

LETTER TO THE EDITOR

Idiopathic Anaphylaxis and Histamine Intolerance

To the Editor,

There has been an increase in the number of pediatric patients with idiopathic anaphylaxis (IA) noted in recent years. IA is a potentially life-threatening syndrome caused by an unknown trigger. It must be properly recognized and treated to prevent a fatal outcome. There have been no previous reports of IA with histamine intolerance (HI) in a pediatric patient. This possible connection of HI with IA requires further investigation. A positive autologous serum skin test (ASST) in our patients with IA—yet with no proof of circulating autoantibodies against IgE and against a subunit of the high-affinity IgE receptor (FcεRIα)—points to the possibility of a different cause of autoreactivity. Thus, autoimmunity could be another cause of IA, which, up to now, has not been sufficiently investigated.

IA is a systemic syndrome of immediate hypersensitivity caused by the release of mediators from mast cells and basophils, where the trigger remains unknown. It is a frustrating condition for patients because they have no means of avoiding a potential trigger, and therefore, events occur spontaneously and unprovoked. IA exerts a profound effect on quality of life. The condition was first described in 1978, by Bacal et al. (1), and since then, much has been learned about the diagnosis, classification, and treatment. Atopy is noted in 48–58% of patients (2). IA is more common in adults and in women.

Clinical manifestations are the same as in allergen-induced anaphylaxis and include urticaria, angioedema, hypotension, tachycardia, bronchial obstruction, stridor, itchy skin, generalized flushing, nausea, vomiting, diarrhea, dysphagia, dizziness, and loss of consciousness. Patients may have a different combination of these symptoms, but tend to have the same manifestations during repeated episodes. The diagnosis is based on a thorough history and clinical examination, and on eliminating other known causes producing the same clinical picture, such as systemic mastocytosis, carcinoid syndrome, pheochromocytoma, hereditary angioedema, and mast cell activation syndrome (2, 3). Treatment recommendations for patients with IA depend on the frequency and severity of attacks. They must carry epinephrine and learn how to manage an acute attack. We present three patients with recurrent episodes of IA, HI, and positive ASST.

Case 1

An 11-year-old boy presented with an episode of acute urticaria, angioedema of the lips, nausea, and vomiting. A second episode occurred 2 months later with similar symptoms

along with headache, nausea, abdominal pain, vomiting, dyspnea, tachycardia, hypotension, and dizziness. At that point, he was hospitalized and an extensive workup was performed. The boy had symptoms of seasonal allergic rhinoconjunctivitis and congenital hypothyroidism and was taking hormone replacement therapy. To confirm the allergy, we performed skin prick tests (SPT) with common aeroallergens, food allergens, and food preservatives, as well as total and specific IgE. Sensitization to house dust mites (HDM), trees, grass, weed, and glutaraldehyde was confirmed by a positive SPT and elevated total serum IgE, as well as by positive specific IgE. His serum tryptase level was elevated during the attack, yet with a baseline level within normal range (5.12 µg/l). Instructed to carry epinephrine autoinjector, he adopted a strict regimen of a histamine-free diet and was advised to begin treatment with 10 mg of cetirizine once daily, which he was not taking regularly. In the following 2.6-year period, he experienced 5 episodes of unprovoked anaphylaxis, requiring the use of epinephrine and emergency room care. Finally, he started taking 10 mg of cetirizine daily on a regular basis and has since been in remission, for one year.

Case 2

A 15-year-old girl presented with urticaria, abdominal cramps, vomiting, and angioedema of the lips. Further episodes occurred 6 and 12 months later, with similar symptoms. During her fourth episode of anaphylaxis (3 months later), she was hospitalized with similar symptoms, along with generalized pruritus of the skin and malaise, followed by a loss of consciousness. The girl has been suffering from pollen-induced allergic asthma and seasonal AR since she was eight. She had symptoms of oral allergy syndrome (OAS) and was allergic to food and beta-lactam antibiotics. Sensitization to HDM, trees, grass, weeds, carrot, lemon, and glutaraldehyde was confirmed by a positive SPT and elevated total serum IgE, as well as by positive specific IgE. OAS symptoms were provoked by fresh fruit (apple, cherry, peach, and melon). She was advised to strictly avoid fresh lemon and carrot, as well as all fresh fruit causing OAS symptoms. Her serum tryptase level during the fourth episode peaked at 120 µg/l, but the baseline level was within normal range (10.34 µg/l). She was instructed on how to use epinephrine autoinjector and advised a histamine-free diet. During the next 2 years, she experienced 3 further episodes of unprovoked anaphylaxis. Based on medical history, OAS and HI were very unlikely causes of these episodes. Unfortunately, after her 18th birthday, the girl was lost to follow-up.

Case 3

In the third patient, the symptoms of anaphylaxis that began manifesting at the age of 12.6 years were itchy skin, generalized flushing, nausea, diarrhea, and loss of consciousness. Episodes

Abbreviations

ASST, autologous serum skin test; DAO, diamine oxidase; FcεRIα, high-affinity IgE receptor; HDM, house dust mites; HMT, histamine N-methyltransferase; IA, idiopathic anaphylaxis; MCAS, mast cell activation syndrome; OAS, oral allergy syndrome; SPT, skin prick test.

repeated up to 4 times monthly, requiring the use of epinephrine, antihistamine, and corticosteroids. She was hospitalized at the age of 13, and workup results showed sensitization to weeds with a positive SPT, elevated total IgE, and specific IgE against *Ambrosia elatior*. Her baseline serum tryptase level was within normal range (4.16 µg/l), but elevated during attacks up to 108.16 µg/l. Instructed on how to use epinephrine autoinjector, and upon advice, she adopted a histamine-free diet. Due to the frequency of attacks, IA was classified as frequent, and the patient was advised to take 120 mg of fexofenadine and 40 mg of methylprednisolone daily. Her parents, however, feared of the side effects of corticosteroid therapy and accepted only antihistamine. After introducing daily antihistamine therapy, unprovoked anaphylaxis attacks occurred 2 more times in a 6-month period, but were significantly milder and required an extra dose of antihistamine and glucocorticoid. Currently taking 120 mg of fexofenadine daily, she has been symptom free for the last 6 months.

The findings for each patient are listed in Table 1. An abdominal ultrasound was normal in all three patients, and chronic inflammatory and autoimmune diseases were ruled out, as well as pheochromocytoma and carcinoid syndrome. Catecholamines in 24-h urine, serum gastrin, and 24-h levels of 5-hydroxyindoleacetic acid were normal. Scintigraphy with somatostatin analogue octreotide was carried out to exclude carcinoid syndrome. Food-dependent exercise-induced anaphylaxis was excluded in all three patients. Reaction to mammalian oligosaccharide α -gal was excluded based on medical history (4). There were no data or signs of tick bites, and no connection of symptoms with ingestion of mammalian food products. Prick-to-prick testing with fresh mammalian meat and an oral challenge test were negative in all patients. Interestingly enough, all three patients had a positive ASST, performed according to the recommendations of the EAACI/GA²LEN task force (5). However, circulating autoantibodies against IgE and against FcεRIα could not be detected; that is, a histamine-release test (carried out according to the previously established method) was negative in all patients (6). There were no other clinical or laboratory signs of chronic inflammatory or autoimmune disease. In all three patients, the activity of histamine-inactivating enzyme, diamine oxidase (DAO) in plasma, was very low—indicating a high histamine intolerance.

Idiopathic anaphylaxis can show up at any age, but the exact incidence is unknown. It is important to recognize this potentially fatal condition so that it may be appropriately treated. Multiple theories on the pathogenesis of IA have been proposed, including dysregulation of cytokines, uncontrolled activation of inflammatory cells with excessive mediator release, uncontrolled increase in bioactive mediators, autoimmune activation of mast cells, and dysregulation of histamine-releasing factor. Based on the current understanding of this disorder and on what is known about mast cell activation, as well as the resulting pathology, a distinct clinical entity named mast cell activation syndrome (MCAS) has been proposed (7, 8). Differentiated by the underlying disease and recognized etiology, MCAS can be primary, secondary, or idiopathic. In primary MCAS, there are 2 well-characterized molecular defects resulting in mast cell proliferation: a point mutation

Table 1 Patient characteristics

Clinical characteristics	Patient 1	Patient 2	Patient 3
Age (years)	11	15	12.6
Gender	Male	Female	Female
Diagnosis	Congenital hypothyroidism AR	Asthma AR Food allergy OAS Drug allergy	AR GERD
Skin prick test			
House dust mite	+	+	—
Trees	+	+	—
Grass	+	+	—
Weed	+	+	+
Food	—	+	—
Preservatives	+	+	—
Total IgE (IU/ml)	427	141	659
Specific IgE—mean (kUA/l)			
House dust mite	Class 1	Class 2	—
Pollen	Class 3	Classes 3–4	Class 4
Food	—	Class 1	—
Tryptase	Normal outside attacks	Normal outside attacks	Normal outside attacks
Bone marrow	Normal	Normal	Normal
ASST	+	+	+
HR-urticaria test	—	—	—
Histamine intolerance	+	+	+
C1-INH	Normal	Normal	Normal

AR, allergic rhinoconjunctivitis; OAS, oral allergy syndrome; GERD, gastroesophageal reflux disease; ASST, autologous serum skin test; HR, histamine release; C1-INH, C1 esterase inhibitor.

D816V in c-KIT associated with mastocytosis and aberrant CD25 expression (9). Secondary mast cell activation occurs in allergic diseases. If neither an allergic or underlying inflammatory process, nor a monoclonal, KIT-mutated mast cell population are detectable in a patient with MCAS, the diagnosis 'idiopathic MCAS' should be established (7). Idiopathic MCAS includes IA, which is a diagnosis made by ruling out possible known causes. We have excluded possible causes of anaphylaxis, such as food, medications, and exercise, as well as systemic diseases that may present with similar symptoms, such as systemic mastocytosis, carcinoid syndrome, pheochromocytoma, and hereditary angioedema. Normal bone marrow with the presence of CD25-negative mast cells, as well as normal baseline serum tryptase levels in our patients, makes the diagnosis of systemic mastocytosis and primary MCAS unlikely. In spite of a positive ASST, there was no evidence of autoantibodies against IgE and FcεRIα. ASST is an *in vivo* test assessing autoreactivity and is characterized by an itchy weal and flare response to intradermally injected autologous serum. It may serve as an indication of mast-cell activating autoantibodies against IgE or an IgE receptor and is most often performed in patients with chronic urticaria. It is recom-

mended that ASST be carried out in conjunction with the basophil histamine-release assay to demonstrate autoantibody specificity (6). The assay was negative in our patients, which could suggest a different possible cause of autoreactivity, although there were no other signs of chronic inflammatory or autoimmune disease.

There have been no previous reports of IA with HI in a pediatric patient. Whether this is pure coincidence or the result of a common underlying pathogenetic mechanism remains to be seen. Histamine is a biogenic amine, affecting human organs and systems in multiple ways. Symptoms of excessive histamine in plasma manifest as acute pseudoallergic illness with skin rash, vomiting, diarrhea, abdominal pain, and/or respiratory distress. HI describes a state where catabolic capacity for endogenously released or exogenously administered histamine is insufficient, leading to histamine-mediated adverse reactions. People with low intestinal histamine inactivation or inhibition of this activity suffer from HI. This diagnosis is based on the careful recording of symptoms and the identification of intestinal or serum activities of DAO and histamine N-methyltransferase (HMT). It may be complemented by an analysis of DAO and HMT gene polymorphisms to identify a possible genetic predisposition. We measured DAO by enzyme immunoassay analysis in serum samples (10). For evaluation, we used the manufacturer's recommended reference values, and all our patients had highly reduced activity of DAO <40 HDU/ml. The only effective therapy for HI is the avoidance of histamine-containing food, and our patients were advised to follow a histamine-free diet. Controlled trials demonstrating the efficacy of DAO substitution with fresh

encapsulated enzymes are still lacking. It has been demonstrated that DAO activity increases in patients on a histamine-free diet, which could be a possible explanation for improvement and remission in case 1 and case 3, respectively.

Symptoms and classifications of IA in the pediatric population are the same as those in adults, and adult treatment regimens have been applied to children (2, 3). Two patients were considered to have generalized infrequent IA, and the third had generalized frequent IA (2, 3). Patients were instructed to carry epinephrine and were taught to self-administer it. We suggested prednisone therapy with antihistamine for the third patient, but the parents, fearing the side effects of corticosteroid, accepted only antihistamine daily. The girl has been in remission for 6 months.

Idiopathic anaphylaxis has been classified and treated successfully, but the underlying mechanism of this disorder has yet to be revealed. The observation that IA is a steroid-responsive disorder indicates a possible autoimmune etiology. Pediatric IA can show up at any age; therefore, it is important to recognize it so that it may be appropriately treated. This potentially life-threatening syndrome can be successfully managed, and in the majority of patients with IA, the frequency of episodes often declines with age.

Irena Ivkovic-Jurekovic

Department of Pulmonology, Allergology, Immunology and Rheumatology,
Children's Hospital Zagreb, Zagreb, Croatia

E-mails: irena.ivkovic-jurekovic@kdb.hr;

irenaivkovicjurekovic@gmail.com

DOI:10.1111/pai.12438

References

1. Bacal E, Patterson R, Zeiss CR. Evaluation of severe (anaphylactic) reactions. *Clin Allergy* 1978; **8**: 295–304.
2. Lenchner K, Grammer LC. A current review of idiopathic anaphylaxis. *Curr Opin Allergy Clin Immunol* 2003; **3**: 305–11.
3. Lieberman PL. Idiopathic anaphylaxis. *Allergy Asthma Proc* 2014; **35**: 17–23.
4. Commins SP, Platts-Mills TA. Anaphylaxis syndromes related to a new mammalian cross-reactive carbohydrate determinant. *J Allergy Clin Immunol* 2009; **124**: 652–7.
5. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CEH. EAACI/GA2LEN task force consensus report: the autologous serum skin test in urticaria. *Allergy* 2009; **64**: 1256–8.
6. Platzer MH, Grattan CE, Poulsen LK, Skov PS. Validation of basophil histamine release against the autologous serum skin test and outcome of serum-induced basophil histamine release studies in a large population of chronic urticaria patients. *Allergy* 2005; **60**: 1152–6.
7. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 2010; **126**: 1099–104.
8. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012; **157**: 215–25.
9. Akin C, Scott LM, Kocabas CN, et al. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with “idiopathic” anaphylaxis. *Blood* 2007; **110**: 2331–3.
10. Mayer I, Missbichler A, Wantke F, et al. Optimierter Radioextraktionsassay zur quantitativen Bestimmung der Aktivität von Diaminoxidase (DAO) in Human Serum und Plasma. *Allergologie* 2005; **28**: 1–8.