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Original investigations

Cow's milk protein allergy and gastro-oesophageal reflux

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Abstract. Evidence for cow's milk allergy was looked for prospectively in 15 children with recurrent vomiting. Whereas radiological examination showed gastro-oesophageal reflux to be present in all patients, 3 out of 15 children presented an enteropathy associated with an increased number of IgE plasmocytes in small intestinal biopsy tissue. These three patients did not improve with conventional medical therapy but a striking improvement occurred within 24 h on a cow's milk-free diet. We conclude that diagnostic confusion between gastro-oesophageal reflux and cow's milk allergy can occur and that the presence of IgE plasmocytes in small intestinal biopsy tissue indicates IgE-mediated cow's milk protein allergy. All cases of "intractable" gastro-oesophageal reflux should be suspected of cow's milk allergy and investigated acordingly.

Key words: Gastro-oesophageal reflux – Cow's milk protein allergy

Introduction

Gastro-oesophageal reflux (GER) and cow's milk protein allergy are two conditions that have many aspects in common. They give rise to similar signs and symptoms such as vomiting, failure to thrive and infantile colics. Both occur most frequently in babies under the age of 6 months and regress by the age of 1 year. Their incidence is similar, between 1%–10% in young infants [2, 4, 5].

Distinction between the two disease entities is quite important. Indeed, whereas most children with GER respond to conventional medical therapy, a diet without cow's milk protein is mandatory in children with cow's milk allergy. The aim of the present prospective study was to look for evidence of cow's milk protein allergy in children presenting with a clinical and radiological diagnosis of GER.

Patients and methods

Patients. Fifteen children with presumed GER were investigated. They were younger than 1 year of age. They presented with recurrent vomiting, (after each feed for most of them). Weight gain was unsatisfactory in seven patients. Slight diarrhoea was present in one patient at presentation. For comparison of histological and immunohistological data the following control groups were available: 16 patients with failure to thrive of unknown aetiology, 5 patients with active coeliac disease, 5 patients with coeliac disease in remission and 1 patient with coeliac disease under gluten challenge.

All patients with presumed GER were treated medically by associated postural therapy and an antacid (Gaviscon). The patients not improving on this regimen received a cow's milk-free diet.

Methods. Radiological examination for GER was performed as previously described [3]. Endoscopy of the upper GI tract: (GIF P_3, Olympus) was performed in all patients. The pre-

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Abbreviation: GER = gastro-oesophageal reflux

Table 1. Small intestinal stereomicroscopic and histological score

Stereomicroscopic aspect	Score
Normal	0
Partial villous atrophy	2
Total villous atrophy	4
Histological features	
Ratio of villous epithelial to crypt epithelial cell hight	
>1	0
$=1$	1
<1	2
Number of intraepithelial lymphocytes	
normal	0
slight increase	1
marked increase	2
Number of mitoses/crypt	
≤ 2	0
$>2<4$	1
≥ 4	2
Inflammatory infiltrate	
absent	0
slight	1
moderate	2
severe	3
	Sum = Total score

sence of oesophagitis and hiatal hernia was looked for. Small intestinal biopsy was performed from the distal duodenum in the 15 GER cases and the 27 other patients. The specimens were examined by stereomicroscopy, histology and immunohistology. A combined stereomicroscopic and histologic score was used to quantitate the mucosal findings (Table 1). It omits the classical villous/crypt ratio which in many cases could not be established confidently in our biopsy material. The score has a range from 0–13, normal values being ≤ 2.

Immunohistology

IgE plasmocytes were stained by the immunoperoxidase technique. Duodenal biopsy specimens were fixed in 4% neutral buffered formaline and processed in paraplast. Five micron sections were cut, dewaxed, rehydrated and blocked for endogenous peroxidase activity in a 0.5% hydrogen peroxidase solution in absolute methanol. After trypsinisation in a $CaCl_2$/trypsin solution [7] sections were subjected to immunostaining according to the unlabelled peroxidase/antiperoxidase technique [12] for the conventional anti IgE antibodies and an indirect procedure for the monoclonal anti IgE. The sections were developed with diaminobenzidine and counterstained with haematoxylin.

Nasal polyps were used as positive control tissue, whereas negative controls were carried out by replacement of the immune anti IgE sera by non-immune rabbit and mouse sera.

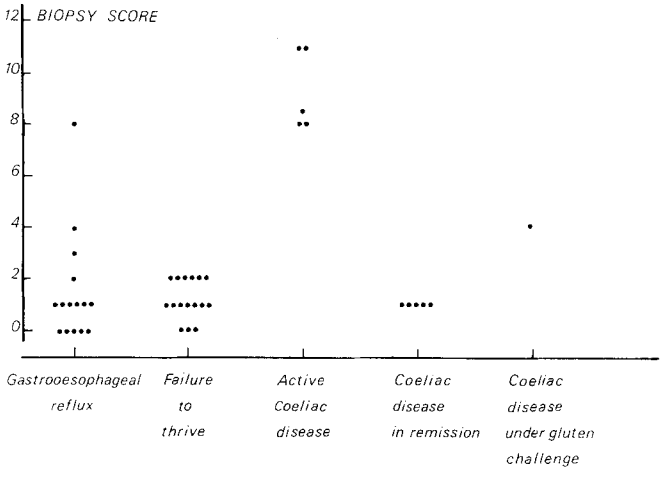

Fig. 1. Small intestinal biopsy score (see Methods) in different patient groups

Results

Radiological findings

Using previously described criteria [3], we found reflux to be present in all our patients with recurrent vomiting.

Endoscopic findings

A normal oesophageal mucosa was found in 2 GER patients, an erythematous oesophagitis in 12 patients and a destructive oesophagitis in only 1. The criteria used were described previously [3]. A constant hiatal hernia was found in the one patient with a destructive oesophagitis.

Small intestinal biopsy findigns

Twelve out of 15 patients with presumed GER presented a normal score (<2) while the 3 others had scores of 3, 5 and 7, respectively (Fig. 1).

Immunohistology showed the presence of IgE plasmocytes in greatly increased numbers in these three last patients. IgE was also present in villous and crypt enterocytes, and in the brush border (Fig. 2). These findings were obtained both with conventional and monoclonal anti-IgE antibodies. Very low numbers of IgE plasmocytes were found in patients from our reference groups. Small intestinal biopsy scores never exceeded 2 in failure-to-thrive patients, without coeliac disease.

In active coeliac disease a score $7 \geq 8$ was always found. A gluten-free diet normalised this score. A gluten challenge resulted in an elevated score in the one patient examined.

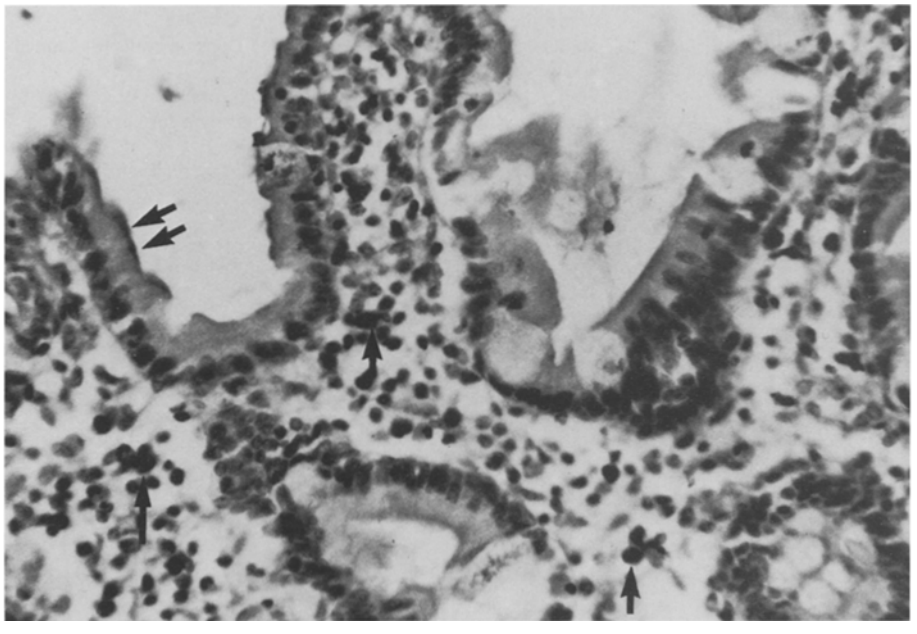

Fig. 2. IgE immunoperoxidase technique applied to small intestinal biopsy tissue of a patient with cow's milk allergy. IgE plasmocytes are present in elevated numbers (→). IgE is also present in enterocytes and brush border (⇉)

Result of treatment

Medical treatment resulted in rapid improvement in all GER patients except in the three patients with elevated scores. In these three patients vomiting stopped within 24 h after eliminating cow's milk protein from the diet. In two of them, a challenge with cow's milk, performed 1 month later, resulted in severe vomiting accompanied by diarrhoea within 5 h.

Discussion

In 15 patients with clinical and radiological features of GER, 3 children showed convincing evidence of cow's milk protein allergy. An enteropathy with both an elevated biopsy score and abundant IgE plasmocytes as well as intraepithelial IgE characterised these three patients. The number of mucosal IgE plasmocytes was very low in all other patients studied. We believe IgE-mediated cow's milk protein allergy caused the symptoms in these three patients. The response to milk elimination and the subsequent milk challenge confirms this.

Clinical data from our three "allergic" patients were reviewed to see whether a correct diagnosis could have been made without small intestinal biopsy. At the time of presentation, one of these patients showed diarrhoea in addition to vomiting and one had eczema. The third one did not show any feature allowing a tentative diagnosis of cow's milk allergy to be made.

Reviewing our X-ray material, the reflux characteristics of our 3 patients with cow's milk allergy did not allow a distinction to be made from the 12 true GER patients. Admittedly, the value of small intestinal biopsy for the diagnosis of cow's milk allergy in disputable. The great majority of children with cow's milk allergy have an enteropathy [6]. This enteropathy, however, is non-specific and could be due to other causes. Little has been published on the value of IgE plasmocytes in the small bowel mucosa in cow's milk allergy. Conflicting results have been obtained by different authors [9–11]. The most extensive study of this problem has been performed in a group of eight babies with cow's milk allergy [8]. All of them showed an enteropathy with drastically elevated levels IgE plasmocytes in the mucosa. Much of the controversy is probably the result of the relative non-specificity of conventional anti IgE antisera, some of which, for example, have been demonstrated to cross-react with IgE.

Use of monoclonal antisera circumvents these problems and therefore our experimental data with monoclonal IgE antibodies lend strong support to the notion that allergic conditions of the digestive tract can be associated with the presence of IgE plasmocytes in the lamina propria and in the enterocytes. This shows that immunoperoxidase examination of small intestinal biopsy tissue for IgE can be a useful method for separating allergic from other types of enteropathies.

Consequently, our study shows that children with GER represent a heterogeneous group of patients. Most have cardia incompetence and should be considered to have primary GER as opposed to children in whom GER has a different origin. All obstructive lesions of the upper gut, antral dystonia [1] and food allergies should be considered as possible, although rare, causes of "secondary" GER.

Quantitative tests for GER, such as prolonged pH monitoring, will not allow a distinction to be made between "primary" and "secondary" GER. In patients for whom this diagnostic puzzle seems likely to be present, a combination of radiology and endoscopy with biopsy is, in our opinion, the most rapid and sure way to a correct diagnosis.

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