Celiac disease and constipation: an uncommon atypical clinical manifestation

Doença celíaca e constipação: uma manifestação clínica atípica e pouco frequente

Enfermedad celíaca y constipación: una manifestación clínica atípica y poco frecuente

Cristiane Boé1, Adriana Chebar Lozinsky1, Francy Reis Patricio2, Jacy Alves B. de Andrade3, Ulysses Fagundes-Neto4

ABSTRACT

Objective: To report two cases of patients with celiac disease (CD) whose main complaint was chronic constipation.

Case description: Two girls, aged 18 and 30 months, had chronic constipation refractory to standard treatment. Both patients concomitantly evidenced low weight gain and short stature. The investigation of the digestive-absorptive function was positive for IgA antibodies against tissue transglutaminase. The diagnosis of CD was confirmed by a small bowel biopsy that showed moderate/severe villous atrophy and increased intraepithelial lymphocytic infiltration. One month after starting the dietary treatment with a gluten-free diet, both patients recovered from constipation, with the passage of soft stools daily.

Comments: CD may be presented in the classical, asymptomatic or atypical forms. In the latter form, isolated manifestations, such as constipation, delay the diagnosis of the disease.

Key-words: constipation; celiac disease; child.

RESUMO

Objetivo: Relatar dois casos de doença celíaca (DC) com manifestação de constipação.

Descrição do caso: Dois pacientes do sexo feminino, com 18 e 30 meses de idade, respectivamente, apresentando história de constipação crônica refratária ao tratamento. Como apresentavam concomitantemente baixo ganho ponderal e estatural, foi realizada investigação da função digestiva-absortiva, que resultou positiva para o anticorpo IgA antitransglutaminase tecidual. O diagnóstico de DC foi confirmado por biópsia de intestino delgado que revelou atrofia vilositária moderada/intensa e infiltrado linfocítico intraepitelial. Um mês após o início do tratamento com dieta isenta de glúten, ambas as pacientes passaram a apresentar fezes pastosas diariamente.

Comentários: A DC pode se apresentar nas formas clássica, assintomática e atípica, em que manifestações isoladas como constipação podem retardar o diagnóstico.

Palavras-chave: constipação intestinal; doença celíaca; criança.

RESUMEN

Objetivo: Relatar dos casos de enfermedad celíaca (EC) con manifestación de constipación.

Descripción del caso: Dos pacientes del sexo femenino, con 18 y 30 meses de edad, respectivamente, presentando historia de constipación crónica refractaria al tratamiento. Como presentaban concomitante baja ganancia de peso

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Fonte financiadora: Bolsa Produtividade em Pesquisa – Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Processo nº 304.150/2009-6

Conflito de interesse: nada a declarar

Recebido em: 27/5/2011
Aprovado em: 18/10/2011
Introduction

Celiac disease (CD) is a permanent intolerance to gluten that occurs in genetically susceptible individuals and is characterized by complete or partial atrophy of the mucosa of the proximal small bowel, hyperplasia of the intestinal crypts and intraepithelial lymphocytic infiltration, leading to malabsorption of dietary nutrients (1). CD is considered a chronic immune-mediated enteropathy (2) and is closely associated with the major histocompatibility complex (MHC) class II molecules HLA-DQ2 and HLA-DQ8 (3).

Classical CD, described in 1888 by Samuel Gee in Sdepanian, Morais & Fagundes-Neto (3), is characterized by chronic diarrhea, abdominal distension, weight loss and/or failure to thrive, vomiting, abdominal pain, irritability, and gluteal wasting (4). Although this is still the most common form of CD, atypical and clinically silent presentations are being reported with increasing frequency.

Constipation is rarely described as an atypical manifestation of CD, particularly in pediatric patients. In 1972, Egan-Mitchell and McNicholl (5) analyzed a series of 112 children with a diagnosis of CD and found that 12 (10.7%) had constipation. On the other hand, Sharma, Poddar and Yachha (6) conducted a study of 18 children with suspected CD in 2007 and found that only one (4%) had constipation as an atypical manifestation.

Within this context, we report two cases of patients with CD who presented with the atypical manifestation of chronic constipation. This report was approved by the Universidade Federal de São Paulo School of Medicine Research Ethics Committee.

Case description

Case 1

A 36-month-old girl presented with an 18-month history of constipation. The patient had been receiving follow-up at the Hospital São Paulo Department of Orthopedics due to a history of “chronic recurrent torticollis” (sic). Due to a concomitant complaint of chronic constipation, she was referred to our service, the Department of Pediatric Gastroenterology of the aforementioned hospital. According to her mother, the patient began to exhibit difficulty with bowel movements at the age of 18 months, with passage of hardened, thick, sausage-shaped stools with cracks on the surface. The patient strained and reported pain during bowel movements, and stools were occasionally coated with strands of bright red blood. These symptoms had thus far been managed unsuccessfully with administration of low-dose lactulose and periodic use of glycerin suppositories.

The patient had been exclusively breastfed until age 6 months. Throughout this period, she reportedly had two to three bowel movements per day, passing soft stools with no difficulty. At age 7 months, the patient was placed on a weaning diet consisting of whole cow’s milk and instant cereal (Mucilon® rice and oat formula) and gluten-containing solids (pasta). Relevant family history included a 6-year-old sibling with difficult-to-control epilepsy since age 3 years.

Physical examination revealed a weight of 11.4 kg and height of 88.5 cm (both within the 3rd percentile for age), mild pallor, and a palpable, hard mass extending across the left lower quadrant and left flank. Inspection of the anus revealed no abnormalities. A small amount of hardened stools was present in the rectal vault.

The following diagnostic hypotheses were considered: wasting and stunting (z scores: weight-for-age, -1.9; height-for-age, -1.6; weight-for-height, -1.5), chronic constipation, and iron deficiency anemia. A comprehensive workup was requested (complete blood count, serum iron and ferritin, thyroid-stimulating hormone and free thyroxine, urinalysis and urine culture, stool ova and parasites, and plain abdominal radiographs). A monosodium/disodium phosphate (Fleet®) enema was prescribed for fecal disimpaction, followed by maintenance lactulose (Lactulona®), 2 mL/kg/day.

The patient returned one month later for follow-up. There had been no improvement in constipation; however, the prescribed therapeutic regimen had not been
followed. Due to the patient’s poor weight and height and low serum iron and ferritin levels (Table 1), further investigation with hydrogen breath testing after glucose, lactose, fructose, and lactulose loading was requested for assessment of digestive-absorptive function (Table 2), as were serum anti-tissue transglutaminase (tTG) antibody and immunoglobulin A (IgA) levels. Glucose, lactose, and lactulose load tests were within normal limits, with elevations in exhaled H$_2$ level <20ppm above fasting (baseline) levels. In the lactulose load test, an increase in exhaled H$_2$ levels is expected at 60 minutes, due to the non-absorbable nature of this carbohydrate (the elevated level reflects the fermentative action of the colonic flora). The fructose load test was indicative of fructose malabsorption, but not intolerance, as the patient did not exhibit any symptoms of the latter. As serum anti-tissue transglutaminase antibody levels were above normal (33.62 units; reference range, <20), an endoscopic small bowel biopsy was scheduled. The patient’s serum IgA level was 111.1mg/dL (reference range, 24–190mg/dL). Histological examination of the biopsy specimen revealed patchy villous atrophy, diffuse intraepithelial lymphocytosis, and slightly increased lymphoplasmacytic infiltration of the lamina propria (Marsh stage 3A) (7) (Figures 1 and 2). In view of these findings, a diagnosis of CD was made and the patient was placed on a gluten-free diet. Within two months of dietary treatment, the patient was having daily bowel movements and passing soft stools.

Case 2

A 30-month-old girl presented with a history of chronic constipation and fecal soiling since age 27 months. According to the patient’s mother, bowel movements were painful and occurred only once every five days; stools were large and hardened, but no blood or other pathological elements were present. Treatment with below-recommended doses of lactulose (Farlac®) had been attempted with no effect. The patient received mixed feeding until age 8 months and, during this period, had two to three daily bowel movements, passing soft stools with no difficulty. A solid diet was introduced at age 6 months, consisting of an age-appropriate cow’s milk formula and age-appropriate solids as recommended by the child’s pediatrician. Wheat-derived flour was introduced at this time. Relevant family history included a grandfather with Crohn’s disease and mother with chronic constipation.

On physical examination, weight was 11.7kg and height was 92cm (z scores: weight-for-age, -1.37; height-for-age, -0.78; weight-for-height, -1.04). The patient appeared

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<th>Case 2</th>
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<td>85</td>
<td>37–170</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>8.4</td>
<td>27.0</td>
<td>11.0–307.0</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (µUI/mL)</td>
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<td>3.68</td>
<td>0.34–5.60</td>
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<td>1.08</td>
<td>0.58–1.64</td>
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<td>Urinalysis</td>
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Table 2 - Hydrogen breath testing – case 1

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Hydrogen breath test after glucose, fructose, lactose, and lactulose load. H2 levels expressed as parts per million (ppm)
Doença celíaca e constipação: uma manifestação clínica atípica e pouco frequente

Era um menino de 7 anos, que no momento da apresentação estava extremamente emagrecido e apresentava distensão abdominal com massa palpável no flanco esquerdo. A hipótese diagnóstica inicial incluía desnutrição e constipação crônica. As radiografias simples do abdômen revelaram arquivamento de gás e fezes pelo colon, com massa de fezes retida no estreito retal. Foi prescrito um enema de fosfato de sódio para disimpacção domiciliar, seguido por manutenção de lactulose (2mL/kg/dia) e óleo mineral (2mL/kg/dia). Apesar de continuar apresentando constipação e restrição do crescimento um ano após a primeira apresentação (peso 13,1 kg; altura 98 cm; índice de peso para a idade z-score, -1,07), foram solicitados mais exames (contagem completa do sangue, hormônio estimulante da tireoide, tireoglobulina livre, ferritina) (Tabela 1). Um panômetro celiaco sérico foi solicitado, consistindo nos seguintes testes: anti-glúten anticorpos (AGA), IgA e IgG; anti-endomisial anticorpos (EMA); anti-tTG anticorpos; e HLA-DQ2 e DQ8 tipagem.

A celiaca sérica foi positiva, conforme: titulações EMA, 1:320 (faixa de referência, não reativo); IgA-AGA, 9,9 (faixa de referência, ≥1); IgG-AGA, 3,6 (faixa de referência, ≥3); anti-tTG, 165; HLA-DQ2, positivo. Diante dessas observações, foi realizada uma biópsia duodenal endoscópica. Exame macroscópico revelou o patamar ou “formato de areia quebrada” da mucosa duodenal, indicativa de CD. O exame histológico under microscopy mostrou atrofia villosa moderada, aumento significativo do número de linfócitos intraepiteliais, aumento significativo da linfoplasmocitose no revestimento da camada propria, e hiperplasia das criptas (Marsh stage 2)(7). O paciente foi instruído a seguir uma dieta livre de glúten. Após um mês de tratamento dietético, a constipação havia resolvido completamente.

**Discussion**

CD é uma condição permanente, de intolerância imune-mediada ao glúten(2). Em Europa e os Estados Unidos, a prevalência do CD varia de 1 em 100 a 1 em 200 (4). Em uma pesquisa de doadores de sangue da cidade de São Paulo, Brasil, Oliveira et al(8) demonstraram que a CD não pode ser considerada uma doença rara, já que sua prevalência na cidade era de pelo menos 1 em 214 população.

Ademais da forma clássica de CD, as outras formas reconhecidas desse distúrbio são: 1) assintomática ou clínicamente silenciosa – típica enteropectia glúten-sensitiva, sem manifestações clínicas. A maioria desses pacientes são parentes de primeiro grau de pessoas com CD e diabetes dependente de insulina (4); 2) não-classificadas ou atípicas – caracterizadas por um ou poucos sintomas, com início em idade avançada; pacientes podem apresentar isoladas manifestações, como estatura curta, resistência ao tratamento anemia de deficiência de ferro, artrite ou artralgia, epilepsia.
seizures, enamel hypoplasia, dermatitis herpetiformis, elevated transaminases, precocious puberty, recurring abdominal pain, and constipation(4). Constipation is consistently cited as one of the presenting symptoms of atypical CD, particularly in review articles; however, it has only rarely been described (with supporting evidence) as a symptom of CD in the literature.

Our extensive review of the literature yielded only two articles describing constipation as a symptom of CD in children(5,6). These rare descriptions of constipation as an atypical manifestation of CD led Hungerford(9), in 1996, to write a letter to the editor of Australian Family Physician in which he revealed his disappointment with the paucity of reports of this symptom in pediatric patients, as, in his personal experience, chronic constipation was not unusual in adult patients with CD.

CD is increasingly recognized in adults with no presenting complaints of diarrhea. An ever greater percentage of patients are asymptomatic; diagnosis is often made during screening. Atypical forms of the disease are becoming more common(10). The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommends that CD be considered in the differential diagnosis of children with persistent gastrointestinal symptoms, including recurring abdominal pain, constipation, and vomiting(11). In 2007, a multicenter U.S. study showed that more widespread CD screening could increase detection of the disease in the country(12). In this study, conducted between 2002 and 2004, 22 cases of CD were diagnosed in a sample of 976 subjects, four of whom reported constipation. This represented a very significant leap in the number of new cases from 0.27 per 1,000 to 11.6 per 1,000 screened.

Both patients described in this case report had chronic constipation and negative weight and height z scores. It is common knowledge that chronic constipation is highly prevalent among pediatric patients seeking specialized gastroenterology care, and that the vast majority of these cases are of functional etiology. However, when constipation presents alongside a variety of red flags, including compromised nutritional status, it should be regarded as an indication of in-depth diagnostic studies. In both patients described herein, constipation and signs of undernutrition persisted during outpatient follow-up, which prompted assessment of digestive-absorptive function, leading to a diagnosis of CD.

To conclude, it bears stressing that CD may present in a variety of forms, namely: classical or symptomatic, asymptomatic, and atypical. Although there have been few descriptions of chronic constipation as a symptom of CD, the prevalence of this atypical manifestation does not appear to be negligible. Therefore, it is essential that healthcare providers be aware of it as a possible atypical presenting symptom of CD and pursue relevant investigations when the disease is suspected.

References