Type I hereditary angioedema in Taiwan – clinical, biological features and genetic study

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Summary

Background: **Hereditary angioedema (HAE) is a rare, autosomal dominant inherited disease which is caused by a genetic deficiency of C1 esterase inhibitor (C1 INH). There have only been a few case reports in Taiwan to date.**

Objective: **To describe the clinical features of type I HAE in Taiwanese patients.**

Methods: **Three unrelated Taiwanese families with type I HAE are reported, and one case of a family from a review of PubMed was reviewed. Clinical manifestations, diagnostic examinations, management and genetic studies were analyzed.**

Results: **Including this report, 19 patients had low C1 INH and low C4 levels and were diagnosed with type I HAE. Only 11 (57.9%) patients were symptomatic. Recurrent skin swelling and edema over the four extremities or trunk were reported in all symptomatic patients (100%). 45.5% of the patients recalled laryngeal attacks and one patient died from asphyxia. 18.2% of the patients experienced abdominal symptoms. The age at the beginning of clinical symptoms ranged from 5 to 30 years (mean ± SD: 20.82 ± 7.88 years). The diagnosis tended to be delayed (range from 1 to 39 years; mean ± SD: 8.45 ± 11.04 years). Nine patients had a mutant *C1 INH* gene, and two patients received long-term prophylaxis with danazol.**

Conclusion: **The prevalence of hereditary angioedema in Taiwan is low. Persons with low levels of C1 INH who were clinically symptomatic accounted for only 57.9% of the cases in our study, which is far lower than previous reports from other countries. Ethnic differences may be the reason for this finding. Further genomic studies are needed to elucidate the genetic penetrance of C1 INH deficiency in Taiwan.** ***(Asian Pac J Allergy Immunol 2011;29:327-31)***

Key words: *HAE, prevalence, asymptomatic, genetic, Taiwan*

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Submitted date: 25/7/2011
Accepted date: 31/10/2011

Introduction

Hereditary angioedema is a rare autosomal dominant disorder resulting from a genetic defect involving the *C1 INH* gene mapping to the long arm of chromosome 11. More than 150 different *C1 INH* gene mutations have been described in HAE[1] and three subtypes of HAE have been defined to date. Type I HAE, which accounts for 85% of cases, is characterized by functional and antigenic C1-inhibitor (C1 INH) deficiency. Type II HAE, which accounts for 15% of cases, is characterized by normal or upper normal C1 INH antigenic levels but no functional activity.[2] Type III HAE, also known as HAE with normal levels of C1 inhibitor, is characterized by a coagulation factor XII gene mutation and is seen primarily in women.[3-5] The prevalence of HAE is about 1 per 50000 to 100000 individuals in Western countries.[6-12] The age of first attack is usually around the first or second decade of life. The three most commonly affected anatomical sites during attacks are the skin, gastrointestinal tract, and upper airway. Prodromes start with a tingling sensation in the sites that are about to experience an attack. A serpiginous, nonpruritic skin eruption, termed erythema marginatum, is noted on some patients.[13] The severity of each attack ranges from uncomfortable skin swelling to life-threatening laryngeal edema. Untreated patients may experience frequent attacks and the attacks do not respond to treatment with epinephrine, antihistamine or glucocorticoids. When available, the treatment of choice for acute severe attacks is C1INHRP (Berinet®) which is an intravenous plasma-derived C1 esterase inhibitor. A kallikrein inhibitor (Kalbitor®)

has also been recently approved by the U.S. FDA for the treatment of acute attacks in patients older than 16 years. The laboratory diagnosis of HAE is established by demonstrating diminished C4 levels and low C1 inhibitor levels or function. Asymptomatic patients are estimated to account for 5% of all patients with HAE[7]. To date, there have only been a few case reports in Taiwan.[14-16] In this report, we describe four unrelated Taiwanese families with type I HAE. All living members of each family underwent thorough history taking, physical examination and laboratory studies. Two families underwent a genetic survey for the *C1 INH* gene.

Methods

This study is a retrospective chart review. From 2003 to 2011, three index patients from three unrelated families were diagnosed with HAE in the Department of Pediatrics of Taipei Mackay Memorial Hospital. Members from each family were recruited to join this program. In total, 24 members from the three different families were surveyed at Taipei Mackay Memorial Hospital. All of the members were contacted by telephone and asked to complete a questionnaire including personal data, age and age at onset of angioedema symptoms, major past medical history including emergency tracheostomy, and whether any family members had suffered sudden death without a definite cause. Levels of C3, C4, and C1 inhibitor were measured in all members and genetic studies were performed in two of the three families. We also reviewed the published literature on PubMed and found one other family study on HAE in Taiwan which included 11 family members.[14] Levels of C3, C4, and both antigenic and functional levels of C1 inhibitor were measured in all members of this family, however genetic studies were not performed. Among these four families, patients with hereditary antigenic or functional C1 inhibitor deficiency confirmed by laboratory analysis were included in this study. Data were analyzed using a statistical software package (SPSS Base for Windows, version 12.0, SPSS Inc., Chicago, IL, USA).

C3 and C4 analysis

C3 and C4 serum levels were measured using nephelometry in all patients.

C1 inhibitor analysis

C1 esterase inhibitor concentrations were measured by radial immunodiffusion assay.

Table 1. The clinical features of the 19 patients with type 1 HAE.

Clinical features	value
Sex, No. (%)	
M	11 (57.9%)
F	8 (42.1%)
Age, range, (mean ± SD), y	
All patients (symptomatic + asymptomatic)	
At diagnosis	5-69 (28.16 ± 15.64)
Symptomatic patients	
At the start of clinical symptoms	5-30 (20.82 ± 7.88)
At diagnosis	6-69 (29.27 ± 16.47)
Delay in diagnosis	1-39 (8.45 ± 11.04)
HAE type	
Type 1	19 (100%)
Genomic mutation	
Exon 5	6 (31.6%)
Exon 3	3 (15.8%)
Not checked	10 (52.6%)
Family history	
Positive	19 (100%)
Negative	0 (0%)
Clinical manifestations and diagnosis	
Asymptomatic	8 (42.1%)
Symptomatic	11 (57.9%)
Skin/extremities/trunk	11 (100%)
Abdomen	2 (18.2%)
Face/larynx	5 (45.5%)
Trigger factors	
Trauma/compression	8 (72.7%)
Stress/emotion	6 (54.5%)
Infection	2 (18.2%)
Pregnancy/menstruation cycle	2 (18.2%)
Unknown	7 (63.6%)
Long-term prophylaxis with attenuated androgens	2 (18.2% of the symptomatic patients)
Mortality due to asphyxia	1 (9.1%)

C1 inhibitor gene sequencing

Genomic DNA was extracted from peripheral blood leukocytes with a genomic blood DNA purification kit (GFX Purification Kit; Amersham Biosciences UK Ltd., Little Chalfont, Buckinghamshire, England). PCR amplification was performed using a thermocycler (Applied Biosystems, 9700 thermocycler, Foster City, California), in a volume of 50 µL with 0.25 mmol/L dNTPs, 1.75 mmol/L magnesium chloride, 0.2 µM of primers, and 0.1 U of Taq polymerase that amplified exons 1 to 8 as well as exon-intron boundaries.[17-19] The steps were as follows: denaturation

of genomic DNA at 95°C for 10 minutes, 35 cycles of denaturation at 94°C for 1 minute, and extension at 72°C for 10 minutes. The amplified product was purified using the GFX PCR DNA and Gel Band Purification Kit (Amersham Biosciences). DNA sequencing was performed with a sequencing kit (Big Dye Terminator cycle sequencing; Applied Biosystems). The reaction products were purified by Multiscreen-HV plates (Millipore) filled with Sephadex G-50 superfine beads (Amersham Biosciences) and analyzed on an automated DNA sequencer (ABIPRISM 3100; Applied Biosystems). Each DNA sample was sequenced in both directions. All mutations were verified with a second independent PCR product.

Results

Clinical Manifestations

The clinical features of the 19 patients belonging to four unrelated HAE-affected families are listed in Table 1. All patients had a family history of HAE. Among the 19 patients, 11 were male (57.9%) and 8 were female (42.1%). The age at the onset of clinical symptoms was 5-30 years (mean ±SD: 20.82 ±7.88 years) and the age at diagnosis was 6-69 years (mean ±SD: 29.27 ±16.47 years), indicating a period of delay in diagnosis (ranged from 1-39 years, mean ±SD: 8.45 ±11.04 years). All 19 patients had type I HAE.

Eleven (57.9%) patients had symptoms, all of which were recurrent, self-limiting, non-inflammatory subcutaneous angioedema. Two patients (18.2%) had experienced recurrent, self-limiting abdominal attacks without a clear organic etiology. Five patients (45.5%) had experienced recurrent facial/laryngeal edema events. The facial/laryngeal attacks were accompanied by shortness of breath, facial swelling, dyspnea, and even asphyxia. Two patients suffered from severe laryngeal edema and survived after emergency tracheostomy. However, after the tracheostomy, one of the two patients died from a subsequent laryngeal attack.

The first and second leading trigger factors were trauma/compression and unknown cause, accounting for 72.7% and 63.6%, respectively. The third leading cause was emotional stress (54.5%). In two patients episodes were triggered by infective episodes: one during pregnancy and one during menstruation.

Only two patients (one male and one female) accepted long term prophylactic treatment with the attenuated androgen danazol, both of whom were from different families. Initially, the female patient was unable to tolerate the virilizing side effects and shifted prophylaxis temporarily to an antifibrinolytic agent (tranexamic acid). The male patient suffered from frequent attacks triggered by trauma, emotional stress and infection episodes and was also a victim of gall stone disease and cholecystitis. After the infection subsided due to cholecystectomy, the attacks occurred less often. To date, the symptoms have been well controlled with danazol 100 mg per day in both patients, and neither has had a recent attack.

Table 2. Major differences between Asian and Caucasian HAE patients.

Prevalence rate of HAE			
Caucasians		Asians	
Bowen et al.[6] (America)	1/50000	Kesim et al.[20] (Turkey)	9.4/10000000
Stray et al.[8] (Norway)	1.5/100000	Current study (Taiwan)	8.2/10000000
Bygum et al.[9] (Denmark)	1.4/100000	Faiyaz et al.[21] (Saudi Arabia)	5.9/10000000
Olga et al.[10] (Spain)	1.1/100000	Iwamoto et al.[22] (Japan)	4.1/10000000
Starsia et al.[11] (Czechoslovakia)	0.6/100000	Kang et al. [23] (Korea)	3.1/10000000
Wais-Nöcker et al.[12] (Switzerland)	0.5/100000	Ren et al. [24] (China)	0.1/10000000
Agostoni et al.[7] (Italy)	0.4/100000		
Percentage of asymptomatic patients			
Caucasians		Asians	
Agostoni et al.[7] (Italy)	5%	Current study (Taiwan)	42.1%
Wais-Nöcker et al.[12] (Switzerland)	5%	Kodama et al.[28] (Japan)	44%
Bygum et al.[9] (Denmark)	6%		
Olga et al.[10] (Spain)	13.7%		
Starsia et al.[11] (Czechoslovakia)	27%		

Laboratory and Genetic studies

The serum levels of C3 in all 19 patients were normal and the serum levels of C4 in all 19 patients were low. The C1 inhibitor antigenic levels were all less than 50% of normal in all 19 patients. The C1 inhibitor functional levels were checked in seven patients and were found to be less than 50% of normal.

Genetic studies were performed in two families, and *C1 INH* gene mutations were found in nine patients. Six patients from one family were heterozygous for a single-base deletion of A at codon 210 in exon 5 causing a frame shift (I210fsX210). This deletion resulted in a non-sense mutation at codon210, ATA to TAA which we recorded as mutation c.628delA, I210fsX210 in exon 5 of the *C1 INH* gene. Three patients from the other family had a 70-base pair deletion in exon 3 causing a frame shift (c.3_73del, p.N1fsX34) which we recorded as mutation c.3_73del, p.N1fsX34 in exon 3 of the *C1 INH* gene.

Discussion

Hereditary angioedema is rare in Taiwan and there have been few studies to date, similar to other neighbouring countries in Asia.[20-24] The prevalence of the disease has been reported to be 1 per 50000 to 100000 population in Western countries,[6-12] however the prevalence seems to be lower in Asia (Table 2).

Sufferers may experience brawny non-pitting angioedema involving any part of the body, which may lead to mortality if laryngeal attacks occur without adequate emergency treatment. Fifty percent of HAE patients experience at least one laryngeal attack during their life time.[7,25] In our study, five patients experienced facial or laryngeal attacks, two of whom experienced life-threatening attacks and survived after tracheostomy. Unfortunately, one of these patients died from a subsequent attack. The proportion of laryngeal attacks in this report was 45.5%, which is consistent with other reports.[7,25] Skin attacks were the most common affecting 100% of our patients, which is also similar to former reports[7,25]. However, abdominal attacks occurred in only two patients accounting for 18.2% of attacks, which is much lower than in the other reports.[7,25] Of note, two members from different families died of sudden onset dyspnea at a young age (18 and 30 years old), one of whom was male and the other female. These two cases were also highly suspected to be victims of HAE, although there was no laboratory evidence to support this diagnosis.

Diagnosis is often delayed in patients with HAE, with a delay ranging from 10 to 22 years.[10,26] In the current study, the average delay in diagnosis was 8.45 years. If a diagnosis can be made earlier, patients will be able to receive adequate prophylactic therapy and therefore suffer from fewer attacks. Patients who have recurrent, unexplained angioedema, especially when combined with recurrent abdominal pain and a positive family history of HAE should be investigated. Serum C4 levels are low in patients with untreated HAE and usually less than 30% of mean normal level. This is an effective screening test for untreated C1 INH deficiency, with 100% sensitivity and 100% negative predictive value.[27]

Asymptomatic carriers accounted for 42% of our cohort, which is similar to a report from Japan,[28] but much higher than in Western countries (Table 2). The reason for this may be related to genotypic and phenotypic variation between different ethnic groups. In the present investigation, the gene mutations were caused by frameshift mutations and large deletions. To date, more than 150 different C1 INH mutations have been identified in HAE patients. The different effects on C1 INH protein function and synthesis may explain the observed clinical differences in disease severity in affected individuals. Extreme phenotypic variability is observed in people with HAE, even in those from the same family. Further analysis of the individual mutations may lead to a clearer understanding of the relationship between structure and function and thereby help to elucidate the causes influencing the clinical severity of HAE.

Plasma-purified C1 inhibitor is the treatment of choice for acute abdominal and facial HAE attacks in adults and adolescents. It is also used for short-term prophylaxis before minor or major medical manipulations, as well as long-term prophylaxis. Epinephrine and FFP have questionable efficacy and attenuated androgen and antifibrinolytic agents are not fast-acting. In the absence of a C1 inhibitor, some off-label therapies are available. Attenuated danazol is indicated in both short-term and routine prophylaxis if C1INHRP is not available. Danazol increases endogenous C1 INH by hepatic stimulation. To date, C1INHRP is not available in Taiwan. Two patients (one male and one female) in the current study accepted long-term prophylaxis. We used attenuated danazol with an initial dosage of 200 mg, gradually tapered to 100 mg per day in the male patient. Danazol was initially used for the female patient, however she was unable to tolerate the virilizing side effects and was temporarily treated with tranexamic acid. Both patient's symptoms were controlled with danazol (both with 100 mg per day) at the end of the study with no further acute attacks noted.

Lack of awareness of this rare disease, with regards to the clinical symptoms and signs for both

clinicians and patients, may be one of the reasons for the low prevalence of type I HAE in Asia and also in Taiwan. However, the currently available data show some differences in prevalence, clinical manifestations and the proportion of asymptomatic individuals between Western and Eastern countries. Ethnic differences may therefore play a critical role. Further investigations should be carried out to identify a more detailed pathway by which gene defects cause different clinical presentations. Through this article, we hope to increase the awareness of this rare disease and enhance the possibility of early diagnosis and proper treatment for the affected patients in Taiwan.

References

1. Kalmar L, Hegedus T, Farkas H, Nagy M, Tordai A. HAEdb: a novel interactive, locus-specific mutation database for the C1 inhibitor gene. Hum Mutat. 2005;25:1-5.
2. Agostoni A. Inherited C1 inhibitor deficiency. Complement Inflamm. 1989;6:112-8.
3. Bork K. Hereditary angioedema with normal C1 inhibitor activity including hereditary angioedema with coagulation factor XII gene mutations. Immunol Allergy Clin North Am. 2006;26:709-24.
4. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. Lancet. 2000;356:213-7.
5. Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. Biochem Biophys Res Commun. 2006;343:1286-9.
6. Bowen T, Cicardi M, Bork K, Zuraw B, Frank M, Ritchie B, et al. Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. Ann Allergy Asthma Immunol. 2008;100:S30-40.
7. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. Medicine (Baltimore). 1992;71:206-15.
8. Stray-Pedersen A, Abrahamsen TG, Froland SS. Primary immunodeficiency diseases in Norway. J Clin Immunol. 2000;20:477-85
9. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. Br J Dermatol. 2009;161:1153-8.
10. Olga Roche, Alvaro Blanch, Teresa Caballero, Noelia Sastre, Daniel Callejo, Margarita Lo'pez-Trascasa. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol. 2005;94:498-503.
11. Starsia Z, Hegyi E, Kuklinek P, Cáp J, Stefanovic J, Lokaj J. Hereditary angioedema in Czechoslovakia. Clinical, immunological, genetic and therapeutic studies of 16 families. Allerg Immunol (Leipz). 1988;34:35-42.
12. Wais-Nöcker B, Steiner U, Späth P, Wuillemin WA. Clinical facets of hereditary Angioedema among Swiss patients. Praxis(Bern 1994). 2010;99:1135-41.
13. Starr JC, Brasher GW. Erythema marginatum preceding hereditary angioedema. J Allergy Clin Immunol. 1974;53:352-5.
14. Yao-Ting Huang, Yung-Zen Lin, Hsin-Lin Wu, Tin-Fang Chiu, Kun-Mei Lee, Hung-Ying Tsai, et al. Hereditary Angioedema: A Family Study. Asian Pac J Allergy Immunol. 2005;23:227-33.
15. Wen DC, Shyur SD, Wu JY, Lin CC, Chiang YC, Huang LH, et al. Hereditary angioedema: A Taiwanese Family with a Novel Gene Mutation. Asian Pac J Allergy Immunol. 2007;25:163-7.
16. Yu TC, Shyur SD, Huang LH, Wen DC, Li JS. Paternal mosaicism and hereditary angioedema in a Taiwanese family. Ann Allergy Asthma Immunol. 2007;99:375-9.
17. Bissler JJ, Aulak KS, Donaldson VH, Rosen FS, Cicardi M, Harrison RA, et al. Molecular defects in hereditary angioneurotic edema. Proc Assoc Am Physicians. 1997;109:164-73.
18. Zuraw BL, Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. J Allergy Clin Immunol. 2000;105:541-6.
19. Blanch A, Roche O, Lopez-Granados E, Fontan G, Lopez-Trascasa M. Detection of C1 inhibitor (SERPING1/C1NH) mutations in exon 8 in patients with hereditary angioedema: evidence for 10 novel mutations. Hum Mutat. 2002;20:405-6.
20. Kesim B, Uyguner ZO, Gelincik A, Mete Gökmen N, Sin AZ, Karakaya G, et al. The Turkish Hereditary Angioedema Pilot Study (TURHAPS): The First Turkish Series of Hereditary Angioedema. Int Arch Allergy Immunol. 2011;156:443-50
21. Faiyaz-Ul-Haque M, Al-Gazlan S, Abalkhail HA, Al-Abdulatif A, Toulimat M, Peltekova I, et al. Novel and recurrent mutations in the C1NH gene of Arab patients affected with hereditary angioedema. Int Arch Allergy Immunol 2010;151:149-54.
22. Iwamoto K, Mihara S, Ikezawa Z, Hide M. National prevalence survey of Hereditary angioedema in Japan. Arerugi. 2011;60:26-32.
23. Kang HR, Yim EY, Oh SY, Chang YS, Kim YK, Cho SH, et al. Normal C1 inhibitor mRNA expression level in type I hereditary angioedema patients: newly found C1 inhibitor gene mutations. Allergy. 2006;61:260-4.
24. Ren HL, Zhang HY. Clinical features of hereditary angioedema: analysis of 133 cases. Zhonghua Yi Xue Za Zhi. 2007;87:2772-6.
25. 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.
26. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. Ann Intern Med. 1976;84:580-93.
27. Gompels MM, Lock RJ, Morgan JE, Osborne J, Brown A, Virgo PF. A multicentre evaluation of the diagnostic efficiency of serological investigations for C1 inhibitor deficiency. J Clin Pathol. 2002;55:145-7.
28. Kodama J, Uchida K, Yoshimura S, Katayama Y, Kushiro H, Yutani C, et al. Studies of four Japanese families with hereditary angioneurotic edema:simultaneous activation of plasma protease systems and exogenous triggering stimuli. Blut. 1984;49:405-18.