

Idiopathic Anaphylaxis

The Evolution of a Disease

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Introduction

The first report of idiopathic anaphylaxis (IA) was published in 1978 (1). Reviewers for the journal to which the manuscript was first submitted rejected it with the recommendation that "the author find the allergen rather than using the term IA." Subsequently, IA became accepted as a disease process. IA is defined as anaphylaxis for which no antigenic or physical stimulus, such as exercise, can be found. Thus, IA is analogous to idiopathic urticaria (2), except urticaria is cutaneous and IA is potentially fatal.

The evolution of knowledge of the syndromes of IA is shown in Table 1, with appropriate references. After extensive experience with IA, publication of the first book on IA occurred (12). The topics listed in Table 1 will be reviewed in this article.

Of interest is that the individual with IA often follows an evolutionary process similar to the steps listed in Table 1. In other words, there is progression from recognition, to classification, to initiation of therapy, and to control of IA by the therapy. Since the description of IA was not accepted by some physicians initially and at present, the diagnosis of IA may not be accepted by the individual patient or the referring physician. After acceptance of the diagnosis and initiation of therapy, the patient may go into remission, may become corticosteroid-dependent, or a fatality may occur. Finally, it may become obvious that the patient believed to have IA has no organic disease and is thus reclassified as having undifferentiated somatiform IA (USIA) (10).

Table 1
Evolutionary Stages in IA

Discovery (1)
Classification (3)
Development of therapy (4)
Demonstration of effectiveness of therapy (5)
Acceptance or denial
Remission (6)
Corticosteroid-dependency (6)
Death (7)
Malignancy (8)
Responsiveness to therapy
Nonresponsiveness to therapy (9)
USIA (10)
Potential mechanisms of IA (11)

Table 2
Differential Diagnosis of IA

IgE-mediated anaphylaxis
Food, venoms, medications
Exercise-induced anaphylaxis
Food- and exercise-induced anaphylaxis
Non-IgE-mediated anaphylaxis owing to medications: aspirin, other nonsteroidal anti-inflammatory drugs, radiographic contrast media, ACE inhibitors, opiates
Hereditary angioedema
Classical or acquired
Systemic mastocytosis
Munchausen's anaphylaxis
USIA
Carcinoid syndrome
Pheochromocytoma
Panic attacks

Classification of IA

As increasing numbers of patients with IA were seen it became possible to classify them as being generalized (G) with urticaria, asthma, gastrointestinal symptoms and hypertension or angioedema (A), where angioedema led to airway obstruction and possible fatality. Additionally, they could be classified as frequent (F), which was arbitrarily defined as the occurrence of more than 6 episodes/yr, and infrequent (I), which was defined as the occurrence of <6 episodes/yr. Other classifications evolved, such as single episode (SE), and unusual presentations as variant (V) or questionable (Q). The latter often were subsequently classified as psychological in nature and termed USIA (10). The differential diagnosis of IA is listed in Table 2.

Treatment of IA

Treatment regimens were based on the successful regimen used to prevent radiographic contrast medium reactions, which consisted of prednisone, an H₁ blocker, and a β -agonist (13). For emergency therapy, epinephrine (self-administered), prednisone (60 mg), and hydroxyzine (25 mg) are given and the patient must have emergency care provided. Infrequent IA uses the same emergency regimen as just described.

For frequent episodes, a regimen of daily prednisone, usually 60 mg, is started plus albutarol, 2 mg three times daily, and 25 mg hydroxyzine, three times daily. The daily prednisone is continued for 2–4 wk. No episodes of IA should occur while the patient is on daily prednisone. After 2–4 wk of daily prednisone, alternate-day prednisone at 80 mg is initiated and a reduction in the dose by 10-mg increments is attempted every 2–4 wk. At 40 mg of prednisone, the reduction can be continued at 10-mg increments or more slowly at 5-mg increments (12). After 9–12 mo of this approach, most patients are off prednisone. Thus, although the prednisone regimen is not pleasing to patients and physicians, the final outcome is usually successful, in contrast to management of severe corticosteroid-dependent asthma, where the outcome will likely be that the asthma will be just as severe 1 yr later.

Corticosteroid-Dependent IA (CSD IA)

After control of IA is achieved with prednisone and taper of prednisone is initiated, a dose of prednisone may be found where further reduction of prednisone is followed by recurrent episodes of IA. This is classified as CSD IA. Ketotifen (Zaditen), a mast cell stabilizer, has been shown to permit further reduction or termination of prednisone (6). Some patients with IA require a maintenance dose of prednisone (9). This is very troublesome to both patients and managing physicians, but, like CSD asthma, the alternative to prednisone therapy may be a fatality (7). The term malignant IA has been applied to IA patients who require very high doses, ≥ 30 mg daily or ≥ 60 mg alternate day, of prednisone for control of disease.

Undifferentiated Somatiform IA

This is a psychiatric disease where the patients report symptoms consistent with IA, but where no objective evidence is found after repeat evaluations of emergency service or hospital records (10), and pharmacotherapy has not reduced the number of episodes. These patients are often overtreated with prednisone, because the managing physician accepts the patient's reports as valid when they are not.

Psychiatric referral is often rejected by these patients who move from one physician to another.

Potential Mechanisms of IA (13)

The mechanism of IA is unknown. The following mechanisms have been suggested. Idiopathic anaphylaxis is likely owing to an immunologic mechanism because IA is responsive to prednisone (although high doses are needed in some patients). IA may be the result of an autoimmune disease. Anti-IgE antibodies have been reported in various urticarial syndromes (14), and such a stimulus could explain IA. An equally interesting postulate is that the various histamine-releasing factors that have been described (15) are released in an uncontrolled manner.

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References

1. Bacal, E., Patterson, R., and Zeiss, C. R. (1978), *Clin. Allergy* **8**, 295–304.
2. Metzger, W. J. (1997), in *Allergic Diseases*, 5th ed., Patterson, R., ed., Lippincott-Raven, Philadelphia, PA, pp. 265–283.
3. Patterson, R. and Harris, K. E. (1997), in *Idiopathic Anaphylaxis*, Patterson, R., ed., Oceanside Publications, Providence, RI, pp. 19–23.
4. Patterson, R., Stoloff, R. S., Greenberger, P. A., Grammer, L. C., and Harris, K. E. (1993), *Ann. Allergy* **71**, 40–44.
5. Wong, S., Yarnold, P. R., Yango, C., and Patterson, R. (1991), *Ann. Int. Med.* **114**, 133–136.
6. Patterson, R. and Harris, K. E. (1997), in *Idiopathic Anaphylaxis*, Patterson, R., ed. Oceanside Publications, Providence, RI, pp. 33–44.
7. Patterson, R., Clayton, D. E., Booth, B. H., Greenberger, P. A., Grammer, L. C., and Harris, K. E. (1995), *Allergy Proc.* **16**, 103–108.
8. Patterson, R., Fitzsimons, E. J., Choy, A. C., and Harris, K. E. (1997), *Ann. Allergy Asthma Immunol.* **79**, 138–144.
9. Patterson, R. (1997), in *Idiopathic Anaphylaxis*, Patterson, R., ed. Oceanside Publications, Providence, RI, pp. 65–68.
10. Choy, A. C., Patterson, R., Patterson, D. R., Grammer, L. C., Greenberger, P. A., McGrath, K. G., et al. (1995), *J. Allergy Clin. Immunol.* **96**, 893–900.
11. Grammer, L. C. (1997) in *Idiopathic Anaphylaxis*, Patterson, R., ed. Oceanside Publications, Providence, RI, pp. 59–64.
12. Patterson, R., ed. (1997), *Idiopathic Anaphylaxis*, Oceanside Publications, Providence, RI.
13. DeSwarte, R. D. and Patterson, R. (1997), in *Allergic Diseases*, 5th ed., Lippincott-Raven, Philadelphia, PA, pp. 317–412.
14. Gruber, B. L., Baeza, M. L., Marchese, M. J., Agnello, V., and Kaplan, A. P. (1988), *J. Invest. Dermatol.* **90**, 213–217.
15. Grant, J. A., Alam, R., and Lett-Brown, M. A. (1991), *J. Allergy Clin. Immunol.* **88**, 683–693.