

Clinical Features of Hereditary Angioedema in Korean Patients: A Nationwide Multicenter Study

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Keywords

Angioedema · Complement C1s esterase inhibitor proteins · Hereditary angioedema types I and II · Koreans · Mortality

Abstract

Background: Hereditary angioedema (HAE) is a genetically heterogeneous autosomal dominant disorder characterized by recurrent episodes of nonpruritic, nonpitting edema increasing after puberty. It can be fatal due to laryngeal or gastrointestinal (GI) involvement with varied and changing fre-

quency of mortality according to studies published from the Western countries. Epidemiological and clinical data of HAE in Asian countries are sparse. We sought to examine the clinical characteristics of HAE patients in Korea. **Methods:** Patients diagnosed with HAE at 15 tertiary hospitals across the country until 2016 were retrospectively reviewed. **Results:** A total of 65 patients diagnosed with HAE by 2016 were identified. The prevalence of HAE was estimated at 1.3/1,000,000

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in Korea. Of the 65 patients, 21 (32.3%) were males. A total of 90.8% patients had type I HAE, while the remaining 9.2% patients had type II HAE. The first symptom developed after 20 years in 73.8% of patients, with a mean age 28.4 ± 14.1 years. The age at diagnosis was 36.5 ± 15.8 years, with a mean time delay of 7.8 ± 10.5 years. While the face (82.3%) and extremities (upper 71.0%, lower 62.9%) were the most frequently involved, the GI tract was affected in 40.5% of Korean HAE patients. Prophylaxis was maintained in 62.5% of patients. There was no reported case of death from HAE so far. **Conclusions:** The clinical manifestation and severity of HAE may vary according to ethnicity. HAE is more infrequent and GI involvement is less likely in Korea compared with Western countries.

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Introduction

Hereditary angioedema (HAE) is an autosomal dominant bradykinin-mediated angioedema characterized by recurrent, episodic angioedema. Its incidence has been reported to be 1:50,000–100,000 [1–3]. HAE is neither associated with urticaria nor responsive to general anti-allergic drugs and is, therefore, distinct from histamine-mediated angioedema [4].

Symptoms of HAE generally disappear within several days with or without medication. The diagnosis of HAE is often delayed, especially in patients who do not manifest facial/laryngeal symptoms or patients with no family history of HAE. However, patients with HAE have a lifetime risk of asphyxiation due to sudden progressive laryngeal edema or occurrence of intestinal obstruction related to wall edema [1]. These emergent conditions can lead to serious consequences unless prompt and accurate diagnosis and appropriate prophylaxis and acute management are provided [4].

Unlike in Europe and North America, only few studies investigating HAE in Asia are available, and the exact prevalence of HAE remains unknown. The prevalence of HAE per 10 million people has been estimated at 4.1 in Japan, 8.2 in Taiwan, and 0.1 in China [5–7]. These rates are relatively low compared to those in Western countries. In Korea, to date, 25 HAE patients have been reported [8–18] since the 1st two cases of HAE were reported in 1994 [8, 9]. In 2011, the Korean Academy of Asthma, Allergy, and Clinical Immunology surveyed all members on the diagnosis and treatment experience of HAE, and the number of patients ever diagnosed with HAE by respondents was 50 [19].

Based on these reports, the prevalence of HAE in Korea might be much lower than in Western countries. However, data clearly depicting the clinical characteristics of HAE in Koreans were not available. Therefore, the purpose of this study was to obtain general clinical information about Korean patients diagnosed with HAE in order to determine its ethnic characteristics.

Methods

Study Subjects

This study was approved by the Institutional Review Board of the Seoul National University Hospital. Inclusion criteria followed the HAE diagnostic guidelines [1]. HAE type I diagnosis required the presence of reduced antigenic C1 inhibitor levels (reference range: 22–39 mg/dL) with characteristic symptoms of HAE. HAE type II was defined as having normal C1 inhibitor levels and a decrease in enzymatic activity of C1 inhibitor to <50% of its normal value in an enzyme immunoassay/functional study.

In 15 tertiary hospitals across the country, patients undergoing C1 inhibitor tests (amount or activity) were recruited based on the above HAE diagnostic criteria. Electronic medical records of patients with confirmed HAE were retrospectively reviewed to obtain information about basic demographic characteristics, age at onset, blood test results, family history, symptoms, etiological factors, treatment modalities, acute exacerbations, and clinical outcomes.

Statistical Analysis

Statistical analysis was performed using SPSS (version 20.0; SPSS Inc., Chicago, IL, USA). Data of continuous variables are expressed as means $\pm$ SD. Paired *t* test was used to compare the frequency of angioedema attacks before and after treatment. Values of *p* < 0.05 were considered statistically significant.

Results

Subjects

A total of 65 patients were diagnosed with HAE at 15 tertiary referral hospitals (Table 1). Of the 65 patients, 44 (67.7%) were females. Of all HAE patients, 37 (58.7%) had a family history of HAE. According to the HAE type, 59 (90.8%) patients had HAE type I and 6 (9.2%) patients had HAE type II.

Delay in Diagnosis

The mean age at the time of first angioedema symptoms was 28.4 ± 14.1 years. Based on age, 5 (7.7%) patients were classified under the age of 10 years, 12 (18.5%) were teens, 16 (24.5%) were in their 20s, 14 (21.5%) were in their 30s, and 8 (12.3%) were in their 40s (Fig. 1a). The mean age at diagnosis was 36.5 ± 15.8 years. The propor-

Table 1. Clinical manifestations of the 65 patients with hereditary angioedema (HAE)

Females	44 (67.7%)
Age at first event, years	28.43±14.09
Age at diagnosis, years	36.51±15.81
Time delay in diagnosis, years	7.75±10.54
Family history of HAE	37 (58.7%)
HAE type I	59 (90.8%)
HAE type II	6 (9.2%)
<i>Maintenance treatment</i>	44 (67.7%)
Treatment duration, years	4.14±4.58
Danazol use	44 (67.7%)
Females	25 (56.8%)
Danazol, mg	231.55±131.02
Adverse drug reactions	12 (27.3%)
Tranexamic acid	6 (9.2%)
Females	5 (83.3%)
Tranexamic acid, mg	666.67±144.34
Adverse drug reactions	0 (0%)
<i>Prognosis</i>	
Emergency department visit	24 (42.9%)
Hospitalization	15 (27.3%)
Death from HAE	0 (0%)

tion of patients who were diagnosed in their 30s was 24.6% (16/65), which was the highest among all age groups (Fig. 1b). The delay from first symptom onset to diagnosis was 7.8 ± 10.5 years.

Clinical Manifestations of HAE

The frequency of symptoms before diagnosis of HAE was 16.9 ± 17.4 per year. The main sites of involvement were the skin of the face and limb, oropharynx or larynx, and gastrointestinal (GI) and respiratory tracts (Fig. 2). In terms of cutaneous involvement, facial involvement was the most common (51/62, 82.3%), followed by upper extremity (71.0%), lower extremity (62.9%), lip (51.6%), chest or abdominal wall (16.1%), and perineal area (10.8%). Internal organ involvement occurred in 43 (69.4%) patients. There were 32 (51.6%) patients with oropharyngeal or laryngeal edema, 25 (40.5%) patients with GI symptoms such as abdominal pain and vomiting, 23 (37.1%) patients with respiratory symptoms, and 6 (8.2%) patients with headache.

In 31 (51.7%) patients, triggering factors preceded angioedema. Symptoms were precipitated by stress in 15 (48.4%) patients. Physical triggers such as surgery, dental treatment, and exposure to nonsteroidal anti-inflammatory drugs also led to the development of sudden angio-

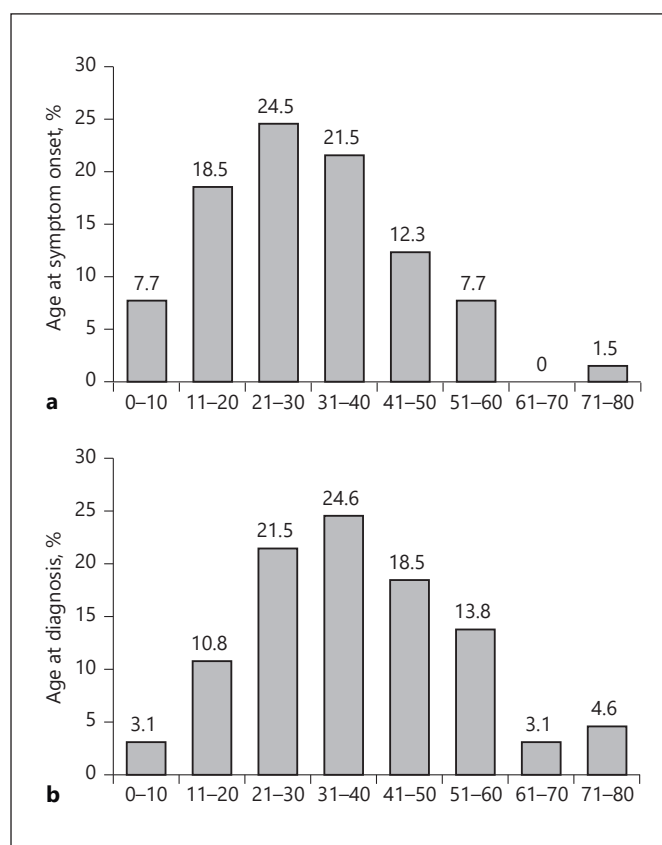


Fig. 1. Ages at the first event and diagnosis of hereditary angioedema. **a** Age at symptom onset. **b** Age at diagnosis.

edema in 5 (16.1%) patients each. Three patients (9.7%) experienced symptom aggravation due to exposure to cold air. Menstruation, exercise, and seasonal changes were described in 2 (6.5%) patients. One patient experienced symptom aggravation after influenza vaccination. The mean time required for resolution of symptoms was 3.8 ± 1.4 days.

Medications for Long-Term Prophylaxis and Related Side Effects

Medication for long-term prophylaxis was administered in 44 (67.7%) patients. All 44 patients had used danazol, a male hormone. Twenty-five patients (56.8%) were females, and the maintenance dose of danazol was 231.55 ± 131.02 mg/day. Twelve (27.3%) out of the 231 patients who received danazol experienced adverse drug reactions. Liver enzyme elevation and androgenic effects (voice change, acne, hair growth on toes, scalp trouble, and menstrual irregularities) were the most common (5 cases each, 41.7%). Headache, pruritus, generalized ede-

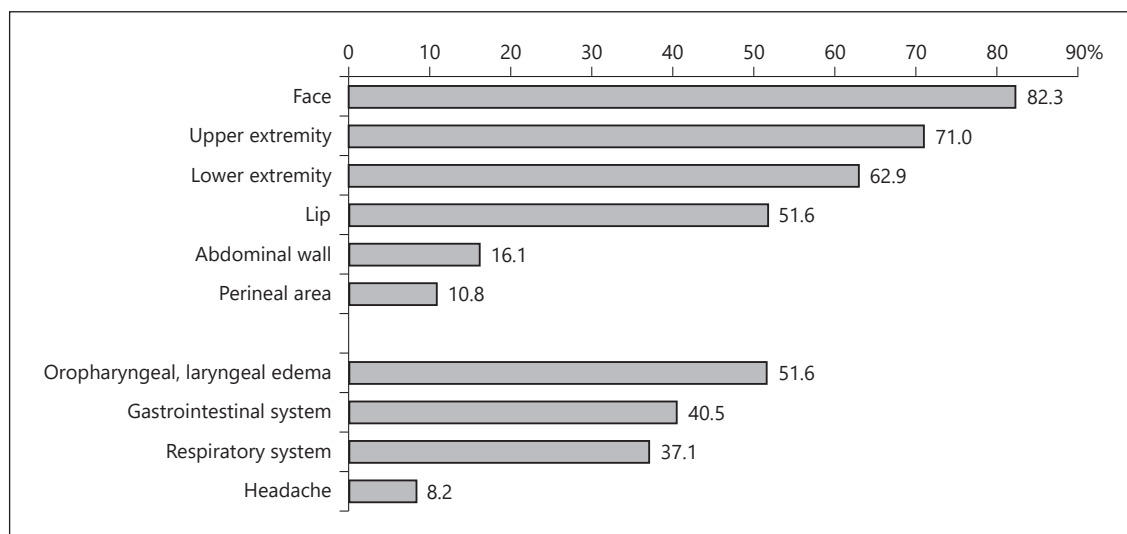


Fig. 2. Cutaneous manifestations of angioedema and internal organ involvement.

ma, weight gain, and digestive system impairment occurred in 1 (8.3%) patient each. In addition, 6 patients were also treated with tranexamic acid at a maintenance dose of 666.67 ± 144.34 mg/day. None of them experienced adverse drug reactions. There was no case treated with other therapeutics such as icatibant or ecallantide, which is not currently available in Korea.

Prophylaxis of Acute Attacks

The incidence of angioedema attacks after surgery, delivery, or dental procedures was investigated. While angioedema developed in 9 (52.9%) of 17 cases without prophylaxis, only 1 of 10 cases (10%) had an attack following prophylaxis. Among 15 cases who underwent operations, angioedema occurred in 5 cases (33.3%); only 1 of the 7 cases treated prophylactically experienced angioedema-related symptoms (14.3%), which is in contrast to 4 cases of angioedema among the 8 prophylaxis-free cases (50%). A total of 4 patients underwent normal vaginal delivery without prophylaxis, and 1 patient had an angioedema attack (25%). After the diagnosis of HAE, 8 patients underwent dental procedures such as extraction or root canal procedure. While none of the 3 patients with prophylaxis had angioedema, 4 of the remaining 5 patients without prophylaxis experienced angioedema.

Prognosis

In the majority ($n = 38$, 86.4%) of these patients, symptoms were decreased after drug administration. When

before and after treatment were compared, the annual attack rate was significantly reduced (before vs. after: 16.9 ± 17.3 vs. 1.2 ± 2.5 , respectively; paired t test, $p < 0.001$, $n = 32$).

Twenty-four (42.9%) patients visited the emergency department due to HAE deterioration, and 15 (27.3%) patients required hospitalization. Three patients underwent surgery or intervention due to laryngeal edema or intestinal obstruction caused by HAE, including tracheostomy due to laryngeal edema ($n = 1$), surgery for intussusception ($n = 1$), and stent insertion due to intestinal obstruction ($n = 1$). There were no deaths due to HAE during the mean follow-up period of 7.4 ± 5.4 years.

Discussion

In this nationwide study of confirmed HAE cases covering all tertiary referral centers in Korea, a total of 65 HAE patients diagnosed at 15 tertiary hospitals in Korea were analyzed. They showed a slightly different clinical profile compared with HAE patients in Western countries. The Korean population had a relatively older age at diagnosis of HAE with a mean age of 36.5 years compared with 15.8 years reported in the literature [3]. The diagnostic delay after the first symptom onset was 7.75 years. According to previous reports in the West, the initial diagnosis of HAE after first symptom onset was delayed around 8.3 years in the USA and around 10 years in Eu-

rope [2, 3, 20]. Although the face and extremities were the most frequently involved sites, the GI tract was involved only in 40.5%, which was decreased compared with the 70–90% reported in Western countries [21–23].

In previous reports, HAE prevalence ranged from 1/50,000 to 4/50,000 in Caucasians [2, 3, 24–27], and about 5,000 people (1/60,000) are affected by HAE in the United States [28]. According to the Spanish HAE patient registry, the minimal prevalence of HAE is 1 in 100,000 inhabitants [2]. However, there are very few reports of the prevalence of HAE in Asia. Although the exact prevalence rate of HAE has not been determined in Asia yet, a few reports have suggested a very low level. In Japan, a total of 52 patients with HAE types I or II were reported in a nationwide survey of 1,128 clinicians in 2009 [5]. The prevalence of HAE in Japan has been estimated at 4.1/10,000,000 [5]. In Taiwan, there were 19 HAE patients, and HAE prevalence rate was estimated at 8.2/10,000,000 [6]. In China, the prevalence rate of HAE has been estimated at 0.1/10,000,000 [7]. In Korea, sporadic case reports have been published since the first 2 cases of type I HAE in 1994 [8–17]. In 2006, 14 HAE type I patients and 18 members in 3 families underwent genetic analysis, and a novel mutation was reported [14]. The first HAE type II case in Korea was reported in 2017 [18]. Altogether, a total of 25 Korean HAE cases have been reported to date in the literature. In 2014, 975 members of the Korean Academy of Asthma, Allergy, and Clinical Immunology surveyed physicians using a questionnaire to assess their clinical experience in managing patients with HAE in Korea [19]. In this survey, the number of patients confirmed as HAE by physicians was 50 [19]. In the current study, a total of 65 patients confirmed as HAE were registered. Based on these results, the estimated minimal prevalence of HAE in Korea is 1.3/1,000,000.

Poor clinical awareness can contribute to the low diagnostic rate of HAE and may be a confounder in ascertaining true national prevalence. However, our estimated time elapsed between symptom onset and diagnosis argues against this rationale. A previous survey of clinical experience in managing Korean patients with HAE has shown a high rate of appropriate recognition and understanding of HAE symptoms, examination, and treatment [19]. Therefore, the low HAE prevalence in Koreans it is not very likely to be due to a lower diagnosis rate.

Another possible contributing factor to the low prevalence is the severity of symptoms. In Asians, the severity of HAE symptoms appears to be milder than in Europeans. In fact, the proportion of asymptomatic patients in

Taiwan and Japan were reported to be 42.1 and 44%, respectively [6, 29]. However, the percentage of asymptomatic Caucasian patients is only 5–27% [3, 24]. Therefore, it is possible that a considerable number of HAE patients in Asia might not seek medical assistance due to milder symptoms.

The timing of the onset of symptoms might also have an effect on the low prevalence of HAE. Most patients experience first attacks in childhood or adolescence, and the frequency of attacks increased after the onset of puberty [30, 31]. In Germany, 51.1% of patients had the first HAE symptoms before 10 years, and 37.8% of patients reported their initial symptoms as teenagers (Fig. 3a) [2, 3, 6, 30, 32]. Interestingly, the first symptoms developed a decade later in Chinese HAE patients than in Caucasians [33]. In this study, Koreans showed a generally delayed peak of onset compared with the Chinese, and only 26.2% of patients had their first HAE symptoms before 20 years of age. In a couple of HAE cases, symptoms eventually occurred in their 60s–70s. An intriguing hypothesis associates age at onset with the severity of HAE in a German group [30], suggesting that cases with an age at onset before 5 years led to a more severe progression than cases with an age at onset after 5 years [30]. Based on their suggestion, the delayed onset in Chinese and Korean HAE patients contributes to the relatively lower rate of GI involvement and mortality and in part to the low prevalence of HAE in these countries. The functional abnormality of gene mutations may show ethnic differences. HAE symptom severity might also be affected by factors other than genetic predisposition in identical twins because HAE incidence and severity are not always correlated with each other [34]. Further research is needed to elucidate the factors associated with the clinical diversity of HAE internationally.

In this study, the mean time required for HAE symptom resolution was 3.8 days, which was similar to the 2–5 days reported in other countries [35]. Korean HAE patients included in this study experienced an average of 16.9 attacks per capita per year, which was lower than the 22.85 attacks per capita per year reported by a German group [30].

The affected body parts were also different according to the study populations. The most frequently involved site in Korean HAE patients was the face (82.3%), while facial involvement was 75.6% in a German study, 55.1% in a Chinese study, and 55% in a Danish study [3, 33]. HAE triggers GI colic, nausea, vomiting, and/or diarrhea due to transient edema of the bowel wall [36]. Recurrent abdominal pain attack is known to occur in 70–90% of

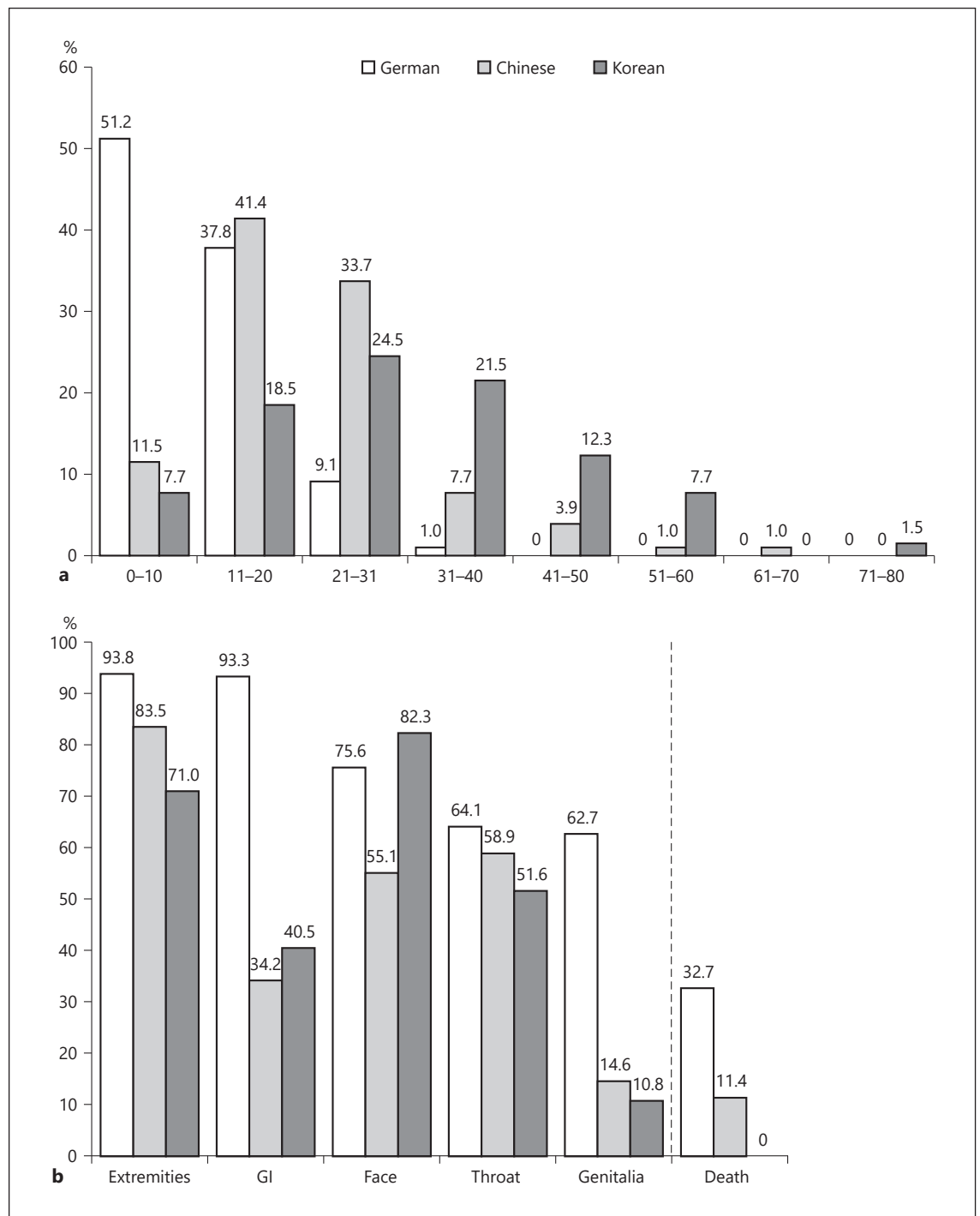


Fig. 3. Clinical manifestations according to country. **a** Age at symptom onset. **b** Distribution of involved sites.

HAEs [21–23]. A German study reported abdominal pain in 93.8% of patients, with a total of 33,671 attacks occurring frequently in 153 patients [23]. Although GI involvement was the main symptom of HAE in Western coun-

tries, GI involvement was only reported in 40.5% of Korean HAE patients. The incidence of GI tract involvement was also low in other East Asian countries: 37% in Japan and 9.53% in China [5, 33]. Meanwhile, orolaryngeal in-

volvement was 51.6% in Koreans, similar to that of Japan and China (42 and 59%, respectively) [5, 33].

HAE can be fatal due to laryngeal or GI involvement, and varied and changing frequency of mortality [1]. Especially, asphyxiation can lead to death. Before effective therapies for HAE were available, one-third of all patients died of asphyxiation [21]. In Germany, 214 out of 728 patients (29.4%) with HAE died and 70 of 214 deaths were attributed to asphyxiation during a laryngeal attack [37]. In the USA, 600 deaths caused by HAE were identified over the 12-year period from 1999 to 2010 [38]. In contrast, the mortality rates of HAE in Japan and China were reported to be 11.7 and 11.4%, respectively [33, 39]. In this study, no mortality due to HAE was found in 65 Korean HAE cases. However, these Asian studies were carried out recently. Therefore, long-term follow-up studies are needed to obtain accurate mortality data of Asian countries.

Aside from allergic angioedema, HAE attack is not responsive to steroids or antihistamines [1]. Therefore, accurate diagnosis is essential for HAE management [1]. Treatment of HAE is divided into maintenance therapy, treatment for an acute attack, and prophylaxis. Patients with frequent recurrence of symptoms (at least once a month) require maintenance therapy for long-term prevention [40]. In this study, maintenance therapy was provided for 67.7% of patients. In Korea, C1 esterase inhibitor therapy was only available at a national orphan drug center, and icatibant and ecallantide have yet to be introduced. Therefore, danazol is used as the primary maintenance treatment in Korea, and tranexamic acid is used in specific cases. Although angioedema attacks are markedly reduced after maintenance treatment with danazol, about one-quarter of patients treated with danazol have

experienced adverse drug reactions. Therefore, introduction of safe alternative drugs is required.

There was only 1 patient (7.1%) with type II HAE in this study, which was relatively low compared with 15–20% reported in the West [41]. The percentage of type II HAE was also low in Japan (5.3%) and China (1.27%) [33, 39]. All 19 patients in a Taiwanese study were type I HAE [6]. These results suggest that the proportion of type II HAE in Asians is relatively low. The percentage of HAE patients with normal C1 inhibitor level has been reported in 1.8% of HAE patients in Japan [39]. However, no such case was found in the present study or previous reports on Korean HAE patients.

The main limitation of this study is its retrospective design. Therefore, there might be differences in the level of detailed records according to the medical staff in charge of the patients. In addition, because no pedigree study was conducted, asymptomatic or mild potential HAEs might have been missed. However, this study was meaningful in that it investigated the general clinical features, treatment status, and progress of HAE patients in Korea for the first time.

We found a low prevalence of HAE in Korea. The onset of HAE in Koreans was delayed, the incidence of GI tract involvement was relatively minor, and mortality was lower compared with those in Caucasians. Future studies of HAE in this population are needed to be able to propagate the guidelines for education, diagnosis, and optimized treatment of Korean HAE patients.

Disclosure Statement

The authors have nothing to disclose.

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