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Original Article

Symptoms, clinical profile and management of pediatric hereditary angioedema: A single-centre experience

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ABSTRACT

Objective: Hereditary Angioedema (HAE) is a rare but life-threatening disease. It is aimed to present data on the clinical characteristics of our pediatric patients with HAE, whose symptoms usually start in childhood, but the delay in diagnosis is still a serious problem.

Method: Clinical and laboratory findings, family histories, and clinical characteristics of 14 patients with HAE diagnosed in our clinic between 1998-2019 were analyzed.

Results: Half of our patients diagnosed with HAE were girls, 78.5% of them were diagnosed with HAE type 1, and 21.4% were HAE type 2. All our patients had a family history, and 10 of them were diagnosed based on their family history. The mean age at diagnosis was 9.7±4.4 years and the mean age at the onset of the first angioedema symptom was 5.3±1.8 years. The delay in diagnosis was 4.4±4.1 years. The swollen areas included extremities (78.5%), abdominal attacks (71.4%), facial edema (57.1%), and laryngeal edema (21.4%). C4 levels were low in all patients. The mean C1 esterase inhibitor level was 0.69±0.08 g/l for HAE type 2 and 0.08±0.04 g/l for HAE type 1. The mean C1 esterase inhibitor functional activity level was 18.6±10.4% in HAE type 2.

Conclusion: Early diagnosis of the disease is critical for reducing morbidity and mortality due to attacks. There are very few studies in Türkiye that focus exclusively on pediatric HAE patients. Sharing our patients' clinical findings and treatment plans for this rare disease is crucial for bringing the disease to light and raising awareness.

Keywords: Hereditary angioedema, pediatric, clinical trial

INTRODUCTION

Hereditary Angioedema (HAE) is an autosomal dominant, life-threatening disease characterized by recurrent swelling of the skin and mucous membranes without pruritus or urticaria.[1] Although the real prevalence of HAE is unknown, the probable prevalence calculated by dividing the number of patients diagnosed in some European countries by the general population is 1/10000-1/50000.[2] Attacks can start at any age, but the first symptom usually appears in childhood and adolescence.

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In a large series of HAE patients, the first episode occurs in approximately 90% of patients by the age of 20.[3] HAE has been reported in both genders in all races.[4]

The main pathophysiological mechanism in HAE is the level or functional deficiency of the C1-inhibitor (C1-INH) glycoprotein. This protein has an inhibitory function in the plasma contact system, kallikrein-kinin system, coagulation system, and complement system.[5] Bradykinin is the primary mediator responsible for the clinical findings in HAE.[6] As a result of the numerical and functional deficiency of C1-INH protein, inhibition of the contact system cannot be achieved, and bradykinin formation increases. The bradykinin B2 receptor is constitutively expressed in vascular endothelial tissues, activation of this receptor loosens adherent junctions between endothelial cells that limit vascular permeability, and subsequently, increase pore sizes between endothelial cells by contraction of the intra-endothelial actin cytoskeleton resulting in angioedema.[7] The SERPING-1 gene, which codes for C1-INH, is found on chromosome 11.[8]

Three HAE variants have been identified: Type 1 HAE is the most common form of HAE associated with C1-INH deficiency, accounting for up to 85% of cases. The expression of the C1-INH protein is low as a result of mutations in the relevant gene, and its function is inadequate. Type 2 HAE is defined as HAE caused by C1-INH dysfunction. Although the C1-INH level is normal in this group, which accounts for 15% of cases, the functional activity of the protein is low.[9] The third group consists of HAE cases with normal C1-INH (nC1-INH-HAE), whose clinical and treatment responses are compatible with HAE despite normal C1-INH levels and function, and was first introduced in 2000.[7]

In this study, we aimed to shed light on the childhood data of this rare disease by analyzing the demographic and clinical data of the HAE patients followed in our clinic.

MATERIAL AND METHODS

Between 1998 and 2019, all patients with HAE diagnosed in Pediatric Immunology Clinic in Dr Behcet Uz Children's Education and Research Hospital were evaluated. The study excluded patients with ACEI/NSAI-related (Angiotensin-converting enzyme inhibitors/non-steroidal anti-inflammatory drugs) angioedema, angioedema associated with chronic spontaneous urticaria, and acquired angioedema.

Clinical and demographic data of the patients were gathered retrospectively from hospital records and out-patients' records. Age, gender, disease type, family history, consanguinity, blood count at admission, biochemical and immunological examinations, treatments, frequency of angioedema attacks, localization of angioedema, family history of angioedema, age of symptom onset, age at diagnosis, and delay in diagnosis were evaluated. The delay in diagnosis was defined as the time between the onset of the symptoms and the patient's diagnosis.

Immunonephelometry (Siemens, Marburg, Germany) was used to determine the levels of C4 (reference range: 10–40 mg/dL) and C1-INH antigen (reference range: 21–39 mg/dL), and a chromogenic assay (Berichrom Siemens, Marburg, Germany) was used to determine the levels of functional C1-INH (reference range: 70%–130%).

The data were analyzed using SPSS18 (Statistical Package for Social Sciences). Descriptive analysis was used, and categorical variables were expressed in numbers and percentages. The chi-squared test was used for comparisons between groups of qualitative variables. The Mann-Whitney U test, which is a nonparametric hypothesis, was used to compare two independent groups. A p-value <0.05 was considered statistically significant.

Study design and ethical approval

This retrospective cross-sectional study was approved by SBU Izmir Dr. Behcet Uz Education and Research Hospital Clinical Research Ethics Committee in 2021 (Decision No:2021/15-15).

RESULTS

Fourteen patients who were followed up in our clinic with the diagnosis of HAE were included in the study (Table 1). Fifty percent of them were female. The mean age at diagnosis was 9.7±4.4 years (min:3, max:10). The mean age at the onset of the first angioedema symptom was 5.3±1.8 years (min:1, max:9.1). The time between the onset of symptoms and the patient's diagnosis is referred to as the delay in diagnosis. The mean delay in diagnosis was 4.4±4.1 years for our patients (min:0, max:13.7). Three of our patients were diagnosed with HAE type 2, and the others with HAE type 1. There was no patient diagnosed with HAE type 3 among our patients. The results of the detailed demographic, clinical, and laboratory analysis are shown in Table 2. The frequency of the attacks varied from almost one week to 1-2 times per year in each patient. When the patients were evaluated based on the swelling patterns, the number of patients and areas of swellings were as follows: extremities in 11 (78.5%); abdominal attacks in 10 (71.4%); facial edema in 8 (57.1%); and laryngeal edema in 3 (21.4%) patients. One patient also had genital edema. All the patients had relatives who had

Table 1. Clinical and demographic characteristics of our patients diagnosed with HAE		
	n (%)	**(min-max)**
Gender		
Female	7 (50%)	
Male	7 (50%)	
Mean diagnosis age (year)	9.7±4.4	(3-10)
Mean first symptom age (year)	5.3±1.8	(1-9.1)
Delay between first symptoms and diagnosis (year)	4.4±4.1	(0-13.7)
Family history	14 (100%)	
Diagnosis based on family history	10 (71.4%)	
Consanguinity between parents	1 (7.1%)	
Swelling patterns		
Laryngeal	3 (21.4%)	
Facial	8 (57.1%)	
Abdominal	10 (71.4%)	
Extremities	11 (78.5%)	
Type of HAE		
HAE Type 1	11 (78.5%)	
HAE Type 2	3 (21.4)	
Mean C4 level (mg/dl)	6.6	
Mean C1 esterase inhibitor level (g/l)		
HAE Type 1	0.08	(0.03-0.15)
HAE Type 2	0.69	(0.60-0.76)
Mean C1 esterase inhibitor functional activity level in HAE Type 2 (%)	18.6	(7-27)
Number of patients who underwent acute attack treatment		
C1 inh (Berinert®/Cetor®/Cinryze®)	8 (57.1%)	
Ecallantide (Kalbitor®)	3 (21.4%)	
Ikatibant (Firazyr®/Icatin®/Heact®)	7 (50%)	
Number of patients who received short-term prophylaxis		
C1 inh (Cetor®/Cinryze®)	2 (14.2%)	
Number of patients who received long-term prophylaxis before		
Tranexamic acid (Transamin®)	7 (50%)	
Androgens (Danazol®/Stanazolol®)	4 (28.5%)	
C1 inh (Cetor®/Cinryze®)	2 (14.2%)	

either been diagnosed with HAE or had similar complaints, as determined after the detailed patient interviews. Nine patients were diagnosed based on one or more cases of HAE in their family, and the appearance of symptoms in the patient. One patient with no symptoms was diagnosed using scanning after the diagnosis of her siblings. Thus, a total of ten patients were diagnosed based on their family history (71.4%).

Table 2. The results of the detailed demographic, clinical and laboratory analysis

	Gender	Type of HAE	Symptom onset age (year)	Diagnosis age (year)	Delay on diagnosis (year)	Diagnosis based on family history	Average attacks per year	Involved sites during the attacks				C4 level (mg/dl)	C1 esterase inhibitor level (g/l)	C1 esterase inhibitory functional activity (%)	Genetic Analysis	Family History
								Larynx	Face	Abdomen	Extremity					
P1	F	Type 2	5	13	8	No	10		+		+	5.8	0.6	7		The grandmother's undiagnosed swellings+ (sudden death)
P2	F	Type 2	1	3	2	No	12		+	+	+	6.8	0.76	22		Father's similar symptoms +
P3	M	Type 1	6	14	8	Yes	*			+		6.9	0.06	-		Father, uncle, aunt, cousins with diagnosis HAE
P4	F	Type 1	-	12	0	Yes	*					6.9	0.08	-		Sibling with diagnosis HAE (diagnosis by scanning)
P5	F	Type 1	6	14	8.5	Yes	50		+	+	+	5.9	0.05	7		Mother, grandmother, aunt with diagnosis HAE +
P6	F	Type 1	7	14.5	7	Yes	12		+	+	+	7.9	0.15	-		Mother's similar symptoms +
P7	M	Type 1	5	12	7.2	Yes	12	+	+	+	+	6.6	0.03	-		Father, grandmother, paternal grandmother, uncle with diagnosis HAE
P8	M	Type 2	4	4.5	1	Yes	1				+	6.6	0.72	27	c.1396C>T	Father's similar symptoms +
P9	M	Type 1	5	6.9	2	Yes	3	+	+	+		6.2	0.13	-	c.431delA	Father with diagnosis HAE+ 1 uncle (53 years), 1aunt (33 years) Larynx edema (death)
P10	M	Type 1	4	17.7	13.7	Yes	6			+	+	6.6	0.08	-		Father, grandmother, paternal grandmother, uncle with diagnosis HAE
P11	F	Type 1	4	4.6	1	No	50			+	+	6.8	0.05	14.3		The grandfather's undiagnosed swellings+ (sudden death), Sibling with diagnosis HAE (diagnosis by scanning)
P12	F	Type 1	9.1	10	1	No	40	+	+	+	+	5.5	0.08	8.7		The grandfather's undiagnosed swellings+ (sudden death)
P13	M	Type 1	5	5	0	Yes	3				+	7.3	0.04	-		Father's similar symptoms +
P14	M	Type 1	5	8	3	Yes	36		+	+	+	7.1	0.14	30	c.1397G>T	Mother with diagnosis HAE, mother's cousin (20 year) sudden death, The grandfather's undiagnosed swellings+ (sudden death

P3 and P4; P11 and P12 are siblings. * Average attacks per year are unknown because because patients were not followed up.

C4 levels were low in all patients. The mean C4 level was 6.6±0.6 mg/dl. The mean C1 esterase inhibitor level was 0.69±0.08 g/l in HAE type 2 patients and 0.08±0.04 g/l in HAE type 1 patients. The mean C1 esterase inhibitor functional activity level in HAE type 2 patients was 18.6±10.4%.

When HAE type 1 and HAE type 2 were compared according to the age at symptom onset, age at diagnosis, delay in diagnosis, levels of C4, and the amounts of functional C1-INH, no significant difference was found between the two groups. When the same criteria were analyzed by gender, there was no significant difference between the two genders. Girls experienced statistically considerably more angioedema attacks annually than boys (p=0.04).

Eight of the patients (57.1%) underwent acute attack treatment with C1-INH, 3 (21.4%) with Ecallantide, and 7 (%50) with Icatibant. Short-term prophylaxis with C1-INH was performed for 2 patients. Tranexamic acid was used in 7 patients (50%), androgens were used in 4 patients (28.5%), and C1-INH in 2 patients (14.2%) for long-term prophylaxis. Androgen prophylaxis was used only in patients whose pubertal stage was Tanner stage 4. Tranexamic acid was preferred when long-term prophylaxis was required in the younger age group.

Genetic analysis was performed in 3 patients. Genetic analysis was not planned for the other patients because they were diagnosed by clinical laboratory results and family history. Patients 1 and 2 had intermittent urticaria accompanied by angioedema. Patient 5 (P5) also had the MEFV R202Q mutation and patient 9 (P9) was also diagnosed with Marfan syndrome.

DISCUSSION

Although HAE attacks can occur at any age, it usually manifests in childhood. In our study, the mean age of symptom onset was 5.3±1.8 years. Except for patient 4 (P4), the first symptom appeared in the first decade. P4 was a screening case diagnosed after her sibling, and she had no symptoms until the time of diagnosis. The median age of symptom onset in a study of pediatric HAE patients in Cincinnati was 5.7 years, which was similar to our findings.[10] The median age of first symptom onset was 12 years in a European study that included patients with HAE type 1 and 2[11] and in a previous pilot study in Türkiye, the mean age of onset of angioedema was found to be 12.5±9.2 years.[12] Symptom onset was under 5 years for 4 patients in our study. Even though it is a hereditary mutation, it is uncommon in infancy and the neonatal period. The first attack, however, was seen in a 4-week-old baby, according to reports.[13]

Suspicion of the illness is the key to the diagnosis of HAE. Mortality from exacerbations is 24 times higher in undiagnosed patients than in diagnosed patients.[14]

In studies, the term “diagnostic delay” refers to the period between the onset of symptoms and the patient’s diagnosis. In our study, the median age at diagnosis was 10.9 years. In our study, the delay in diagnosis was 4.4±4.1 years, which is much lower than the value reported in the literature. The delay in diagnosis, which has been found to range from 8.5 to 16.5 years in recent studies, is still quite long and is not at an acceptable level, even though it has been claimed that this period has shortened recently compared to previous years.[15] In the TURHAPS study conducted in Türkiye, the interval between the onset of symptoms and diagnosis was determined as 26±14.4 years.[12] In the European study, the median age at diagnosis was 24.3 years, and the median delay in diagnosis was 8.5 years in type 1 and type 2 HAE patients.[11] According to this study, the diagnostic delay varied significantly between countries, ranging from 2.0 years (Germany) to 15.0 years (Italy).[11] The difference in diagnostic delay between countries, however, was not statistically significant. When the literature was reviewed, it was stated that the median delay in the diagnosis was 3 years, which was close to our study, according to the Hungarian experience.[16]

Although 20% of cases may occur as a result of sporadic mutations[17], there are cases with similar clinical findings or a family history of HAE when questioned in detail, owing to the autosomal dominant inheritance pattern. Ten of our patients (74.1%) were diagnosed based on the family history of an individual with HAE and when questioned in detail, it was learned that all patients had individuals with HAE or similar symptoms in their families. The rate of patients diagnosed based on family history was 73% in a Hungarian study, similar to our study.[16]

The frequency and severity of HAE symptoms vary from person to person and may even differ between different members of the same family. Extremity edema (90%) and abdominal pain (80-90%) are defined as the most common findings in studies[18], and as in our study, patients most frequently reported experiencing extremity swelling (78.5%) and abdominal attacks (71.4%). The majority of abdominal attacks do not appear to be associated with concurrent skin edema.[13] This situation directs the focus on more common etiological reasons such as surgical causes such as appendicitis, or other causes such as FMF, which is very common in Türkiye, and causing the diagnosis of HAE to be delayed. However, in addition to the diagnosis of HAE, one of our patients (patient 5) had a genetic mutation related to FMF and had been treated with colchicine for several years. Laryngeal edema is

the most detrimental and life-threatening attack. In an adult study evaluating 55 patients with HAE, laryngeal attacks were reported in 19 patients (34.5%).[19] If untreated, the risk of death from airway obstruction is estimated to be 30%.[13] Additionally, 3 of our patients (21.4%) had laryngeal attacks.

HAE is classically defined as an angioedema attack without urticaria. This is a crucial distinction from histaminergic angioedema in terms of clinical presentation. Urticaria is very rare, even though erythema marginatum may occasionally be present in patients as a prodromal finding prior to an attack. Intermittent urticaria, on the other hand, was present in two of our patients. Recurrent urticaria was reported in 7.3% (n = 3) of patients in the HAE group in a study comparing the clinical characteristics of hereditary angioedema and histaminergic angioedema.[20] In the foreground, this was thought to be an incidental histaminergic urticaria.

A study reported that the gender of pediatric patients changed the clinical presentation of the disease but there was no significant difference between the genders in terms of the age of onset of the first symptoms, similar to our study.[21] According to this study, HAE attacks in places other than genitals were reported more frequently in girls than in boys.[21]

The C4 (complement 4) level is the first laboratory parameter to be examined in suspected cases. The diagnosis of type 1 and type 2 HAE is ruled out by a normal C4 level during attacks, despite the fact that it may be normal in a very small percentage of cases (2%) between attacks.[1] As a result, a screening test for type 1 and type 2 HAE can be performed by measuring the C4 level during an attack. In our study, it was found that all the patients had low C4 levels.

Genetic analysis is not mandatory to diagnose HAE type 1 and type 2. The diagnosis can be made by evaluating the C1 esterase inhibitor levels and functional activity in the presence of clinical findings. If necessary, the diagnosis can be supported by genetic analysis. HAE type 1 and type 2 are associated with mutations in the SERPING1 gene. Mutations in the SERPING1 gene were identified in 3 of our patients. In HAE type 3, the diagnosis can only be made by demonstrating the mutation with genetic analysis in patients with clinical findings of HAE, although the C1 esterase level and functional activity are at normal levels.

Since HAE patients were evaluated over a period of 20 years, the type of drugs used in the treatment of acute attacks and prophylaxis varied according to their availability in our country, Türkiye. For the treatment of acute attacks, 57.1% of the patients received C1-INH concentrate, 50% Icatibant, and 21.4% Ecallantide. Two patients received C1-INH concentrate as short-term prophylaxis prior to the intervention. Tranexamic acid was used in 50% of the patients for long-term prophylaxis. Androgens were used in 4 (28.5%) patients in the post-pubertal period. C1-INH concentrate was preferred for long-term prophylaxis in 2 patients.

CONCLUSION

Early diagnosis and rapid treatment of this disease, which is lifesaving, is the most important step of the disease. The possibility of HAE should be considered if a patient has a family history of similar symptoms, experienced the onset of symptoms during childhood or adolescence, suffers from recurrent and painful abdominal attacks, generally lacks urticaria, exhibits accompanying prodromal symptoms, and has angioedema that does not respond to antihistamine, steroid, or adrenaline treatments. The delay in diagnosis between the onset of symptoms and the diagnosis of patients is still quite long in recent studies. Therefore, the awareness of physicians and patients with HAE about this disease should be increased.

Ethical approval

This study has been approved by the İzmir Dr. Behçet Uz Education and Research Hospital Clinical Research Ethics Committee (approval date 07/10/2021, number 2021/15-15). Written informed consent was obtained from the participants.

Author contribution

Concept: SÖB, FG, NG; Design: SÖB, FG, NG; Data Collection or Processing: SÖB, ÖA, İT, İAH, MSK, FCC, ÖS, CŞK, NG, FG; Analysis or Interpretation: SÖB, FG, NG; Literature Search: SÖB, ÖA, İT, İAH, MSK, FCC, ÖS, CŞK, NG, FG; Writing: SÖB, FG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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