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# Review article: chronic constipation and food hypersensitivity – an intriguing relationship

A. CARROCCIO* & G. IACONO†

*Internal Medicine, University Hospital of Palermo, Palermo; †Pediatric Gastroenterology, 'Di Cristina' Hospital of Palermo, Palermo, Italy

Correspondence to:
Dr A. Carroccio, Internal Medicine, Policlinico di Palermo, via del Vespro 141, 90127 Palermo, Italy.
E-mail: acarroccio@hotmail.com

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## SUMMARY

### Background
Chronic constipation is common in the general population. Some studies have shown that in children cow's milk protein hypersensitivity can cause chronic constipation unresponsive to laxative treatment.

### Aims
To review the literature and summarize the data that point to a relationship between refractory chronic constipation and food hypersensitivity, and to discuss the hypothesis that the pathogenesis of constipation due to food hypersensitivity.

### Methods
A search in the U.S. National Library of Medicine was performed, matching the key words 'chronic constipation, food intolerance and allergy'.

### Results
Thirty-three papers were found but only 19 of them were related to the topic of this review. Most of the data indicated a relationship between constipation and food allergy in a subgroup of paediatric patients with 'idiopathic' constipation unresponsive to laxative treatment. There was only one study in adults that demonstrated the resolution of chronic constipation on hypoallergenic diet in four patients.

### Conclusions
An increasing number of reports suggest a relationship between refractory chronic constipation and food allergy in children. Similar data in adults are scarce and need to be confirmed. Further studies should be performed to obtain firmer evidence for the role of allergy in constipation and clarify the pathogenetic mechanisms involved.

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## INTRODUCTION

Chronic constipation is extremely common in the general population, with a reported prevalence as high as 20%.[1] The disease is also very common in children, the frequency ranging between 3% and 16% of the paediatric population.[2] The role of internists, gastroenterologists or paediatricians is, first of all, to exclude the possibility that the constipation may be secondary to another condition, including cancer of the colon in adults. After this first step, if there are no data indicating secondary constipation a therapeutic trial with fibre and/or simple laxatives is proposed. If further treatment is required, several laxatives at progressively higher dosages can be used. However, this approach does not cure the constipation in a considerable number of patients. In children, indeed, it has been reported that at the end of a 5-year follow-up study, 35–45% of the patients had not recovered.[3] Furthermore, it has been demonstrated that childhood constipation can persist into adulthood, as a recent study showed that one-third of the children followed up beyond puberty continued to have complaints of severe constipation.[4] This finding contradicts the general belief that childhood constipation gradually disappears before or during puberty.

Furthermore, adult patients unresponsive to laxative treatment normally undergo a complete diagnostic study, but very few patients are treated effectively.[1]

Our previous studies have shown that in children with chronic constipation unresponsive to laxative treatment the symptom can be due to cow's milk protein hypersensitivity (CMPH) and in these patients an elimination diet is able to correct the constipation.[5, 6]

This review summarizes the literature regarding the relationship between refractory chronic constipation and food hypersensitivity and discusses the hypothesis of the pathogenesis of constipation due to food hypersensitivity.

## METHODS

We identified and selected eligible literature irrespective of publication status, language, study design and type of publication (clinical trial, case report, review, etc.). Electronic searches included MEDLINE (1970 to June 2006; at the website http://www.ncbi.nlm.nih.gov), looking for the following words (all fields): ('chronic constipation' or 'constipation') and ('food intolerance' or 'allergy'). References from reviews on chronic constipation or food allergy and from the articles selected for our study were also examined in search of relevant articles. We also identified papers via the bibliographies in relevant articles and hand searches of specialist journals and conference proceedings.

## RESULTS

Thirty-three references were identified through electronic searches of which 14 references were excluded after scanning the abstracts. Nineteen references were thus included and others were identified through bibliographies (Table 1).

### Chronic constipation and food hypersensitivity: evidence of a relationship in children

Although the association between cow's milk (CM) protein and chronic constipation had already been reported by Buisseret in 1978,[7] until our first prospective study[5] there were only two case reports in the literature indicating that constipation might be the only clinical manifestation of CMPH.[8, 9] However, it is interesting that many years before, Davidson *et al.* had reported that constipation in paediatric patients considerably improved when treatment included the exclusion of CM and its derivatives from the diet.[10]

We performed our first study as we had observed that several patients suffering from diarrhoea, atopic dermatitis or bronchospasm because of CMPH during the first year of life began to suffer from chronic constipation unresponsive to conventional laxative treatment (refractory constipation) at the age of 2–3 years. It was an open study, not placebo-controlled, and showed that 21 of 27 patients with refractory constipation responded to a CM-free diet. Figure 1 shows two of the main findings of that work: (i) most of the patients with chronic constipation responding to CM-free diet had a previous history of CM allergy; (ii) there was no significant difference in serum levels of total immunoglobulin (Ig)E or specific IgE between patients with or without CMPH.

An important confirmation of the data observed in that first study came from a subsequent study with a double-blind crossover design,[6] comparing CM with soy milk in 65 children with refractory chronic constipation (one bowel movement every 3–15 days). All patients had been previously treated with laxatives without success. After a 15-day observation period they received CM or soy milk for 2 weeks and, after a

**Table 1.** Summary of the main studies which have investigated the relationship between chronic constipation and CMPH

Studies investigating the constipation–CMPH relationship

| Author, year | Number of cases | Type of study | Evidence of the relationship | Reference |
|---|---|---|---|---|
| Chin, 1983 | 1 | Case report | Yes | 8 |
| McGrath, 1984 | 1 | Case report | Yes | 9 |
| Iacono, 1995 | 27 | Prospective, uncontrolled trial | Yes | 5 |
| Iacono, 1998 | 65 | Prospective RCT | Yes | 6 |
| Iacono, 1998 | 1 | Case report | Yes | 43 |
| Daher, 1999 | 25 | Not specified | Yes | 12 |
| Shah, 1999 | 14 | Prospective | Yes | 11 |
| Bloom, 1999 | 4 | Case report | Yes | 36 |
| Daher, 2001 | 25 | Prospective | Yes | 13 |
| Loening-Baucke, 2001 | Not specified | Unpublished personal experience | No | 4 |
| Vanderhoof, 2001 | 12 | Retrospective | Yes | 14 |
| Turunen, 2004 | 35 | Prospective | Yes | 15 |
| Carroccio, 2005 | 52 | Prospective with DBPC challenge | Yes | 23 |
| Iacono, 2006 | 26 | Prospective with DBPC challenge | Yes | 35 |
| Carroccio, 2006 | 4 | Case reports | Yes | 27 |

Other studies on allergy and constipation

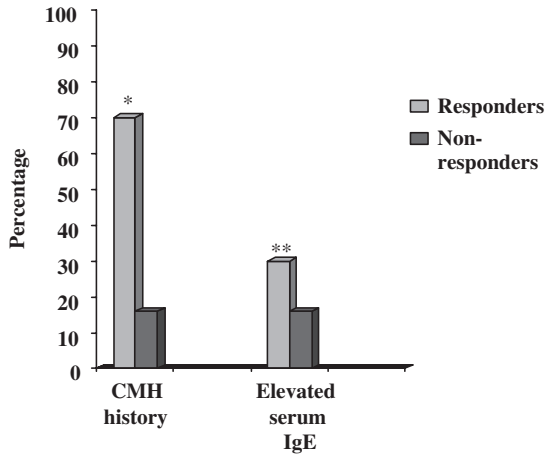
| | Main conclusions | |
|---|---|---|
| Andiran, 2003 | Children with chronic constipation and anal fissures consumed larger amounts of CM, had shorter duration of breast feeding and earlier bottle feeding than children with normal bowel habits | 45 |
| Rokaite, 2005 | One hundred and four of 164 children with atopic dermatitis complained of gastrointestinal disorders due to food allergy. Constipation was one of the most common gastrointestinal disorders | 18 |
| Yimyaem, 2003 | None of 10 patients with CMPH showed constipation | 17 |
| Aanpreung, 2003 | 4 of 20 infants with haematemesis due to CMPH showed constipation during a follow-up of 2.6 years | 19 |
| Romanczuk, 2003 | IgE-mediated food allergy may significantly prolong colonic transit in patients with chronic constipation | 20 |

RCT, randomized-controlled trial; DBPC, double-blind placebo-controlled; CMPH, cow's milk protein hypersensitivity.

1-week wash-out period, the feeding regimens were reversed. In 44 of the 65 children (68%) constipation resolved while they were receiving soy milk (see Table 2). Anal fissures and pain on defecation, which were present in all these patients at the beginning of the study, were cured. None of the children receiving CM had a positive response. In the 44 responders, the relation with CMPH was confirmed in all cases by a double-blind challenge with CM. The children with symptom resolution on soy milk diet had a higher frequency of coexistent rhinitis, dermatitis or bronchospasm than non-responders ($P < 0.05$). Anal fissures, erythema and oedema were other characteristics of the patients with constipation responding to a CM-free diet.

Immediately after this study, two other groups confirmed the constipation–CMPH association,[11, 12] reporting a frequency of 30% and 55% respectively. In a more extensive paper, one of these groups confirmed our observation[5, 6] that a rectal histology characteristic of patients with chronic constipation responding to CM-free diet was eosinophil infiltration of the mucosa.[13] Furthermore, Daher *et al.* confirmed that the IgE-mediated mechanism had only a secondary role (if any) in the pathogenesis of the disease as there was no difference in serum IgE levels between CMPH and non-CMPH patients (Figure 2).

Further confirmation of the refractory chronic constipation–CMPH relationship was given by Vanderhoof *et al.*[14] In a retrospective study they reported the




* $P < 0.05$

** Not significant

**Figure 1.** Percentage of patients with previous history of cow's milk hypersensitivity (CMH) and of elevated serum immunoglobulin E levels among subjects with refractory chronic constipation. The patients had been divided into two groups according to response to the cow's milk-free diet: 21 patients responded and six did not respond to CM-free diet.[5]

clinical history of a small group of children, and their data were fully in agreement with our first reports.[5, 6] In particular, they showed that most of their patients with chronic constipation and CMPH had already shown symptoms suggesting CMPH during infancy: eight of the 12 cases reported had suffered from significant irritability as infants, four had diarrhoea, three chronic emesis and one poor growth (one or more symptoms were present in each patient). As regards the histology findings of the rectal biopsies, Vanderhoof *et al.*[14] confirmed that refractory constipation because of CMPH is characterized by eosinophil infiltrate in the mucosa.[5, 6, 13]

Although the number of reports from different researchers confirming the chronic constipation–CMPH association is increasing,[5, 6, 11–15] not all are in agreement. In particular, Loening-Bauche reported that in her centre none of the children with chronic constipation and a previous history of CMPH who were placed on a CM-free diet showed a symptom resolution on this regimen.[3] However, she had previously reported that in her experience, when children suffering from chronic constipation were switched from a CM formula to a protein hydrolysate formula the symptom completely regressed in most of them.[16] Recently, Yimyaem *et al.* reviewed the records of 10 CMPH patients observed from 1997 to 2001 and did not find patients with constipation.[17] However, the very small size of the sample and its low mean age (3.5 months) do not permit this study to be considered a valid argument against the constipation–CMPH relationship.

## Other indirect evidence in favor of the constipation–CMPH relationship

Constipation has been indicated as one of the most common gastrointestinal disorders in patients with

| | Placebo (cow's milk) | Treatment (soy milk) | *P*-value |
|---|---|---|---|
| Number of bowel movements (median) | 4 | 10 | <0.001 |
| Qualitative faecal score | | | |
| 1 | 0 | 2 | <0.001 |
| 2 | 0 | 42 | |
| 3 | 65 | 21 | |
| Number of patients who reached the end point | 0/65 (0%) | 44/65 (68%) | <0.001 |

Number of bowel movements and qualitative faecal scores during the study periods are reported. The end point of the study, designed as crossover, was a number of bowel movements ≥8 during the 2 weeks of treatment.
A qualitative faecal score of 1 indicates mushy or liquid stools, a score of 2 soft faeces and no pain on passing tools, and a score of 3 hard stools and difficulty and pain on passing stools.

**Table 2.** Detail of the results obtained in the unique randomized-controlled trial performed on the effectiveness of the elimination diet in patients with chronic constipation[6]

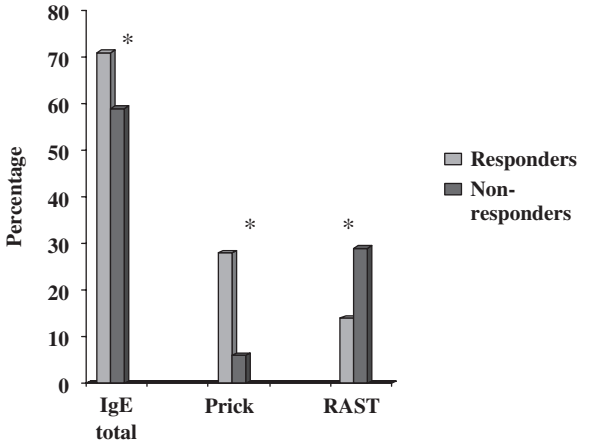



**Figure 2.** Percentage of positive serum total immunoglobulin (Ig)E, skin prick tests and serum-specific IgE values in 25 children with chronic refractory constipation. The patients had been divided into 'responders' and 'non-responders' according to the effectiveness of the cow's milk-free diet.[13]

atopic dermatitis and food allergy.[18] In one study, 20 infants with a diagnosis of haematemesis because of CMA were followed for a mean period of 2.6 years and four patients (20%) developed constipation.[19] Another study including more than 300 subjects with chronic constipation demonstrated that patients with an IgE-mediated food allergy showed a significantly longer total colonic transit time than patients without food allergy.[20]

## Difficulties in making a diagnosis of chronic constipation due to CMPH

There are several elements which contribute to make the diagnosis of constipation because of CMPH difficult.

First, although a previous history of CMPH is very common in patients with chronic constipation because of CMPH and can be considered an important element for suspecting this disease, it is interesting to underline that both in the study of Vanderhoof *et al.*[14] and in our patients series,[5, 6] the previous symptoms of CMPH observed during infancy were other than chronic constipation. We suggest that an 'allergic march' is present in many patients suffering from food hypersensitivity, but a changing pattern of clinical CMPH manifestations is a common characteristic of patients with food allergy persisting beyond the first 2–3 years of age.[21] This concept should be kept in mind by clinicians to prevent a delay in diagnosing CMPH in older children.

A second important factor is the lengthy time lapse between the reintroduction of CM into the diet and the reappearance of chronic constipation on diagnostic challenge. In one of our studies,[6] constipation and discomfort on defecation reappeared after 5–10 days of CM-containing diet. In these patients, when the diagnosis of CMPH was first made, on CM challenge the general time lapse between CM administration and the onset of symptoms had been under 12 h. When the patients began to suffer from constipation and were put on a CM-free diet, the subsequent reintroduction of CM caused the reappearance of constipation after 4–14 days. This change in reaction time between consumption of the food allergen and the clinical reaction is another finding which has been previously underlined.[22] In fact, a percentage of cases of CMPH have been reported with patients reacting to CM administration more than 72 h after challenge. In a previous study on a cohort of children suffering from CMPH, at first observation this 'very delayed reaction' was observed in 5% of patients, whereas 3 years after diagnosis, during a yearly challenge to evaluate the possibility of reintroducing CM into the diet, 35% of the patients of the cohort with persistent CMPH had a 'very delayed reaction'.[22] The results of that study and the observation of the patients with chronic constipation because of CMPH should advise clinicians to use great caution and a long clinical follow-up before excluding a diagnosis of food hypersensitivity in patients who have benefited from an elimination diet.

A third difficulty is the obvious possibility that the patients could be suffering from multiple food intolerance and not simply from CM hypersensitivity. In a recent study[23] we enrolled 52 patients with chronic constipation unresponsive to laxative treatment. All patients underwent the CM protein-free diet period and during the first 2 weeks of this treatment bowel movements normalized in 24 subjects. The remaining 28 patients were then placed on a more restricted, oligoantigenic diet and on this regimen bowel movements normalized in another six patients. The double-blind, placebo-controlled CM challenge confirmed that all 30 patients with a resolution of the symptom on an elimination diet were suffering from CM allergy and six of them from multiple food intolerance. In these latter six subjects, the following foods caused the reappearance of constipation: wheat, egg, tomato, fish,

cocoa, goat's milk, soy, oranges, legumes. For each of these foods open challenges confirmed intolerance, with the reappearance of constipation 1–4 days after reintroduction. On the basis of these results, it can be affirmed that constipation can be due to intolerance to several foods and the introduction of an oligoantigenic diet must be proposed in children who do not respond to a CM-free diet.

In view of all the above-quoted diagnostic difficulties, we strongly agree that a diagnosis of CMPH in patients showing chronic constipation must be exclusively based on a double-blind, placebo-controlled oral food challenge, although the presence of perianal lesions, histological abnormalities and signs of hypersensitivity had likelihood ratios of 2.2, 2.4, and 3.7, respectively, and post-test probabilities of 83%, 84%, and 88%, respectively.[24]

## Can food hypersensitivity cause chronic constipation in adults?

Adult patients suffering from chronic constipation are treated with fibre and laxatives as the first-line therapeutic approach, but often there is only a slight improvement in bowel movements.[25] Furthermore, patients unresponsive to this treatment require a more accurate evaluation in a tertiary care clinic with consequently elevated economic costs.[26] Very recently, we showed that some patients with chronic constipation unresponsive to laxatives were suffering from multiple food intolerance and their constipation was successfully treated with an oligoantigenic diet.[27] Briefly, we reported chronic constipation in four women aged between 30 and 52 years. In all cases there was no response to dietary fibre supplements plus several laxative treatments (milk of magnesia or/and lactulose or/and polyethylene glycol). However, on an oligoantigenic diet, bowel habits normalized in these patients and a double-blind placebo-controlled food challenge triggered the reappearance of constipation. The foods which caused the constipation were: CM (four cases), wheat (four cases), egg (four cases), tomato (three cases), beef (three cases), cocoa (three cases), soy (three cases), oranges (two cases), goat milk (two cases), fish (one case), legumes (one case), peas (one case), cauliflower (one case), beans (one case). The constipation reappeared 1–4 days after the reintroduction of these foods into the diet.

In comparison with other cases of refractory chronic constipation not because of food hypersensitivity, the patients with food hypersensitivity-related constipation presented the following characteristics: a longer duration of illness, lower body mass index, higher frequency of self-reported food intolerance, higher frequency of nocturnal abdominal pain and anal itching. As regards the duodenal and rectal mucosa histology of these patients, there was lymphocyte and eosinophil infiltration and the duodenal villi were flattened in two cases. These latter findings could also be associated with a diagnosis of celiac disease, but we excluded this because of the lack of clinical improvement after excluding only wheat proteins from the diet, as well as the negativity of the serum antitransglutaminase antibodies and the absence of the human leucocyte antigen (HLA) alleles that predispose to celiac disease (DQ2 or DQ8). Furthermore, similar severe intestinal mucosa damage has been reported in food protein hypersensitivity with a cell-mediated immune response.[28]

## Constipation in CMPH patients: persisting doubts and indications for further research

The association between chronic constipation and food hypersensitivity seems by now to have been accepted by the gastroenterologist community. A few years ago, a position statement of the American Gastroenterology Association on food allergy listed chronic constipation as a 'possible' disorder linked to food allergy but added that further studies were needed to confirm this association.[29] More recently, a review on food allergy and gastrointestinal symptoms included chronic constipation among the manifestations of food allergy.[30] However, several points should be further investigated.

A first question is whether or not there is an immunological mechanism underlying the constipation because of CM ingestion and what this is. In fact, some believe that evidence for a possible activation of the immune system is still insufficient.[31] In particular, it could be hypothesized that the exclusion of CM from the diet is effective in some patients not because of an underlying CMPH condition but rather due, for example, to a profound change in the patients' dietary habits after the beginning of the CM-free diet. Although few studies seem to contrast this hypothesis,[6, 23] further research should be addressed to clarify the role of the different dietary components (proteins, fats, carbohydrates, fibre, calcium, etc.) on the bowel movements of chronic constipated patients undergoing a CM-free diet. Furthermore, there are no studies on

the effects of an exclusion diet in constipated patients who do respond to conventional laxative therapy, so that the specificity of the CM-free diet has not been fully assessed.

However, the 'allergic hypothesis' is, by now, strong. All the studies on rectal histology in patients with chronic constipation because of CMPH have shown the presence of an elevated number of eosinophils in the lamina propria and in the epithelium[5, 6, 13–15, 23, 27] and these cells are considered markers of allergic inflammation.[32] Furthermore, the inflammatory changes in the rectal mucosa are directly linked to food ingestion, as it has been demonstrated that both the eosinophil and the lymphocyte mucosa infiltration regressed during elimination diet.[23, 27] Other markers of food allergy have also been shown to be present in constipation because of CMPH. In fact, Turunen *et al.*[15] showed that lymphoid nodular hyperplasia of the colon and an increase in intraepithelial $\gamma/\delta$ T lymphocytes of the rectal mucosa are frequent in these cases. Both of these phenomena are considered an indication of enhanced local immune responses against food antigens and are clearly associated with food hypersensitivity.[33, 34] However, despite the above evidence, we agree that most of the allergic mechanisms involved in the non-IgE-mediated gastroenterology manifestations of food allergy still remain to be clarified, and future *in vitro* studies should be performed on the *ex vivo* mucosa of patients with chronic constipation and food allergy to clarify the cytokine pattern and what kind of inflammatory cells are activated to determine this disease.

Another important point is to understand the mechanism which leads from an 'allergic' inflammatory condition of the mucosa to an alteration in intestinal motility. In a very recent study we showed that anal sphincter resting pressure was significantly higher in patients with constipation because of food intolerance than in patients with constipation unrelated to food intolerance.[35] Fifteen of 17 patients with food intolerance-related constipation had an anal sphincter resting pressure above the higher cut-off value for our laboratory, but on elimination diet only one of the 17 patients showed values higher than the normal limit. This high anal sphincter pressure could be an important factor, which contributes to the pathogenesis of constipation in CMPH patients. However, in the same study we found another manometric characteristic in the opposite direction; in fact, at baseline eight of the 17 patients with food intolerance had critical volume values (minimum volume required to produce the sensation of an urge to defecate) lower than the minimum cut-off. Furthermore, there was a significant increase in critical volume over baseline values on elimination diet. Consequently, it is difficult to understand why this reduced rectal compliance does not cause chronic diarrhoea instead of constipation. However, reduced rectal compliance is another typical feature of inflammatory bowel diseases and these results added convincing data in favour of the hypothesis that the food intolerance constipation may be related to proctitis.[35]

The severity of the rectal motility disorder can sometimes recall that of Hirschprung's disease, when constipation appears in very young infants. In four infants barium enemas revealed irregular narrowing of the rectum and a transition zone. Rectal biopsies in each case demonstrated ganglion cells and evidence of allergic colitis. In these cases a diagnosis of milk allergy colitis was made and symptoms resolved after removal of milk from the diet.[36]

In general, it must be remembered that one of the typical histology findings in constipation because of CMPH – the eosinophil infiltrate – is clearly associated with allergic dysmotility in various tracts of the gastrointestinal tube, such as the oesophagus and the stomach.[37, 38] Furthermore, in animal models the eosinophil recruitment disrupts enteric nerve function, as demonstrated by electron microscopy.[39] Other cells of the immune system, activated in a food hypersensitivity condition, can play an important role in determining a 'myenteric ganglionitis' with the consequent effects of intestinal dysmotility. In patients with irritable bowel syndrome this has been demonstrated, i.e. for low-grade inflammatory infiltration and activation of mast cells in proximity to nerves in the colon mucosa,[40, 41] or for T lymphocyte-driven inflammation.[42]

The presence and the pathogenetic role of the perianal lesions should also be further investigated. Anal erythema and/or fissures are very often present in patients with chronic constipation associated with CMPH.[6] In patients showing these findings it is obvious to hypothesize that pain on defecation can cause retention of faeces in the rectum with consequent dehydration and hardening of the stools, thus aggravating constipation. Albeit rarely, the severity of anal lesions can determine the formation of perianal abscesses and fistulas.[43] All these lesions, including the most severe ones, disappeared on CM-free diet and reappeared 2–10 days after the reintroduction of CM into the diet,[6, 43] suggesting that they could be

considered manifestations of CMPH. It could be advanced the hypothesis that an anal, perianal atopic dermatitis could be a contributory pathogenetic factor. It could also induce/contribute to an increase in anal sphincter pressure as a pain-limiting mechanism (to avoid painful defecation); in turn, high anal sphincter pressure can facilitate the appearance of anal fissures, thus aggravating pain and constipation. The hypothesis of a perianal atopic dermatitis, in the absence of other skin lesions, can be considered; in fact, we recently described atopic dermatitis lesions exclusively limited to the periumbilical skin as a sign of CMPH.[44] Interestingly, it has been reported that young children with chronic constipation and anal fissures consumed larger amounts of CM than children with normal bowel habits. Moreover, they had a shorter duration of breast feeding and earlier bottle feeding with CM, possible factors facilitating CMPH onset.[45]

Another point which warrants further investigation is the pathogenetic role of the thickness of the mucus gel layer of the rectal mucosa on constipation. In fact, in previous studies[23, 35] we found that the patients suffering from food intolerance had a marked reduction in mucus gel layer thickness with a significant difference in comparison with the patients not suffering from food intolerance. These data are in agreement with the previous observation of a reduction in goblet cell mucin in some cases of food intolerance-related constipation.[5, 6] On an elimination diet, the subjects suffering from food intolerance showed a significant increase in mucus gel layer thickness over baseline values. The mucus deficiency seemed because of a marked reduction in or the disappearance of the non-sulphated sialomucins in most of the food-intolerant patients, whereas sulphated mucins were less frequently reduced. More rarely, a reduction in mucus gel layer thickness on the rectal mucosa has also been found in patients with constipation unrelated to food intolerance. It is interesting that we recorded significant inverse correlations between the inflammatory infiltrate of the rectal mucosa (intraepithelial eosinophils and lymphocyte count) and mucus layer thickness.[23] Thus, as occurs in ulcerative colitis, a classical inflammatory bowel disease,[46, 47] we found that in patients with food intolerance-related constipation there was a concomitant, correlated presence of mucosa inflammation and reduced mucus barrier function. From a pathogenetic point of view, it must be remembered that the surface-active phospholipids forming the outermost layer of the mucus gel display excellent high load-bearing lubrication. Accordingly, we have speculated that in patients with chronic constipation the loss of the adherent rectal mucus layer may reduce the physiological lubricating role and could contribute to the pathogenesis of the constipation. Further studies would clarify whether the mucus thickness reduction can represent a potential target for treatment.

## CONCLUSIONS

There is abundant evidence from various groups of researchers which has clearly shown that a CM-free diet or a more restricted oligoantigenic diet can resolve constipation in paediatric patients with chronic constipation refractory to laxative treatment. A limited number of other studies, but not including randomized-controlled trials, have contradicted these data. A great deal of histology data strongly suggests that there is an underlying immune mechanism involved, but further studies must be performed to better understand the pathogenesis of the constipation because of food allergy. There has also been recent evidence that a few cases of refractory constipation in adults have been resolved on an oligoantigenic diet and, consequently, studies on the 'allergic hypothesis' should be encouraged, involving a greater number of adults with chronic constipation unresponsive to laxatives. At present, although several aspects must be further investigated, a therapeutic attempt with elimination diet is to be advised in all children with constipation unresponsive to correct laxative treatment. Adult patients with refractory constipation could also be placed on an oligoantigenic diet if they show some of the clinical characteristics recently underlined.

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