

## Acute Pancreatitis in the Context of Abdominal Attack of Hereditary Angioedema

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Hereditary angioedema (HAE) is a rare autosomal dominant disease (1:50 000 individuals) [1]. The most common forms of HAE result from mutations in the C1 esterase inhibitor (C1-INH) gene (*SERPING1*) that lead to a quantitative or qualitative C1-INH deficiency. The 3 types of C1-INH that have been described to date are as follows: C1-INH-HAE type 1, which is characterized by C1-INH quantitative deficiency; C1-INH-HAE type 2, which is characterized by C1-INH qualitative deficiency; and nl-C1-INH-HAE, which is characterized by normal C1-INH levels and function and is due to a heterogeneous gene mutation that includes FXII-HAE (*F12* gene), ANGPT1-HAE (angiopoietin 1), PLG-HAE (plasminogen), KNG1-HAE (kininogen 1), and UNK-HAE (unknown) [1]. Clinically, HAE is characterized by recurrent, nonpruritic edema, which typically involves subcutaneous tissue (face, extremities) and mucosal tissue (oropharyngeal, laryngeal, and gastrointestinal) and may last up to 3-5 days without treatment [1]. Involvement of the upper airways and gastrointestinal system can lead to airway obstruction, asphyxia, and abdominal attack [1,2]. Early diagnosis is therefore fundamental.

Abdominal attack is characterized by abdominal pain with or without other symptoms such as nausea, vomiting, diarrhea, and abdominal distension. These symptoms are secondary to transient edema of the wall of the intestinal tract and fluid shifts into the intestinal lumen or the peritoneal cavity [2]. In rare cases, abdominal attack manifests with signs of pancreatitis. Our aim was to increase physicians' awareness of pancreatitis as a sign or complication of abdominal attack in HAE. We

report a case of acute pancreatitis due to abdominal attack of HAE with exclusively pancreatic edema and elevation of pancreatic enzymes in which C1-INH therapy was essential for clinical resolution. A 39-year-old woman with type 2 C1-INH-HAE and a history of multiple episodes of angioedema of the extremities since age 16 years was seen in our Outpatient Department at age 25 years. Her laboratory values were as follows: C3, 140 mg/dL (90-180); C4, 3 mg/dL (10-40); C1-INH, 56 mg/dL (18-32); and functional C1-INH, 30% (>68). She was initially treated with aminocaproic acid, which partially controlled the angioedema. At age 35 years, she presented with several episodes of abdominal pain and vomiting and started treatment with stanazolol 2 mg/d, which improved her symptoms. At age 39 years, under irregular treatment with stanazolol, she went to the Emergency Department with a new episode of intense and colicky epigastric pain in association with nausea and vomiting. She has no history of alcohol consumption or trauma and was not taking other medications. Abdominal ultrasound revealed a globular and swollen pancreas, with a heterogeneous and hypoechoic structure. There were no other relevant findings, including no free intraperitoneal fluid. C-reactive protein (CRP) had increased by 17.3 mg/dL and pancreatic enzyme values were elevated (lipase, 512 U/L; amylase, 374 U/L). No other analytical changes were recorded (leukocytes, hematocrit, bilirubin, and transaminases). The patient was treated with several analgesics (acetaminophen, butylscopolamine, and tramadol), although her symptoms did not improve. HAE was accepted as being the cause of the acute pancreatitis and, 8 hours after the onset of abdominal attack, 1000 U of C1-INH concentrate (Berinert, CSL Behring) was administered; her symptoms resolved within about 30 minutes. She was hospitalized for observation without the need for analgesics. After 24 hours, a second abdominal ultrasound scan did not reveal pancreatic changes but did reveal the presence of a moderate amount of free fluid in the Morrison space and in the pouch of Douglas that were not evident in the first scan. CRP and pancreatic enzyme levels had decreased. The patient was discharged 96 hours later; she was asymptomatic and had been diagnosed with abdominal attack of HAE with exclusively pancreatic involvement.

Gastrointestinal tract involvement is one of the most common features of HAE, and attacks affecting the abdomen are almost as common as those affecting the skin (>90% of patients) [3]. The difficulty in associating gastrointestinal symptoms with an abdominal attack of HAE often leads to an incorrect diagnosis, such as irritable bowel syndrome or renal colic. Appendicitis, intestinal obstruction, and cholecystitis may be suspected and consequently lead to unnecessary surgical procedures. One study concluded that one third of HAE patients with abdominal symptoms underwent unnecessary abdominal surgeries [2]. In rare cases, abdominal

Table. Recently Published Cases of Pancreatitis Secondary to Abdominal Attack of Hereditary Angioedema (Adapted From Lopes-Veronez et al, *Front Med (Lausanne)*. 2019;6:80

Paper	Gender, Age	Lipase, U/L	Amylase, U/L	Treatment	Clinical Evaluation	Gastrointestinal Surgeries
Our case	F, 39	512	374	C1 inhibitor	Improvement in 30 min	No history
Lopez-Veronez et al [3]	M, 21	1.159	292	Icatibant	Improvement in 3 h	No history
	F, 47	ND	210	Icatibant	Improvement in 1 h	Appendectomy
Loudin et al [4]	F, 56	663	ND	C1 inhibitor	Improvement in 30 min	Cholecystectomy
Maamer et al [5]	F, 73	1235	869	Danazol	Improvement in 5 d	No history
Czaller et al [6]	F, 29	1452	2615	C1 inhibitor (2 times)	Improvement in 4 h	Appendectomy
Cancian et al [7]	F, 32	ND	470	C1 inhibitor	Improvement in 30 min	ND

Abbreviations: F, female; M, male; ND, not determined.

attacks of HAE are associated with acute pancreatitis. Although this association is not fully documented, it is thought that pancreatic edema may cause obstruction of the pancreatic duct or the ampulla of Vater, leading to episodes of pancreatitis [3]. The Table shows several published cases [3-8] of acute pancreatitis due to abdominal attack of HAE. All patients were treated with specific HAE therapy, and symptoms improved. This improvement was faster in patients undergoing treatment of an acute attack.

The unspecific symptoms of abdominal attack of HAE can hamper diagnosis and, in the absence of clinical suspicion, treatment may be postponed altogether. In addition, laboratory parameters remain largely unchanged, except for an increase in hematocrit, which is probably secondary to hemoconcentration, dehydration, and translocation of fluid into the intestinal wall, as well as leukocytosis [9]. A recent study [10] found a correlation between CRP levels and abdominal attack of HAE: increased CRP levels during the attack are found mainly in patients with abdominal locations. In the absence of an attack, increased CRP levels may alert the physician to severe inflammation. Imaging may prove useful in the initial investigation of abdominal pain episodes. During an abdominal attack, endoscopy may show ascites and/or visceral edema and frequently edema of the intestinal wall [2]. Since intestinal swelling associated with acute HAE attacks could induce pancreatitis, serum amylase and lipase should be monitored, as management of the attack could vary depending on the results.

The therapies currently available for treatment of HAE attacks comprise C1-INH concentrate, hr-C1-INH, icatibant, and ecallantide [1]. As no specific biomarker of this condition has been identified, rapid improvement in symptoms after administration of specific therapy enables us to differentiate between abdominal attacks of HAE and other etiologies.

Although rare, HAE is associated with significant comorbidity, and a history of unnecessary abdominal surgeries is not unusual in abdominal attack of HAE. Health professionals should be aware of the existence of this entity to perform early diagnosis and institute appropriate therapy. Since HAE is a potential cause of acute abdomen (eg, acute pancreatitis), HAE-specific therapy should be considered a therapeutic option.

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### Conflicts of Interest

The authors declare that they have no conflicts of interest.

### Previous Presentations

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