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.

(Arch Dis Child 1996;75:141–144)

IMMUNOLOGICAL STUDIES
Patients underwent skin prick tests with a 1:20 (wt:vol) concentration of food extracts (Bayropharm, Milan, Italy). In patient 3, fresh food skin prick tests were done by a prick + pricking technique with garlic and pine nut, which were not commercially available. The size of the skin test 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.

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. 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. The exercise test was performed if both the baseline forced expiratory volume during the first second of expiration (FEV₁) and peak expiratory flow rate (PEFR) were greater than 90% of mean predicted value. Blood pressure was monitored before and after exercise challenge and during reactions. β₂ Agonists and inhaled corticosteroids were withheld for...
Table 1 Clinical features of food dependent exercise induced anaphylaxis

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

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

<table>
<thead>
<tr>
<th>Case</th>
<th>Foods</th>
<th>Skin prick test</th>
<th>RAST score</th>
<th>Total IgE (U/ml)</th>
<th>Food-exercise combination challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prodomal symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Tomato</td>
<td>+</td>
<td>3</td>
<td>167</td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Chestnut</td>
<td>+</td>
<td>3</td>
<td></td>
<td>Neg</td>
</tr>
<tr>
<td>2</td>
<td>Tomato</td>
<td>-</td>
<td>1</td>
<td>6</td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Egg</td>
<td>-</td>
<td>0</td>
<td></td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Beans</td>
<td>+</td>
<td>0</td>
<td></td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Peas</td>
<td>+</td>
<td>0</td>
<td></td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Rice</td>
<td>+</td>
<td>0</td>
<td></td>
<td>Neg</td>
</tr>
<tr>
<td>3</td>
<td>Garlic</td>
<td>+</td>
<td>2</td>
<td>287</td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Tomato</td>
<td>+</td>
<td>3</td>
<td></td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Soy</td>
<td>+</td>
<td>2</td>
<td></td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Basil</td>
<td>-</td>
<td>nd</td>
<td></td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Pine nut</td>
<td>+</td>
<td>nd</td>
<td></td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Rice</td>
<td>+</td>
<td>2</td>
<td></td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>Meal with above foods</td>
<td>+</td>
<td>3</td>
<td>95</td>
<td>Neg</td>
</tr>
</tbody>
</table>

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 PEFR and FEV<sub>1</sub> were expressed in absolute terms and as percentage of predicted values. Postexercise values of PEFR and FEV<sub>1</sub> were expressed as percentage changes from baseline at individual time points. Maximum percentage drop in PEFR as well as in FEV<sub>1</sub> was calculated as follows: (100 × (pre-exercise value - lowest value after exercise) / pre-exercise value). The exercise test was considered positive for bronchospasm if it caused a fall of PEFR 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 pruritis 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
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Discussion
Food dependent EIAn has not been reported previously in children less than 12 years old,7–10 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.7–10 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.20,21 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.5,9,10,13–16 Such challenges failed to provoke a clinical reaction in patient 3. Because an episode does not necessarily occur each time a child exercises,7 negative exercise challenge results do not rule out EIAn.15 We offer two explanations: first, exercise conditions in a laboratory setting may be insufficiently severe to induce reactions.7 Second, other factors could be associated with the development of symptoms, but we took care to exclude such provoking factors as drug intake,15,19 cold temperatures,16 dental amalgam,10 or weather conditions.19,20

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,2,4,9,10,16 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.7 This is indicated by the following observations: (1) exercise without food ingestion increased plasma histamine concentration in some patients both with food dependent EIAn7 or with EIAn4,10,13; (2) in a few cases, histamine concentration was higher after the food–exercise combination challenge than after the exercise challenge alone7; (3) our data showed that patients had atopic backgrounds and an in vivo 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.


