COW’S MILK INTOLLERANCE AND CRONIC CONSTIPATION IN CHILDREN. ACLINAL AND HISTOLOGY STUDY

Introduction

Chronic constipation is a very common problem in children\(^1\), but despite its high prevalence its cause remains unknown in the majority of cases. Our previous works indicated a clear relationship between CM-intolerance and chronic constipation in part of the patients\(^3\), and it is now accepted that these children can be cured with a CM-free diet. However, the pathogenesis of the CM-intolerance-related constipation is unknown and the existence of an inflammatory condition is still debated\(^4\).

In the present study we considered a new series of consecutive patients suffering from chronic constipation and unresponsive to previous standard treatment to evaluate the histology characteristics of the cases of constipation due to CM-intolerance.

Patients and methods

The study included all the consecutive infants and children with chronic constipation unresponsive to previous treatments examined at the out-
patients clinic of the Pediatric Gastroenterology Division of the “Di Cristina” Hospital, Palermo, between January and December 2000. Chronic constipation was defined as < 3 bowel movement per week with painful elimination of hard stools.

**Inclusion criteria were:**
- a history of chronic constipation lasting at least three months;
- lack of response to a previous increase in dietary fiber intake and/or to laxative treatment (milk of magnesia 1 to 2 ml per kilogram of body weight);
- regular dietary intake of cow’s milk and derivatives.

**Exclusion criteria were:**
- previous evaluation for chronic constipation;
- anatomical/neurological causes of constipation (Hirschsprung’s disease 1 case, psychomotor retardation 1 case);
- constipation due to another disease (celiac disease 1 case, hypothyroidism 1 case);
- prior anal surgery;
- use of medications that can cause constipation;
- referral for reasons other than chronic constipation (15 cases).

All patients included were being fed a normal diet, without any restrictions. In accordance with the above criteria 39 patients were recruited, (23 females, aged 9 months-12 years, median 4.6 years). When the patients were first examined a detailed chart was compiled containing the results of the physical examination and case-history information.

The infants’ parents 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.

**Results**

**Clinical data**

After the two-week observation period, all patients underwent the cow’s milk protein-free diet period and during the first two weeks of this treatment the number of bowel movements normalized in 17 subjects. The remaining 22 patients were then placed on a more restricted, oligoantigenic diet. On this regimen, bowel movements normalized in another three patients, while nineteen did not improve. These nineteen patients were considered to be suffering from chronic constipation unrelated to food intolerance. The double-blind placebo-controlled cow’s milk challenge confirmed that all the seventeen patients cured on elimination diet suffered from CM-allergy.

In all cases the cow’s milk re-administration caused the reappearance of constipation, very often associated with abdominal pain and perianal erythema, within five days after commencement of the challenge (median 2 days, range 1-5 days) and these symptoms disappeared on returning to the CM-free diet or to the oligoantigenic diet in the three patients with multiple food intolerance.

In these three subjects, other foods were progressively reintroduced into their diet and the following caused the reappearance of constipation: wheat (three cases), egg (two cases), tomato (two cases), fish (two cases), cocoa (one case), soy (one case). For each of these foods, open challenges confirmed intolerance, showing the reappearance of constipation 1-4 days after reintroduction.

According to the above results, we diagnosed chronic constipation due to CM-intolerance in the 14 children and chronic constipation due to multiple food intolerance in the three patients.

**Histology data**

At entry to the study, endoscopy showed mild rectal inflammation with mucosal erythema and friability, without ulcerations or erosions in all the 17 patients with food intolerance and in 2 of the 19 with constipation unrelated to food intolerance (P< 0.001). Hematoxylin-eosin staining showed erosions of the mucosa in 16/17 patients with food intolerance and only in 1/19 of the subjects who did not suffer from food intolerance (P< 0.001). There was not crypts’ distortion or branching.

In the patients with food intolerance, inflammation was characterized by mucosal infiltration of eosinophils, lymphocytes and plasma cells with the aspect of both follicular and diffuse inflammation. Patients with food intolerance showed a significantly higher number of intra-epithelial lymphocytes and eosinophils and of eosinophils in the lamina propria than the patients with constipation unrelated to food intolerance.

On elimination diet, all the seventeen patients with food intolerance-related constipation showed normal rectal endoscopy. At this time, histology did not show mucosa erosions in any of the cases and was absolutely normal in 8 of the 17 patients and...
inflammation was greatly reduced in the others. Morphometry revealed a significant decrease in the number of intra-epithelial lymphocytes and eosinophils and of eosinophils in the lamina propria over baseline.

The study of the surface mucus gel layer on rectal mucosa, performed at entry to the study, showed that the patients suffering from food intolerance had a marked reduction in the thickness of the mucus gel layer. There was a reduction or the disappearance of the non-sulphated sialomucins in most cases (14/17), whereas sulphated mucins were reduced in 2/17 cases. Only 2 of the 19 patients with constipation unrelated to food intolerance showed a reduction in the thickness of the mucus gel layer on rectal mucosa. On elimination diet, the subjects suffering from food intolerance showed a significant increase in the thickness of the mucus gel layer over baseline values.

Finally, we recorded significant correlations between the histology inflammatory parameters and the manometry data.

**Discussion**

Although our and others’ studies have the relation between cow’s milk protein intolerance (CMPI) and chronic constipation, very little is known about the pathogenesis of chronic constipation due to CMPI. Consequently, we performed this study to investigate the histology aspects in patients with chronic constipation due to CMPI.

Seventeen of the thirty-six patients (48%) who completed the study showed a CM-intolerance-related or a multiple food intolerance-related chronic constipation. In these subjects, the symptom disappeared on CM-free or oligoantigenic diet and subsequent food challenges demonstrated that these patients were suffering from CM-intolerance or multiple food intolerance. In fact, in these cases constipation reappeared when the various foods were reintroduced and disappeared on elimination diet. According with the European Society Pediatric Gastroenterology Hepatology and Nutrition diagnostic criteria for food intolerance/allergy, we can affirm that half of the patients included in the study (17 out of 36) were suffering from food intolerance which caused chronic constipation.

As studies from other centres showed a frequency of constipation due to CM-intolerance ranging between 28% and 70%, it can be concluded that in patients unresponsive to conventional treatments or with a personal history of CM-intolerance, constipation is quite frequently a manifestation of food intolerance.

In our series the immunological assays performed to evidence an IgE-mediated hypersensitivity were very often negatives, whereas the IgG anti-betalactoglobulin assay was positive in more than 50% of the cases. This result is in keeping with the reported lack of sensitivity of specific IgE assay in patients with food intolerance and irritable bowel syndrome-like symptoms and with the very recent observation that IgG antibodies to food help to identify dietary intolerances.

Furthermore, the observation that the constipation reappeared as a delayed clinical reaction (in mean 48 hours after CM-reintroduction) indicates that a cell-mediated hypersensitivity seems to be the more probable immune mechanism. This seems confirmed by histology: the rectal biopsies of the patients suffering from chronic constipation due to food intolerance showed inflammation in all subjects, with mucosa erosions in 16 of the 17 patients. These alterations were clearly food-dependent as they completely disappeared on elimination diet. It is also interesting the behaviour of the mucus gel layer of the rectal mucosa: our data showed that in food-intolerant patients there was a severe reduction in the thickness of the mucus layer on the rectal mucosa.

**Conclusion**

Our findings have shown eosinophil infiltrate as the main histology characteristic of the proctitis in patients with constipation due to food intolerance. Furthermore, there has been recent confirmation that eosinophil recruitment could disrupt enteric nerve function in sensitized mice as electron microscopy showed areas of neural damage adjacent to degranulating eosinophils in the gastric mucosa.

It is noteworthy also the correlation between the eosinophils infiltrate and the reduction of mucus gel layer on the rectal mucosa. We speculate that in patients with chronic constipation the loss of the adherent rectal mucus layer reduces the physiologic lubricating role and could contribute to the pathogenesis of the constipation.

In summary, the main conclusions of our study were:

- chronic constipation in children can be due both to CM-intolerance and to multiple food intolerance;
• the constipation of food intolerant patients is associated with proctitis;
• reduced mucus gel layer can be considered contributory factors in the pathogenesis of the constipation.

Bibliography