

Criteria positive and criteria negative anaphylaxis, with a focus on undifferentiated somatoform idiopathic anaphylaxis: A review and case series

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ABSTRACT

Background: Undifferentiated somatoform (US) idiopathic anaphylaxis (IA) is considered a psychogenic disorder characterized by a lack of observable physical findings and poor response to treatment. Although failure to diagnose true anaphylaxis can have disastrous consequences, identification of US-IA is crucial to limit unnecessary expenses and use of health care resources.

Objective: To better define the presentation and understand the potential relationship between US-IA and underlying psychiatric comorbidities.

Methods: We retrospectively reviewed 110 visits by 107 patients to our institution for evaluation and management of anaphylaxis over a 1-year period. The patients were classified as having either criteria positive (CP) or criteria negative (CN) anaphylaxis based on whether they met Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium criteria for the clinical diagnosis of anaphylaxis. Patient characteristics, including objective and subjective signs and symptoms, and the presence of psychiatric diagnoses were collected and analyzed. Statistical significance was assessed by using the Fisher exact test. A literature review of US-IA and other psychogenic forms of anaphylaxis was performed.

Results: Patients with CP anaphylaxis were more likely to present with hypotension, wheezing, urticaria, and vomiting than were patients with CN anaphylaxis. The patients with CN anaphylaxis were more likely to present with subjective symptoms of sensory throat tightness or swelling compared with patients with CP anaphylaxis. No significant difference was detected in the prevalence of psychiatric conditions between the two groups.

Conclusion: Patients who met previously established diagnostic criteria for anaphylaxis were more likely to present with objective physical findings than those who did not meet criteria for true anaphylaxis. CN patients who presented for treatment of anaphylaxis were more likely to present with subjective symptoms. Formal diagnostic criteria should be used by clinicians when evaluating patients with suspected anaphylaxis.

(Allergy Asthma Proc 41:436–441, 2020; doi: 10.2500/aap.2020.41.200076)

Anaphylaxis is a severe, systemic allergic reaction that arises quickly after exposure to an allergen.¹ An increased incidence of true anaphylaxis and related emergency department visits has been documented, with almost 2500 deaths reported in the United States between 1999 and 2010.^{2,3} Efforts within the medical community have been made to arrive at a consensus definition of anaphylaxis, which has subsequently been validated.^{1,4,5} However, several nonorganic etiologies remain difficult to diagnose and are rarely described in the

literature. These include undifferentiated somatoform (US) idiopathic anaphylaxis (IA) and Munchausen or factitious anaphylaxis, which are primarily psychogenic.⁶ IA, a systemic reaction that occurs without a clear inciting trigger, was first documented in 1978.⁷ Due to highly variable presentations, algorithms have been proposed to facilitate efficient recognition and diagnosis.⁸

Similar to IA, US-IA has been difficult to identify in an acute setting. It is distinguished from IA by a lack of objective physical findings, poor response to treatment, and that it fulfills *Diagnostic and Statistical Manual of Mental Disorders* criteria for somatic symptom disorder.⁹ In a series of 11 patients, published in 1995, a diagnostic algorithm was used to identify US-IA in patients with questionable diagnoses of IA, which was used to create diagnostic criteria for US-IA.¹⁰ However, this diagnosis and the proposed criteria have been mostly overlooked, without larger, more recent studies published in the literature. Munchausen syndrome, a factitious disorder first described by Richard Asher, M.D., in 1951, was initially documented in three

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The authors have no conflicts of interest to declare pertaining to this article

No external funding sources reported

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patients who frequented hospitals despite no identifiable etiology for their highly variable symptoms. The disorder is named after Baron von Munchausen, known for telling dramatic and untruthful stories.¹¹ Since the identification of Munchausen syndrome, the literature generally only contains case reports that addressed factitious anaphylaxis.^{12,13} Despite a lack of large-scale studies, case reports have been documented over the years.^{14–16}

In 1990, Patterson *et al.*¹⁷ subdivided Munchausen anaphylaxis into three categories. These included immunoglobulin E (IgE) mediated symptoms purposely induced by deliberate allergen exposure, purposely simulated laryngeal stridor, and prevarication anaphylaxis. Prevarication anaphylaxis was described in four cases that involved vague, evasive symptoms.¹⁷ These included a lack of documented physical findings of anaphylaxis, despite self-reported events, involvement of multiple physicians, lack of treatment response, “unusual personality traits,” and health care profession.¹⁷ It is important to distinguish this psychosomatic condition from vocal cord dysfunction (VCD).

The presentation of VCD may overlap with anaphylaxis and Munchausen stridor. Direct rhinolaryngoscopic visualization of paradoxical inspiratory vocal cord adduction while the patient is symptomatic is the diagnostic criterion standard for VCD.¹⁸ Bronchoprovocation challenge and laryngeal fiberoptic examination were used in a small case series to distinguish patients with laryngeal spasm secondary to environmental irritation from patients with psychosomatic illness.¹⁹ One case report¹² of a patient who presented with presumed anaphylaxis was found to have resolution of inspiratory stridor after being instructed to cough. Normal inspirations were observed before and after the cough, which indicated that the stridor was nonorganic or simulated.¹² A more recent report¹³ illustrated two patients misdiagnosed with recurrent anaphylaxis based on subjective laryngeal symptoms, despite extensive negative allergic evaluations. After further testing with placebo (saline solution) induced severe stridor, these patients were diagnosed with Munchausen stridor.¹⁴ These cases illustrate the necessity of astute diagnostic skills in distinguishing true anaphylaxis and organic disease from somatoform disorders.

A systematic review of somatoform disorders stressed the importance of early detection to limit the use of unnecessary health care resources and to prevent patient harm.²⁰ Difficulty to effectively diagnose somatoform anaphylaxis stems partly from a lack of evidence-based research. The clinician faces considerable challenges when tasked with ruling out organic disease in patients convinced that they have life-threatening symptoms in the absence of objective evidence.¹⁰ The aim of our study was to perform a retrospective review of patients treated for anaphylaxis to identify clinical characteristics of those

with somatoform anaphylaxis. We also explored the unique challenges that clinicians face with that diagnosis and its management. This may improve identification of somatoform anaphylaxis and potentially allow the development of improved objective diagnostic criteria.

METHODS

Medical records of all children and adults (ages 11 months to 89 years) admitted to our institution's inpatient service or evaluated at our emergency department with anaphylaxis were reviewed. Patient visits assigned *International Classification of Diseases, Tenth Revision (ICD-10)* codes for “anaphylaxis” were initially included in this study. The ICD-10 codes included anaphylactic reaction due to unspecified food (T7800XA), peanuts (T7801XA), shellfish (crustaceans) (T7802XA), other fish (T7803XA), fruits and vegetables (T7804XA), tree nuts and seeds (T7805XA), milk and dairy products (T7807XA), eggs (T7808XA), other food products (T7809XA), other serum (T8059XA), adverse effect of correct drug or medicament properly administered (T886XXA); and anaphylactic shock, unspecified (T782XXA).

Medical records with these codes during the 1-year period from March 2018 to March 2019 were reviewed. All the patients were classified as having either “criteria positive (CP) anaphylaxis” or “criteria negative (CN) anaphylaxis,” based on whether they met the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium (Second Symposium) criteria¹ for the clinical diagnosis of anaphylaxis. Patient characteristics, including age, gender, chief concern, symptoms, time from exposure to symptom onset, objective signs, occupation, suspected triggers, treatment administered, treatment response, final disposition, allergic and immunologic history, previous allergy testing history, psychiatric history, procedures performed (if applicable), laboratory test findings, chronic medical conditions, number of unscheduled health care visits, epinephrine use and frequency, and any other notable clinical findings or behavior patterns, were collected. Results are presented as counts and percentages, with significance assessed by using the Fisher exact test (two-tailed; $\alpha = 0.05$). A review of the literature was conducted by using Google (Google, LLC, Mountain View, California), Google Scholar (Google, LLC, Mountain View, California), and PubMed search engines by entering the following search terms: “anaphylaxis,” “Munchausen syndrome,” “Munchausen stridor,” “factitious disorders,” “somatoform disorders,” “psychogenic,” “psychosomatic,” and “fictitious.” The institutional review board of the Albany Medical Center approved this study (approval 5488).

RESULTS

Discrepancy between Anaphylaxis Diagnosis and Number of Patients Who Met the Second Symposium Criteria

Medical records for 110 visits for suspected anaphylaxis by 107 patients were reviewed based on screening criteria over a 1-year period. Eight patients were excluded from the study due to suspicion for nonallergic causes of symptoms, including intraoperative and/or postoperative complications (four patients [4%]), renal comorbidities (two patients [2%]), transfusion reaction (one patient [1%]), and acute coronary syndrome (one patient [1%]). Thirty-eight cases (37%) of patients with true CP anaphylaxis were identified based on the Second Symposium criteria,¹ 19 (19%) of whom were adults (ages 18 to 75 years) and 19 (19%) of whom were children (ages 11 months to 17 years).

Sixty-four patient visits (63%) were assigned a final diagnosis of "anaphylaxis" but did not meet the Second Symposium criteria¹ and thus were classified as having CN anaphylaxis. The signs and symptoms reported and/or observed in both patients with CP anaphylaxis and patients with CN anaphylaxis are listed in Table 1. Patients with CP anaphylaxis were more likely than patients with CN anaphylaxis to present with hypotension (13% versus 0%; $p = 0.006$), wheezing (21% versus 3%; $p = 0.005$), urticaria (60% versus 31%; $p = 0.007$), and vomiting (39% versus 5%;

$p < 0.001$). The patients with CN anaphylaxis were more likely than the patients with CP anaphylaxis to present with subjective concerns of sensory throat tightness or swelling (41% versus 10%; $p = 0.001$). The rates of other signs and symptoms were not found to be significantly different between the two groups.

Relationship between Anaphylaxis Diagnosis and Psychiatric Comorbidities

Five patients (13%) who fulfilled the Second Symposium criteria¹ were noted to have comorbid psychiatric diagnoses. The prevalence of psychiatric illness among the patients coded for anaphylaxis are shown in Table 2. These included bipolar disorder (two patients [5%]), schizoaffective disorder (two patients [5%]), anxiety disorder (two patients [5%]), depression (one patient [3%]), and attention-deficit and/or hyperactivity disorder (one patient [3%]).

Thirteen patients (20%) who did not meet the criteria for anaphylaxis were noted to have comorbid psychiatric diagnoses. This is not statistically significantly different from those who met the criteria ($p = 0.43$). These included anxiety disorder (eight patients [13%]), depression (six patients [9%]), posttraumatic stress disorder (three patients [5%]), bipolar disorder (two patients [3%]), conversion disorder (two patients [3%]), chronic pain disorder (one patient [2%]), schizoaffective disorder (one patient [2%]), pseudoseizures (one patient [2%]),

Table 1 Signs and symptoms associated with CP and CN anaphylaxis

	CP Anaphylaxis, % (n = 38)	CN Anaphylaxis, % (n = 64)	p
Cardiovascular			
Hypotension	13 (5)	0	0.006
Syncope	8 (3)	1 (1)	NS
Chest tightness and/or pain	8 (3)	14 (9)	NS
Respiratory			
Shortness of breath	58 (22)	41 (26)	NS
Wheezing	21 (8)	3 (2)	0.005
Sensation of throat: tightness and/or swelling	10 (4)	41 (26)	0.001
Cough	10 (4)	6 (4)	NS
Stridor	10 (4)	9 (6)	NS
Dysphagia	5 (2)	3 (2)	NS
Voice changes	8 (3)	6 (4)	NS
Dermatologic			
Urticaria	60 (23)	31 (20)	0.007
Lip and/or tongue angioedema	26 (10)	19 (12)	NS
Facial and/or other angioedema	26 (10)	20 (13)	NS
Gastrointestinal			
Vomiting	39 (15)	5 (3)	<0.001
Nausea	2 (1)	12 (8)	NS
Diarrhea	0	3 (2)	NS

CP = Criteria positive; CN = criteria negative; NS = not significant.

Table 2 Prevalence of psychiatric comorbidities among patients coded for anaphylaxis

Psychiatric Comorbidities	CP Anaphylaxis, % (n = 38)	CN Anaphylaxis, % (n = 64)	p
None	87 (33)	80 (51)	NS
Anxiety disorder	5 (2)	13 (8)	NS
Depression	3 (1)	9 (6)	NS
Posttraumatic stress disorder	0	5 (3)	NS
Bipolar disorder	5 (2)	3 (2)	NS
Schizoaffective disorder	5 (2)	2 (1)	NS
Conversion disorder	0	3 (2)	NS
ADHD	3 (1)	0	NS
Chronic pain disorder	0	2 (1)	NS
Pseudoseizures	0	2 (1)	NS
Hypomanic episodes	0	2 (1)	NS
Alcohol use disorder	0	2 (1)	NS
Panic disorder	0	2 (1)	NS

CP = Criteria positive; CN = criteria negative; ADHD = attention-deficit/hyperactivity disorder; NS = not significant.

hypomanic episodes (one patient [2%]), alcohol use disorder (one patient [2%]), and panic disorder (one patient [2%]). The difference in psychiatric comorbidity prevalence between the patients with CP anaphylaxis and the patients with CN anaphylaxis was not found to be statistically significant. No patients with CP or with CN anaphylaxis were found to have a formal diagnosis of US-IA listed in their chart.

Variation of Treatment of Anaphylaxis and Epinephrine Use

Discrepancies in anaphylaxis treatment are displayed in Table 3. Twenty-three patients (23%) of all the patients coded for anaphylaxis did not receive treatment with intramuscular (IM) epinephrine. Six patients (6%) received nebulized epinephrine, and, in two cases, did not also receive IM epinephrine. One patient (1%) was started on a continuous intravenous epinephrine infusion due to the lack of clinical improvement after four doses of IM epinephrine. One

patient (1%) received an intentional “half dose” of IM epinephrine due to the attending physician’s perception of low symptom severity, although true anaphylaxis was correctly recognized.

Thirty-one patients (30%) reported using self-administered IM epinephrine at least once before their hospital visit. Twenty-four (77%) of those did not meet the Second Symposium criteria¹ for anaphylaxis at the time of their visit or in the prehospital setting. The highest number of epinephrine autoinjector use among the patients without anaphylaxis was 24 doses in 7 months compared with three lifetime doses in the true anaphylaxis group. Fourteen patients (14%) with clinician-diagnosed anaphylaxis did not receive systemic corticosteroid treatment. Five (5%) of them met criteria for anaphylaxis, whereas 9 (9%) did not. 6 patients (6%) did not receive treatment with any antihistamines, with two (2%) of those meeting criteria for true anaphylaxis. Seventeen patients (17%) were admitted to the hospital, with five patients (5%) admitted to the intensive care unit. Eleven of all the admitted patients (65%) met

Table 3 Variation of anaphylaxis treatment

Anaphylaxis Treatment	CP Anaphylaxis, % (n = 38)	CN Anaphylaxis, % (n = 64)	p
Epinephrine (IM)	84 (32)	72 (46)	NS
Epinephrine (IM and nebulized)	3 (1)	8 (5)	NS
Epinephrine (nebulized only)	0	3 (2)	NS
Epinephrine (continuous IV infusion)	3 (1)	0	NS
Epinephrine (IM half dose)	3 (1)	0	NS
Corticosteroids (oral or IV)	87 (33)	83 (53)	NS
Antihistamines (oral or IV)	92 (35)	89 (57)	NS

CP = Criteria positive; CN = criteria negative; IM = intramuscular; NS = not significant; IV = intravenous.

criteria for true anaphylaxis, including four of all the patients (80%) admitted to the intensive care unit.

Four of 38 patients with CP anaphylaxis (11%) had a serum tryptase level obtained; however, one of these was measured 24 hours after the initial presentation and was found to be normal. Two patients with CP anaphylaxis (5%) were found to have elevated serum tryptase levels, of 23 ng/mL and 33.2 ng/mL, respectively. One of 64 patients with CN anaphylaxis (2%) had a serum tryptase level obtained and was found to be normal. Four patients with CN anaphylaxis (6%) had previously documented normal serum tryptase levels in the years before their acute presentation, with one patient having had five normal measurements over the past decade. No patients with CP anaphylaxis had documented previous encounters which included serum tryptase measurements.

DISCUSSION

The majority of patients in this study did not meet the Second Symposium criteria,¹ despite receiving treatment for anaphylaxis and having the corresponding ICD-10 code. The Second Symposium criteria¹ were composed predominantly of objective clinical dermatologic, cardiovascular, respiratory, and gastrointestinal factors. Most patients in the CP and CN groups presented with multiple organ system involvement. Many patients diagnosed with anaphylaxis by a clinician did not receive IM epinephrine, and their management varied, even in cases of correctly diagnosed anaphylaxis. Few patients had serum tryptase levels measured, which may have provided objective data that suggest whether an episode of true anaphylaxis occurred. This highlights the opportunity for meeting the educational gap on the recognition and management of anaphylaxis in the emergency department and inpatient hospital setting.

Given the paucity of previous data on US-IA, diagnostic criteria remain difficult to validate. Large multicenter studies or case series with a clear diagnosis of US-IA do not exist. We attempted to analyze patients in our series who did not meet criteria for true anaphylaxis and found a small number of patients who had clinical characteristics consistent with US-IA. These included a high number of self-administered epinephrine events, repeated emergency health care visits, psychiatric comorbidities, suspected triggers not consistent with accepted models of IgE-mediated hypersensitivity reactions (e.g., smelling certain foods), and preoccupation with vague allergic diagnoses not formally made (e.g., self-diagnosed mast cell activation syndrome after reading articles on the Internet).

The prevalence of psychiatric disorders was higher among patients who did not fulfill criteria for true anaphylaxis; however, this study did not have adequate

power to detect a statistically significant difference. As a result of a relatively small sample size, we could not exclude the possibility of a type II error. In addition, greater varieties of psychiatric disorders were found compared with those patients who did meet true anaphylaxis criteria. Although we could not conclude that an underlying mental illness was responsible for the presenting symptoms, obtaining a thorough psychiatric history should be an important component of the evaluation.

Additional study is needed to determine the best approach to patients with US-IA. This chronic condition often involves many unscheduled visits for nonorganic symptoms. Long-term strategies are needed to prevent unnecessary visits, reduce costs of care, and provide lasting patient reassurance and support. Schechter and Nurko²¹ recently suggested the use of a “biopsychosocial model,” in which functional disease occurs due to a combination of intrinsic and extrinsic factors, and gives rise to symptoms. This allows for a multidisciplinary approach to rehabilitation without minimizing the patient or being dismissive.

The role of medications specifically for the treatment of US-IA is poorly understood. Patients who are affected may use unnecessary medications to treat anaphylaxis, but the few previous reports¹⁰ rarely discussed long-term management. Perhaps a promising approach may be found in the dermatology literature, which has previously found effective use for psychotropic medications, e.g., selective serotonin-reuptake inhibitors. These medications play an effective role in the treatment of factitious, delusional, and other psychogenic dermatologic conditions in a patient population resistant to suggestions of psychiatry referral.²²

We acknowledge several limitations of this study. Our reliance on emergency department and hospitalist documentation during the chart review process introduced an element of potential inaccuracy in recording actual events and symptoms. A lack of time, resources, and specialized allergy training may not have allowed for the detection of objective markers of anaphylaxis through direct visualization and laboratory testing. Such objective data were not obtained as part of the majority of our patients' evaluations. Important aspects of patients' history were either not obtained or not documented in many cases, such as details of past allergy evaluation. It is possible that certain objective and subjective findings may have been under- or overreported given these limitations. This may partly account for inconsistencies between our data and previous reports of more frequent skin involvement in patients with true anaphylaxis.¹ On a few occasions, discrepancies were found between emergency department and hospitalist clinician documentation with regard to the timeline and prehospital course. Also, there may have been additional patients excluded from this study if the relevant

ICD-10 codes were not assigned, even if they met all other inclusion criteria.

CONCLUSION

The diagnosis and management of anaphylaxis and US-IA remain inconsistent. US-IA is a diagnosis of exclusion and requires a thorough history taking and workup to rule out organic causes of the disease. Use of objective diagnostic criteria for somatoform anaphylaxis would improve identification and may help reduce unnecessary medical costs and medication use. Routinely available data from electronic medical records (EMR) are often not sufficient to retrospectively diagnose US-IA. To develop a streamlined treatment approach to US-IA and other anaphylaxis masqueraders, discrepancies in the recognition, evaluation, and treatment of true anaphylaxis must first be addressed.

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