

Idiopathic anaphylaxis in children

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Background: Idiopathic anaphylaxis is a disease where no identifiable antigen or disease initiates an anaphylactoid reaction. Unlike classic IgE antibody-mediated anaphylaxis, severe idiopathic anaphylaxis is treatable with corticosteroids. To date, only 22 pediatric cases from one referral center have been reported.

Objective: To describe the characteristics of children with idiopathic anaphylaxis

Methods: A retrospective review of medical records for children presenting to the pediatric allergy clinic with the diagnosis of idiopathic anaphylaxis was performed.

Results: The review identified eight children with idiopathic anaphylaxis. All eight patients had a cutaneous finding of either urticaria, angioedema, or generalized flushing. Six of the eight patients were noted to have wheezing or angioedema of the airway causing respiratory difficulties. Diarrhea was noted among six patients. Many of the children clearly had life threatening events. Response to appropriate therapy was generally good.

Conclusions: Pediatric idiopathic anaphylaxis can present at any age. It may be that many pediatric cases are assumed to be anaphylaxis due to some unknown antigen, and the correct diagnosis is never appreciated. It is important to recognize this disease in children so that it may be appropriately treated, because its specific therapeutic regimen has been shown to prevent the potentially fatal consequences of this disease.

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INTRODUCTION

Anaphylaxis is characterized by acute episodes of urticaria, angioedema, bronchospasm, diarrhea, and hypotension which are life threatening in nature. Usually there is an identifiable antigen initiating IgE antibody-mediated mast cell release of histamine and other immunologic mediators. Idiopathic anaphylaxis was first described in 1978.¹ It is a disease characterized by all of the features of anaphylaxis but without an identifiable exogenous antigen or other cause.¹ Fatalities have been reported due to idiopathic anaphylaxis.² Unlike antigen-induced anaphylaxis, idiopathic anaphylaxis is treatable with a tapering course of oral glucocorticosteroids.³

The prevalence of idiopathic anaphylaxis in the United States has been estimated to be 20,000 to 40,000 cases

across all age groups.⁴ Over 90% of the reported cases of idiopathic anaphylaxis have been in adults.⁵ To date, only 22 pediatric cases from one referral center have been reported.⁶ We describe the clinical manifestations of eight patients who presented to our Pediatric Allergy clinic with idiopathic anaphylaxis.

METHODS

The charts of eight patients evaluated and/or managed by members of the Pediatric Allergy/Immunology Division at West Virginia University were reviewed. The Pediatric Department accepts new pediatric patients who are under the age of 21. These patients presented to our service for evaluation during the time period of January 1993 through December 1997.

RESULTS

Eight patients with idiopathic anaphylaxis were evaluated by our service. In all patients, no identifiable allergen such as medications, latex, food, or

insect sting could be identified as the possible cause of the anaphylaxis episodes. In addition, no other disease state could be identified as a cause of the systemic reactions of these patients. Table 1 is a synopsis of each patient's clinical course.

The actual anaphylactic events these patients had were quite similar. All eight patients had a cutaneous finding of either urticaria, angioedema, or generalized flushing. Six of the eight patients were noted to have wheezing or angioedema of the airway causing respiratory difficulties. Diarrhea was noted among six patients.

Many of the children clearly had life threatening events. Patient 1 was treated with an inadequate amount of epinephrine (0.15 mL) and experienced a more severe biphasic event. Eight hours after treatment the patient returned to the emergency room with a blood pressure of 50/20. Patient 3 had one episode of anaphylaxis associated with loss of consciousness presumably due to vascular compromise. Patient 6 lost consciousness and had no obtainable blood pressure at the time of the arrival of an emergency medical crew. He was resuscitated with three doses of epinephrine. Patient seven was found unresponsive and was resuscitated with epinephrine and intravenous fluids on two occasions. Patient 8 had hypotension and loss of consciousness on two occasions.

Some patients had other difficulties due to their idiopathic anaphylaxis. Patient 4 was being placed in home bound schooling as school officials were afraid of their liability concerning potential exposure to an exogenous antigen. After the school nurse realized that a triggering antigen did not cause anaphylaxis in this case, patient 4 returned to public school. An emergency rescue plan was implemented.

Patient 6 developed malignant idiopathic anaphylaxis when his prednisone dose could not be lowered be-

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Table 1. Clinical Characteristics* of Children with Idiopathic Anaphylaxis

Patient	Sex	Onset Age	Current Age	Characteristics of Episodes	Classification	Current Status	Other Diseases	Additional Comments
1	F	15 yr	16 yr	Hives, wheezing, angioedema, hypotension	IA-GI	No episodes in 20 mo	Asthma	Single episode, biphasic anaphylaxis
2	M	10 yr	11 yr	Diarrhea, hives, wheezing	IA-GI	3 episodes/yr	Asthma	
3	M	9 yr	39 yr	Hives, flushing, angioedema, respiratory compromise, diarrhea, LOC	IA-GI	2 episodes/yr	Gastro-esophageal reflux	Remission from 12 years of age to 33 yr
4	F	11 mo	6 yr	Hives, angioedema, airway compromise	IA-AI	4 episodes/year at presentation; no episodes in past 2 years	None	Youngest reported patient at time of onset, biphasic anaphylaxis
5	F	13 yr	14 yr	Hives, diarrhea	IA-GI	3 episodes at presentation; local pediatrician assumed care	Allergic rhinitis, nasal polyposis	No CF, no NSAID hypersensitivity
6	M	19 yr	20 yr	Hives, bloody diarrhea, wheezing, LOC	IA-GF to Malignant IA-GF to IA-GI	Off oral steroids for 6 mo.	Asthma, allergic rhinitis, hemophilia A	Five episodes associated with documented sinusitis. Requires factor VIII after epi-pen use.
7	M	11 mo	17 mo	Irritable, flushing, diarrhea, vomiting, LOC	IA-GI	4 episodes/yr	Zinc deficiency	Youngest reported patient at time of onset, supplemented zinc levels normal
8	M	12 yr	17 yr	Wheezing, LOC, diarrhea, angioedema, hypotension	IA-GI	1 episode/yr	None	Elevated tryptase during episode, lost to follow-up

* LOC, loss of consciousness; IA-GI, idiopathic anaphylaxis generalized infrequent; IA-AI, idiopathic anaphylaxis angioedema infrequent; and IA-GF, idiopathic anaphylaxis generalized frequent.

low 60 mg alternate day. The parents refused to initiate ketotifen in an attempt to lower the maintenance prednisone dose. Shortly afterwards, a chart review revealed that five of the six anaphylactic episodes after his original diagnosis were associated with documented infections on sinus radiographs or observable pus after dental extraction. His infections were treated. He has been off oral steroids for 6 months without recurrence of his anaphylactic episodes.

Patient 6 had initial difficulties complying with the emergency rescue plan and pharmacologic plan of oral steroids. In spite of having a previous anaphylactic episode at which no blood pressure was recorded. One subsequent episode of anaphylaxis was treated in the emergency room because the patient could not self-treat himself with an epi-pen at the time of the episode. A serious talk with the family while the patient was in the emergency room temporarily corrected the pa-

tient's lack of compliance with the emergency and treatment plans. The patient once again was non-compliant with therapy after leaving for college. The patient's girlfriend had to be recruited by the family to assist in monitoring compliance while away from home.

The parents of patient 8 refused to believe that no antigen or disease process was responsible for the anaphylactic episodes. Extensive education by both the managing allergist and pedia-

trician failed to reassure the parents. The patient has been subsequently lost to follow-up.

DISCUSSION

The diagnosis of idiopathic anaphylaxis is a diagnosis of exclusion. A careful history is taken to identify antigens such as foods, insect stings, latex, ingestion of medications including non-steroidal anti-inflammatory agents, and triggers such as exercise. In addition, rare diseases such as hereditary angioedema or mastocytosis should be considered in the differential diagnosis. Idiopathic anaphylaxis is responsive to oral steroid therapy unlike anaphylaxis induced by an antigen.^{2,7} It has been hypothesized that this disease is a result of either an inability to appropriately control histamine release at a cellular level⁸ or secondary to T lymphocyte activation.⁹

Classification of the disease is necessary to determine the appropriate treatment course. If episodes occur at a rate of every 2 months or more the label of "frequent" is added to the classification. These patients are started on hydroxyzine, albuterol, and oral prednisone with a gradual taper. Failure of the disease to respond to steroids is strong evidence that the diagnosis of idiopathic anaphylaxis is incorrect.⁷ Patients with infrequent episodes (less than six per year) are treated at each episode with epinephrine, hydroxyzine, and systemic steroids and then sent to the emergency department.

Pediatric idiopathic anaphylaxis can present at any age. Two patients presented with their first anaphylactic episode at 11 months of age. The youngest child previously reported with idiopathic anaphylaxis was 3 years of age at presentation.⁶ The majority,

however, of pediatric patients in the series reported by Patterson et al⁶ and our series appear to be over 10 years old at the time of their first anaphylactic episode.

In addition, it appears that the disease process may fluctuate as these patients get older. In the one previously reported adult patient whose disease presented during childhood, the patient's disease at onset was characterized as idiopathic anaphylaxis angioedema infrequent.⁶ The classification was subsequently changed as episodes began to occur more than every 2 months. In our adult patient, the anaphylactic episodes occurred infrequently from the age of 9 to the age of 12. He then experienced a remission of 21 years before symptoms began to recur. It appears prudent to inform these pediatric patients and their parents that this disease may wax and wane over time, but there is no guarantee that the disease will be "outgrown."

As there have been only 22 reported pediatric idiopathic anaphylaxis cases in the literature, it's presumed to be a rare condition. Our experience suggests there may be many more unrecognized cases. We report that pediatric idiopathic anaphylaxis also occurs at institutions that are not referral centers for idiopathic anaphylaxis. It may be that many of these cases of pediatric idiopathic anaphylaxis are assumed to be anaphylaxis due to an unknown antigen, and the correct diagnosis is never appreciated. Although this disease is lifethreatening, a specific therapeutic regimen exists to prevent the potentially fatal consequences of this disease. It is therefore important to identify the disease so that it may be appropriately treated.

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