Scandinavian Journal of Gastroenterology, 2006; 41: 498–504

Taylor & Francis
Taylor & Francis Group

CASE REPORT

Multiple food hypersensitivity as a cause of refractory chronic constipation in adults

ANTONIO CARROCCIO[1], LIDIA DI PRIMA[1], GIUSEPPE IACONO[2], ADA M. FLORENA[3], FRANCESCO D'ARPA[4], CARMELO SCIUMÈ[5], ANGELO B. CEFALÙ[1], DAVIDE NOTO[1] & MAURIZIO R. AVERNA[1]

[1]*Internal Medicine, University Hospital of Palermo, Italy,* [2]*Paediatric Gastroenterology, Di Cristina Hospital, Palermo, Italy,* [3]*Pathology Department, University Hospital of Palermo, Italy,* [4]*Emergency Surgery Department, University Hospital of Palermo, Italy* [5]*Surgery Department, University Hospital of Palermo, Italy*

Abstract

Chronic constipation that is unresponsive to laxative treatment is a severe illness, but children unresponsive to laxatives have been successfully treated with an elimination diet. We report the first cases of refractory chronic constipation caused by food hypersensitivity in adults. Four patients with refractory constipation who were unresponsive to high doses of laxatives were put on an oligo-antigenic diet and underwent successive double-blind, placebo-controlled, food challenges (DBPFC). Routine laboratory tests, immunological assays, colonoscopy, esophago-gastroduodenoscopy and rectal and duodenal histology were performed. While on an elimination diet, bowel habits normalized in all patients and a DBPFC challenge triggered the reappearance of constipation. In comparison with another 13 patients with refractory constipation unresponsive to the elimination diet, observed over the same period, the patients with food-hypersensitivity-related constipation had the following characteristics: longer duration of illness ($p < 0.03$), lower body mass index ($p < 0.03$), higher frequency of self-reported food intolerance ($p < 0.01$), higher frequency of nocturnal abdominal pain and anal itching ($p < 0.01$). In patients with food hypersensitivity, hemoglobin concentrations and peripheral leukocytes were lower than those in controls ($p < 0.03$). The duodenal and rectal mucosa histology showed lymphocyte and eosinophil infiltration, and the duodenal villi were flattened in two cases. In adult patients, refractory chronic constipation may be caused by food hypersensitivity and an elimination diet is effective in these subjects.

Key Words: *Chronic constipation, diet, duodenal histology, food hypersensitivity, rectal histology*

Introduction

Chronic constipation is a frequent illness, affecting between 2% and 28% of the general population [1–6]. As a first approach, an organic or secondary cause must be ruled out, and subsequently therapeutic trials with fiber supplements and/or simple laxatives can be attempted. Patients who are unresponsive to these treatments normally undergo a complete diagnostic work-up to evaluate the possibility of surgical treatment. However, even after a correct diagnostic study, very few patients are treated effectively [7]. We have shown that in children with chronic constipation unresponsive to laxative treatment, the symptoms can be due to cow's milk protein intolerance and in these patients an elimination diet can correct constipation [8,9].

Here we present the first reports of refractory chronic constipation caused by food hypersensitivity in four adult patients.

Material and methods

The four cases described were observed between January 2000 and December 2002, at the outpatient clinic of the Internal Medicine Department of the University Hospital of Palermo. These patients were

Correspondence: Antonio Carroccio, MD, Medicina Interna, Policlinico di Palermo, Via del Vespro 141, IT-90127 Palermo, Italy. Tel: +39 091 6552860. Fax: +39 091 6552 936. E-mail: acarroccio@hotmail.com

(Received 22 July 2005; accepted 21 September 2005)

ISSN 0036-5521 print/ISSN 1502-7708 online
DOI: 10.1080/00365520500367400

diagnosed as suffering from refractory chronic constipation as they had the following characteristics: a) fewer than three bowel movements per week over at least 6 months, b) difficult and painful evacuation of hard stools, c) patient's impression that evacuations were incomplete, d) lack of response to dietary fiber supplements plus several laxative treatments (milk of magnesia 15–50 ml b.i.d., or/and lactulose 15–50 ml b.i.d., or/and polyethylene glycol 20–120 g/day); patients were instructed to adjust the dose to achieve soft stools).

In accordance with the standard diagnostic work-up performed in our hospital, at first contact an accurate clinical history and physical examination, routine laboratory tests, immunology tests and colonoscopy with rectal biopsies were performed. As these patients were also suffering from dyspepsia, they underwent esophago-gastroduodenoscopy (EGDS) with biopsies. After 4 weeks of laxative treatment, the unresponsive patients underwent defecography to evaluate pelvic floor dysfunction. Subsequently, they were enrolled in a 4-week treatment period with an oligo-antigenic diet to test the hypothesis of an association between constipation and food intolerance. The patients who improved on the oligo-antigenic diet were considered to be suffering from probable food hypersensitivity. After at least 8 weeks, all the patients who improved on the oligo-antigenic diet underwent a period of food challenges with the suspected foods. Food-hypersensitivity diagnosis was based exclusively on the relapse of constipation during the food-challenge period and its subsequent disappearance on the elimination diet. The patients with normal stool habits on the oligo-antigenic diet and who already showed constipation during the various food challenge periods were considered as having multiple food-hypersensitivity-related constipation.

The patients gave their informed consent to all the diagnostic and therapeutic procedures described in this study. The study protocol was approved by the Ethics Committee of the University Hospital of Palermo.

Elimination and food challenge diets

On the basis of our previous experience [10,11] the oligo-antigenic diet was designed to contain rice, lamb, carrots, ass's milk, olive oil, salt and sugar. After 4 weeks, the subjects who responded to this regimen were introduced to new foods carefully and singly, with at least 8 days between the introduction each new food. The tolerated foods were kept in the diet. If after the introduction of a new food the patients observed any symptoms, particularly the reappearance of constipation, the food was excluded from the diet. If bowel movements normalized again, a second challenge was performed after at least 2 months to confirm the intolerance.

The first challenge was performed at home in an open fashion, with the patient aware of the foods introduced. Any food that had previously caused an acute reaction in the personal clinical history of the patients was avoided. The second challenge was begun in hospital as previously described [8,9] using the double-blind placebo-controlled (DBPC) method for cow's milk and wheat and again in open fashion for the other foods. If no symptoms were observed within 12 h after commencement of the challenge, the patient was discharged and the challenge continued at home. DBPC for cow's milk was performed by administering capsules coded as A or B containing milk proteins (whey from bovine milk, 15 g daily divided into three administrations; Sigma W1500) or polyethylene glycol (PEG, 10 g daily in three administrations; Sigma P3015) respectively. DBPC for wheat proteins was performed with capsules containing wheat (untreated wheat germ, 20 g daily in three administrations; Sigma W0125) or PEG. Capsules A or B were given for 2 consecutive weeks and then, after one week of washout, the patients received the other capsules for 2 weeks. The order of capsule administration was randomly assigned by a computer-generated method and the researchers were also unaware of the order of the treatments.

During the 2-week DBPC period, the patients recorded the number of bowel movements and any clinical symptoms.

Dietary assessment

During the study period the patients were asked to record the amount and type of food they had eaten each day. These diaries were analyzed at the end of the study to evaluate adherence to the diet and the quantity of fiber consumed.

Laboratory tests

At entry to the study, routine hemato-chemical, thyroid function and immunological tests were performed. Serum levels of total IgE (Phadebas IgE paper radioimmunosorbent test kit, Pharmacia Diagnostics, Uppsala, Sweden) were assayed and specific IgE tests were performed on whole cow's milk, wheat, egg and other food allergens. In addition, skin prick tests (Lofarma Diagnostic, Milan, Italy) were carried out with food antigens. Serology tests for diagnosis of celiac disease and serum C4 levels (for C1 esterase inhibitor deficiency

diagnosis) were also assayed. Methods and reference values have been described previously [12–14].

Histology study

Rectal biopsies were performed at entry to the study. Biopsy specimens (at least three) were obtained at 5 to 10 cm from the anus. Mucosa specimens were fixed in 10% neutral buffered formalin, embedded in paraffin wax and stained with hematoxylin-eosin, Schiff's periodic acid and Masson's trichrome. Morphometric studies were performed with a Leica interactive image analyzer (model Q500 MC; Leica, Heerbrugg, Switzerland). Intraepithelial and lamina propria lymphocytes and eosinophils were counted as previously described [15]. In brief, intraepithelial lymphocytes and eosinophils in the rectal mucosa were counted per 100 deep-crypt cells. The number of eosinophils in the lamina propria was given as a percentage per 1000 lamina propria cells per section.

Subjects with concomitant dyspepsia underwent EGDS with duodenal biopsies. Duodenal histology was classified according to Oberhuber et al. [16]. The number of intraepithelial lymphocytes was counted per 100 villous epithelial cells.

The pathologist was unaware of the clinical and laboratory data of the patients, including response to the elimination diet and the immunology study.

Case reports

The four subjects with food-hypersensitivity-related constipation were women with a mean age (SD) of 40.2 ± 11.5 years (range 30–52 years). At baseline, they had no more than two bowel movements per week (median 1.5, range 1–2), always after a cleanout and despite their assuming high doses of laxatives. They all reported abdominal pain and nausea which were exacerbated by some foods (self-reported intolerance to: cow's milk and derivatives 4 cases, eggs 4 cases, wheat 2 cases, tomatoes 2 cases, beef 1 case, cocoa 1 case, oranges 1 case, fish 1 case, legumes 1 case). However, none of them reported food hypersensitivity as a possible cause of the constipation.

In all cases, the diagnostic procedures, including defecography, did not show any cause of secondary constipation. When the hypoallergenic elimination diet was commenced, all medications were suspended. Bowel habits normalized in all patients within 10 days after commencement of this diet: stools became soft, there was no pain on defecation and abdominal pain and nausea disappeared. During the 8 weeks of elimination diet the patients had a median of 5.5 bowel movements/week, range 4–7, (in comparison with the baseline $p < 0.01$, the Wilcoxon rank sum test).

The double-blind, placebo-controlled cow's milk and wheat challenges confirmed that all four patients cured on elimination diet suffered from cow's milk and wheat hypersensitivity. In fact, cow's milk caused coughing and bronchospasms in two patients within 10 min after its administration and in these cases the challenge was suspended. In the other two cases, the readministration of cow's milk and wheat in all four patients caused the reappearance of constipation, always associated with abdominal pain, within 5 days after commencement of the challenges (median 2 days, range 1–5 days) and these symptoms disappeared on returning to the oligo-antigenic diet. Furthermore, open challenges showed hypersensitivity to other foods (eggs 4 cases, tomatoes 3 cases, beef 3 cases, cocoa 3 cases, soy 3 cases, oranges 2 cases, goat's milk 2 cases, fish 1 case, legumes 1 case, peas 1 case, cauliflower 1 case, beans 1 case), as constipation reappeared 1–4 days after reintroduction.

Analysis of the daily calory intake and of the main constituents of the diet (proteins, carbohydrates, fats and fiber) did not show any significant quantitative variations during the different dietary regimens. In accordance with these results, we diagnosed chronic constipation due to multiple food hypersensitivity in the four patients with normalized bowel movements on the oligo-antigenic diet.

All the patients had a long history of constipation and in three cases the onset was during childhood. All patients reported that some foods had exacerbated abdominal pain and they had tried to self-limit their consumption. A previous diagnosis of food intolerance had been made in all cases during childhood, but based on the presence of symptoms other than constipation: two patients had had chronic diarrhea and one patient vomiting due to cow's milk allergy before the age of 2 years, while one patient had had asthma and atopic dermatitis due to egg ingestion until the age of 20 years. All of them were considered to be no longer suffering from food intolerance. When food-hypersensitivity-related constipation was diagnosed, all four patients had one or more manifestations of allergy due to respiratory allergens: asthma (2 cases), atopic dermatitis (1 case) and rhinitis (1 case). Finally, three patients had hypersensitivity to medications: salicylates (3 cases), penicillin and derivatives (2 cases), non-steroidal anti-inflammatory drugs (2 cases).

Dyspepsia was also present in all four patients with food-hypersensitivity-related constipation and they underwent EGDS with duodenal biopsies. The final EGDS diagnosis was erosive esophagitis in all cases, with one case of Barrett's esophagus; according to

the Los Angeles classification system for the endoscopic assessment of reflux esophagitis [17], two patients had grade A and two patients had grade B esophagitis. Other clinical signs present in all the patients with food-hypersensitivity-related constipation were nocturnal abdominal pain and anal itching. Body mass index (weight/height^2) was lower than the normal limit in three patients.

Concerning the laboratory data, skin prick tests were negative and none of the IgE-related assays for food allergy evaluation was positive. Two patients showed above-normal values of antigliadin IgG antibodies. Celiac disease was excluded in these patients as they were negative for anti-transglutaminase antibodies and did not show the HLA alleles DQA1*0501, DQB1*02 or DQB1*0302, codifying for the haplotypes predisposing to celiac disease. All patients had hemoglobin levels lower than the normal limit (range 9–11.5 g/dl) and two showed peripheral leukocytes counts below 4000/mm^3. All the other routine laboratory tests were normal, including serum C4 assay and those exploring liver, thyroid and kidney function.

At entry to the study, rectoscopy showed mild rectal inflammation with erythema of the mucosa and friability, without ulcerations or erosions in all four patients with food hypersentivity. Hematoxylin-eosin staining of the rectal biopsies showed that there was no crypt distortion or branching in any of the cases, but a diffuse inflammation of the mucosa with infiltration of eosinophils, lymphocytes and plasma cells as well as edema. Duodenal histology showed that two patients with food-hypersensitivity-related constipation had partial and focal villous atrophy, with a villi/crypt ratio between 1 and 2 (normal value >3.5) and diffuse mucosa infiltration of lymphocytes and plasma cells. The same infiltration was seen in the other two patients with food hypersensitivity, but their villi/crypt ratios were normal.

Follow-up of the patients

The mean duration of follow-up was 3 years (range 2–4 years). On elimination diet, bowel movements remained normal with painless evacuations of soft stools. The frequency and severity of abdominal pain dramatically decreased, as did the associated symptoms of allergy, but they did not completely disappear. Pain-disturbed sleep and anal itching disappeared. Dyspepsia also improved, but not completely. Some manifestations reappeared on the occasional, often involuntary, consumption of foods causing constipation. Formal open cow's milk (in two patients) and wheat (in all patients) challenges were performed yearly during the follow-up period. They confirmed the persistence of the cow's milk and wheat hypersensitivity. In fact, they caused the reappearance of constipation, always associated with abdominal pain and nausea, within 5 days after commencement of the challenges.

As for laboratory examinations, hemoglobin concentration increased but remained below 12 g/dl in one patient and a leukocyte count below 4000/mm^3 occasionally persisted in two patients. Rectal histology was re-evaluated after the subjects had been on an oligo-antigenic diet for at least one year. Histology showed no mucosal erosions and inflammation was greatly reduced: the number of intraepithelial lymphocytes and eosinophils was significantly lower than at baseline (both $p = 0.04$, Mann-Whitney test). EGDS and duodenal histology were also repeated while subjects were on an elimination diet. Esophagitis persisted in all patients but was less severe than on entry to the study: there was mucosal hyperemia without erosions and no change in the patient with Barrett's esophagus. Duodenal histology showed normal villi and crypts in all patients and the intraepithelial lymphocyte count was lower than at baseline.

Retrospective analysis

During the same study period we observed another 13 patients with chronic refractory constipation not due to secondary causes who were treated with an oligo-antigenic diet but did not improve on this treatment. In comparison with this group, the patients with food hypersensitivity showed the following differences: longer duration of illness ($p < 0.03$; Mann-Whitney test), lower body mass index ($p < 0.03$), higher frequency of previous history of cow's milk intolerance and of concomitant allergic manifestations ($p < 0.01$ the Fisher test), higher frequency of self-reported food hypersensitivity ($p < 0.01$), higher frequency of nocturnal abdominal pain and anal itching ($p < 0.01$), lower hemoglobin concentration and peripheral leukocytes count ($p < 0.03$) (see Table I). Both the duodenal and rectal mucosal histology showed a more severe inflammation in patients with food hypersensitivity than in the others with constipation unrelated to food hypersensitivity (see Table II).

Discussion

In this report we showed that some patients with chronic constipation unresponsive to laxatives were suffering from multiple food hypersensitivity and their constipation was successfully treated with an oligo-antigenic diet. In fact, in these patients bowel habits normalized on elimination diet while constipation with severe abdominal pain reappeared on

Table I. Clinical characteristics at baseline of the 4 patients suffering from refractory chronic constipation due to food hypersensitivity (Group A) and of 13 patients with refractory constipation unrelated to food hypersensitivity (Group B). (Plus-minus values are means ± SD).

	Group A ($n=4$)	Group B ($n=13$)	p-value
Age (years)	40.2 ± 11.5	41 ± 19.1	NS
Sex (males/females)	0/4	6/7	NS
Body mass index	21.1 ± 1.15	26.7 ± 4.31	0.03
Duration of illness (years)	39.2 ± 7.2	24.9 ± 10.5	0.03
Self-reported food intolerance (number)	4/4	0/13	0.01
Family history of food intolerance (number)	2/4	0/13	NS
Previous personal history of food intolerance (number)	4/4	0/13	0.01
Concomitant symptoms of food intolerance (bronchospasm, dermatitis, urticaria, rhinitis) (number)	4/4	0/13	0.01
Allergy to medications	3/4	1/13	0.04
Soiling (number)	0/4	1/13	NS
Nocturnal abdominal pain (number)	4/4	0/13	0.01
Fecal mass on rectal examination	4/4	13/13	NS
Anal itching	4/4	0/13	0.01
Dyspepsia	4/4	10/13	NS

Body mass index was calculated as patient's weight (in kg)/height^2 (in meters); normal range is 20–25.

DBPC challenge with wheat and cow's milk. Furthermore, several other foods caused constipation and abdominal pain, as confirmed by open challenges and several episodes of involuntary food consumption. As food hypersensitivity diagnosis is based on the clinical observation of the relationship between food ingestion and symptom onset on DBPC challenge and the subsequent disappearance of symptoms on returning to an elimination diet [18], we can reasonably affirm that chronic constipation may be a manifestation of food hypersensitivity in adults, as has been shown in children [8,9,19–21]. Moreover, the hypothesis that the resolution of the chronic constipation could be related to an unspecific property of the hypoallergenic diet is excluded by the evidence that this diet did not modify stool frequency, consistency and form in another 13 patients who underwent this dietary treatment. Furthermore, as no spontaneous fluctuation of the disease was observed during the six months before the study and no medications were administered during the dietary trial, there can be no doubt that the improvement in stool frequency was due to the elimination diet.

Although the present report is the first description of chronic constipation caused by food hypersensitivity in adults, we think that the clinical presentation of these cases led to a "self-made diagnosis". All four

Table II. Histology findings in the rectal and duodenal mucosa of the 4 patients with food-hypersensitivity-related constipation (Group A) and in 13 patients with refractory constipation unrelated to food hypersensitivity (Group B) at entry to the study. Only 10 patients in Group B, suffering from dyspepsia, underwent duodenal biopsies and were included as controls for duodenal histology.

Rectal histology	Group A $n=4$	Group B $n=13$	p-value
Crypt distortion	0/4	0/13	N.S.
Lymphoid nodules	1/4	7/13	N.S.
Interstitial edema	4/4	1/13	0.04
Intraepithelial lymphocytes (× ± SD)	4.6 ± 1.5	3.1 ± 0.6	0.01
Intra-epithelial eosinophils (× ± SD)	4.1 ± 1.4	2.0 ± 1.5	0.03
Eosinophils in the lamina propria (× ± SD)	6.3 ± 2.4	3.9 ± 2.0	0.05
Duodenal histology	$N=4$	$N=10$	
Inflammation score	3.5 ± 0.5	1.5 ± 0.5	0.01
Intraepithelial lymphocytes (× ± SD)	45 ± 13	23 ± 8	0.01

The scores for the villi/crypt ratio and duodenal mucosa inflammation [16] were: normal villi/crypt ratio, without inflammatory infiltration of the lamina propria (score 1); normal villi/crypt ratio, but presence of inflammatory infiltration of the lamina propria (score 2); reduced villi/crypt ratio due to crypt hypertrophy, but with normal villi, and presence of inflammatory infiltration of the lamina propria (score 3); reduced villi/crypt ratio due to crypt hypertrophy plus mild villus atrophy, and presence of inflammatory infiltration of the lamina propria (score 4); flattened mucosa (marked villous atrophy) plus crypt hypertrophy and presence of inflammatory infiltration of the lamina propria (score 5). Intraepithelial lymphocytes in the duodenal mucosa were counted per 100 villous cells.

The Fisher test was used to compare the frequency of the different histological findings in the two groups. The Mann-Whitney U-test was used to compare the data of the patients with food hypersensitivity-related constipation and the patients not suffering from food hypersensitivity.

patients we diagnosed had been previously diagnosed for food intolerance during childhood. These patients had been considered cured because the specific symptom of intolerance had disappeared on a normal diet. However, the appearance of constipation some time later confirmed our previous observation that, in some patients with food hypersensitivity, the disease persists with a different clinical manifestation [22]. Furthermore, at the time of our observation, all the patients with food-hypersensitivity-related constipation had other symptoms of hypersensitivity: asthma, urticaria, dermatitis and rhinitis. Hypersensitivity to medications was also more frequent in these patients than in the others studied. Finally, all the patients with constipation due to food hypersensitivity self-reported that some foods caused abdominal pain and consequently they had reduced ingestion of these foods.

Other clinical characteristics of the subjects with food-hypersensitivity-related constipation were a longer history of constipation, a lower body mass index and a higher frequency of anal itching and severe abdominal pain along with sleep disturbance. The association between constipation and abdominal pain generally suggests a diagnosis of irritable bowel syndrome (IBS) [7,23]. However, the severity of abdominal pain (nocturnal and sleep-disturbing) observed in our patients is uncommon in IBS, and previous treatments were not effective (data not shown). We hypothesize that in these patients the intestinal mucosal inflammation alters function in the deeper neuromuscular tissue determining slow motility, as has been demonstrated also in clinical conditions characterized by mild and superficial inflammation restricted to the mucosa or lamina propria [24,25].

Laboratory assays showed that none of the patients with food hypersensitivity had an IgE-mediated allergy mechanism, although some of the associated allergy manifestations (asthma and urticaria) appeared only a few minutes after food ingestion. However, it is known that most of the gastrointestinal symptoms due to food allergy are not linked to an IgE reaction [18] and we have described cases of anaphylactic shock a few minutes after rice ingestion, without any evidence of an IgE-mediated mechanism [26]. Two patients with wheat hypersensitivity were positive for IgG AGA, a result in keeping with the useful role of the IgG food antibodies in addressing an elimination diet in patients with suspected food intolerance [27,28]. Although this finding can be associated with a diagnosis of celiac disease [16], we excluded this possibility because of the lack of clinical improvement after excluding only wheat proteins from the diet (data not shown) as well as the negativity of the serum anti-transglutaminase antibodies and the absence of the HLA alleles, which predispose to celiac disease. Among the other laboratory tests, the slightly low hemoglobin level, as well as the low body mass index, may be due to damage to the duodenal mucosa documented by the duodenal histology. Similar intestinal mucosa damage has been reported in food-protein hypersensitivity with a cell-mediated immune response [29]. Rectal histology confirmed that the patients with food hypersensitivity had more frequent signs of inflammation than the others [30]. Rectal and duodenal histology and the evidence of esophagitis in all four subjects with constipation due to food hypersensitivity show that this clinical condition is characterized by food-dependent inflammation of the entire gastrointestinal tube.

In conclusion, this report shows that in adult patients chronic constipation can be caused by multiple food hypersensitivity. These cases presenting constipation that is unresponsive to laxative treatment can be successfully treated with an oligoantigenic diet.

Acknowledgements

We thank Mrs Carole Greenall for revision of the English. This work was supported by grants from the Ministry of Universities and Scientific Research (decr 86 Ric dated 30/01/2002) and from the Ministry of Agriculture of Italy (DM 224/7303/02 dated 10/06/2002) (project "ALICE").

References

[1] Sonnenberg A, Koch TR. Epidemiology of constipation in the United States. Dis Colon Rectum 1989;32:1–8.
[2] Everhart JE, Go VLW, Hohannes RS, Fitzsimmons SC, Roth HP, White LR. A longitudinal study of self-reported bowel habits in the United States. Dig Dis Sci 1989;34:1153–62.
[3] Locke GR III. The epidemiology of functional gastrointestinal disorders in North America. Gastroenterol Clin North Am 1996;25:1–19.
[4] Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, et al. US householder survey of functional gastrointestinal disorders. Dig Dis Sci 1993;38:1569–80.
[5] Jones R, Lydeard S. Irritable bowel syndrome in the general population. Br Med J 1992;304:87–90.
[6] Stewart WF, Liberman A, Sandler RS, Woods MS, Stemhagen A, Chee E, et al. Epidemiology of constipation (EPOC) Study in the United States: relation of clinical subtypes to socio-economic features. Am J Gastroenterol 1999;94:3530–9.
[7] Locke GR III, Pemberton JH, Phillips SF. American Gastroenterological Association medical position statement: guidelines on constipation. Gastroenterology 2000;119:1761–6.
[8] Iacono G, Carroccio A, Cavataio F, Montalto G, Cantarero MD, Notarbartolo A. Chronic constipation as a symptom of cow milk allergy. J Pediatr 1995;126:34–9.

[9] Iacono G, Cavataio F, Montalto G, Florena A, Soresi M, Tumminello M, et al. Intolerance of cow's milk and chronic constipation in children. N Engl J Med 1998;338:1100–4.
[10] Carroccio A, Cavataio F, Montalto G, D'Amico D, Alabrese L, Iacono G. Intolerance to hydrolysed cow's milk proteins in infants: clinical characteristics and dietary treatment. Clin Exp All 2000;30:1597–603.
[11] Iacono G, Carroccio A, Cavataio F, Montalto G. Multiple food allergy. J Ped Gastroenterol Nutr 1993;16:472–3.
[12] Iacono G, Carroccio A, Cavataio F, Montalto G, Kazmierska I, Lorello D, et al. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. J Allergy Clin Immunol 1996;97:822–7.
[13] Carroccio A, Iacono G, Montalto G, Cavataio F, Soresi M, Kazmierska I, et al. Immunologic and absorptive tests in celiac disease: can they replace intestinal biopsies? Scand J Gastroenterol 1993;28:673–6.
[14] Carroccio A, Vitale G, Di Prima L, Chifari N, Napoli S, La Russa C, et al. Comparison of anti-transglutaminase ELISAs and anti-endomysial antibody assay in the diagnosis of celiac disease: a prospective study. Clin Chem 2002;48:1546–50.
[15] Carroccio A, Volta U, Di Prima L, Petrolini N, Florena AM, Averna MR, et al. Autoimmune enteropathy and colitis in an adult patient. Dig Dis Sci 2003;48:1600–6.
[16] Oberhuber G, Granditsch G, Vogelsang H. The histopathology of celiac disease: time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol 1999;11: 1185–94.
[17] Armstrong D, Bennett JR, Blum AL, Dent J, De Dombal FT, Galmiche JP, et al. The endoscopic assessment of oesophagitis: a progress report on observer agreement. Gastroenterology 1996;111:85–92.
[18] Sampson HA, Sicherer SH, Birnbaum AH. AGA technical review on the evaluation of food allergy in gastrointestinal disorders. Gastroenterology 2001;120:1026–40.
[19] Daher S, Sole D, de Morais MB. Cow's milk and chronic constipation in children. N Engl J Med 1999;340:891.
[20] Shah N, Lindley K, Milla P. Cow's milk and chronic constipation in children. N Engl J Med 1999;340:891–2.
[21] Vanderhoof JA, Perry D, Hanner TL, Young RJ. Allergic constipation: association with infantile milk allergy. Clin Pediatr 2001;40:399–402.
[22] Iacono G, Cavataio F, Montalto G, Soresi M, Notarbartolo A, Carroccio A. Persistent cow's milk protein intolerance in infants: the changing faces of the same disease. Clin Exp All 1998;28:817–23.
[23] Talley NJ, Zinsmeister AR, Van Dyke C, Melton LJ. Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology 1991;101:927–34.
[24] Collins SM. The immunomodulation of enteric neuromuscular function: implications for motility and inflammatory disorders. Gastroenterology 1996;111:1683–99.
[25] Tornblom H, Lindberg G, Nyberg B, Veress B. Full thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterology 2002;123:1972–9.
[26] Cavataio F, Carroccio A, Iacono G, Montalto G. Isolated rice intolerance: clinical and immunologic characteristics in four infants. J Pediatr 1996;128:558–60.
[27] Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. Gut 2004;53: 1459–64.
[28] Iacono G, Carroccio A, Cavataio F, Montalto G, Lorello D, Kazmierska I, et al. IgG anti–betalactoglobulin (betalactotest): its usefulness in the diagnosis of cow's milk allergy. Ital J Gastroenterol 1995;27:355–60.
[29] Iyngkaran N, Yadav M, Boey C, Lam K. Severity and extent of upper small bowel mucosal damage in cow's milk protein-sensitive enteropathy. J Pediatr Gastroenterol Nutr 1988;8: 667–74.
[30] Carroccio A, Scalici C, Maresi M, Di Prima L, Cavataio F, Noto D, et al. Chronic constipation and food intolerance: a model of proctitis causing constipation. Scand J Gastroenterol 2005;40:33–42.