

Original Article

Cholinergic Urticaria with Anaphylaxis: An Underrecognized Clinical Entity

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What is already known about this topic? Cholinergic urticaria may sometimes be accompanied by multisystem allergic reactions with cardiorespiratory involvement.

What does this article add to our knowledge? In a cohort of patients with anaphylaxis triggered by high ambient temperatures, strenuous exertion, and stress, we note a strong female predominance with moderate to severe reactions recurring about once per month.

How does this study impact current management guidelines? This study highlights the occurrence, demographic characteristics, and clinical characteristics of patients with multisystem reactions accompanying cholinergic urticaria. Typical cholinergic triggers, especially high ambient temperatures, should be considered in the investigation of anaphylaxis.

BACKGROUND: Cholinergic urticaria is a form of physical urticaria triggered by high ambient temperature, strenuous physical activity, and strong emotion. These same triggers may cause multisystem reactions that can be life-threatening. A study of patients with cholinergic urticaria with anaphylaxis was undertaken to describe the demographic and clinical features of this form of anaphylaxis.

OBJECTIVE: To describe a cohort of patients with anaphylaxis triggered by high ambient temperature, exertion, and stress.

METHODS: Patients from an academic allergy practice in a university teaching hospital were identified by retrospective chart review.

RESULTS: A total of 19 patients with recurrent episodes of anaphylaxis due to cholinergic triggers were identified. The female:male ratio was 15:4 (79% females). The mean age of onset was 27.5 years. Patients experienced a mean of 9.41 episodes per year. All 19 patients (100%) reported anaphylaxis triggered by high ambient temperature, 89.5% reported anaphylaxis triggered by strenuous exertion, and 78.9% reported anaphylaxis triggered by stress. Cutaneous involvement was present in 94.7%; 78.9% had upper airway obstructive symptoms, 78.9% had lower airway involvement, 57.9% had gastrointestinal involvement, and 78.9% had cardiovascular manifestations. Anaphylaxis severity scores were grade 1 (mild) in 11.1%, grade

2 (moderate) in 44.4%, and grade 3 (severe) in 44.4%. Baseline tryptase levels were normal in all but 1 patient.

CONCLUSIONS: Anaphylaxis due to cholinergic triggers is underreported, with only several case reports in the literature. Reactions are multisystem with cutaneous, upper and lower airway, and cardiovascular involvement in most patients. Manifestations may be life-threatening, and reactions are often severe. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

Key words: Anaphylaxis; Cholinergic; High Ambient Temperature; Exercise; Exertion; Urticaria; Idiopathic; Mast cell; Mastocytosis

Cholinergic urticaria is a form of inducible urticaria, distinct from other physical urticarias. It is triggered by passive elevation of core body temperature and often by active elevation of core body temperature or by strong emotion.^{1,2} These triggers will typically lead to the sudden appearance of crops of intensely itchy papular urticarial lesions on a base of large erythematous flares.³

High ambient temperatures, such as hot baths or showers, hot summer days or saunas, or sleeping in a warm room with too many blankets, may bring on cholinergic urticaria. Strenuous exertion resulting in elevation of core body temperature will also give rise to cholinergic urticaria, but exertion in a warm environment need not necessarily be very strenuous in order to bring on a reaction. For example, a casual walk on a hot summer day may be sufficient to raise the core body temperature to bring on symptoms. Patients with cholinergic urticaria may note that strong emotional reactions, such as stress, anxiety, or embarrassment, will bring on reactions. The lesions of chronic idiopathic urticaria typically appear overnight, whereas cholinergic urticaria will often be more prominent during the daytime by virtue of the nature of typical triggers.

As with many types of allergic reactions, patients with this form of physical urticaria may manifest symptoms that span a spectrum from isolated cutaneous involvement to multisystem involvement with urticaria, angioedema, gastrointestinal manifestations, and cardiorespiratory compromise. There have been a

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number of case reports describing patients with typical cholinergic triggers who have experienced multisystem reactions.³⁻⁵ In this study, we describe a group of patients with anaphylaxis exclusively brought on by triggers of cholinergic urticaria.

METHODS

Patients included in this study were identified by retrospective chart review from a single referral practice at a university teaching hospital. Institutional research ethics board approval was obtained for this study. Patients were included when they fulfilled the criteria for anaphylaxis⁶ triggered by those factors known to cause cholinergic urticaria and when other causes of recurrent urticaria were ruled out. These included other forms of physical urticaria, chronic idiopathic urticaria, and anaphylaxis due to foods, drugs, insect stings, mast cell disorders, and catamenial anaphylaxis.⁷

Demographic characteristics of patients were compiled. The contributions of typical cholinergic triggers were analyzed, and the severity of anaphylaxis was graded as reported previously by Brown.⁸

Organ system involvement was defined as follows: cutaneous (papular urticaria, flushing, angioedema); upper airway obstructive symptoms (throat constriction, dysphagia, dysphonia, inspiratory stridor); lower airway symptoms (wheezing, cough, chest tightness, dyspnea); gastrointestinal involvement (nausea, vomiting, crampy abdominal pain, diarrhea); and cardiovascular manifestations (presyncope, syncope, palpitations).

RESULTS

Demographic features of patients with cholinergic anaphylaxis are summarized in Table I. Nineteen patients were identified with recurrent episodes of anaphylaxis due to cholinergic triggers. The female:male ratio was 15:4 (79% females). The mean age of onset of symptoms was 27.5 years (range, 12-48 years). The mean number of episodes per year was 9.41. Triggers of cholinergic urticaria with anaphylaxis are presented in Table II. All the 19 patients (100%) reported anaphylaxis triggered by high ambient temperature, 88.9% reported anaphylaxis triggered by strenuous exertion, and 83.3% reported anaphylaxis triggered by stress. Some anaphylactic reactions began overnight, with 3 of 19 patients (16.67%) reporting reactions that awakened them from their sleep.

Signs and symptoms reported by each patient are presented in Table III, as are medications taken at the time of their reactions. Organ system involvement was as follows: 18 of 19 (94.7%) had cutaneous involvement, 15 of 19 (78.9%) had upper airway obstructive symptoms, 15 of 19 (78.9%) had lower airway involvement, 11 of 19 (57.9%) had gastrointestinal involvement, and 14 of 19 (78.9%) had cardiovascular manifestations. Cardiovascular manifestations included palpitations, lightheadedness, and presyncope. Seven of 19 patients experienced loss of consciousness. Anaphylaxis severity scores were grade 1, 11.11% (2 of 19); grade 2, 44.4% (8 of 19); and grade 3, 44.4% (8 of 19). Body temperatures at the time of presentation to the emergency department were normal in 18 of the 19 patients. One patient had a body temperature of 37.1°C. Baseline tryptase levels were available for 12 of the 19 patients (Table III). Tryptase levels were normal in 11 of 12 patients tested. The 1 patient with a slightly elevated tryptase level of 12.2 ng/mL (reference range, <11.4 ng/mL) underwent a bone marrow biopsy, which proved to be normal.

TABLE I. Demographic characteristics of patients with cholinergic urticaria with anaphylaxis

Characteristic	Median (y)	Mean ± SD	Range
Age at presentation (y)	31.00	31.95 ± 11.49	13-58
Age of onset of symptoms (y)	27.0	27.5 ± 12.6	12-48
Male:female ratio	4:15 (79% females)		
Family history of atopic disease	78.9% (15 of 19)		

One patient, a 24-year-old female biomedical engineering student, was referred for investigation of recurring anaphylaxis. She reported a total of 8 stereotypic reactions beginning with difficulty swallowing, followed by tightness in her throat and chest, inspiratory stridor, itching of her arms and chest, and increasingly labored breathing and dyspnea. With some reactions, she would get a red blotchy rash or scattered hives and felt lightheaded. At least 1 reaction began with strenuous exertion. While engaging in a strenuous workout, she developed itchy, red, blotchy rashes, itching and tightness in her throat, labored breathing, mild cough, chest tightness, and lightheadedness. All the symptoms resolved as she stopped exercising. Following informed consent, she was challenged to high ambient temperature in a 90°C sauna. Core body temperature readings were taken at 3-minute intervals and corresponding symptoms were recorded (Table IV). The high ambient temperature of the sauna reproduced the symptoms described above, in the absence of physical activity.

DISCUSSION

Cholinergic urticaria with anaphylaxis is a phenomenon observed predominantly in females. Female predominance is also seen in patients with chronic idiopathic urticaria and other autoimmune conditions^{9,10} as well as in patients with idiopathic anaphylaxis.¹¹⁻¹³ Pathogenesis is poorly understood, but some data point to a mast cell-mediated mechanism. During provocation of cholinergic reactions, increases in serum histamine levels and eosinophil and neutrophil chemotactic activities were noted.⁵ Although anaphylaxis to foods is most commonly observed in children and teens,^{14,15} and drug- and venom-induced anaphylaxis in middle-aged and older individuals,^{16,17} cholinergic urticaria with anaphylaxis was seen mainly in young adults in our cohort as well as in patients reported in an earlier study.³

Patients with cholinergic urticaria with anaphylaxis all reported reactions caused by high ambient temperatures causing passive elevation of core body temperature. However, core body temperatures appear to have returned to normal at the time of presentation to the emergency department, presumably due to removal from a location with high ambient temperature or cessation of strenuous activity. Most of the patients also had reactions brought on by strenuous activity and stress. Episodes typically occurred several times per year, but less than once per month. However, in female patients, recurrences did not coincide with menstrual periods, thereby ruling out catamenial anaphylaxis⁷ or heightened sensitivity to triggers at the time of menses.¹⁸

Because of the relative lack of familiarity with this condition, patients reported a delay of 4 to 5 years between the onset of symptoms and diagnosis. This condition had a major impact on

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