Hereditary angioedema (HAE) is a rare, autosomal dominant disease with a prevalence of 1 in 10,000 to 50,000 people. Approximately 20% are de novo mutations, without family history of the disease. HAE usually begins in childhood and persists throughout life. The disease is characterized by recurrent and unpredictable attacks of subcutaneous and/or submucosal swelling that usually last 2 to 5 days and resolve spontaneously. The anatomic sites may involve the face, extremities, upper airways, and gastrointestinal or genitourinary system. HAE that affects the tongue or larynx can cause suffocation and death. Sometimes a rash that looks similar to urticaria (erythema marginatum) can occur, although it is not raised or pruritic.1

Hereditary angioedema (HAE) may manifest with swelling of the face, extremities, and upper airways. Gastrointestinal symptoms are also common and may include abdominal pain, vomiting, and diarrhea. However, pancreatic involvement is rare and has been reported only in a few adults with previously diagnosed HAE. We describe a 6-year-old boy who presented with recurrent severe abdominal pain accompanied by an elevation in pancreatic enzyme levels, without subcutaneous or cutaneous angioedema. His symptoms had begun 18 months earlier, and he was hospitalized several times before the present admission with a diagnosis of acute pancreatitis. More comprehensive analysis yielded low levels of C2, C4, CH50, and C1 esterase inhibitor, establishing the diagnosis of HAE. One year after diagnosis, swelling of the extremities appeared for the first time. This is the first report of a child in whom pancreatic disease was the presenting symptom of HAE. HAE should be included in the differential diagnosis of recurrent pancreatitis in children.

Typical symptoms of gastrointestinal involvement are anorexia, vomiting, diarrhea, and crampy abdominal pain. The abdomen is tender to palpation but without guarding in most cases. Fever and leukocytosis are unusual, and their presence should raise suspicion of another diagnosis, such as appendicitis.

We describe a child in whom HAE was diagnosed after several attacks of pancreatitis. To our knowledge, this presentation has not previously been reported in patients with HAE.

CASE PRESENTATION

A 6-year-old boy with an unremarkable family history presented to the Pediatric Surgery Department with complaints of abdominal pain, nausea, and vomiting, without fever. This was his 10th hospitalization for similar symptoms in the previous 18 months. The time between attacks ranged from a few days to a few weeks. During all episodes, laboratory workup revealed high levels of amylase in blood (up to 1440 U/L; normal, 10–100 U/L) and urine (up to 913
U/L; normal, 0–460 U/L). Blood lipase level was also elevated (up to 180 U/L; normal, 16–65 U/L). There were no pathologic signs on abdominal ultrasonography, endoscopic retrograde cholangiopancreatography, and magnetic resonance cholangiopancreatography. The diagnosis at each presentation was acute pancreatitis, and the patient was treated conservatively with fluids and papaverine, followed by a low-fat diet. This led to an alleviation of the symptoms accompanied by normalization of amylase and lipase levels.

At the fourth hospitalization, an abdominal ultrasound scan showed an enlarged edematous hyperechogenic pancreas, compatible with acute pancreatitis. Endoscopic ultrasound demonstrated stones in the gallbladder. Treatment with ursodeoxycholic acid was started, followed 2 months later by laparoscopic cholecystectomy. Gallstones were not found in the removed gallbladder, and the histologic findings were consistent with mild chronic cholecystitis. However, 2 months after the procedure, the patient experienced another attack with the same clinical features.

At the 10th admission, given the persistence of the attacks, a broader investigation was undertaken, including blood tests for complement components: C2 was 0.6 mg/dL (normal, 1.8–3.0 mg/dL), C4 was 2.1 mg/dL (normal, 10–25 mg/dL), and C3 was 80 mg/dL (normal, 80–180 mg/dL). There were only traces of CH50 activity. C1 esterase inhibitor (C1-INH) was <6 mg/dL (normal, 15–35 mg/dL). These findings, together with the clinical picture, led to a diagnosis of HAE. The next 3 episodes were treated with purified C1-INH (Berinert). The child responded well, with disappearance of symptoms within minutes. Approximately 1 year after HAE was diagnosed, angioedema of the upper limb developed for the first time, in addition to abdominal pain.

**DISCUSSION**

The 2 main types of HAE present with a typical laboratory finding of abnormal serum level and/or function of C1-INH. Type 1 HAE occurs in 80% to 85% of affected patients and is characterized by a decrease in the production of C1-INH. Type 2 HAE occurs in the remaining 15% to 20% patients and is characterized by normal or elevated levels of functionally impaired C1-INH. HAE usually manifests for the first time during the first and second decades of life. The median age according to several reports ranges from 6.6 to 12.5 years. Approximately 90% of patients experience their first attack before age 20 years. The number and severity of attacks typically increase around puberty in both genders. According to 1 large series, swelling of the extremities occurs in all patients, involvement of the gastrointestinal system in 97%, and involvement of the larynx in ~50% of the patients. In contrast to attacks of cutaneous angioedema, which may last for days, attacks of gastrointestinal tract angioedema usually last 12 to 24 hours. However, involvement of the pancreas, presenting as acute pancreatitis, is rarely seen in HAE.1,2

Acute pancreatitis is the most common pancreatic disorder in children. It may be caused by infections, metabolic disorders, immunologic conditions, blunt abdominal injuries, biliary stones, and drug toxicity.3 Recurrent pancreatitis in children may be caused by hereditary disorders such as Shwachman syndrome, Pearson syndrome, mutation in CFTR (cystic fibrosis transmembrane conductance regulator), SPINK 1 (serine protease inhibitor, Kazal type 1) or PRSS1 (serine protease 1; trypsin 1). It manifests as severe upper quadrant abdominal pain, vomiting, and sometimes fever, accompanied by an increase in serum lipase and amylase levels. Children with uncomplicated acute pancreatitis do well and recover within 4 to 5 days, usually with only conservative treatment.3

To the best of our knowledge, no case of HAE presenting as acute pancreatitis has been described to date in a child. Our review of the medical literature yielded 4 reports of adults in whom acute pancreatitis presented as an expression of already diagnosed HAE. The patients included a 40-year-old man with known C1-INH deficiency since age 2 years,4 a 73-year-old woman with a 10-year-history of HAE,5 a 32-year-old woman with a history of recurrent cutaneous swelling and decreased C1-INH level,6 and a 44-year-old woman with a known C1-INH deficiency.7 All complained of abdominal pain, nausea, and vomiting, and all were found to have elevated amylase and/or lipase levels.

We propose the following pathologic mechanism for the formation of pancreatitis in HAE: swelling of the pancreatic duct, as part of the HAE, is followed by obstruction of the duct, resulting in an accumulation of pancreatic enzymes and the formation of acute pancreatitis.

**CONCLUSIONS**

We describe a rare presentation of HAE that has not yet been reported in children. HAE may present as recurrent events of pancreatitis, possibly due to edema or swelling of the pancreas that interferes with normal pancreatic drainage. Clinicians should be alert to this possibility and include HAE in the differential diagnosis of unexplained recurrent events of abdominal pain or acute pancreatitis.
ABBREVIATION
HAE: hereditary angioedema

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Hereditary Angioedema Presenting as Recurrent Acute Pancreatitis
Tal D. Berger and Ben-Zion Garty

*Pediatrics* originally published online January 26, 2016;

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Pediatrics originally published online January 26, 2016;

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