Report on the First Survey of Iranian Patients with Hereditary Angioedema

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ABSTRACT

Background: Hereditary angioedema (HAE) is a rare autosomal dominant primary immunodeficiency with complement system defect characterized by recurrent episodes of angioedema involving the skin or mucosa of the upper respiratory and gastrointestinal tracts. **Objective:** To characterize the clinical and laboratory data of hereditary angioedema in Iran. **Methods:** Patients with probable diagnosis of angioedema were enrolled in this study. Demographic and clinical data were documented in the designed questionnaire including history of attacks, triggering factors and laboratory data such as C4, C1 esterase inhibitor level and function. **Results:** Among 63 patients who were clinically suspicious for angioedema (23 males and 40 females), 8 cases (12.7%) were diagnosed with HAE. Among these 8 HAE patients, 3 were diagnosed with HAE type 1 and five patients were diagnosed with HAE type 2. The mean ages of HAE type 1 and type 2 patients were 25.6 ± 13.5 and 22.4 ± 12.32 years. The mean age of onset in HAE type 1 group was 8 ± 5 years and in HAE type 2 group was 18.8 ± 11.84 years. The mean diagnosis delay was 17.6 years in HAE type 1 patients and 2.6 years in HAE type 2. The most common clinical manifestation was facial swelling presented in all HAE patients followed by swelling of extremities which was present in 7 patients with HAE. **Conclusion:** The clinical criteria of the Iranian patients with HAE were consistent with the known clinical patterns of the disease.

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INTRODUCTION

Angioedema is characterized by localized swelling that is generally asymmetric. This complication results from increased vascular permeability with leakage of plasma which involves mucosal layers and subcutaneous tissues. However in the respiratory tract, it can cause potentially life-threatening distress leading to upper airway constriction or obstruction or even asphyxiation (1-3).

Angioedema is classified into the following causative groups: hereditary angioedema (HAE), acquired angioedema (AAE), allergic angioedema, ACE inhibitor induced angioedema and chronic idiopathic angioedema (4). HAE is a known primary immunodeficiency with complement system defect. There are three major forms of HAE including; Type 1 is HAE due to decreased level of C1 esterase inhibitor (C1INH) and type 2 results from dysfunction of C1INH protein by normal or elevated protein levels (5-8). Different mutations in SERPING1 gene which codes for C1INH are responsible for both type1 and 2, in which for 85% result in HAE-1 and 15% result in HAE type 2 (9). Type-3 of HAE is presented with normal level and function of C1INH especially in women and is associated with mutation of the *FXII* gene (11-14). It has been estimated that prevalence of HAE is 1 case per 50,000 persons with reported ranges from 1: 10,000 to 1: 150,000 (2).

Attacks of angioedema are frequently precipitated by minor trauma and stress. The attacks may also be triggered by surgery, invasive medical procedures or medications. However, many episodes occur without any definite stimulus (10-12). Although symptoms of HAE often begin in early childhood and persist throughout the life diagnosis is frequently delayed because of extremely low awareness about this condition leading to mismanagement of patients (13).

Since no study has been conducted on angioedema in Iran, there are no data available about the clinical properties of these patients in our country. The aim of this study is to get more information about the clinical manifestation and triggering factors of hereditary angioedema in Iran.

MATERIALS AND METHODS

Patients. The current study was performed at the Children's Medical Center Hospital, Pediatrics Center of Excellence in Tehran, Iran affiliated with the Tehran University of Medical Sciences between the March, 2010 and the March, 2013. Patients with clinical manifestations of HAE such as recurrent swelling of skin of face or extremities and submucosal tissues (without urticaria) associated with pain syndromes, nausea, vomiting, diarrhea and positive family history of angioedema (14) referred to the immunology and dermatology clinic and enrolled in this hospital-based case-series study. Then laboratory evaluation was performed and diagnosis of HAE was established using International Consensus Algorithm for HAE (14),i,e., in the presence of decreased serum C4 and C1INH antigenic proteins, early age of onset (<20 years) and positive family history of angioedema, the diagnosis is compatible with HAE type 1. If serum C4 and C1INH were decreased with no family history and later onset of symptoms (age over 40), then acquired angioedema was possible therefore we tested serum C1q level to differentiate HAE from AAE. If C1q revealed normal it was also compatible with HAE

type 1. If C1INH functional activity was low with normal or elevated C1-INH antigenic protein and normal C1q, this was compatible with HAE type 2.

For ethical considerations, patients' names were replaced with codes in the database. Moreover, written informed consents were obtained from the adult patients and children's parent(s) or their legal guardians after explaining the process of the study. This study was reviewed and approved by research ethics committee of Tehran University of Medical Sciences.

Methods. Demographic and clinical data were documented in the designed questionnaire. History of attacks and special triggering factors were also recorded including minor trauma, stress, infection, menstruation, pregnancy, alcohol consumption, change in temperature, exercise, and the use of drugs or contraceptives. Physical examination was performed for all patients by a trained specialist. Laboratory tests were performed in all of the cases to determine different subtypes of angioedema and to identify any other co-morbidity as follows: C3, C4, CH50, C1INH level and function, immunoglobulin levels and erythrocyte sedimentation rate. C1q level was also measured if the patients had decreased level of C1INH and C4 without family history of angioedema or late age of onset. Complement laboratory tests were performed when the patient did not receive treatment or the treatment was delayed until next attack because drugs could change the results. Immunoglobulins, C3 and C4 were measured by an immunoturbidimetric assay. C1 inhibitor and C1q level were assayed by nephelometry using a commercial kit (binding site) and functional assay of C1 inhibitor was performed using the Enzyme-linked immunosorbent (ELISA) kit form Quidel (San Diego, USA). The diagnosis of HAE was made according to the recently published international consensus algorithm for the diagnosis, therapy and management of this disease (14).

Statistical Analysis. Statistical analysis was performed using a commercially available software package (SPSS Statistics 17.0, SPSS, Chicago, Illinois). One-sample Kolmogrov-Smirnov test estimated whether data were normally distributed. Parametric and nonparametric analyses were performed based on the finding of this evaluation. A p value of 0.05 or less was considered statistically significant in our study.

RESULTS

Patients' Characteristics. A total number of 63 cases (23 males and 40 females), fulfilled the clinical diagnostic criteria of angioedema and were enrolled in the current study. Male to female ratio was 0.57. The mean age of the patients at the time of study was 26.5 ± 14.4 years.

Out of 63 cases, 8 cases (12.7%) were diagnosed with HAE. Among these 8 HAE patients, 3 were diagnosed with HAE type 1 and they were two female and one male. Five patients were diagnosed with HAE type 2, one male and four females. The mean age of HAE type 1 patients was 25.6 ± 13.5 and 22.4 ± 12.32 years for type 2. The mean age of onset in HAE type 1 was 8 ± 5 years and in type 2 HAE was 18.8 ± 11.8. The mean diagnosis delay in HAE type 1 and type 2 patients were 17.6 and 2.6 years, respectively. Family history was present in two HAE type1 and two HAE type 2 patients.

Table 1. Demographic, clinical and laboratory data of HAE patients.

Code	G	Age (y)	AOO (y)	FH	DD (y)	MCM	C4 Level (mg/dl)	C1INH Level (mg/dl)	C1INH Function	C1q (mg/dl)	Dx
1	M	24	3	+	20	Swelling of face and extremities	8	12	Not indicated	NM	HAE 1
2	F	40	8	+	32	Swelling of face and extremities	0.8	0.44	Not indicated	NM	HAE 1
3	F	13	13	_	1	Swelling of face and extremities	8	0.08	Not indicated	NM	HAE 1
4	M	3	1	+	1	Swelling of face	25	29	Decreased	NM	HAE 2
5	F	23	21	_	1	Swelling of face and extremities	8	27	Decreased	230	HAE 2
6	F	36	34	+	0	Swelling of face and extremities	7	14	Decreased	NM	HAE 2
7	F	21	21	_	1	Swelling of face and extremities	36	27	Decreased	128	HAE 2
8	F	29	17	_	10	Swelling of face and extremities	4	15	Decreased	142	HAE 2

G: gender, AOO: age of onset, FH: family history, DD: diagnosis delay, MCM: main clinical manifestation, C1INH: C1 inhibitor, Dx: diagnosis

Table 2. Characteristic of 8 hereditary angioedema patients comparing to 55 patients with non hereditary angioedema .

Type of Disease	NA	HAE	P Value	HAE 1	HAE 2	P Value Between NA & HAE 1	P Value Between NA & HAE 2	P Value Between HAE 1 & HAE 2
Number of patients	55	8	-	3	5	-	-	-
Mean age ± SD, years	26.62 ± 14.6	23.6 ± 11.9	0.83	25.6 ± 13.5	22.4 ± 12.32	0.80	0.82	0.68
Sex (male/female)	22/33	2/6	0.23	1/2	1/4	0.28	0.64	1
consanguinity	25.4%	12.5	0.66	0	20%	1	1	1
Mean onset age ± SD, years	22.43 ± 14.14	14.7 ± 10.8	0.58	8 ± 5	18.8 ± 11.84	0.97	0.86	0.98
Mean diagnosis delay, years	4.54 ± 3.02	8.2	0.53	17.6	2.6	0.34	0.93	0.34
Family history (%)	10 (18.1)	3 (37.5)	0.36	2 (66.6)	2 (40)	0.51	0.27	1
Clinical presentation								
Swelling of extremities (%)	23 (41.8)	7 (87.5)	0.02*	3 (100)	4 (80)	0.08	0.15	1
Facial swelling (%)	49 (89.0)	8 (100)	1	3 (100)	5 (100)	1	1	
Abdominal pain attacks (%)	6 (10.9)	2 (25)	0.28	1 (33.3)	1 (20)	0.33	0.43	0.52
Genital swelling (%)	9 (16.3)	2 (25)	0.62	1 (33.3)	1 (20)	0.45	1	0.52
Laryngeal swelling (%)	5 (9.0)	1 (12.5)	1	1 (33.3)	0	0.29	1	0.16
Voice change (%)	3 (5.4)	2 (25)	0.12	1 (33.3)	1 (20)	0.20	0.31	1
Erythema (%)	50 (90.9)	5 (62.5)	0.06	2 (66.7)	3 (60)	0.29	0.08	1
Itching (%)	46 (83.6)	4 (50)	0.04*	2 (66.7)	2 (40)	0.41	0.033*	1
Pain (%)	6 (10.9)	2 (25)	0.28	1 (33.3)	1 (20)	0.29	0.43	1
Predisposing factor								
Attack after infection (%)	3 (5.4)	1 (12.5)	0.40	0	1 (20)	1	0.32	1
Attack after stress (%)	11 (20.0)	1 (12.5)	1	1 (33.3)	0	0.36	0.57	0.37
Attack after trauma (%)	6 (10.9)	3 (37.5)	0.06	2 (66.7)	1 (20)	0.04*	0.38	0.20
Laboratory parameter								
C1 esterase inhibitory ± SD, mg/dl	26.5 ± 5.8	15.5 ± 11.5	<0.001*	4.1 ± 6.7*	22.4 ± 7.2	<0.001*	0.38	0.008*
CH50± SD, U/dl	126.5 ± 20.3	107 ± 37.6	<0.001*	117.6 ± 43.4*	100.6 ± 37.4	0.047*	0.023*	0.81
C3± SD, mg/dl	108.8 ± 27.6	106 ± 45.3	0.18	86.9 ± 76.1*	117.6 ± 16.0	0.008*	0.83	0.014*
C4±SD, mg/dl	22.7±8.7	12 ±12	0.008*	5.3 ± 4.5*	16.1 ± 13.8	0.023*	0.294	0.30

*: statistically significant P<0.05, HAE: hereditary angioedema, NA : non hereditary angioedema

The Pattern of attack in relatives of patients was swelling of face and extremities but no Family history of laryngeal edema or death due to angioedema attack was detected. Demographic, clinical and laboratory data of HAE patients are summarized in Table 1 and analysis of these data is summarized in Table 2.

Clinical Evaluation. Out of the total number of 63 patients, the most common clinical manifestation was facial swelling in 57 patients (90.4%) which followed by erythema in 55 (87.3%), itching in 50 (79.3%) and swelling of extremities in 29 patients (47.6%). There was statistically significant difference of itching and swelling of extremities in HAE and non-HAE group. Itching was significantly less in HAE patients (p=0.04). Swelling of extremities was more in HAE patients (p=0.02). All of the HAE patients presented facial swelling. Except for one of HAE patients others experienced swelling of extremities. Swelling of extremities was significantly higher in those with HAE than others (p=0.02). History of laryngeal swelling was positive for one HAE patient but no asphyxiation or airway obstruction was observed during the period of investigation. The median interval of the attacks was different for every patient, ranging from 1 day to 2 years and a median of 30 days.

Out of 8 HAE patients, tranexamic acid was considered as long term prophylaxis for five patients according to their age and sex (one prepubertal boy and four young adult girls); attenuated androgens (danazol and stanasol) were recommended for two other patients who experienced more attacks and remained symptomatic despite receiving tranexamic acid. Both of regimens successfully prevented the attacks in all of the patients.

Para-Clinical Evaluation. The mean level of C1INH in patients with HAE type 1 was 4.1 ± 6.7 mg/dl and in HAE type 2 was 22.4 ± 7.2 mg/dl (p<0.001). Figure 1 shows the level of C1INH among different groups of this study. Mean Serum level of C4 in HAE type 1 was 5.3 ± 4.5 mg/dl and in HAE type 2 was 16.1 ± 13.8 mg/dl. The mean level of C3 was 86.9 ± 76.1 mg/dl in HAE type 1 and 117.6 ± 16.0 in HAE type 2. The mean level of functional C1INH in HAE type 2 was 35.7 ± 24.6 which was two SD below the normal population.

The mean level of CH50 of patients with HAE type 1 and HAE type were 117.6 ± 43.4 mg/dl and 100.6 ± 37.4 mg/dl, respectively.

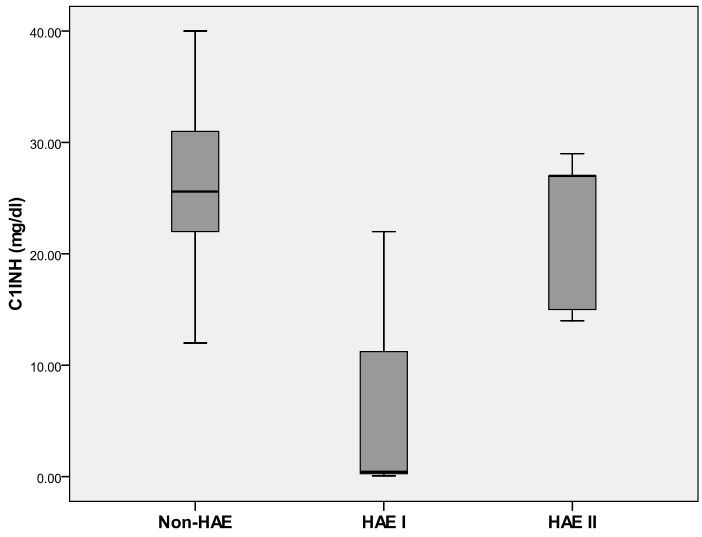

Figure 1. Levels of C1INH among different types of angioedema. HAE I: hereditary angioedema Type 1, HAE II: hereditary angioedema Type 2, Non-HAE: non-hereditary angioedema.

DISCUSSION

Angioedema could be classified into two general groups: rare hereditary angioedema (HAE) and the more common non-hereditary angioedema (non-HAE) (15) but in this study we have focused on HAE especially HAE type 1 and 2. Prevalence of non-HAE is estimated to be about 1:14 and prevalence of HAE to be 1:50,000 which is rare in comparison to non-HAE (15,16). However, 8 (12.6%) of our patients were diagnosed with HAE. The high percentage of HAE diagnosed patients in this survey may be due to some limitations; our study was conducted in only one hospital, this hospital is a tertiary referral center and also is specialized for children. Moreover high rate of consanguinity in the Iran as well as other middle eastern country may lead to severe symptomatic clinical presentation of HAE in contrast to patient with single allele defect with limited manifestation (17).

Although many of HAE patients have de novo mutations and a negative family history of HAE (9), positive family history of angioedema is a very important suggestive factor for HAE (4). The diagnosis of HAE type 1 can be confirmed with decreased C4 and C1INH and positive family history of angioedema. The diagnosis of HAE type 2 is also confirmed with normal or elevated level of C1INH but the function is abnormal (14). In our study, positive family history was recorded in two (66.6%) of patients with HAE type I and also two (40%) of patients with HAE type II had positive family history. In this study evaluation of family was almost based on the history taking, but for further studies we propose detailed evaluation of family members with the history of angioedema with laboratory tests such as C1INH and C1q.

The age of onset of clinical manifestations of angioedema is very important and HAE has earlier age of onset compared with AAE (4). The reported mean age at onset of symptoms in HAE patients is 8-12 years (17,18). In our study the age of onset for HAE type 1 was in the first decade in two patients and in the second decade of life in one of them. The clinical manifestations of Iranian patients with angioedema were, in general, consistent with the clinical patterns previously described (3). Facial swelling and swelling of extremities were the most common clinical manifestations in HAE patients without presence of itching. According to our results, presentation with skin swelling and attack after trauma and absence of itching is a relatively common finding in patients with HAE. These clinical findings are important to differentiate HAE from acquired forms of angioedema and assessment of complement system, because the management and treatment of these patients can be quite different and should be considered by purified or recombinant C1INH as well as bradykinin receptor antagonist in this life-threatening condition. Moreover, HAE is refractory to commonly used drugs for acute allergic attacks, adrenalin and steroids (17,19). However, serum C4 level is an excellent screening test for C1INH deficiency which is reduced in almost 100% of patients during attacks.

Abdominal attack is another complication of HAE (3) which was seen in 2 cases (1 with type 1 and 1 with type 2). It should be considered that if it occurs in the absence of other manifestations it would be challenging to differentiate from acute abdomen that need surgical procedures and abdominal ultrasonography would be helpful (20). Recently, Cugno *et al*. (21) demonstrated high prothrombin fragment F1 and 2 and D-dimer levels during acute angioedema attacks in HAE and proposed that these measurements may have an important diagnostic value.

The coincidence of angioedema and common variable immunodeficiency has been described previously (22). However, we did not find any case of antibody immunodeficiency in our series (data is not presented). Moreover, patients with HAE show an increased susceptibility to autoimmunity, especially glomerulonephritis, whereas there was no case of autoimmunity in this survey (23).

An important point from this study was the long duration between first clinical manifestation of angioedema and exact diagnosis. This delayed diagnosis is probably due to the fact that patients are not refered to the immunologist or subspecialist while they have signs and symptoms of angioedema. This might be due to the lack of knowledge about differential diagnosis and management of angioedema in medical community. All of our patients were on close observation and were placed on patient education including avoidance of trigger factors such as minor trauma, emotional stress, strong exercise, surgery or diagnostic manipulation of the head and neck region, specific food stuffs, use of estrogen-containing drugs, alcohol and infection (19,24).

This study was performed to respect the importance of differentiation between HAE and other types of angioedema because they have completely different therapeutic approaches and its very important not to miss HAE patients because commonly used drugs for acute allergic attacks such as adrenalin and steroids are not effective in HAE (19,25-27). Success in appropriate diagnosis and prophylactic management of HAE could decrease morbidity and mortality especially due to asphyxiation (3,28). This study showed that it is possible to do this process by attention to clinical manifestations and decreased level of complement proteins or dysfunction of C1INH in laboratory tests of patients. Absence of coexisting relevant urticaria and equal frequency of facial and peripheral involvement for cutaneous attacks are clinical characteristics which help to differentiate angioedema due to C1INH deficiency from allergic angioedema (29).

Although presence of this mutation in HAE type 3 is controversial, we propose further studies to evaluate the relationship between HAE type 3 and mutations of *FXII* gene especially in patients with positive family history of angioedema, parental consanguinity and early age of onset presentation and normal serum level and function of C1INH. Therefore, in rare cases, patients with HAE who have normal C1INH level and function some but not all of these patients are found to have a factor XII dysfunction. Since our investigation was performed in pediatric hospital further studies are needed for the diagnosis and differentiation of this type of HAE in rest cases and how to distinguish this type from other forms of angioedema including lymphoma or drug induced angioedema in othe cases (30).

In conclusion, the clinical properties of the Iranian patients with HAE were consistent with the known clinical patterns of the disease. An important point in this study was the delay between first clinical manifestations of angioedema and the exact diagnosis. This is probably due to the fact that patients are not refered to the immunologist or subspecialist while they have signs and symptoms of angioedema. Also it can be due to the lack of enough knowledge about differential diagnosis and management of angioedema in medical community. Attention to clinical manifestation and early age of onset and positive family history of angioedema could be extremely helpful in the diagnosis of HAE.

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