

## Recurrent Abdominal Pain Attacks; Hereditary Angioedema

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**ABSTRACT** Hereditary angioedema (HAE) is an important disease characterized by recurrent episodes of angioedema without urticaria, which most often affects the skin or mucosal tissues of the upper respiratory, genitourinary and gastrointestinal tracts. The angioedema is mostly self-limited and resolves in a few days without treatment, however in some conditions such as upper respiratory involvement, may cause fatal asphyxiation. Gastrointestinal attacks are experienced by a majority of patients with HAE and can be the principal presentation. The diagnosis of hereditary angioedema may be delayed in many cases. Many patients with undiagnosed HAE may undergo inappropriate abdominal surgery. In this study, we are presenting a 14 years-old patient and his mother who are diagnosed with type 1 HAE, predominantly suffering from abdominal pain attacks due to intestinal angioedema. The patient underwent appendectomy and two times diagnostic laparotomy at different times due to unexplained abdominal pain. With this case report we wanted to raise awareness of physicians about HAE.

**Keywords:** Angioedema; hereditary angioedema; C1 inhibitor; abdominal pain

Hereditary angioedema (HAE) is an important disease characterized by recurrent episodes of angioedema without any urticaria, which most often affects the skin or mucosal tissues of the upper respiratory, genitourinary and gastrointestinal tracts. The swelling is mostly self-limiting and resolves in five days without any treatment, however, it may cause fatal asphyxiation in some conditions such as laryngeal involvement.

The angioedema observed in HAE results from excessive production of bradykinin, a potent vasodilatory mediator. Bradykinin is elevated in HEA because of the deficiency or the dysfunction of C1 inhibitor (C1INH). Nevertheless, there are other forms of HAE in which C1INH is normal.<sup>1</sup>

In this study, we are presenting a 14 years-old patient and his mother who were diagnosed with type 1 HAE, predominantly suffering from abdominal pain attacks due to intestinal angioedema.

### CASE REPORT

A 14 years-old male patient has been admitted since he was complaining from abdominal pain. He had been suffering from recurrent severe abdominal pain since he was 10 years old. He had abdominal pain attacks 4-5 times a year. Abdominal pain was accompanied by vomiting, and lasted approximately 2-3 days. The patient underwent appendectomy nine years ago and had diagnostic laparotomy twice at different times due to unexplained abdominal pain. Since nine years old, he experienced a small number of mild swellings upon trauma in a year. Numerous laboratory and imaging tests have been performed by pediatricians and general practitioners for 10 years, but no anomaly has been detected. His parents did not have consanguineous marriage. He and his 2 brothers were not diagnosed with any diseases before. There were no findings in physical examination.

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Peer review under responsibility of Türkiye Klinikleri Journal of Case Reports.

**Received:** 05 Sep 2019

**Received in revised form:** 22 Oct 2019

**Accepted:** 31 Oct 2019

**Available online:** 22 Nov 2019

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There were no significant findings in laboratory tests including complete blood count, serum electrolytes, liver function tests, erythrocyte sedimentation rate, viral serology, stool microscopy, *Helicobacter pylori* antigen stool test, thyroid autoantibodies, and antinuclear antibody test.

There were no significant findings in abdominal ultrasound and abdominal computerized tomography.

The patient was admitted to our clinic with this history. C4 level was tested, and determined to be low (1.4 mg/dl). Afterwards, C1INH level was checked, and it was also determined to be low. The patient was diagnosed with type 1 HAE.

The patient was treated with C1INH concentrate, and abdominal symptoms resolved within five minutes after the infusion.

Over the follow-up, although abdominal pain attacks were decreased in frequency and severity since starting C1INH concentrate prophylaxis, they continued. Therefore, we added tranexamic acid to his medication regimen as recommended by guidelines. During the four-month follow-up period, he didn't experience any abdominal angioedema attack.

Family members were questioned for hereditary angioedema symptoms. Patient's mother has been suffering from the same abdominal pain attacks since she was 8 years old. She only had abdominal pain attacks, there was no skin or upper airway edema. She has been receiving treatment for irritable bowel syndrome for a long time. C4 and C1INH levels were tested, and low levels were detected (C4:0.0 mg/dl, reference interval: 15-50 mg/dl; C1INH: 0.03 g/l, reference interval: 0.15-0.35 g/l). She was diagnosed with type 1 HAE like her son. Danazol treatment was started. She responded to treatment. Abdominal pain was resolved. The medications that she was taking for irritable bowel syndrome were discontinued. She experienced one abdominal angioedema attack in the follow-up, and treated in this acute attack with C1INH concentrate.

Written consent was obtained from the patient and legal representative for the preparation of this case.

## DISCUSSION

HAE has a number of sub-types. Two forms of the disorder arise due to C1INH deficiency or dysfunction (type I and II, respectively). Type 1 HAE can be detected by abnormal C4 and C1INH complement protein levels. Meanwhile, type 2 HAE is diagnosed by abnormal C4 and C1INH function levels. The other types of familial angioedema are characterized by normal C1INH level and normal complement studies. Some patients have identifiable variants in factor XII.<sup>2,3</sup>

Patients with HAE have these complement defects from birth, and generally present with recurrent angioedema in childhood or young adulthood. There is also an acquired form of C1INH deficiency which presents in older patients who do not have a family history of angioedema, and it is associated with underlying disorders or autoantibodies in most cases.

The age of onset for angioedema attacks is variable. Approximately 40 percent of the patients experience their first attack before the age of 5, and 75 percent by age 15, and as a result, it can be said that the disease first presents in childhood or adolescence in the majority of patients.<sup>1,2,4</sup>

Our cases were diagnosed in puberty and adulthood, but their symptoms had started many years ago and were overlooked.

Most often affected anatomical locations of angioedema are characteristically the skin, gastrointestinal tract, upper airway, and genitourinary tract. Attacks involve only one site at a time, or they are experienced as combination attacks, such as cutaneous attacks that spread to involve the larynx.<sup>4,5</sup>

Patients with HAE due to decreased level of C1INH typically present with a history of discrete episodes of nonpruritic, nonpitting angioedema involving the extremities, genitourinary tract, abdomen, face, or oropharynx.<sup>2</sup> Both of our cases have presented with abdominal attacks.

Gastrointestinal attacks are presented as varying degrees of gastrointestinal colic, nausea, vomiting, and diarrhea. Similarly with our cases, gastrointestinal attacks are experienced by a majority of HAE patients, and they can be the principal presentation in one-quarter of the patients.<sup>6</sup>

Fever, peritoneal signs, or elevated white blood cell count are important differential findings, and they are not associated with HAE. However, elevated neutrophils, hypovolemia due to fluid loss, or hemoconcentration have been reported.<sup>3,7</sup> Patients with HAE were found to have an elevated C-reactive protein level at baseline during the asymptomatic period. The C-reactive protein levels increased during attacks, and were more likely to be elevated in abdominal attacks compared to the other anatomical locations.<sup>8</sup>

Gastrointestinal attacks can be difficult to diagnose, and the clinician must determine if the abdominal symptoms are due to angioedema, or to an unrelated condition. Many patients with undiagnosed HAE may undergo inappropriate abdominal surgery as in our case.<sup>9</sup> In some cases, it may be difficult to distinguish abdominal angioedema from the conditions requiring surgery even if the HAE diagnosis is already known.<sup>10</sup> Patients should be questioned and examined carefully due to the clinical similarities between intestinal attacks of angioedema and true surgical emergencies.

HAE typically presents with edema in different parts of the body such as extremities, genitourinary tract, abdomen, face, or oropharynx. Physicians should keep in mind that there may be no visible skin or mucosal edema in some HAE cases. They may present with only intestinal or genitourinary symptoms for many years.

HAE may be considered in unexplained isolated abdominal pain attacks upon excluding other medical conditions in patients, and these patients should be directed to allergy-immunology specialists. With this approach, the patients can be protected from unnecessary surgical procedures and complications due to delayed diagnosis.

#### **Source of Finance**

*During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.*

#### **Conflict of Interest**

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

#### **Authorship Contributions**

*All authors contributed equally while this study preparing.*

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