Prevalence and Clinical Manifestations of Hereditary Angioedema in Untested Close and Distant Blood Relatives of Hereditary Angioedema Index Patients in a City, Turkey

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ABSTRACT

Objective: Hereditary angioedema (HAE) is a rare autosomal-dominant disease characterized by recurring attacks of nonpruritic, nonpitting edema caused by an inherited deficiency or dysfunction in the C1 esterase inhibitor (C1 INH). Symptoms present years before an accurate diagnosis is made. Our aim was to determine the prevalence and clinical manifestations of HAE in untested blood relatives of HAE index patients in a city of Düzce province, Turkey.

Methods: Overall, 4 index patients with HAE and 60/118 blood relatives enrolled in the study. The mean age of the enrolled untested subjects (29 female+31 male) was 41 years. The enrolled subjects underwent complement testing (C4, C1 INH antigen, and functional C1 INH). If the laboratory tests were abnormal, the enrolled subjects were questioned on clinical manifestations and scheduled for a follow-up visit.

Results: Except for 4 index cases, 60 relatives enrolled in the study underwent complement testing, and 36.6% of them were diagnosed Type 1 and 1.6% Type 2. HAE could not be ruled out in 6.6% of the subjects. In 55% of the untested blood relatives, the HAE disorder was ruled out. Of 23 (22; type 1+ 1; type 2) newly diagnosed subjects, 9 (39%) reported having experienced symptoms that may have been related to HAE, such as swelling in the face, genitourinary region, extremities or abdominal pain. The median age of 9 symptomatic patients was 42 (25-75) years, whereas newly diagnosed asymptomatic subjects had a median chronological age of 17 (9-74) years.

Conclusions: This study's findings reinforce the importance of screening family members and relatives of index patients with HAE to detect this hereditary condition.

Keywords: C1 esterase inhibitor, hereditary angioedema, screening, questionnaires, C4

INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant disease caused by an inherited deficiency or dysfunction of the plasma protein C1 esterase inhibitor (C1 INH). It is characterized by recurring attacks of nonpruritic, nonpitting subcutaneous edema, or submucosal edema of the small/large intestines or upper/lower airways (1). Symptoms typically present during childhood; however, the diagnosis could be delayed for a decade or more, even in developed countries (2-5). The offspring (children) of a diseased parent with a mutation of the C1 INH gene will have a 50% chance of inheriting the HAE disorder. Because of the scarcity of the disease, clinicians do not think of HAE in the first plan of their differential diagnosis (6). Additionally, despite its high probability due to familial predisposition, many family members of HAE patients are not searched for the disease. With new and effective therapeutic products, screening of family members has increasingly been given emphasis as a means to diminish the significant morbidity and mortality related to HAE (7).

Aim

This study was designed to determine the prevalence and occurrence of clinical manifestations of hereditary angioedema (HAE) in previously unevaluated blood relatives of known (index) patients with HAE in a few villages of a city in a province (Düzce) in Turkey.

METHODS

Study Design

In the beginning, after this study was approved by the relevant ethics committee (number: 162 214 662/050.01.04/90), we informed the local administration about our survey and got their approval as well. Later, we reached out to the recorded 4 (index) cases diagnosed with HAE and their untested relatives. A pedigree drawing was performed for the 4 index cases diagnosed with HAE (Figure 1). In addition, through public meetings with the permission of the local administration, the patients and relatives were informed about the disease. Besides close rela-

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tives of the index cases, distant relatives of the index case were also of interest. Close and distant blood relatives that wanted to enroll in the study were identified. These patients and their relatives were first informed of the nature of the study by telephone and were then visited. During this visit, the untested relatives were given a questionnaire (Table 1). The questionnaire was used to collect information on the demographics, screening status of blood relatives according to the HAE index patient, pregnancy, medication use, and past medical history including specific questions about swelling and symptoms that could be consistent with an angioedema attack. During the visit, permission by filling the informed consent form was obtained from all the blood relatives of the 4 index cases who agreed to enroll in the study. During this visit, after completing the questionnaire, blood samples were drawn and complement tests were performed to verify the diagnosis. If the complement testing (C4, C1 INH antigen level, and C1 INH activity) was normal in a suspected person, the diagnosis of HAE was excluded, and the results were provided to them. If the complement test results were abnormal or HAE could not be ruled out, the subjects were telephoned. They were asked the same questionnaire about the symptoms of HAE, the time of the onset of symptoms, swelling attacks, and drug use, and new complement testing was planned. In addition, through correspondence with the local health authorities, the medical/laboratory records of the newly diagnosed HAE patients were passed to their family physicians. (A diagram of participation from the index cases to the identification of untested relatives with laboratory results compatible with the diagnosis of HAE is shown in Figure 2).

Complement Tests

Fresh serum blood samples were collected in a red top Vacutainer tube for complement testing. Within six hours of blood collection, 3 mL of serum from the untested relatives was obtained and stored at −20°C. Frozen serum samples were tested within 72 hours for C4, antigenic and functional C1 INH levels. C4 was evaluated using the Cobas C4-2 kit (Roche, Rotkreuz, Switzerland) by Cobas c 501 nephelometry (C4 reference range: 0.1-0.4 g/L), and the C1 INH antigen level was measured using the N AS C1IN kit (Siemens, Marburg Germany) by BN Prospec nephelometry (C1 INH antigen normal range: 0.21-0.39g/L). The functional C1 INH was measured using a chromogenic Berichrom C1-Inhibitor kit (Siemens, Marburg Germany) by BCS coagulometer (C1 INH function normal range: 70-130%). Results were defined as low for C4: ≤0.1g/L, antigenic C1 INH: ≤0.21g/L, and functional C1 INH: ≤%70 (8-10).

Questionnaire

Questions were developed by collaborating with HAE experts to characterize the current state of screened subjects for HAE disorder. Nine questions were categorized into several broad areas, including patient characteristics, burden of disease, and treatment options (Table 1).

Statistical Analysis

Data from our study group were pooled and presented as descriptive (summary) statistics using the IBM Statistical Package for the Social Sciences 21.0 (IBM Statistics; Armonk, NY, USA) software package program in the form of group means, rates, and proportions.

RESULTS

Demographics

One hundred and eighteen blood relative subjects were identified from pedigree charts of 4 index patients with HAE. Nine out of 118 blood relatives of HAE patients had already died. Six of them were diagnosed with HAE before death. From the remaining 109 living relatives, 64 (including 4 index cases) elected to enroll in the study and underwent complement testing. Forty-five untested blood relatives did not want to enroll in the study. Twenty-nine enrolled blood relatives (29/60: 48.3%) were female, and 31/60 (51.6%) of them were male. The median age of all untested subjects, including the index cases, was 41 (range: 4-75) years (Table 2).

Prevalence of HAE in Close and Distant Relatives

C1 INH antigen levels were significantly low in 22/60 (36.6%) of the untested blood relatives of 4 index patients. These subjects were thought to have Type 1 HAE disorder. The C1 INH activity was significantly low in just 1/60 (1.6%) untested subject. This one was thought to have Type 2 HAE disease. In the remaining 4 subjects, HAE could not be ruled out during the study due to borderline low complement results. These suspicious results will be repeated in the near future. As a result, of the 60 relatives who enrolled in the study and underwent complement testing,

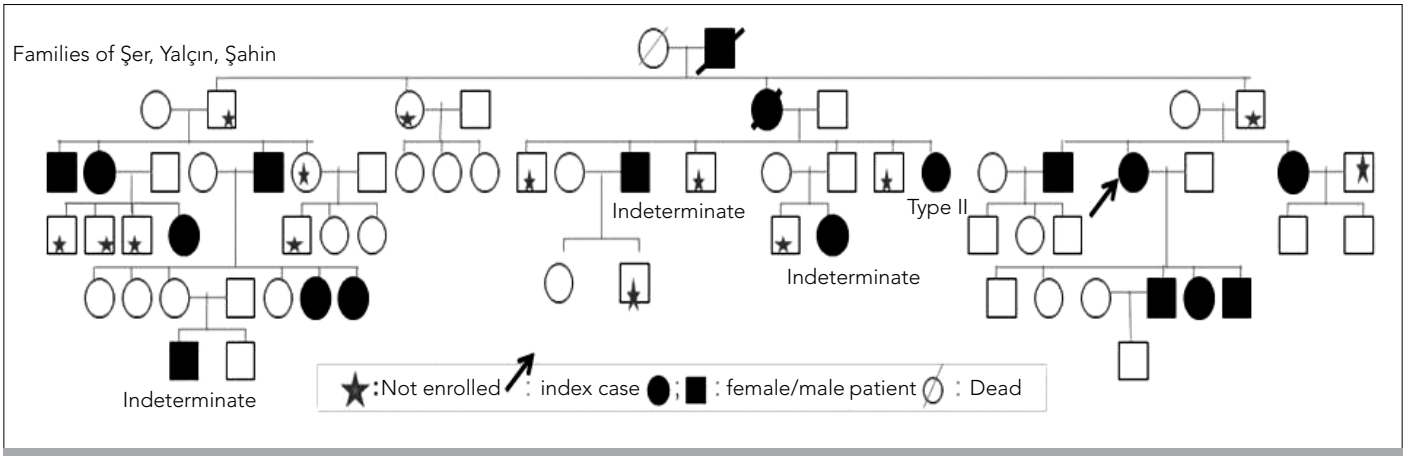

Figure 1. The sample pedigree for 3 families of untested relatives of an index case with hereditary angioedema

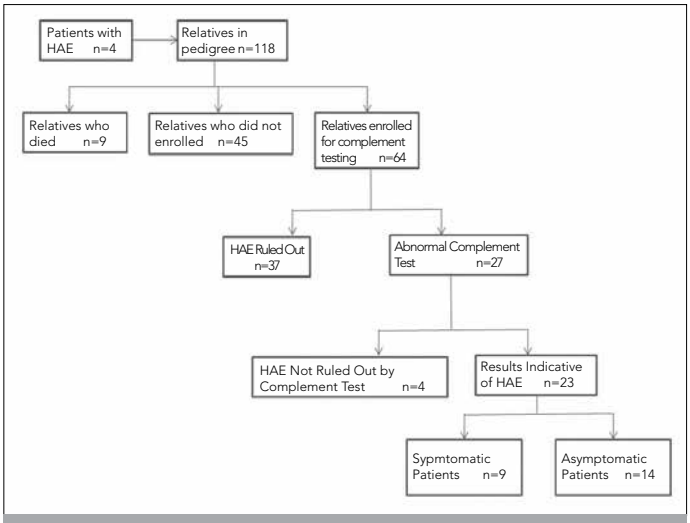

Figure 2. Algorithm of participation from the index cases to the identification of untested blood relatives with laboratory results compatible with the diagnosis of HAE
HAE: hereditary angioedema

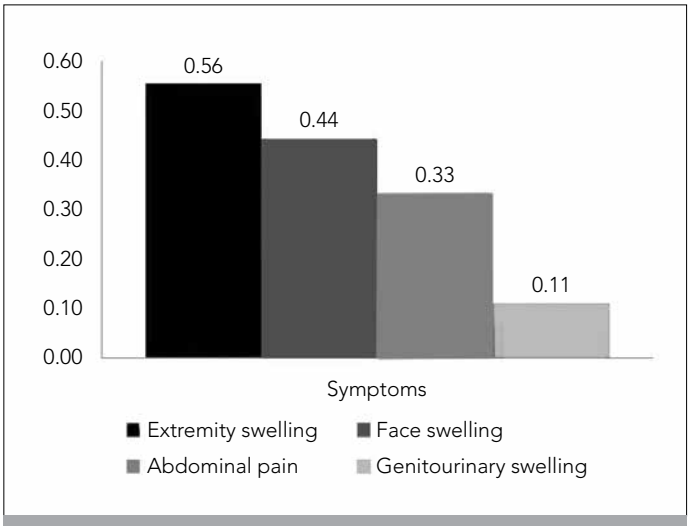

Figure 3. Distribution of symptoms in newly diagnosed patients in our survey

36.6% of them were found to have laboratory results indicative of Type 1 and 1.6% of them has results indicative of type 2 HAE. The complement tests could not rule out the diagnosis of HAE (indeterminate cases) in 4 patients (4/60: 6.6%). In 33/60 (55%) of the untested blood relatives, the HAE disorder was ruled out (Table 2).

The median age of the 4 patients (indeterminate cases) whose complement tests could not rule out the diagnosis of HAE was 33.5 (range: 4-71) years. The mean C1 INH protein levels of these subjects was detected as 0.17±0.01 g/L (0.20, 0.15, 0.17, and 0.17 g/L). The C1 INH activity and C4 levels were within normal limits. There was not a symptom that might have been related to HAE in the indeterminate cases. This suggests that indeterminate cases/subjects might need some more time to develop symptoms since the median age of the 9 symptomatic patients was 42 years. Complement testing of these patients will be performed again.

According to the index cases, 10/23 newly diagnosed patients (43.5%) were first-degree relatives and 13/23 (56.5%) of them were more distant (second/third degree) relatives. In the 60 subjects who enrolled in our study, 17 of them were first-degree relatives, and the remaining 43 were more distant relatives. The HAE diagnosis rate in the first degree relatives of the index cases was 58.8% (10/17), and it was 30.2% (13/43) in the more distant relatives (Table 2).

History of Symptoms

Of 23 (22; type 1+1; type 2) newly diagnosed subjects, 9 (39.1%) subjects reported symptoms that may be related to HAE, such as swelling in the face, genitourinary region or extremities, and abdominal pain. These 9 symptomatic patients reported a few swelling episodes per year persisting for a couple of days. The attacks were mostly reported to be triggered by stress and/or trauma. Most of the 9 patients did not recall the time when the first attack happened. Swelling in extremities was observed in 5 (55.5%) of them, swelling in the face (lip) was reported in 4 (44.4%), swelling in the testis in 1 (11.1%), and abdominal pain was reported in 3 (33.3%) of them (Figure 3). The median age of the 9 symptomatic patients was 42 (range: 25-75) years, whereas the newly diagnosed asymptomatic subjects had a median chronological age of 17 (range: 9-74) years (Table 2).

DISCUSSION

Hereditary angioedema (HAE), caused by C1-INH deficiency, is a rare disease with an estimated frequency of 1:10.000-1:150.000 (11, 12). The clinical features of HAE consist of recurrent episodes of edema, which usually last for 2-5 days. The skin, gastrointestinal tract, and upper airway are most commonly affected in the recurrent edema attacks (13). A diagnosis of HAE should be suspected in any patient with recurrent angioedema attacks on the skin as well as upper airways or abdominal pain. There have also been recent reports of attacks manifesting as headaches, temporary neurologic deficits, swelling and spasms of the urethra and bladder, joint swelling, chest tightness and pain, and renal colic (14, 15). Laryngeal edema is the most serious complication and can become life threatening, but it is a relatively rare event. Only 0.9% of all edema episodes of HAE disease involved laryngeal edema (16). In this study, symptoms such as swelling in the face, genitourinary region or extremities, and abdominal pain were present in our tested subjects. We found symptoms that might have been related to HAE in 39% of subjects. As mentioned above, the newly described clinical findings, such as headaches, described in the literature and outside the classic findings were not observed. A history of laryngeal edema development was not reported in our newly diagnosed patients. Symptoms appeared at an advanced age (median: 42 years) in our study population.

Although HAE is an autosomal dominant disorder, approximately 25% of disorders inherited in this manner may represent de novo mutations (17). HAE is a genetically heterogeneous disease, with more than 100 C1 INH gene mutations described to date spanning all the exons and exon/intron boundaries (18). However, genetic testing is rarely necessary, and, in fact, a negative test result cannot be used to exclude the diagnosis because new mutations that have not been previously identified are possible. In addition, a positive test result is consistent with the diagnosis but cannot

Table 1. The questionnaire of our survey

Volunteer (candidate)'s Name / Last name: …… Age: …… Sex: …… ID Number: ……..
Village / Neighborhood: ……..... Address: ..... Phone: 0….....
1- Are you one of the untested blood relatives of HAE index patients?
Yes ( )
No ( )
2- Did you have any hand-arm-foot-eye-lip swelling without urticaria? Swelling: repeated; unknown cause; longer than 24 hours?
Yes ( )
No ( )
3- Did you have any trauma-, stress-triggered or unknown swelling?
Yes ( ) Which region: .....
No ( )
4- Have you been referred to any health center with similar complaints?
Yes ( ) Diagnosis: ……
No ( )
5- Is there any person in the family diagnosed with HAE?
Yes ( ) Degree of relationship: ……
No ( )
6- Do you have a family member who died from HAE disease and/or complications?
Yes ( ) Degree of relationship: ……
No ( )
7- Do you have another disease (autoimmune, connective tissue disease, vasculitis, etc.)?
Yes ( ) Which disease: ……
No ( )
8- Are you pregnant?
Yes ( )
No ( )
9- Do you use any medications?
Yes ( ) (androgens, antifibrinolytic, fresh frozen plasma, etc.)
No ( )

be used to predict the natural history of the disease because the same genotypes present with various phenotypes (19). Laboratory testing (complement testing: C4, C1 INH activity, and C1 INH antigen level) is needed to confirm or rule out the diagnosis of HAE (11, 20). Even if a patient does not exhibit HAE symptoms, a confirmed diagnosis will allow them to prepare for the possibility of a future attack. The early diagnosis will also provide patients with the necessary education and knowledge to manage the HAE disorder during their daily life, including identification and avoidance of triggers and how to properly react to lethal complications, such as an airway obstruction (19). In this study, 14/23 (61%) of the newly diagnosed subjects did not have any symptoms/signs suggestive of HAE in their past medical history until our survey. Proving their diagnosis of HAE during our study will let unscreened blood relatives be aware of the disease and prepare for a possible HAE attack in the future.

Hereditary angioedema is caused by mutations in the C1-INH gene that result in reduced C1-INH antigen levels (type I) or dysfunction (type II) of the C1-INH protein (21). Unique among the inherited deficiencies of the complement system, HAE types I and II are inherited as an autosomal dominant disorder, with equal occurrence in men and women. Low levels of the C1 INH protein and decreased function of the protein distinguish type I HAE, which accounts for approximately 80% to 85% of all HAE cases. Type II HAE, which occurs in 15% to 20% of patients, results from decreased functional activity of the C1 INH gene

Table 2. Clinical, demographic and laboratory findings of screened untested relatives of HAE index patients

Case	Age	Sex	C4 (g/L)	C1 Esterase Inhibitor Activity (%)	C1 Esterase Inhibitor (g/L)	Type	Relationship of parents	Swelling Symptoms
1	46	F	0.12	45	0.02	I	Yes	Face (lip)- Extremity
2	42	F	0.03	34	0.05	I	No	Extremity
3	25	M	0.06	38	0.12	I	No	Face - Abdominal pain
4	51	F	0.40	86	0.13	I	Yes	Face (lip)
5	75	F	0.03	38	0.06	I	No	Extremity
6	41	M	0.12	51	0.09	I	Yes	Abdominal pain
7	41	M	0.07	32	0.05	I	Yes	Extremity- Abdominal pain
8	55	M	0.07	34	0.08	I	No	Genitourinary- Extremity
9	32	M	0.37	99	0.17	I	No	Face (lip)
10	18	F	0.05	38	0.06	I	No	No
11	58	F	0.23	60	0.33	II	No	No
12	74	M	0.11	35	0.08	I	No	No
13	26	F	0.06	41	0.07	I	No	No
14	9	M	0.10	37	0.16	I	No	No
15	14	F	0.07	46	0.09	I	No	No
16	13	M	0.07	40	0.08	I	No	No
17	13	F	0.06	43	0.09	I	No	No
18	16	F	0.06	34	0.08	I	No	No
19	11	F	0.12	45	0.09	I	No	No
20	52	M	0.10	44	0.09	I	No	No
21	10	M	0.09	44	0.10	I	No	No
22	46	M	0.05	37	0.05	I	Yes	No
23	42	F	0.09	36	0.06	I	No	No
24	51	M	0.20	78	0.21	Indeterminate	Yes	No
25	71	M	0.25	85	0.15	Indeterminate	No	No
26	4	M	0.21	92	0.17	Indeterminate	Yes	No
27	16	F	0.23	87	0.17	Indeterminate	No	No
28	42	F	0.10	39	0.06	I (Index case)	No	Extremity
29	41	F	0.15	31	0.31	II (Index case)	No	Extremity
30	46	F	0.03	21	0.05	I (Index case)	No	Extremity- Face (eye, lip)
31	25	F	0.26	81	0.19	I (Index case)	No	Face (lip)

F: female; M: male

but with a normal C1 INH protein level in the serum (22, 23). Recently, a new subtype of HAE, type III, has been described in the literature (19, 24). Type III HAE was out of the scope of this study. In this study, 22 out of 23 (95.6%) patients diagnosed by the complement tests had type 1 HAE disorder, and 1/23 (4.3%) of the patients was diagnosed as type 2 HAE. This is consistent with the literature.

Because of the rarity of HAE disease and the fact that its symptoms overlap with those of other forms of angioedema and, in cases of abdominal attack, it can appear to be a surgical emergency, it is frequently misdiagnosed. Consequently, HAE patients may experience considerable delays in diagnosis (5, 25, 26). Without an accurate diagnosis, HAE patients may not receive an appropriate treatment that can effectively manage their attacks. Inappropriate treatment could result in higher

morbidity and mortality, adverse events, and unnecessary surgical interventions (27, 28). Especially, delayed treatment of laryngeal swelling can cause death (11, 13). Zanichelli et al. (28) reported that the median age of the first symptoms was 12.0 years, and the corresponding median age at diagnosis was 24.3 years (29). In our survey, the median age at diagnosis of untested blood relatives was too late (41 years). The median age at diagnosis was 42 years in symptomatic patients, and 17 years in asymptomatic patients.

Although HAE is inherited as an autosomal dominant disorder, it is known that testing family members and close/distant relatives for the disorder is not common practice worldwide. It is prudent to test family members or relatives of affected individuals to ensure appropriate education and treatment of HAE. This will decrease the time from the initial symptoms to diagnosis. Screening family members/ blood relatives for HAE may also be cost-effective by decreasing the number of physicians seen and the number of unnecessary tests and procedures ordered. Detecting the median age at diagnosis as 42 years in this study proves that screening/testing family members and close/distant blood relatives of these index patients for the HAE disorder must be a common practice. Ten out of 23 newly diagnosed patients (44%) were first-degree relatives of the index cases and 13/23 (57%) of them were more distant relatives. Of the subjects who enrolled in the study, 17 of them were first-degree relatives and 43 tested subjects were more distant relatives. The HAE diagnosis rate in first degree relatives was 59% (10/17), and it was at 30% (13/43) in the more distant (second and third degree) relatives (Table 2).

CONCLUSION

This study shows us that screening untested close and distant family members for the HAE disorder is very prudent and should be done. Validating their diagnosis of HAE will let the untested relative subjects be aware of the disorder earlier in life and prepare for a possible HAE attack in the near future.

Key Messages

HAE is a rare otosomal dominant disease caused by an inherited deficiency or dysfunction of the plasma protein C1 INH.

Despite its high probability of familial predisposition, many family members of HAE patients are not usually searched for the disease.

With new and effective therapeutic products, screening of family members has increasingly been given emphasis as a means to diminish the significant morbidity and mortality related to HAE.

Inappropriate treatment could result in higher morbidity and mortality, adverse events, and unnecessary surgical interventions. Especially, delayed treatment of laryngeal swelling can cause death.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Sakarya University.

Informed Consent: Written informed consent was obtained from patients and patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.Ö., B.E.; Design - Ö.Ö., B.E.; Supervision - Ö.Ö., B.E.; Resources - Ö.Ö., B.E.; Materials - Ö.Ö., B.E.; Data Collection and/or Processing - Ö.Ö., B.E.; Analysis and/or Interpretation - Ö.Ö., B.E.; Literature Search - Ö.Ö., B.E.; Writing Manuscript - Ö.Ö., B.E.; Critical Review - Ö.Ö., B.E.

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REFERENCES

1. Bernstein JA. HAE update: Epidemiology and burden of disease. Allergy Asthma Proc 2013; 34: 3-6. [CrossRef]
2. Martinez-Saguaer I, Escuriola Ettingshausen C. Delayed diagnosis of hereditary angioedema: Thirty nine years of inadequate treatment. Ann Allergy Asthma Immunol 2016; 117: 554-6. [CrossRef]
3. Lunn ML, Santos CB, Craig TJ. Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients? Ann Allergy Asthma Immunol 2010; 104: 211-4. [CrossRef]
4. Roche O, Blanch A, Caballero T, Sastre N, Callejo D, López-Trascasa M. Hereditary angioedema due to C1 inhibitor deficiency: Patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol 2005; 94: 498-503. [CrossRef]
5. Zanichelli A, Magerl M, Longhurst H, Fabien V, Maurer M. Hereditary angioedema with C1 inhibitor deficiency: Delay in diagnosis in Europe. Allergy Asthma Clin Immunol 2013; 9: 29. [CrossRef]
6. Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al. on behalf of HAWK under the patronage of EAACI (European Academy of Allergy and Clinical Immunology). Classification, diagnosis, and approach to treatment for angioedema: Consensus report from the Hereditary Angioedema International Working Group. Allergy 2014; 69: 602-16. [CrossRef]
7. Riedl MA, Lumry WR, Busse P, Levy H, Steele T, Dayno J, et al. Prevalence of hereditary angioedema in untested first-degree blood relatives of known subjects with hereditary angioedema. Allergy Asthma Proc 2015; 36: 206-12. [CrossRef]
8. Thomas L. The complement system. In: Thomas L, ed. Clinical Laboratory Diagnostics. Frankfurt: TH- Books Verlagsgesellschaft 1998; 794-806.
9. Wagner C, Dati F. Fibrinogen. In: Thomas L, ed. Clinical Laboratory Diagnostics. Frankfurt: TH- Books Verlagsgesellschaft 1998; 609-12.
10. Tietz NW, ed. Clinical guide laboratory tests. 3rd ed. Philadelphia, PA: WB Saunders Company 1995; 164-5.
11. Zuraw BL. Hereditary angioedema. N Engl J Med 2008; 359: 1027-36. [CrossRef]
12. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med 2001; 161: 2417-29. [CrossRef]
13. Zilberberg M, Jacobsen T, Tillotson G. The burden of hospitalizations and emergency department visits with hereditary angioedema and angioedema in the United States, 2007. Allergy Asthma Proc 2010; 31: 511-9. [CrossRef]
14. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med 2006; 119: 267-74. [CrossRef]
15. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med 2001; 161: 2417-29. [CrossRef]
16. Xu YY, Zhi YX, Liu RL, Craig T, Zhang HY. Upper airway edema in 43 patients with hereditary angioedema. Ann Allergy Asthma Immunol 2014; 112: 539-44. [CrossRef]
17. López-Lera A, Garrido S, Roche O, López-Trascasa M. SERPING1 mutations in 59 families with hereditary angioedema. Mol Immunol 2011; 49: 18-27. [CrossRef]

18. Tosi M. Molecular genetics of C1 inhibitor. Immunobiology 1998; 199: 358-65. [CrossRef]
19. Lunn ML, Santos CB, Craig TJ. Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients? Ann Allergy Asthma Immunol 2010; 104: 211-4. [CrossRef]
20. Ohsawa I, Honda D, Nagamachi S, Hisada A, Shimamoto M, Inoshita H, et al. Clinical manifestations, diagnosis, and treatment of hereditary angioedema: survey data from 94 physicians in Japan. Ann Allergy Asthma Immunol 2015; 114: 492-8. [CrossRef]
21. Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angio-oedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol 2004; 114: S51-131. [CrossRef]
22. Zuraw BL, Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. J Allergy Clin Immunol 2000; 105: 541-6. [CrossRef]
23. Bowen B, Hawk JJ, Sibunka S, Hovick S, Weiler JM. A review of the reported defects in the human C1 esterase inhibitor gene producing hereditary angioedema including four new mutations. Clin Immunol 2001; 98: 157-63. [CrossRef]
24. Riedl MA. Hereditary angioedema with normal C1-INH (HAE type III). J Allergy Clin Immunol Pract 2013; 1: 427-32. [CrossRef]
25. Cardarelli W. Managed care implications of hereditary angioedema. Am J Manag Care *2013;* 19: s119-24.
26. Roche O, Blanch A, Caballero T, Sastre N, Callejo D, López-Trascasa M. Hereditary angio-oedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol 2005; 94: 498-503. [CrossRef]
27. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. Br J Dermatol 2009; 161: 1153-8. [CrossRef]
28. Zanichelli A, Vacchini R, Badini M, Penna V, Cicardi M. Standard care impact on angio-oedema because of hereditary C1 inhibitor deficiency: a 21- month prospective 2 study in a cohort of 103 patients. Allergy 2010; 66: 192-6. [CrossRef]
29. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol 2012; 130: 692-7.[CrossRef]