

## CASE REPORT

# Hereditary Angioedema: A Family Study

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**SUMMARY** Hereditary angioedema (HAE) is a rare, life-threatening, autosomal dominant disease characterized by recurrent episodes of angioedema, and caused by a deficiency of the plasma protein C1-esterase inhibitor (C1-INH). Clinical manifestation of HAE may first develop during childhood but typically presents around puberty with nonpruritic and non-pitting edema of the subcutaneous and mucosal tissues. Up to now, there has been no published report of HAE case in Taiwan. We reported a 33 year-old female patient who had recurrent painful swelling of face and hands since 27 years of age. She first suffered from sudden onset of painful swelling of the eyelids and lips in August 1998 when she was pregnant for the first time. Subsequently, similar episodes recurred for a few times. Her blood test disclosed that her C3 and C4 were 125 mg/dl and 6 mg/dl, respectively. Her uncle died of laryngeal edema at the age of 30 years. Her father and elder brother also had the similar history of recurrent facial and hand swelling. The C4 levels of her elder brother were 6 mg/dl and 13.3 mg/dl on two separate occasions. The C1-INH antigen serum level and functional assay of the index patient and ten other family members were studied. A total of seven members of the family were confirmed to have type 1 HAE as evidenced by the low C4 and low C1-INH antigenic level and functional activity. Two of the seven cases were asymptomatic up to the date of our report.

Hereditary angioedema (HAE), first described clinically by Osler in 1888, is a rare autosomal dominant disorder of complement system with multiple clinical manifestations.<sup>1</sup> The clinical features of the disease are recurrent transient episodes of nonpruritic and non-pitting cutaneous edema and mucosal swelling of the extremities, face, and larynx. These transient edemas usually last 2 to 5 days, and they regress spontaneously. However, angioedema can develop in subcutaneous tissue or involve the mucous membranes of the upper airway and the gastrointestinal tract. The intestinal wall edema may be accompanied by transient ascites.<sup>2</sup>

HAE is caused by a deficiency (type 1) or dysfunction (type 2) of complement C1-esterase inhibitor (C1-INH). The underlying pathophysiology was discovered by Donaldson and Evans<sup>3</sup> in 1963. The cause is a defective C1-INH gene that produces

either a deficient C1-INH or a dysfunctional C1-INH. HAE is characterized by recurrence of subcutaneous and mucosal swellings appearing early in life and usually accompanied by a strong family history.<sup>4</sup> HAE type 1, found in 85% of patients with HAE, is characterized by low C1-INH antigenic level and functional activity. Patients have a deficiency in C1-INH. The defect is transmitted as an autosomal dominant trait but can occur spontaneously as well. In HAE type 2, which comprises 15% of HAE cases, the circulating C1-INH concentration is normal, but the C1-INH does not have normal functional activity. In HAE type 3, which is rather rare, the C1-INH has a structural abnormality that binds to albumin, forming an inactive complex.<sup>5</sup>

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This type affects primarily women and is exacerbated by estrogens.<sup>6,7</sup> The exact prevalence of HAE is unknown; current estimates suggest that the disease affects between 1 in 10,000 to 50,000 persons.<sup>8</sup> Mortality as high as 30% has been reported, and asphyxiation resulting from obstruction of the upper airways due to acute laryngeal edema is the most common cause of mortality.<sup>9</sup> In addition, obstetricians should be aware of the disease because it affects women in the reproductive years. HAE during pregnancy typically follows a benign course, but an increase trend in acute attacks of HAE during pregnancy has been previously reported.<sup>10</sup> It is also an important issue for the dentists because manipulation within the oral cavity may precipitate an acute attack.<sup>11</sup> In HAE patients, the C4 level is typically decreased.<sup>12</sup> C1-INH antigenic and functional level should be measured to confirm the diagnosis.

We report a case of a 33-year-old female patient suffering from recurrent painful swelling of face and hands since she was pregnant at 27 years of age. Furthermore, the paucity of relevant information and case reportage in Taiwan prompted us to conduct and extend pedigree analysis of her family. Serological assay of C4 and C1-INH antigenic and functional assay were performed in her family members to identify afflicted relatives. The literature was also reviewed.

### CASE REPORT AND FAMILY STUDY

This 33-year-old female was in her usual state of health until August 1998, when she suffered from painful swellings of her face and hands for a few times starting at 25 years of age when she was pregnant for the first time. The symptoms would subside a few days later. On February 14<sup>th</sup>, 2000 she presented to the Emergency Department of Zhongxiao Branch of Taipei City Hospital with impressive urticaria-like lesion over face and hands. Antihistamine (diphenhydramine) therapy was given without much improvement. The symptoms subsided spontaneously a few days later. Subsequently, similar episodes occurred for a few times. On few occasions, the larynx and feet were involved, and she presented with shortness of breath. She was referred to the Allergy and Immunology Department on February 25<sup>th</sup> 2000, where the laboratory data showed white blood cell count 7,600 cells/ $\mu$ l (neutrophils 67.8%, lym-

phocytes 26.4%), hemoglobin 11.4 g/dl. The electrolytes showed sodium 134 meq/dl and potassium 4.6 meq/dl. The blood chemistry showed serum glucose level 95 mg/dl, total protein 7.2 g/dl, albumin 4.1 g/dl, urea nitrogen 9.1 mg/dl, creatinine 0.6 mg/dl, serum glutamic oxaloacetic transaminase (SGOT) 26 U/l, serum glutamic pyruvic transaminase (SGPT) 19 U/l, cholesterol 162 mg/dl, and triglyceride 111 mg/dl. The IgE was 141 IU/ml, complement factor 3 (C3) was 125 mg/dl, and complement factor 4 (C4) was very low at 6.0 mg/dl. Specific IgE test showed no reaction to house dust mites, cat or dog dander, cockroach, or ragweed. Her father and elder brother also suffered from recurrent painful facial edema. The 37-year-old elder brother also has frequent abdominal pain since 14 years of age. On one occasion in 1994, the elder brother suffered from severe facial and laryngeal edema after a minor facial injury by a steel rope. The symptoms progressed even though antihistamine and steroid were given for treatment. Finally, a tracheostomy had to be conducted by an Otolaryngologist to secure the airway due to severe airway obstruction and dyspnea. A blood test disclosed his C3 was 94.1 mg/dl and the C4 was only 6.0 mg/dl at the time of presentation. He was admitted three additional times due to facial swelling, dysphonia, odynophagia and dysphagia. Each time, the laryngeal examination showed edematous change. A repeat blood test disclosed a low C4 level of 13.3 mg/dl. Her father also suffered from recurrent symptoms of sudden onset of hoarseness and edema of four limbs. The laryngeal examination showed vocal cord swelling on several occasions. Her uncle died of sudden onset of dyspnea at the age of 30 years without the details being known. Based on the clinical symptoms and family history, the diagnosis of HAE was made in the index patient. The family members were interviewed for their disease history and the serums were collected for detection of C3, C4 and C1-INH.

### Laboratory methods

The C3 and C4 complement fractions were determined by nephelometry (Dade Behring Marburg GmbH, Marburg, Germany). The C1-INH antigenic level was determined by "Human C1 inactivator (C1-INH) Bindarid<sup>TM</sup> radial immunodiffusion kit" (The Binding Site Ltd., Birmingham, UK). In short, the serum was diffused radially from a cylin-

drical well through an agarose gel containing a mono-specific antibody (anti C1-INH antibody). The antigen-antibody complexes formed a precipitin ring. A calibration was constructed by measuring the ring diameter produced by a number of samples of known concentration. The concentration of the antigen in an unknown sample was then determined by measuring the ring diameter produced by the sample and reading off the calibration curve. The C1-INH functional activity was determined by "Human C1 inactivator (C1-INH) Bindarid™ functional activity kit" (The Binding Site Ltd., Birmingham, UK). A heat aggregated  $\gamma$ -globulin (HAGG) was added to the serum samples, the complement system was then activated. C1-INH bound to activated C1r masking many of C1r's antigenic sites. This was demonstrated on a radial immunodiffusion plate containing C1r antibodies, as a deterioration in ring quality following incubation with HAGG, compared to the same serum incubated with saline. This effect is not observed in patients with functional C1-INH deficiency. Measurement of serum C1r levels, before and after addition of HAGG, therefore provides an indicator of functional C1-INH activity in the test samples.

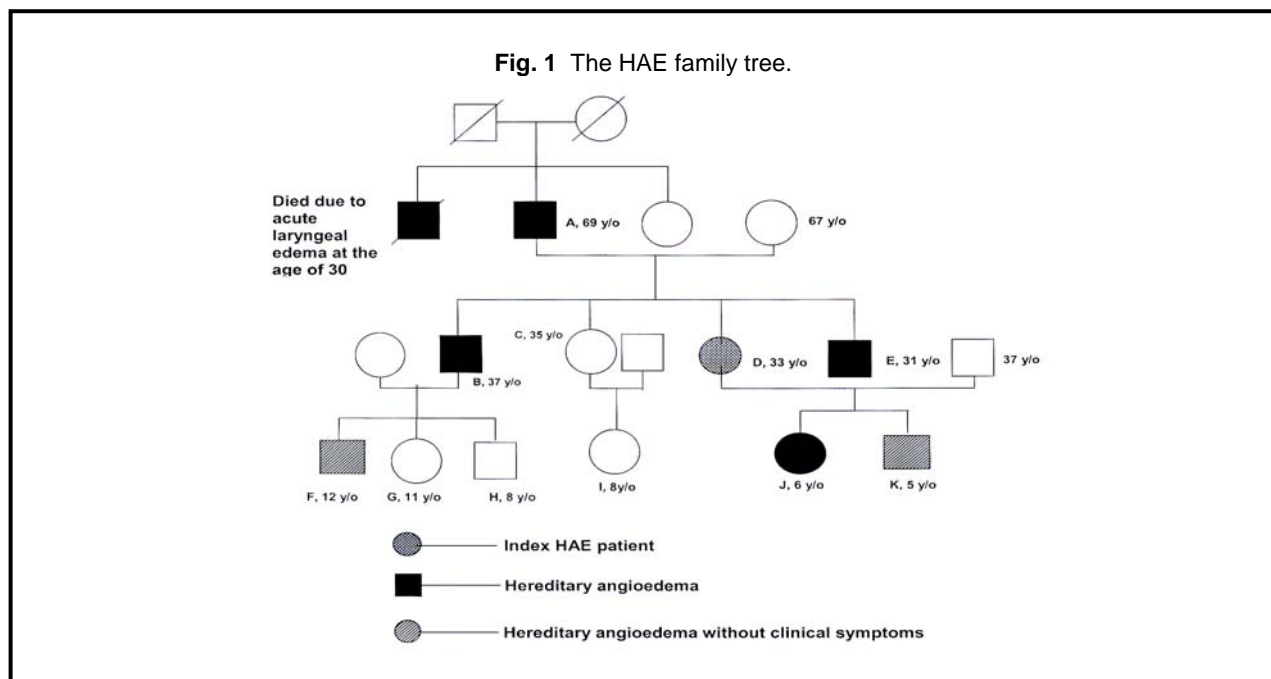
## RESULTS

The family pedigree is shown in Fig. 1. The family members with no mark of English character could not be reached and thus were not studied. A to-

tal of 11 family members were included in the study, and seven members were confirmed to have HAE, as evidenced by the low C4 and C1-INH levels. The uncle of the index patient was also highly suspected to be a case of HAE, since he died of laryngeal edema at the age of 30, although, there was no laboratory data to support the diagnosis. The HAE-related laboratory data of the family are presented in Table 1. The clinical characteristics of the seven HAE patients are shown in Table 2. Two (cases F and K) of the seven cases are still asymptomatic. All the symptomatic cases had subcutaneous involvement. The youngest symptomatic case (case J) was only 6 years old. Gastrointestinal manifestations occurred in 2 cases, and laryngeal edema also developed in 3 cases.

## DISCUSSION

There has been no published report of HAE cases in Taiwan. Our report is the first to demonstrate the familial HAE cases in Taiwan. In this study, a total of seven cases in a family were identified to suffer from HAE. In addition, the uncle of our index patient was highly suspected to be an additional HAE case since he died of laryngeal edema at the age of 30, although there was no laboratory data to support the diagnosis. All of the seven confirmed cases had decreased C4 level and low C1-INH antigenic level and functional activity. The youngest



**Table 1** HAE related laboratory data of the family

Case	Age (years)	C3 (mg/dl) <sup>a</sup>	C4 (mg/dl) <sup>b</sup>	C1-INH	
				Antigen level <sup>c</sup>	Functional activity <sup>d</sup>
A	69	119	12.9	59.3	-
B	37	94	6.0	48.4	-
C	35	142	47.2	205	+
D	33	145	5.4	38	-
E	31	148	12.4	59.3	-
F	12	102	11.2	53.8	-
G	11	100	25.9	238	+
H	8	116	38.6	247	+
I	8	115	42.5	164	+
J	6	134	5.4	88.8	-
K	5	129	13.0	95	-

a, reference values: 90-180 mg/dl; b, reference values: 3 months-10 years: 10-40 mg/dl, adults: 15-45 mg/dl; c, reference values: 174 - 240 mg/l; d, "-" functionally inactive; "+" normal activity.

**Table 2** Clinical characteristics of the 7 HAE cases

Case	Onset age (years)	Site(s) involved			Precipitating factors			
		Subcutaneous	Laryngeal	Abdominal	Trauma	Stress	Infection	Pregnancy
A	30	+	+	+	+	+	-	-
B	25	+	+	+	+	+	-	-
D	25	+	+	-	+	+	+	+
E	28	+	-	-	-	-	-	-
F	-	-	-	-	-	-	-	-
J	5	+	-	-	-	-	-	-
K	-	-	-	-	-	-	-	-

"-", no symptoms till the day of this study.

symptomatic case (case J) was only six years old, with onset of symptom started at five years of age. Our HAE cases all had low C1-INH antigenic level and low functional activity; thus, they are properly classified to HAE type 1.

Owing to the rarity of HAE and the common occurrence of idiopathic angioedema, HAE patients are insufficiently recognized and often overlooked and misdiagnosed under limited laboratory data and clinical history. To confirm the diagnosis of HAE, it is necessary to have good laboratory data in addition to a positive family history. It is also essential that the initial result be confirmed and interpreted by an appropriately trained and experienced specialist. In a review of the literature, it was noted that 15% to

33% of untreated angioedema patients died from acute airway obstruction as a result of laryngeal edema.<sup>13</sup> The potentially fatal outcome of this disease can be avoided if the proper evaluation and treatment are rendered.

HAE patients usually begin to become symptomatic during their childhood and experience increase in symptoms at the time of puberty.<sup>10</sup> Studies have shown that 50-70% of patients have their first episodes under the age of 12 years.<sup>14</sup> No occurrence has been reported in newborns, and the youngest symptomatic case is 19 months old.<sup>15</sup> Our six-year-old case should be the youngest reported symptomatic HAE patient in Taiwan at present. Affected individuals typically continue to experience recurrent

attacks throughout the remainder of their lives. Patients have local swellings at three predominant sites: subcutaneous tissues (face, hands, arms, legs, genitals, and buttocks); mucosal surface of the abdominal organs (stomach, intestines, bladder), which can mimic surgical emergencies; and the mucosal surface of the upper airway (larynx), which may result in life-threatening laryngeal edema. Abdominal symptoms generally subside spontaneously within 12 to 24 hours, whereas the subcutaneous lesions may last for two to five days. Laryngeal edema in HAE may be fatal. Most patients who asphyxiate by airway obstruction die between their 20th and 50th years of life. Fatal airway obstruction may happen not only in patients with frequent edema attacks but also in those with rare episodes of swelling. Even the first episode of laryngeal edema may be fatal.<sup>16,17</sup> Perioral and periorbital involvements, which are often observed in allergic (idiopathic) angioedema, are not specific characteristics of HAE.<sup>4</sup> In the review of 30 patients with HAE by Frank *et al.*<sup>10</sup> noted that 26% of the patients reported nonpruritic rashes with their attacks. Erythematous mottling, erythema multiforme, and erythema marginatum have all been described in association with attacks. The presence of urticarial lesions should not rule out a diagnosis of HAE. Precipitating factors of attacks may include trauma, anxiety, stress, menstruation, pregnancy, some drugs or infection.<sup>10, 18</sup> Furthermore, oral contraceptives may precipitate an acute attack and are therefore not recommended for women with HAE.<sup>4</sup> During pregnancy, symptoms may intensify or diminish. There is an increased incidence of autoimmune diseases among patients with HAE.<sup>4</sup> As many as 2% of patients with HAE may have systemic lupus erythematosus.<sup>19</sup>

Hereditary angioedema related to C1-INH deficiency is transmitted by a well-defined autosomal dominant trait. Its variants include type 1 and 2 HAE, which are caused by heterozygous defects in the C1-INH gene (C1NH or SERPING1). This gene is located in the q12-q13.1 subregion of chromosome 11.<sup>20,21</sup> A wide variety of deletions, translocations, stop codons, and point mutations of the gene that lead to disease have been identified and are discussed. Unfortunately, the gene study was not performed because of the disagreement of the family. C1-INH is a heavily glycosylated single-chain polypeptide with a reported molecular weight of ap-

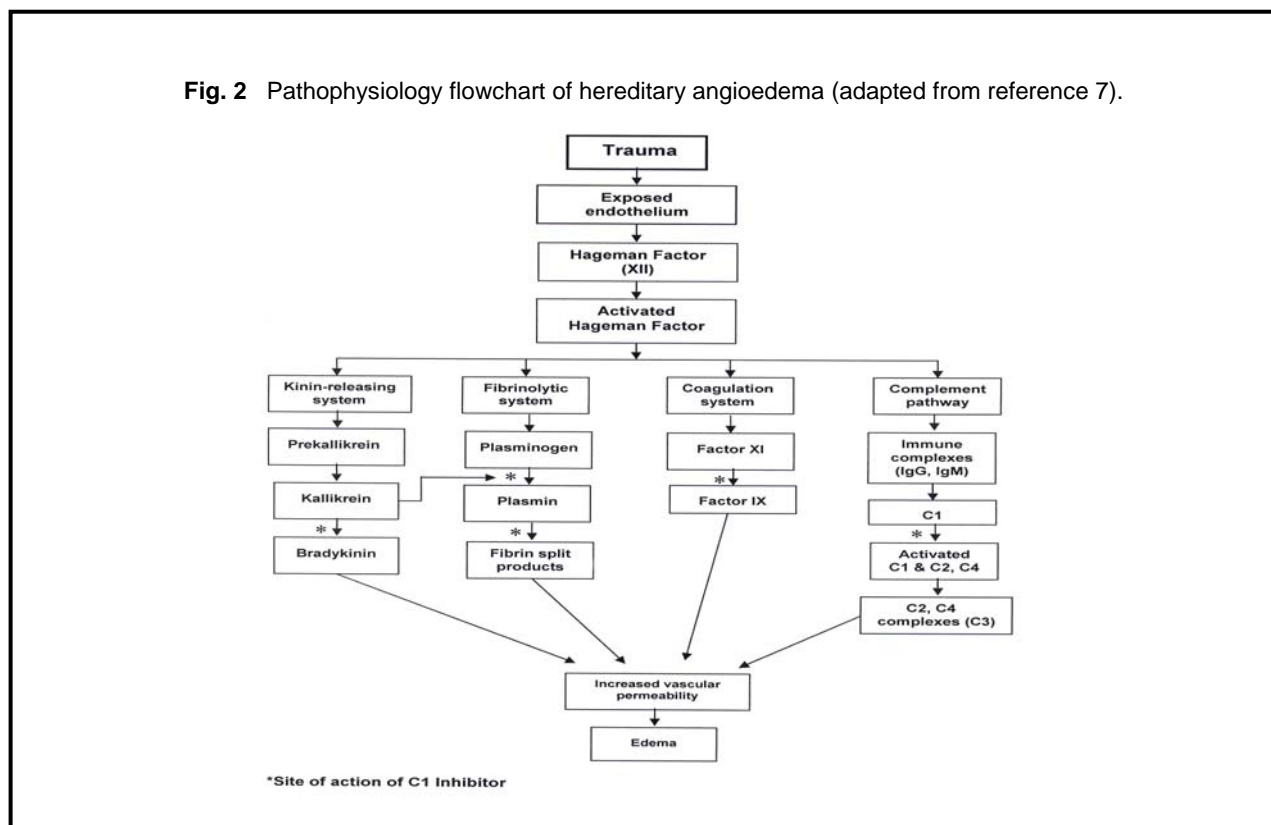
proximately 108 kDa.<sup>17</sup> It is a multifunctional serine protease inhibitor that is normally present in high concentrations in plasma. This protein is produced in the liver and in activated monocytes.<sup>22</sup> Accumulating evidence suggests that bradykinin, released from high molecular weight kininogen by plasma kallikrein, is the major mediator of the angioedema in HAE.<sup>23-26</sup> The whole mechanism of pathophysiology of HAE is shown in Fig. 2.<sup>11</sup>

Clinical diagnosis is made on the basis of typical clinical presentation and positive family history of angioedema as specified above. However, up to 20% of HAE patients have de novo mutation.<sup>27</sup> Diagnosis of HAE is confirmed by establishing a low level of C1-INH antigen or function and low levels of the complement protein C4 and/or C2. A low C4 level at the time of presentation is a reliable and useful indicator and is invariably below 40% of normal value.<sup>28</sup> The differential diagnosis of HAE includes angioneurotic edema, de Quervain's disease, and nonhereditary angioedema.<sup>29</sup>

The treatment of HAE is divided into three categories, acute medical, long-term medical, and short-term surgical prophylaxis. Long-term prophylaxis has been successful with the use of synthetic anabolic androgens such as Stanozolol and Danazol.<sup>30</sup> These drugs increase the hepatic production of C1-INH. The use of anabolic androgens, however, is associated with multiple side effects including weight gain, liver dysfunction, amenorrhea, virilization, fatigue, and headaches. Anabolic androgen used for long-term prophylaxis must be heavily weighed against these risks. Interferon- $\gamma$  ( $\gamma$ -IFN) has been shown to stimulate C1-INH RNA, thus allowing greater C1-INH production.<sup>31</sup> Antifibrinolytic agents, such as  $\epsilon$ -aminocaproic acid (EACA) or tranexamic acid (AMCA), are frequently effective in decreasing the number and severity of the attacks.<sup>32</sup> EACA appears to inhibit C1 and plasmin activation. The side effects include thrombus formation, fatigue, muscle aches and nausea, which mitigate the benefits of EACA. AMCA has better tolerability with reduced gastrointestinal discomfort.<sup>33</sup> Synthetic anabolic steroids remain the treatment of first choice for long-term prophylaxis.<sup>32</sup>

In the management of an acute episode, fresh frozen plasma (FFP) has been shown to resolve the

Fig. 2 Pathophysiology flowchart of hereditary angioedema (adapted from reference 7).



attack within minutes. FFP contains C1-INH and provides a sudden boost in its circulating concentration. The potential drawbacks to FFP are twofold. The first is the possible introduction of viral contaminants contained within the preparation. The second is that the high concentration of many complement proteins may worsen symptoms during the acute phase.<sup>5,10</sup> The newest treatment modality is the use of purified pasteurized C1-INH preparations, which currently is regarded as the most appropriate therapy for life-threatening HAE attacks.<sup>18,34</sup> An acute HAE attack does not respond well to epinephrine and steroid therapies as does a classic allergic reaction.

Surgical (short-term) prophylaxis of patients with HAE undergoing oral and maxillofacial surgery procedures is strongly recommended.<sup>10</sup> The use of FFP has been shown to be effective in surgical prophylaxis.<sup>11,35</sup> Treatment begins the night before surgery with one unit of FFP. A second unit is administered before surgery. The use of C1-INH preparations for surgical prophylaxis is currently being intensely studied and has been used in patients undergoing oral and maxillofacial surgery without compli-

cations or side effects.<sup>34</sup> Alternatively, high-dose anabolic androgen therapy (stanozolol 2 mg three times daily or danazol 200 mg three times daily) beginning 7-10 days before the procedure affords excellent protections.<sup>36</sup> The C1-INH preparations will likely become the treatment of choice for both acute attacks and surgical prophylaxis of HAE.

This case report, a familial HAE study, and literature review demonstrate the complexity of diagnosing and treating HAE. HAE is often overlooked as a differential diagnosis of patients suffering from diffuse swelling or abdominal discomfort. A clinician of medicine or dentistry should be aware of these entities of HAE to ensure inclusion within the differential diagnosis. A thorough history and clinical assessment is required for a patient who displays symptoms consistent with angioedema. The laboratory tests, including C4 level, C1-INH antigenic level and functional activity, help to confirm the diagnosis of HAE. This literature review has also described currently available treatment modalities of HAE. Proper identification and prophylactic treatment will ensure a favorable outcome.

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