

Undifferentiated somatoform idiopathic anaphylaxis: Nonorganic symptoms mimicking idiopathic anaphylaxis

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Background: Northwestern University's Division of Allergy and Immunology has had experience with the diagnosis and treatment of more than 350 patients with idiopathic anaphylaxis (IA). In 1992 we reported a group of patients with IA whose presentations mimicked IA, but IA and other organic causes were later excluded. Psychologic factors were suspected as the underlying problem. These patients were classified as IA-variant. Management of these cases was extremely difficult. There was significant morbidity and high and unnecessary costs.

Objective: We aim to distinguish the nature of this disease and to highlight the evaluation and treatment of this group of patients.

Methods: Their cases are reviewed and reported.

Results: Common features included (1) presenting symptoms mimicking IA, (2) no objective findings that correlated with I, (3) no response to the therapeutic regimen for IA, (4) meeting the Diagnostic and Statistical Manual of Mental Disorders criteria for undifferentiated somatoform disorder, and (5) significant wasted health care expenditure.

Conclusions: This group of patients were better defined as having undifferentiated somatoform-IA. An algorithm was proposed to expedite the diagnosis of the disease so that with early recognition of the disease, unwarranted repetitive consultations, tests, and inappropriate therapy can be avoided. (*J ALLERGY CLIN IMMUNOL* 1995;96:893-900.)

Key words: Idiopathic anaphylaxis, somatoform, prednisone

Idiopathic anaphylaxis (IA)¹ was first recognized 17 years ago and has since been well established as a clinical entity. It refers to the syndrome of idiopathic urticaria or angioedema with at least one of the following symptoms: collapse, shock,

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Abbreviations used

IA: Idiopathic anaphylaxis
NUAI: Northwestern University's Division of Allergy and Immunology
US-IA: Undifferentiated somatoform idiopathic anaphylaxis

bronchospasm, or gastrointestinal symptoms including pain and acute diarrhea such that a potentially life-threatening medical emergency occurs. The angioedema can involve the upper airway so that pharyngeal or uvular edema or acute laryngeal swelling occurs, resulting in voice change or documented vocal cord swelling. In 1993 an algorithm for the diagnosis, classification, and management of IA was published.² More than 350 patients with this diagnosis have been treated successfully by Northwestern University's Division of Allergy and

TABLE I. Classification of idiopathic anaphylaxis

Disease	Symptoms
IA-G-F	Urticaria or angioedema with bronchospasm, hypotension, syncope, or gastrointestinal symptoms with or without airway compromise with frequent episodes (≥ 6 episodes each year)
IA-A-I	Urticaria or angioedema with upper airway compromise, such as laryngeal edema, or massive tongue edema without other systemic manifestations with infrequent episodes (< 6 episodes per year)
IA-A-F	Urticaria or angioedema with upper airway compromise such as laryngeal edema, severe pharyngeal edema, or massive tongue edema without other systemic manifestations with frequent episodes (≥ 6 episodes per year)
IA-Q	This diagnosis is applied for a patient whose history of episodes of IA are inconsistent with IA-G or IA-A; diagnosis is questionable until further documentation can be achieved.
IA-V	This diagnosis is applied for a patient whose history and physical findings do not completely fit IA-G or IA-A and may later be changed to IA-G, IA-A, or IA-Q.
US-IA	This diagnosis is applied for a patient whose history mimics IA but lacks correlating objective physical findings, shows no response to the therapeutic regimen for IA, and meets the <i>DSM</i> ⁴ criteria for undifferentiated somatoform disorders.

Modified from Wong et al. Idiopathic anaphylaxis: a clinical summary of 175 patients. *Arch Intern Med* 1990;150:1324.

G-F, Generalized-frequent; A-I, angioedema-infrequent; A-F, angioedema-frequent; Q, questionable; *DSM*, *Diagnostic and Statistical Manual of Mental Disorders*.⁴

Immunology (NUAI). No fatalities caused by IA have occurred in our series.

In our initial development of the classification of IA (Table I), we used the term IA-variant (IA-V)³ to include a group of patients with histories compatible with IA but in whom the diagnosis of IA was excluded. These patients had nonorganic symptoms mimicking anaphylaxis.³ The evaluation and management of these cases may be more difficult, time-consuming, and expensive in terms of health care costs than in patients with true IA. It is important to form a diagnosis early in the patient's illness so that appropriate psychiatric management can be instituted and inappropriate therapy discontinued.

Since the publication of the study of nine patients with the classification of IA-V in 1992,³ the number of such cases referred to our program has continued to increase. We review the characteristics of the presentation of 11 additional patients, an algorithm we have successfully used to expedite the diagnosis, and the recommendations for future management.

METHODS

Patients

Ten patients were referred to NUAJ for evaluation and diagnosis of their anaphylactic symptoms. One additional patient was referred to the private office of an attending physician of NUAJ. Four of the patients also had the diagnosis of asthma, and one had the diagnosis of C1 inhibitor deficiency for 12 years. All patients were seen by one or more of the authors in an outpatient setting between 1990 and 1993.

Clinical assessment

Each patient was questioned regarding the presence of urticaria and swelling associated with potentially life-threatening symptoms such as dizziness, passing out, lower airway obstruction, upper airway obstruction leading to voice change, difficulty in breathing, abdominal cramps, diarrhea, and nausea. The onset, frequency, and duration of the episodes were noted. All trigger factors such as alcohol, food, exercise, medication, drugs, menstruation, and animals were elicited or excluded.

Each patient received a complete physical examination. If the patient's symptoms were suggestive of IA, but the diagnosis was questionable because no objective findings were documented to correlate to these symptoms, a diagnostic trial of the therapeutic regimen (prednisone, hydroxyzine, albuterol) for IA^{2,3} was initiated on the patient's agreement (Fig. 1). The regimen included a minimum of 60 mg of prednisone each morning and 25 mg of hydroxyzine and 2 mg of albuterol three times daily (or as tolerated by the patient). When IA episodes disappeared, the prednisone was converted to 60 mg every other day. The emergency regimen, which consisted of an EpiPen (Center Laboratories, Port Washington, N. Y.), 60 mg of prednisone, and 25 mg of hydroxyzine was carried by the patient at all times. The patients were given access to a 24-hour emergency service and were instructed to call the service, return to our clinic for evaluation, or go to the nearest emergency department for each episode of IA. If they visited the emergency department during an acute attack, they were instructed to ask the emergency department physician to communicate with our service. Objective findings of the patient after the physician's evaluation and response to treatment of an acute attack were ascertained. The prednisone regimen was intensified

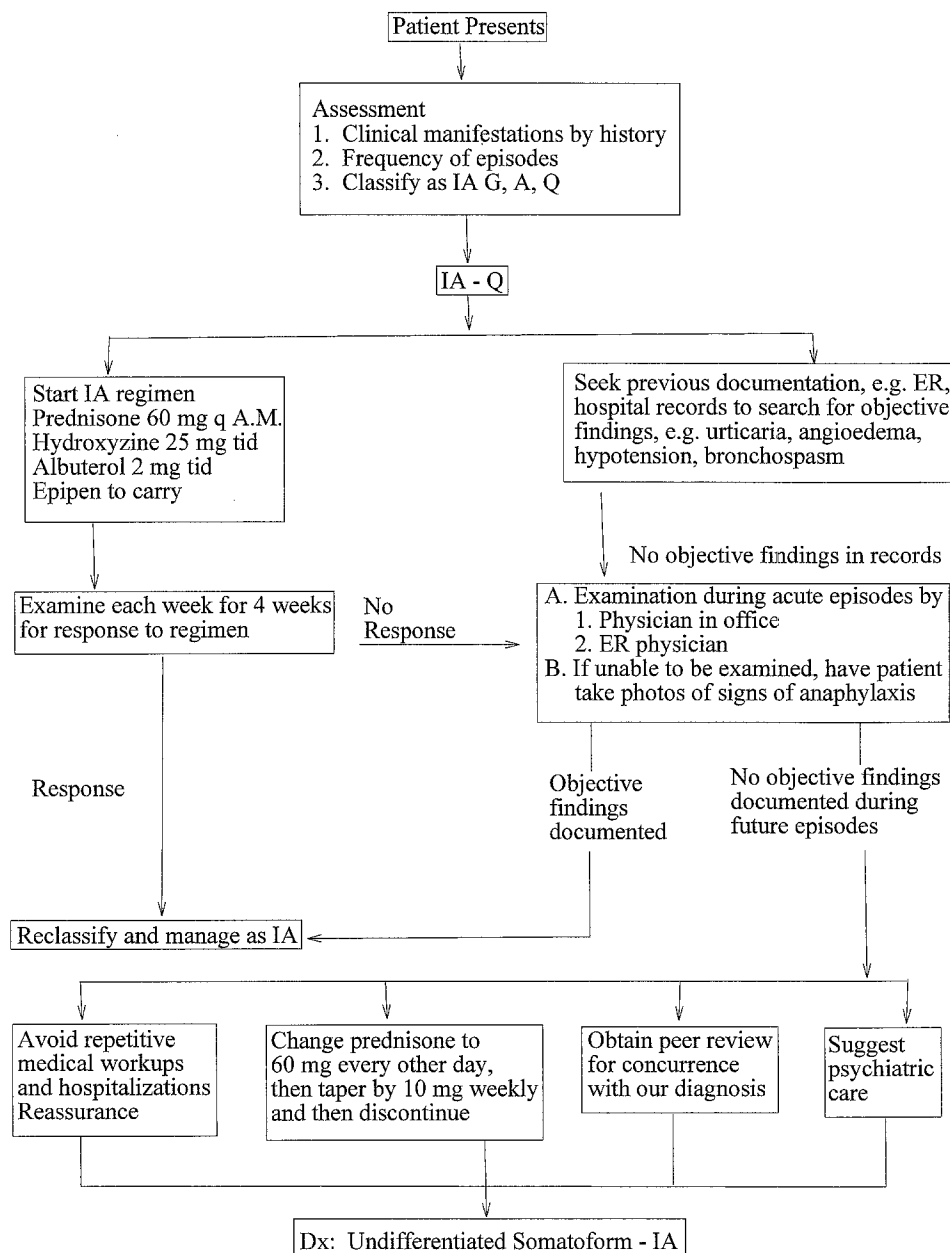


FIG. 1. Algorithm for the diagnosis of US-IA. G, Generalized; A, angioedema; Q, questionable; ER, emergency room; Dx, diagnosis.

when insufficient control of episodes of IA occurred. Usually prednisone in daily doses of 60 to 80 mg should prevent IA episodes within a week.⁵ Occasionally 2 weeks of therapy is required; 3 weeks may rarely be needed. In exceptional cases 4 weeks of therapy is necessary. The prednisone dose was tapered and discontinued when no control of the apparent clinical symptoms occurred and other evidence suggested that the recurrent symptoms were not due to IA.

Medical records

Requests for all previous documentation of IA episodes and past medical evaluations of each patient were made. Evidence of objective physical findings consistent with anaphylaxis were sought in all emergency department records and inpatient and outpatient medical records. Attention was placed on possible triggers of anaphylaxis including foods, medications, and results of radiologic and laboratory tests.

TABLE II. Summary of evaluations

Patient no.	Negative test results	Estimated costs*	Referral diagnosis
1	5HIAA, SK, GI, C, R	\$7500	IA
2	PFT, L, CT, L on exposure to acetone	\$5000 per patient	Vocal cord dysfunction
3		\$3000 per patient	IA
4	L, B, GI, XR, PFT	\$5500	Vocal cord dysfunction, asthma, allergic rhinitis
5	5HIAA, PFT, GI, V/Q, L	\$100,000	IA, asthma
6	GI, 5HIAA, R, PFT, C, XR, B, CT	\$10,000	
7	5HIAA, CT, SK, GI, C.R	\$150,000	C1 inhibitor deficiency
8	PFT	\$2500 per patient	Allergic reaction, asthma
9	5HIAA, C, PFT, SK, GI, R, XR, CT, B	\$40,000	IA, Crohn's disease
10	5HIAA, XR, C, R, GI, PFT, L	\$9500 per patient	IA
11	5HIAA, XR, C, R, PFT, H, open food challenges	\$3000	Allergic reaction, asthma

SK, Skin biopsy; R, rheumatologic studies; GI, gastrointestinal workup: esophogastric-duodenofiberscopy, upper gastrointestinal studies, small bowel follow-through studies, colonoscopy; C, complement studies; B, bronchoscopy; H, histamine; 5-HIAA, 5-hydroxyindoleacetic acid; XR, x-ray studies; CT, computed tomographic scan; PFT, pulmonary function tests; V/Q, ventilation perfusion scan; L, laryngoscopy.

*Calculated either by author's estimation of cost or by patient's estimation.

Despite the therapeutic-diagnostic regimen, at each recurrent episode of IA, all available medical records were obtained to verify objective physical findings.

Immediate cutaneous testing

Immediate cutaneous testing for aeroallergens was performed to help determine whether a patient was atopic. Allergens used included trees, grasses, ragweed, dust mites, selected fungi, cat, and dog. Percutaneous and intradermal testing⁶ were carried out. Tests with a panel of 13 screening food extracts were performed with the percutaneous method in nine of 11 patients. The foods included whole wheat, soybean, whole cow's milk, fish mix (codfish, salmon, tuna, haddock, and mackerel), shellfish mix (clam, crab, oyster, lobster, and shrimp), peanut, cereal grain mix (barley, corn, oat, wheat, rye, and rice), almond, chestnut, walnut, brazil nut, filbert nut, and cashew. Additional food extracts were tested in two patients (patients 3, 11) as indicated by history.

Laboratory tests

Hematologic, biochemical, and immunologic tests were performed as necessary to exclude other possible explanations for symptoms. Food challenges were performed on patient 11 to rule out food-induced anaphylaxis. Direct laryngoscopy was performed on patient 2 during an open challenge with acetone.

Estimated costs of evaluation

The total expenses incurred from the accumulated evaluations of each patient throughout the duration of his or her illness up to presentation at NIAI and excluding the expense of our evaluation were estimated. This estimation was done in one of two ways, as indicated in Table II. The patients were requested to total their billing sheets from health insurance companies on

all charges relating to their IA illness. When this was not possible, the author tabulated all procedures, evaluations, emergency department visits, and hospitalizations that the patients reported during the course of their IA illness. The cost was then estimated according to the current fee for services at Northwestern Memorial Hospital-McGaw Medical Center, Chicago, Illinois, a tertiary care facility. The cost of medication and loss of work days and remuneration were excluded because of complexity in gathering these data.

RESULTS

Demographic information

Table III lists the features of the 11 patients with IA in whom the diagnosis of IA could not be established. This series showed a clear female preponderance (10:1) with a mean age of 46.0 ± 11 years at the time of presentation. The duration of symptoms before presentation to NIAI varied from 1 to 15 years (mean, 5.2 ± 6 years). Only one patient was in the health care profession.

Patients' symptoms at presentation

Table IV summarizes the patients' symptoms at presentation to NIAI. Dermatologic symptoms were present in all 11 patients, and these were urticaria, soft-tissue swelling, pruritus, or flushing. The second most frequent complaint (eight of 11 patients) was symptoms in the respiratory tract and the larynx. The patients reported shortness of breath, tightness in the chest, and wheezing. Laryngeal symptoms included throat swelling, difficulty in swallowing, choking, voice hoarseness, or loss of voice that precipitated visits to the emergency department. Pa-

TABLE III. Patient demographics

Patient no.	Sex	Age at presentation (yr)	Duration of symptoms before presentation (yr)	No. of physicians seen before NUI	Hospitalizations	ED visits	Occupation as health professional
1	F	41	2	5	0	1	No
2	F	62	2	3	1	3	No
3	F	39	1	2	0	1	No
4	F	32	15	4	0	2	No
5	F	57	4	5	12	1	No
6	F	57	1	3	1	3	No
7	F	30	12	6	5	0	Nurse
8	F	38	2	1	0	0*	No
9	F	55	15	7	2	0	No
10	F	46	1	6	1	9	No
11	M	49	3	1	0	1	No
Mean		46.0 ± 11	5.2 ± 6	3.9 ± 2	2.0 ± 4	1.9 ± 3	

ED, Emergency department.

*Was diverted from emergency department to NUI and evaluated immediately.

TABLE IV. Summary of symptoms at presentation

Patient no.	Skin	Dizziness	Respiratory system	Larynx	Gastroenterological system
1	+	+	—	—	+
2	+	—	+	+	—
3	+	+	+	+	+
4	+	—	—	+	—
5	+	—	+	+	—
6	+	—	+	+	—
7	+	+	—	+	+
8	+	+	+	+	—
9	+	+	+	—	+
10	+	+	+	+	—
11	+	+	+	—	—

+, Present; —, absent.

tient 7 underwent intubation three times because of these symptoms. Other symptoms included dizziness and various gastrointestinal disturbances. The frequency of the episodes of these symptoms was greater than six per year. Thus the diagnosis of the patients at initial presentation was consistent with IA-generalized-frequent (Table I). All patients sought immediate medical attention for their symptoms. Emergency department visits or hospitalizations occurred at an average rate of 0.7 per year of illness. The patients consulted an average of four physicians, and multiple tests were done by each physician.

Lack of documentation of objective physical findings

On review of all medical records there was no proven hypotension, laryngeal or pharyngeal

angioedema, urticaria, or abnormal result of lung examination (e.g., wheezing or decreased air entry) that was consistent with anaphylaxis. All documentation revealed subjective complaints even when patients were evaluated during an acute episode. Four patients (patients 4, 5, 8, 11) had asthma as diagnosed by the NUI service. The asthma, however, could not explain all the symptoms of IA reported by the patients.

In patients with laryngeal symptoms laryngoscopy was performed when possible and failed to demonstrate any anatomic or functional abnormalities.⁷

In one patient (patient 10) photographs of rashes and swelling revealed linear lesions consistent with excoriations in a patient with dermatographism (Fig. 2).



FIG. 2. Dermatographic lesions stimulating lesions in photographs of patient 10, which she said were her hives during acute IA episodes.

Laboratory evaluation

Table II summarizes the extensive evaluations undertaken in the patients.

All patients, at various times of their illness, had complete blood cell count and differential levels of serum electrolytes, blood glucose, creatinine, blood urea nitrogen, calcium, phosphorus, and liver function tests. No significant result was noted. Patient 7 was given a diagnosis of C1 esterase inhibitor deficiency at another health care facility, but all complement levels documented in the charts were within normal or near-normal limits, including our laboratory results. C1 inhibitor was normal as determined by both quantitative and qualitative evaluation. Other evaluations included multiple 24-hour urinary 5-hydroxyindoleacetic acid measurements to rule out carcinoid syndrome, skin biopsies to rule out systemic mastocytosis, and various radiologic bowel series performed to rule out gastrointestinal disease. Only patient 9 showed a questionable abnormality, and further evaluation revealed Crohn's disease. However, this finding could not explain her systemic reports of coughing, flushing, chest tightness, and breathing difficulties.

Associated atopic disorders

Eight of 11 patients had cutaneous testing performed with both aeroallergens and food allergens. Of the remaining three patients, patient 10 had previous cutaneous testing with food allergens to exclude the diagnosis of food anaphylaxis. Cutaneous testing for aeroallergens was not performed for this patient, because she was unable to discontinue her antihistamine and antidepressant medications, which would affect the results of her cutaneous tests. There was no indication from

history to perform these tests on patients 4 and 7, because their chief difficulties had no correlating triggers. Three of the patients were atopic with allergic rhinitis and asthma (patients 4, 8, 11). One patient had allergic rhinitis alone (patient 6), and one had intrinsic asthma (patient 5). Results of food skin tests were nonreactive in eight of 10 patients. Patient 11 had positive food test responses to spinach and rye, but no clinical correlation was found. He received multiple open food challenges (soybeans, kidney beans, wheat, orange, water chestnut, asparagus, cauliflower, cheese, cantaloupe) despite having no cutaneous reactivity to these foods because of his persistent reports of anaphylactic symptoms after their ingestion. No anaphylactic symptoms were observed during these challenges. No venom or drug testing was performed, because there was no indication for doing so according to the patient's history.

Diagnoses by other physicians

Five of the 11 referring physicians who examined the patients on multiple visits had concluded that the patients had IA; these patients were sent to our clinic for further evaluation and treatment. The rest of the patients were given various probable diagnoses and were referred to NIAI for consultation.

It was not apparent, on review of the records or in our communication with these referring physicians, that they had insight into the nonorganic nature of their patient's disease. They had accepted the patient's history of anaphylactic symptoms and pursued extensive evaluations. Several of these physicians had not treated patients with IA previously.

Response to therapeutic-diagnostic regimen of prednisone, hydroxyzine, and albuterol

Ten of the 11 patients received the therapeutic-diagnostic regimen for a minimum of 4 weeks. None of these patients had any reduction in their symptoms during this period.

Patient 9 received daily prednisone (30 mg alternating with 20 mg) from her local physicians for her difficulties despite our diagnosis of undifferentiated somatoform IA made 2 years earlier. No reduction in her symptoms occurred during her prednisone therapy.

Patient 4 refused a trial of the therapeutic-diagnostic regimen for her attacks of choking, throat closure, facial swelling, pruritis, and rashes. Her attacks were sudden in onset and resolved within seconds to minutes. Although she had in-

sisted on carrying an EpiPen for the past 16 years, she had never used it for her continued problems.

Estimated costs

The estimated cost of evaluation of the patient ranged from \$2500 to \$150,000, with an average of \$30,545 per patient. The cost was higher in those patients who had a longer duration of symptoms. We wish to emphasize that the estimated costs were calculated conservatively, including only those items that were documented in the records.

Response to suggestion of psychiatric care

When the diagnosis of undifferentiated somatoform-idiopathic anaphylaxis (US-IA) was made, the disease was explained to the patient in a manner that was individualized to his or her needs. After receiving reassurance of absence of life-threatening disease, two patients (patients 1 and 8) had resolution of their symptoms. Nine patients were offered psychiatric consultation. Five patients were hostile and angry at our suggestion; only three patients (5, 10, and 11) would agree to this option. The psychiatric evaluations confirmed the diagnosis of undifferentiated somatoform disorder in patients 10 and 11. We were unable to get permission from patient 5 to discuss her psychiatric diagnosis with her psychiatrist. Patient 2 agreed to receive speech therapy and sessions on behavior modification after negative results of laryngoscopy were obtained during an open challenge with acetone. Her symptoms have since been under control, and she has been able to return to work. Follow-up by phone calls of the patients who refused psychiatric care revealed the continuation of their "anaphylactic" symptoms with recurrent emergency department visits. Some of the referring physicians of these patients accepted the nonorganic nature of the symptoms, whereas others rejected the concept of nonorganic disease.

DISCUSSION

This series of 11 patients were first seen with systemic symptoms mimicking the clinical presentation of IA. They were primarily female with an average age of 46 years at presentation and significant duration of symptoms of 5.2 years. Health care profession was not a dominant feature, in contrast to the first nine cases reported.³ Results of routine studies and extensive workup were unremarkable. The incidence of atopy was no higher than that in the general population. As in our previous series, the prominent features in these 11 patients were the lack of objective physical findings

TABLE V. Diagnostic criteria for undifferentiated somatoform disorder

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- A. One or more physical complaints, for example, fatigue, loss of appetite, gastrointestinal or urinary difficulties
 - B. Either (1) or (2):
 - 1. Appropriate evaluation reveals no organic disease to account for the physical problems.
 - 2. When there is related organic disease, the physical problems or resulting social or occupational impairment is grossly in excess of what would be expected from physical findings.
 - 3. Symptoms are of at least 6 months' duration.
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Modified from *Diagnostic and Statistical Manual of Mental Disorders*.⁴

during an acute attack and failure to respond to the therapeutic-diagnostic regimen of prednisone, hydroxyzine, and albuterol. IA is prednisone responsive.^{8,9} Only a very small number of patients require more than 60 mg every other day to control their IA symptoms.^{5,10} Although their IA symptoms might not have been completely resolved, these patients did show some reduction of their symptoms.

The clinical picture of these patients, after the exclusion of IA and other organic disease, meets the criteria for undifferentiated somatoform disorder in *Diagnostic and Statistical Manual of Mental Disorder*⁴ (Table V). Certainly, it would have been advantageous to have demonstrated the presence of environmental or personality factors that contributed to the persistence of anaphylactic symptoms. But four patients did accept psychiatric referral, and two had their symptoms abated on realizing the absence of life-threatening disease. The hostile reaction encountered in the remaining five patients reflected a defensive reaction, which is consistent with psychiatric causes. Of note, two psychiatric evaluations agreed with our diagnosis. Although we have previously used the term IA-variant to classify these patients, we now propose the term US-IA to be a more appropriate description.

US-IA represents a significant problem, not only because of the frustration and difficulties encountered in the process of diagnosis, but also because of the morbidity and significant amount of wasted health care expenditure inherent in the patients' care. The diagnosis is difficult because the physician is challenged with the uncertainty regarding the true existence of organic disease for these extremely convincing life-threatening symptoms.

Sometimes open challenges such as in the case of patient 2⁹ with acetone or food challenges, despite negative cutaneous testing in the case of patient 11, have to be undertaken to verify the absence of objective findings. Other objective measures of assessment (e.g., tryptase, urinary methyl histamine, or full serum histamine), if available, could be helpful in ascertaining the presence or absence of anaphylaxis. The costs reported in the current review may be an underestimation. Additional charges might not be immediately apparent on review of medical records, and procedures that were inaccurately documented were not included in our estimates. With the current concern about health care costs in our society, it has become important to establish the diagnosis of somatoform disease early to avoid inappropriate treatments and costs. It should be emphasized that the hospitalizations of these patients before our evaluation was performed did not aid in the diagnosis or alter the course of the problem and were thus wasting financial resources.

An algorithm has been developed to help physicians recognize and expedite the diagnosis of patients with US-IA (Fig. 1). Because the initial step of evaluation is to prevent fatal anaphylaxis, every effort must be made to control IA by response to therapy, to teach patients to self-administer epinephrine for acute episodes, and to document objective IA findings. The patient must be seen either by the physician in the clinic or by the emergency department physician, who should discuss all objective findings with the managing physician. If the patient cannot be evaluated during the acute episode, we recommend that photos of subjective problems such as purported edema of the tongue, face, or skin be taken and be brought to the clinic at a later date. Once the diagnosis of IA seems unlikely, prednisone administration should be switched to an alternate-day regimen, and the dose should be tapered. We recommend referral to a psychiatrist or psychologist to verify the diagnosis and treatment of undifferentiated somatoform disorder. It is recognized that this is not always

possible. As shown in this series, five patients were hostile to the suggestion of psychiatric care, and four of these patients continued to seek medical care elsewhere. Consultation of a peer specialist for review of the case to concur with the diagnosis and supportive approach in care of the patient is recommended. The patient should be reassured with regard to the absence of risk of fatality and urged to return to the maintenance of a functional life.

Finally, because most of the patients in this series show continued preoccupation with their symptoms, it is important that the managing physician become knowledgeable about IA and its difference from US-IA so that appropriate care can be provided for the patient and wasteful health care expenditure can be minimized.

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