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ORIGINAL ARTICLE

Pattern of food intolerance in patients with gastro-esophageal reflux symptoms

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ABSTRACT

BACKGROUND: Many food items have been involved in gastro-esophageal reflux disease pathogenesis and dietary modification has been proposed as first-line treatment. Test-based exclusion diets have shown to significantly reduce reflux symptoms. We aimed to assess the patterns of food intolerance in a series of patients with typical gastro-esophageal reflux symptoms (GERS).

METHODS: We retrospectively evaluated all patients with typical reflux symptoms, attending the Centre Study Association on Food Intolerance and Nutrition of Ferrara from January 2010 to October 2015, who resulted positive to at least one food item at the Leucocytotoxic Test. The presence and severity of typical GERS (heartburn and/or acid regurgitation) were assessed using the Gastro-esophageal Reflux Disease Impact Scale (GIS) questionnaire. Only individuals with a GIS Score of at least 5 points were included.

RESULTS: Almost all patients (91.1%) were intolerant to at least 5 food items. The most frequent food intolerance (more than 33% of patients) were found for milk (55.4%), lettuce (46.4%), coffee (43.7%), brewer's yeast (42.9%), pork (42.9%), tuna (37.5%), rice (35.7%), sole (34.8%), asparagus (34.8%) and eggs (33.9%). Nine different clusters of food intolerance were detected.

CONCLUSIONS: Patients with typical gastro-esophageal reflux symptoms seem to have intolerance to multiple food items, some of which (lettuce, brewer's yeast, tuna, rice, sole and asparagus) have not yet been associated to gastro-esophageal reflux disease.

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Key words: Food - Malabsorption syndromes - Gastro-esophageal reflux.

Gastro-esophageal reflux disease (GERD) is a common condition with increasing prevalence in the last decades.^{1, 2} GERD affects patients' quality of life with high costs for health care, causing a major concern for public health.³ Despite the size of the problem, the pathogenesis of GERD remains largely unknown. Several studies have focused on the role of food in the pathogenesis of GERD. In-

deed, several foods, such as chocolate, coffee, peppermint and citrus fruit, have been shown to decrease lower esophageal sphincter (LES) pressure and/or increase the number of reflux episodes.⁴⁻⁹ The associations between these foods and GERD symptoms has also been confirmed by surveys based on validated questionnaires.¹⁰

Recently, we evaluated the possible correla-

TABLE I.—Proportion of patients with typical gastro-esophageal reflux symptoms and intolerance to more than one food.

Number of food intolerances	Patients N.=112 N. (%)
<3	0
3	2 (1.8)
4	8 (7.1)
5	32 (28.6)
6	34 (30.4)
7	23 (20.5)
8	10 (8.9)
9	1 (0.9)
10	2 (1.8)

tion between food intolerance and the development of typical GERS (heartburn and regurgitation) using the Leucocytotoxic Test with a panel of 60 food extracts.^{11, 12} We found that leucocytotoxic reactions seem to be more frequent in GERD patients than in control subjects.¹¹ We also showed that test-based exclusion diets significantly reduced GERS in up to 50% of patients, suggesting that food intolerance may play a role in the pathogenesis of GERD. Indeed, our randomized controlled trial showed that patients with typical reflux symptoms following exclusion diets based on the leucocytotoxic results had a significant reduction of symptoms compared with patients undergoing control diets.¹² A better knowledge of the pattern of food intolerance in patients with gastro-esophageal reflux symptoms may help improving the management of these patients and reduce disease-related public health costs.

The aim of the present study was to assess the patterns of food intolerance in a series of patients with typical gastro-esophageal reflux symptoms.

Materials and methods

Patients

We retrospectively evaluated all patients with typical gastro-esophageal reflux symptoms, attending the Centre Study Association on Food Intolerance and Nutrition of Ferrara from January 2010 to October 2015, who resulted positive to at least one food item at the

TABLE II.—Intolerance to different types of food items diagnosed by the leucocytotoxic test in 112 patients with typical gastro-esophageal reflux symptoms.

Food	Patients with positive reaction, N. (%)		
	Total	Level II	Level III
Milk	62 (55.4)	25 (22.4)	37 (33.0)
Lettuce	52 (46.4)	25 (22.3)	27 (24.1)
Coffee	49 (43.7)	23 (20.5)	26 (23.2)
Brewer's yeast	48 (42.9)	27 (24.1)	21 (18.7)
Pork	48 (42.9)	28 (25.0)	20 (17.9)
Tuna	42 (37.5)	31 (27.7)	11 (9.8)
Rice	40 (35.7)	35 (31.2)	5 (4.5)
Sole	39 (34.8)	30 (26.8)	9 (8.0)
Asparagus	39 (34.8)	35 (31.2)	4 (3.6)
Eggs	38 (33.9)	26 (23.2)	12 (10.7)
Aubergine	33 (29.5)	24 (21.4)	9 (8.0)
Wheat	32 (28.6)	21 (18.7)	11 (9.8)
Chemical yeast	24 (21.4)	20 (17.9)	4 (3.6)
Crawfish	22 (19.6)	20 (17.9)	2 (1.8)
Tomato	7 (6.2)	6 (5.4)	1 (0.9)
Banana	5 (4.5)	5 (4.5)	-
Potato	5 (4.5)	4 (3.6)	1 (0.9)
Chicory	5 (4.5)	5 (4.5)	-
Mixed mushrooms	5 (4.5)	5 (4.5)	-
Beans	5 (4.5)	4 (3.6)	1 (0.9)
Cocoa	5 (4.5)	3 (2.7)	2 (1.8)
Orange	3 (2.7)	3 (2.7)	-
Sweet pepper	3 (2.7)	2 (1.8)	1 (0.9)
Celery	3 (2.7)	3 (2.7)	-
Carrot	3 (2.7)	3 (2.7)	-
Cod	3 (2.7)	3 (2.7)	-
Barley	3 (2.7)	3 (2.7)	-
Kiwi	2 (1.8)	2 (1.8)	-
Spinach	2 (1.8)	-	2 (1.8)
Onion	2 (1.8)	2 (1.8)	-
Turkey	2 (1.8)	2 (1.8)	-
Beef	2 (1.8)	1 (0.9)	1 (0.9)
Legumes	2 (1.8)	2 (1.8)	-
Grapes	1 (0.9)	1 (0.9)	-
Apple	1 (0.9)	1 (0.9)	-
Lemon	1 (0.9)	1 (0.9)	-
Walnut	1 (0.9)	1 (0.9)	-
Olive	1 (0.9)	1 (0.9)	-
Courgette	1 (0.9)	1 (0.9)	-
Cabbage	1 (0.9)	1 (0.9)	-
Salmon	1 (0.9)	1 (0.9)	-
Tea	1 (0.9)	1 (0.9)	-

No patients with positive reaction to pear, plum, strawberry, apricot, peach, almond, peanuts, chicken, rabbit, lamb, soya, peas, spelt, sugar, honey, mix cephalopods.

Leucocytotoxic Test. The presence and severity of typical GERS (heartburn, acid regurgitation, pain) were assessed using the Gastro-esophageal Reflux Disease Impact Scale (GIS) questionnaire.¹³ Only individuals with a GIS Score of ≥ 5 points were included.

TABLE III.—Factor loading of 33 food items with positive reaction in more than one patients with typical gastro-esophageal reflux symptoms. Bolt values indicate the loading values of higher than 0.5 for each food item factor.

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
Milk	-0.1264	0.2723	-0.0069	0.2023	-0.0418	-0.0747
Lettuce	-0.2100	-0.1540	0.1120	-0.1094	0.2234	0.1264
Coffee	0.2682	0.0953	0.1679	0.2306	0.2815	-0.2737
Brewer's yeast	0.0110	-0.0416	0.5139	0.2470	-0.1720	-0.1349
Pork	0.1270	-0.1210	0.0806	-0.2078	-0.0947	-0.2848
Tuna	-0.0590	-0.1993	0.0182	-0.1891	-0.0665	0.3465
Rice	-0.0636	0.2754	-0.3796	-0.2263	-0.2159	0.1165
Sole	-0.1668	-0.1068	-0.6254	-0.0976	-0.1812	-0.3026
Asparagus	-0.0754	-0.1703	-0.1110	-0.0517	-0.1060	-0.0447
Eggs	-0.0739	0.0659	-0.1188	-0.0196	0.0133	0.0405
Aubergine	0.0929	-0.1242	0.0554	-0.0778	-0.0002	-0.1239
Wheat	-0.2170	0.0243	0.0488	-0.0585	-0.1414	-0.1631
Chemical yeast	-0.1122	0.1344	0.7732	-0.0852	0.0037	-0.1800
Crawfish	0.0205	-0.0831	-0.1612	0.0336	-0.0052	-0.1711
Tomato	-0.0337	0.2183	0.0954	-0.1491	-0.1182	-0.1109
Banana	-0.0642	-0.0626	-0.1300	-0.0759	-0.0222	-0.0040
Potato	-0.0146	-0.0239	-0.0662	-0.0007	0.1586	-0.0068
Chicory	0.0008	0.6635	-0.0167	0.1809	-0.0376	0.4113
Mushrooms	-0.0090	-0.0747	-0.2449	0.4334	0.4517	-0.1001
Beans	0.5540	0.4710	-0.1763	-0.0988	-0.0634	-0.0590
Cocoa	-0.0589	0.7755	0.2184	0.0057	0.0969	-0.0804
Orange	-0.0397	-0.0408	-0.0680	0.0049	0.7535	0.0799
Sweet pepper	-0.0265	0.1091	0.1761	-0.1055	0.7575	-0.0908
Celery	-0.0025	0.0458	-0.1458	-0.0359	-0.0197	0.5238
Carrot	-0.0093	-0.0706	0.0449	-0.0069	-0.0641	-0.0062
Code	-0.0512	0.2420	0.0921	0.7671	-0.0598	0.0102
Barley	-0.0076	-0.1377	-0.0231	0.7317	-0.0281	-0.0118
Kiwi	-0.0383	-0.0285	0.0771	-0.0169	-0.0031	-0.0248
Spinach	0.7954	-0.0450	-0.0148	-0.0246	-0.0205	-0.0020
Onion	-0.0132	-0.0404	-0.0144	0.0155	-0.0295	-0.0248
Turkey	-0.0116	0.0499	-0.0383	-0.0259	-0.0210	0.8068
Beef	0.8218	-0.0584	0.0452	-0.0016	-0.0148	0.0041
Legumes	-0.0293	-0.0100	-0.0239	-0.0591	-0.0750	-0.0265

Bolt values indicate the loading values of higher than 0.5 for each food item factor.

Only patients who were no longer assuming proton-pump inhibitors treatment at the time of enrolment were included. Patients with celiac disease or lactose intolerance were excluded.

Leucocytotoxic test

The Leucocytotoxic Test with a panel of 60 food items (Antigenia srl, Bologna, Italy) has been described elsewhere.¹² Briefly, the buffy coat obtained by centrifuging patient's blood samples was suspended in a mixture of sterile distilled water and serum and then placed in a siliconized microscope slide previously coated with the dried extract of the food to be tested. A staff member (N.L. or E.Z.) evaluated the unstained leukocytes at various time intervals by optical microscopy (40x zoom), up to

two hours. The level of positivity of the test depended on: 1) the state of the leukocytes; and 2) the total number of leukocytes that react. In particular, we rated as follow: level 0 (negative: no alterations in leukocytes structure), level I (slightly positive: mild alterations of leukocytes shape), level II (moderately positive: swelling of leukocytes and cellular membrane rupture), level III (highly positive: severe membrane lesion, with cytoplasm leakage, or leukocyte disintegration). According to our previous studies, we considered as positive only moderate-severe reactions (level II and level III).^{11, 12} Considering level I reactions as negative we improved the specificity of the test, whose major criticism was related to the very low specificity showed in a previous study,¹⁴ and eliminated any possible

Factor 7	Factor 8	Factor 9	Factor 10	Factor 11	Factor 12	Factor 13	Factor 14
-0.0324	0.0891	0.5884	0.0339	0.0145	-0.0237	0.3496	0.1379
-0.1601	0.1391	0.3917	0.3282	0.1086	-0.0169	0.3132	0.0297
-0.2520	-0.0149	-0.3122	-0.1602	-0.0178	0.0459	0.0875	0.1436
-0.0186	-0.2607	0.3590	-0.2203	0.0380	0.0615	0.1344	0.0259
-0.1090	0.0055	-0.1125	-0.0761	-0.6487	0.2242	0.1243	-0.0429
0.4661	0.3176	-0.2801	-0.0918	-0.0592	-0.0834	0.0054	0.0081
-0.3159	-0.1143	-0.1236	-0.1665	-0.1163	0.0793	-0.0617	-0.2151
0.1450	-0.2379	0.1245	-0.1224	0.0489	0.2087	0.1798	-0.0081
-0.6148	0.3079	0.0209	-0.2178	-0.0245	0.1257	-0.3310	-0.0105
0.0321	-0.1295	-0.0490	-0.1364	-0.0122	-0.2340	-0.7229	0.0194
-0.0948	0.0641	-0.1171	-0.0563	0.8084	0.0076	0.0348	-0.0615
0.1492	-0.1538	-0.5921	0.0509	0.2883	-0.0110	0.1354	-0.1235
-0.0187	-0.0815	-0.0168	0.0159	0.0343	0.1131	0.1284	-0.1043
0.7406	0.0193	-0.0528	-0.1517	-0.0486	0.1713	-0.2131	-0.0151
0.1206	0.4663	0.2648	0.4787	0.0060	-0.0330	-0.1246	-0.1103
-0.0433	-0.0668	0.0483	-0.2100	-0.3554	-0.3074	0.5020	-0.1301
0.1268	0.4756	-0.0442	-0.0642	0.0781	-0.0068	0.0478	0.6408
-0.1667	-0.0285	-0.0807	-0.0817	-0.0999	0.0531	-0.0671	0.0439
-0.0532	-0.0189	0.1113	0.4787	-0.0506	0.0378	-0.0226	-0.1050
0.2287	0.0331	0.0061	0.0556	-0.0131	-0.0520	-0.0540	-0.0586
0.0230	-0.0214	0.1244	-0.0182	0.0036	-0.0344	-0.0026	-0.0420
0.1671	0.0681	-0.1931	0.0244	-0.1310	-0.0448	0.0325	0.0980
-0.1004	-0.1019	0.2199	-0.0935	0.2041	0.0162	-0.0385	-0.0980
-0.0475	-0.0802	0.1416	-0.0207	0.0982	0.6475	0.1394	-0.0107
-0.0411	-0.0932	-0.0643	0.7936	-0.0023	-0.0147	0.1010	0.0358
-0.0817	0.0453	-0.1086	0.0034	0.0803	-0.0043	0.1449	-0.0212
0.1384	-0.0766	0.2424	-0.0334	-0.0541	-0.0536	-0.1655	-0.0576
0.0690	0.0204	-0.0669	-0.0115	-0.1348	0.8222	0.0215	-0.0301
-0.1595	-0.0467	-0.0144	-0.0040	0.0561	-0.0299	-0.0848	-0.0201
-0.0827	0.8351	0.0626	-0.0507	0.0462	-0.0038	0.0932	0.0053
-0.0519	-0.0324	0.0138	-0.0286	-0.0155	0.0810	-0.0395	-0.0407
0.1243	0.0044	0.0167	-0.0330	-0.0173	0.0058	0.1150	-0.0084
-0.0538	-0.1068	0.0903	0.0207	-0.0626	-0.0233	-0.0466	0.8604

subjective interpretation of optical results, as levels II and III of reaction present so evident optical changes that make impossible any mis-interpretation.

Statistical analysis

The frequency of each food item intolerance in the study sample was defined as percentage of patients with either level II or level III positive reaction. Food item intolerance was defined as frequent when present in more than 33% of patients. Similarly, we assessed the percentage of patients with intolerance to more than one food item. In addition, an exploratory factor analysis was applied to assess for the presence of correlations between differ-

ent types of food items which may reflect complexes of food intolerance. The 33 food items that positively reacted in more than one patient were included. The principal component analysis method of data extraction was applied. According with the Kaiser criterion, an Eigenvalue higher than 1 was used to determine the number of components needed to represent the study data. Principal factor methods with Varimax rotation was used. Only loading of 0.5 or higher were considered in the interpretation of factors.

Results

A total of 112 patients, mean age 49.7 (standard deviation: 5.1) years, 67 (60%) females, with typical GERS and positive (moderate or

severe reaction) to at least one food item at the Leucocytotoxic Test were evaluated.

Of the 112 patients with typical gastro-esophageal reflux symptoms, 102 (91.1%) showed concomitant intolerance to at least 5 food items (Table I). All patients resulted positive at least to three food items, with a mean number of food items intolerance of 6 (SD 1.29).

Table II shows the type and frequency of food item intolerance in the study sample. Frequent intolerance among 112 patients was found for the following 10 items: milk (55.4%), lettuce (46.4%) and coffee (43.7%) were the most frequent, followed by Brewer's yeast (42.9%), pork (42.9%), tuna (37.5%), rice (35.7%), sole (34.8%), asparagus (34.8%), eggs (33.9%). For the remaining food items, intolerance was rare for 28 items being present in less than 6.2% of patients, whereas it was absent for 16 food items.

The factor analysis showed the presence of a 14-factor structure of food item intolerance (Table III). The following clusters of food intolerance were found: beans, spinach and beef (factor 1); chicory and cocoa (factor 2); brewer's yeast and chemical yeast (factor 3); cod and barley (factor 4); orange and sweet pepper (factor 5); celery and turkey (factor 6); kiwi and celery (factor 12); potato and legumes (factor 14). No correlation with other food items was reported for crawfish, onion, milk, carrot, aubergine and banana (Table III).

Discussion

Many food items have been involved in the pathogenesis of typical gastro-esophageal reflux symptoms, and dietary modification has been proposed as first-line treatment for these patients in both general and specialized settings.^{5, 10} The American College of Gastroenterology recommends to reduce fat intake, chocolate, alcohol, citrus, tomato, coffee and tea consumption, and to implement lifestyle changes such as to stop smoking and lose weight.¹⁵ Thus, dietary modification may represent a substantial opportunity for a non-pharmacologic approach to patients with typical GERS. However, a recent population-based

study reported that patients with more severe gastro-esophageal reflux symptoms adhere less to dietary recommendations.¹⁶

Although the underlying pathogenic mechanisms of the association between food and reflux symptoms are still unclear,¹⁷ there is some evidence that food intolerance may play a role in their pathogenesis. We have previously reported that food intolerance was significantly more frequent in patients with GERS compared with healthy controls.¹¹ We have also found that Leucocytotoxic Test-based exclusion diets were effective in reducing GERS.¹²

To our knowledge, this is the first study exploring the patterns of test-based food intolerance in patients with typical symptoms of gastro-esophageal reflux. The most frequent intolerance in patients with GERS were found for milk, lettuce, coffee, brewer's yeast, pork, rice, sole, asparagus and eggs. Moreover, almost all patients with GERS were intolerant to at least five food items. The factor analysis showed a correlation between particular types of food intolerance: beans, spinach and beef; chicory and cocoa; brewer's yeast and chemical yeast; cod and barley; orange and sweet pepper; celery and turkey or kiwi; potato and legumes. In agreement with previous studies, we found that food intolerance in patients with GERS involves food items not usually included in GERD dietary recommendations,^{11, 12} such as milk, lettuce, brewer's yeast, rice, sole, asparagus and eggs. Among the foods traditionally related with GERD, only coffee and pork meat presented a moderate-severe reaction at the Leucocytotoxic Test. Therefore, our data supports the hypothesis that many other food items, different from those commonly considered in GERD recommendations, may play a role in the pathogenesis of this very common clinical condition. This would suggest that excluding specific food items from a patient's diet based on food intolerance tests may help improving GERS. Furthermore, test-based exclusion diets could also be considered as a possible therapeutic approach in patients with GERS.

These observations underline the complexity of GERD pathogenesis, which might involve patient's susceptibility and possible underlying

immune-mediate mechanisms. The role of specific receptors and specialized cells of innate immunity in the recognition of food antigens has become evident. When an antigen is not recognized, a kind of adaptive immune response may be activated, closely dependent on the effectiveness of T-regulatory cells (T-reg cells).¹⁸ On the basis of these findings, we have previously suggested that an up-regulation of T-reg cells may induce an increase of both IgG4 and toxic reactions in blood leucocytes, involved in the pathogenesis of intolerance.^{11, 12} As a result, an up-regulation of these cells is also the most probable reason for the moderate-severe reactions seen in the Leucocytotoxic Test.¹²

Limitations of the study

This study has some limitations. The main limitation is the retrospective design. Another limitation may be the use of the Leucocytotoxic Test to assess the presence of food intolerance. The Leucocytotoxic Test has been considered to have poor sensitivity and specificity.¹⁴ However, we considered as positive only the highest grades of reactions, such as level II and level III, to improve the specificity of the test.

Conclusions

In conclusion, patients with typical symptoms of gastro-esophageal reflux seem to have intolerance to multiple food items, some of which have not yet been described in patients with GERD. Clinical studies providing evidence of a causal association between food intolerance and typical symptoms of gastro-esophageal reflux are certainly needed.

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