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Prevalence of atopy in children with chronic constipation

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ABSTRACT

Objectives: To evaluate the prevalence of chronic constipation (CC) in unselected children, its association with atopy and the efficacy of a cow's milk protein (CMP) elimination diet on refractory constipation.

Study design: The study was conducted by six primary care paediatricians, serving a population of 5113 children aged from birth through to 12 years; only 2068 children were 6 months to 6 years. During a 3-month period, prevalence of CC was determined for the entire study population, ages 0–12 years. In the second part of the study, all patients aged 6 months to 6 years with CC, and age- and sex-matched controls, were evaluated for atopy and its association with CC. A questionnaire was completed including personal and family history of atopy and bowel-movement characteristics. Patients were tested for atopy by specific serum IgE and/or skin-prick tests. Constipated patients, refractory to osmotic laxatives, underwent a 4-week CMP elimination diet.

Results: 91 (1.8%) children had CC, and 69 (3.3%) of the 6 months to 6 years age group fell into the atopy study age range. All 69 constipated children (mean age 34.9 (18.0) months) and 69 controls completed the questionnaire. Twelve of the 69 constipated children (17.3%) and 13 out of the 69 control children (18.8%) had a diagnosis of atopy. Eleven out of 69 (15.9%) constipated children were refractory to constipation treatment, and three (27.3%) of these had atopy. The 4-week trial of dietary elimination did not result in improvement in any of these 11 children.

Conclusions: In our study group, prevalence of atopy among children with CC is similar to that in the general population. The level of refraction of CC does not seem to be related to cow's milk allergy.

In several studies, chronic constipation (CC) in children has been reported as a clinical manifestation of cow's milk allergy (CMA).^{1–5} Iacono *et al* found that in children with CC, 68% demonstrated improvement in their bowel habit when treated for 2 weeks with dietary elimination of cow's milk protein (CMP). In these children, faecal retention was associated with pain on defecation, possibly related to allergic proctitis.² Supporting this hypothesis was the presence of eosinophils in the lamina propria of 59% of these patients.

Shah *et al* reported that 78.5% of 14 children with refractory constipation and atopy responded to dietary changes, whereas no change was seen in non-atopic patients (0/16) after withdrawal of cow's milk.⁶ In another study,⁷ although an association between CC and CMA was reported, no correlation was found between the clinical response to elimination diet, specific IgE levels and/or prick test for milk proteins.

What is already known on this topic

- ▶ Chronic constipation in children has been reported as a clinical manifestation of cow's milk allergy but existing data are conflicting.

What this study adds

- ▶ The strength of this study is the large unselected population that has been evaluated for the association of CMA and chronic constipation.
- ▶ For the first time we demonstrate a very low prevalence (0.2%) of refractory chronic constipation, unresponsive to conventional therapies.
- ▶ The level of refraction of chronic constipation does not seem to be related to cow's milk allergy.

There are dissenting voices and conflicting data, however. Loening-Baucke states that her patients with CC and a history of CMP allergy or atopy did not improve on a 2-week elimination diet.⁸ Also, poor adherence to traditional osmotic laxative therapy is a common and well-described cause of therapeutic failure in patients with constipation. In a study of 174 patients of 5 years of age and younger, only 2% failed to respond to appropriately administered osmotic therapy.⁹

Is CMA, and not poor compliance with treatment, one of the most common causes of chronic refractory constipation in children? In a recent review of the relationship between CC and food hypersensitivity, the authors concluded that a CMP elimination diet should be attempted in constipated patients refractory to conventional treatments.⁵

The pathogenesis of CMA recognises several immunological mechanisms: IgE-mediated or cell-mediated pathogenesis or both.¹⁰ The hypoallergenic diet, followed by a re-challenge with CMPs, represents the gold standard for the diagnosis.^{10 11} Evaluation of specific IgE levels (radioallergosorbent test, RAST) and the skin-prick test are useful for the identification of allergens implicated in IgE-mediated disorders.¹⁰ Until now, atopy patch tests were not considered sufficiently specific for cell-mediated reactions.¹² Atopic disease is characterised by increased production of IgE against

common environmental allergens and usually manifests with symptoms of asthma, allergic rhinitis or conjunctivitis, urticaria or atopic dermatitis.¹³ A recent investigation estimated the prevalence of atopy as 20% in developed countries.¹⁴

The aims of the present study were to evaluate (1) the prevalence of CC in an unselected population of children, (2) its relation with atopy and (3) the efficacy of a CMP elimination diet for constipation refractory to conventional treatments.

METHODS

In Italy, all children age from birth through to 12 years are enrolled in the National Health Service (NHS). Approximately 800 children are assigned to each primary care paediatrician; these paediatricians are evenly distributed across the country, so that the needs of the entire paediatric population are satisfied. Six randomly selected paediatricians from the Campania region of Italy agreed to participate in the study. From 1 March until 30 May 2005 each paediatrician recorded the number of children examined per day in the office for routine, acute, chronic or follow-up care and completed a detailed questionnaire for each patient affected by CC. Prevalence was determined for the entire study population, ages 0–12 years.

In the second part of the study, all patients aged 6 months to 6 years with CC were evaluated for atopy. The diagnosis of CC was based on a history of at least 3 months (Rome II) of painful defecation and/or reduced bowel movement frequency (≤ 2 /week) and/or faecal incontinence.¹⁵ Patients affected by developmental delay, hypothyroidism, Hirschsprung disease, anorectal malformations and those taking medications known to cause constipation were excluded. The controls were randomly chosen from patients who presented for routine well-child checks and were matched for age and sex. The random selection from the pool of healthy controls was based on the evenly numbered children provided from the waiting list of daily ambulatory visits. A detailed questionnaire was completed for each subject and control, including details of family and personal history of atopic disease, the presence of allergic symptoms, duration of breastfeeding and age at first introduction of CMP. In addition, we evaluated the presence, during the first months of life, of symptoms related to CMA, such as diarrhoea, vomiting, abdominal pain and failure to thrive. Questions also covered the number and consistency of bowel movements per week, the presence of abdominal pain, painful defecation and the presence of anal fissures or erythema. A detailed dietary history was also recorded.

All 69 constipated study subjects and 69 controls of 2068 children aged 6 months to 6 years were tested for specific serum IgE levels using standard radioimmunoassay techniques,¹⁶ and/or skin-prick tests for common inhalational (*Dermatophagoides pteronyssinus* and *farinae*, *graminacea*, *parietaria* and cat dander) and dietary allergens (whole milk, alpha-lactalbumin, beta-lactoglobulin, casein, albumin, egg yolk and fish). These tests were performed by one physician who was not aware of the subject's clinical history (DS).

Specific IgE levels were considered positive if greater than 0.70 kU/l, as the reported reference ranges for the commercial test used in our laboratory (Unicap specific IgE allergen immuno cap, manufactured by Pharmacia). Skin tests were read as positive if the wheal was at least 3 mm larger the control antigen.¹⁷ Subjects with specific IgE and/or prick tests positive for at least one allergen and a personal history of atopy (such as recurrent symptoms of rhinitis, dermatitis and bronchospasms) were considered atopic children.¹⁸ Subjects were defined as affected by refractory constipation if they were unresponsive to

osmotic laxatives (lactulose or lactitol at a maximum dose of 2 g/kg/day) given in increasing doses over a period of 4 weeks.

During the study period, parents of 69 constipated study patients and 69 controls were asked to complete a defecation diary, in which the number and consistency of bowel movements were recorded. Consistency was recorded on a three-point scale: hard (3), soft (2) or liquid (1).

Atopic and non-atopic patients who also had refractory constipation were started on a hypoallergenic diet, substituting soy milk for cow's milk, and were re-evaluated after 30 days. A detailed list of food containing milk proteins was given to each patient to avoid them during the elimination diet period. A dietary diary was filled in for each patient. These children were evaluated 15 and 30 days after the beginning of the diet. They also kept a defecation diary. These patients were categorised as responsive to the elimination diet if their stool frequency increased to >3 stools a week.

Statistical analysis

For continuous variables, the Kolmogorov–Smirnov statistic with a Lilliefors significance correction was used for testing normality, and data were analysed with paired Student's *t* test (patients and controls matched for age and sex, and data before and after diet). Categorical variables were evaluated by the χ^2 test. A *p* value of <0.05 was considered statistically significant. All analyses were run using SPSS 15.0.0 (SPSS Inc., Chicago, IL, USA).

Informed consent for participation in this study was obtained from the parents, and the investigation was approved by the Ethics Committee of the University of Naples "Federico II".

RESULTS

Six primary care paediatricians took part in the recruitment and evaluation of constipated patients and controls from a pool of 5113 patients. The average patient population was 852 for each paediatrician; the average number of ambulatory visits each day during the study period was 19.3.

Ninety-one out of 5113 (1.8%) children satisfied the diagnostic criteria for CC. The mean age of this group of subjects was 3.7 (1.3) years. Sixty-nine out of 2068 (3.3%) subjects aged 6 months to 6 years presented with CC. All of them agreed to participate in the atopy study. The study subjects included 34 males and 35 females, with a mean age of 34.9 (18) months (range 6–72 months). Sixty-nine age- and sex-matched controls were chosen randomly; there were 34 males and 35 females, with a mean age of 34.3 (19.3) months (range 9–71 months). Clinical characteristics of the constipated patients and controls are summarised in table 1. Family history of atopy was present in 18 subjects (26%) and 15 controls (21.7%).

On the basis of the criteria listed under the methods section, 12 subjects (17.3%) and 13 controls (18.8%) also satisfied the diagnostic criteria for atopy. The clinical characteristics of 12 constipated atopic patients are reported in table 2. Positive laboratory results consistent with atopy for these patients are summarised in table 3. None of the patients had symptoms of CMA. Symptoms and signs in our patients with CC included abdominal pain in 45 (65.8%), painful defecation in 62 (89.9%), daily faecal incontinence in 14 (20.3%), anal fissure in 28 (40.6%) and perianal erythema in 39 (56%). Eleven of the 69 constipated subjects were refractory to treatment (15.9%); three of these patients were atopic, and they, along with eight other refractory patients who were not atopic, were treated with dietary elimination of CMP for 30 days. The dietary diaries were evaluated 15 and 30 day after the elimination diet was started.

Table 1 Clinical characteristics of constipated patients and control population

	Patients (n = 69)	Controls (n = 69)	p Value
Age (months) (mean (SD))	34.9 (18.0)	34.3 (19.3)	NA
Sex (M/F), n	34/35	34/35	NA
No of bowel movements/week	1.9 ± 1.0	5.0 ± 1.7	<0.01
Duration of breast feeding (months)	3.9 ± 2.5	3.8 ± 2.5	0.2
Introduction of cow's milk (months)	2.9 ± 2.0	3.1 ± 2.2	0.1
Family history of atopy, n (%)	18 (26)	15 (21.7)	0.09
Atopy, n (%)	12 (17.3)	13 (18.8)	0.2

NA, not applicable.

Data are mean (SD) except when otherwise indicated.

All patients were compliant with the dietary restrictions. None of these eleven patients had any significant improvement in their constipation, as measured by stool frequency and consistency (mean number of bowel movements/week: before diet 1.8 (1.6), after diet 1.9 (1.3); faecal consistency score: before diet 2.5 (0.8), after diet 2.4 (1.2)).

DISCUSSION

Our prospective data show a prevalence of 1.8% for CC in this unselected Italian pediatric population. The prevalence of atopy in the constipated patients was not significantly different from controls (17.3% versus 18.8%). Eleven of 69 (15.9%) constipated children were refractory to constipation treatment, and three (27.3%) of these had atopy. The 4-week trial of dietary elimination did not result in improvement in any of these 11 children.

Previously published prevalence of CC in children ranges from 0.3% to 8%.⁹

The wide range of values reported can be attributed to differences in the study population, study method and definition of constipation. Our prevalence for CC is within this range of reported values.

During infancy, allergy to CMP can be diagnosed in 0.3% to 7.5% of the population.¹⁹ The persistence of CMA symptoms

has been evaluated in several studies. Bishop *et al* reported that CMP allergy may persist in up to 22% of affected children who undergo antigen challenge at 6 years of age.²⁰ Host *et al*²¹ evaluated 1749 Danish children and reported that oral tolerance by the age of 3 years developed in 100% and in 75% of children affected by IgE-mediated and non-IgE mediated CMA, respectively. Most infants affected by CMP allergy present with gastrointestinal symptoms, such as enterocolitis, proctocolitis, esophagitis and malabsorption; these infants rarely demonstrate an IgE-mediated pathogenesis of their symptoms.²² An IgE-mediated pathogenesis is much more common in children whose symptoms do not resolve in the first 2 years of life and in those who present with extraintestinal symptoms, such as urticaria, angioedema, atopic dermatitis or asthma.

Recently, several studies have noted an association between CMA and CC, and authors have postulated that constipation may be the only manifestation of CMA in these children.¹⁻⁴ Iacono *et al*¹ reported that the majority of children responsive to a CMP elimination diet complained of symptoms of CMA during the first year of life. No correlation was reported between the specific IgE levels for milk allergens and the response to the restriction diet.

Evidence supporting the role of atopy or CMP allergy in the pathogenesis of CC has come from a prospective study in which

Table 2 Clinical characteristics of constipated atopic patients

Patient	Age (months)	Sex	Prick (mm)	*RAST (kUA/l)	Perianal erythema	Associated symptoms
1	27	M	<i>Dermatophagoides pteronyssinus</i> (4)	<i>Dermatophagoides pteronyssinus</i> (0.9)	Present	Urticaria
2	24	F		Beta-lactoglobulin (1.2) <i>Beta-lactoglobulin</i> (14.1) Cat dander (1)	Present	Asthma
3	29	M		Beta-lactoglobulin (1.3)	Present	Atopic dermatitis
4	24	M	Egg (6)		Absent	Asthma
5	19	M	<i>Dermatophagoides pteronyssinus</i> (4)	Beta-lactoglobulin (0.8)	Present	Atopic dermatitis
6	21	M	<i>Dermatophagoides pteronyssinus</i> (4)		Present	Atopic dermatitis
7	9	M	Cat dander (3)		Absent	Urticaria
8	42	M	<i>Dermatophagoides pteronyssinus</i> (4)		Absent	Atopic dermatitis
9	26	F		<i>Dermatophagoides pteronyssinus</i> (1) Beta-lactoglobulin (1.3)	Present	Atopic dermatitis
10	25	M	Egg (3)		Present	Asthma
11	27	F	Beta-lactoglobulin (4)	<i>Dermatophagoides pteronyssinus</i> (0.9) Beta-lactoglobulin (1.6)	Absent	Atopic dermatitis
12	14	M	<i>Dermatophagoides pteronyssinus</i> (4)		Absent	Urticaria

Specific IgE (KU/l) with values <0.35 were considered absent; 0.35–0.70 low; 0.70–3.50 medium; 3.5–17.5 high; 17.5–50 very high; 50–100 extremely high. RAST, radioallergosorbent test.

Table 3 Laboratory results in patients and controls who satisfy criteria for atopy

	Constipated patients (n = 12)	Controls (n = 13)
RAST		
Beta-lactoglobulin	6	1
<i>Dermatophagoides pteronyssinus</i>	3	3
Grass pollens	–	1
Cat dander	1	1
Prick		
<i>Dermatophagoides pteronyssinus</i>	5	4
Parietaria	–	1
Grass pollens	–	2
Egg white	2	3
Cat dander	1	1
Casein	–	1
Beta-lactoglobulin	1	1

RAST, radioallergosorbent test.

refractory constipation was commonly associated with mucosal eosinophilia, normal oro-rectal but delayed oro-anal transit with recto-anal hold up of the stool passage.⁶

In a further study, Iacono *et al*² reported that 18 (40%) out of 44 children who were responsive to a CMP elimination diet showed high levels of specific IgE antibodies to cow's milk antigens. Ten (22.7%) out of 44 had a positive skin-prick test result for milk antigens, even if the evidence of inflammation of the rectal mucosa on biopsy, characterised by infiltration of the lamina propria by eosinophils, indicated a non IgE-mediated reaction. No association has recently been reported between CC and allergy in allergic children affected by irritable bowel syndrome.²³

These studies all describe selected patients referred to tertiary care paediatric gastroenterology clinics, and they analyse refractory patients or patients who have not adhered to therapy prescribed by their primary care paediatricians. Many refractory children have been treated with laxatives either on an as needed basis or with inadequate doses or may have received ineffective stool softeners. Many parents discontinue laxative therapy prematurely out of fear that the laxatives will become habit forming. Adherence to chronic maintenance therapy is therefore known to be very poor.

The strength of our study lies in the large unselected population that we evaluated for the association of CMA and CC. As noted above, if a food allergy is suspected, an elimination diet is needed and should be followed by a re-challenge to confirm the diagnosis.⁹ The 4-week elimination diet did not improve bowel habit in either atopic and non-atopic constipated children in our unselected population. This data do not confirm an association between constipation and CMA.

Our results show no difference in the prevalence of atopy in children with or without constipation. Our reported prevalence of CC and atopy among this unselected population are in the same range as in previous studies.⁸

Our study has some limitations. First of all, our prevalence could be an apparent prevalence, underestimating the true prevalence (the proportion of a population that is actually affected by CC), since not all subjects were seen by a paediatrician. Moreover, the number of patients a paediatrician can see in any given day is limited, therefore the number of constipated cases may be incomplete and this could affect any estimate of true prevalence. Secondly, another limitation is the very small number of patients¹¹ with CC refractory to conventional treatments. CMA is to be thought to be a cause

of constipation in the subgroup of patients who fail to respond to conventional management and have a history of atopy. In our study, only three children (0.05%) of our screened population fulfilled such criteria. Because of the large number of screened subjects (5113), we strongly believe that if we continued the study, we would find similar results. We believe our study to be important because for the first time it demonstrates a very low prevalence (0.2%) of refractory CC, unresponsive to conventional therapies.

Furthermore, because we had negative results (ie, we did not find a statistical difference) and the sample size of the cohorts is somewhat small, it is likely that the lack of significant difference occurred by chance. However, because there are no trends towards significance we doubt that there is any risk of a type II statistical error in our study. Therefore, we believe that the refractory constipation is not associated with CMA in the general paediatric population.

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