

Original articles

Exercise-induced anaphylaxis

Albert L. Sheffer, M.D., and K. Frank Austen, M.D. Boston, Mass.

Sixteen patients were seen because of possibly life-threatening exercise-associated symptoms similar to anaphylactic reactions. Asthma attacks, cholinergic urticaria and angioedema, and cardiac arrhythmias are recognized as exertion-related phenomena in predisposed patients but are distinct from the syndrome described here. A syndrome characterized by the exertion-related onset of cutaneous pruritus and warmth, the development of generalized urticaria, and the appearance of such additional manifestations as collapse in 12 patients, gastrointestinal tract symptoms in five patients, and upper respiratory distress in 10 patients has been designated exercise-induced anaphylaxis, because of the striking similarity of this symptom complex to the anaphylactic syndrome elicited by ingestion or injection of a foreign antigenic substance. There is a family history of atopic disease for 11 patients and cold urticaria for two others and a personal history of atopy in six. The size of the wheals, the failure to develop an attack with a warm bath or shower or a fever, and the prominence of syncope rule against the diagnosis of conventional cholinergic urticaria. There is no history or evidence of an encounter with an environmental source of antigen during the exercise period.

During the past 10 yr 23 patients have come to our attention because of possibly life-threatening, exercise-associated symptoms similar to anaphylactic reactions. Sixteen of these patients were seen by us directly; the other seven were identified by correspondence with their personal physicians. Asthma attacks, cholinergic urticaria and angioedema, and cardiac arrhythmias are recognized as exertion-related phenomena in predisposed patients but are distinct from the syndrome described here. This report summarizes the precipitating events and symptoms and signs in the 16 patients who have experienced exercise-induced anaphylactic reactions and were later assessed by us.

From the Departments of Medicine, Harvard Medical School, and the Robert B. Brigham Hospital Division of the Affiliated Hospitals Center, Inc.

Supported by Grants AI-07722, AI-10356, HL-17382, and RR-05669 from the National Institutes of Health.

Presented in part at the annual meeting of the American Academy of Allergy, New Orleans, La., March 1979.

Received for publication Dec. 18, 1979.

Accepted for publication Feb. 11, 1980.

Reprint requests to: Albert L. Sheffer, M.D., Robert B. Brigham Hospital, 125 Parker Hill Ave., Boston, MA 02120.

RESULTS

The patient population (Table I) consisted of 16 individuals (11 men and five women) ranging in age at the time of assessment from 12 to 54 yr (mean of 24 yr). In most cases symptoms had been present for several years prior to assessment. The episodes of exercise-induced systemic reactions have varied from a single occurrence to several attacks annually over a period of 16 yr. The symptoms and signs experienced by these patients during the peak of an attack (Table I) include, in decreasing frequency, generalized itching, hives and giant hives, cutaneous angioedema, collapse, choking with respiratory distress, gastrointestinal colic, headaches, and wheezing. Generalized pruritus and urticaria were the initial manifestations in almost every instance of an attack, and exercise-induced urticaria is the hallmark of the syndrome. Patients 9 and 11 experienced small hives of about 2-mm diameter characteristic of cholinergic urticaria, but all others developed typical hives of the usual size, approximately 1 cm in diameter. In 12 patients the urticaria progressed to angioedema involving the face, palms, and soles. Cutaneous urticaria-angioedema persisted throughout the attack, which

usually lasted for from 30 min to 4 hr. Twelve patients collapsed after interruption of the exercise. Vertigo was present in each of these instances, and tinnitus was present in one. Upper respiratory tract manifestations characterized by choking developed in 10 patients, six of whom collapsed. Gastrointestinal tract symptoms including colic, nausea, or diarrhea occurred in five patients. Disabling headaches occurred in four patients and usually persisted for several days. Wheezing was experienced by seven patients during the exercise period and was usually evanescent and not incapacitating.

The usual sequence of the symptomatology of an attack was consistent and could be divided into prodromal, early, and fully established manifestations; late or postexertional sequelae were also present. The premonitory symptoms often included a feeling of fatigue, generalized warmth, and itching, and the person may have noted cutaneous erythema. The subsequent early manifestations of an attack were highlighted by an urticarial eruption that was generalized and became confluent and even angioedematous. The face, palms, and soles were commonly involved. Collapse, with transient brief periods of loss of consciousness, occurred in 12 patients as exercise was interrupted because of the cutaneous discomfort. Choking, respiratory stridor, gastrointestinal colic, nausea, and vomiting were noted with fully developed attacks but occurred with equal frequency in the absence of or subsequent to a syncopal period. The fully developed attack symptom complex had a duration of 30 min to 4 hr. Late sequelae in the form of headaches persisted for 24 to 74 hr. Wheezing and occasional chest tightness were inconstant and evanescent, occurring in eight patients after completion of the exercise; it differed from the other symptoms and signs in its failure to occur with regularity in the same patient.

All patients were accomplished athletes when they experienced their first exercise-induced symptom. Exertion was daily for all patients except for patient 7 who exercised three times per week, and patient 12 who exercised once per week. The number of attacks ranged from a single episode to monthly episodes occurring over 9 yr. The types of exercise preceding the attacks (Table I) ranged from mild tennis warmups and dancing to strenuous events. Four athletes developed symptoms while sprinting in track events and nine others while jogging or running from $\frac{1}{2}$ to 15 mi. Symptoms developed in five patients while playing basketball or soccer and in three during tennis matches.

Detailed physical examination at the site of the attack was never performed; however, in 10 instances

physicians did attend the patients during an emergency room visit. Under these circumstances the attacks were no longer at their height, and the physical findings revealed hypotension in three patients, tachycardia in three, and bradycardia in two others.

Factors possibly associated with or predisposing to attacks (Table I) included personal and family history of atopy, aspirin and food ingestion, and weather conditions. Four patients experienced allergic rhinitis, and two had eczema; eleven patients had family histories of atopy. Five (patients 3, 4, 10, 13, and 14) who ingested aspirin and two (patients 9 and 15) who had taken caffeine before exercising experienced symptoms that seemed out of proportion to the modest exercise and that did not occur without exercise. Three (patients 3, 5, and 11) thought their symptoms were worse when exercise was conducted after eating. Heat-accentuated symptoms in eight (patients 1, 2, 5, 7, 8, 10, 12, and 15) and reactions were generally more common or worse in the summer months. Prolonged collapse occurred twice in patient 14 while exercising in the rain.

Routine hematology studies and measurements of whole-complement activity (CH50), C3 and C4 complement proteins, immunoglobulin classes, and blood chemistries (SMA-12) were within the normal range. Serum IgE concentrations were not elevated in the four atopic patients assessed.

Treatment was directed to the reversal of symptoms and to the prevention of future attacks. The therapeutic approaches to acute reactions resembled the treatment for an anaphylactic reaction precipitated by allergens. The usual emergency therapy for collapse included subcutaneous administration of epinephrine. Fluid replacement and oxygen therapy were used in several instances. Antihistaminic drugs administered systemically appeared to reduce the pruritus, warmth, and erythema. Therapeutic intervention usually interrupted an attack within 1 hr, although occasionally urticaria, angioedema, or both persisted for several hours. Headaches lingered for several days in four instances. Modification of the exercise program by patient willingness to reduce the intensity of the exertion, to avoid exercise on warm and humid days, and to interrupt the exercise at the first evidence of itching seemed to reduce the severity, duration, and frequency of attacks. Antihistaminic agents administered over time in 14 patients or before strenuous exercise have been considered to be helpful but were never totally effective in preventing attacks. Beta agonists and phosphodiesterase-inhibiting agents have provided no apparent benefit when administered prophylactically.

TABLE I. Exercise-induced anaphylaxis: Population and clinical spectrum

Patient	Sex	Age at onset (yr)	Attacks/ history (mo)	Type of exertion*	Prodromal manifestation
1	F	19	2/5	Jogging 15 mi	Nausea, pruritus, warmth
2	M	19	1/15	Running 2 mi	Fatigue, pruritus, warmth
3	M	45	5/84	Playing tennis, ice skating 1 hr	Pruritus, warmth
4	F	13	2/34	Running 1 mi, playing soccer	Pruritus
5	F	35	36/72	Dancing, playing tennis	Erythema, pruritus
6	M	13	3/19	Running 1 mi, playing basketball	Angioedema
7	M	26	2/164	Running ½ mi	Angioedema
8	M	13	2/12	Running 3 mi	Pruritus
9	M	19	50+/92	Jogging	Pruritus, small urticaria
10	F	13	3/29	Sprinting 50 yd	Pruritus
11	M	15	60+/192	Sprinting, dancing, playing soccer and basketball	Flushing, pruritus, small urticaria
12	F	26	3/24	Jogging, playing tennis	Flushing, warmth
13	M	17	3/12	Running, sprinting, playing basketball	Erythema, pruritus
14	M	12	108/108	Playing basketball, sprinting	Erythema, pruritus
15	M	39	3/23	Jogging	Pruritus
16	M	26	4/36	Jogging 1 mi	Angioedema, urticaria, vertigo

*Exertion daily for all but patient 7, who exercises three times per week, and patient 12, who exercises once per week.

†Family history of allergic rhinitis in all instances plus additional family history of eczema for patient 4 and asthma for patients 4, 7, and 8.

‡Parent with past history of cold urticaria.

§Cousin with past history of cold urticaria.

DISCUSSION

A syndrome characterized by the exertion-related appearance of cutaneous pruritus and warmth, the development of generalized urticaria, and the appearance of such additional manifestations as syncope, abdominal colic, and upper respiratory tract distress has been designated exercise-induced anaphylaxis, because of the striking similarity of this symptom complex to the anaphylactic syndrome elicited by ingestion or injection of a foreign antigenic substance. The characteristic features of allergen-induced systemic anaphylaxis in humans include cutaneous pruritus and erythema, the development of well-

circumscribed pruritic hives, which may coalesce to form giant hives, and a localized, nonpitting, poorly demarcated deeper cutaneous angioedema. When the angioedematous process involves the gastrointestinal tract there is nausea, vomiting, abdominal pain of a crampy nature, and diarrhea, whereas its presence in the upper respiratory tract mucosa is experienced as a "lump in the throat," hoarseness of voice, or stridor. A combination of mucosal edema and smooth-muscle spasm in the lower respiratory tract is characterized by feelings of tightness in the chest and audible wheezing. Cardiovascular collapse in patients with allergen-induced anaphylaxis is secondary to the

Complete clinical syndrome	Atopic history	
	Personal	Family†
Angioedema, collapse, nausea, urticaria		Parent
Angioedema, collapse, nausea, urticaria		Parent
Chest tightness, collapse, urticaria		
Angioedema, choking, collapse, urticaria, wheezing	Allergic rhinitis	Parents, siblings
Angioedema, choking, nausea, urticaria, vomiting		Child
Choking, headache, pruritus, urticaria, wheezing		Sibling
Choking, rhinitis, urticaria, wheezing	Allergic rhinitis, asthma	Parent, sibling
Angioedema, collapse, headache, urticaria	Eczema	Parent
Angioedema, choking, urticaria	Eczema, asthma	Parents, siblings
Angioedema, colic, collapse, tinnitus, urticaria		‡
Angioedema, choking, colic, collapse, wheezing	Rhinitis	Parents, sibling, cousin
Collapse, headache, urticaria, wheezing	Rhinitis, asthma	§
Choking, collapse, urticaria, wheezing		Parent
Angioedema, choking, collapse, headache, urticaria		Parent
Choking, collapse, urticaria		
Choking, collapse, rhinitis, urticaria, wheezing		

hypoxia of respiratory insufficiency or can be primary without antecedent hypoxia from respiratory insufficiency.¹ Whether this latter group experiences collapse as a result of cardiac arrhythmia or a critical reduction in plasma volume is not established.¹⁻³ That syncope occurs without severe antecedent respiratory difficulty and without clinical evidence of cyanosis suggests that this aspect of the syndrome can represent a reversible response of the cardiovascular system, but at present there is no basis for distinguishing between a central or peripheral mechanism. An isolated cardiovascular catastrophe or a reversible arrhythmia would not be associated with the dominant features of pruritic erythema and urticaria. Similarly, exercise-induced asthma would be dominated by the pulmonary insufficiency aspect of the syndrome with prominent wheezing and would lack the other muco-

cutaneous characteristics of the exercise-induced anaphylactic syndrome. The exertion-related collapse syndrome presents the essential ingredients of the allergen-induced human anaphylactic syndrome except for the introduction of an exogenous antigen just before the onset of the adverse response.

Certain adverse responses to physical stimuli are termed physical allergy, because the reproducible symptom complex appears to be mediated by IgE-dependent activation of host mast cells. In some instances a local urticarial reaction can be passively transferred by injecting serum from an affected individual into a skin site of a normal recipient and then after an appropriate interval challenging the injection site of the normal recipient with the appropriate physical stimulus. In some patients with cold-induced urticaria and dermographism, the responsible serum factor has been shown by the physicochemical and immunochemical criteria to be of the IgE class,^{4, 5} whereas in solar urticaria elicited by certain wavelengths of light and in cholinergic urticaria the passive transfer of the local response by a heat-labile substance⁴⁻⁸ represents presumptive evidence for the involvement of IgE. The passive transfer approach with serum is not uniformly positive, and additional circumstantial evidence that these reactions are mast cell-mediated includes their variable suppression by such pharmacologic agents as antihistamines, hydroxyzine, and cyproheptadine,⁹⁻¹² degranulation of mast cells in skin biopsy specimens from patients with cold urticaria,¹³ and elevations in plasma histamine in relation to the regional site of elicitation of an attack of cold¹⁴⁻¹⁶ or solar¹⁷ angioedema-urticaria. Syncope is not part of these syndromes unless the physical stimulus is applied over a very large body surface, as would occur when a patient with cold urticaria was suddenly or persistently exposed to a source of ambient cold such as a cold-water stream or ocean or winter wind.¹⁸

Generalized heat urticaria, known as cholinergic urticaria, develops after a warm bath or shower, after exercise, and with fever and is a form of physical allergy that must be considered for its possible relationship to the exercise-induced anaphylactic syndrome. The skin lesions appear as pruritic tiny wheals surrounded by large areas of erythema, and occasionally they become confluent; systemic manifestations are rare and include syncope, abdominal pain, and, uncommonly, wheezing.¹⁸ Elevations in plasma histamine occur in relation to experimentally exercise-induced attacks¹⁹ manifested by the cutaneous lesions^{19, 20} and reversible alterations in pulmonary function.¹⁹ A single patient has been reported with exertion-induced tiny wheals without pruritus or

erythema, hypotension, and alterations in plasma levels of 5-hydroxytryptamine but not histamine.¹⁴ Although the exercise-induced anaphylactic syndrome has some features in common with generalized heat urticaria, there are a number of important differences. Only two of the 16 patients with the exercise-induced anaphylactic syndrome reported that the attacks began with tiny pruritic wheals rather than the characteristic 10 to 15-mm urticarial response. Further, the patients with exercise-induced anaphylactic syndrome did not experience this event in response to a warm bath or shower or a fever. Finally, the associated collapse in 12 of the 16 patients represents a high frequency of this clinical manifestation, as compared with the rarity of a syncopal response in patients with classic cholinergic urticaria. Thus, although exercise-induced anaphylaxis resembles cholinergic urticaria in perhaps being an example of a generalized physical allergy, it represents a distinct syndrome in terms of the precipitating event and the overall clinical presentation.

An important aspect of the syndrome is that it does not occur with each exercise experience, yet has a sufficient degree of recurrence and of uniformity of presentation to suggest to the dedicated athletes experiencing the syndrome that the event is a repetition of a previous experience. The irregularity of exercise-induced anaphylaxis in individuals judged to be susceptible suggests that there may well be additional important variables in determining whether the syndrome is expressed. Maulitz et al.²¹ have reported a patient in whom they felt a hypersensitivity to oysters and shrimp was a factor in a subsequent adverse reaction to strenuous exercise; the patient exhibited a positive skin response to prick testing with a variety of seafoods including shrimp. In none of the 16 patients grouped under the exercise-induced anaphylactic syndrome was it possible by history or by the usual allergy skin test procedures to invoke a specific exogenous allergen as relevant to the exercise-related attacks, although atopy was a prominent associated condition in the patients and their families. Similarly, although adverse reactions to nonsteroidal anti-inflammatory agents and certain food additives²² include urticaria, angioedema, wheezing, and even syncope, it was not possible to establish that exposure to these agents was a consistent variable in the experience of the 16 patients described here. Nonetheless, the irregularity of the episodes in the susceptible population strongly suggests that there are additional variables that may not be the same in every individual experiencing this exercise-induced syndrome.

Treatment of an attack should include those maneuvers efficacious in the management of conven-

tional anaphylactic syndrome, including the administration of epinephrine. Persistent hypotension is best managed in an emergency facility where oxygen and the appropriate vasoactive drugs are available. Life-threatening laryngeal edema has not been documented as yet in this syndrome but, if recognized, would require maintenance of the airway by emergency measures. Relief of the cutaneous manifestations can be accelerated with the administration of an antihistamine with or without epinephrine. Prevention of attacks is the most logical approach to the management of this syndrome. Prevention may be achieved with limitation of the exercise program or interruption of the program at the appearance of the first prodromal signs. The exercise program should always include the presence of an associate with knowledge of the problem and its short-term management. Variables such as eating, the ingestion of a nonsteroidal anti-inflammatory agent, or certain weather conditions should be avoided whenever they have been identified by a patient as a factor in the elicitation of the symptom complex. In no case to date has a continued exercise program, even when associated with the recurrence of the exercise-induced anaphylactic syndrome, led to a serious medical illness. Thus modification of the exercise program is preferred to complete interruption of a vocation that has generally become an essential part of the lifestyle of the healthy, young individuals afflicted with this adverse syndrome.

REFERENCES

1. James LP, Austen KF: Fatal systemic anaphylaxis in man. *N Engl J Med* **270**:597, 1964.
2. Petsas AA, Kotler MN: Electrocardiographic changes associated with penicillin anaphylaxis. *Chest* **64**:66, 1973.
3. Hanshiro PK, Weil MH: Anaphylactic shock in man: Report of two cases with detailed hemodynamic and metabolic studies. *Arch Intern Med* **119**:129, 1967.
4. Houser DD, Arbesman CE, Ito K, Wicher K: Cold urticaria: Immunologic studies. *Am J Med* **49**:23, 1970.
5. Newcomb RW, Nelson H: Dermographia mediated by immunoglobulin E. *Am J Med* **54**:174, 1973.
6. Sherman WB, Seebohm PM: Passive transfer of cold urticaria. *J ALLERGY* **21**:414, 1950.
7. Harber LC, Holloway RM, Wheatley VR, Baer RL: Immunologic and biophysical studies in solar urticaria. *J Invest Dermatol* **39**:439, 1963.
8. Illig L, Heinicke A: Zur Pathogenese der Cholinergischen Urticaria IV: Zur Frage einer echten Antigen-Antikörper Reaktion. *Arch Klin Exp Dermatol* **229**:360, 1967.
9. Matthews CNA, Kirby J, James J, Warin RP: Dermographism: Reduction in wheal size by chlorpheniramine and hydroxyzine. *Br J Dermatol* **88**:279, 1973.
10. Wanderer AA, Ellis EF: Treatment of cold urticaria with cyproheptadine. *J ALLERGY CLIN IMMUNOL* **48**:366, 1971.
11. Baer RL, Harber LC: Reactions to light, heat, and trauma, *in*

- Samter M, editor: Immunological diseases, ed. 2. Boston, 1971, Little, Brown and Co., pp. 973-984.
12. Ive H, Lloyd J, Magnus EA: Action spectra in idiopathic solar urticaria: A study of 17 cases with a monochromator. *Br J Dermatol* **77**:229, 1965.
 13. Juhlin L, Shelley WB: Role of mast cell and basophil in cold urticaria with associated systemic reactions. *JAMA* **177**:371, 1961.
 14. Kaplan AP, Gray L, Shaff RE, Horakova Z, Beaven MA: In vivo studies of mediator release in cold urticaria and cholinergic urticaria. *J ALLERGY CLIN IMMUNOL* **55**:394, 1975.
 15. Soter NA, Wasserman SI, Austen KF: Cold urticaria: Release into the circulation of histamine and eosinophil chemotactic factor anaphylaxis. *N Engl J Med* **294**:687, 1976.
 16. Wasserman SI, Soter NA, Austen KF: Cold urticaria: Recognition and characterization of a neutrophil chemotactic factor which appears in serum during experimental cold challenge. *J Clin Invest* **60**:189, 1977.
 17. Soter NA, Wasserman SE, Pathak MA, Parrish JA, Austen KF: Solar urticaria: Release of mast cell mediators into the circulation after experimental challenge. *J Invest Dermatol* **72**:282, 1979. (Abstr.)
 18. Soter NA, Austen KF: Urticaria, angioedema, and mediator release in humans in response to physical environmental stimuli. *Fed Proc* **36**:1736, 1977.
 19. Soter NA, Wasserman SE, Austen KF, McFadden ER Jr: Release of mast cell mediators and alterations in lung function in patients with cholinergic urticaria. *New Engl J Med* **302**:604, 1980.
 20. Kaplan AP, Beaven MA: In vivo studies of the pathogenesis of cold urticaria, cholinergic urticaria, and vibration-induced swelling. *J Invest Dermatol* **67**:327, 1976.
 21. Maulitz RM, Pratt DS, Schocket AL: Exercise-induced anaphylactic reaction to shellfish. *J ALLERGY CLIN IMMUNOL* **63**:433, 1979.
 22. Samter M, Zeitz HJ: The aspirin triad and the prostaglandins, in Samter M, editor: Immunological diseases, ed. 3. Boston, 1978, Little, Brown & Co., pp. 900-916.