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Celiac disease is overrepresented in patients with constipation

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Abstract

Objective: It is suggested that patients with constipation should be screened for celiac disease. Similarly, it is recommended to investigate these patients for hypothyroidism and hypercalcemia. However, no evidence for these recommendations is available so far. We therefore set out to determine the prevalence of celiac disease, hypothyroidism, and hypercalcemia in children with constipation.

Methods: Prospective cohort study of 370 consecutive patients who met the Rome III criteria for constipation. These patients were referred by a general practitioner to a pediatrician because of failure of laxative treatment.

Results: Seven of these patients had biopsy-proven celiac disease. This is significantly higher ($p < 0.001$) than the 1:198 prevalence of celiac disease in the Netherlands. Two patients had auto-immune thyroiditis. No patient had hypercalcemia.

Conclusions: We conclude that celiac disease is significantly overrepresented in patients with constipation who are referred by a general practitioner to a pediatrician because of failure of laxative treatment. All such patients should, therefore, be screened for celiac disease.

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Introduction

Celiac disease (CD), a chronic inflammatory disease characterized by flattened villi in the small bowel mucosa, is induced in genetically susceptible people by the ingestion of the gluten containing proteins of wheat, rye, and barley.[1,2] Classical presentation is with chronic diarrhea, abdominal distension, and failure to thrive. However, other symptoms, such as abdominal pain, weight for height lower than percentile 10, and lassitude or anemia are encountered

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with increasing frequency.[3] Constipation might also be the presenting symptom of CD, although the frequency of this phenomenon is unknown.[4] Nevertheless, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) suggests testing for CD in constipated infants and children when oral laxative treatment is not successful.[5] In addition, testing for hypothyroidism and hypercalcemia is recommended for this group.[5] However, formal evidence that CD is overrepresented in patients with constipation is lacking. Similarly, the frequency of hypothyroidism or hypercalcemia in pediatric patients with constipation is unknown.

The aim of the present study was, therefore, to determine the prevalence of CD in children with constipation who were referred by a primary care physician to a pediatrician. At the same time, these patients were screened for hypothyroidism and hypercalcemia.

Patients and methods

Between October 2006 and October 2008, 370 prospectively consecutive patients with constipation were included. Eight pediatric centers in the Netherlands participated: Catharina Hospital Eindhoven, Flevo Hospital Almere, St. Elisabeth Hospital Tilburg, Elkerliek Hospital Helmond, Máxima Medical Center Veldhoven, St. Jansdal Hospital Harderwijk, Gelre Hospital Apeldoorn, and Wilhelmina Children's Hospital Utrecht. The study was executed in accordance with the guidelines of the institutional ethics committees. The Medical Ethics Review Committee (METC) of the Catharina Hospital approved the above mentioned trial. The METC reviewed the research protocol in accordance with the rules laid down in the Medical Research Involving Human Subjects Act (WMO).

Patients included were referred by a general practitioner to a pediatrician because initial laxative treatment of constipation had failed. All 370 patients included met the Rome III criteria[6,7] for constipation: patients between 1 and 4 years of age had to have at least two of the following symptoms for 1 month: two or fewer defecations per week; at least one episode per week of incontinence after acquisition of toileting skills; history of excessive stool retention; history of painful or hard bowel movements; presence of a large fecal mass in the rectum and history of large-diameter stools that may obstruct the toilet; patients from 4-18 years of age had to meet these criteria for at least 2 months instead of 1 month and also had to have insufficient criteria for the diagnosis of irritable bowel syndrome (IBS). All patients were between 1 and 18 years of age, and had had at least 3 months of gluten ingestion. Primary screening for CD was done by determining total serum IgA, and IgA-human tissue transglutaminase (Celikey tTG Elisa kit, Pharmacia and Upjohn Diagnostics, Freiburg, Germany). All patients with an abnormal IgA-tTG, or a low serum IgA, underwent a small intestinal biopsy. Final evaluation was done by a single, experienced pediatric pathologist (PN), and biopsies were assessed according to the Marsh criteria.[8] In this classification, an increased number of intraepithelial lymphocytes is seen in stage 1; in stage 2, an increase in crypt depth is seen additionally, but without villous flattening. In stage 3, both an increased number of intraepithelial lymphocytes and an increase in crypt depth is seen, as well as a reduction of villus height, which is graded into a, b and c, with c meaning total villous atrophy. Only patients with Marsh 3, either a, b or c, were judged as having CD. Apart from screening for CD, serum calcium, serum free thyroxine (fT4), and serum thyroid stimulating hormone (TSH) were also determined.

To determine whether the frequency of CD is indeed increased among patients with constipation, a two tailed Fisher's exact test was used.

Results

In the 2 years time interval between October 2006 and October 2008, a total of 370 patients with constipation were included. Seven of these patients had biopsy proven CD (Marsh 3, Table 1). This is significantly higher ($p < 0.001$) than the 1:198 prevalence of CD in the Netherlands, as determined in a survey of 6,127 Dutch children.[9] Both height and weight growth of these seven children were normal before the biopsy. Laxatives were no longer necessary after the initiation of gluten-free diet in two of the seven children; in three, the laxatives could be reduced; and two needed the same amount of laxatives as before.

In two patients (both girls, 8 and 9 years of age) a low serum fT4 and an increased serum TSH were found. On further testing both had an increased titer of thyroid peroxidase (TPO) antibodies, so a diagnosis of auto-immune thyroiditis was made. Constipation for 3 months before referral was the only complaint. There were no other clinical signs of hypothyroidism. Treatment with thyroxin and a laxative was started. Laxatives could be withdrawn after some time in both patients. No patients were diagnosed with hypercalcemia.

Discussion

Our study did show an increased prevalence of CD in pediatric patients with constipation referred by the general practitioner to a pediatrician because of initial failure of laxative treatment. This implies that in each child with constipation and a failure to respond to treatment, CD should be excluded, as well as other well-known causes of constipation (e.g., Hirschsprung disease). The cause of this relation between CD and constipation is unclear, but we do suggest that the mucosal inflammation in CD might affect normal bowel motility, as it is seen in an extreme form in celiac crisis.[10]

Table 1 - Patients with celiac disease who presented with constipation

Sex	Age at diagnosis (years)	Biopsy	Symptoms and treatment of constipation after starting gluten-free diet
Male	1 ¼	Marsh 3b	No constipation anymore; no laxative use
Female	12	Marsh 3b	No constipation anymore; no laxative use
Male	3	Marsh 3b	Constipation improved; needs less laxatives
Female	3 ½	Marsh 3a	Constipation improved; needs less laxatives
Female	8	Marsh 3a	Constipation improved; needs less laxatives
Male	1 ½	Marsh 3c	Still constipated; needs same amount of laxatives
Male	2 ¼	Marsh 3b	Still constipated; needs same amount of laxatives

Two of our patients with childhood constipation had auto-immune thyroiditis. Although CD and auto-immune thyroiditis are associated, neither of these two children had CD. Furthermore, auto-immune thyroiditis in children is fairly rare, with a prevalence of 0.3%.[11] Therefore, the frequency we found (2/370) seems to be increased, although not significantly. Even though the number of patients included in our study was designed to find an answer to the question whether CD is overrepresented in pediatric patients with constipation, the power was insufficient to detect an overrepresentation of thyroid problems. As both our patients were symptom-free, apart from the constipation, screening for thyroid problems can be considered for any child with constipation who is seen by a pediatrician.

No child in our study had hypercalcemia, which might induce constipation through a reduced neuromuscular excitability by high calcium levels.[12] However, only a single child with hypercalcemia associated with constipation has been described so far,[13] so the low frequency we found (0/370) is not a surprise.

In conclusion, CD is significantly overrepresented in patients with constipation who are referred from a general practitioner to a pediatrician because of failure of laxative treatment. All such patients should, therefore, be screened for CD.

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