mastocytosis or mastocyte activation syndrome unlikely, the DAO was instead very low (0.54 U/mL (vn>10) suggesting a DAO deficit. The patient started supplementation of rhDAO without showing further reactions to food, although she continued to avoid fish and shellfish.

For unclear histamine food content and the istamino-liberating power of some cofactors (drugs, heat, alcohol consumption) the patient has been prescribed self-injectable adrenaline to be used in case of new reactions.

Conclusions: Severe DAO deficiency can manifest itself with symptoms and signs suggestive of anaphylaxis. In patients with symptoms suggestive of allergic reactions to food and a negative test for food allergy it is important consider DAO deficiency as a possible alternative diagnosis.

Introduction

The anaphylactic reactions are the more serious systemic allergic reactions, they are more frequently in the woman and often under-recognized with immediate repercussions on prompt administration of therapy. The atypical symptoms such as pain could aggravate the diagnostic delay [1]. The foods allergic reactions are the most frequent causes accounts between 1 to 3% of the cases. Actually, four phenothype are recognized 1) Type I reactions (endotypes IgE and not IgE mediated, 2) cytokine storm reactions (cytokine releasing) 3) mixed reactions (endotype T-cell macrophage, and basophil mast cell mediated, 4) complement mediated reacrtion (endotype mast cell and basophils). They are triggered by different stimuli [2]. The histamine intolerance defined as the icreased level of histamine deriving from an impaired metabolism. It affects 1% of the population, 80% of which are of middle age. The normal range of histamine level in the organism is 0.3-1.0 ng/ml when exceeding it could elicit a series of manifestation mimic an allergic reaction, with effects that are directly proportionated with its concentration conducing to cardiac arrest [3]. Hyperhistaminemia has been correlated with recurrent anaphylaxis but any case, in our knowledge, up to date has been described [4]. We would describe a case of 46 years old woman presenting pseudoanaphylaxis reactions due to a very low DAO activity.

Case presentation

A 46-year-old woman was admitted to the hospital for syncope. She is affected by thalassemia major which had required splenectomy at an early age and secondary hemochromatosis with hypogonadism and diabetes mellitus. Since 2013, she had received the diagnosis of undifferentiated mixed connective tissue disease, she also has a muscle tensive cervicalgia. Her pharmacological therapy includes eutirox insulin, hydroxychloroquine, supplements of calcium and magnesium, foline and vitamin B6, oral chelating iron, finally sirdalud from June 2016. She drank alcohol occasionally, had smoked in the past, and did not use illicit drugs or over-thecounter herbal preparations. On examination PA 80/40 mmHg, HR 157 bpm sinusal ad a diffuse redness skin rash were detected. She had eaten 30 minutes ago a grilled fish and shellfish at the restaurant. No other cases occurred among other commences. The adrenaline was administered with completely recover. She was referred to the Allergology department for a more in-depth investigation regarding disease assessment. She complains various acute allergic manifestations: in 2005 at the end of a course of antibiotic therapy with amoxicillin-clavulanate for pharyngo-tonsillitis had experimented a sense of constriction in the throat treated with prednisone in an emergency setting. Futher study failed to detect the presence of specific penicilline IgE and cutaneous tests for penicillins, cephalosporins and latex were negative. A similar episode occurred about seven years later followed a rich lunch with saffron risotto, red tuna with radishes, cherry tomatoes, and white wine, when she complained of palpitations, flushing, hands erythema following by diarrhea and vomiting with spontaneous resolution. A the scombroid syndrome was hypothesized. Since July 2016, she had recurrent episodes of skin itching and paresthesia, especially in Kiwifruit and apples cause lingual itching and burning and watery rhinorrhea. The hemochromocytometric formula showed a number of eosinophils in the limits. Serum tryptase was 3.44 [cut] and REMA test 1. The total serum IgE was 5.7 (cut off), specific IgE for fish, shellfish, mites, prup 3 (LTP) and anisakis were negative, skin prick tests with extracts and fresh foods were negative too. So, considering the serological characteristics we have searched a basophil activation performing BAT for foods and sulfites but it gave a negative result. Oral Double blinding challenge with placebo, regarding as gold standard, being within 12 months from the last manifestation, was still contraindicated. Reconsidering her history, we decided to dose DAO activity that was found very low. The patient started a diet at low histamine content combined with oral supplementation of DAO with an improvement of symptoms.

Discussion

The histamine intolerance is an underestimate disorder due to impaired histamine metabolism. The increased levels of histamine could be attributable to pathological conditions such as allergy, mastocytosis, gastrointestinal bleeding associated with an increased endogenous histamine level, or to an increase exogenous intake rather than medications or wine that interfere with its catabolism, but the most frequent cause of histamine intolerance is DAO deficiency. Numerous single nucleotide polymorphisms of the DAO gene are associated with various pathological conditions, among them also with a food allergy, and could explain the high interindividual variability. Moreover, an impaired DAO activity could have repercussions on HNMT activity, the second enzyme involved in histamine metabolism. The diagnosis must be considered, after the exclusion of mastocytosis and food allergy, in patients with two or more symptoms of hyperhistaminasemia and that have some beneficial from starting a low histamine diet. The DAO activity could be measured with REA methods giving a probability whereas, the definitive diagnosis derives from double-blinded with placebo oral challenge with histamine in a protected setting [5-7]. Interestingly in our patient, we could not exclude a coexistence of both, food allergy and DAO deficiency, considering the very low total serum IgE, it is really likely [8]. Moreover, the food allergy is frequently associated with increased histamine levels, impaired DAO and HNMT activity that could explain the allergic symptoms in the interval period between major episodes [4-10].

Conclusion

The DAO deficiency should be considered in the differential diagnosis of patients with anaphylaxis symptoms especially in the case of negativity of all available diagnostic tests.

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