Idiopathic Anaphylaxis

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Idiopathic anaphylaxis is a perplexing problem that accounts for approximately 30% to 60% of cases of anaphylaxis in ambulatory adults and perhaps 10% of cases in children. Advances in our knowledge of idiopathic anaphylaxis have occurred over the past decade with the elucidation of mast cell activating disorders and the discovery of episodes of anaphylaxis caused by galactose-alpha-1,3-galactose. Most patients do well because fatalities can usually be prevented with proper therapy, and many individuals, for reasons not understood, undergo spontaneous remission. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:243-50)

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The first report of patients with multiple episodes of anaphylaxis without discernible cause was published in 1978.[1] The investigation originated at the Northwestern University Medical School, Division of Allergy-Immunology, under the direction of the late Roy Patterson, MD. Many of the subsequent reports that deal with this disorder have come from the same institution. Since the original article, there have been a total of 102 published articles that deal directly with this condition or that indirectly clarify its diagnosis, natural history, and treatment.[2-92] The diagnosis of idiopathic anaphylaxis is one of exclusion. Patients with idiopathic anaphylaxis also may have experienced anaphylaxis from recognizable causes such as foods (5%)[17] or exercise (11%).[17] Pre-existing urticaria and/or angioedema had occurred in 23% of the Northwestern series of 335 patients with idiopathic anaphylaxis, and, during episodes, all the patients had either urticaria, angioedema, or both.[17] The typical attack began suddenly and reached a peak over minutes to a few hours. But a few patients reported urticaria for 3 days before anaphylaxis occurred.[7] Furthermore, from the series of 335 patients, 15 patients (4.5%) had known reactivity to nonselective nonsteroidal anti-inflammatory agents, and 65 (19%) reported penicillin allergy.[17] But, episodes of idiopathic anaphylaxis were distinct and not explained by such exposures or alternative diagnoses.[7] These findings imply that the physician may need to reassess the working diagnosis of idiopathic anaphylaxis.

It was noted early on that the manifestations of idiopathic anaphylaxis are identical to those that occur during episodes with known cause.[4-6] As more patients were reported, other key features were discovered. Many patients had severe life-threatening events,[9,10] and fatalities occurred.[18] Patients with idiopathic anaphylaxis were found to have a high incidence of atopy, as high as 58% in 1 series,[32] and there was a significantly higher incidence in women, than in men,[26,32] after puberty and until menarche at which time the incidence became equal. For many years, reports of idiopathic anaphylaxis were limited to the United States. However, beginning in the 1990s, reports began to appear from other countries, including Spain,[29] France,[31,32] Ireland,[33] Germany,[34] and Brazil.[35]

INCIDENCE

The exact incidence of idiopathic anaphylaxis is unknown. In 1995, Patterson et al[16] estimated the incidence in the United States (population 263,000,000) to be between 20,592 and 47,024 cases based on a survey of allergists and extrapolation to 4,000 allergists in the United States. At that time, the current total number of identified cases of idiopathic anaphylaxis by allergists in the United States was 1020. Thus, it was assumed that the majority of cases went unreported.

An insight into the incidence can be obtained by ascertaining the percentage of cases of patients who presented with anaphylaxis to an allergist-immunologist and remain idiopathic after an extensive evaluation to determine the cause. In a population skewed to adults, approximately one-third[11] to two-thirds[26] of episodes have no known cause. It should be noted that in the study that shows a two-thirds incidence, episodes due to allergen immunotherapy and insect stings were excluded.[26] This exclusion would tend to produce a higher incidence than if these causes were included in the series. In children, the incidence of idiopathic anaphylaxis is much lower, but episodes in children have been reported.[21,22,45] Regardless of the overall incidence, in any given patient, idiopathic anaphylaxis can have a profound effect on quality of life because there is no known way for a patient to avoid a potential trigger.

THEORIES OF PATHOGENESIS

Serum tryptase is elevated acutely but is usually normal, <11.4 ng/mL, at baseline. Similarly, urine histamine or its

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TABLE I. Theories offered to explain episodes of idiopathic anaphylaxis

Hidden allergen
Aberrant cytokine profile lowering the threshold for mast cell degranulation
Female hormone effect on mast cells and/or basophils
An alteration in the T-cell population
Increased sensitivity to histamine at the target organ site
Presence of serum histamine releasing factor
Presence of IgE autoantibodies

metabolite can be elevated acutely. Several attempts have been made to discern the underlying cause of mast cell activation. Theories that resulted from these attempts are summarized in Table I. Perhaps the earliest hypothesis as to the origin of idiopathic anaphylaxis was the postulation that episodes were really antigen and/or allergen related, with failure to detect the culprit. Such a "hidden allergen" might exist as a food additive because there was no test to detect the presence of specific IgE to such ingredients. Investigators pursued this hypothesis by performing oral challenge tests with food additives in a blinded manner. They found that food additives, for example, potassium metabisulfite, failed to trigger episodes with patients in whom they were suspected to be responsible.[56] In addition, studies carried out to identify reproducible reactions to monosodium glutamate[87] and aspartame[88] could not confirm reactions even if people were emphatic about the connection. Alternatively, 2 health care workers were referred with a provisional diagnosis of idiopathic anaphylaxis and were found to have latex allergy such that avoidance of latex was associated with no additional episodes of anaphylaxis.[93]

Extensive food testing has been shown to uncover the culprit in some cases of anaphylaxis previously diagnosed as or suspected to be idiopathic.[37] In a study of 102 patients initially diagnosed as having experienced episodes of idiopathic anaphylaxis, a battery of 79 food-antigen skin prick tests were selected to include foods reported or suspected of provoking episodes. Previously, a detailed history, results of a physical examination, and results of conventional laboratory tests had ruled out all known causes of anaphylaxis. Thirty-two patients (31%) had positive tests to one or more food antigens. With 5 of these patients, subsequently eating a food that elicited a positive test provoked an anaphylactic event. Two patients who eliminated the foods completely stopped having reactions. The researchers concluded that a battery of selective food-antigen skin prick tests can provide a useful method for identifying an offending allergen. In their series, this occurred in 7% of individuals evaluated.[37]

The possibility that enhanced mast cell "releasability" due to the extracellular cytokine milieu bathing these cells might be present has also been investigated. The fact that a large number of patients with idiopathic anaphylaxis are atopic suggested that perhaps an increase in Th2 cytokines could lower the threshold dose for mast cell degranulation to exogenous stimulus. Reed et al[55] did find that patients with idiopathic anaphylaxis exhibited higher levels of Th2 cytokines (IL-4, IL-5, and IL-13) produced by lymphocyte stimulation when compared with nonatopic individuals and individuals with allergic rhinitis. In fact, even patients who were nonatopic but who had episodes of idiopathic anaphylaxis were found to have higher levels of interleukins associated with a Th2 response.

Because episodes are more common in females patients, investigators looked at whether female hormones could lower mast cell and basophil degranulation thresholds. Results of these studies have been inconclusive.[57] Two of 4 women were reported to have developed remission of anaphylaxis when treated with a luteinizing hormone-releasing hormone agonist, and the responders had experienced anaphylaxis within 30 to 60 minutes of infusion during provocation testing.[59] These patients should not be labeled as having idiopathic anaphylaxis because another explanation was identified. Grammer et al[61] found that patients with idiopathic anaphylaxis exhibited the presence of activated T cells. They found that, when comparing patients with acute idiopathic anaphylaxis with those in remission, those experiencing episodes had a higher percentage of $CD3^+HLA^-DR^+$ cells. They also noted that patients who experienced episodes while on prednisone as well as patients who were in remission had a significantly higher percentage of activated B cells ($CD19^+CD23^+$) than did normal volunteers, but it was unclear as to whether these findings were a result of events or were part of the underlying pathology.[61]

Investigators tested whether idiopathic anaphylaxis might be from increased target organ sensitivity and reported that some patients with idiopathic anaphylaxis had increased sensitivity to the injection of histamine.[62] In contrast, there was no evidence for cutaneous hypersensitivity (threshold reactive concentration for a reproducible 5-mm wheal and/or erythema from histamine, leukotriene D4, and platelet activating factor) in idiopathic anaphylaxis compared with patients with chronic idiopathic urticaria[89] and actually less reactivity than for patients with allergic rhinitis or asthma.[90] These data are consistent with receptor downregulation from mediator release. In addition, it remains to be established whether patients with idiopathic anaphylaxis have impaired inactivation of platelet activating factor by platelet activating factor acetyl hydrolase as has been described in severe or fatal anaphylaxis from peanuts[94] and in survivors of anaphylaxis, including 5 patients with idiopathic anaphylaxis.[95] Histamine releasing factors have been found in patients with idiopathic anaphylaxis.[63] Finally, autoantibodies to the IgE receptor also have been noted.[28] But it is unclear as to whether these antibodies are active in producing the degranulation of mast cells.

The number of mast cells/mm^2 in biopsy specimens of skin has been reported as follows: normal, 38 cells/mm^2; idiopathic anaphylaxis or unexplained flushing, 72 cells/mm^2; urticaria pigmentosa or indolent systemic mastocytosis, nonlesional skin, 168 cells/mm^2; urticaria pigmentosa, lesional skin, 597 cells/mm^2; and indolent systemic mastocytosis, lesional skin, 721 cells/mm^2.[91] So, although the number of mast cells in nonlesional skin is higher than found in normal skin, it is approximately 10% of that found in lesional skin from patients with indolent systemic mastocytosis.[9] Thus, an increased mast cell burden does not appear to play a role, at least in the majority of patients.

When considering theories of pathogenesis, it is important to note that empiric treatment with prednisone has proved effective in reducing the number and severity of episodes of idiopathic anaphylaxis, consistent with a steroid-responsive condition.[8,17,68,72,75] The positive findings were of patients classified as having frequent episodes, which means 6 or more per year or 2 episodes in 2 months.[72] The decision to administer prednisone was made because empiric treatment with H1- with or without