

# Food related, exercise induced anaphylaxis

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## Abstract

**Four children under 12 years of age with food dependent, exercise induced anaphylaxis (EIAN) were investigated. These children and five controls performed exercise challenges when fasting and one hour after a meal without food suspected to predispose to the reaction. Patients then performed exercise tests after intake of each suspected food. Three out of 15 food-exercise combination challenges were positive, but no reactions were provoked after exercise without prior intake of suspected foods. Patients underwent skin prick tests to foods and serum total and specific IgE antibodies were measured. Skin prick test results were positive and RAST results were positive in two of three instances. In case 3, food-exercise combination challenges did not provoke any clinical reaction. The diagnosis of food dependent EIAN should be considered in young children with EIAN of unknown origin.**

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Keywords: food dependent exercise induced anaphylaxis, exercise challenge, preadolescents.

Exercise induced anaphylaxis (EIAN) is a recently described syndrome, characterised by erythema, urticaria, upper respiratory tract obstruction, and/or collapse in association with exercise.<sup>1</sup> In a few cases, symptoms occur only when exercise is preceded by eating.<sup>2</sup> Two subsets of food dependent EIAN have been described.<sup>3</sup> Several patients have EIAN only when they ingest a meal before exercise (non-specific food dependent EIAN).<sup>3,4</sup> In other patients, EIAN occurs only after eating a particular food (specific food dependent EIAN).<sup>2</sup> Foods incriminated include celery,<sup>3</sup> shellfish,<sup>2,4-6</sup> wheat,<sup>5,8-12</sup> grapes,<sup>5</sup> nuts,<sup>13</sup> peach,<sup>13</sup> egg,<sup>7,14</sup> orange,<sup>15</sup> apple,<sup>16</sup> hazelnut,<sup>17</sup> cheese,<sup>18</sup> and cabbage.<sup>19</sup>

Food dependent EIAN has been described previously only in adults and adolescents.<sup>2-18</sup> We present characteristic features of four children with food dependent EIAN.

## Methods

### PATIENT POPULATION

All children were evaluated at the department of paediatrics, University Hospital of Parma, Italy, where prospective studies of children with food dependent EIAN were in progress. Of seven patients with food dependent EIAN seen from January 1992 to December 1994, four were children under 12 years of age. Clinical

and laboratory data were recorded prospectively in all patients from the time of admission to the study.

Patients were diagnosed with EIAN according to the following features<sup>1,5,19-21</sup>: (1) episodes of upper respiratory tract obstruction or collapse with rash or urticaria precipitated by exercise, or both; (2) anaphylaxis was not experienced in response to warm baths, showers, fever, or other events increasing core body temperature.

### IMMUNOLOGICAL STUDIES

Patients underwent skin prick tests with a 1:20 (wt:vol) concentration of food extracts (Bayerpharm, Milan, Italy). In patient 3, fresh food skin prick tests were done by a prick + prick technique<sup>22</sup> with garlic and pine nut, which were not commercially available. The size of the skin test weal was compared with histamine, 1 mg/ml, and the diluent. The test was considered positive when antigens elicited a weal greater than 3 mm, after subtracting the diameter of the negative control weal and at least half the area of the histamine standard.<sup>23,24</sup>

Blood was taken to measure both specific IgE antibodies to foods by RAST (Pharmacia, Uppsala, Sweden) and total IgE levels by PRIST (Pharmacia, Uppsala, Sweden).

### EXERCISE CHALLENGES

Patients followed a 15 day elimination diet before the exercise challenge when food suspected of inducing EIAN was avoided. On the first day of the study, patients underwent a control exercise test after 12 hours of fasting. An exercise test was then performed one hour after a meal which did not contain suspected foods and one hour after eating each suspected food. As a control, five healthy children performed the exercise challenge both fasting and one hour after a meal. Exercise challenge tests were performed on separate days.

The exercise test consisted of free running back and forth along a 45 m straight corridor for six minutes, increasing heart rate to at least 170 beats/min.<sup>25</sup> Lung function was measured with a computerised spirometer (Microloop-Markos). Measurements were performed before running and at 3 min, 6 min, 10 min, and 15 min intervals after beginning to exercise.<sup>26</sup> The exercise test was performed if both the baseline forced expiratory volume during the first second of expiration (FEV<sub>1</sub>) and peak expiratory flow rate (PEFR) were greater than 90% of mean predicted value.<sup>27</sup> Blood pressure was monitored before and after exercise challenge and during reactions.  $\beta_2$  Agonists and inhaled corticosteroids were withheld for

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Table 1 Clinical features of food dependent exercise induced anaphylaxis

	Patient			
	1	2	3	4
Age (years)	7	9	9	11
Sex	M	M	M	M
Age of onset (years)	6	6	8	11
No of attacks	2	15	4	2
Suspected foods eaten before exercise	Tomato, chestnut	Tomato, peas, rice, egg, beans	Wheat, peas, potato, tomato, spinach, garlic, lettuce, basil, pine nut	Tomato
Type of exercise	Running	Running	Soccer	Gymnastic
Length of exercise	5'	5'	10'	10'
Distance food-exercise	30'	45'	60'	30'
Symptoms	Urticaria, angio-oedema, vomiting, dyspnoea with the feeling of 'lump in the throat'	Pruritus, urticaria, angio-oedema, sneezing, rhinorrhea, lacrymation, conjunctival injection	Urticaria, angio-oedema, difficult breathing with feeling of throat closure	Urticaria, angio-oedema, dyspnoea, hoarseness
Personal atopic history	Negative	Oculorhinitis due to artemisia	Negative	Oculorhinitis, asthma due to artemisia and grasses
Family atopic history	Negative	Brother: oculorhinitis due to grasses, urticaria	Brother: urticaria, paternal grandfather: asthma due to grasses and mites	Maternal grandmother: asthma due to mites

Table 2 Results of skin prick tests, circulating IgE, and food-exercise combination challenges to suspected foods

Case	Foods	Skin prick test	RAST score	Total IgE (U/ml)	Food-exercise combination challenges			
					Prodromal symptoms	Complete symptoms	Max % FEV <sub>1</sub> fall	Max % PEF <sub>R</sub> fall
1	Tomato	+	3	167	Neg	Neg	2	4
	Chestnut	+	3		Generalised pruritus	Wheezing, urticaria	24.8	46
2	Tomato	-	1	6	Neg	Neg	4	8
	Egg	-	0		Neg	Neg	0	0
	Beans	+	0		Neg	Neg	0.4	0.7
	Peas	+	0		Neg	Neg	0.5	0.7
	Rice	+	0		Neg	Oculorhinitis, pruritus, wheezing, angio-oedema	21	18
3	Garlic	+	2	287	Neg	Neg	0	1.7
	Tomato	+	3		Neg	Neg	0	-0.9
	Soy	+	2		Neg	Neg	0	-1.4
	Basil	-	nd		Neg	Neg	0	-3.9
	Pine nut	+	nd		Neg	Neg	5.2	-2.2
	Rice	+	2		Neg	Neg	-5.2	-3.3
	Meal with above foods	+	2		Neg	Neg	-5.2	0.3
4	Tomato	+	3	95	Neg	Urticaria, angio-oedema, dyspnoea, hoarseness	25.9	10.8

nd = not done; neg = negative.

at least 12 hours before each testing session and oral steroids and antihistamines for eight days.

All exercise challenges were conducted in the same conditions of temperature (20-22°C) and humidity, at the same time of day.

Baseline values of PEF<sub>R</sub> and FEV<sub>1</sub> were expressed in absolute terms and as percentage of predicted values.<sup>27</sup> Postexercise values of PEF<sub>R</sub> and FEV<sub>1</sub> were expressed as percentage changes from baseline at individual time points. Maximum percentage drop in PEF<sub>R</sub> as well as in FEV<sub>1</sub> was calculated as follows:  $(100 \times (\text{pre-exercise value} - \text{lowest value after exercise}) / \text{pre-exercise value})$ . The exercise test was considered positive for bronchospasm if it caused a fall of PEF<sub>R</sub> of > 12% or of FEV<sub>1</sub> of > 10%.<sup>28</sup>

## Results

### PATIENT CHARACTERISTICS

These are summarised in table 1.

Before exercising, all patients had eaten specific foods which were suspected to trigger the reaction. Intake of specific foods not followed by exercise provoked no adverse reaction. Similar exercise never resulted in symptoms without ingestion of suspected foods. No child

was reported as having episodes at rest. No prodromal manifestation was reported by children or parents.

No patient experienced anaphylactic reactions following warm baths, fever, or other events increasing core body temperature, drug intake, cold temperature, weather conditions, or exposure to dental amalgam.

The interval between clinical onset and diagnosis varied from three years, in patient 2, to two months in patient 4.

### EXERCISE CHALLENGE

In the patients, no reactions were provoked by exercise tests performed on fasting or after taking a meal without suspected foods.

Three out of 15 food-exercise combination challenges were positive (table 2). In three patients a particular food triggered the reaction. Reactions always developed immediately after running. In one child there was prodromal diffuse pruritus on test challenge. Symptoms elicited by test challenges were urticaria in two cases, angio-oedema in two, oculorhinitis in one, wheezing in two, and dyspnoea and hoarseness in one. Airway obstruction on lung function testing was found after all positive exercise tests. After challenges, blood pressure

did not fall below resting values. Patients were treated with antihistamines, corticosteroids, adrenaline, and inhaled salbutamol to resolve the episodes.

Patient 3 had neither clinical reactions nor changes in lung function following food-exercise combination challenges (table 2) despite there being a previous history that food intake before exercise was a predisposing factor. Moreover, parents denied any previous episode in association with exercise not preceded by a meal. An exercise test performed after a meal containing all suspected foods was negative.

In controls, neither symptoms nor significant changes in lung function were provoked by exercise challenges.

In table 2, total IgE values, skin prick tests and RAST results of suspected foods are listed. Eleven of 14 skin prick test results and four of 12 RAST results to suspected foods were positive. Skin prick test results to foods predisposing the reaction were positive; RAST results were positive in two of three instances.

### Discussion

Food dependent EIAN has not been reported previously in children less than 12 years old,<sup>2-18</sup> either because it was unrecognised or is uncommon in this age group. The first hypothesis seems to be likely since, in our population, case ascertainment occurred some years after the first attack when there was heightened awareness of this syndrome because of local publicity about our research. The latter hypothesis is speculative because the prevalence of the disease is unknown.

Although the sample size was far too small for any definitive conclusion, these children's symptoms differed from those seen in adolescent and adult onset patients.<sup>2-18</sup> For example, no child had collapse, and wheezing was more common in childhood onset patients.

EIAN must be distinguished from cholinergic urticaria and exercise induced asthma. In our study, we concluded that no child had cholinergic urticaria because cutaneous lesions did not occur after warm baths, fever, or emotional distress.<sup>20 21</sup> Furthermore, wheezing occurred after food-exercise combination challenges, but not after control exercise tests, so it was not due to exercise induced asthma.

Precipitating foods have been identified by exercise tests performed after intake of each food.<sup>5 9 10 15-18</sup> Such challenges failed to provoke a clinical reaction in patient 3. Because an episode does not necessarily occur each time a child exercises,<sup>2</sup> negative exercise challenge results do not rule out EIAN.<sup>15</sup> We offer two explanations: first, exercise conditions in a laboratory setting may be insufficiently severe to induce reactions.<sup>5</sup> Second, other factors could be associated with the development of symptoms, but we took care to exclude such provoking factors as drug intake,<sup>15 19</sup> cold temperature,<sup>16</sup> dental amalgam,<sup>29</sup> or weather conditions.<sup>19 20</sup>

We found the parents' history helpful in determining suspect foods. However, parents were able to identify a relation between a

particular food intake and anaphylactic reaction only if the food was uncommon in the children's diet.

Consistent with previous reports,<sup>2 4 6 9 15 16</sup> we found that skin prick test results to foods had excellent sensitivity but poor specificity.

In this small series, RAST results were less accurate than skin prick test results to foods. Therefore the food-exercise combination challenge seems to be a more reliable diagnostic test in food dependent EIAN.

The mechanism of food dependent EIAN is not clear. It is probable that a food dependent IgE mediated reaction may lower the threshold for mediator release from mast cells induced by exercise.<sup>3</sup> This is indicated by the following observations: (1) exercise without food ingestion increased plasma histamine concentration in some patients both with food dependent EIAN<sup>5 7</sup> or with EIAN<sup>21 30 31</sup>; (2) in a few cases, histamine concentration was higher after the food-exercise combination challenge than after the exercise challenge alone<sup>5 7</sup>; (3) our data showed that patients had atopic backgrounds and an in vivo and in vitro immediate hypersensitivity reaction to the foods which predisposed the attacks.

We conclude that unexplained EIAN should prompt consideration of the precipitating role of foods in preadolescents. Early diagnosis in this age group may avoid unnecessary reduction of physical exertion and long periods of restricted diet, and prevent serious reactions.

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