Frequency of food hypersensitivity in patients with Functional Gastrointestinal Disorders

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Abstract

Background and study aims : **Food hypersensitivity (FH), irritable bowel syndrome (IBS) and functional dyspepsia (FD) have many overlapping symptoms, including abdominal discomfort, bloating, and altered bowel habits. We aimed to determine the frequency of FH in patients with IBS and functional FD.**

Patients and Methods **: Adult patients of either gender diagnosed with IBS and/or FD as per the Rome ш criteria were recruited. Patients underwent serological testing against 6 food allergens: beef, shrimp, egg white, milk, peanut, and soy-bean. Those testing positive were subjected to a food elimination diet for 4 weeks. Those showing improvement on elimination diet were subjected to re-challenge. Changes in symptoms were documented by the Global overall improvement scale (GOS) and Gastrointestinal symptom rating scale (GSRS).**

Results **: Two hundred patients were screened. Average age of the patients was 38.6, and 55 % were male. Nineteen (38%) patients tested positive, and were subjected to a food elimination diet. The most common food hypersensitivity was shrimp (17/89%), followed by 4/21% for egg-white, and peanut. Off these, 8 showed improvement. They were re-challenged, and were evaluated 2 weeks later, when all suffered symptom relapse. These 8 (4%) patients were diagnosed with FH. There was a statistically significant difference in both GSRS (total and component) and GOS scores at baseline between patients testing (+) and (-) on food allergen testing, mainly for diarrhoea (p=0.001), abdominal pain (p=0.001) and indigestion p=<0.001)**

Conclusions **: FH is present in 4 % of patients with a functional gastrointestinal disorder.** (Acta gastroenterol. belg., **2018,** 81, **253-256).**

Introduction

Food Hypersensitivity (FH) is an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food (1). The predominant symptoms of FH are post –prandial nausea, fullness, reflux, occasional vomiting, abdominal pain and diarrhoea.

Irritable bowel syndrome (IBS) is a gastrointestinal syndrome characterized by chronic abdominal pain and altered bowel habits in the absence of any organic cause. It is the most commonly diagnosed gastrointestinal condition[2]. Functional dyspepsia (FD) is a complex syndrome, characterized by postprandial fullness, early satiation, epigastric pain and/or burning and no evidence of structural disease. The reported prevalence of IBS is 15-20% (2) , while that of FD is 10-15 % (3) .These are among the commonest conditions encountered in gastroenterology practice, and thus are extremely important disease conditions. IBS and FD may coexist in up to 15 % of patients (3, 4)

Mucosal immune activation is an important factor in the development of hypersensitivity and pain in IBS. The immune activation that results from ingesting food antigens in FH may be an important cause of symptoms in patients with IBS/FD (5, 6).

IBS, FD and FH reactions have many overlapping symptoms, including abdominal pain and discomfort, bloating, and altered bowel habits, making it challenging to distinguish between the disorders (6). However, symptoms of food hypersensitivity are reduced or disappear when patients are placed on diets that specifically omit certain foods (elimination diets), which does not happen in IBS/FD. These symptoms return when patients are exposed to the same antigen subsequently (food challenge) (4).

While some studies report no significant association, recent studies report that up to 25% of patients with IBS have FH (7, 8, 9). Thus a significant number of patients have been erroneously diagnosed with IBS, when in fact they suffer from FH. However, these have universally been Caucasian populations, in which the type of food consumed, and the tendency to form antibodies against these common foods may be completely different as compared with the south Asian population (10).

The diagnosis of FH requires a compatible clinical history, a positive allergen test, and improvement of symptoms on an elimination diet. The reappearance of the same symptoms on an oral food challenge with the culprit allergen is not mandatory, but makes the diagnosis more supportive (4). We aimed to determine the frequency of food hypersensitivity in patients with irritable bowel syndrome and functional dyspepsia.

Materials and Methods

Patient population

Adult patients of either gender visiting the out-patient gastroenterology clinics of the Aga Khan University hospital from December 2013 till August 2015 diagnosed with irritable bowel syndrome and/or functional dyspepsia as per the Rome ш criteria were recruited.

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Process

The study protocol was approved by the hospital ethics committee, and all subjects gave their written informed consent to participate. The well-validated Global overall improvement scale (11) (GOS) and the gastrointestinal symptom rating scale (12) (GSRS) was filled at baseline. Patients underwent serological testing against the 6 main food allergens: beef, shrimp, egg white, milk, peanut, and soy-bean (Chemiluminescent Allergen Specific IgE Test-Immulite 2000 Siemens inc (13).), which tests for antibodies that are highly specific for human IgE and exhibit no cross reactivity to other human immunoglobulin classes. 5 ml clotted blood or 1 cc serum was required for testing. Titre`s of 0.35-0.69 and above, corresponding to 'low' and above were considered positive.

Patients who did not test positive on serum testing were diagnosed as not having food hypersensitivity, and were discharged to routine follow-up. Those who tested positive were subjected to a food elimination diet for 4 weeks. Diet was restricted to as many allergens as the patient showed sensitivity to on testing. Dietary information for food elimination was provided in the form of hand-outs in the language of their choice (English or Urdu), which included details of the foods to avoid, and their alternatives. In addition, there was verbal counselling by 2 trained research officers regarding food elimination, and the advice to maintain a food diary. This was done in consultation with a dietician, and the resource of the USDA food and nutrition centre (http://fnic.nal.usda.gov/nal_display/index.php) (14).

After 4 weeks of elimination diet, these patients were reviewed in clinic, and filled the 2nd round of GSRS and GOS forms, to document change in symptoms post food elimination. Those who did not report improvement were told to stop the elimination diet, and were discharged to follow-up. Those who had improved were subjected to re-challenge, by advising to consume a normal diet.

After 2 weeks of the re-challenge, patients were evaluated in clinic with the 3rd round of GSRS and GOS forms to document change in symptom scores post re-challenge.

Figure 1 describes the flow of the study

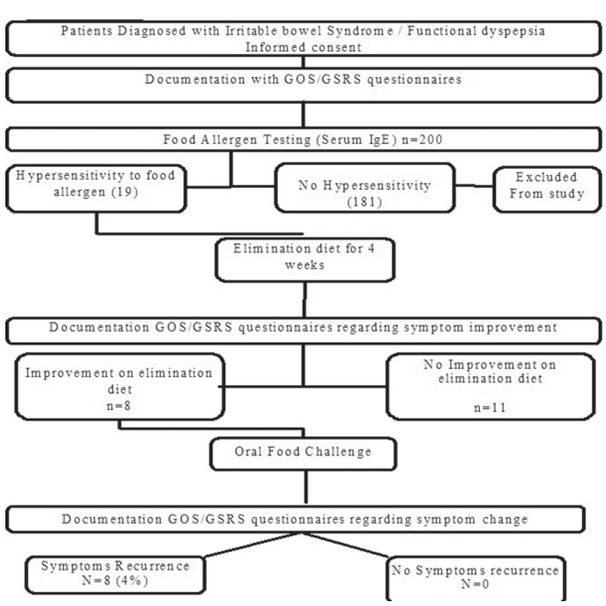

Fig. 1. — Study flowchart and results

Data analysis

Prevalence of positive food hypersensitivity in IBS with 95% confidence Interval (CI) were calculated with Epi-Info version 6.04 (CDC, USA 2016). Continuous variables are presented as mean ± SD, and categorical variables as percentage.

Paired t-test was applied to determine if there was a significant change in food hypersensitivity test from baseline to completion. Overall significant difference between the means at the different time points was measured through repeated measures ANOVA. Line graphs shows the relapsed symptoms of patients with food elimination were subjected to a re-challenge for 2 weeks. All p-values were based on two-sided tests and significance was set at a p-value less than 0.05. The analysis was performed using SPSS (Statistical Package of Social Sciences 2012) version 19.

Results

A total of 200 hundred patients with IBS-D and FD were screened. The average age of the patients was 38.6 ± 13.6, and the majority were male (55 %), 181 were negative on screening, and were diagnosed as not having any food hypersensitivity.

Nineteen (9.5%) patients tested positive, and were subjected to a food elimination diet. The most common food hypersensitivity was shrimp (17/89%), followed by 4/21% for egg-white, and 2 (10%) each for peanut and soya bean. Four patients had allergies to 3 food products, while 1 had a hypersensitivity to 4 food allergens.

Apart from 1 patient who tested positive for 4 food allergens who reported some tingling in the lips and tongue, none of the patients reported any other symptom, apart from their GI symptoms.

Off 19 patients at follow-up, 11 (58%) patients said that the symptoms persisted despite food avoidance, while 8 (42 %) showed improvement. These 8 were re-challenged, and were evaluated 2 weeks later, when all said that they had suffered symptom relapse. These 8 patients were diagnosed with food hypersensitivity. (Fig 1)

There was a statistically significant difference in both GSRS (total and component) and GOS scores at baseline between patients testing (+) and (-) on food allergen testing. The main components that were the most significant were diarrhoea (p=0.001), abdominal pain (p=0.001) and indigestion p=<0.001) (Table 1).

Table 1. — **Comparison of total and component GSRS and GOS scores at baseline between patients with true food hypersensitivity and no food hypersensitivity (including 11 false (+))**

	True positive, n=8	No food allergies, n=192	p value
Total	30.1 ± 2.5	24.4 ± 5.1	<0.001
Abdominal pain	5.1 ± 0.6	4.1 ± 0.8	0.001
Reflux	4.1 ± 0.9	3.6 ± 0.9	0.19
Diarrhoea	5.2 ± 0.4	4.3 ± 0.7	0.001
Indigestion	10.8 ± 0.6	8.3 ± 2.1	<0.001
constipation	4.7 ± 0.7	3.9 ± 1.0	0.02
GOS score	6 ± 0.5	4.4 ± 1.1	<0.001

GOS: Global overall improvement scale
GSRS: Gastrointestinal symptom rating scale

Table 2. — **Difference from baseline in GSRS/GOS scores in patients with (8) and without (11) FH after 4 weeks of elimination diet (n=19)**

	Baseline GSRS	After 4 weeks GSRS	Mean difference	p value
Positive, (8)	30.1 ± 2.5	17.8 ± 2.1	12.3	<0.001
Negative, (11)	25.1 ± 4.0	22.7 ± 3.8	2.4	0.06
	Baseline GOS	After 4 weeks GOS	Mean difference	p value
Positive, (8)	6 ± 0.5	2.7 ± 0.46	3.3	<0.001
Negative, (11)	4.4 ± 1.1	4.3 ± 0.92	0.1	0.8

GOS: Global overall improvement scale
GSRS: Gastrointestinal symptom rating scale

Table 3. — **Pre and post Comparison of GSRS (total and component) and GOS scores after 4 weeks of elimination diet (ED) and re-challenge (RC) (n=8)**

	Baseline	Follow up post ED	Follow up post RC	p value
Total	30.1 ± 2.5	17.8 ± 2.1	29.5 ± 3.1	<0.001
Abdominal pain	5.1 ± 0.6	2.5 ± 0.5	5.1 ± 0.9	<0.001
Reflux	4.1 ± 0.9	1.7 ± 0.7	4 ± 1.0	<0.001
Diarrhoea	5.2 ± 0.4	3.5 ± 0.9	5.3 ± 0.5	<0.001
Indigestion	10.8 ± 0.6	7.5 ± 0.9	10.6 ± 0.7	<0.001
Constipation	4.7 ± 0.7	2.6 ± 0.5	4.3 ± 1.0	<0.001
GOS score	6 ± 0.5	2.7 ± 0.4	5.8 ± 0.6	<0.001

GOS: Global overall improvement scale
GSRS: Gastrointestinal symptom rating scale

If the 19 patients who underwent a food elimination diet for 4 weeks are considered, 11 did not show improvement, while 8 did. This was confirmed in the GOS and GSRS scores, where there was a statistically significant decrease in GSRS and GOS scores in the patients with food hypersensitivity, which was not observed in those without hypersensitivity (Table 2).

The 8 patients who improved on food elimination were subjected to a re-challenge for 2 weeks. All the patients relapsed with symptoms, with scores almost returning to baseline levels (Table 3).

The individual variations in the patients with FH in the GSRS scores and GOS scores are depicted in Fig. 2 and 3 respectively.

Discussion

Functional gastrointestinal disorders are common disorders both in general and specialist practice. However food allergies are also not uncommon, having being reported in up to 5 % of the population (15). A growing body of work is reporting a link between IBS and FH, and recommending that an attempt should be made to diagnose and treat FH in this cohort (6, 15, 16).

In this study we utilized a standard procedure for the diagnosis of a FH in IBS-D and FD patients. Of the cohort of 200, 19 patients tested positive for a FH to at least 1 agent, shrimp being the most common. This is in keeping with literature reports that in adults the most common food hypersensitivity is crustacean (15).

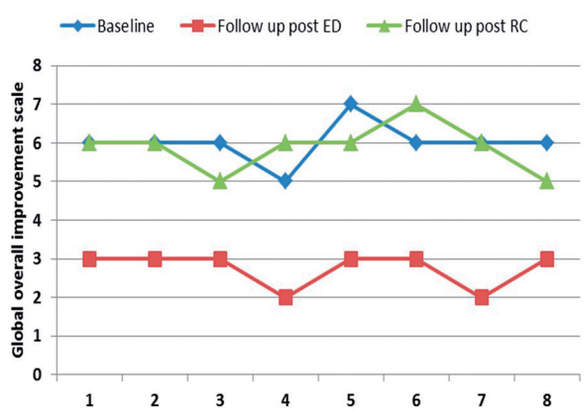

Fig. 2. — Individual variations in the patients with FH in the GOS scores

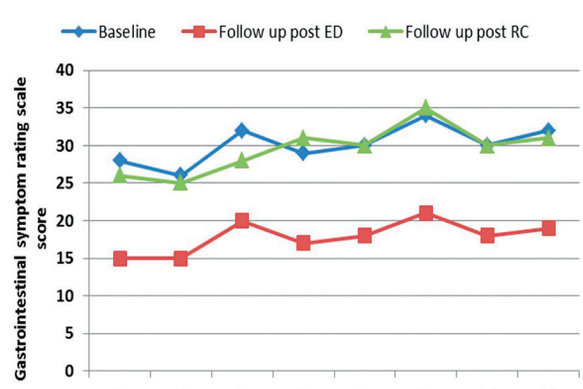

Fig. 3. — Individual variations in the patients with FH in the GSRS scores

These 19 patients were subjected to an elimination diet, on which 8 reported symptom improvement. The other 11 did not report any improvement in symptoms, likely reflecting a process of sensitization, i.e. the presence of antibody without it being responsible for clinical manifestations (4).

Eight patients were diagnosed with FH (4 %). This is compatible with reported literature that reports a range from 1.7-5.3% using robust methods of diagnosis (15). However, it is lower in this particular cohort than had been previously reported (8, 9). This may be due to the fact that varying methodologies have been adopted to establish a diagnosis of FH in other published studies, ranging from questionnaire based studies to cytometric assays, and fecal assays for tryptase, and calprotectin

IBS with FH is significantly more symptomatic than IBS without FH. Comparison of GOS/GSRS scores of these 8 patients with FH compared to the rest of the cohort without FH show that their baseline scores were higher, indicating that they were more symptomatic. Main component scores of the GSRS that were high were those relating to indigestion, diarrhoea and abdominal pain (Table 1). However, these scores decreased significantly both total and component, when subjected to an elimination diet. This did not occur in those with evidence of sensitization (Table 2). This indicates that serological evidence of a positive test, even in the presence of a compatible clinical history is not sufficient for a diagnosis of FH to be made.

The 8 patients who improved on the elimination diet were subjected to the re-challenge. All reported worsening of symptoms, as evidenced by GOS and GSRS scores returning to baseline (Fig 2 and 3) respectively. All sub-components of the GSRS showed worsening (table 3), thus supporting a diagnosis of FH.

If a comparison is made of the group ultimately diagnosed with a FH (n=8) and those who did not have a FH (n=192), then the group with a FH had higher GSRS scores for abdominal pain, diarrhoea and indigestion (table 1). This may be an early indicator of a possible FH in these patients.

Our study had the following limitations. Since the GSRS/GOS forms were filled after the elimination diet and re-challenge, there may have been recall bias. All meals were not provided by the investigators, so therefore there is always a chance that cross-contamination may have occurred.

We tested against the six main ingredients responsible for most FH, but it is possible that the patients may be allergic to other ingredients in foods against which we did not test.

The use of spices is common place in the local diet, and its contribution to symptoms is not known. And finally, the food challenge was not a double-blind challenge which is the gold standard, hence was open to patient bias regarding relapse of their symptoms.

However, despite these limitations we believe that this is important data in this subgroup of patients with IBS / FD. This is the first study of its kind in this specific group of patients from this region using robust methods of diagnosis of FH. Given the low rate of prevalence of FH in this group of patients, we do not recommend testing all patients with IBS/FD for FH. However, if there is a history of similar, recurrent symptoms on exposure of the same food in a patient on multiple occasions, it is worth screening with a food allergen test, with consideration of an elimination diet in those who test positive (17).

Conclusion

FH is present in 4 % of patients with a functional gastrointestinal disorder. Exclusion of a FH may be helpful in a subset of patients with a compatible clinical history, and intractable symptoms.

References

1. BOYCE J.A., ASSA'AD A., BURKS A.W. *et al.* Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel. *J. Allergy Clin. Immunol.*, 2010 Dec., **126** (6 Suppl) : S1-58.
2. DROSSMAN D.A. Rome Foundation Diagnostic Algorithms. *Am. J. Gastroenterol.,* 2010 Apr., **105** (4) : 741-2.
3. EL-SERAG H.B., TALLEY N.J. The prevalence and clinical course of functional dyspepsia. *Aliment. Pharmacol. Ther*., 2004 Mar. 15, **19** (6) : 643-54.
4. HUNGIN, A.P., CHANG L., LOCKE G.R., DENNIS E.H., BARGHOUT V. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. *Aliment. Pharmacol. Ther*., 2005 Jun 1, **21** (11) : 1365-75.
5. COLLINS S.M., PICHE T., RAMPAL P . The putative role of inflammation in the irritable bowel syndrome . *Gut*., 2001 Dec., **49** (6) : 743-5.
6. ATKINSON W., SHELDON TA., SHAATH N., WHORWELL P.J. Food elimination based on IgG antibodies in irritable bowel syndrome : a randomized controlled trial. *Gut*., 2004, **53** (10) : 1459-1464.
7. LIED G.A., LILLESTØL K., LIND R. *et al.* Perceived food hypersensitivity: a review of 10 years of interdisciplinary research at a reference center. *Scand. J. Gastroenterology,* 2011, **46** : 1169-78.
8. CARROCCIO A., BRUSCA I., MANSUETO P. *et al.* A Cytologic Assay for Diagnosis of Irritable Bowel Syndrome. *Clin. Gastroenterol. Hepatol.*, 2010, **8** : 254-60.
9. CARROCCIO A., BRUSCA I., MANSUETO P. *et al.* Fecal Assays Detect Hypersensitivity to Cow's Milk Protein and Gluten in Adults With Irritable Bowel Syndrome. *Clin. Gastroenterol. Hepatol.*, 2011, **9** (11) : 965-971.
10. LEE A.J., THALAYASINGAM M., LEE B.W. Food allergy in Asia : how does it compare? *Asia Pacific. Allergy,* 2013, **3** (1) : 3-14.
11. VELDHUYZEN VAN ZANTEN S.J., CHIBA N., ARMSTRONG D. *et al.* Validation of a 7-point Global Overall Symptom scale to measure the severity of dyspepsia symptoms in clinical trials. *Aliment. Pharmacol. Ther*., 2006 Feb. 15, **23** (4) : 521-9.
12. KULICH K.R., MADISCH A., PACINI F. *et al.* Reliability and validity of the Gastrointestinal Symptom Rating Scale (GSRS) and Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire in dyspepsia: A six-country study. *Health Qual. Life Outcomes*, 2008 Jan. 31, **6** : 12.
13. IMMULITE 2000 XPI IMMUNOASSAY SYSTEM. (n.d.). Retrieved March 09, 2017, from http://usa.healthcare.siemens.com/immunoassay/systems/immulite-2000-xpi-immunoassay-system/assays.
14. DIETARY GUIDANCE. (n.d.). Retrieved March 09, 2017, from https://www.nal.usda.gov/fnic/dietary-guidance-0
15. SKYPALA I. Adverse food reactions--an emerging issue for adults. *J. Am. Diet Assoc*.,. 2011 Dec., **111** (12) : 1877-91.
16. VIVINUS-NÉBOT M., DAINESE R., ANTY R. *et al.* Combination of allergic factors can worsen diarrheic irritable bowel syndrome: role of barrier defects and mast cells. *Am. J. Gastroenterol*., 2012 Jan., **107** (1) : 75-81.
17. DRISKO J., BISCHOFF B., HALL M., MCCALLUM R. Treating irritable bowel syndrome witha food elimination diet followed by food challenge and probiotics. *J. Am. Coll. Nut*r., 2006 Dec., **25** (6) : 514-22.