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ORIGINAL ARTICLE

Clinical and Laboratory Characteristics That Differentiate Hereditary Angioedema in 72 Patients with Angioedema

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ABSTRACT

Background: Hereditary angioedema (HAE) is a rare but life-threatening condition that results from mutations in C1-inhibitor (C1-INH). Since distinguishing HAE from other causes of angioedema (AE) is a critical problem in emergencies, the objective of the present study was to clarify the differences between HAE and other forms of AE.

Methods: Seventy-two patients with AE were enrolled in this study. The medical history and laboratory data of patients with HAE at the first visit were compared to those with other types of AE.

Results: Subjects included 23 patients with HAE, 33 with mast cell-mediated AE, 5 with drug-induced AE and 11 with idiopathic AE. The average age of HAE onset (19.5 ± 8.0 years old) was significantly lower than in other groups. A family history of AE was noted in 82.6% of HAE patients, which was significantly higher than other groups. Swelling affecting the extremities and gastrointestinal (GI) tract was observed in the majority (60 to 80%) of HAE patients. Life threatening laryngeal edema was observed in 30.4% of HAE patients. In 95.6% of HAE patients serum levels of C4 were less than the lower limit of the normal range. In our subjects, the sensitivity and specificity of low C4 for HAE were 95.6% and 93.8%, respectively.

Conclusions: Early onset of AE, positive family history, recurrent AE in the extremities and GI tract, and suffocation are distinctive characteristics of HAE. A low serum level of C4 is a useful marker for making a differential diagnosis of HAE.

KEY WORDS

C1-inhibitor, C4, d-dimer, hereditary angioedema (HAE), suffocation

INTRODUCTION

Angioedema (AE) is clinically characterized by self-limiting attacks of marked edema involving the skin, airway, gastrointestinal (GI) tract and other organs,[1] and may or may not have a trigger event.[2] Hereditary angioedema (HAE) is an autosomal dominant disease caused by an inherited deficiency of the functionally active C1-inhibitor (C1-INH). Spontaneous new mutations often occur, and are related to about 20% of HAE cases.[1,2] C1-INH belongs to the serpin family and regulates the contact, complement and fibrinolysis systems via its serine protease inhibitory effect. Excessive bradykinin formation due to the pathological activation of the factor XII-driven plasma contact system is a consistent finding in acute episodes of HAE. Since plasma-derived C1-INH concentrate is available for first-line treatment of acute HAE attacks, such as life-threatening laryngeal edema and GI tract edema, the discrimination of HAE from other causes of AE is critical for effective treatment. However, correct diagnosis of HAE is, in some cases, made after a delay of

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approximately 20 years following the initial symptoms.[3,4] Recently, we investigated the difficulties associated with initial diagnosis in cases of severe abdominal attack with leukocytosis and high hematocrit without CRP elevation, as such cases can be confused with an acute abdomen, which can require an emergency surgical procedure.[4]

According to the World Allergy Organization (WAO) Guideline for the Management of HAE, HAE patients can be screened for low serum levels of C4 and diagnosed by low functional and antigenic levels of C1-INH.[5] However, the measurement of functional levels of C1-INH requires commercial testing that can take up to 10 to 14 days and evaluation of antigenic levels of C1-INH is not approved by the Japanese health insurance system. Therefore, we undertook this retrospective clinical study of various AE patients with the aim of identifying useful characteristics that can differentiate HAE from other types of AE.

METHODS

SUBJECTS

At the outpatient clinic of Juntendo University Hospital (Tokyo, Japan), 72 AE patients were enrolled from February 2010 to August 2013. All patients had a confirmed AE occurrence from their own self-photographs of the AE site and/or had introduction letters from their general physician. The HAE diagnosis criteria described by Agostoni, *et al.*[6] were used in this study. The major clinical criteria are: (1) self-limiting, non-inflammatory subcutaneous angioedema without major urticarial rash, often recurrent and often lasting more than 12 hours, (2) self-remitting abdominal pain without clear organic etiology, often recurrent and often lasting more than 6 hours, and (3) recurrent laryngeal edema. The minor clinical criteria are: a family history of recurrent angioedema and/or abdominal pain and/or laryngeal edema. Laboratory criteria are: (1) C1 inhibitor antigenic levels <50% of normal at two separate determinations with the patient in a basal condition and after the first year of age, (2) C1 inhibitor functional levels <50% of normal at two separate determinations with the patient in a basal condition and after the first year of age, and (3) a mutation in the C1 inhibitor gene altering protein synthesis and/or function. Diagnosis of HAE can be established with the presence of one major (1-3) clinical criterion and one laboratory criterion.

CATEGORY OF ANGIOEDEMA

All patients were divided into four groups: HAE, mast cell-mediated AE with urticaria and/or anaphylaxis (mast-AE), drug-induced AE (d-AE), and idiopathic AE (i-AE) according to the "International consensus on hereditary angioedema and acquired angioedema".[7] Additionally, 5 asymptomatic patients with a C1-INH deficiency (as-HAE), who were relatives of HAE patients, were also enrolled.

EVALUATION OF CLINICAL BACKGROUND AND DATA

All historical locations of AE occurrences on the patient were recorded. Blood samples were obtained from patients at the first consultation for a diagnosis of AE to be made under normal conditions (no swelling and no medication). The laboratory data for white blood cells, eosinophils (Eo), red blood cells, hemoglobin, hematocrit, serum creatinine (Cr), total protein (TP), albumin (Alb), immunoglobulin (Ig) G, IgM, IgA, and IgE, C3, C4, total hemolytic complement activity (CH50), C-reactive protein (CRP), fibrinogen and d-dimer were collected. For the purpose of differential diagnosis, serum concentration of immune complex (IC) [using a C1q-binding assay], C1q and cryoglobulin were evaluated, and genetic analysis of C1-INH was performed in some patients with low functional levels of C1-INH and no family history of AE. Functional levels of C1-INH were determined using a chromogenic assay (Sysmex, Hyogo, Japan). For differentiating collagen disease, anti-nuclear antibody (ANA) in sera was also measured. The study was conducted in accordance with the Declaration of Helsinki (1995) and was approved by the Institutional Review Board at Juntendo University. Written informed consent was obtained from all participating patients.

STATISTICAL ANALYSIS

GraphPad Prism 5 software for Windows (version 5.04; GraphPad, San Diego, CA, USA) was used for statistical analysis and a two-sided p-value < 0.05 was taken as the level for statistical significance. The relationship between categorical variables was analyzed using a χ^2 test. In the comparisons between grouped items, one-factor analysis of variance (ANOVA), followed by pair-wise comparisons with Bonferroni's correction was used when total ANOVA indicated a significant difference. All data were expressed as mean ± standard deviation (SD). Percentages shown in Table 1-4 are rounded down to one decimal place.

RESULTS

SUBJECTS' BACKGROUND

Subjects in this study included 23 HAE patients, 33 mast-AE patients (including 2 cases of IgE-mediated anaphylaxis), 5 d-AE patients, 11 i-AE patients and 5 as-HAE patients (Table 1). The occurrences of d-AE were due to enalapril, loxoprofen, an estrogen-containing contraceptive drug, and candesartan; two Chinese traditional herbs (*Shakuyaku-Kanzo-To* and *Boiogi-to*) were suspected of causing d-AE. There were no patients with acquired angioedema due to a C1-INH deficiency or normal C1-INH with positive inheritance. Age at the first visit in the d-AE group was high but there were no statistical differences between

Table 1 Characteristics of patients in the study

	n	Age of first visit (years)	M : F	Age of AE onset (years)	Family history of AE (% with history)
HAE	23	42.3 ± 14.3	10 : 13	19.5 ± 8.0†	82.6‡
mast-AE	33	41.2 ± 13.6	8 : 25	34.3 ± 14.0	9.0
d-AE	5	57.0 ± 21.0	1 : 4	55.0 ± 21.1	0.0
i-AE	11	47.2 ± 20.5	5 : 6	41.4 ± 26.6	9.0
as-AE	5	34.4 ± 17.5	3 : 2	-	100.0

† Significantly lower than other groups (ANOVA: $p < 0.0001$, Bonferroni's analysis: $p < 0.05$).

‡ Significantly higher than that of mast-AE, d-AE and i-AE groups (χ^2 test: $p < 0.0001$).

Data presented above describe the number, mean (±SD) age at onset and first visit, the percentage of patients with a family history, and the gender ratio of the patients in the study, divided into groups according to the etiology of their condition.

Abbreviations: AE, angioedema; HAE, hereditary AE; mast-AE, mast cell mediated AE with urticaria and/or anaphylaxis; d-AE, drug induced AE; i-AE, idiopathic AE; as-AE, asymptomatic C1-inhibitor deficiency.

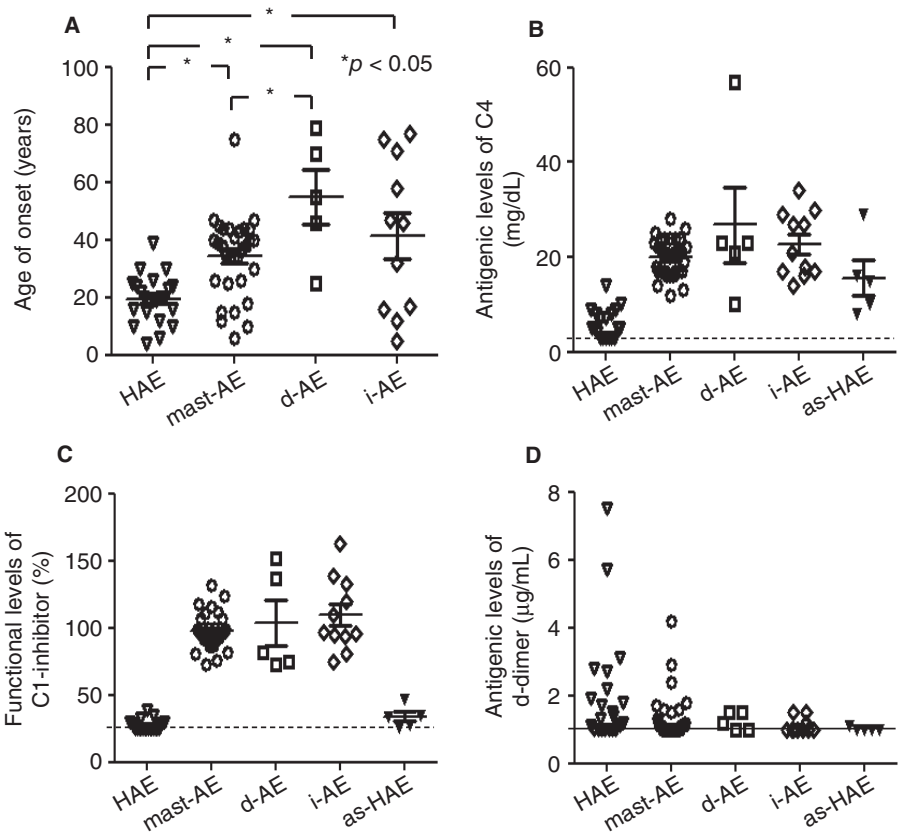

Fig. 1 Distribution of age of onset and serum parameters. **A**: The age of the first symptoms of angioedema (ANOVA: $p < 0.0001$, *Bonferroni's analysis: $p < 0.05$). **B**: Antigenic serum levels of C4. **C**: functional levels of C1-inhibitor. The horizontal broken line represents the limit of quantitation. **D**: Antigenic levels of d-dimer. The horizontal line represents the upper limit of normal range. Abbreviations: HAE, hereditary angioedema; mast-AE, mast cell-mediated angioedema with urticaria and/or anaphylaxis; d-AE, drug-induced angioedema; i-AE, idiopathic angioedema; as-HAE, asymptomatic relatives of HAE.

any groups. However, the age of AE onset in the HAE group (19.5 ± 8.0 years) was significantly lower than that of the mast-AE, d-AE and i-AE groups (Fig. 1A). A family history of AE was noted in 19 of the 23 HAE patients (82.6%), which was a significantly higher rate than that of the mast-AE, d-AE and i-AE groups (χ^2 test: $p < 0.0001$). Four AE cases with low functional levels of C1-INH, low concentration of C4 and having

Table 2 Laboratory data of HAE patients with no family history of AE

Pt no.	Age of AE onset (years)	C3 (mg/dL)	C4 (mg/dL)	CH50 (IU/mL)	C1-inhibitor		CRP (mg/dL)	IC-C1q (μg/mL)	Cryo	ANA (dilution)	anti-dsDNA ab (IU/mL)	C1q (mg/dL)	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)	IgE (IU/mL)
					antigen (mg/dL)	activity (%)										
18	39	106	7	33	8	29	0.2	<1.5	-	20	<10	12.5	962	88	98	129
28	16	97	5	25.1	<6	<25	0.1	40.8	±	20	<10	6.3	1000	207	245	142
53	6	76	<2	<7	n.t.	<25	0.1	1.8	-	40	<10	n.t.	1215	381	125	173
64	12	87	8	32.3	7	37	0.1	<1.5	-	20	<10	n.t.	800	56	360	35
Normal range		69-128	14-36	25-54	21-39	70-130	<0.3	0-3	-	<80	<12	8.8-15.3	870-1700	110-410	46-260	0-500

Parameters of HAE with no family history are shown above.

Abbreviations: AE, angioedema; HAE, hereditary AE; Pt, patients; no., number; CRP, C-reacting protein; IC-C1q, immunecomplex (C1q-binding assay); Cryo, cryoglobulin; ANA, anti-nuclear antibody; anti-dsDNA ab, anti-double stranded DNA antibody; n.t., not tested.

no family history of AE were diagnosed with HAE with additional findings (Table 2). Patient number (no.) 18, (a 54-year old female) had no positive results in evaluations of immunecomplex (IC), cryoglobulin (Cryo), ANA, anti-double stranded DNA antibody (anti-dsDNA ab) and C1q. Patient no.28, (a 35-year old female) presented with high concentration of IC, but hetero-deletion of exon4 of C1-INH gene was demonstrated (genetic analysis was performed by Professor Takahiko Horiuchi, Internal Medicine, Kyusyu University Beppu Hospital, Oita, Japan). She did not present with any symptoms commonly associated with autoimmune disease and/or infectious disease. The remaining two cases visited our hospital seeking a second opinion. Patient no. 53, (a 42-year old female) presented with repeated severe AE attacks of her face and larynx from the age of 6 and has been treated with C1-INH concentrate three times on demand at a local hospital. Her blood examination showed no positive results for evaluation of IC, Cryo, ANA and anti-dsDNA ab. We could not evaluate the concentration of C1q due to the patient having emigrated. Patient no.64, (a 32-year old male) had experienced abdominal attacks since the age of 12, and had previously been treated with C1-INH concentrate on demand in another hospital. His blood examination showed no positive findings; however, C1q concentration could not be measured. There was only one case of i-AE (a 26-year old female) whose mother occasionally experiences AE attacks on her eye lids, from age 5, and abdomen, from age 24. She showed no efficacy with H_1-blockade and corticosteroids. There was also no diagnostic evidence in her blood examination. There were no differences in the laboratory data, such as blood cell counts, Eo, TP, Alb, Cr, CRP and IgE, between AE groups (data not shown).

ANGIOEDEMA LOCATION

Facial edema, including lips, were common in all groups of AE (Table 3). Extremities and GI tract AE were noted in the majority (60 to 80%) of HAE patients, in comparison to other AE types (10 to 20%). Tongue and/or oral cavity AE were remarkable symptoms present in 80% of patients with d-AE. Laryngeal edema was most frequently observed in the HAE group (39.1%) compared to mast-AE (18.1%), d-AE (20%) and i-AE (18.1%). Suffocation (subjects had undergone airway management) was observed in 30.4% of HAE patients and 2 of them had undergone tracheotomy. Genital AE was observed in HAE and i-AE patients but not mast-AE and d-AE patients. Amongst our subjects, there were no patients who had undergone abdominal surgery due to abdominal pain.

EVALUATION OF BIOMARKERS

Except for one as-HAE patient whose serum C3 level was slightly below normal (67 mg/dL), serum C3 lev-

Table 3 Details of angioedema location

	Subcutaneous AE						Mucosal AE at air way				Mucosal AE at GI tract	
	Hand *n* (%)	Foot *n* (%)	Trunk *n* (%)	Face *n* (%)	Neck *n* (%)	Genital *n* (%)	Laryngeal *n* (%)	Tongue, oral cavity *n* (%)	Nasal cavity *n* (%)	Suffocation *n* (%)	Admission *n* (%)	Symptoms of abdominal pain *n* (%)	Admission *n* (%)
HAE	18 (78.2)	16 (69.5)	3 (13.0)	9 (39.1)	5 (21.7)	5 (21.7)	9 (39.1)	3 (13.0)	-	7 (30.4)	3 (13.0)†	14 (60.8)	4 (17.3)
mast-AE	7 (21.1)	7 (21.1)	4 (12.1)	27 (81.8)	2 (6.0)	-	6 (18.1)	4 (12.1)	-	3 (9.0)	1 (3.0)	5 (15.1)	1 (3.0)
d-AE	-	-	-	4 (80.0)	1 (20)	-	1 (20)	4 (80)	1 (20)	-	-	-	-
i-AE	1 (9.0)	1 (9.0)	-	6 (54.5)	1 (9.0)	1 (9.0)	2 (18.1)	4 (36.3)	-	2 (18.1)	-	3 (27.2)	1 (9.0)

† Including 2 patients who had history of emergency tracheotomy.

The percentage of patients suffering subcutaneous angioedema in different areas of skin, as well as mucosal angioedema in different sections of the airway and in the gastrointestinal tract are shown above. Patients are divided into groups based on the etiology of their condition.

Abbreviations: AE, angioedema; GI, gastrointestinal; HAE, hereditary AE; mast-AE, mast cell mediated AE with urticaria and/or anaphylaxis; d-AE, drug induced AE; i-AE, idiopathic AE.

els in all patients were within the normal range (Table 4). In 22 of 23 patients with HAE (95.6%) the serum C4 levels were below the lower limit of the normal range (14 mg/dL) and 4 HAE patients (17.3%) presented extremely low levels of C4 below the limit of quantitation (LOQ, <2 mg/dL) (Fig. 1B). In 2 of 5 patients with as-HAE (40%) serum C4 levels were less than the lower limit of the normal range. In 2 of 33 patients with mast-AE (6.0%) and 1 of 5 patients with d-AE serum C4 levels were low (12, 13 and 10 mg/dL respectively). Patients with low CH50 levels were limited to the HAE and as-HAE groups. A total of 11 of 23 patients with HAE (47.8%) and 1 of 5 patients with as-HAE (20%) presented CH50 levels below the lower limit of the normal range (25 U/mL). Levels of CH50 were lower than the LOQ (<7 U/mL) in 2 of 23 patients with HAE (8.6%) but none of the as-HAE patients had serum CH50 levels that were extremely low. A functional level of C1-INH less than 50% of normal was the diagnostic criterion used to diagnose HAE, and patients with HAE and as-HAE fulfilled that criterion (Fig. 1C). Furthermore, 14 of 23 (60.8%) patients with HAE presented functional levels of C1-INH below the LOQ (<25%).

DIFFERENTIATION OF SUBJECTS

Figure 2 shows the differentiation of all subjects. The results show that low C4 levels have a high sensitivity and specificity for the diagnosis of HAE (95.6% and 93.8%, respectively) irrespective of whether the patients have a family history of AE. Of the four exceptions, the first was a 17-year old female who had a family history of AE and low C4 (13 mg/dL), but who was not diagnosed with HAE (labeled 'a' in Fig. 2). Since she had multi-drug allergy, and H_1-blockade was successful at treating swelling on her facial region and legs, she was diagnosed as having mast-AE. The second was an HAE patient who had a positive family history of AE and who was within the lower limit of serum levels of C4 (14 mg/dL), but whose low serum C4 concentration (7 mg/dL) was obtained during an attack ('b' in Fig. 2). The third was a 19-year old male who had no family history of AE but had low C4 (12 mg/dL), and was diagnosed with mast-AE because lip and GI tract AE occurred after urticaria. His symptoms responded well to H_1-blockade treatment ('c' in Fig. 2). Finally, a 46-year old female, who had no family history of AE but had low C4 (10 mg/dL), was diagnosed with d-AE because her facial AE attacks disappeared after discontinuation of loxoprofen ('d' in Fig. 2).

Serum concentration of fibrinogen was distributed within a normal range and showed no statistical difference between each group (data not shown). In contrast to fibrinogen, 16 cases of HAE (69.5%), 19 of mast-AE (57.5%), 3 of d-AE (60%), 3 of i-AE (27.2%) and 4 of as-AE (40%) presented a higher concentration of d-dimer than the normal range of <1 μg/mL

Table 4 Biomarkers in HAE

	C3 (mg/dL)		C4 (mg/dL)				CH50 (U/mL)				C1-INH activity (%)			
	Results	BNR *n* (%)	Results†	Within NR *n* (%)	Below NR *n* (%)	Below LOQ *n* (%)	Results†	Within NR *n* (%)	Below NR *n* (%)	Below LOQ *n* (%)	Results†	Within NR *n* (%)	<50% *n* (%)	Below LOQ *n* (%)
HAE	105.5 ± 18.9	0 (0.0)	6.3 ± 4.6	1 (4.3)	22 (95.6)	4 (17.3)	27.4 ± 13.3	13 (56.5)	11 (47.8)	2 (8.6)	31.0 ± 15.6†	0 0	23 (100.0)	14 (60.8)
mast-AE	98.5 ± 15.5	0 (0.0)	19.9 ± 4.0	31 (93.9)	2 (6.0)	0 (0.0)	41.9 ± 7.2	33 (100.0)	0 (0.0)	0 (0.0)	97.5 ± 13.4	33 (100.0)	0 (0.0)	0 (0.0)
d-AE	114.2 ± 21.2	0 (0.0)	26.8 ± 17.7	4 (80.0)	1 (20.0)	0 (0.0)	48.5 ± 11.3	5 (100.0)	0 (0.0)	0 (0.0)	103.8 ± 37.6	5 (100.0)	0 (0.0)	0 (0.0)
i-AE	97.1 ± 22.3	0 (0.0)	22.7 ± 6.8	11 (100.0)	0 (0.0)	0 (0.0)	43.6 ± 8.6	11 (100.0)	0 (0.0)	0 (0.0)	109.3 ± 26.8	11 (100.0)	0 (0.0)	0 (0.0)
as-HAE	106.3 ± 17.0	1 (20.0)	20.3 ± 4.5	3 (60.0)	2 (40.0)	0 0	27.3 ± 10.9	4 (80.0)	1 (20.0)	0 (0.0)	34.0 ± 8.2	0 (0.0)	5 (100.0)	0 (0.0)
Normal range	69-128		14-36				25-54				70-130			

† Mean ± SD was calculated from the patients whose results were within measurement sensitivity.

The mean levels of C3, C4, CH50 and C1-inhibitor (C1-INH) levels measured in patients with various angioedema etiologies are shown above.

Abbreviations: NR, normal range; LOQ, limit of quantitation; AE, angioedema; HAE, hereditary AE; mast-AE, mast cell mediated AE with urticaria and/or anaphylaxis; d-AE, drug induced AE; i-AE, idiopathic AE; as-AE, asymptomatic C1-inhibitor deficiency.

(Fig. 1D).

DISCUSSION

Early diagnosis and treatment is key in patients with HAE although the low awareness of HAE amongst medical staff in Japan is a serious problem.[8] Recent national reports have suggested a similarity between Japanese HAE patients and patients in other countries, in terms of a slight female predominance, age of onset, percentage of sporadic cases, and frequencies of abdominal and respiratory symptoms.[3,4] However, the many classifications of AE, defined from clinical symptoms and pathophysiological viewpoints, have led physicians to confuse the differential diagnosis of AE.[5,7] Thus, the predominance of HAE in all types of AE has been not clarified. A Japanese national survey indicated the prevalence of HAE was 13% among 41 patients of AE.[9] Our observations in this retrospective study have highlighted characteristics that may aid physicians in correctly diagnosing HAE in patients during the first contact.

Evaluating the past histories, age of onset and location of AE in patients is very informative. The mean age of onset in the HAE group was significantly lower than that in other groups with a range of 4 to 39 years. However, some patients with a young age of onset were observed in mast-AE and i-AE, and therefore the age of onset of AE was not a decisive indicator for differential diagnosis of HAE. In patients with HAE, 82.6% had a positive family history of AE and the remaining cases of HAE would involve de novo mutation. Previous western studies have also estimated that HAE patients with autosomal dominant trait account for 75 to 80% and de novo mutations account for at least 20 to 25% of all HAE patients.[1,2,5,10] In order to confirm a diagnosis of HAE, patients with acquired AE have to be excluded. Although the Japanese health insurance system does not cover evaluation of the antigenic level of C1-INH and C1q, we performed further blood examination for differential diagnosis of acquired AE using research budget. Although patient no.28 had a confirmed genetic abnormality of C1-INH, she presented with high serum concentration of IC. Looking forward, we have to be aware of the signs of autoimmune disease which are often associated with HAE.[11] Both patients no.53 and 64 had a history of early onset of AE. Although we could not evaluate the concentration of C1q, they presented no other positive findings of acquired AE and activators of the classical pathway. Because new onset of acquired AE after the age of 40[12] and positivity of low concentration of C1q for acquired AE have been reported 70%,[13] we provisionally diagnosed them with HAE.

All types of AE share facial AE, the so-called "Quincke's edema". By contrast, extremities and genital AE were observed in over 65% and 20% of patients with HAE, respectively, therefore attention

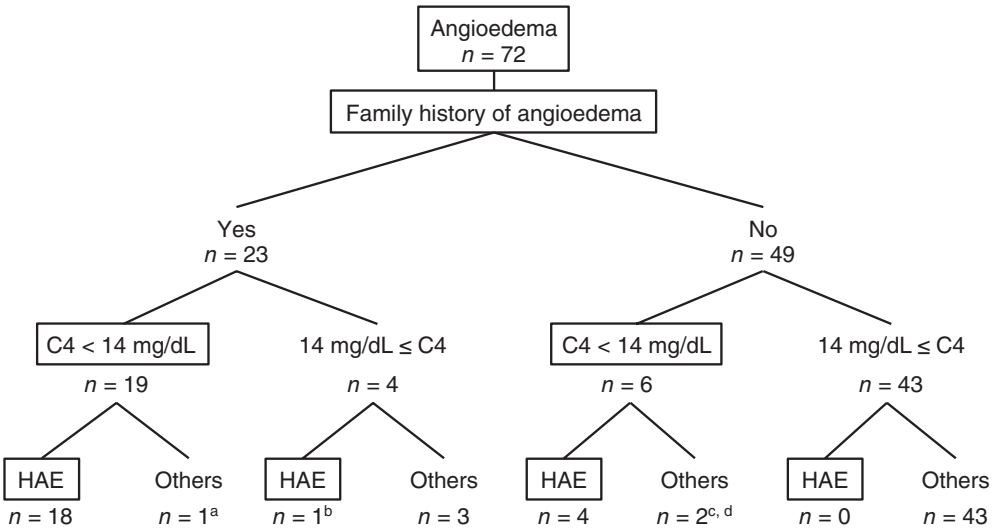

Fig. 2 Differentiation of subjects. With the possible exception of acquired AE, low C4 is a distinctive characteristic for differentiating HAE. Details of each patient (a, b, c, d) refer to results in the text.

should be paid to swelling in these areas of a patient's body. Oral cavity and laryngeal AE were observed in all groups of AE but suffocation was observed in HAE and mast-AE. Thus, a history of tracheotomy is an important indicator for the diagnosis of HAE. As abdominal attacks were observed in over 60% of patients with HAE, repeated abdominal attacks and any admissions for abdominal pain might become diagnostic hallmarks. In a patient survey among 209 German HAE patients, the frequencies of AE in the extremities, genitalia and larynx were 93.8%, 62.7% and 54% respectively.[2] Although the frequency in our subjects was less than this report, we can state that the location of AE in Japanese and German patients shows the same tendency.

As the results of serum C4 concentration tests can be obtained within several hours to a day, the World Allergy Organization (WAO) guideline recommends C4 as the single best screening test, and repeating C4 tests during an attack increases the probability that a low C4 concentration will be found.[5] In our results, the low serum levels of C4 showed a high level of sensitivity (95.6%) and specificity (93.8%) for HAE. In only one case of HAE were C4 levels slightly higher than the lower limit of the normal level of C4, but even in this case, the second measurement showed a low C4 concentration during an attack. Although the WAO did not include Japanese data, the measurement of serum C4 levels may be useful for screening HAE in Japanese patients. Low titers of CH50 were only observed in HAE (47.8%) and as-HAE patients (20%), and 8.6% with patients of HAE presented a CH50 titer value below LOQ. Since as-HAE presented a low prevalence of low serum C4 levels, complement classical and lectin pathways might be relatively well controlled regardless of the low functional levels of C1-INH. In the context of differentiating between types of AE, we have to first check for acquired AE by observing a patient's symptoms and laboratory findings. However, as it is difficult to discriminate HAE from mast-AE, low serum C4 levels are a useful indicator of HAE that can be tested quickly ahead of the results of C1-INH activity.

C1-INH has several inhibitory activities as a "serpin"; it inhibits not only the contact system but also the complement and fibrinolytic systems. Since d-dimer is a fibrin degradation product, HAE patients in remission often present with a high serum level of d-dimer, and during attacks, HAE patients present with a further elevation of d-dimer.[14,15] In our results, HAE and mast-AE patients presented relatively higher serum levels of d-dimer than patients with other types of AE, but there were a few cases with high serum d-dimer levels in d-AE or i-AE groups. Previous reports have indicated that a high serum d-dimer concentration may be present in patients with chronic urticaria,[12,16] indicating that there are common mechanisms that lead to elevated serum d-dimer concentrations. The measurement of d-dimer therefore was not a decisive differentiator for HAE.

In conclusion, this study underlines the importance of clinical characteristics of HAE for diagnosis, such as the early onset of AE, a family history of AE, and recurrent AE located in the extremities, genitals and GI tract. In laboratory findings, a low serum C4 level is an excellent marker for the differential diagnosis of HAE over other types of AE.

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