

Review Article

Pediatric Idiopathic Anaphylaxis: 3 Case Reports and A Systematic Review of Literature

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Citation: Scheyver SD, SK, Ben-Shoshan M, Chan ES (2017) Pediatric idiopathic anaphylaxis: 3 case reports and a systematic review of literature. Int J Allergy Asthma: IJAA-102. DOI: 10.29011/IJAA-102.100002

Received Date: 28 July, 2017; **Accepted Date:** 07 August, 2017; **Published Date:** 17 August, 2017

Abstract

Background: Idiopathic Anaphylaxis (IA) is a diagnosis of exclusion and represents a major diagnostic and management challenge, especially in children. There are no current guidelines for diagnosis and management of pediatric IA. We aim to present a series of 3 cases of pediatric IA followed by a systematic review of the literature.

Methods: We describe 3 cases of pediatric IA and conducted a systematic review of original articles published in the past 22 years regarding diagnosis and management of pediatric IA.

Results: The current proposed diagnostic approach and treatment regimens are based on a few small studies. Future large-scale studies are required. IA is a diagnosis of exclusion and should be made only after extensive evaluation excluding potential triggers of anaphylaxis as well as non-allergic conditions with a similar presentation. The current proposed treatment regimens recommend prophylactic treatment with continuous prednisone for patients with frequent episodes. However, daily treatment with systemic steroids have well recognised serious adverse effects such as obesity, poor growth, osteoporosis and behavioural disturbances that are of paramount importance in the pediatric age group. More recently the use of biologics was suggested to benefit patients with IA although the optimal management protocol is not yet established.

Conclusion: Future studies are needed to optimize diagnosis and treatment strategies in pediatric cases of IA. Omalizumab may be a promising novel therapeutic option for pediatric IA.

Introduction

Idiopathic Anaphylaxis (IA) is a diagnosis of exclusion after known causes for anaphylaxis and other diseases that mimic anaphylaxis have been ruled out [1]. The condition was first described in 1978 [2]. The exact prevalence is not known but has been estimated to be between 20,000 and 47,000 cases in the United States [3].

IA accounts for up to 60% of cases of anaphylaxis in adults and 10% of pediatric cases [4]. Given that as per the definition there are no identifiable triggers of IA, there are substantial challenges related to the diagnosis and management of these cases. There are currently no guidelines regarding the diagnostic approach includ-

ing assessment for underlying diseases and use neither of confirmatory tests nor on the best management of pediatric cases of IA. The current approach to treatment is based on disease frequency; short-term treatment for infrequent attacks, but prophylactic treatment with glucocorticoids is recommended for patients with frequent episodes. It is well known however that long-term treatment with systemic glucocorticoids is associated with multiple side effects that may be particularly worrisome in the pediatric population including growth failure and adrenal suppression. Although several case series have been published regarding IA, only a few small descriptive studies have focused on pediatric idiopathic anaphylaxis. We aim to present a series of 3 cases of pediatric IA followed by a

systematic review of the literature published in the past 22 years regarding IA in children, with a focus on diagnosis and management.

Methods

We searched the PubMed database for original scientific studies pertinent to the clinical diagnosis and management of idiopathic anaphylaxis in children. We used the search terms “Idiopathic anaphylaxis” AND “Children” and then limited the results to articles published between May 12, 1995 and May 12, 2017, that were written in English or French.

The abstracts of the resulting papers were reviewed and those relevant to the diagnosis and management of idiopathic anaphylaxis in children were included. The initial PubMed search yielded 58 articles, which was reduced to 19 after applying previously mentioned filters and then further narrowed to 8 articles after the first and last authors (SD and MBS) assessed the abstracts and discussed their relevancy to the systematic review. (Figure 1)

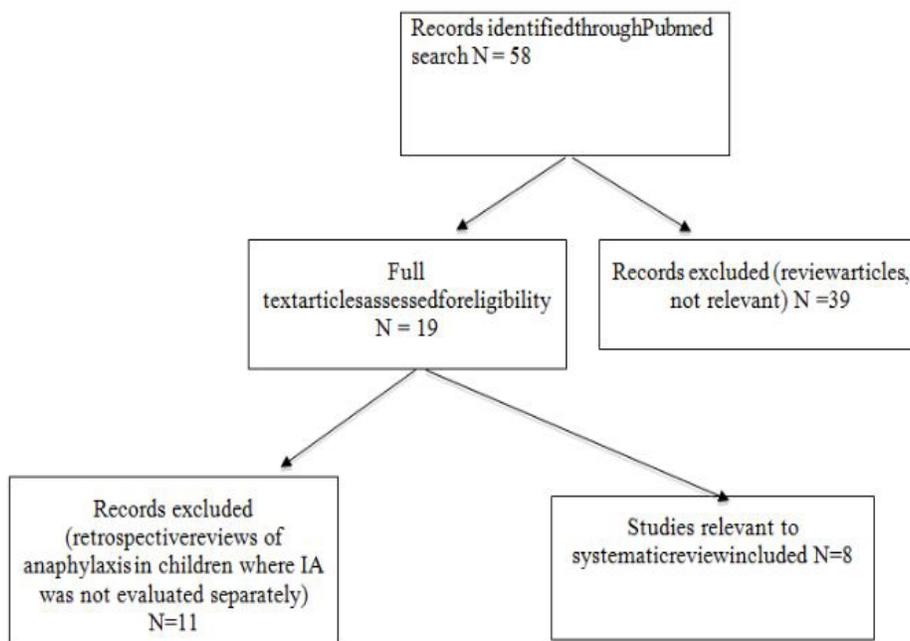


Figure 1: Results of the systematic review using PubMed database. Excluded papers were either review articles rather than original papers or not relevant to the diagnosis or management of idiopathic anaphylaxis in children.

Type of Study	Author, Journal Pub yr	Peds/ Adults	Findings	Comments
Retrospective chart review	Krasnick et al 1996	A > C	<p>Charts of 225 patients diagnosed with idiopathic anaphylaxis (IA) were reviewed at a single center and 61 patients were available for long-term F/U.</p> <p>Diagnosis: based on history, PE, serology, radiology, SPT food and aeroallergens, challenges with food additives</p> <p>Age range was between 10-68 years old, mean 39 yo, the majority was female.</p> <p>Treatment based on frequency of symptoms:</p> <p>Infrequent: treatment of acute attacks only with Epi, Pred 60 mg, antihistamine</p> <p>Frequent: Pred 60-100 mg x 1 week, alternate day, tapering by no more than 5 mg per month; daily antihistamines and sympathomimetics (albuterol)</p> <p>Long-term F/U</p> <p>65% of patients with frequent attacks and 91% of patients with infrequent attacks went in remission.</p> <p>Significant decrease in ED visits (except IA-AE-F), hospital admission and ICU admission after evaluation and treatment by allergy service</p> <p>Reduction 184 740 \$ saved by program for 546 patient-years (estimated 11 million \$ saved for 33 000 cases of IA in US)</p> <p>Cromolyn not effective</p> <p>Ketotifen effective in reducing amount of prednisone and in some stop prednisone</p> <p>Greatest clinical benefit IA-G (F and IF): significant decrease in ED visit</p>	<p>Small N of pediatric patients</p> <p>No specific information regarding children in this study (percentage, clinical presentation, management?)</p> <p>High remission rate for patients with infrequent episodes</p> <p>Spontaneous remission vs aggressive treatment of acute episodes decreases frequency and severity of future episodes</p> <p>A number of patients in remission were still on daily antihistamines which may have an effect on disease control</p> <p>No control group with placebo for ethical reasons</p>
Case series	Ditto et al, Ann All, 1996	Adults > Children	<p>335 patients were evaluated for episodes of anaphylaxis of unknown origin. N=132 were evaluated</p> <p>Diagnosis: R/O food, drug, exercise 4 hours prior to Rx, R/O pheochromocytoma and mastocytosis, SPT to aeroallergens if atopic history, complement levels R/O AE</p> <p>Treatment according to previous protocol and based on frequency of symptoms:</p> <p>Infrequent: treatment of acute attacks only with Epi, Pred 60 mg, antihistamine</p> <p>Frequent: Pred 60-100 mg x 1 week, alternate day, tapering by no more than 5 mg per month; daily antihistamines (hydroxyzine) and sympathomimetics (albuterol)</p> <p>N=14/335 children (4.2%) were included</p> <p>N=4 between 0-9 yr (1.2%)</p> <p>N=28 between 10-19 yr (8.4%)</p> <p>Increasing incidence in children (9 new cases since previous study) increasing prevalence vs increasing awareness</p> <p>Children on same treatment protocol as adults and similar response as adults</p> <p>64% frequent episodes requiring prednisone (3/56 cortico-steroid dependent IA) vs 36% infrequent</p> <p>Remission rate overall 65% (57/132)</p> <p>Time to remission 1-14 years</p> <p>48% atopy, 23% pre-existing urticaria/AE, 5% unrelated food allergies, 11% exercise induced episodes</p>	<p>Small N of pediatric patients</p> <p>No specific description of pediatric cases</p> <p>Food SPT, laboratory test (CBC, complement and serum chemistry) non contributory - not recommended except in selected patients</p> <p>No control group</p>

	Ditto et al, JACI 1997	Children	<p>22 cases of IA in children (9 new, 13 previously described in study published by Ditto in 1996) were evaluated</p> <p>Diagnosis: Thorough history and PE, R/O food, drug, exercise 4 hours prior to Rx, R/O pheochromocytoma and mastocytosis, SPT to aeroallergens if atopic hx</p> <p>Complement levels R/O AE</p> <p>Treatment according to previous protocol and based on frequency of symptoms:</p> <p>Infrequent: treatment of acute attacks only with Epi, Pred 60 mg, antihistamine</p> <p>Frequent: Pred 60-100 mg x 1 week, alternate day, tapering by no more than 5 mg per month; daily antihistamines (hydroxyzine) and sympathomimetics (albuterol)</p> <p>Age at onset 3 - 17 yo, majority were female F > M 13:9</p> <ul style="list-style-type: none"> - 12/22 frequent attacks, 9/22 infrequent, 1/22 undifferentiated somatoform idiopathic anaphylaxis - 2/22 CSD-IA (Tx with Ketotifen, 1 went in remission, 1 tapering daily corticosteroids) - 4/22 isolated throat angioedema Tx (inhaled beclomethasone dipropionate) with success - 3/22 malignant IA uncontrolled with alternate day prednisone (1/3 in remission, 1/3 Ketotifen: improved, 1/3 US-IA (non-organic disease), no improvement despite high dose CS) 	<ul style="list-style-type: none"> • Comment on specific psychosocial problems interfering with care of pediatric patients with IA (parents refuse to follow tx with steroids, corticophobia, low awareness from local physician,...) • Non-organic causes presenting as IA should be considered • Treatment outcomes similar as in adults for disease control and remission
Retrospective chart review	Hogan, Annals 1998	Children	<p>Charts of 8 children with IA were evaluated</p> <p>No identifiable allergen, no other systemic disease</p> <p>7/8 infrequent 1/8 frequent (tx with steroid; off steroids since 6 months)</p> <p>All cutaneous sx</p> <p>6/8 resp sx (wheezing or AE w breathing difficulties)</p> <p>6/8 diarrhea</p> <p>Many had life-threatening events: hypotension or LOC</p> <p>Other difficulties:</p> <p>Non compliance, non-belief, taken out of school</p> <p>Can start at any age, majority after 10 y of age</p>	<p>Small study</p> <p>None in remission</p> <p>2 young patients at time of onset (11 months)</p>
1. Cross-sectional	Tejedor Alonso Annals 2002	Adults > Children	<p>Documentation of clinical characteristics of IA in 81 cases</p> <p>Clinical data related to episodes, presence of atopy, 1st visit.</p> <p>2nd part prospective longitudinal evaluation after 1st visit</p> <p>N=81 cases of IA 1990-1995</p> <p>13/81 (16%) children less than 14 yrs</p> <p>Mean age 30 +/- 17.3 yrs</p> <p>Age range 5-73; Median 24 years</p> <p>68%F</p> <p>Median N of episodes during a year was 2, range 1-130</p> <p>Median F/U = 24 months</p> <p>N=74/81 f/U until 12/1995</p> <p>Remission 56/74 (76%)</p> <p>N18/81 (22%) frequent episodes and proposed to start maintenance w corticosteroids</p> <p>12/18 agreed, 2/18 refused, 4/18 had history of use of cs with improvement</p> <p>Patients who received corticosteroids had a significant decrease in attacks between 1 year before and after F/U</p> <p>15% other anaphylaxis (food, exercise, drugs)</p> <p>48% atopy</p> <p>58% acute or CSU or AE</p>	<p>Small N of pediatric patients</p> <p>No specific description of pediatric cases</p>

Retro-Spective chart review + Follow-up	Lieberman et al Annals 2006	Adults > Children	To examine natural history, clinical manifestations and factors compliance to Tx Retrospective chart review 25 years + F/U question N=601 cases of anaphylaxis of unknown origin Age range 1-79 years, mean 37 yrs, F 62% Causes in 41% of patients (food, drug, exercise) Mastocytosis N=3/601 IA 59% increasing N of idiopathic anaphylaxis Attacks decrease in time	Small N of children, no specifics about pediatric population
Case report	Warrier, Annals 2009	Child	Omalizumab in IA; 1 st case report in child 12 yo uncontrolled asthma requiring multiple courses of oral steroids, AR, multiple FA, recurrent episodes of anaphylaxis of unknown origin (4 to 5 per month); Atopic; Total IgE 1848 IU/ml Tx Omalizumab 375 mcg q 2weeks: resolution of acute episodes, anaphylaxis and asthma exacerbations; Improved QOL	
Case series	Ivkovic PAI 2015	Children	Report of 3 patients with IA, HI and positive ASST Age at presentation 11, 15, 12.6 years Diagnosis: All 3 had positive ASST to assess auto-reactivity (Indication of mast-cell activating auto-antibodies against IgE or high affinity receptor) Basophil histamine release assay was negative in 3 patients to demonstrate auto-antibody specificity Maybe different cause for auto-reactivity DAO (histamine-deactivating enzyme Diamine Oxidase) levels decreased; indicating high level of histamine Intolerance Treatment Patient 1: generalized infrequent episodes, Epi PRN, on histamine free diet alone no improvement, started with antihistamines (Cetirizine 10 mg QD) and improved Patient 2: generalized infrequent, on histamine free diet, Epi PRN, lost to F/U Patient 3: frequent episodes tx with Epi, antihistamines and steroids; advised a histamine free diet and oral steroid on maintenance but refused; on daily antihistamines (Fexofenadine) decrease in frequency and severity of attacks; in remission since 6 months	First reports of positive ASST in children and decreased DAO levels (histamine intolerance) Treatment with histamine free diet, antihistamines (Cetirizine 10 mg QD)

Table 1: The articles that were reviewed are summarized in table.

Case presentations

Case 1

An 11 year-old boy presented initially with an episode of cough and eyelid swelling 15 minutes after completing exercise (hockey game). He had eaten pasta 2 hours prior to his exercise.

A year later he developed a similar episode with angioedema, difficulty breathing and abdominal pain after eating pizza. He had done exercise 6 hours prior to eating the pizza. At that point he was seen at the emergency department and he was treated with 3 doses of IM epinephrine. An extensive work-up was performed. The boy had symptoms of seasonal rhino conjunctivitis. Skin prick tests were performed with common aeroallergens and sensitizations to ragweed and tree pollens was confirmed. Skin prick tests with suspected food allergens were negative as well as

specific IgE to possible food allergens including ω-5 gliadin and alpha-gal (Alpha gal testing was performed at Thomas Platts-Mill laboratory, University of Virginia, United States). A challenge with the suspected meal was negative.

He had an elevated total IgE (571 kU/L) and his tryptase level was within normal range (3.5 - 4.5 µg/L) at baseline. Tryptase levels were not documented during his attacks. He had normal levels of C3, C4 and C1 inhibitor esterase. (1.57 g/L, 0.20 g/L, 0.32 g/L respectively). Further investigation revealed no mutation for the cKIT 816 on peripheral blood (conduct based on PCR levels - Thomas Kristiansen laboratory, Dept. of Pathology, Odense University Hospital, Denmark).

Parents refused bone marrow biopsy.

Given the association with exercise we performed an exercise

and food-dependent exercise challenge that was normal.

He was instructed to carry an Epipen auto-injector and in the following year he had 3 other similar episodes. The last episode occurred at 15 years of age. He had no new reactions over the last 24 months.

Case 2

A 14 year-old girl presented with 2 episodes of anaphylaxis with abdominal cramps, flushing and hives. The first episode occurred in the context of exercise after eating tree-nuts and wheat. One month later she presented with a second episode occurring 1 hour after eating meat. She was treated with Epinephrine and Reacting. Specific IgE levels were negative to all suspected foods including tree-nuts, wheat, milk and alpha-gal. Tryptase levels during the reaction (17.2 µg/L), with baseline levels within normal range (7.5 µg/L).

Further investigation revealed undetectable levels of alpha-gal (Thomas Platts-Mill laboratory, University of Virginia, United States) and no mutation for the cKIT 816 on peripheral blood (Thomas Kristensen laboratory, Dept. of Pathology, Odense University Hospital, Denmark). Exercise challenge test (with and without prior exposure to the suspected meal) and spirometry revealed no abnormalities.

She was instructed to carry an Epipen auto-injector and we advised to begin a treatment with Reactine 20 mg daily. Parents refused a bone marrow biopsy at this point. At a 24-month follow-up she remained in remission.

Case 3

The third patient presented at 16 years of age with recurrent anaphylaxis. Her episodes were characterized by acute abdominal pain, vomiting, diarrhea followed by itchiness and hives. The episodes would occur 6 to 7 times per month, usually at night between 10-11 pm (2 hours after eating). She would do exercise 1 hour prior to eating (30 min on a stationary bike). The episodes seemed to occur in the context of her menstruation (a few days before, during or a few days after). Otherwise, no clear triggers could be identified. In between episodes she was symptom-free and had no constitutional symptoms.

She had an extensive work-up with negative skin prick tests and specific IgE for the relevant food allergens. Her total IgE was significantly elevated (4032 kU/L) and tryptase levels were elevated during attacks (17.4 µg/L) and normal at baseline (3.4 µg/L). There were undetectable levels of alpha-gal (Thomas Platts-Mill laboratory, University of Virginia, United States) and the cKIT816 mutation was not detected in peripheral blood (Thomas Kristensen laboratory, Dept. of Pathology, Odense University Hospital, Denmark).

Given the severity of episodes and the prominent gastrointestinal manifestations, an abdominal ultrasound was done and revealed no abnormalities. Urine collection over 24 hours for 5HIAA and VMA was normal. A bone marrow biopsy was

performed revealing no abnormal mast cell infiltrates and normal staining for cKIT and tryptase.

She was instructed to carry an Epipen auto-injector and we advised to begin treatment with Reacting 20 mg daily that did not improve her symptoms.

Treatment with Omalizumab 300 mg monthly was started and she has been in remission since then, for one year. Four months after stopping Omalizumab treatment she has not experienced new episodes consistent with anaphylaxis. The findings for each patient are listed in (Table 2).

Clinical characteristics	Patient 1	Patient 2	Patient 3
Age at presentation (years)	11	14	16
Gender	Male	Female	Female
Presence of atopy	Yes	No	Yes
Frequency of attacks	Infrequent	Infrequent	Frequent
SPT			
Ragweed	+	NA	NA
Tree	+	NA	NA
Grass	-	NA	NA
House dust mite	NA	NA	+
Wheat	-	NA	-
Soy	-	NA	NA
Almonds	-	NA	NA
Peanut	NA	NA	-
Celery	NA	NA	-
Tomatoe	NA	NA	-
Prick to prick			
Fresh shrimp	-	NA	NA
Pizza	-	NA	NA
Fresh noodles	-	NA	NA
Total IgE	571	804	4032
(IU/ml)			
sIgE			
(IU/ml)			

Milk	NA	< 53.0	NA
Cashew	NA	< 53.0	NA
Pistacchio	NA	< 53.0	NA
Walnut	NA	< 53.0	NA
Pecan	NA	< 53.0	NA
Hazelnut	NA	< 53.0	NA
Peanut	NA	NA	0.33
Shrimp	< 01.0	NA	NA
ωνιδαιλγ-5-	< 01.0	NA	0.33
Alpha gal	< 01.0	< 01.0	< 01.0
Oral food challenge to suspected food(s)	Negative	Negative	Negative
Exercise challenge	Negative	Negative	Negative
Tryptase	Normal baseline levels	Elevated during attacks	Elevated during attacks
cKIT mutation on peripheral blood	Negative	Negative	Negative
Bonemarrow aspirate	NA	NA	Negative
C1 inhibitor	Negative	NA	NA
Treatment	Epinephrine auto-injector PRN	H1 antihistamines Epinephrine auto-injector PRN	H1 antihistamines Epinephrine auto-injector PRN Omalizumab
Follow-up	Remission	Remission	Remission

Table 2: Patient characteristics.

Results

Diagnosis of IA

Idiopathic anaphylaxis is a diagnosis of exclusion and should be made only after extensive evaluation to exclude other potential causes of anaphylaxis and other diseases with similar manifestations. The classification of IA is based on frequency of episodes and clinical manifestations.

The majority of studies included in this review (Table 1) describe an extensive evaluation in adults and children with anaphylaxis of unknown origin including diagnostic testing

for possible triggers of IgE mediated anaphylaxis such as food, drugs and exercise 4 hours prior to reaction. In patients with an atopic history, Skin Prick Tests (SPT) to aeroallergens is usually performed. C1-inhibitor levels are measured in patients presenting with angioedema to rule out hereditary angioedema. Rare diseases such as systemic mastocytosis, carcinoid syndrome or pheochromocytoma are usually considered. The extensive diagnostic work-up makes the diagnosis of IA highly probable in those series [4,5].

In a large cases series of 335 patients, including adults and children, authors concluded that SPT for foods and laboratory testing (CBC, complement and serum chemistry) were non-contributory and should be reserved for selected patients [6].

In a case series published by Hogan et al, 8 children were evaluated for IA when no identifiable allergen was found and in the absence of other systemic disease. However, the diagnostic tests performed were not elaborated on in the manuscript [7].

In a Spanish series published in 2005, including mostly adults and a small proportion of children (mean age 30.0 ± 17.3 years, age range 5-73 years), all patients had an extensive evaluation as previously described as well as excluding insect bites, latex and other rare causes such as anaphylaxis attributed to Anisakis simplex or rupture of hydatid cyst. Psychiatric disorders were ruled out as well as other known mimickers such as systemic mastocytosis and pheochromocytoma [8].

In a large retrospective review of 601 cases of anaphylaxis of unknown origin with a majority of adult patients, an identifiable trigger was found in 41% of cases including food, drugs and exercise. IA accounted for 59% of cases and 3 patients (0.005%) were diagnosed with systemic mastocytosis in contrast to previously mentioned studies in which no systemic diseases were found [4]. More recently, 3 case reports of IA were published in which all 3 patients had a thorough investigation as previously described [5].

The authors suggest that rare disorders that may mimic IA include delayed anaphylaxis to red meat. In contrast with immediate food-mediated anaphylaxis, symptoms may occur more than 2 hours after exposure. Reaction to mammalian oligosaccharide α-gal in these 3 cases was excluded based on medical history (no data or signs of tick bites, and no symptoms related to ingestion of mammalian products). Interestingly all 3 patients were found to have a positive Autologous Serum Tests (ASST), but a histamine release test was negative and the presence of circulating auto-antibodies against IgE and FcεRIα could not be confirmed.

In addition they determined the activity of histamine-inactivating enzyme (DAO) which was very low in all three patients, indicating low histamine intolerance. Histamine intolerance describes a state with decreased ability to catabolize endogenous or exogenously administered histamine, leading to histamine-mediated adverse reactions. Diagnosis is based on careful clinical history and identification of intestinal or serum activities of DAO and histamine N-methyl transferase. However, there are

no large scale studies published, establishing the sensitivity and specificity of these tests [5]

Management

Classification of the disease is necessary to determine the appropriate treatment course for IA. Frequent episodes are defined as at least 2 episodes in the preceding 2 months or at least 6 episodes in the preceding year [9].

All the studies included in this review recommend a treatment for patients with frequent episodes with continuous prednisone at a dose of 40-60 mg, antihistamine (e.g. Hydroxyzine 25-50 mg or Cetirizine 10 mg) and sympathomimetics (e.g. Albuterol) with gradual taper [4-8,10]. Patients with infrequent episodes are treated when episodes occur with epinephrine, antihistamines and oral steroids.

The same treatment regimens have been recommended for children with pediatric dose adjustments [7,10]

The authors in published studies suggest that the current treatment regimens are successful in controlling the disease and induce remission in the majority of patients, although no large-scale studies have been conducted to assess the adequacy of control. The proposed regimens of prophylaxis are based on previous clinical experience in the treatment of reactions to radio-contrast media, which represent nonspecific, non-immunologic mast cell activation.

Given ethical considerations in withholding treatment in patients presenting with anaphylaxis, placebo-controlled trials are lacking to support this evidence. Further, patients requiring long-term prophylactic treatment with prednisone are at risk for side effects. Alternative prophylactic management strategies are limited. A few reports suggest that Ketotifen, a mast cell stabilizer, is effective in patients with cortico-steroid dependent IA [6,10]. More recently the use of biologics was suggested to benefit patients with IA.

A first case report was published more recently describing a 12-year-old boy presenting with uncontrolled asthma, multiple food and environmental allergies, recurrent episodes of anaphylaxis of unknown origin and elevated IgE. He was treated with Omalizumab at a dose of 375 mcg every 2 weeks for 10 months with a rapid resolution of acute episodes and asthma exacerbations [11]. Three recent case reports reveal that a histamine free diet is not beneficial in cases of IA. Symptoms did not seem to improve upon histamine-free diet alone, in any of the patients studied. However, after introducing daily antihistamines symptoms improved in all patients. One of the three patients presented with frequent episodes of IA. A treatment with continuous prednisone was recommended which the parents refused given the increased risk of side effects. She started a treatment with daily antihistamines, after which her symptoms improved and she went in to remission [5].

Discussion

Although IA accounts for only 10 % of anaphylaxis cases

in children, it represents a major diagnostic and management challenge given the lack of confirmatory tests inability to avoid potential triggers. Based on the existing literature, a diagnosis and management algorithm specifically targeting pediatric cases of IA is required. Based on current literature we suggest considering the following diagnostic tests when evaluating a patient with possible IA:

A thorough clinical history and physical exam should be performed followed by laboratory investigations. Immediate skin testing and/or in vitro tests for specific IgE to potentially relevant drugs or foods may help to confirm or exclude food or drug allergy as a possible trigger including sIgE to ω -5 gliadin and alpha-gal in the case of a suggestive history.

Delayed anaphylaxis to red meat is a rare disorder that may mimic IA. It should be suspected as a culprit in any case of anaphylaxis of an unknown origin, especially in events occurring 3 to 6 hours after eating, particularly when reactions start in the early morning hours. Our 3 patients had negative sIgE to the relevant oligosaccharide galactose- α -1,3-galactose. Other potential causes that should be considered are exercise and food-dependent exercise-induced anaphylaxis.

Exercise and/or food-dependent exercise challenges should thus be considered in the case of a suggestive history.

Other disorders that may mimic IA are systemic mastocytosis, monoclonal mast cell activation syndrome and mast cell activation syndrome.

Elevated serum tryptase levels during attacks are suggestive for IA and patients with elevated levels both at baseline and during attacks should be evaluated with a bone marrow biopsy to rule out mastocytosis or other clonal mast cell disorders.

Given studies supporting the comparison of serum tryptase levels at baseline and during reaction to confirm the presence of anaphylaxis [12], patients with IA should have tryptase levels done at these two time points. All 3 of our patients had a normal baseline tryptase and a negative cKit 816 mutation analysis on peripheral blood. Our third patient who presented with generalized frequent episodes of IA had a normal bone marrow biopsy.

Pheochromocytoma and carcinoid syndrome are rare disorders in which patients may present with symptoms similar to anaphylaxis, such as flushing induced by release of vasoactive substances (vanillylmandelic acid or VMA in pheochromocytoma and 5-hydroxyindoleacetic acid or 5HIAA in carcinoid syndrome). Detection of these mediators in 24-hour urine may help exclude or confirm the diagnosis in patients with a suggestive history. Our third patient had a normal abdominal ultrasound as well as a normal 24 urine for 5HIAA and VMA and hence repeated tests are required if symptoms persist and suspicion is high.

Hereditary angioedema may mimic IA presenting with recurrent episodes of angioedema as principal symptom. Laboratory findings should include serum levels of C4 and C1 inhibitor in selected patients. More recently, 3 previously described case

reports with IA were reported with positive autologous serum skin testing suggestive of mast-cell activating auto-antibodies against IgE or IgE receptor. However, the basophil histamine-release assay was negative in all 3 patients and specific auto antibodies could not be demonstrated, suggestive of a different possible cause of auto-reactivity.

More interestingly, decreased DAO levels, indicative of histamine intolerance were demonstrated in all 3 patients [5]. Whether these findings are coincidental or play a role in the underlying pathogenesis of IA remains to be further evaluated. Given the small number of patients, it would be interesting to confirm these findings in larger studies and to look at ASST and DAO levels in patients presenting with IA. (Table 3) summarizes diagnostic testing to consider in patients with possible IA.

Diagnostic test	Comment
Skin prick test and/or sIgE for food, intradermal test for insect stings or drug	Based on suggestive clinical history, to confirm or exclude other causes of IgE mediated anaphylaxis
sIgE for alpha-gal	When suggestive history to confirm or exclude alpha-gal allergy
Exercise challenge	When suggestive history, to confirm or exclude exercise-induced anaphylaxis
Oral food challenge plus exercise challenge	When suggestive history, to confirm or exclude food-dependent exercise-induced anaphylaxis
Serum tryptase	At baseline and during reaction; suggestive for IA when elevated during reaction; suggestive of mastocytosis when elevated at baseline and during reaction
Bone marrow biopsy	To exclude or confirm systemic mastocytosis
cKIT 816 mutation on peripheral blood	To exclude or confirm systemic mastocytosis
24 h - urine for VMA/5HIAA	To exclude or confirm pheochromocytoma/carcinoid syndrome
Abdominal ultrasound	To exclude or confirm pheochromocytoma/carcinoid syndrome
Complement levels	To confirm or exclude hereditary angioedema when suggestive history
C1 inhibitor levels +/- function	To confirm or exclude hereditary angioedema when suggestive history
Autologous serum skin test (ASST) and diamine oxidase (DAO) levels	To be considered

Table 3: Diagnostic tests to consider in a patient with possible IA.

The current proposed treatment regimens are based on small studies from long ago, and daily treatment with systemic steroids in children is associated with an increased risk of long-term side effects. As the risks of systemic steroids often outweigh the benefits

in children, we do not recommend systemic steroids for treatment of IA in children. Based on recently published case reports and our own clinical experience, we would suggest the following algorithm for the management of pediatric IA:

All patients should be instructed on the management of acute episodes and should be prescribed an epinephrine auto-injector. In patients with frequent episodes, daily H1-antihistamines at regular doses should be prescribed and the patient should have close clinical follow-up. If no improvement after 1 month the physician should consider increasing the daily dose to 2 times and up to 4 times the regular dose.

If no improvement upon increased daily anti-histamines after 1 or 2 months, treatment with Omalizumab should be considered. Omalizumab is a 95% humanized monoclonal antibody that recognizes and binds to the FC portion of IgE. Allergen specific IgE plays a central role in IgE mediated anaphylaxis. Cross-linking of receptor bound IgE on mast cells and basophils by allergens leads to activation of those cells and subsequent release of inflammatory mediators causing anaphylaxis. The exact mechanism in IA remains unknown but it has been postulated that the high affinity IgE receptors may be cross-linked by autoimmune mechanisms.

Omalizumab may prevent IgE expression on effectors cells and subsequent cross-linking of IgE. It has been a successful treatment in other IgE-mediated conditions such as asthma and chronic urticaria. Here we report a second case of pediatric IA successfully treated with Omalizumab. Although we could argue that time could have played a role in achieving remission, the rapid and significant improvement supports the positive therapeutic effect of Omalizumab.

Conclusion

In conclusion few studies have evaluated diagnosis and management of pediatric idiopathic anaphylaxis. Future studies are needed to optimize treatment regimens for IA in children, who are particularly at risk for potential side effects of oral steroids.

Omalizumab maybe a therapeutic option for pediatric IA as a novel approach to treatment. Based on our clinical experience we would recommend treatment of acute attacks with epinephrine for patient with infrequent episodes and a stepwise approach for patients using a potential algorithm we have constructed for the diagnosis and management of IA. The usefulness and accuracy of these algorithms should be assessed in future large-scale studies.

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Citation: Scheyver SD, SK, Ben-Shoshan M, Chan ES (2017) Pediatric idiopathic anaphylaxis: 3 case reports and a systematic review of literature. *Int J Allergy Asthma: IJAA-102*.

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