

Risk factors for diagnostic delay in Chinese patients with hereditary angioedema

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ABSTRACT

Background: Hereditary angioedema (HAE) is still underdiagnosed or diagnosed after a serious delay. This study aimed to evaluate the diagnostic delay (DD) and misdiagnosis of HAE, and to explore the risk factors associated with a longer DD.

Methods: An Internet-based survey was sent to 129 patients with type 1 and 2 HAE who presented to the Allergy Department, Peking Union Medical College Hospital between 1983 and 2017; 107 patients (82.9%) responded, among whom, a total of 96 patients provided complete information about medical visits. DD was divided into two subperiods according to the lower quartile, i.e., $DD \leq 6$ years and $DD > 6$ years.

Results: The median DD of all 96 patients with HAE was 11.04 years (interquartile range [IQR], 6.06–18.27 years). A significant difference ($p < 0.001$) in the median DD was found between different decades of onset, i.e., before 1999 (19.75 years [IQR, 13.58–29.50 years]), between 2000 and 2009 (8.67 years [IQR, 5.67–11.04 years]), and between 2010 and 2017 (3.79 years [IQR, 2.29–5.71 years]). Patients with a previous misdiagnosis experienced a longer median delay to complement 1 inhibitor HAE diagnosis (13.17 years [IQR, 7.40–20.50 years]) compared with patients without a previous misdiagnosis (median 6.96 years [IQR, 2.83–10.65 years]; $p \leq 0.001$). According to the logistic regression analysis, a younger age of onset and earlier decade of onset were significant predictors of a DD of >6 years. The most frequently visited departments and most frequently misdiagnosed diseases were summarized.

Conclusion: The median DD of patients with HAE was 11.04 years (IQR, 6.06–18.27 years). A younger age of onset and earlier decade of onset were predictors of a DD of >6 years. Seventy-five percent of the patients reported receiving more than one previous misdiagnosis. The patients with a previous misdiagnosis had longer DDs compared with patients without a misdiagnosis.

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Hereditary angioedema (HAE) is a rare autosomal dominant disorder that is characterized by unpredictable and recurrent attacks of painful swelling that typically involve the extremities, bowel mucosa, genitals, face, and upper airway.¹ The following three forms of HAE have been recognized: (1) type 1 HAE, which is due to a complement C1 inhibitor (C1-INH) deficiency and is characterized by low C1-INH levels

and function; type 2 HAE, which is caused by C1-INH dysfunction and is characterized by normal or slightly higher C1-INH levels but impaired function; and (3) HAE with normal C1-INH levels and function, which involves a mutation in either the F12 gene, the angiotensin-converting enzyme gene, or the plasminogen gene.² HAEs due to C1-INH (types 1 and 2) have an estimated prevalence of 1/50,000, with no gender difference.³

The heterogeneity of the disease manifestation and the difficulties in differentiating HAE symptoms from those of more common angioedema subtypes account for the tendency of misdiagnosis and lead to DDs that are typically 8–10 years.^{4–6} When considering the high lifelong risk of laryngeal edema, the delayed diagnosis and treatment of HAE constitute a danger to patients.⁷ Delayed diagnoses and inappropriate treatment cause great economic and psychological burdens for patients, which gives rise to higher morbidity and mortality, adverse events, and unnecessary treatment and procedures.^{8,9}

A previous study reported the mean (range) DD for HAE to be 12.64 years (1 month to 45 years) on the Chinese mainland.¹⁰ However, the percentage of misdiagnoses, number of medical visits before diagnosis, frequently visited departments, and risk factors associated with a longer DD were not explored. Thus, the aim of our study was to systematically

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evaluate the trend to misdiagnose HAE in China and to identify putative risk factors that are associated with a longer DD.

METHODS

Study Population

Patients who presented to the Department of Allergy, Peking Union Medical College Hospital, from 1983 to 2017 with a final diagnosis of HAE type 1 or 2 were identified through medical records. The inclusion criteria were as follows: (1) a history of recurrent angioedema without urticaria, and/or recurrent attacks of abdominal pain and vomiting, and/or laryngeal edema; (2) decreased C1 inhibitor levels and function confirmed by repeated measurements for type 1 HAE; or (3) normal or slightly increased serum C1 inhibitor levels and lower function confirmed by repeated measurements for type 2 HAE. Although some patients described their family members as having similar symptoms, only patients with medical records in our center were included in this study. Among the 400 patients with HAE identified, 129 were followed up regularly in our center. Most of these patients were probands, which means that they usually presented with more severe symptoms than their family members. An Internet-based questionnaire and informed consent were sent to the 129 patients, and a total of 107 patients completed the Internet-based questionnaire, independently or with the help of others. The study protocol was approved by the research and ethics board of the Peking Union Medical College (S-K661). Informed consent was obtained from all patients before the study questionnaires were completed. S. Liu, X. Wang, and Y. Zhi conceptualized the study; S. Liu and Y. Xu acquired the data; S. Liu, X. Wang, Q. Xu, and Y. Zhi interpreted the data; and S. Liu and Y. Zhi prepared the manuscript. All the authors participated in reviewing and editing the manuscript and in the approval of the finalized manuscript.

Questionnaire Development

The questionnaire was developed by using the wxj online survey platform (Changsha Ranxing Information Technology Co., Ltd., Changsha, P.R.C.). The questionnaire contained a majority of close-ended questions with defined response categories. A small number of questions asked participants to provide descriptive information in the open-ended text box. A pilot questionnaire was sent to seven patients who volunteered to develop the final version. The final version of the questionnaire was sent to the 129 patients with HAE. The participants were informed of the information about the survey, including the purpose, the agency conducting the research, and privacy protection. The survey had five sections that measured the demographic data, body measurement,

clinical characteristics, socioeconomic issues, and health-related quality of life.

DD

We calculated the DD as the time lapse between the onset of symptoms indicative of HAE and the final diagnosis. The DD was divided into two subperiods (≤ 6 years and > 6 years) according to the lower quartile to further explore its risk factors. We also evaluated the number of medical visits before the correct diagnosis, the most frequently visited medical departments, and the percentage and type of misdiagnoses.

Severity Evaluation

We proposed a scoring system to evaluate the clinical severity of patients with HAE before a definite diagnosis. This evaluation system takes into account the edema location, frequency, and need for emergency treatment. Patients with skin edema only and an attack frequency of fewer than once a month are defined as having mild HAE. Patients with a skin edema frequency of more than once in a month or patients with mucosal (laryngeal, gastrointestinal) edema without needing emergency treatment are defined as having moderate HAE. Severe HAE is defined as being those patients who have mucosal edema and need emergency treatment.

Statistical Analysis

The data were exported *via* the wxj online survey platform and was checked through internal error detection. All statistical analyses were performed by using SPSS 23.9 software (SPSS, Inc., Armonk, New York, U.S.). The results are expressed as either the median and the interquartile range (IQR) for non-normal data, or the mean $\pm$ standard deviation for normally distributed data. Categorical data are summarized as the percentage of the total group. Differences in quantitative data distributions between patient subgroups were compared by using the Student's *t*-test for normally distributed data or the Wilcoxon rank sum test for non-normal data. Differences in frequencies for categorical data were compared by using the χ^2 test. Pearson correlation analysis was applied to explore the correlation between two variables. Full-model logistic regression analysis was used to determine the value of gender, education level, onset age, onset decade, skin edema, laryngeal edema, gastrointestinal edema, severity, and family history in predicting a longer DD in patients with HAE. A *p* value of < 0.05 (two-tailed) was considered statistically significant.

RESULTS

Baseline Patient Characteristics

Among the 107 patients with HAE who responded to the Web-based survey, 96 patients (89.7%) sought med-

ical help before eventually receiving a diagnosis of HAE. Eleven patients did not present to hospitals for evaluation until their family members received a diagnosis of HAE and then were finally diagnosed as having HAE according to the criteria. These 96 patients with HAE were included in the study. Baseline demographics and clinical characteristics are shown in Table 1.

Length of DD

The median DD of all 96 patients with HAE was 11.04 years (IQR, 6.06–18.27 years). We stratified the patients into subgroups according to different factors. The median (IQR) DD of each subgroup is shown in Table 2. A significant positive correlation was detected between DD and age at diagnosis (correlation coefficient = 0.647; $p \leq 0.001$), whereas a significant negative correlation was revealed between DD and age of onset (correlation coefficient = -0.319; $p = 0.002$) in all the patients with HAE.

Patient Distribution in the DD Subperiods

When we analyzed the results according to the two DD lengths (≤ 6 years and >6 years divided by lower quartile), we detected certain significant differences in the features of patients with HAE between the two subgroups (Table 3). The onset age of patients with a DD of ≤ 6 years was higher than in patients with a longer DD. In the DD of the ≤ 6 years subgroup, more patients had their first edematous attack after 2010. A higher percentage of gastrointestinal edema was detected in the patients with a DD of >6 years. The severity distribution also differed between the subgroups, with significantly more patients with severe HAE in the DD >6 years subgroup. Gender, diagnostic era, education level, attack frequency, and family history did not significantly differ between the subgroups.

Risk Factors for a Longer DD in the Past 3 Decades

Logistic regression analysis was applied to explore the relationship between DD (≥ 6 years versus <6 years subgroups) and potential risk factors, such as gender (female versus male), education level (tertiary education versus primary or secondary education), age of onset (per year), decade of onset (after 2000 versus before 1999), the presence of laryngeal edema (positive versus negative), presence of gastrointestinal edema (positive versus negative), severity (mild as reference), and family history (positive versus negative). According to this logistic regression analysis (Table 4), a younger age of onset and earlier decade of onset were shown to be significant predictors of a DD of >6 years.

Table 1 Baseline characteristics of the 96 patients with HAE

Characteristic	Result
C1-INH HAE diagnosis, <i>n</i> (%)	
Type 1	92 (95.8)
Type 2	4 (4.2)
Gender, <i>n</i> (%)	
Male	43 (44.8)
Female	53 (55.2)
Education, <i>n</i> (%)	
Primary or secondary education	65 (67.7)
Tertiary education	31 (32.3)
Age in the baseline survey, <i>n</i> (%)	
11–30 y	29 (30.2)
31–44 y	46 (47.9)
45–68 y	21 (21.9)
Age at symptom onset, <i>n</i> (%)	
0–10 y	15 (15.6)
11–20 y	52 (54.2)
21–40 y	29 (30.2)
Decade of onset, <i>n</i> (%)	
Before 1999	45 (46.9)
2000–2017	51 (53.1)
Decade of diagnosis, <i>n</i> (%)	
Before 2009	21 (21.9)
2010–2017	75 (78.1)
Ever had skin edema, <i>n</i> (%)	
Yes	95 (99.0)
No	1 (1.0)
Ever had gastrointestinal edema, <i>n</i> (%)	
Yes	74 (77.1)
No	22 (22.9)
Ever had laryngeal edema, <i>n</i> (%)	
Yes	33 (34.4)
No	63 (65.6)
Severity before the diagnosis, <i>n</i> (%)	
Mild	11 (11.5)
Moderate	11 (11.5)
Severe	74 (77.0)
Annual attack frequency, median (IQR), no. attacks	8 (3.1–12)
No. attacks in past 4 wk, median (IQR)	1 (1–2)
Family history, <i>n</i> (%)	
Yes	64 (66.7)
No	32 (33.3)

HAE = Hereditary angioedema; C1-INH = complement 1 inhibitor; IQR = interquartile range.

Most Frequently Visited Medical Departments and Reported Misdiagnoses

The patients reported visiting median 4 hospitals (IQR, 3–8 hospitals) and median 6 physicians (IQR, 4–10.75 physicians) before confirming the diagnosis of

Table 2 Lengths of diagnostic delay in different subgroups of the patients

		<i>p</i>
C1-INH HAE type		0.140
1	11.38 (6.33–19.40)	
2	4.88 (2.04–14.65)	
Gender		0.199
Male	9.25 (5.50–16.50)	
Female	11.92 (7.46–21.54)	
Education		0.590
Primary or secondary education	11.67 (5.42–21.54)	
Tertiary education	9.83 (6.92–16.50)	
Decade of onset		<0.001
Before 1999	19.75 (13.58–29.50)	
2000–2017	6.91 (4.58–9.83)	
Decade of diagnosis		0.193
Before 2009	9.75 (3.58–16.04)	
2010–2017	11.08 (6.58–20.25)	
Ever had laryngeal edema		0.016
Yes	12.75 (7.33–21.25)	
No	8.17 (4.50–16.04)	
Ever had gastrointestinal edema		0.013
Yes	13.17 (7.40–20.50)	
No	6.79 (3.56–13.35)	
Previous misdiagnosis		<0.001
Yes	13.17 (7.40–20.50)	
No	6.96 (2.83–10.65)	
Family history of HAE		0.506
Yes	10.75 (6.33–16.75)	
No	12.21 (5.88–21.83)	

C1-INH = Complement 1 inhibitor; HAE = hereditary angioedema.

HAE. Seventy-five percent of the patients received more than one previous misdiagnosis. The most frequently visited medical departments are summarized in Fig. 1. The most popular departments that patients with HAE went to were the emergency department (90.6%), dermatology (71.9%), allergy (61.5%), gastroenterology (52.1%), health centers or clinics (42.7%), rheumatology (34.4%), and otolaryngology (34.4%). The most frequent misdiagnoses reported by patients are listed in Supplemental Table 1. The most common misdiagnoses received by patients with HAE included acute gastroenteritis, allergy (unspecified), urticaria, gastrointestinal disease (unspecified), and appendicitis.

DISCUSSION

To our knowledge, this was the first study to explore the DD of HAE and the associated risk factors in Chinese patients with HAE across an extended period. The median DD of patients of HAE in this survey was 11.04 years (IQR, 6.06–18.27 years). For comparison, a U.K.

national audit in 2013 reported an average DD of 10 and 18 years for type 1 and type 2 HAE, respectively.⁵ A multinational study of 418 patients in 2016 identified a DD of 8.5 years for C1-INH HAE.¹³ Also, an improvement of DD over time was observed in two studies.^{11,12} The median DD was reduced from 12.64 years in 2013 to 11.04 years in the current study which also indicated a reduction in DDs.¹⁰

Frequent initial misdiagnoses was considered as a major driver of the long delays.¹³ The Icatibant Outcome Survey study group reported that 185 of 418 patients (44.3%) had received at least one misdiagnosis.¹³ In the current study, 75% of the patients reported receiving more than one misdiagnosis, and patients with an initial misdiagnosis experienced longer median delays to the C1-INH HAE diagnosis compared with those without an initial misdiagnosis. Patients with laryngeal edema reported a longer DD compared with those without laryngeal edema in the current study. However, when stratifying the patients according to the lower DD quartile, the difference in

Table 3 Distribution of clinical features in two subgroups according to the length of DD

	DD		<i>p</i>
	≤6 Years (<i>n</i> = 24)	>6 Years (<i>n</i> = 72)	
Gender, <i>n</i> (%)			0.305
Male	13 (54.2)	30 (41.7)	
Female	11 (45.8)	42 (58.3)	
Onset age, mean ± standard deviation, y	22.3 ± 8.0	16.1 ± 6.2	<0.001
Age at diagnosis, median (IQR), y	26.0 (18.8–30.0)	29.5 (26.0–40.0)	0.003
Decade of onset, <i>n</i> (%)			<0.001
Before 1999	2 (8.3)	43 (59.7)	
2000–2017	22 (91.7)	29 (40.3)	
Decade of diagnosis, <i>n</i> (%)			0.318
Before 2009	7 (29.2)	14 (19.4)	
2010–2017	17 (70.8)	58 (80.6)	
Education level, <i>n</i> (%)			0.409
Primary or secondary education	14 (58.3)	35 (48.6)	
Tertiary education	10 (41.7)	37 (51.4)	
Attack location, <i>n</i> (%)			
Skin edema	23 (95.8)	72 (100.0)	0.082
Laryngeal edema	12 (50.0)	51 (70.8)	0.063
Gastrointestinal edema	14 (58.3)	60 (83.3)	0.012
Severity before diagnosis, <i>n</i> (%)			0.001
Mild	7 (29.2)	4 (5.6)	
Moderate	5 (20.8)	6 (8.3)	
Severe	12 (50.0)	62 (86.1)	
Annual attacks, no. attacks, median (IQR)	4.5 (1.5–12.0)	9.0 (4.1–12.0)	0.119
Family history of HAE, <i>n</i> (%)	15 (62.5)	49 (68.1)	0.617

DD = Diagnostic delay; IQR = interquartile range.

Table 4 Predictors of a diagnostic delay of >6 years in patients with hereditary angioedema (logistic regression)

	Multivariate Logistic Regression	
	Odds Ratio (95% confidence interval)	<i>p</i>
Female vs male	1.00 (0.26–3.84)	0.998
Tertiary education vs primary or secondary education	1.23 (0.30–5.00)	0.773
Age at onset (year)	0.86 (0.77–0.96)	0.006
Decade of onset: after 2000 vs before 1999	0.05 (0.01–0.30)	0.001
Laryngeal edema: yes vs no	2.56 (0.48–10.66)	0.305
Gastrointestinal edema: yes vs no	3.06 (0.56–16.63)	0.196
Severity: moderate or severe vs mild	0.38 (0.02–9.38)	0.553
Family history of HAE: yes vs no	0.39 (0.09–1.75)	0.219

laryngeal edema percentage between the subgroups was only borderline significant ($p = 0.063$). Further validation based on a larger population is warranted.

Logistic regression revealed that a younger age of onset and an earlier decade of onset were significant predictors of a DD of >6 years. Earlier onset age was

associated with longer DDs in previous studies.^{6,7} Besides, patients with a higher age of onset may be able to describe and research their symptoms better. As for the onset decade, the advancement of medical knowledge access and progress of awareness among clinicians in recent years may account for the improvement.

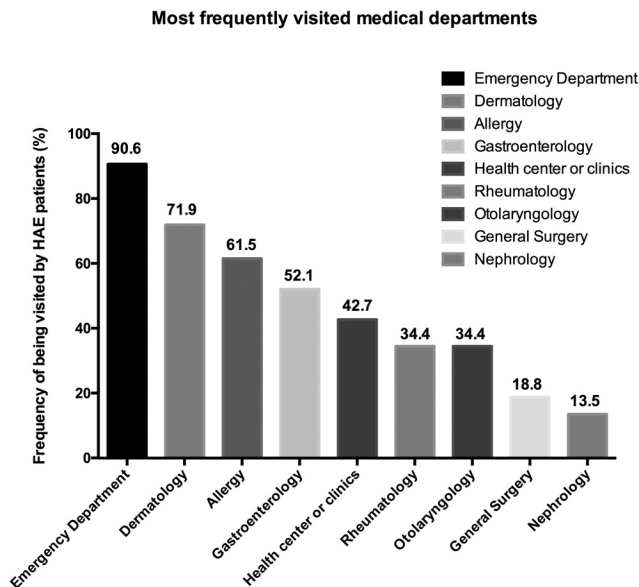


Figure 1. The most frequently visited departments that patients with HAE reported to have gone to were the emergency department (90.6%), dermatology (71.9%), allergy (61.5%), gastroenterology (52.1%), health centers or clinics (42.7%), rheumatology (34.4%), otolaryngology (34.4%), general surgery (18.8%), and nephrology (13.5%).

Results of previous studies indicated that testing family members of patients who are proband could help decrease the DD and should be performed as a routine.^{14,15}

Misdiagnoses also lead to a range of improper treatments, such as antihistamines, corticosteroids, and immunosuppressants, which have substantial adverse effects while exerting little clinical efficacy. More importantly, when considering that the lifetime incidence of laryngeal edema is high among patients with HAE, a DD may increase the risk of death.^{9,10} A correct diagnosis, however, could help clinicians to select the appropriate treatment for acute attacks and to initiate long-term prophylaxis treatment, which may partially relieve the personal disruption, economic burden, quality-of-life influence, and medication costs associated with acute attacks.^{16,17}

We summarized the most frequently visited medical departments and the most frequently misdiagnosed disorders. In real-world settings, the substantial heterogeneity in clinical manifestation and the overlap of symptoms with other more common diseases leads to a low clinical suspicion of HAE. Thus, we make the following suggestions to correct the DD. First, with a mechanism to inform clinicians who missed the correct diagnosis of the final diagnosis of HAE, the diagnostic level could be improved to shorten this delay. Second, listing HAE as a differential diagnosis for certain diseases in clinical guidelines may also help physicians and surgeons maintain suspicion of this disease. Third,

future integration of clinical decision support system in practice has the potential to better recognize patients with HAE at initial medical contact.

There were several limitations of the present study. First, <100 patients were included in the analysis, although this was not a small number when considering the rarity of HAE. Second, most of the participants were probands and tended to have more serious conditions, which may have led to an overestimation of the severity of disease. Third, there may be a time lag between improvements in the recognition of the disease and the observation of a decrease in DDs, which may account for certain deviations in the analysis.

CONCLUSION

Analysis of our data indicated that the median DD of patients with HAE was 11.04 years (IQR, 6.06–18.27 years). A younger age of onset and earlier decade of onset were predictors of a DD of >6 years. Seventy-five percent of the patients reported more than one previous misdiagnosis. The patients with a previous misdiagnosis had a longer DD compared with patients without a misdiagnosis. However, further investigations that incorporate more representative subjects are warranted.

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