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Multiple intolerance to food additives

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To the editor:

Numerous studies claiming that food additives are responsible for an array of clinical conditions, including urticaria, angioedema, anaphylaxis, asthma, and even behavior disturbances, have appeared in the medical literature.^{[1](#) [2](#)} However, because most of these studies were either anecdotal or heavily biased by the lack of appropriate diagnostic procedures, the exact role of food additives in allergic diseases is still unclear. It is now generally accepted that only double-blind, placebo-controlled studies using multiple and randomized placebos are able to reduce bias and lead to reliable conclusions. A case of multiple intolerance to food additives causing both perennial rhinitis and worsening of chronic urticaria is reported here.

A 44-year-old woman with a 12-year history of both chronic urticaria and perennial rhinitis (obstruction, rhinorrhea, and sneezing) was recently seen. Her symptoms responded well to cetirizine 10 mg daily. Skin prick testing with both airborne allergens and food allergens had been carried out several times, always with negative results. Routine blood counts and chemistry investigations revealed only a slight eosinophilia (5%). The patient had never observed a clear relationship between her symptoms and food intake.

After 3 days without cetirizine, an intradermal test with 0.05 mL of fresh autologous serum induced a marked wheal-and-flare reaction, whereas the injection of 0.05 mL of saline solution did not elicit any skin reaction. An elimination/additive-free diet regimen was started. During the 4-week diet period, the patient was asked to record and grade the severity of both cutaneous and nasal symptoms on a VAS and was left free to use cetirizine on demand.

At the follow-up visit, the patient reported a total and persistent disappearance of rhinitis and a 60% decrease in urticaria severity beginning 4 to 5 days after the diet was started. The slight residual pruritus was easily controlled with one half of a cetirizine tablet (5 mg) every 4 to 7 days. Both cutaneous and nasal symptoms relapsed some days after an open challenge (unrestricted diet for 3 weeks) was performed, and at the next follow-up visit the patient had to take 10 mg of cetirizine daily again.

After the total disappearance of the rhinitis and a marked reduction in urticaria severity were obtained by a new elimination diet period, peroral double-blind, placebo-controlled challenges (DBPCC) with food additives (Table I ■)

Table I. Food additives used in challenge tests

Additive	Dose (mg)
Sodium metabisulfite	25
Sodium benzoate	50
Monosodium glutamate (MSG)	100
Sodium nitrate	10
Tartrazine	10
Erythrosine	10
Sorbic acid	100
Butylated hydroxyanisole	10
Talc (placebo)	100

were carried out. All preparations were given in identical opaque capsules in a randomized sequence; talc capsules were used as placebos. A total of 8 active substances and 4 placebos were used in challenges given at 1-week intervals. The patient was controlled for 2 hours after each challenge; she had given an informed written consent before the procedure was started. She was asked to avoid antihistamines throughout the whole challenge period unless their use was strictly necessary.

Approximately 30 minutes after the administration of butylated hydroxyanisole 10 mg, severe rhinitis (sneezing and watery rhinorrhea) appeared. Symptoms disappeared

approximately 30 minutes after the intramuscular administration of chlorphenamine 10 mg. Similarly, severe rhinitis appeared approximately 4 hours after the ingestion of sodium metabisulfite 25 mg; symptoms were controlled by cetirizine 10 mg. Finally, severe urticaria appeared approximately 45 minutes after the ingestion of monosodium glutamate (MSG) 100 mg. Chlorphenamine 10 mg was given intravenously to control symptoms. No reaction was induced by the remaining substances or by the placebos. As a control, another series of DBPCCs with the 3 positive substances as well as with 3 placebos was carried out. Severe rhinitis again appeared, 30 minutes and 4 hours after the administration of butylated hydroxyanisole 10 mg and sodium metabisulfite 25 mg, respectively, and generalized urticaria followed by 45 minutes the administration of MSG 100 mg. No reaction was induced by the placebo capsules. Intolerance to all 3 substances was finally diagnosed.

Although food additive intolerance rarely represents the primary cause of chronic urticaria, additives can sometimes worsen an underlying idiopathic urticaria.¹ This patient had chronic idiopathic (probably autoimmune) urticaria.⁴ The finding that her urticaria was markedly worsened by MSG is surprising, inasmuch as glutamate intolerance has been associated with so-called Chinese restaurant syndrome and with asthma² but not with urticaria. A single case of delayed angioedema induced by this substance has been reported.⁵

Although the natural history of chronic urticaria itself, with periods of activity followed by periods of remission, might pose a challenge in the detection of the role played by food additives, the fact that this patient specifically reacted to MSG in 2 distinct series of DBPCCs should have minimized any possible bias. The amount of sodium glutamate that induced a flare of hives in this patient was relatively low (100 mg), given that glutamate intake during a meal at a Chinese restaurant can reach 6 g.^{1 2}

We recently demonstrated that intolerance to food additives might sometimes present as chronic rhinitis⁶; in our previous report, the culprit additive was sodium benzoate.⁶ In the present case, rhinitis was caused both by butylated hydroxyanisole and by sodium metabisulfite. Again, bias should have been minimized by the diagnostic procedure that was used (DBPCCs with multiple placebos) and by the performance of a second series of confirmatory challenges. Sodium metabisulfite intolerance has been associated with asthma,^{1 2} whereas the role of the antioxidant butylated hydroxyanisole has been investigated in patients with chronic urticaria with conflicting results.² This is probably the first study reporting that these 2 additives might induce perennial rhinitis. The pathogenesis of these adverse reactions is unclear. The fact that antihistamines were able to provide adequate control of both respiratory and cutaneous symptoms, together with the marked chemical differences between the 3 offending additives, suggests a mechanism based on direct histamine release from mast cells and basophils.

We recently found that subjects with histories of multiple intolerance to NSAIDs or with multiple drug allergy syndrome are characterized by circulating histamine-releasing factors,

as shown by their reactivity on autologous serum skin tests.^{[7](#) [8](#)} The reasons that single additives appear to induce histamine release from only 1 specific target organ (skin or nose) remain obscure.

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