



Anaphylaxis and sport

Matteo Bonini and Paolo Palange

Purpose of review

This article aims to review the most relevant studies on exercise-induced anaphylaxis, published in the last year, in order to provide comprehensive and updated evidence and hopefully contribute to a better definition of its pathophysiological mechanisms and treatment strategies.

Recent findings

The search strategy was performed from 1/2/2013 to 31/1/2014 by scanning the principal electronic bibliographic database and by hand-searching the main scientific publications in Allergy and Clinical Immunology. Among the identified articles, 17 articles were selected to be part of the systematic review. Eligible studies included five experimental trials, eight case reports and four letters.

Summary

The overall collected evidence was of very low quality. No randomized controlled trials were identified by the searching process. Most of the data derived from reports performed in small population samples or even in individual cases. Except for one article addressing issues related to the preventive management of exercise-induced anaphylaxis, all other articles focused on prevalence rates, causative triggers and pathogenetic mechanisms. More interesting findings were related to the influence of the IL-4-C590T polymorphism on the onset of wheat-dependent exercise-induced anaphylaxis and to the usefulness of the immuno solid-phase allergen chip technique in the allergic screening of polysensitized athletes at risk of severe reactions.

Keywords

anaphylaxis, exercise, food, sport

INTRODUCTION

Exercise-induced anaphylaxis (EIA) is a rare, unpredictable and potentially fatal clinical syndrome in which anaphylaxis occurs in conjunction with exercise or other physical activities [1]. Since 1979 when Maulitz *et al.* [2] described the first case of EIA related to the ingestion of shellfish, several hundreds of cases have been reported, and the incidence of EIA appears to be increasing, possibly because of the popularity of practicing physical activity in developed countries. It has been estimated that 5–15% of anaphylactic episodes are caused by or are associated with exercise [3]. EIA may occur independently of food-allergen ingestion or may require the ingestion of a food allergen around the time of exercise, known as food-dependent exercise-induced anaphylaxis (FDEIA). In FDEIA, both the food allergen and exercise are independently tolerated [4].

The clinical presentation of EIA includes cutaneous manifestations such as pruritus, flushing, urticaria and angioedema; laryngeal oedema or bronchospasm; abdominal pain and nausea; and vascular collapse. Symptoms may vary in severity, although fatalities are rare (approximately 1/1000

cases). The largest cohort of patients with EIA includes 279 individuals identified through a medical questionnaire and followed up for 10 years [5,6]. In this study sample, females predominated with a ratio of 2:1 and a mean age of 37.5 years. However, EIA may occur in all ages and in both sexes. Furthermore, EIA has been reported to be more common in atopic individuals [7]. A heritable predisposition has been suggested by the presence of several affected members within families [8]. EIA generally occurs following submaximal exercise of a relatively short duration. Attacks have been more frequently associated with jogging, running, dancing, tennis, cycling, swimming and skiing [9]. Even minimal exertion, such as walking, was noted as a

Department of Public Health and Infectious Diseases, 'Sapienza' University of Rome, Rome, Italy

Correspondence to Matteo Bonini, Department of Public Health and Infectious Diseases, 'Sapienza' University, Viale dell'Università, 37, 00185, Rome, Italy. Tel: +39 3926852127; e-mail: matteo.bonini@uniroma1.it

Curr Opin Allergy Clin Immunol 2014, 14:323–327

DOI:10.1097/ACI.0000000000000074

KEY POINTS

- EIA is a rare, unpredictable and potentially fatal clinical syndrome in which anaphylaxis occurs in conjunction with exercise or other physical activities.
- EIA may occur either independently or in the presence of food-allergen ingestion (FDEIA).
- The pathophysiology of EIA remains to be fully elucidated.
- Overall, the scientific evidence on EIA published in the last year and collected in the present systematic review appears to be of very low quality.
- Future trials on EIA should be based on more robust study designs and should consider the creation of multicenter networks to increase population samples.

precipitant factor in many cases. EIA has been described in both elite athletes and non-competitive exercisers. There are no consistent exercise associated risk factors. However, extreme ambient temperature or humidity, hormonal changes and concomitant use of medication (i.e. aspirin) may represent additional triggers. Although wheat is the most commonly reported food allergen associated with FDEIA [10], many other food allergens have also been reported. Foods most frequently associated with FDEIA are given in the following list [9].

- (1) Grains/cereals: wheat (particularly the w-5 gliadin allergen), buckwheat, barley and oats
- (2) Foods contaminated with aero-allergens: house dust mite, penicillium mould
- (3) Seafood: fish and shellfish
- (4) Seeds: mustard and sesame
- (5) Nuts: peanut and tree nuts
- (6) Vegetables and fruit: celery, onion, soy, red bean, tomato orange and grape
- (7) Meat: pork and beef
- (8) Miscellaneous: cow's milk, wine and mushrooms

Diagnosis of EIA is mainly clinical. However, when symptoms and signs are not typical, the broad list of differential 'exercise-induced' (i.e. physical urticaria, mastocytosis, vasovagal episodes, exercise-induced bronchoconstriction, vocal cord dysfunction, and panic disorders) and 'exercise-related' (i.e. hidden food allergens in rehydration fluids, nut allergens in massage oils and contact skin reactions to latex) diagnoses should be considered. In particular, a diagnosis of exercise-induced bronchoconstriction should be thought for patients who experience predominantly respiratory symptoms in the absence of allergic systemic manifestations.

Investigations include skin-prick testing, as well as total and specific immunoglobulin-E (IgE) serum testing. Broad panels of allergens may be required, not to miss less common food sensitizations. Recently, the immuno solid-phase allergen chip (ISAC) microarray technique has shown additional diagnostic values in a real-life setting of polysensitized patients [11[¶]]. High serum tryptase levels are associated with anaphylaxis and have been shown to correlate with the severity of the symptoms, but are rarely tested in clinical practice [12]. A challenge-proven diagnosis is indicated to unequivocally establish the presence of EIA in a well-tolerated setting [13]. A diagnosis of food-independent EIA can only be made once FDEIA has been excluded thorough an accurate clinical history and the execution of a modified exercise food challenge test.

Mast cells have been shown to be implicated in the pathophysiology of EIA, although specific mechanisms remain to be fully elucidated. Current working hypotheses involve alterations in plasma osmolality, gastrointestinal permeability and pH, tissue enzyme activity, blood flow redistribution and facilitated epitope recognition/allergen binding [14]. The natural history of EIA is hardly predictable, but a gradual return to exercise can be safely achieved with careful management.

If a diagnosis of FDEIA has been made, dietary management is required. In view of the literature data and supposedly involved pathophysiological mechanisms [10], the allergen ingestion should be avoided at least 3 h prior to and 1 h following exercise. However, to successfully achieve a complete separation of food ingestion from exercise, it may be necessary to totally eliminate the causative allergen from the diet. The prophylactic use of antihistamines, leukotriene antagonists and oral steroids may attenuate symptoms, but their role needs to be further clarified [4]. A personalized emergency plan and medication kit are required for EIA patients, who should be trained in the identification and management of anaphylaxis [4]. Avoidance of beta-blockers, angiotensin converting-enzyme inhibitors and angiotensin-receptor blockers should be considered, because these drugs may increase the severity of anaphylaxis. It also seems prudent for food allergic individuals to avoid aspirin and alcohol, since they may alter gastrointestinal permeability, prior to exercise.

This article aims to review the most relevant studies, on exercise-induced anaphylaxis, published in the last 12 months, in order to provide comprehensive and updated evidence, which may hopefully contribute to a better understanding of involved pathophysiological mechanisms and to an improved disease management.

METHODS

The search strategy was performed from 1/2/2013 to 31/1/2014 using the following key terms: 'anaphylaxis', 'exercise', 'sport', 'physical activity' and 'athlete'. Articles were identified by scanning the principal electronic bibliographic database (Medline, Embase, CENTRAL), as well as by hand-searching the main scientific journals and meeting abstracts in the area of Allergy and Clinical Immunology. Titles and abstracts of identified articles were screened independently by two reviewers, and those consensually considered eligible for the review were retrieved in full. Reference lists of included studies, recent reviews and textbooks were also screened for relevant citations. No language restrictions were applied.

RESULTS

The performed search strategy identified 138 articles. After having removed overlaps and excluded nonpertinent and nonoriginal manuscripts, as well as texts published as abstract only, 16 articles were selected in agreement by the two reviewers to be included in the systematic review. One further article was added through the hand-searching process. Eligible studies included: five experimental trials, eight case reports and four letters. Below are summarized the most relevant findings emerging from the collected evidence.

Cai and Yin [15[■]] performed an interesting case-control study, with the aim to investigate the association between single nucleotide polymorphisms (SNPs) of three cytokine-related genes (IL-4-C590T, IL-4RA A1727G and IL-10-A627C) and the onset of wheat-dependent exercise-induced anaphylaxis (WDEIA). The authors recruited and genotyped 51 patients with only WDEIA (case-subset), 17 patients with WDEIA associated with other allergic diseases (control 1), 18 patients with FDEIA (control 2), 72 patients with other allergic disease (control 3) and 203 healthy people (control 4). Statistically significant differences in genotype frequencies of IL-4-C590T were found between cases and controls 1 and 4 ($P=0.03$ and 0.001 , respectively), under the model of CC versus CT versus TT. Comparing with healthy subjects, the homozygote CC [CC versus (CT + TT)] conferred an increased risk of inducing WDEIA [OR = 5.22 (95% CI = 1.67–16.31), $P=0.006$]. Tests of homozygote of TT [TT versus (CC + CT)] revealed that TT genotype offered significant protection for WDEIA cases as compared with controls 1, 3 and 4. All other genotype associations studied showed no statistically significant differences. Interestingly, no study had been previously published to explore the genetic background of WDEIA.

Thirty-six patients with suspected WDEIA were enrolled in the study of Kohno *et al.* [16] and divided into three different groups according to the results of wheat and exercise and/or aspirin challenge testing and serum gliadin levels. Serum gliadin concentrations were determined using an ELISA kit for wheat gliadin. All measurements were performed in duplicate, setting the detection limit of serum gliadin level at 15 pg/mL. Patients who were evaluated as having a positive result in the challenge tests received a definite diagnosis of WDEIA (Group I). In contrast, patients with negative challenge test results were divided into either an undetectable or a detectable group (Groups II and III, respectively) according to their serum gliadin concentration. Patients in Group II were considered insufficiently challenged and were required to undergo retesting. Patients with a positive retest were considered as definite WDEIA, whereas those with a negative retest were followed with a diet management. Patients in Group III maintained a normal diet for 1 year, and during this time-period, their allergic symptoms were carefully monitored. If a patient in this group had no symptoms during the year, a diagnosis of non-WDEIA was given. The presence of symptoms with wheat and exercise and/or NSAIDs suggested a diagnosis of probable WDEIA or other food allergies. Results provided evidence that serum gliadin monitoring may be a useful tool to extract the patients with false-negative results, since a lack of increased serum gliadin can identify an insufficient challenge test for the diagnosis of WDEIA.

In an article published in *Allergy* [17], our group aimed at evaluating whether the ImmunoCAP ISAC might provide additional useful information to those obtained by conventional IgE tests in identifying different sensitization profiles in polysensitized allergic athletes. ISAC represents a microarray technology of recent introduction, which allows the detection of IgE antibodies to more than 100 molecular components of allergens, including molecules indicating a genuine sensitization (e.g. Phl p 1, 2, 4, 5, 6, 11 for grass; Der p 1 and Der p 2 for mites; Amb a 1 for Ambrosia; etc.), cross-reacting molecules present in different allergen sources (pathogenesis-related protein family 10 proteins; profilins; tropomyosins; cross-reacting carbohydrate determinants; calcium-binding proteins) and markers of sensitizations potentially responsible for severe allergic reactions, such as EIA (Arah 1, 2, 3; Pru p 3; Cor a 8; omega-5 gliadin; lipid transfer proteins). Among the 435 athletes selected for the Beijing Olympics, 72 polysensitized athletes were chosen for being representative of different atopic phenotypes on the basis of clinical history, results of a specific allergy questionnaire (AQUA) [18], physical examination, skin-prick tests,

pulmonary function tests and specific IgE determination. Two age-matched and sex-matched control groups (polysensitized sedentary individuals and healthy athletes) were also included in the study design. Among data obtained, it may be interesting to report that IgE antibodies to allergens at risk for severe allergic reactions were found in a relevant percentage of athletes (4/72, 6%), mostly in those with oral allergy syndrome, but even in asymptomatic athletes. ISAC might therefore represent a useful additional allergy test to detect athletes at risk for severe allergic reactions and to adopt appropriate preventive measures.

Two publications produced by a Japanese group of authors addressed the role of causative allergens, as well as the sensitivity and clinical course of patients with WDEIA sensitized to hydrolyzed wheat protein (HWP) in facial soap [19,20]. In the first study, sera were obtained from 22 patients with HWP-sensitized WDEIA. The allergenic activities of HWP and six recombinant wheat gluten proteins, including α/β -gliadin, γ -gliadin, ω 1,2-gliadin and ω 5-gliadin and low-molecular weight and high-molecular weight (HMW) glutenins, were characterized by immunoblot analysis and histamine releasing test. IgE-binding epitopes were identified using arrays of overlapping peptides synthesized on SPOTs membrane. Immunoblot analysis showed that IgE antibodies (Abs) from HWP-WDEIA bound to α/β -gliadin, γ -gliadin and ω 1,2-gliadin. Recombinant γ -gliadin induced significant histamine release from basophils in eight of 11 patients with HWP-WDEIA, binding with IgE antibodies more strongly compared with the native epitope-peptide. These findings were suggested as of potential usefulness to develop tools for diagnosis and desensitization therapy for HWP-WDEIA. The second manuscript is based on a retrospective study in 30 HWP-WDEIA patients. Data analysis revealed that patients with HWP-WDEIA were mainly women (28/30) with a mean age of 40.3 ± 16.9 years. Duration of use of HWP-containing soap was from <1 month to 48 months. Symptoms were mainly represented by urticaria (90.0%), dyspnea (78.6%) and angioedema (75.8%). Skin prick tests were positive in 18/22 patients for wheat and in 17/22 for bread. All patients were positive against HWP in the histamine release test, glutenins inducing the highest histamine release from basophils. The sensitivity of patients was reduced over months, along with the discontinuance of HWP-soap.

Among the eight collected case reports [21–28], the most interesting findings were related to the description of a mite ingestion associated EIA, to the proposal of a new EIA pathological mechanism associated with the inhibitory effects of exercise on

gastric acid secretion and to the induction of specific oral tolerance using IFN-gamma in two cases of FDEIA.

The four included letters focused on unconventional cases of EIA. An episode of FDEIA by nectarine was described in a 14-year-old boy with weakly positive nectarine prick-by-prick and negative specific IgE to Pru p 3 [29]. Occurrence of WDEIA was reported in three patients in whom the causative allergen was a 9-kDa wheat lipid transfer protein and in a 51-year-old woman without filaggrin mutations [30,31]. A premature onset of EIA in a 6-year-old Indian boy was also presented [32].

At last, although not included in the present systematic review because of their nonoriginal study design, a deserved mention should be made to the 2013 Update of the World Allergy Organization Anaphylaxis Guidelines [33[¶]] and to the article of Morita *et al.* [34[¶]] on recent advances of in-vitro tests for the diagnosis of FDEIA for their innovative contents, clinical relevance and potential interest for readers.

CONCLUSION

Seventeen original studies have been included in the present systematic review. The overall collected evidence appears to be of very low quality. No randomized controlled trials were identified by the searching process. Apart from the five experimental studies (three case-control studies, one cohort study and one retrospective study), all other data derived from reports performed in extremely small population samples or even in individual cases. The majority of the articles focused on prevalence rates, causative triggers and pathophysiological mechanisms of EIA. Only one article addressed issues related to the management of EIA, by reporting the successful use of specific oral tolerance induction with IFN-gamma in two patients with WDEIA. The most interesting findings, for the potential development of future research lines and for the improvement of diagnostic flow charts, were those related to the genetic results showing the influence of the IL-4-C590T polymorphism on the onset of WDEIA, as well as those related to the reliability of the ISAC technique in the allergic screening of athletes, especially if polysensitized and at risk of severe reactions. In order to improve the quality of available evidence, new trials should be based on more robust study designs and should consider the creation of multicenter networks to increase the number of included individuals, strengthening the power of the trials.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Castells MC, Horan RF, Sheffer AL. Exercise-induced anaphylaxis. *Clin Rev Allergy Immunol* 1999; 17:413–424.
 2. Maulitz RM, Pratt DS, Schocket AL. Exercise-induced anaphylactic reaction to shellfish. *J Allergy Clin Immunol* 1979; 63:433–434.
 3. Du Toit G. Food-dependent exercise-induced anaphylaxis in childhood. *Pediatr Allergy Immunol* 2007; 18:455–463.
 4. Robson-Ansley P, Toit GD. Pathophysiology, diagnosis and management of exercise-induced anaphylaxis. *Curr Opin Allergy Clin Immunol* 2010; 10:312–317.
 5. Wade JP, Liang MH, Sheffer AL. Exercise-induced anaphylaxis: epidemiological observations. In: Tauber AI, Weintraub BU, Simon A, editors. *Biochemistry of the acute allergic reaction. Fifth international symposium. Atlanta: RLiss; 1989. pp. 175–182.*
 6. Shadick NA, Liang MH, Partridge AJ, et al. The natural history of exercise-induced anaphylaxis: survey results from a 10-year follow up study. *J Allergy Clin Immunol* 1999; 104:123–127.
 7. Sheffer AL, Soter NA, McFadden ER Jr, et al. Exercise-induced anaphylaxis: a distinct form of physical allergy. *J Allergy Clin Immunol* 1983; 71:311–316.
 8. Grant JA, Farnam J, Lord RA, et al. Familial exercise-induced anaphylaxis. *Ann Allergy* 1985; 54:35–38.
 9. Castells MC, Horan RF, Sheffer AL. Exercise-induced anaphylaxis. *Curr Allergy Asthma Rep* 2003; 3:15–21.
 10. Aihara Y, Takahashi Y, Kotoyori T, et al. Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior-high-school students. *J Allergy Clin Immunol* 2001; 108:1035–1039.
 11. Passalacqua G, Melioli G, Bonifazi F, et al. The additional values of microarray allergen assay in the management of polysensitized patients with respiratory allergy. *Allergy* 2013; 68:1029–1033.
- An interesting article for the potential usefulness of the innovative ISAC microarray technique in EIA.
12. Schwartz HJ. Elevated serum tryptase in exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1995; 95:917–919.
 13. Sheffer AL, Austen KF. Exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1980; 66:106–111.
 14. Robson-Ansley P, Bonini M, Delgado L, et al. Pathophysiological mechanisms of exercise induced, anaphylaxis: an EAACI position statement. 2014 submitted to *Allergy*.
 15. Cai PP, Yin J. Association between single nucleotide polymorphisms and wheat-dependent exercise-induced anaphylaxis in Chinese population. *Chin Med J (Engl)* 2013; 126:1159–1165.
- First genetic study on WDEIA.
16. Kohno K, Matsuo H, Takahashi H, et al. Serum gliadin monitoring extracts patients with false negative results in challenge tests for the diagnosis of wheat-dependent exercise-induced anaphylaxis. *Allergol Int* 2013; 62:229–238.
 17. Bonini M, Marcomini L, Gramiccioni C, et al. Microarray evaluation of specific IgE to allergen components in elite athletes. *Allergy* 2012; 67:1557–1564.
 18. Bonini M, Braidò F, Baiardini I, et al. AQUA: allergy questionnaire for athletes. Development and validation. *Med Sci Sports Exerc* 2009; 41:1034–1041.
 19. Yokooji T, Kurihara S, Murakami T, et al. Characterization of causative allergens for wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat proteins in facial soap. *Allergol Int* 2013; 62:435–445.
 20. Hiragun M, Ishii K, Hiragun T, et al. The sensitivity and clinical course of patients with wheat-dependent exercise-induced anaphylaxis sensitized to hydrolyzed wheat protein in facial soap – secondary publication. *Allergol Int* 2013; 62:351–358.
 21. Adachi YS, Itazawa T, Okabe Y, et al. A case of mite-ingestion-associated exercise-induced anaphylaxis mimicking wheat-dependent exercise-induced anaphylaxis. *Int Arch Allergy Immunol* 2013; 162:181–183.
 22. Ahanchian H, Farid R, Ansari E, et al. Food-dependent exercise-induced anaphylaxis due to wheat in a young woman. *Iran J Allergy Asthma Immunol* 2013; 12:93–95.
 23. Chen JY, Quirt J, Lee KJ. Proposed new mechanism for food and exercise induced anaphylaxis based on case studies. *Allergy Asthma Clin Immunol* 2013; 9:11.
 24. Jaqua NT, Peterson MR, Davis KL. Exercise-induced anaphylaxis: a case report and review of the diagnosis and treatment of a rare but potentially life-threatening syndrome. *Case Rep Med* 2013; 610726.
 25. Mobayed HM, Ali Al-Nesf M. Two cases of food-dependent exercise-induced anaphylaxis with different culprit foods. *Ann Thorac Med* 2014; 9:42–44.
 26. Noh G, Lee JH. Specific oral tolerance induction using IFN-gamma in 2 cases of food-dependent exercise-induced anaphylaxis. *Case Rep Med* 2013; 259692.
 27. Pérez-Rangel I, Gonzalo-Garijo MA, Pérez-Calderón R, et al. Wheat-dependent exercise-induced anaphylaxis in elderly patients. *Ann Allergy Asthma Immunol* 2013; 110:121–123.
 28. Tritar F, Matoussi N, Daghfous H, et al. Food-induced anaphylaxis exercise in children: a report of two cases [in French]. *Revue française d'allergologie* 2014; 54:30–33.
 29. Miceli Sopo S, Monaco S, Giorgio V, et al. Food-dependent exercise-induced anaphylaxis (FDEIA) by nectarine in a paediatric patient with weakly positive nectarine prick-by-prick and negative specific IgE to Pru p 3. *Allergol Immunopathol (Madr)* 2013; 41:201–203.
 30. Pastorello EA, Farioli L, Stafylaraki C, et al. Wheat-dependent exercise-induced, anaphylaxis caused by a lipid transfer protein and not by ω -5 gliadin. *Ann Allergy Asthma Immunol* 2014; 112:386–387.
 31. Iga N, Tanizaki H, Endo Y, et al. Hydrolyzed wheat protein-containing facial soap-induced wheat-dependent exercise-induced anaphylaxis in a patient without filaggrin mutations. *J Dermatol* 2013; 40:494–495.
 32. Mittal P, Singla S. Exercise induced anaphylaxis. *Indian Pediatr* 2013; 50:249.
 33. Simons FE, Arduzzo LR, Dimov V, et al. World allergy organization anaphylaxis guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol* 2013; 162:193–204.
- Updated and evidence-based guidelines on anaphylaxis.
34. Morita E, Chinuki Y, Takahashi H. Recent advances of in vitro tests for the diagnosis of food-dependent exercise-induced anaphylaxis. *J Dermatol Sci* 2013; 71:155–159.
- Elegant review on diagnostic in-vitro tests for FDEIA.