

The natural history of exercise-induced anaphylaxis: Survey results from a 10-year follow-up study

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Background: Exercise-induced anaphylaxis (EIA) is a unique physical allergy that is triggered by exertion, the clinical spectrum and modifying factors of which have been previously studied. At the time of initial description, it was postulated that other factors contributed to this disorder.

Objective: We sought to determine the clinical course and potential modifying factors in EIA.

Methods: In 1993, we conducted a cross-sectional analysis of 671 individuals with exercise-associated symptoms for more than a decade using a validated 75-item questionnaire. Subjects met criteria for EIA if they had anaphylactic symptoms, including hypotension or upper airway obstruction, urticaria, or angioedema with physical exertion but without a passive increase in core body temperature.

Results: Of 365 (54%) questionnaire respondents, 279 (87%) met criteria for EIA (199 females and 80 males). At the time of study entry, subjects with EIA (mean age, 37.5 years; range, 13 to 77 years) had an average of 10.6 years of symptoms, which were most frequently triggered by aerobic activities such as jogging or brisk walking (78% and 42%, respectively). On average, subjects reported that the frequency of attacks had decreased (47% of subjects) or stabilized (46% of subjects) since onset. One hundred (41%) subjects reported being completely free of attacks in the past year. Subjects reduced their attacks by avoiding exercise during extremely hot or cold weather (44%), avoiding ingestion of certain foods before exercise (37%), and restricting exercise during their allergy season (36%) or humid weather (33%). The most common pharmacologic agents used to manage symptoms were H1 antagonists (56%) and/or epinephrine (31%). However, 28% used no treatment at all.

Conclusion: EIA is an episodic condition in which the frequency of attacks tends to stabilize or decrease over time. Improvement appears to result from individual modification of exercise and avoidance of known environmental and ingestible precipitants. (*J Allergy Clin Immunol* 1999;104:123-7.)

Key words: Anaphylaxis, urticaria, physical allergy, exercise, exercise-induced anaphylaxis, food allergy

Exercise-induced anaphylaxis (EIA) is a unique physical allergy characterized by flushing, generalized pruritus with urticaria, and occasionally upper respiratory obstruction and/or cardiovascular collapse.¹⁻³ EIA has become increasingly recognized as more people become engaged in physical activity. The clinical manifestations are indistinguishable from allergen-induced systemic anaphylaxis.³ Patients with EIA challenged by exercise have a rise in serum histamine with clinical symptoms and elevated serum levels of mast cell-derived tryptase compared with those of asymptomatic patients with EIA and control subjects.^{2,4}

The clinical manifestations of this disease have been described in detail^{1-3,5}; however, little is known about its duration and recurrence. We surveyed a large cohort of patients with a mean of more than a decade of exercise-associated symptoms to determine the natural history of this disorder.

METHODS

Identification of subjects

Since 1980, 671 individuals with exercise-associated symptoms were identified through a variety of sources at the Brigham & Women's Hospital Asthma and Allergic Diseases Center (BWH-AADC) and entered into the EIA registry. Some individuals were referred from other medical centers, and others were individuals who wrote to the Center after hearing about EIA through the media. Inclusion criteria included being 18 years of age or older, speaking English, and having appropriate symptoms of anaphylaxis.

Development of questionnaire

A questionnaire modified from Wade et al⁵ was constructed based on elements of published clinical criteria for EIA^{2,3} amenable to a questionnaire format. In addition to questions on the clinical elements of EIA, the survey included questions on the type of exercise most likely to trigger an attack (ie, walking, aerobics, and tennis), other modifying conditions (ie, heat, humidity, cold, and fever), specific food triggers, and avoidance maneuvers. The participants were also asked to report on their symptom history (ie, frequency and duration of attacks). This standardized 75-item questionnaire was pretested on 14 subjects for clarity and comprehension before being sent to the study participants.

In March 1993, questionnaires were mailed to 671 subjects. To maximize response rates, up to 3 separate mailings at 4-week intervals took place, which included a cover letter describing the study, a refusal response card, and the questionnaire. This protocol was

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Abbreviations used

BWH-AADC: Brigham & Women's Hospital Asthma and Allergic Diseases Center

EIA: Exercise-induced anaphylaxis

approved by the Brigham & Women's Hospital Committee for Research on Human Subjects.

Diagnostic criteria for EIA

On the basis of published clinical criteria,²⁻⁴ an algorithm for identifying EIA was used. Subjects were defined as having EIA if they reported anaphylactic symptoms, had urticaria and/or angioedema with symptoms consistent with upper respiratory obstruction, or had cardiovascular collapse associated with exercise. The algorithm excluded subjects with symptoms in relation to an elevation in core body temperature without exercise (ie, fever or hot shower).

Validation of the questionnaire

For the questionnaire validation substudy, a sample of 29 BWH-AADC patients, with a clinical diagnosis of EIA identified through BWH-AADC diagnosis code and then confirmed by one author (ALS), were selected and asked to fill out the questionnaire. One control group of 8 subjects from BWH-AADC with other allergic diseases (6 with cholinergic urticaria and 2 with exercise-induced asthma) were enrolled also and administered the EIA questionnaire.

Statistical methods

Data on participants with EIA were analyzed by using variables of interest in univariate analyses with SAS software.⁶ For the validation substudy, the sensitivity of the EIA questionnaire (the proportion of subjects fulfilling EIA criteria among those with clinical EIA) and the specificity (the proportion of subjects not fulfilling criteria among those without clinical EIA) were determined. Likelihood ratios (the ability of the test to distinguish between diseased and nondiseased subjects) for the subjects were calculated as follows: sensitivity/1 – specificity.⁷

RESULTS**Sensitivity and specificity of questionnaire**

In the validation substudy, of 29 subjects with a clinical diagnosis of EIA, 25 met survey criteria, indicating an overall sensitivity of 83%. In the control group of subjects with other allergic disorders, the overall specificity was 88%. The likelihood ratio, the ability of the survey to distinguish between diseased and nondiseased subjects, was 6.9.

Survey response rates

Of 671 subjects sent questionnaires, 365 (54%) responded. Two hundred forty questionnaires were returned with no forwarding address, and 66 individuals did not respond after 3 mailings. Forty five respondents declined participation. Of those who could be located by mail, there was an excellent participation rate of 88%.

Characteristics of the study population

Of the 365 respondents, 279 (76%) met criteria for EIA. The demographic profile of the 279 subjects with

EIA is outlined in Table I. The majority of respondents to the survey were female. The group had an average of 10.6 years of symptoms when surveyed for this study.

Clinical spectrum

The most common activities reported to cause EIA in 279 subjects were aerobic activities, such as jogging, walking at a brisk pace, tennis or racquetball, and dancing (Table II). Activities with less cardiovascular demand, such as raking leaves, volleyball, and horseback riding, also triggered attacks but in fewer subjects (<2%). There was no reliably safe exercise; however, only 6 subjects reported that shoveling snow, 5 that exercising on the stairmaster, and 5 that horseback riding triggered an attack. For the subjects who reported jogging as the main trigger of EIA, symptoms developed in 90% within 30 minutes of initiating exercise.

The most frequently occurring symptoms at the time of an EIA attack were generalized pruritus and urticaria, flushing, and angioedema (Table III). However, symptoms suggesting vascular compromise, such as tachycardia and loss of consciousness, headache, gastrointestinal colic and nausea, upper respiratory obstruction, and even dysphagia, were also described. Fainting or loss of consciousness occurred in 90 (32%) individuals. One quarter of the subjects experienced symptoms of upper respiratory obstruction with their attacks.

Clinical course

Subjects were asked to judge whether the frequency of their EIA attacks had decreased, increased, or remained the same since the onset of their disease. The majority of participants, 105 (47%), stated that the frequency of attacks had decreased since onset. In 102 (46%) individuals the frequency of attacks had remained the same. Only 17 individuals (7%) stated that frequency had increased since onset.

An average of 8.3 attacks occurred (range, 0 to 365) in respondents in the year preceding the study. However, 100 (41%) individuals stated that they were completely free of EIA symptoms within the year of survey response. Nearly all subjects (97%) reported 12 or less attacks at the time of survey response. Subjects estimated an average of 14.5 attacks per year when their illness first began.

The natural history of subjects who experienced upper airway obstruction, described as choking, hoarseness, or difficulty swallowing, did not differ from those without symptoms of upper airway obstruction in terms of both the usual number of attacks per year (*t* test, 18.3 (SD 66.3) vs 11.5 (SD 32.3); *P* = .40), as well as the number of attacks recorded in the year before study (*t* test, 11.3 (SD 51.4) vs 6.4 (SD 22.7); *P* = .38).

A logistic regression model was run to identify predictors of a decrease in symptoms over time. In a model that included age, sex, the presence of precipitating conditions, and a history of other allergic conditions, having a history of other allergies (*P* = .14), specifically a history of eczema (*P* = .023), or having family members with allergies (*P* = .006) predicted fewer attacks than usual.

TABLE I. Patient characteristics in 279 subjects with EIA

Sex	
F, n (%)	199 (71)
M, n (%)	80 (29)
Age (y)	
Mean (SD)	37.5 (12.1)
Range	13-77
Age at onset of symptoms (y)	
Mean (SD)	26 (9.0)
Range	3-66
Duration of symptoms (y)	
Mean (SD)	10.6 (9.1)
Range	0.3-60

TABLE II. Activities associated with symptoms of EIA in 279 subjects

Subjects	n (%)
Jogging	219 (78)
Walking	117 (42)
Tennis/racquetball	78 (28)
Dancing	73 (26)
Bicycling	68 (24)
Downhill skiing	18 (6)
Yardwork	17 (6)
Basketball	12 (4)
Stairmaster	5 (2)

Food-associated EIA

Shellfish, tomatoes, and wine or liquor were the most frequently reported precipitants, but dairy products (eg, cheese and milk) and celery were reported as triggers as well. The frequencies of food triggers reported by subjects are further detailed in Table IV. Overall, one third of the cohort (37%) reported that there were one or more food triggers that contributed to an attack.

Other atopic disorders were common in the subjects. Nearly one half of the cohort had seasonal rhinitis or dust or pet allergies. Nineteen percent reported concurrent asthma, and 10% had eczema. Ten subjects reported anaphylactic symptoms in settings independent of exercise.

Pregnancy and EIA

Data was available on 7 subjects who had EIA symptoms during pregnancy. All subjects had reduced their exercise regimen during pregnancy. Only one subject who continued exercising during most of her pregnancy reported worsening of her symptoms. In 5 women the frequency and severity of attacks increased when they resumed exercising postpartum. Three women reported improvement in their EIA symptoms during their second or third pregnancies. One woman, during labor, had mild pruritus and urticaria without other anaphylactic manifestations. Her delivery was without incident.

Management

Prophylaxis (Table V). Successful strategies for preventing attacks included avoiding exercise during extremely hot or cold weather, during the subjects' aller-

TABLE III. Frequency of EIA symptoms in 279 subjects

Symptom	n (%)
Pruritus	257 (92)
Urticaria	241 (86)
Angioedema	201 (72)
Flushing	194 (70)
Shortness of breath	141 (51)
Dysphagia	94 (34)
Chest tightness	92 (33)
Loss of consciousness	90 (32)
Diaphoresis	90 (32)
Headache	78 (28)
Nausea/diarrhea/colic	77 (28)
Choking/throat constriction/hoarseness	71 (25)

TABLE IV. Most commonly reported food triggers in 279 subjects with EIA

Food	n (%)
Shellfish	45 (16)
Alcohol	31 (11)
Tomatoes	23 (8)
Cheese	22 (8)
Celery	18 (7)
Strawberries	15 (5)
Milk	13 (4)
Wheat products	14 (5)
Peaches	13 (5)

gy season, or during humid weather. Avoiding ingestion of specific foods, aspirin, or nonsteroidal anti-inflammatory drugs before exercise helped as well.

Pharmacotherapy. Subjects most commonly used antihistamines (56%) and epinephrine (31%) to treat their attacks; however, corticosteroids (5%), β -agonist inhalers (5%), and cromolyn (2%) were used by some subjects. Twenty-eight percent of the subjects reported that they did not use medication to manage their attacks.

DISCUSSION

This series of subjects with symptoms of EIA recurring for longer than a decade suggests that in the majority of individuals the frequency of EIA attacks tends to decrease or remain the same over time. The average number of episodes per year at the time of presentation was 14.5 but decreased to 8.3 in the year of analysis. Moreover, one third of the subjects with EIA reported not experiencing any attacks in the year before the survey follow-up. Although remission of disease has been observed in other physical allergies (eg, cholinergic urticaria, in which symptoms predominate in adolescence and young adulthood but over time can remit completely⁸), it is likely that individual strategies, from modifying one's exercise regimen to avoiding known precipitants, mitigates symptoms.

Although a number of inciting agents have been suggested in EIA, no single antigen or allergen has been identified as a predictable trigger. A range of physical

TABLE V. Avoidance behaviors in 279 subjects with EIA

	n (%)
Avoid exercise during:	
Extremely hot or cold weather	124 (44)
Allergy season	101 (36)
Humid weather	91 (33)
Avoid eating before exercise	102 (37)
Modify exercise location (indoors vs outdoors)	68 (24)
Avoid specific drugs (aspirin or NSAIDs)	37 (13)

NSAID, Nonsteroidal anti-inflammatory drug.

activities have been associated with EIA. Although jogging was reported by 78% of subjects in our cohort to provoke an episode of EIA, less intensive physical activities, including bicycling and doing yard work, were also identified as triggers. Our results are similar to a previous investigation, in which activities requiring more cardiovascular demand were more likely to provoke an attack than less strenuous activities.^{1,5} The particular exercises reported to cause an episode may reflect, however, the popularity of a particular activity rather than necessarily identifying it as a definitive trigger.

Previous investigators have found that exercising during ambient temperature extremes and in humid conditions are frequently cited as provoking factors with regard to EIA.^{1,5} To reduce the occurrence of EIA, more than one third of the respondents in the current study avoided exercising during extremely warm or cold temperatures or during periods of high humidity. Avoidance of exercise during periods with high levels of seasonal aeroallergens was an effective way to reduce the severity and frequency of attacks for one third of subjects. This finding may be partially explained by the fact that many subjects had atopic disorders. Seventy-one percent of the subjects had at least one atopic disorder or a family history of atopy.

The ingestion of specific fruits, vegetables, grains, nuts, and fish have all been implicated as inciting attacks of EIA, but in some individuals the ingestion of any food before exercise can be a trigger.⁹⁻¹⁹ The most commonly reported food triggers were shellfish, nuts, tomatoes, celery, and dairy products. One third of the cohort reported that one or more foods appeared to trigger an attack. Wheat products were identified by only 5% of respondents as contributing to an episode of EIA. This contrasts with the data of investigators from Europe and Japan, who have reported a frequent association of EIA with wheat ingestion and specific IgE to wheat demonstrated by skin tests, RASTs, or CAP testing.^{11,12}

Antihistamines (H1 antagonists) and cromolyn taken before exercise may prevent or ameliorate symptoms in certain individuals with EIA, but β -agonists and xanthines offer little clinical benefit.^{1,2,13} In these subjects H1 antagonists were the most commonly used medications and, like epinephrine, used by 31% of the cohort, they were used on an emergent basis and not prophylactically. The other agents (ie, corticosteroids, β -agonists, and antidiarrheals) were also used, mostly to manage

symptoms once an attack occurred. Only 2% of the group used cromolyn as a prophylactic agent. More formal studies are necessary to determine the efficacy of a prophylactic regimen in EIA, but the episodic nature of this disease makes such evaluations difficult.

The course of EIA during pregnancy is not well studied. One report describes a woman with a long history of EIA and symptomatic dermatographism who experienced anaphylaxis during delivery of her 2 children.²⁰ Only 1 of 7 subjects who became pregnant in this report had a mild EIA attack during labor. It would be useful to recommend that postpartum patients with EIA consider resuming exercise gradually.

The EIA survey is based on previously published clinical criteria adapted to a questionnaire format. It is sensitive and specific for EIA and has a high likelihood ratio. In excluding individuals with urticaria in response to a passive increase in core body temperature, the questionnaire improves its specificity at the expense of sensitivity; however, this report does not likely include data from individuals with cholinergic urticaria or other "overlap" syndromes, the frequency of which may be high in clinical practice. Nevertheless, the EIA questionnaire may be a good screening tool for case finding in larger epidemiologic studies.

Several limitations in this study require comment. First, the natural history of EIA may be less severe than this study reflects because subjects with severe disease may have been selected. In support of this, the most common reason cited for nonparticipation was that the individual had been free of symptoms for many years. Second, the frequency of exercises that induce attacks are more reflective of the frequency of persons engaged in the exercise rather than a direct etiologic role. The limitations of a mail questionnaire should be recognized; many of the questions refer to symptoms experienced years before the survey. Some data may be prone to recall bias.

In summary, EIA is a chronic, episodic condition in which the frequency of attacks in most individuals tends to stabilize or decrease over time. Patients alleviate their symptoms by modifying their exercise program during allergy season and times of temperature extremes and by avoiding certain foods or drugs before exercising. Antihistamines and epinephrine are the most commonly used therapeutic agents, suggesting their emergent use for relief of symptoms. These results suggest that recognition of specific precipitating factors may allow the physician and patient to develop individual management strategies for controlling this condition.

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Correction

The following correction applies to an abstract that appeared in volume 103, number 1, part 2, p S142, 1999, of the Journal.

539 Ataxia-Telangiectasia (AT) Clinical and Laboratorial Evaluation of 11 Patients. *Pastorino AC, Almeida AG, Marques-Dias MJ, Jacob CMA, Duarte AS, Grumach AS*, Department of Pediatrics and Immunogenetic and Experimental Transplantation Laboratory (LIM73), University of São Paulo, Brazil.

Ataxia-telangiectasia (AT) is a recessive autosomic disease characterized by progressive cerebellar degeneration, chromosomal instability, which predispose to cancer and combined immunodeficiency, leading to recurrent respiratory infections.

Objective: Describe clinical and laboratorial evaluation of 11 AT patients followed at Allergy and Immunology and Neuropediatric Unit.

Methodology: Retrospective analysis of 11 patients (5M:6F) affected by AT and submitted to immunological investigation. Laboratorial evaluation included: blood count, serum alpha-feto protein and immunoglobulins (IgG,IgM,IgA,IgE), anti-poliovirus I, II and III antibodies titres, anti-A and/or anti-B Isohemagglutinins, lymphocyte subpopulations (CD4,CD8 and CD4/CD8 ratio), late cutaneous hypersensitivity tests and proliferative lymphocyte response (mitogens and Candida).

Results: Definitive AT diagnosis occurred at a mean of 82,4months (median=75m), first infections were present at 15,7 months and neurologic symptoms at 49,6 months. Main recurrent infections were: otitis, pneumonia and sinusitis and 3 patients had no infections. Failure to gain weight were detected in 5 patients. Alfa-feto protein levels were elevated in 10/11 patients and above 200 ng/ml in five. IgA deficiency (values < 5 mg/dl) was detected in 4/11 patients. The following values were below the 5th percentile for age: absolute number of lymphocytes (5/10), CD4+ (7/10), CD8+ (4/10) and CD4+/CD8+ ratio (4/10). Proliferative lymphocyte response was decreased in 4/8 patients. Prophylatic antibiotics were given to eight patients and gammaglobulin was replaced in three patients.

Conclusion: Variable clinical and immunological spectrum in AT patients has been observed. Atypical forms should be investigated in this combined immunodeficiency .