

Pediatric idiopathic anaphylaxis: Experience with 22 patients

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Idiopathic anaphylaxis in the pediatric population is being increasingly recognized, with symptoms (and therefore classifications) the same as those described in adults. We present a series of 22 patients with special attention to considerations relatively unique to the pediatric population. Prednisone, hydroxyzine, and albuterol were used to control symptoms and induce remission. No deaths occurred during treatment. One adolescent who presented with corticosteroid-dependent idiopathic anaphylaxis was diagnosed with undifferentiated somatoform-idiopathic anaphylaxis. Local physician reluctance to participate in management complicated care for some patients. (*J Allergy Clin Immunol* 1997;100:320-6.)

Key words: Anaphylaxis, idiopathic anaphylaxis, pediatric, airway obstruction, urticaria, angioedema

Idiopathic anaphylaxis (IA) is a well-described syndrome of anaphylaxis with no recognized external stimulus.¹⁻⁴ First reported in 1978,¹ this condition is estimated to affect 30,000 people in the United States alone⁵ and is recognized internationally.⁶⁻⁸ Although initially described in adults,¹ it has subsequently been reported in pediatric populations.⁹⁻¹¹ We extend our findings in pediatric patients with IA, adding 9 new patients for a total of 22.

METHODS

Twenty-one patients were evaluated and treated by faculty and fellows of the Division of Allergy-Immunology at Northwestern University. One patient was diagnosed and managed at the Medical College of Wisconsin. Twelve of these patients have been reported previously.⁹⁻¹¹

All patients underwent a thorough history and physical examination directed at identifying a precipitating allergen or inciting event. Emphasis was placed on food ingestion, medications, and exercise. The foods and additives ingested in the 4 hours preceding an anaphylactic episode were assessed as

Abbreviations used

IA:	Idiopathic anaphylaxis
CSD-IA:	Corticosteroid-dependent idiopathic anaphylaxis
MIA:	Malignant idiopathic anaphylaxis
US-IA:	Undifferentiated somatoform-idiopathic anaphylaxis

possible causes of acute episodes. Rare diseases such as pheochromocytoma and mastocytosis were considered. Aeroallergen skin testing was performed on patients with atopic histories. Food skin testing was performed on patients whose histories were suggestive of food-induced anaphylaxis. Exceptions included patients who were referred after having received skin testing. Patients whose histories and symptoms were suggestive of hereditary angioedema had complement levels evaluated. Because of the life-threatening nature of IA and its proven response to treatment,¹¹⁻¹³ no attempt was made to study the natural history of this disease without pharmacotherapy.

TREATMENT AND STATUS OF PATIENTS

Data from these 22 patients diagnosed with IA and classified as previously described¹² are presented in Table I. For a patient to be diagnosed with IA, no cause was identified at the initial visit or at subsequent visits. Patients were treated with prednisone, albuterol, and hydroxyzine per the protocol previously reported¹⁴ (Table II). Three patients (Table III, Nos. 12, 16, 22) received ketotifen because of difficulty in tapering the prednisone. Ketotifen has been shown to decrease prednisone requirements in corticosteroid-dependent IA (CSD-IA).^{15, 16} Four patients (Table III, Nos. 6, 9, 13, 14) presented with throat angioedema as the predominant or only symptom. The condition was treated with inhaled beclomethasone dipropionate in addition to the described protocol. This treatment was added to address a possible local antiinflammatory effect and appears to be successful (three cases reported separately¹⁷). Personal use epinephrine (0.15 ml of 1:1000) was available for emergency intramuscular administration. The patients, their ages, presenting symptoms, classifications, and current status are outlined in Table III. Special problems are noted in Table IV.

DISCUSSION

Pediatric IA is being seen with increasing frequency by our service. The reasons for this are unclear and likely

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TABLE I. Classification of idiopathic anaphylaxis

Classification	Description
Idiopathic anaphylaxis-generalized-infrequent (IA-G-I; <i>n</i> = 7)	Urticaria or angioedema with bronchospasm, hypotension, syncope, or gastrointestinal symptoms with or without upper airway compromise, with infrequent episodes (<6/yr)
Idiopathic anaphylaxis-generalized-frequent (IA-G-F; <i>n</i> = 9)	As above, with frequent episodes (≥ 6 /yr)
Idiopathic anaphylaxis-angioedema-infrequent (IA-A-I; <i>n</i> = 2)	Urticaria or angioedema with upper airway compromise such as laryngeal edema, severe pharyngeal edema, or massive tongue edema without other systemic manifestations, with infrequent episodes (<6/yr)
Idiopathic anaphylaxis-angioedema-frequent (IA-A-F; <i>n</i> = 3)	As above, with frequent episodes (≥ 6 /yr)
Idiopathic anaphylaxis-questionable (IA-Q)	Applied to a patient whose history of episodes of idiopathic anaphylaxis are inconsistent with idiopathic anaphylaxis-generalized or idiopathic anaphylaxis-angioedema, and whose diagnosis is questionable until further documentation can be achieved.
Idiopathic anaphylaxis-variant (IA-V)	Applied when symptoms and physical findings of idiopathic anaphylaxis vary from classic findings of idiopathic anaphylaxis. Idiopathic anaphylaxis-variant may subsequently be classified as idiopathic anaphylaxis-questionable, idiopathic anaphylaxis-angioedema, idiopathic anaphylaxis-generalized, undifferentiated somatoform-idiopathic anaphylaxis, or idiopathic anaphylaxis may be excluded.
Undifferentiated somatoform-idiopathic anaphylaxis (US-IA; <i>n</i> = 1)	Applied for a patient whose history mimics idiopathic anaphylaxis but lacks correlating objective physical findings, shows no response to the therapeutic regimen for idiopathic anaphylaxis, and meets the criteria for undifferentiated somatoform disorders as defined in the Diagnostic and Statistical Manual for Mental Disorders.
Malignant idiopathic anaphylaxis (MIA)	Idiopathic anaphylaxis that cannot be controlled on <30 mg of prednisone daily or <60 mg of prednisone on alternate days.
Corticosteroid-dependent idiopathic anaphylaxis (CSD-IA)	Idiopathic anaphylaxis that requires continuing prednisone for control of symptoms at doses less than that required for MIA.

multifactorial, but the increasing awareness of this condition, particularly in the pediatric population, is likely a significant factor. The symptoms of anaphylaxis are the same as in the adult population, ranging from upper airway obstruction only to severe gastrointestinal symptoms and shock. The classifications based on symptoms and frequency of episodes, initially described in the adult population,¹² are used in this population and the same algorithm¹⁴ for treatment is applied. Prednisone, hydroxyzine, and albuterol are given to control symptoms in patients with frequent episodes and in those with severe reactions but infrequent episodes, with the expectation of inducing a remission. Emergency treatment is the same for any classification of IA.

This medical regimen was derived initially from our experience in the treatment of anaphylaxis secondary to radiocontrast media administration.¹⁸ It has been shown to be successful in treating IA in both adults and children as well as in inducing a remission of the disease.^{13, 16} (Remission is defined as control of symptoms for 1 year after discontinuation of prednisone.)

The mechanisms involved in the pathogenesis of IA

are not clear. Several mechanisms have been proposed, including: (1) dysregulation of cytokines, (2) uncontrolled activation of inflammatory cells with resultant mediator release, (3) uncontrolled increase of bioactive mediators, (4) autoimmune activation of mast cells, and (5) dysregulation of histamine releasing factor. Very limited evidence for these mechanisms has been presented.¹⁹ Elevated urine histamine levels and elevated serum tryptase levels have been shown during acute episodes in patients with IA.^{4, 20} However, plasma histamine levels have been noted to be normal during asymptomatic periods.²¹ Although evidence suggests histamine release as a cause for the symptoms, studies have shown that patients with IA are not more sensitive to histamine than control subjects, nor is their dermal response to the nonspecific mast cell release by morphine sulfate any different.²² Recently, increased B cell activation has been described.²³ Continued observation and investigations are needed.

As a condition, pediatric IA appears to be similar to that seen in adults. However, some medical and psychosocial problems unique to the pediatric population were

TABLE II. Treatment regimens for idiopathic anaphylaxis

Disease	Symptoms	Treatment
Frequent episodes		
Idiopathic anaphylaxis-generalized-frequent (IA-G-F)	Urticaria, angioedema, hypotension, syncope, gastrointestinal symptoms, with or without airway compromise, in any combination. Episodes occur ≥ 6 /yr.	Acute: Epinephrine*, prednisone, hydroxyzine, go to emergency room. Subsequent management: Prednisone, 1-2 mg/kg orally, daily for 1 week or until signs and symptoms are controlled, then convert to alternate-day prednisone, 1-2 mg/kg, with cautious tapering by no more than 5-10 mg per month. Continuous antihistamine (e.g., hydroxyzine HCL, 25-50 mg three times daily). Continuous sympathomimetic agents (e.g., albuterol, 2 mg three times daily). Dosages must be adjusted for children.
Idiopathic anaphylaxis-angioedema-frequent (IA-A-F)	Angioedema with laryngeal, tongue, and pharyngeal involvement and airway compromise. Episodes occur ≥ 6 /yr.	Same as IA-G-F
Infrequent episodes		
Idiopathic anaphylaxis-generalized infrequent (IA-G-I)	Same symptoms as IA-G-F but occur < 6 /yr.	Acute treatment: Same as outlined for IA-G-F. For patients with very severe infrequent episodes, the subsequent management can be the same as for IA-G-F, otherwise acute treatment only.
Idiopathic anaphylaxis-angioedema-infrequent (IA-A-I)	Same symptoms as IA-A-F but occur < 6 /yr.	Same as above.

*If appropriate for body weight; Epi-Pen Jr. Auto-Injector may be appropriate in nonmedical settings or for pediatric patients (delivers 0.15 ml of 1:1000 epinephrine).

encountered by our service and deserve mention. Four patients (three published separately)¹⁷ presented with angioedema of the throat as either the only or the predominant symptom. These children were treated per the protocol but inhaled beclomethasone dipropionate was added to their regimens, with apparent success. The local antiinflammatory effect of topical inhaled steroids was proposed as helpful in decreasing upper airway inflammation. The differential diagnosis for upper airway obstruction in the pediatric groups is somewhat different from that of adults and must be considered before a diagnosis of IA can be made.

One patient's medical course was also complicated by cystic fibrosis and allergic bronchopulmonary aspergillosis (reported separately).⁹ Specific problems including psychosocial problems that interfere with the care of pediatric patients with IA are listed in Table V. Many of these were destructive to our pediatric population because of the direct and necessary involvement of the parents and because of the increasing number of long-distance referrals.

One patient was classified as having corticosteroid-dependent IA (CSD-IA) requiring alternate-day prednisone at doses < 30 mg to control symptoms. Ketotifen, a mast cell stabilizer used widely in Europe and Canada, was added to this patient's medical regimen and he is now in remission. Another patient had repeated anaphylactic episodes while receiving alternate-day prednisone and therefore continued to receive daily prednisone. Ketotifen was added to his regimen and tapering with

daily prednisone has been successful. He is currently taking 10 mg/day of prednisone. These steroid-sparing effects of ketotifen in the treatment of CSD-IA have previously been described.¹⁵

Symptoms in three children were unable to be controlled at a dosage of < 30 mg of prednisone on alternate days; these patients were classified as having malignant idiopathic anaphylaxis (MIA).²⁴ The treatment regimen in one patient was eventually tapered with no additional medication and the patient's disease is currently in remission. Ketotifen has been added to another child's regimen and prednisone dosing is being tapered successfully. The third patient was reclassified as having undifferentiated somatoform-IA (US-IA) when she continued to have symptoms of dyspnea, throat closure, and angioedema but no objective findings while taking high doses of prednisone. Although this adolescent initially had objective findings and responded to treatment, the ensuing loss of control of the disease was in fact due to nonorganic disease. US-IA has been described recently in adults²⁵ and should be considered when symptoms do not respond to treatment, especially if objective findings cannot be documented. A multidisciplinary approach including psychiatric or psychologic evaluation should be taken with patients with US-IA; however, great caution should be exercised as these patients may be very resistant to psychiatric referrals. All of these problems are documented in Tables III and IV. Patient No. 16 already had been under therapy by a psychologist before developing IA. Repeated episodes of dyspnea in chem-

TABLE III. Diagnosis and course of patients with idiopathic anaphylaxis

Case no.	Sex	Current age (yr)	Age at onset (yr)	Characteristics of episodes	Classification	Current status	Atopy	Additional comments*
1	M	14	9	Urticaria, angioedema, diarrhea, nausea, abdominal pain, dyspnea, hypotension	IA-G-F	In remission	Asthma	
2	M	15	10	Throat angioedema, emergency service visits required, 8 episodes in 3 months	IA-A-F	In remission	None	
3	F	9	7	Chronic urticaria, single episode of hoarseness and wheezing	Urticaria, IA-G-single episode	In remission for 2½ years	None	Lost to follow-up 4 years ago
4	F	13	9	Urticaria, hypotension, severe gastrointestinal symptoms, three episodes	IA-G-I	Last episode 2 years ago	None	Child very frightened until program initiated
5	F	24	11	Eye, tongue and throat angioedema	IA-A-I to IA-A-F†	Uncontrolled	None	Special problems; see Table IV
6	F	10	5	Angioedema with laryngeal obstruction, intermittent urticaria	IA-G-F	Was in remission; recently treated for an acute episode but then lost to follow up	Asthma, rhinitis	Special problems; see Table IV; reported separately ¹⁰
7	F	6	3	Urticaria, wheezing, severe gastrointestinal symptoms	IA-G-F	Recurring 3 months after stopping prednisone; treated again and now without prednisone 3 weeks without symptoms	None	See Table IV; youngest patient at time of onset of IA in this series
8	F	12	11	Chronic severe urticaria, episodic severe gastrointestinal symptoms and angioedema	Malignant IA-G-F to IA-G-F†	Without prednisone <1 year, no episodes	None	See Table IV
9	M	12	5	Upper airway obstruction	IA-A-I	Recurring 2 months after stopping prednisone; treated again and now taking only inhaled beclomethasone dipropionate; without prednisone 10 months, no episodes	Mild asthma	C ₁ inhibitor normal; intubated with first two episodes
10	M	13	13	Urticaria, tongue and facial angioedema, one episode of stridor and wheezing	IA-G-F	In remission	None	

TABLE III. Cont'd

Case no.	Sex	Current age (yr)	Age at onset (yr)	Characteristics of episodes	Classification	Current status	Atopy	Additional comments*
11	F	16	15	Urticaria, wheezing, shortness of breath, light-headedness, one episode of loss of consciousness	IA-G-I	Without prednisone <1 year, no episodes	Asthma, allergic rhinitis	Child intubated for 16 hours with first episode
12	F	15	15	Urticaria, angioedema, hypotension, wheezing	IA-G-I to IA-G-F to MIA†	Recurred 2 months after prednisone discontinued; reclassified as MIA; ketotifen added and prednisone tapered; patient currently without prednisone	Asthma, allergic rhinitis	Severe acne; patient depressed
13	F	15	14	Stridor, wheezing, throat tightness	IA-A-F	Lost to follow-up	None	Noncompliant
14	F	11	9	Urticaria, facial angioedema, wheezing, bronchospasm	IA-G-I	In remission	Asthma, allergic rhinitis	Intubated twice
15	M	15	10	Urticaria; throat, lip, and facial angioedema; hypotension; near syncope, syncope one episode, wheezing one episode	IA-G-F	In remission	None	Managed from a distance with local personal physician
16	F	15	14	Urticaria, throat tightness, lip angioedema	IA-G-F to MIA to US-IA†	Tapering off prednisone and ketotifen therapy	Asthma	See Table IV
17	F	19	11	Facial angioedema, throat tightness, shortness of breath, wheezing, voice change	IA-G-I	Taking hydroxyzine and albuterol; took prednisone 2 weeks for breakthrough syndromes (9/89)	Mild asthma, allergic rhinitis	Some episodes associated with eating celery or carrot followed by exercise
18	F	16	12	Shortness of breath, wheezing, urticaria, throat swelling, flushing, hypotension	IA-G-I	Taking hydroxyzine and albuterol; last episode 6/95; without prednisone since 12/93		Several episodes associated with food followed by exercise; Raynaud's syndrome
19	F	15	14	Shortness of breath, pruritis, rash, erythema, eye swelling, difficulty swallowing	IA-G-I	Without prednisone <1 year; tapering hydroxyzine and albuterol from initial therapy	Potato skin test positive, not tested for aeroallergens	Exercise-associated episodes; also potato food allergy (three of four episodes associated with french fries)
20	F	14	12	Urticaria; throat tightness; lip swelling; hands, knee, and ankle swelling; one episode of chest tightness; hoarseness; two episodes of diarrhea	IA-G-F	Taking hydroxyzine and albuterol (tapering from initial therapy)	Food panel negative	

TABLE III. Cont'd

Case no.	Sex	Current age (yr)	Age at onset (yr)	Characteristics of episodes	Classification	Current status	Atopy	Additional comments*
21	M	27	17	Hand, foot, throat, and lip angioedema; throat tightness; difficulty swallowing	CSD-IA to IA-A-I†	Hydroxyzine for lip angioedema only	Asthma, allergic rhinitis, eczema	Went into remission taking ketotifen previously; did have CSD-IA, now takes hydroxyzine only for occasional lip angioedema
22	M	16	15	Urticaria, dyspnea, syncope	IA-G-F	Tapering prednisone; currently taking ketotifen, albuterol, hydroxyzine, cimetidine, and procardia	None	

*Cases 1 through 12 were previously reported (reference 11) and cases 1 through 3 were previously reported (reference 9).

†Indicates change in classification during continued observation and management. This may be due to a change in frequency or response to therapy.

TABLE IV. Special problems of patients with pediatric IA

Case No.*	Other diseases	Severity of IA	Behavioral concerns
5	None	Corticosteroid-dependent IA; requires prednisone at dose of 10 mg on alternate days	For more than 12 years has been only intermittently compliant; stops medication, changes physicians
6	Cystic fibrosis, ABPA-CB-Stage II	IA rapidly controlled but exacerbations of asthma, ABPA, and respiratory infections complicate management	Patient and mother concerned about possible recurrences of airway obstruction (previously published ¹⁰)
7	None	IA rapidly controlled with IA protocol but difficulty with completing prednisone taper; recurrence of symptoms 3 months after prednisone was discontinued; treated again per the initial protocol. Without prednisone for 2 weeks without symptoms	With initial prednisone dose of 20 mg daily and then on alternate days, patient had mood changes and marked irritability; these symptoms abated on doses of prednisone <10 mg on alternate days
8	None	Required 30 mg prednisone on alternate days for control; has seen 10 physicians for opinion and management; diagnosis changed from malignant IA to IA; patient is now in remission	Use of prednisone to control IA for >1 year resulted in Cushingoid facies and weight gain that was very disturbing to child and parents; dietary control urged for weight management
12	None	Unable to taper prednisone dosage below 30 mg on alternate days; ketotifen added and prednisone successfully tapered.	
16	Attention deficit disorder	Very difficult to control; diagnosed as MIA; ketotifen added to regimen; initial improvement followed by increasing symptoms with episodes coinciding with the start of school as well as with a particular class; these episodes were without physical findings and the diagnosis was changed to US-IA	
22	None	Unable to tolerate alternate-day prednisone; ketotifen added and currently taking prednisone 10 mg/day	

ABPA-CB, Allergic bronchopulmonary aspergillosis-central bronchiectasis; CF, cystic fibrosis.

*Refers to cases listed in Table III; there were no special problems with those cases not listed in Table IV.

TABLE V. Specific problems interfering with the care of pediatric patients with IA

Parents refuse to follow treatment plan as outlined
Excessive number of physicians, distrust of local physicians, management by parent(s) at times instead of physicians
Local physician does not accept diagnosis and does not support IA pharmacotherapy
Local physician expresses disinterest and lack of desire to treat patient locally
Prednisonephobia: parents, local physician, or adolescent patients

istry class and dyspnea and syncope in the restroom were not accompanied by objective findings. She was reclassified as having US-IA but attacks continued.

Nonorganic disease presenting as IA in children (i.e., US-IA) must be considered as it is in adults, especially if the patient does not respond to therapy. Munchausen's by proxy, a problem relatively unique to the pediatric population, must also be considered if a patient's symptoms cannot be controlled. This could be the result of the administration of a known allergen by an adult. Munchausen's disease presenting as IA has been described in adults.²⁶

We continue to see increasing numbers of patients with IA, with a notable increase in the pediatric population in the past few years. Symptoms and classifications are the same as those seen in adults, including MIA, CSD-IA, and US-IA. Although some problems were seen as fairly unique to the pediatric population, others were similar to those in adults (i.e., compliance issues, acceptance of disease, fear of prednisone). Treatment regimens outlined for adults have been applied to children, with similar success in controlling the disease and in inducing remission in most cases.

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