A Possible Role of Food Intolerance in the Pathogenesis of Gastroesophageal Reflux Disease

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To the Editor: Gastroesophageal reflux disease (GERD) is an extremely common condition characterized by symptoms of heartburn and acid regurgitation. The etiopathogenetic steps of GERD remain largely unknown even though up to 20% of the adult population in Western countries is thought to be affected by reflux symptoms on a weekly basis (1), natural-history studies indicate that patients with GERD symptoms suffer from a chronic relapsing course of disease, with at least 50% remaining on continuous medical therapy (2), and the condition is known to predispose to an increased cancer risk. We know that GERD is caused by an abnormal contact of gastrointestinal contents with esophageal mucosa, and insufficient clearance of the esophageal body, lower esophageal sphinter incompetence, and delayed gastric emptying have been identified as putative pathophysiological mechanisms of disease, but the exact etiology of this backward displacement of gastrointestinal contents has yet to be elucidated.

Because a possible role for food intolerance in the etiology of GERD has not, to our knowledge, been investigated, and the so-called typical symptoms are considered specific, although not sensitive, for the diagnosis (3), we decided to retrospectively evaluate the results of a leukocytotoxic test for food intolerance using a panel of 60 foods (Allergoline Biotech & Research, Modena, Italy). The test was performed at the local center of a food research group, ACSIAN (Associazione Centro Studie Ricerche delle Intolleranze Alimentari e della Nutrizione) , from the date of the opening of the center in April 2007 to April 2008, in 16 patients suffering from typical GERD symptoms (heartburn and regurgitation, in the absence of dysphagia) and 7 healthy subjects. This test is based on the optical evaluation of leukocytes in a blood sample that has come into direct contact with specific food substances. On the basis of observation of the leukocytes, degrees of reaction to the food extracts are rated according to the following scale: level 0 = negative, level 1 = slightly positive, level 2 = moderately positive, and level 3 = highly positive. These levels correspond to (i) the state of the leukocytes, which react by swelling, then developing

Table 1. Patients with GERD symptoms

No	Sex	Age	Positive reaction degree III	Positive reaction degree II	Efficacy of exclusion diet[a]
1	M	26	—	Coffee	Moderate
2	F	56	Coffee, spinach	Mushroom, onion	Complete
3	M	51	—	Eggs, milk	Moderate
4	F	70	—	Bean, almond	Complete
5	M	47	—	Coffee, wheat, strawberry, peach, plum	Moderate
6	F	36	Milk	Brewer's yeast, shellfish, octopus, lettuce	Complete
7	F	44	—	Brewer's yeast, celery, banana	Complete
8	F	63	—	Coffee, celery, pea, bean	Complete
9	M	53	—	Milk, brewer's yeast	Complete
10	M	87	—	Lettuce, celery, plum	Complete
11	M	64	—	Coffee, lettuce, bean	Moderate
12	F	45	—	Coffee, potato, lettuce	Moderate
13	M	34	—	Milk, turkey, onion, sugar	Complete
14	M	74	—	Wheat, pea, bean, carrot, lettuce	Complete
15	M	45	Nut, lamb, strawberry, peach, almond	Rabbit, eggs	Complete
16	M	36	—	Milk, lettuce, onion, carrot,coffee, mushroom, potato, tomato, pepper, aubergine, turkey, chicken	Moderate
Control subjects					
1	F	42	—	—	
2	M	35	—	—	
3	F	45	—	Grapes	
4	M	38	—	—	
5	F	57	—	—	
6	M	44	—	—	
7	F	22	—	—	

[a]Evaluation of exclusion diet efficacy: none–mild–moderate–complete.

vacuoles, and finally deteriorating, and (ii) the total number of leukocytes that react. None of the GERD patients was on proton pump inhibitor therapy, either at the time of the test or during the period of the exclusion diet (described below). The success level of the exclusion diet was graded as mild, moderate, or complete, and the evaluation was performed at least 3 months after the beginning of the diet.

All the patients with GERD symptoms presented a moderate to severe positive reaction, whereas only one control subject exhibited a moderate reaction to a food (grapes, for which none of the GERD patients tested positive). Coffee, lettuce, and milk were the foods that most frequently provoked a reaction. The exclusion diet proved to be effective in all the patients for ameliorating symptoms (it was completely effective in 10 patients and moderately effective in 6 patients). Results are summarized in the **Table 1**.

Tests for food intolerance are currently not recommended as a diagnostic tool; not only are they expensive but both the leukocytotoxic test and antigen-specific immunoglobulin 4 (IgG4) evaluation are considered to have very poor clinical specificity and sensitivity (4). The lack of an accepted test for this purpose is the likely reason that little consideration has been given to a possible role of food intolerance in the etiopathogenesis of diseases. On the other hand, recent insights into the role of innate immunity in the intestinal tract might help to answer two fundamental open questions: what are the mechanisms underlying nonallergic food intolerance, and why should the evaluation of leukocytotoxicity or IgG4 level be used for the diagnosis of food intolerance? In recent years, the role of specific receptors and specialized cells of innate immunity in the recognition and identification of antigens has become evident. Complete recognition of an antigen by this receptorial system is the basis of tolerance to a food or a microorganism. When an antigen is not suitably recognized, a kind of adaptive immune response may be activated—allergy or intolerance, both of which closely depend on the efficiency of the T-regulatory cell (T-reg cell) system. Consistent with this, recent and very intriguing data (5) indicate that T-reg cells induce suppression of allergic disease by suppressing IgE and inducing IgG4, whereas IgA production appears to be independent of T-reg cell activity. We suggest that an upregulation of T-reg cells may induce an increase in both IgG4 and toxic reactions in blood leukocytes as a result of T-reg-cell activity, and these phenomena may be the pathogenetic basis of intolerance. The regulation state of T-reg cells may be the key point; whereas an allergic reaction may depend on a downregulation of T-reg cells, an intolerance reaction may result from an upregulation of T-reg cells. More insights into the pathogenetic mechanisms of food intolerance are needed. Although we realize that to date the proposed association between food intolerance and GERD is open to criticism, our experience leads us to believe that further retrospective and prospective studies in GERD patients should be carried out to better elucidate this intriguing and exciting possibility.

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