

Food additives intolerance: does it present as perennial rhinitis?

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Purpose of review

A case report published in 2001 raised the possibility that some patients with long-lasting 'nonallergic' perennial rhinitis might in effect have food additives intolerance. The recent literature published in English was reviewed to find controlled studies able to confirm this observation.

Recent findings

Two double-blind, placebo-controlled studies published between August 2002 and July 2003 confirmed the above observation. The prevalence of additives intolerance among individuals with 'nonallergic' perennial rhinitis is about 5%. The pathogenic mechanisms involved remain unclear.

Summary

Intolerance to food additives may sometimes present as perennial rhinitis. Clinicians should consider this possibility before they definitively dismiss patients as 'nonallergic'.

Keywords

rhinitis, food additives, food intolerance, food allergy

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Abbreviation

DBPCC double-blind, placebo-controlled oral challenge

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Introduction

Thousands of agents including dyes, sweeteners, anti-oxidants, preservatives, emulsifiers, conditioners, stabilizing agents, and thickeners are added by the food industry to the foods that we consume [1]. Although food additives must be 'nonharmful' by law, in most cases their long-term toxicity is unknown. Thus, it is not surprising that public opinion (often following incorrect information provided by the media) has been much concerned about the safety of such an impressive number of substances and that researchers from all over the world have devoted much work to ascertain whether additives may directly cause or worsen specific clinical conditions. Altogether, the number of additives that have been implicated in adverse reactions is very small. Moreover, despite all efforts, adverse reactions to food additives remain one of the most debated and controversial issues in allergology. During the last 30 years a number of papers claiming an association between the intake of specific food additives and an impressive array of clinical disorders including urticaria, angioedema, anaphylaxis, asthma, atopic eczema, and even behavioral disturbances have appeared in the medical literature (for a revision, see [2,3]). Unfortunately, since most of those studies were either anecdotal or heavily biased by the lack of appropriate diagnostic procedures, and clinical conditions studied were in some cases spontaneously recurrent or long lasting (e.g. chronic urticaria and asthma), results have often been contradictory and not reproducible. Altogether, with the exception of rare, well documented cases of asthma exacerbated by the ingestion of metabisulfite, tartrazine, or monosodium glutamate [2–4], or of chronic pruritus induced by nitrate intolerance [5,6], one must conclude that the role played by food additives in several allergic disorders remains largely undefined. It is presently clear, and generally accepted, that the flaws of most of the older studies can only be overcome by well designed studies carried out using stringent clinical criteria aiming to detect an unequivocal cause/effect relationship between the intake of a certain food additive and the onset of a specific clinical condition. To this end, the clinical criteria to be fulfilled should include the following.

- (1) The total and persistent disappearance of the clinical condition under investigation shortly after an elimination diet (free of food additives) is started [7,8].
- (2) A relapse in the primary clinical condition shortly after the normal diet is resumed [7,8].

- (3) An unequivocal response (i.e. a relapse of the primary clinical condition) on double-blind, placebo-controlled oral challenges (DBPCCs) with food additives. DBPCCs should be carried out only if patients are completely symptom-free and if they are still following the additive-free diet. Also, precise formalities such as the use of multiple and randomized placebos should be followed [2,4,7,8].

If these criteria are adopted as a prerequisite to diagnosing intolerance to food additives, the number of clinical conditions for which a possible association with additives intolerance has been established drops dramatically. In effect (and not surprisingly), after much initial enthusiasm, intolerance to food additives has virtually disappeared from the stage of medical literature during the last 10 years. Nonetheless, some recent studies provide sufficient evidence that perennial rhinitis should be included in the restricted list of clinical disorders, possibly induced by food additives intolerance.

Additive-induced perennial rhinitis

A possible association between upper airways disease and intolerance to food additives was first noted in 1977 by Rosenhall [9] who reported 104 patients with chronic rhinitis, 4% of whom had a positive reaction with nasal symptoms upon oral challenges. Sodium benzoate was responsible for most reactions in patients with rhinitis [9,10]. Unfortunately, as in most other older studies, this study was flawed by poor control. Much more recently, a case of occupational rhinitis caused by sensitization to carmine red (a natural dye obtained from cochineal) was reported in an employee of a factory where natural dyes were made [11]. The pathogenesis of this disorder was IgE-mediated, as shown by strongly positive skin tests with the offending dye. This probably remains the only example of a food additive able to induce truly allergic (IgE-mediated) disorders. The first case of perennial rhinitis induced by food additives intolerance diagnosed using the clinical criteria discussed above was reported in 2001 [12]. This case was a 33-year-old woman with a 7-year history of perennial rhinitis characterized by watery rhinorrhea, itching of the nasal mucosa, and episodes of sneezing paroxysm that showed little response to antihistamines and local corticosteroids. Nasal symptoms totally and persistently disappeared 5 days after the start of an elimination, additive-free diet and relapsed 3 days after the unrestricted diet was resumed. On DBPCC rhinitis recurred about 1 h after the administration of 50 mg of sodium benzoate and symptoms lasted for about 36 h. Benzoate intolerance was confirmed on a second series of DBPCCs. The patient's unrestricted diet frequently included soft cheeses and wine; these foods may contain sodium benzoate as an antimycotic/antibacterial preservative.

A second case was reported in September 2002 [13[•]]. The patient, a 44-year-old woman, had a 12-year history of both chronic urticaria and perennial rhinitis that responded well to cetirizine 10 mg daily. Rhinitis totally and persistently disappeared about 4–5 days after an elimination, additive-free diet regimen was started, and relapsed some days after the unrestricted diet was resumed. On DBPCC rhinitis recurred approximately 30 min after the administration of butylated hydroxyanisole 10 mg and about 4 h after the administration of sodium metabisulfite 25 mg. Since in both cases antihistamines were given to control the reactions the duration of symptoms induced by a single dose of the offending additives was not evaluated. A second series of DBPCCs confirmed intolerance to both mentioned substances.

Finally, a mini-series of patients with additive-induced rhinitis was recently reported [14[•]]. Three out of 54 (6%) patients with perennial rhinitis fulfilling four admission criteria (see below) responded to the elimination, additive-free diet. On DBPCC these three patients turned out to have monosodium glutamate (two cases) and sodium benzoate (one case) intolerance, respectively. In all patients rhinitis relapsed 4–6 h after the administration of the offending additive, and lasted for 2 days in monosodium glutamate-intolerant patients and for 7 days in the benzoate-intolerant patient.

The clinical features of patients with additive-induced rhinitis reported so far are compared in Table 1. Interestingly, in all cases rhinitis appeared within 6 h of a single provoking dose of the offending additive and symptoms lasted for at least 2 days.

Selection criteria and additive-free diet

The prevalence of additive-induced rhinitis is presently unknown. On the basis of previous studies [9,14[•]] one can infer that about 5% of patients classified as having 'nonallergic' perennial rhinitis might show additives intolerance. Since intolerance to food additives probably occurs only in a small minority of patients with perennial rhinitis, clinical criteria are needed to select the candidates suitable for the elimination diet. Based upon the experience of this allergy center we suggest employing the following criteria.

- (1) Long-lasting (>6 months) perennial rhinitis characterized by 'allergic' features such as sneezing, watery rhinorrhea, and itching of the nasal mucosa.
- (2) Diagnosis of 'allergic rhinitis' in the absence of nasal polyps and structural deformities on ENT investigation.
- (3) Normal plain radiograph or computed tomography scan.
- (4) No reactivity on skin tests with a series of seasonal and perennial airborne allergens including pollen

Table 1. Clinical features of five patients diagnosed as having food additives-induced rhinitis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/sex	33/F	44/F	51/M	45/F	58/M
Duration of rhinitis	7 years	12 years	4 years	6 months	3 years
Response to antihistamines	Poor	Yes	Yes	Yes	Yes
Time for healing	4–5 days	4–5 days	5 days	3 days	4 days
Time to relapse (normal diet)	3 days	3 days	2 days	2 days	3 days
Time to relapse (DBPCC)	1 h	30 min (BHA), 4 h (MBS)	4 h	6 h	4 h
Duration of the effect of single dose of offending additive	2 days	NA	2 days	2 days	7 days
Offending additive	Benzoate	BHA & MBS	MSG	MSG	Benzoate

DBPCC, double-blind, placebo-controlled oral challenges; BHA, butylated hydroxyanisole; MBS, sodium metabisulfite; MSG, monosodium glutamate; NA, not available.

(grass, mugwort, ragweed, plantain, birch, olive, cypress, and pellitory) mites, animal dander (cat, dog, plus others in the presence of a history of specific contacts), and molds (*Alternaria*, *Aspergillus*, *Cladosporium*).

Patients fulfilling all four criteria should start an elimination diet (free of food additives) to be followed for at least 3 weeks. Since dietary habits show marked geographical differences it is difficult to suggest an additive-free diet that can be easily complied with in every country. In the Mediterranean area, where the traditional cuisine is based almost exclusively on the use of natural ingredients, the task of building up an additive-free diet could turn out to be much simpler than in other geographical areas. In order to optimize compliance and to reduce the risk of an inadvertent ingestion of foods containing additives, the elimination diet should be, as far as possible, clear, varied, and rich in foods. The elimination diet adopted at this allergy center has undergone a number of revisions over the years; the currently employed version is shown in Table 2. The experience of this center suggests that patients succeed in complying with this diet quite easily, even when they are unable to prepare and consume all their meals at home [5,6]. During the additive-free period, patients should record both the severity and the frequency of nasal symptoms on specific forms or on a visual analog scale. At the end of the 3-week period patients reporting only partial benefit or no benefit at all should be dismissed as 'not intolerant to food additives', whereas those reporting a complete and persistent disappearance of their rhinitis should undergo an open challenge (unrestricted diet for 3 weeks). Patients showing a relapse of rhinitis on an unrestricted diet followed by a new disappearance of symptoms during a further 3-week period free of additives should finally be started on a DBPCC.

Oral challenges (double-blind, placebo-controlled oral challenges)

Some relevant questions relating to oral challenges include the following: how many and which of the

thousands of available additives should be tested on DBPCCs and which doses should be given? An essential requirement of a diagnostic test is certainly sensitivity; however, diagnostic procedures should also be reproducible, easy to perform, and not too time-consuming. Based on a series of review articles of food additives intolerance [2–4,7,8] we have chosen a restricted panel of eight substances to be challenged regularly (Table 3). These eight additives are those that have been more frequently implicated in adverse reactions, are among those most frequently employed by the food industry, and represent the main dyes, antioxidants, preservatives, and thickeners. Previous studies [5,6,12,13*,14*] have shown that if the clinical conditions under investigation are not life threatening, as is the case for chronic pruritus or chronic rhinitis, it is possible to challenge substances safely as single provocative doses, thus avoiding the time-consuming administration of multiple increasing doses. Single provocative doses employed at this center (Table 3) have been derived from a review of the literature and represent a possible mean daily intake for each substance. Active substances and placebos are challenged 1 week apart in a randomized sequence, and the patient should be kept under control for at least 2 h after the last provocative dose. The appearance of unequivocal rhinitis within 24 h of a challenge session will be considered as a positive response. Clearly, it is essential that patients continue to comply with the additive-free diet throughout the study period.

In the presence of an unequivocal response to both an elimination diet and an open challenge (unrestricted diet) followed by a negative DBPCC, the possibility that the responsible substance was not included in the list of challenged additives should be considered. In this case open challenge tests carried out at home with single preserved foods that the patient used to consume before the elimination diet was started, along with a thorough examination of labels, may be useful in detecting one or more putative offending additives to be subsequently challenged double blind.

Table 2. Suggested additive-free diet*Flours, pasta, bread, and cereals*

Allowed: fresh bread, pasta (both commercial and home made), rice, barley, flours (wheat, maize, rice), home made cookies and pizza

Forbidden: commercial biscuits and cookies, precooked ready to use frozen pastas, canned pastas, commercial filled-up pastas ('ravioli', 'tortellini' etc.), commercial sauces and condiments for pastas, commercial pizzas, corn flakes and other breakfast cereals

Fruits & vegetables

Allowed: all fresh vegetables and fruits but walnut; it is advisable to peel fruits whenever possible

Forbidden: jam, marmalade, commercial juices, canned fruits and vegetables, pickles, vegetables in oil, ketchup, mustard and other sauces

Dairy products

Allowed: fresh milk, natural yogurt, butter, true parmesan cheese

Forbidden: margarine, all cheeses other than parmesan, yogurts with fruits or cereals or malt

Eggs

Allowed: fresh eggs

Forbidden: commercial mayonnaise, egg-based sauces and seasonings

Meat & fish

Allowed: fresh meats (beef, pork, poultry), fresh fish and shellfish (but not crustaceans)

Forbidden: salami, bacon, ham, and all other kinds of preserved meats, corned beef, commercial precooked meatballs, bouillon cubes, meat extracts, smoked fish, pickles, stock fish, canned fish, caviar, etc.

Oils

Allowed: olive oil

Forbidden: all other oils

Beverages

Allowed: water, freshly brewed coffee and tea

Forbidden: wine, beer, alcohols, soft drinks, vinegar

Sweeteners

Allowed: cane sugar

Forbidden: white sugar, sweeteners (aspartame, etc.)

Note: All complex preparations (cookies, pizza, sauces, etc.) must be made at home using allowed ingredients.

Table 3. Additives and doses given on double-blind, placebo-controlled oral challenges

Additive	Dose (mg)
Sodium metabisulfite	25
Sodium benzoate	50–200
Monosodium glutamate	100
Sodium nitrate	10
Tartrazine	10
Erythrosine	10
Sorbic acid	100
Butylated hydroxyanisole	10

Pathogenesis of additive-induced rhinitis

The pathogenic mechanism of additive-induced rhinitis (as well as that of most other conditions induced by food additives) remains unclear. Unlike previously reported cases of IgE-mediated sulfite sensitivity [7,15], skin prick tests and patch tests with the offending food additives that have been tentatively carried out at this allergy center in some intolerant patients have always produced negative results (unpublished). Moreover, in contrast to IgE-mediated rhinitis induced by foods [16,17], the effect of a single dose of the offending additive(s) was rather long lasting in patients with additive-induced rhinitis. As far as we know, the mechanisms of these adverse reactions are nonimmunologic. The fact that antihistamines were effective in controlling symptoms in most of the recently reported patients [12,13*,14*] suggests that histamine played a part in the pathogenesis of their disorder. In view of the

marked chemical differences between offending additives, a mechanism based upon direct histamine release (and other mediators) from mast cells seems the most likely explanation for additive-induced rhinitis. How and why offending additives succeed in causing histamine release only at the level of a single target organ, and which patient-related factors are implicated in these adverse reactions, are questions that presently remain unanswered.

Conclusion

There is some evidence that a small proportion of patients diagnosed as having 'chronic vasomotor rhinitis' or 'perennial nonallergic rhinitis' might in effect have food additives intolerance. Allergologists should consider this possibility before patients with a long-lasting disorder of the upper airways are definitively dismissed as nonallergic and referred to the ENT specialist.

References and recommended reading

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- of special interest
- of outstanding interest

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