CASE REPORT

Acute Pancreatitis in Association with *Campylobacter jejuni*-Associated Diarrhea in a 15-Year-Old with *CFTR* Mutations: Is There a Link?

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ABSTRACT

Context Acute pancreatitis has occasionally been reported in association with *Campylobacter jejuni* infection in humans. However, the mechanism linking *Campylobacter jejuni* infection and pancreatitis is unclear. Acute pancreatitis in association with an infectious illness may be related to underlying genetic mutations. For instance, studies show that mutations in the cystic fibrosis transmembrane conductance regulator gene increase the susceptibility for acute and chronic pancreatitis.

Case report We describe a patient with *Campylobacter jejuni* infection who developed acute pancreatitis in the setting of an underlying cystic fibrosis transmembrane conductance regulator gene mutation.

Discussion In this patient with an underlying mutation in the *CFTR* gene, we propose that the interaction between the mutant gene and an environmental factor, *Campylobacter jejuni* infection, resulted in pancreatitis.

INTRODUCTION

We report a case of acute pancreatitis associated with *Campylobacter jejuni* (*C.*

jejuni) enteritis in a 15-year-old female who has compound heterozygous mutations involving the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Studies in adults have shown that compound heterozygous severe/mild-variable C*FTR* genotypes increase the susceptibility to pancreatitis [1, 2, 3]. The attacks of acute pancreatitis occur infrequently and are likely triggered by strong environmental stressors [4, 5]. In this patient, the likely stressor is *C. jejuni infection*, a common cause of diarrhea accounting for 3.2 % to 6.1 % of the cases [6, 7]. Importantly, *C. jejuni* infection has been reported in association with acute pancreatitis in humans [8, 9, 10, 11, 12, 13]. Given this background, we propose a novel model of pancreatic hyperstimulation leading to acute pancreatitis as a collateral consequence of a neurally-mediated secretory defense mechanism against an enteric infection.

CASE REPORT

A 15-year-old Caucasian female presented to Children's Hospital of Pittsburgh with acute right lower quadrant and periumbilical abdominal pain and an 8 day history of diarrhea described as 3-4 watery stools per day. She had a 2 kg weight loss, bilateral knee pain and fever. She had used acetaminophen and ibuprofen as needed for abdominal pain

and fever. Family history was significant for celiac disease in a second cousin. She had unpasteurized milk one week prior to onset of diarrhea.

Her past medical history was significant for poor growth (weight and height below 5th percentile adjusted for age) and recurrent episodes of abdominal pain since 4 years of age. Previous evaluation for abdominal pain including an abdominal ultrasound, CT scan, upper gastrointestinal and small bowel series were unremarkable. Upper endoscopy with biopsies at 4 years of age showed chronic gastritis and she was treated with ranitidine. Celiac disease antibodies and duodenal biopsies were normal. At 4 and 7 years of age, she had mildly elevated serum lipase to 271 IU/L (reference range: 0-200 IU/L) and normal serum amylase levels. Repeat upper endoscopy and bile analysis in response to cholecystokinin stimulation for cholesterol and bilirubin crystals was negative. Sweat chloride test at 11 years of age showed elevation of sodium to 69 mEq/L and chloride to 60 mEq/L on two occasions (reference range: 0-40 mEq/L for both). Pulmonary function tests, and fat soluble vitamin levels were normal. Seventy-two hour fecal fat analysis showed no evidence of steathorrea.

On admission, her temperature was 36.2°C, heart rate was 80 per minute, respiratory rate was 18 per minute and blood pressure was 100/70 mmHg. She weighed 36.2 kg (below the 3rd percentile adjusted for age), height was 160 cm (25 percentile) and body mass index was 13.5 (less than 3 percentile). She had mild epigastric tenderness and the rest of the exam was normal. Serum amylase was 103 IU/L (reference range: 0-90 IU/L) and serum lipase was 3,663 IU/L (reference range: 0-200 IU/L). Complete blood count, serum electrolytes, serum calcium, liver function tests, and fasting serum triglyceride levels were normal. Pain management was begun with meperidine, feedings were held and intravenous fluids with 5% dextrose were started. Abdominal ultrasound did not reveal any abnormalities. Abdominal pain and watery stools continued, serum amylase increased to 465 IU/L and lipase increased to

19,051 IU/L on the fourth day of hospitalization.

Stool studies were negative for occult blood, parasitic and *C. difficile* infections. However, heavy growth of *C. jejuni* was detected on stool culture and she was treated with azithromycin 500 mg daily. Naso-jejunal feeds with Ensure (Abbott Laboratories, Abbott Park, IL, USA) were started on fifth day of hospitalization. Over the next couple of days serum amylase peaked to 554 IU/L and lipase peaked to 21,047 IU/L. The degree and duration of lipase and amylase elevation was most consistent with a diagnosis of acute pancreatitis. Contrast CT scan of the abdomen showed a normal appearing pancreas. Magnetic resonance cholangiopancreatography revealed normal pancreatic, intrahepatic and common bile ducts. Over the next several days her abdominal pain and diarrhea improved. Due to a history of borderline sweat chloride test at 11 years of age and pancreatitis on admission, a buccal swab was sent for *CFTR* genetic mutation analysis. She was found to have a compound heterozygote R117H/delF508 *CFTR* genotype.

Azithromycin was continued for a total of 7 days; serum amylase and lipase decreased to 513 IU/L and 17,345 IU/L and she was discharged on the tenth hospital day. Serum amylase decreased to 308 IU/L and lipase decreased to 650 IU/L four weeks after discharge and she remained asymptomatic.

DISCUSSION

Elevations of serum amylase or lipase have been reported in association with bacterial infections of the intestine [14, 15, 16]. In most patients the elevations are less than three times the upper limits of normal making it unclear if they had pancreatitis or if the enzyme elevation occurred by a separate mechanism. Others more clearly had acute pancreatitis associated with the enteric infection. The mechanism by which enteric infections contribute to acute pancreatitis in these cases is unclear. The association of mutations in the *CFTR* gene and an enteric infection in our patient suggests a possible mechanism.
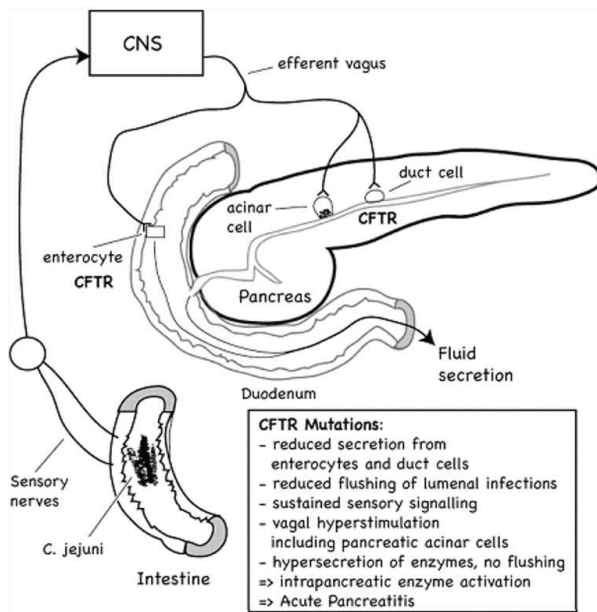
Figure 1. Hypothetical model linking *C. jejuni* enteritis to acute pancreatitis through a hyperstimulation mechanism. In this model the normal feedback loop to eliminate the luminal stimulus of *C. jejuni* with increased fluid secretion (manifested by watery diarrhea) is blocked at the level of dysfunctional *CFTR*. Hyperstimulation of the pancreas leads to acinar cell stimulation but duct cell dysfunction limits digestive enzyme elimination from the duct. Trypsinogen activation within the pancreas leads to generalized digestive enzyme activation, pancreatic injury, and acute pancreatitis.

One of the pathophysiological mechanisms of *C. jejuni* involves an increase in intracellular cyclic adenosine monophosphate (cAMP) and calcium that induces release of 5-hydroxytryptamine initiating a secretory reflex in the afferent limb of the enteric nervous system [17]. This activates efferent neurons via cholinergic and non-cholinergic interneurons thereby liberating vasoactive intestinal peptide and acetyl choline at bases of the enterocytes [18]. In more severe cases the symptoms extend beyond the local region, with systemic inflammatory symptoms and possible activation of long nervous reflexes. Cystic fibrosis is an autosomal recessive disorder caused by mutations in the *CFTR* gene, which encodes a cAMP activated anion channel that is important for chloride and bicarbonate secretion in the intestine and pancreas. Mutations in CFTR can eliminate function (severe) or diminish function (mild-variable) [19, 20]. Individuals with two functionally severe *CFTR* mutations (e.g., delF508) have cystic fibrosis whereas individuals with a mild-variable mutation combined with a severe *CFTR* mutation may retain pancreatic function but are susceptible to acute and chronic pancreatitis [1, 2, 3, 21, 22, 23].

In our model, intraluminal *C. jejuni* activated inflammatory and sensory responses that were sufficient to cause systemic responses, including long-neural reflexes (Figure 1). As part of the defense against enteric pathogens, there is a proximal, efferent vagus-mediated secretory response resulting in diarrhea and elimination of the intestinal contents. Since this patient had both severe and mild-variable *CFTR* mutations the *CFTR*-dependent chloride efflux would be markedly limited from enterocytes and pancreatic duct cells. Failure to effectively eliminate the enteric pathogen may lead to prolonged and intense stimulation resulting in hyperstimulation of the efferent vagus. The pancreatic acinar cells, which are also driven by efferent vagal stimulation, would respond with exocytosis of digestive enzymes, but their clearance from the duct would be limited by the *CFTR* dysfunction. Activation of the digestive enzymes within the pancreas by hyperstimulation or failed clearance would lead to pancreatic injury and acute pancreatitis [24, 25].

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