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Characteristics of patients with C1 esterase inhibitor deficiency: a single center study

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Summary

Hereditary angioedema (HAE) is a primary complement factor deficiency, characterized by recurrent submucosal/subcutaneous swelling episodes. SERPING1 gene defects encoding C1 esterase inhibitor (C1INH) are responsible from the disease.

Fifteen patients with HAE are retrospectively evaluated in this study. All patients (n = 15) had HAE type I, 13 were from the same family, other two from two different families. Median age at onset of symptoms was 7 years (2-20); median age on diagnosis, 12 (0,5-41) and median delay in diagnosis, 3 years (0-33). Clinical symptoms were extremity edema(92,3%), facial edema(46%), abdominal pain (46%), genital edema (46%), and laryngeal edema (23%). Some patients suffered from recurrent abdominal pain, had been empirically given colchicine with familial mediterranean fever (FMF) when they admitted. One presented with bullous skin eruption, soon after developed extremity edema. Both resolved spontaneously after C1INH concentrate therapy. Two females suffered from recurrent genital edema after sexual activity. One patient experienced compartment syndrome-like swelling of extremity after playing football. One patient diagnosed with panic attack due to fear of death by asphyxiation, and was diagnosed with HAE disease. A nonsense mutation in exon 8, a missense mutation in exon 2 in SERPING1 gene was present in Family 1 and another patient (P14) from the other family, respectively. Sporadic autosomal dominant inheritance ratio was 2/3 in the families present in our series.

Patients with HAE presents with a large spectrum of symptoms. In mediterranean countries, patients with abdominal attacks may be misdiagnosed with FMF. Thus, health-care professionals should be alert, and put HAE in the first line of differential diagnoses when the disease symptoms are present. Consequently, morbidity/mortality will decrease with effective treatment options.

Introduction

Hereditary angioedema (HAE) is an autosomal dominant disease that occurs due to the mutations in SERPING1 gene encoding the serine protease C1 esterase inhibitor (C1INH). It is characterized by recurrent episodes of submucosal or subcutaneous swelling, most often affecting skin or mucosal tissues. The more common form, HAE type I, (85% of patients) results from C1INH deficiency and shows low C1INH function, while HAE type II is caused by C1INH dysfunction with normal or elevated C1INH levels (1). In HAE type III, there is no change in C1INH, and the disease includes patients with FXII, plas-

minogen and angiotensin-1 gene mutations, as well as cases with unknown causes.

The diagnosis of HAE is based on clinical history, physical findings during episodes, a family history of angioedema, and analysis of C1INH concentration and activity in plasma. Genetic analysis is also necessary to make a definite diagnosis of HAE. The treatment is based on prevention of the attacks, reduction of morbidity and mortality and improvement in life quality. The gold standard treatment for acute attacks is plasma derived nano-filtered C1INH concentrate. Recombinant C1INH concentrate, icatibant (bradykinin B2 receptor inhibitor) and ecallantide (kallikrein inhibitor) is also used for acute attacks. Attenuated

androgens and plasmins are highly effective despite the side effects and they are the mainstay of the long term prophylaxis. The aim of this study is to investigate the characteristics, clinical and laboratory findings of patients with HAE.

Patients and methods

Patients who were diagnosed with HAE during 2009-2019 period in pediatric immunology department are enrolled into the study. The clinical and laboratory findings retrospectively reviewed from the files of the patients.

The level and the activity of C1INH protein were recorded. The genetic defect was analyzed by the help of primary immunodeficiency diseases (PID) next generation sequencing (NGS) panel (2).

Results

There were totally 15 patients, 13 from the same family (**figure 1 A**). P14 and P15 are from different families. All patients had HAE type I. Demographic, clinical and laboratory characteristics of the patients are given in **table I**. The median age at onset of symptoms was 7 years (2-20). The median age on diagnosis was 12 (0.5-41). The median delay in diagnosis was 3 years (0-33). The most common clinical symptom was extremity edema (92,3%). Facial edema (46%), abdominal pain (46%), genital edema (46%) and laryngeal edema (23%) were the other most frequent symptoms. The proband in Family 1, P1 (38 year-old), first admitted to our clinic with facial edema after trauma. After he was diagnosed with HAE, the pedigree was overviewed for the analysis of the family members with similar complaints. The father of P1, P2 (53 year-old) had recurrent laryngeal edema. P2's brothers P3 and P4, and P4's daughter, P5, had

suffered from recurrent abdominal pain for years. They were given colchicine empirically for recurrent abdominal pain with the possible diagnosis of familial mediterranean fever (FMF). MEFV analysis was performed to P4 and P5, and found to be normal. Upon low C1INH level, he and his daughter were diagnosed as HAE type I respectively. P1's daughters, P6, 9, 10, P1's brother P7 and his son, P1's sister P8 and her children P12 and P13 were diagnosed with HAE type I.

P1, P2, P3, P6, and P7 were suffering from recurrent laryngeal edema. P2 and P3 had recurrent abdominal pain for 25 and 33 years, respectively. P1, P7 and P8 had recurrent peripheral edema. P6,9,10,12, and 13 were diagnosed before symptoms occurred. Despite low C1INH levels, P12 and P13 are asymptomatic. Once P7 presented with bullous skin eruption in the distal part of right upper extremity occurred as an early symptom of angioedema, resolved spontaneously after therapy (**figure 2**). P5 and P8 had suffered recurrent genital edema after sexual activity. A compartment syndrome of right leg developed in P6 after playing football, responded to medical therapy.

Molecular analysis of Family 1 was a previously defined non-sense mutation in SERPING1 gene (c.1450 C > T (p.Gln484Ter) (**figure 1 B**) (3). P14 was diagnosed when she was admitted to hospital with extremity edema at the age of 2,5 years. Low complement C4 and C1INH level was observed. Mutational analysis demonstrated a novel missense mutation in SERPING1 gene by NGS panel (c.5C > T (p.Ala2Val) (**figure 1 A**)). P15 suffered from recurrent skin and laryngeal edema after the age of ten. He admitted to hospital with the complaint of hard breathing and he was diagnosed as panic attack. He was diagnosed as HAE with 9 years delay.

All patients have low serum C1INH and complement C4 levels that compatible with HAE type I. Mean serum levels of C1INH was $7,0 \pm 2,7$ mg/dl (normal range: 15-35 mg/dl) ranging from

Figure 1 - (A) Pedigree of the Family 1. **(B)** The position of the genetic defects.

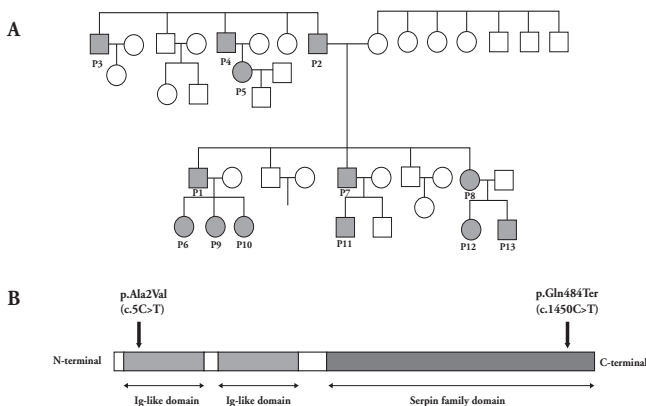


Figure 2 - Bullous skin eruption in the distal part of right upper extremity of P6, occurred one time before extremity angioedema.



Table I - Demographic, clinical and laboratory features of patients.

Patient No	Gender (M/F)	Age	Age at onset of symptoms	Age at diagnosis	Sites involved during angioedema attacks	Treatment	Severity of disease	C4 (mg/dl) (16-38 mg/dl)	C1INH (mg/dl) (15-35 mg/dl)
P1	M	39	20	23	Extremities, abdominal, genital	Danazol	Mild	5	3,5
P2	M	60	8	41	Extremities, abdominal	C1INH concentrate (during attacks)	Mild	4,7	2,8
P3	M	51	7	32	Extremities, facial, laryngeal, genital	C1INH concentrate (during attacks)	Severe	9,2	7,2
P4	M	53	10	34	Extremities, facial, genital		Mild	3,2	8,8
P5	F	25	7	12	Extremities, facial, abdominal, genital	C1INH concentrate (during attacks)	Severe	4,6	10,2
P6	F	11	5	1	Extremities, abdominal	Tranexamic acid	Mild	5,5	4,3
P7	M	41	10	22	Extremities	Danazol	Mild	5,3	4,9
P8	F	32	18	20	Extremities, facial, laryngeal	Tranexamic acid	Mild	3,4	5,9
P9	F	10	7	2	Abdominal	C1INH concentrate (during attacks)	Moderate	10	6,5
P10	F	3	2	0,5	Ekstremities	C1INH concentrate (during attacks)	Mild	5,6	11
P11	M	10	5	5	Extremities, facial	Danazol	Mild	8,7	8,5
P12	M	1,5	No symptoms developed	1			Asymptomatic	3,4	7,4
P13	F	5	No symptoms developed	2			Asymptomatic	3,8	6,9
P14	F	14	2,5	2,5	Extremities, abdominal		Moderate	5,6	5,3
P15	M	20	10	19	Extremities, laryngeal, genital		Mild	6	12,4

2,8 to 12,4. Because of having multiple attacks, danazol was started to P1 and P7, and tranexamic acid was started to P6 and P7. No patients had angioedema attacks after prophylaxis treatment. P4 refused the treatment. P2, P3, P5, P9 and P10 receive C1INH concentrate when attacks occur, and refused to receive long term prophylaxis treatment due to side effects. P12 and P13 are asymptomatic.

Discussion

HAE is characterized by recurrent episodes of submucosal or subcutaneous swelling, most often affecting skin or mucosal tissues and developing after trauma. In some cases clapping of hands, prolonged sitting on a hard surface may cause an attack. In this study angioedema occurred in 13 out of 15 patients. P6 was suffered from compartment syndrome of the leg and improved with medical therapy, however in some cases fasciotomy might be

necessary (4). Bullous skin eruption, which was reported before in HAE (5), also developed once in P6 before extremity angioedema. As it resolves spontaneously, there is no need for diagnostic workup and treatment. Other rare clinical presentations were previously reported such as transient ischemic attack symptoms due to local cerebral edema and reduced cerebral perfusion, recurrent episodes of pancreatitis due to pancreatic edema and pancreatic duct obstruction, hypovolemic shock due to abdominal ascites, tetany due to hyperventilation during the abdominal pain, hemorrhagic diarrhea due to massive bowel edema, hematuria due to submucosal edema of vesical walls (6-8).

HAE is a rare disease, and most of the patients are diagnosed years after onset of symptoms. P4 and his daughter were first misdiagnosed as having FMF and administered colchicine treatment for years. They didn't benefit from treatment as expected. The transient edema of the bowel wall may cause gastrointestinal pseudoobstruction, and is generally characterized with ab-

dominal pain, vomiting and diarrhea. Bork *et al.* reported that 28% of patients presented with abdominal attacks long before they noted swelling of their skin (7). For this reason, abdominal angioedema without skin swelling may be misdiagnosed as FMF, in FMF endemic countries, like Turkey. FMF is an autosomal recessive disorder characterized with recurrent fever, serositis, erysipelas like skin rash in the lower extremities and elevated acute phase reactants. Most of the patients have biallelic MEFV gene mutation, and achieve complete remission with colchicine (9). Thus, the physicians should suspect about the diagnosis of HAE, unless the patients diagnosed previously with FMF respond to colchicine therapy.

P15 admitted to emergency department with the complaint of dyspnea, he was misdiagnosed as panic attack and received psychiatric treatment. Laryngeal attacks not only cause fear of death by asphyxiation, but also lead to depression and anxiety. On the contrary, depression and anxiety may trigger initiation of attacks. Therefore HAE should be considered as a disease having a psychosocial dimension. Misdiagnoses of HAE according to symptoms are shown in **table II** (10, 11).

In this study, the laboratory workup of all patients were consistent with HAE type I, low C4, C1INH level, and C1INH function were recorded. After the proband was diagnosed, the other 13 patient were diagnosed subsequently. Thus, five family members had a chance of having diagnosis before the onset of symptoms due to the autosomal dominant inheritance pattern of the disease.

A nonsense mutation and a missense mutation in SERPING1 gene were found by the help of NGS in the first family and P14, respectively. Previously Kesim *et al.* reported an initial codon change in exon 2 and a nonsense mutation and 9-bp deletion in exon 8 (12). Although first family has the same mutation, the onset of the symptoms, the tissues affected (skin, mucosa, larynx, abdomen, extremities) and the severity of the disease among family members are different, showing that there is no genotype-phenotype relationship. P14 and P15 were thought to be sporadic cases as there was no family history. The prevalence of the HAE is known to be about 0,2-1/10000 (12, 13). However, the ratio of sporadic and AD inherited cases to all cases is unknown. Previously Pappalardo suggested that 45 out of 137 patients diagnosed with HAE in his series were sporadic (14). According to this study, 2/3 of the cases have AD inheritance pattern, and 1/3 of the cases are sporadic. This ratio was 1/3 in our series. Among three families, AD inheritance was present in Family 1, and other two patients were sporadic cases. So, genetic counseling and information about the preimplantation genetic study should be offered to cases, except sporadic ones. As soon as patients are diagnosed with HAE, they have access to effective treatment options. Consequently, morbidity and mortality decreases.

Table II - Misdiagnoses in HAE according to symptoms (10, 11).

Symptoms	Differential diagnoses
Laryngeal edema	Anaphylaxis Tonsillitis Panic attack
Lip edema	Cheilitis granulomatosa Melkersson-Rosenthal syndrome
Facial edema	Superior vena cava syndrome Autoimmune conditions (SLE, polymyositis, dermatomyositis, Sjogren syndrome) Allergic contact dermatitis
Pretibial mixedema	Thyroid disorders
Extremity edema	Autoimmune conditions (SLE, polymyositis, dermatomyositis, Sjogren syndrome) Allergic contact dermatitis Compartment syndrome
Abdominal edema	Familial mediterranean fever Appendicitis GERD Irritable bowel disease Peptic ulcer Endometriosis
Genital edema	Orchitis

GERD, gastroesophageal reflux disease; SLE, systemic lupus erythematosus.

The gold standard treatment for acute attacks is plasma derived nanofiltered C1NH concentrate. Recombinant C1INH concentrate, icatibant (bradykinin B2 receptor inhibitor) and ecallantide (kallikrein inhibitor) are also used for acute attacks (15). Because of being recently available in Turkey, we didn't have opportunity to use these therapies for the treatment of acute attacks. Anabolic steroids are the mainstay of HAE prophylactic treatment of, however side effects like hepatoma and virilization in women may cause discontinuation of therapy. Additionally, the risk of growth retardation restricts its use in children. Plasmin inhibitors are less effective than anabolic steroids, but are preferred in children and women in longterm prophylaxis after the evaluation for the risk of thrombosis. Some of our patients refused the prophylaxis of danazol due to concerns about the side effects, such as hepatic toxicity and hepatic disease. They may be preferred in adult male patients. Regular control for liver disease is needed. However, others benefited from danazol and tranexamic acid used for long term prophylaxis, and after treatment no attacks and side effects were recorded. Other long term prophylaxis options, such as lanadelumab is not available in Turkey and

C1INH concentrate for long term prophylaxis treatment is not cost effective. Fresh frozen plasma is safe and effective for acute exacerbations of HAE, and can be used when C1INH concentrate can not be obtained (15). However improvement with FFP is slower. Although we used FFP with success, Nzeako *et al.* suggested that tissue swelling may increase with FFP as it involves other complement factors and kinins (16).

Conclusions

The diagnosis of HAE is based on clinical history, physical findings during episodes, a family history of angioedema, and analysis of C1INH concentration and activity in plasma. Anabolic steroids and plasmin inhibitors are effective for long term prophylaxis, but require close monitoring for side effects. There is a need to raise awareness of HAE among clinicians as the patients may be misdiagnosed as FME, or panic attack. The health care professionals should consider that laryngeal attacks not only cause life threatening asphyxiation, but also have a psychosocial dimension. Genetic counseling and preimplantation genetic testing should be offered to patients except sporadic ones.

Author's contributions

Deniz Çağdaş, İlhan Tezcan and Elif Soyak Aytekin contributed to follow-up of patients. Elif Soyak Aytekin involved in collecting data and samples. Elif Soyak Aytekin and Deniz Çağdaş contributed in writing the manuscript. Elif Soyak Aytekin, Deniz Çağdaş, and İlhan Tezcan involved in the analysis and interpretation of the findings. Cagman Tan did the molecular genetic studies. Deniz Çağdaş and İlhan Tezcan reviewed the manuscript. All the authors read and approved the final draft of this manuscript.

Conflict of interests

The authors declare that they have no conflict of interests.

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