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Hereditary angioedema: a Chinese perspective

Hereditary angioedema (HAE) is a rare autosomal dominant disorder of vascular permeability associated with heterogeneous clinical manifestations, with prevalence estimated at 1/50,000. Most disease-causing variants lie within the *SERPING1* gene, while *FXII12, PLG* and *ANGPT1* gene variants are also reported to associate with HAE. Research on HAE in China began in the 1980s, and later studies identified some clinical characteristics of Chinese HAE patients that differ from the western population. Type 1 HAE (98.73%) accounts for the majority of Chinese HAE patients while no type 3 HAE patient has been diagnosed in China to date. Compared with other populations, the onset age (21.25 years) of Chinese HAE patients is older and the percentage of abdominal attacks (34.18%) is lower. A spectrum of mutations within *SERPING1* has been established and a total of 56 mutations have been reported among Chinese patients. Currently, there is no approved drug for acute attacks on the Chinese market, and the choices for long-term prophylaxis are limited to danazol and tranexamic acid. Danazol has demonstrated good efficacy and is tolerated in most Chinese patients, although it has some side effects, especially at the beginning of the treatment with higher doses. Oedematous attacks are effectively prevented with a dosage of $\leq$200 mg/day in 80% patients. This article provides a brief update of HAE and reviews the research progress in the Chinese population within the past 30 years.

Key words: hereditary angioedema, China, clinical features, genetic, therapeutic intervention

Hereditary angioedema (HAE) is a rare condition characterized by unpredictable and recurrent attacks of painful swellings which typically affect the extremities, bowel mucosa, genitals, face, and upper airway [1]. The inherited form of angioedema was first described by Osler in 1888 [2]. In 1963, Donaldson and Evans identified the deficiency of esterase inhibitor (C1-INH) as the underlying mechanism of HAE [3]. So far, there are several defined forms of HAE [1]: (1) type 1 HAE caused by C1-INH deficiency and characterized by low C1-INH level and function; (2) type 2 HAE resulting from C1-INH dysfunction, characterized by a normal C1-INH level but impaired function;(3) HAE with normal C1-INH level and function, with mutation either in the F12 gene (HAE-FXII), the angiopoietin-1 gene (HAE-ANGPT1), the plasminogen gene (HAE-PLG) and (4) HAE due to unknown mutations (HAE-UNK)

Inherited in an autosomal dominant manner, HAE due to C1-INH (type 1 and 2) has an estimated prevalence of 1/50,000 with no gender difference. HAE is highly heterogeneous in terms of both genotype and phenotype. Trauma and fluctuation of hormones are regarded as the common triggers, although the triggers for many attacks still remain unidentified [4]. With a better understanding of HAE, more therapeutic and prophylactic measures are becoming available [5].

Since the first Chinese HAE case was reported in 1980 [6], C1-INH concentration testing and related research on HAE have been conducted at the Peking Union Medical College Hospital (PUMCH). To date, more than 400 patients from 120 different families have been registered at the PUMCH HAE centre. Here, we review the current update of HAE and summarise some of the research progress in Chinese HAE patients.

Clinical features

The onset age of HAE varies in patients. It is generally accepted that HAE begins in childhood and is aggravated during puberty [7]. Previous studies have indicated that 40% patients have experienced a first attack before the age of five, and this number mounts to 75% at age 15 [8-10]. Bork *et al*. observed 131,110 oedema episodes and found that clinical symptoms start at 11.2 ± 7.7 years old [8]. They also proposed that women patients and early-onset patients suffer a more severe disease course than others. For untreated patients, attacks are estimated to occur every 7-14 days [8]. Oedematous episodes can be precipitated by psychological stress, physical trauma, and infection, or occur spontaneously [11]. The oestrogen-mediated increase in attack frequency and severity has been early recognized, however, the molecular mechanism needs further clarification [12]. Pregnancy can lead to aggravation, despite the

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fact that the disease conditions remain the same during pregnancy in some patients [7].

The characteristic symptom of HAE is non-pitting and non-pruritic tissue swelling, which typically affects the skin, gastrointestinal tract, and upper respiratory tract [13]. Involvement of the extremities is estimated to be over 90%, and occurs more frequently than involvement of the genitalia and trunk during skin attacks [13]. Abdominal swelling, which is frequently misdiagnosed as appendicitis, may cause moderate to severe abdominal pain, nausea, and vomiting [14]. Failure to recognize gastrointestinal oedema as HAE often leads to unnecessary abdominal surgery [15]. Laryngeal involvement is the most dangerous form and is associated with a lifetime mortality rate of 40%; it is experienced by 50% HAE patients at least once in their lives [22]. Usually, the swellings develop slowly in the first 24 hours and undergo a 48-72-hour time course of resolution despite considerable heterogeneity between individuals [8]. Premonitory symptoms or prodromes, including a tingling sensation, skin change or discomfort such as fatigue, nausea, and myalgia, may precede the swelling episode [16]. Erythema marginatum, the only objective prodrome of acute oedematous attacks, occurs in approximately 25% patients, thereby allowing prophylaxis for acute attacks [17].

The first likely HAE case in China was described by Xie in 1980 [6]; clinical history of three young male patients from the same family revealed details of recurrent non-pitting swellings without urticaria that affected the skin and larynx. Testing for serum and inhibitor complement was not available in China at that time. Serum C1-INH concentration and functional tests were introduced to mainland China in 1980 and 2001, respectively. Since this time, Chinese physicians have gradually established a standard practice for diagnosis. In 1988, Zhang *et al*. conducted a study of 88 HAE patients, and noted that 9/88 (10.2%) had complications associated with chronic glomerulonephritis, implying a correlation between HAE and chronic glomerulonephritis [18]. With the advance of more diagnostic technologies, more HAE patients were identified. Zhi [19], Ren [20], and Tang [21] summarized the clinical characteristics of HAE patients at the Peking Union Medical College Hospital in 2003, 2007, and 2010, respectively.

In 2013, Xu *et al*. [22] reviewed 158 symptomatic HAE patients at the Peking Union Medical College Hospital from 1982 to 2011. The authors reported clinical characteristics of Chinese HAE patients that differed from other populations, indicating the probable role of the environment in modifying disease phenotype as well as differences between ethnic groups. The proportions of different types were found to deviate from those previously reported; among the 158 patients analysed, 156 were diagnosed as type 1 HAE (98.73%), whereas type 1 HAE was reported to account for 85% cases in western countries; only two (1.27%) patients were type 2 HAE, while the percentage of type 2 HAE is approximately 15% in the literature. No type 3 HAE patient was identified in this study, and there is no report regarding type 3 patients in China. The mean onset age was 21.25 years (ranging from two to 63 years), and most patients experienced their first attack in their 20 s (42%) or 30 s (32%). The onset age was later compared to previously reported data in other populations. A comparison of onset age between Chinese and German patients is shown in *figure 1*. Only 34.18% patients experienced abdominal

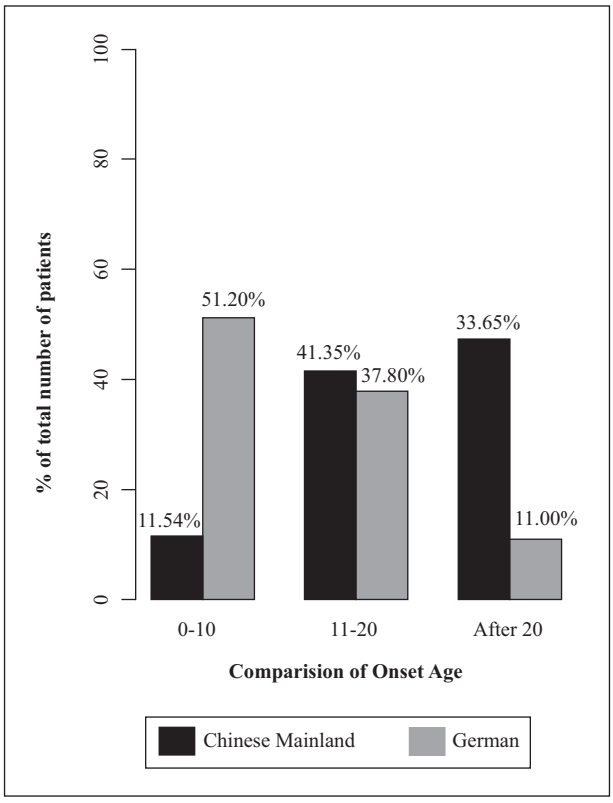

Figure 1. The distribution of onset age differs between mainland Chinese and German HAE patients. The majority of Chinese patients experience their first oedematous attack during their second or third decade.

attacks [22], while the frequency of abdominal involvement is much higher in the western population. *Figure 2* shows the frequency of swelling at different sites in different populations. Other major clinical manifestations are similar to those documented. In addition, Xu *et al*. [22] also identified several rare complications, including melena, gastric mucosa inversion, pleural effusion, dysuria, and syncope. Among 47 pregnancies in 38 women, the frequency of episodes remained stable in 29 (61.70%) pregnancies while others were accompanied by an exacerbation in frequency (3; 6.38%) and severity (15; 31.91%) [22].

Xu *et al*. in 2013 investigated the features of patients with upper airway oedema (UAE) [23]. Unlike the typical slow time course of HAE episodes, UAE usually starts spontaneously and progresses rapidly, and can progress from an initial awareness of symptoms to maximum airway involvement within 30 minutes. Patients with a positive UAE family history are prone to experience UAE, while men develop more asphyxiation than women. Since UAE can result in significant morbidity and mortality, it is important for patients, physicians, and other caregivers to be aware of the early symptoms of UAE.

Pathophysiology

HAE is considered as a heterogeneous disorder with complex pathophysiology [24]. Bradykinin, which induces

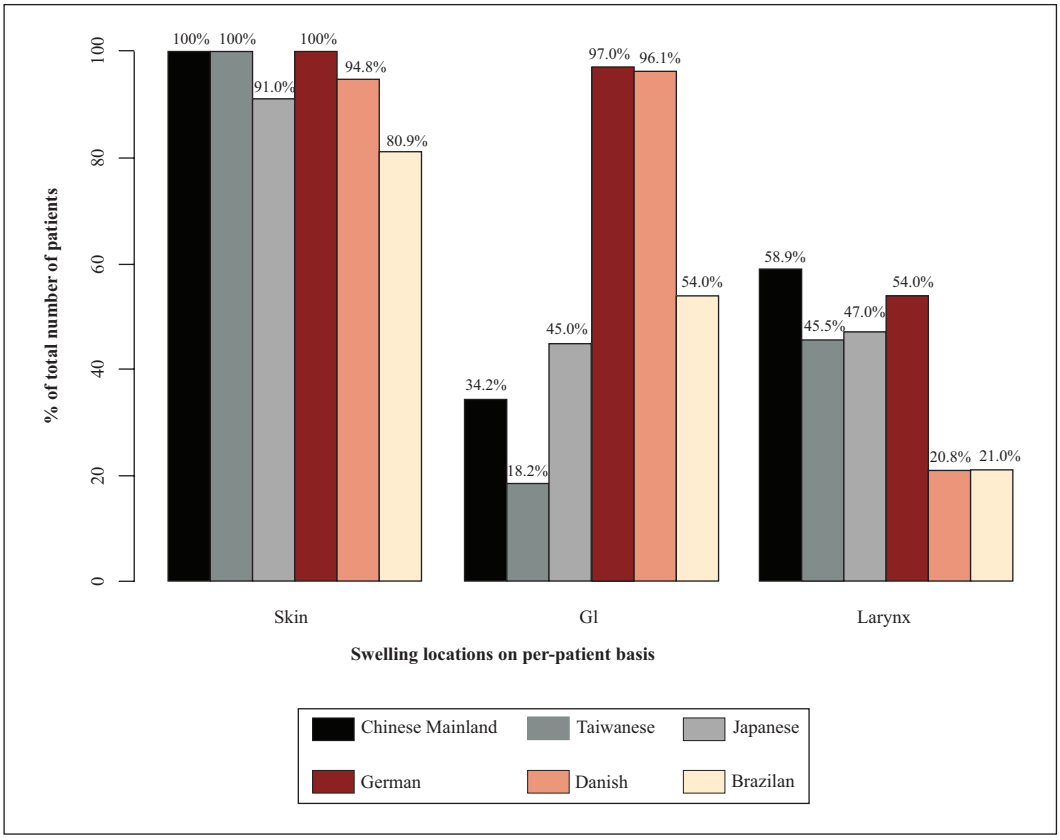

Figure 2. The frequency of swelling at different sites in mainland Chinese, Taiwanese, Japanese, German, Danish, and Brazilian patients. East Asian (mainland Chinese, Taiwanese, and Japanese) patients present with a lower frequency of gastrointestinal involvement (GI) than other populations.

smooth muscle cell relaxation and increases vascular permeability, serves as a central mediator in HAE. For the majority of HAE patients, the underlying pathology is the deficiency (type 1 HAE) or dysfunction (type 2 HAE) of C1-INH [25]. *Figure 3* illustrates the basic pathophysiological aspects of HAE.

Activation of the plasma enzyme system and vasoactive peptides has been observed in HAE patients or during oedematous attacks [26-28]. Up-regulation of C-reactive protein (CRP) and certain cytokines during attacks has also been reported [27, 29-32]. Recent studies also indicate a possible role of the ficolin-dependent lectin complement pathway [33, 34] in the pathogenesis of HAE. Possible involvement of the neuroendocrine and immune system increases the potential complexity of HAE. Research concerning the pathophysiological mechanisms of HAE in China is limited.

Genetics

The gene encoding C1-INH is *SERPING1* (OMIM no. 606860; GenBank NM_000062.2), which is located on chromosome 11q12-q13.1 and comprises eight exons and seven introns. The traditional research strategy to screen *SERPING1* is to amplify all exons and exon/intron boundaries by PCR and further detect mutations by direct sequencing. *SERPING1* exhibits considerable genetic variability. Over 510 *SERPING1* mutations related to C1-INH have been identified [35], and most of these can result in the premature truncation of protein synthesis [36]. It has been previously estimated that at least 25% HAE patients have *de novo SERPING1* mutations [37]. To date, it remains controversial whether all *SERPING1* alterations are responsible for HAE [36]. Mutation in the *SERPING1* coding region is not detected in approximately 5% of C1-INH HAE patients, which indicates that a defect hidden in intronic or untranslated regions may modify C1-INH expression [36], or that there are contributory mutations in other genes. In 2017, Bafunno *et al*. reported a mutation in the angiopoietin-1 gene (*ANGPT1*) in a family with HAE with an unknown genetic defect (U-HAE) [38].

For HAE-nC1INH, a significant percentage of patients have mutations in the *FXII* gene (OMIM no. 610619; GenBank NM_000005.10), which increases FXIIa activity and results in the uncontrolled activation of bradykinin generation [39]. In 2017, Bork *et al*. detected a mutation in the plasminogen gene (*PLG*; OMIM no.173350; GenBank NM_000006.12) in HAE-nC1-INH patients [40]. This *PLG* mutation led to the identification of a novel type of HAE which is transmitted in an autosomal dominant manner, and is associated with a high risk of tongue swelling [40].

Individuals with the same gene mutations may present with different disease severity [41, 42], and 14% *SERPING1* mutation carriers remain asymptomatic throughout their lives [43]. However, correlation between *SERPING1* mutation and HAE phenotype is poor, and previous studies have

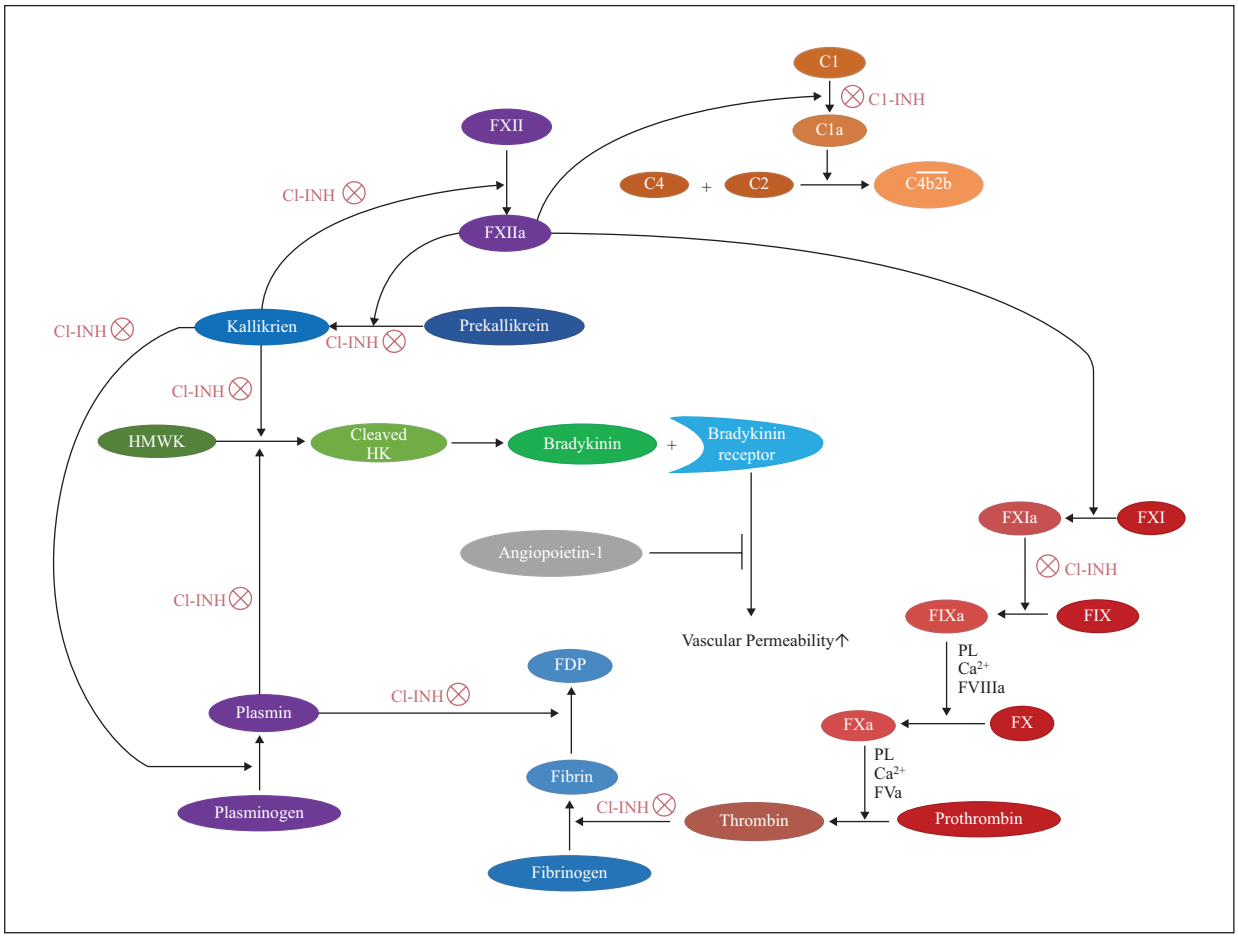

Figure 3. Molecular pathways involved in the pathophysiology of C1-INH hereditary angioedema. Bradykinin-receptor complex stimulates cGMP production, resulting in an enhancement of PGI2 and nitric oxide, which mediates vasodilation and increases permeability. C1-INH, which belongs to the serine protease inhibitor (SERPIN) superfamily, inhibits a variety of molecules including kallikrein, plasmin, thrombin, activated coagulation factor XII, and activated coagulation factor XI. Absence or defective function of C1-INH leads to continuous activation of the plasma complement system, contact (kallikrein-kinin) system, fibrinolytic system, and intrinsic coagulation system, generating the characteristic swelling in HAE.

failed to correlate polymorphisms in other genes with C1-INH HAE severity [36]. The factors that modify phenotype remain unclear.

Genetic research in China, in general, emerged in 2003. Zhi *et al*. performed DNA sequencing in 34 patients from nine families and 16 unrelated healthy individuals; all eight exons of the *SERPING1* gene were sequenced and six mutations were identified [19]. Several small-scale genetic studies involving one or more families were later published in China [44-47]. In a relatively large population study with 48 HAE patients from 48 unrelated families, 35 mutations and seven SNPs were identified, of which 25 mutations and three SNPs were reported for the first time [48]. Researchers also investigated the potential correlation between genotype and phenotype and found that patients with nonsense, frame shift, and Arg466 mutations tended to have a lower level of C1-INH antigen than those with missense and in-frame mutations, although the difference in C1-INH antigen did not affect severity. Other investigators have performed genetic analyses on a single or several affected families and reported mutations within the *SERPING1* gene. The genetic studies of HAE patients in China are summarised in *supplementary table 1* and *figure 4*.

Diagnosis

The first global guideline for HAE management was drafted by the World Allergy Organization (WAO) HAE International Alliance in 2012 [49] and revised in 2017 [1]. Based on these documents, experts from different countries have established respective practice guidelines for HAE according to the specific circumstances in their respective nations [1, 50]. However, there is currently no national guideline or expert consensus document for HAE in China. Characteristic clinical manifestations and a positive family history lead to further examination of C4 and C1-INH levels. *Figure 5* shows the general diagnostic process for HAE in China. Although international consensus and practice guidelines are regularly updated, a considerable delay in diagnosis has also been reported in the literature. The mean delay for Chinese patients from first attack to the diagnosis of HAE was reported to be 12.64 years, ranging from one month to 45 years [22], which is longer than the average of 8.5 [0-62] years in Europe [51]. The diagnostic delay hinders patients from receiving appropriate and immediate treatment [14].

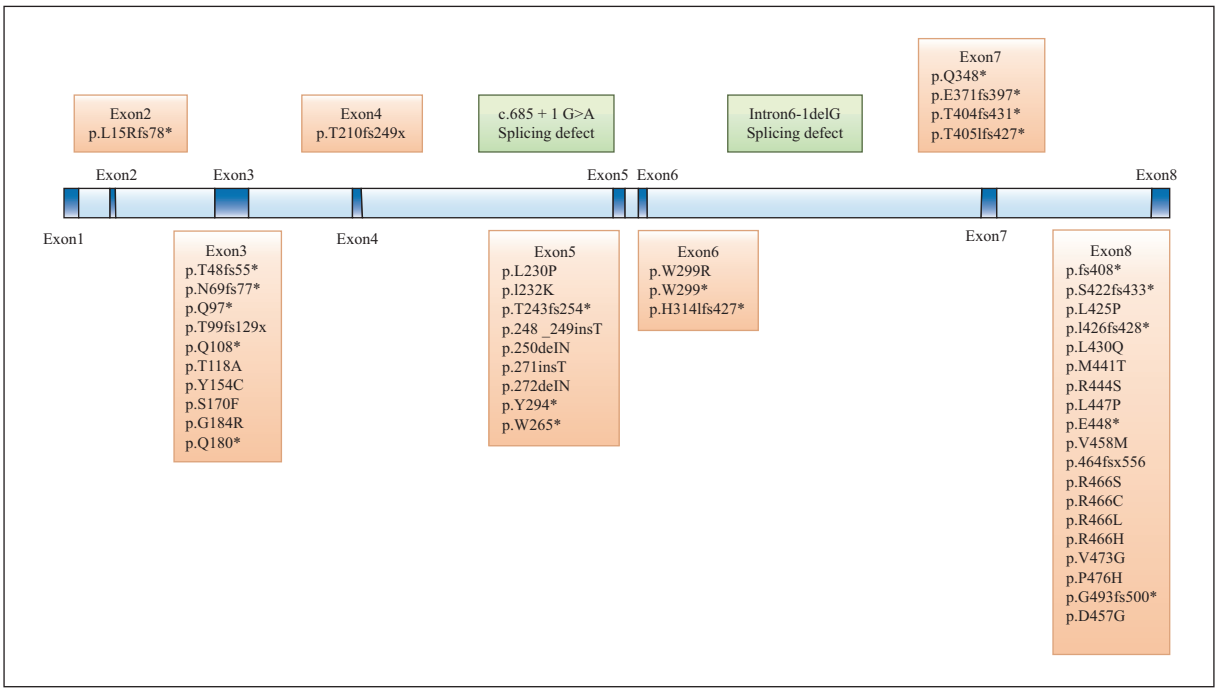

Figure 4. Genetic mutations identified in Chinese C1-INH HAE patients. The exons and introns of *SERPING1* are drawn in proportion. The amino acid changes for disease-causing mutations listed in *supplementary table 1* are also illustrated.

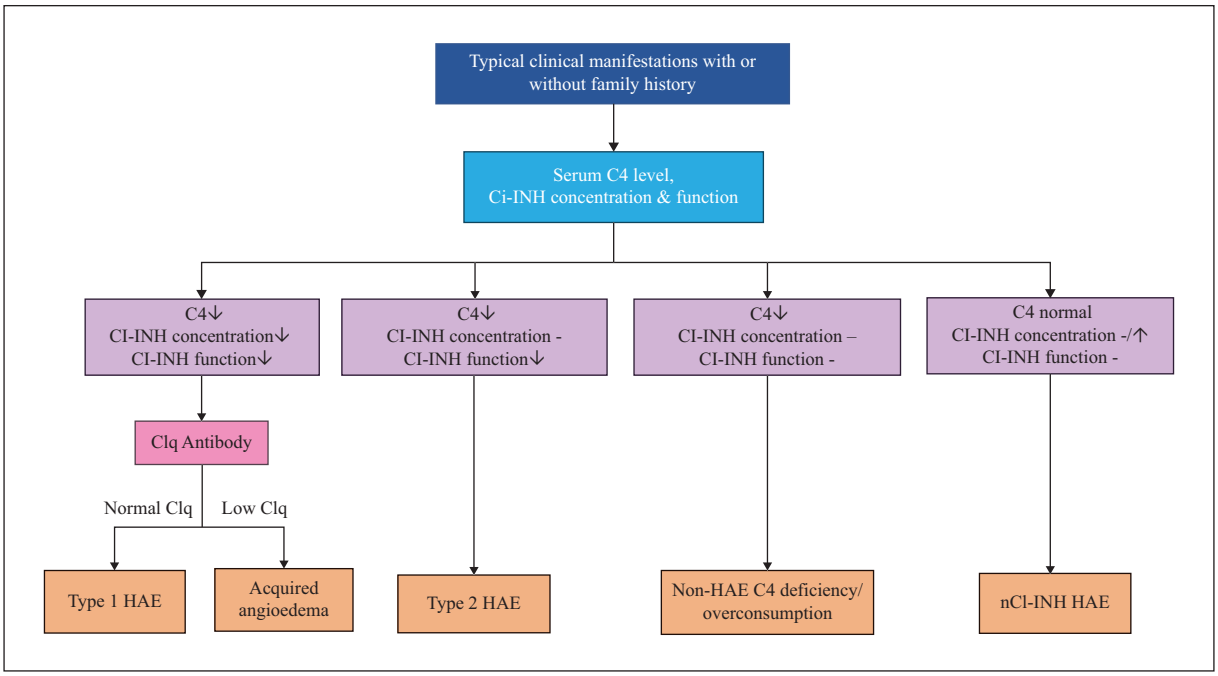

Figure 5. General diagnostic process for HAE. For patients with typical clinical manifestations, including recurrent angioedema without urticaria, recurrent attacks of abdominal pain and vomiting, and laryngeal oedema, the diagnostic possibility of hereditary angioedema should be considered. Serum C4 and C1 inhibitor level and function are measured for further diagnosis. A family history of angioedema is an important indicator of HAE. Genetic testing can be a useful tool for prenatal diagnosis and for children under one year old.

Therapeutic intervention

Considering the heterogeneity of clinical manifestations, a highly specialised and multi-disciplinary approach is required for HAE care. Since oestrogen exerts great influence on the frequency and severity of HAE attacks, management of women is more complicated. A guideline/international consensus for female [52] and paediatric patients [53] has been published to guide better management.

The management of HAE is often divided into three categories, including the treatment of acute attacks, the long-term prophylaxis of recurrent attacks, and the short-term prophylaxis of attacks induced by invasive medical and surgical procedures. Some experts recommend that prophylactic agents should be given before surgery. Several drugs targeting different pathophysiological processes have been launched onto the market in Europe and the US. However, no clinical trial has been conducted in China, and most treatments are mainly based on the experience of experts and evidence from other countries. The officially approved therapeutic options are limited to fresh frozen plasma (FFP), danazol (an attenuated androgen), and tranexamic acid (an antifibrinolytic agent) in China.

An acute attack of HAE is an emergency, which often requires timely management in the emergency room or intensive care unit. Supplementation of C1-INH (FFP, plasma-derived or recombinant C1-INH concentrates) or inhibition of related molecules (kallikrein inhibitor and bradykinin-2 receptor antagonists) may alleviate the acute symptom. Intubation and emergency tracheostomy must be performed timely in order to ensure adequate breathing for patients with laryngeoedema.

Treatment for acute attacks is currently limited in China, and mainly includes FFP and supportive therapy. Tang *et al*. reviewed 16 cases of FFP treatment for acute HAE attacks [54]; 15/16 (93.75%) patients benefited from the FFP transfusion while one patient stopped the treatment because of adverse reactions during transfusion. Patients benefited from FFP treatment in terms of a decrease in time to full remission from 6.7 ± 27.0 to 2.0 ± 12.0 hours. In clinical practice, certain traditional Chinese medicines (*e.g. Xueyuganlu* cream, from Tibet Medicine) were observed to accelerate remission in some patients. However, the exact mechanisms remain poorly understood and the efficacy and side effects also require further study based on a large HAE population.

As for long-term prophylaxis, attenuated androgen (danazol) is still the main drug in some areas, especially in places where other drugs are not available. Its safety has been evaluated by several research groups, which show a mild virilizing effect [55] and sporadic erythrocytosis and polyglobulia [56] following long-term prophylaxis. Besides danazol, antifibrinolytic agents (tranexamic acid) and many drugs for acute attacks can also be applied to prevent recurrent attacks, such as the plasma-derived C1-INH, Cinryze.

In mainland China, the attenuated androgen is the main drug for long-term prophylaxis, and administration is initially with high dosage of danazol at 400/600 mg per day for three or four weeks with tapering to the minimum effective level. The maintenance dosage varies from patient to patient. Research has shown a dosage of $\leq$200 mg/day to be effective for 80% of patients. The side effects of danazol, which are mainly liver dysfunction and androgen-related manifestations, were well tolerated and became mild under maintenance doses. One aspect that deserves special attention is that the attack may occur even with regular and long-term prophylaxis, which makes it necessary for C1-INH HAE patients with acute attacks [57].

A series of drugs for HAE are under investigation, and optimization of administration (developing oral or subcutaneous dosage forms, *etc*.) would be an important direction for research into treatment for HAE. In addition, studies on monoclonal antibodies and gene therapy also show great promise for the future.

Conclusion

In the past three decades, studies of HAE in China have mainly focused on clinical features, identifying mutations, and therapeutic intervention. Chinese HAE patients show different clinical characteristics from those of western populations, which indicates the important role of genetic and environmental factors in the pathogenesis of HAE. Further studies concerning different aspects of HAE according to ethnic variation are expected in the future. A spectrum of *SERPING1* mutation in Chinese patients has now been established, laying a foundation for future genetic therapy. Currently, there is still no approved drug for acute attacks on the Chinese market, and choices for long-term prophylaxis are limited to danazol and tranexamic acid. Thus, medication for acute attacks and prophylaxis with minor side effects are anticipated. Further investigation on molecular mechanisms and therapeutic interventions including traditional medicine are warranted in the future. ■

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Supplementary data

Supplementary data (table 1) associated with this article can be found, in the online version, at doi:10.1684/ejd.2018.3487.

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