

Food intake in combination with a rise in body temperature: A newly identified cause of angioedema

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We report a case in which a combination of non-allergenic factors induced angioedema, which has not been described before in the literature.

CASE REPORT

In a 43-year-old woman with a 15-year history of recurrent attacks of severe periorbital angioedema, all efforts by numerous specialists to identify the causative agent had failed. By means of careful reevaluation of the history and the use of several different provocation tests, we found that food intake in combination with a rise in body temperature was the cause.

Within 2 hours after food intake, a rise of body temperature of 0.9° to 1.1° C as a result of either exercise or a hot water bath (40° C, 15 minutes) induced a most impressive periorbital angioedema that lasted for 24 to 48 hours. In contrast, the same rise in body temperature on an empty stomach caused no angioedema. The angioedema was not accompanied by extracutaneous symptoms such as bronchoconstriction or a decrease in blood pressure. Typical food allergy was considered unlikely after negative results of prick test and RAST were obtained. A 3-day trial of ingestion of only unseasoned rice, potatoes, and mineral water revealed the patient's tolerance to these foods. However, on the fourth morning, the reaction could be provoked when a breakfast of cold cooked rice was followed by a warm bath. On the other hand, angioedema was never observed after food intake without subsequent rise in body temperature, regardless of the kind of food eaten. Provocation tests with full meals that consisted of common allergens such as dairy products were equally ineffective on their own as were provocation tests with encapsulated food additives known as pseudoallergens.

The symptoms could not be suppressed by antihistamines, but the anticholinergic drug pirenzepine was effective.

An important observation, regarding the therapeutic approach, was the occurrence of a refractory period. After provocation on an empty stomach, which did not result in angioedema, neither exercise nor a warm bath after food intake induced angioedema for the rest of the day. We therefore suggested that this effect could be used therapeutically. To the patient's satisfaction, daily exercise for 20 minutes before breakfast has kept her free of symptoms for nearly half a year.

DISCUSSION

Angioedema could only be provoked when food intake was followed by an active or passive rise in body temperature. Food allergy could be excluded as a cause. Antihistamines were not effective, but the reaction could be blocked by pirenzepine, an anticholinergic drug, which suggests that the parasympathetic nervous system played a crucial role. An additive or synergistic effect of two incomplete stimuli, a rise in body temperature and the release of neurogenic mediators after food intake, appears to be a possible explanation.

A similar combination of two incomplete stimuli is sometimes seen in exercise-induced anaphylaxis in which vigorous exercise is the trigger, though in some patients only in combination with preceding food intake.¹ In contrast to our case, exercise-induced anaphylaxis cannot be induced by elevating the body temperature.

In our patient a refractory period could be induced by exercising on an empty stomach or by taking a hot bath before breakfast. Neither stimulus elicited angioedema by itself. There is a similarity to the refractory period seen in some patients with exercise-induced asthma.² Refractoriness can be induced by moderate exercise that does not lead to bronchoconstriction. There seems to be a threshold. A weak stimulus is not

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Accepted for publication Dec. 18, 1992.

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J ALLERGY CLIN IMMUNOL 1993;91:1226-7.

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0091-6749/93 \$1.00 + .10 1/54/45213

strong enough to cause perceivable symptoms, but it can induce a refractory period. The mechanism responsible for this is unknown. Prostaglandin release might be involved, since in patients with asthma, refractoriness can be inhibited by indomethacin.³

Although we cannot explain the exact pathomechanism of the refractory period, it was satisfying to make use of it. Curing a disease with early morning exercise is probably the most wholesome therapy conceivable.

REFERENCES

1. Casale TB, Keahey TM, Kaliner M. Exercise-induced anaphylactic syndromes: insights into diagnostic and pathophysiologic features. *JAMA* 1986;255:2049-53.
2. Bierman CW. Management of exercise-induced asthma. *Ann Allergy* 1992;68:119-22.
3. O'Byrne PM, Jones GL. The effect of indomethacin on exercise-induced bronchoconstriction and refractoriness after exercise. *Am Rev Respir Dis* 1986;134:69-72.

Ocular challenge and hyperresponsiveness to histamine in patients with allergic conjunctivitis

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Nonspecific hyperreactivity to physical, chemical, and pharmacologic agents is a common characteristic of allergic subjects, which is strictly related to the inflammatory events consequent to allergic reaction.^{1, 2} Histamine challenge is a common nonspecific test to evaluate hyperreactivity in subjects with asthma and rhinitis.¹ Recently, Bonini et al.³ demonstrated a conjunctival hyperresponsiveness to histamine in patients with vernal conjunctivitis by evaluating conjunctival hyperemia.

We evaluated the possible evidence of ocular hyperresponsiveness to histamine in patients with allergic conjunctivitis on the basis of several parameters: clinical evidence (i.e., ocular hyperemia), cellular inflammatory infiltrate, and CD54 expression on conjunctival epithelial cells. Particularly, we focused our attention on CD54 (Intra-

Abbreviations used

Dp: *Dermatophagoides pteronyssinus*
Par j: *Parietaria judaica*
PD: Provoking dose

cellular Adhesion Molecule-1), an adhesion molecule with an immunoglobulin-like structure present on activated immunocompetent cells, endothelia, and inflamed epithelium. We have recently demonstrated CD54 expression on conjunctival epithelial cells after allergen challenge in allergic subjects.⁴

METHODS

Twenty patients who were free of symptoms (11 men and 9 women, aged 18 to 54 years) with a previously documented diagnosis of allergic conjunctivitis due to *Parietaria judaica* (Par j) (10 subjects) or *Dermatophagoides pteronyssinus* (Dp) (10 subjects) were selected. All allergic subjects had positive history (for at least 2 years), positive skin prick test results (more than + + +, histamine + + +), positive RAST results (more than class III) and positive allergen-specific conjuncti-

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J ALLERGY CLIN IMMUNOL 1993;91:1227-30

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