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EDITORIAL COMMENT

Persistent elevated tissue-transglutaminase in cystic fibrosis

Cystic Fibrosis (CF) and Celiac Disease (CD) are the most common causes of chronic intestinal malabsorption in childhood.[1] Although pancreatic exocrine insufficiency is relatively common in patients with CD,[2] the coexistence of CF and CD is rarely reported. Here we report a case of CF in a child with presumed CD, who failed to respond clinically to a gluten-free diet and had a persistent elevated anti-transglutaminase (tTG) test.

A 6-year-old Caucasian male with known congenital hypothyroidism was referred to the Gastrointestinal (GI) clinic with a history of loose stool, abdominal bloating and an IgA anti-tTG test >200 units (screening cut-off <20 units). He was born at term, delivered by spontaneous vaginal delivery. His birth weight was 3.1 kg. At 3 months of age, he experienced poor weight gain and was diagnosed with congenital hypothyroidism. He was placed on levothroxin 50 µg daily with good response. At the GI visit, he was determined to have a long-standing history of passing up to three loose oily bowel movements per day. He had associated abdominal distension, irritability and skin pallor. His past medical history included a possible food allergy during infancy that failed to respond to dairy-free and wheat-free diets. He was known to have asthma and allergic rhinitis responsive to Salbutamol and Fluticasone. He had chronic cough with intermittent wheezing. Physical examination revealed little fat subcutaneous and muscle mass, finger clubbing and mild nasal obstruction without respiratory distress. His weight and height were both on the 10th percentile for age. Abdominal examination revealed quite marked abdominal distension, but no hepatosplenomegaly, palpable masses or ascites. The rest of the examination was unremarkable. The initial laboratory investigations were as follows: hemoglobin 130 g/L (range 118–146), anti-tTG IgA >200 units (negative screen <20 units), serum IgA 1.2 (range 0.34–3.05), albumin 34 g/L (range 35–50), total protein, AST, ALT and ALP were normal. As a result of nasal obstruction with increased respiratory distress following IV sedation in the endoscopy suite, the upper GI endoscopy was aborted. A presumed diagnosis of celiac disease was made and as the family lived a long distance from the hospital he was placed on a Gluten-Free Diet (GFD).

He returned to the GI clinic 1 year later on a GFD. He had ongoing symptoms. The repeated tTG was 185 units. Anti-endomysial antibody was not done. He underwent an upper GI endoscopy under propofol anaesthesia, which showed a macroscopic normal upper GI tract. Histological assessment revealed unremarkable villi, no evidence of crypt hyperplasia and no increase in intraepithelial lymphocytes or lamina propria mononuclear cells. A duodenal aspirate done at the time of endoscopy and sent for bacterial culture grew *Staphylococcus aureus* and *Pseudomonas aeruginosa*. A subsequent sweat test confirmed the diagnosis of CF with sweat chloride and sodium of 111 and 121, respectively. Stool for fat globules >100/low power field (range <50), faecal chymotrypsin 40 units/min/g (range 60–400), stool pancreatic elastase 1 <15 ug/g (range 200–500), serum immunoreactive trypsin <5 ug/L (range 10–57). On genetic testing he was homozygous for the DNA ΔF508 mutation. He was taken off the GFD and placed on pancreatic enzymes. His symptoms resolved and he demonstrated good weight gain and growth.

He was re-referred to the GI clinic 2 years after resumption of the gluten-containing diet. He continued to demonstrate good weight gain and growth, but had persistently elevated tTG levels with levels remaining above 200 units on two occasions. Repeat upper GI endoscopy showed a macroscopic normal upper GI tract. Histological assessment revealed normal duodenal biopsies except for a small amount of inspissated mucin as seen in CF. HLA-DQ typing was negative for HLA-DQ2 (0201, 0202), but positive for HLA-DQ8 (0302).

A child with CD may present with impaired growth, abnormal stools, abdominal distension, muscle wasting and behavioural changes. These features are also commonly seen in infants with CF. In untreated CD, nutrient malabsorption is attributed mainly to impaired absorptive function of the damaged intestinal mucosa[3], however, concurrent exocrine pancreatic dysfunction may also contribute.[2,4] In small studies, reduced pancreatic secretory capacity has been reported in up to 40% of newly diagnosed CD cases.[2] These abnormalities are multifactorial and likely result from inadequate cholecystokinin[5] release by the damaged small bowel mucosa, disruption of the normal trophic relationship between intestinal mucosa and exocrine pancreas and direct impairment of pancreatic enzyme synthesis associated with prolonged malnutrition.[4] Where most studies suggest pancreatic function recovery in response to GFD,[2,3] several studies have suggested that treatment failure might be related to impaired pancreatic intrinsic secretory function.[4]

In our case with presumed CD, persistent diarrhea, elevated tTG levels and normal biopsy did not indicate poor compliance or an inexperienced pathologist. Rather, exocrine pancreatic insufficiency and small intestinal bacterial overgrowth (SIBO) were considered. We could not apply the definition of SIBO in our patient because his bacterial load in small bowel <10 000 000 CFU/mL. D-lactate and glucose breath test were not done to support the diagnosis of SIBO.

The presence of SBIO is supported by an adult CD study demonstrating a high prevalence of SIBO in 66% (10/15) of cases unresponsive to a GFD.[6] The determination of a duodenal aspirate culture positive for *S. aureus* and *P. aeruginosa* (commonly found in the sputum of CF patients) alerted us to a possible diagnosis of CF, further supported by the presence of chronic diarrhea, nasal obstruction and finger clubbing.

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A recent publication suggests a high prevalence of SIBO in CF patients.[7] The reason for SIBO in our patient was likely multifactorial, including impaired flushing of the intestine because of reduced pancreatic, biliary and enterocyte fluid secretions, an acidic environment, a poorly hydrated thickened mucus layer, impaired Paneth cell innate defenses, reduced intrinsic antibacterial activity as a result of reduced pancreatic secretions and slowed intestinal transit allowing bacterial proliferation and adhesion.[7]

The persistent tTG elevations in association with HLA-DQ8 positivity, despite normal histology, raise the possibility of the coexistence of CF with latent CD. To date, the coexistence of these two conditions has only been indicated in case reports.[8] The presence of HLA-DQ2 or HLA-DQ8 in patients with positive serologic test results while strongly suggestive of CD is not pathognomonic.[9] Nevertheless, it remains possible that this child will eventually develop histological evidence of CD, and further monitoring is required.

The case described raises important issues including the possible coexistence of these two relatively common pediatric conditions and highlights the need to consider alternative diagnoses such as CF in patients with positive CDe serology and apparent CD unresponsive to GFD.

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