

Hereditary angioedema with a focus on the child

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ABSTRACT

Hereditary angioedema (HAE) is a rare disease that causes recurrent mucosal and cutaneous swelling. Skin swelling, abdominal pain, and airway swelling cause significant morbidity and potential mortality. Symptoms often appear early in life and accelerate around puberty. Despite this, there is a paucity of both data and treatment options for HAE in children in the United States. Our objective was to summarize the published data and perform a retrospective chart review on children with HAE to improve care of the child with the disease. A retrospective chart review study was performed after Institutional Review Board approval. A search of electronic medical records from 2001 to 2011 was performed for children aged 1 to 18 years with a confirmed diagnosis of HAE. Demographic patient information was obtained and analyzed. Twenty-five pediatric patients were identified with the diagnosis of HAE: 13 female and 12 male. The median age at diagnosis was seven years. The most common initial presenting symptom was swelling of the upper extremity, followed by abdominal pain, swelling of the face and/or lower extremity, and scrotal swelling. Three patients reported no previous symptoms and were diagnosed due to family history of HAE and positive laboratory testing. The majority of patients (84%) reported a family history of HAE. Accurate and timely diagnosis of HAE is imperative for children to prevent further morbidity and mortality associated with the disease.

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Hereditary angioedema (HAE) is an autosomal dominant, potentially life-threatening disease that induces recurrent episodes of edema of the face, extremities, gastrointestinal tract, and urogenital areas of the body. The swelling is nonwhealing and nonpruritic and is refractory to treatment with antihistamines and corticosteroids.¹ Most cases are caused by the deficiency, or functional inactivity, of the C1 esterase inhibitor (C1-INH), a plasma protein that prevents bradykinin activation. HAE type 3, commonly referred to as HAE with normal C1-INH, has been reported but is an extremely rare disease and will not be included in our manuscript, because there is no diagnostic test.² In all three types of HAE, bradykinin is recognized as the primary mediator of the edema as a result of increased activity of kallikrein in the plasma.³

Diagnostic algorithms suggest, in the presence of characteristic clinical symptoms or family history of HAE, initial screening for low C4 levels with subsequent measurement of C1-INH protein levels and function is indicated.^{4,5} Due to the immaturity of the complement and kallikrein/bradykinin systems early in life, testing for C4 and C1-INH is generally deferred until age one year in children suspected of having the

disease, most commonly because of a family history of HAE.^{6–9} HAE patients often visit multiple physicians and go many years with recurrent symptoms before their condition is correctly diagnosed.¹⁰ Prompt and accurate diagnosis has been proven to reduce morbidity and mortality in HAE.^{6,11}

Once a diagnosis of HAE has been established, proper management is paramount due to the significant morbidity and mortality associated with the disease. Although targeted therapies have been available for the past three decades in Europe,¹² they had been absent from the United States until a few years ago. There are currently only four Food and Drug Administration (FDA) approved therapies available in the United States (Table 1).¹ For children, FDA-approved treatments are even more limited. Before recent approvals, the lack of targeted therapy left adult patients and their physicians with a limited armamentarium and often exposed the patient to significant adverse effects of medications. Children, however, are still limited in therapeutic options that are FDA approved, often resulting in inadequate therapy.

Over the past few years, the conclusion of several United States FDA phase II and phase III trials has made specific therapies available to physicians to prescribe. In particular, new therapeutic options are available that directly address the C1-INH deficiency and subsequent downstream kallikrein activation and bradykinin generation that is responsible for the symptoms of HAE.^{3,13–18} The recent availability of these safe and efficacious drugs for adults has changed the treatment paradigm for HAE as reflected in the current guidelines^{1,6} and will continue to change based upon both patient and drug-specific factors, including pref-

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Table 1. FDA-approved treatments for HAE in children

Generic Name	Trade Name	FDA Approval	Approved Age	Administration
Plasma-derived C1-inhibitor	Berinert	Acute attacks	12 years and up	Intravenous
Ecallantide	Kalbitor	Acute attacks	12 years and up	Subcutaneous
Icatibant	Firazyr	Acute attacks	18 years and up	Subcutaneous
Plasma-derived C1-inhibitor	Cinryze	Prophylaxis	12 years and up	Intravenous

FDA = Food and Drug Administration; HAE = hereditary angioedema.

erence, cost, efficacy, and availability. Early treatment has been shown to result in improved outcomes, reinforcing international recommendations to treat HAE attacks as early as possible for optimal control of symptoms, including using self-administered approved therapies.^{11,19}

Despite the majority of HAE attacks occurring spontaneously, some commonly reported triggers include stress/anxiety, trauma, surgery, and illness. Other causes include prolonged physical activity, menstruation, pregnancy, the use of angiotensin-converting enzyme inhibitors and oral contraceptives or other hormone therapies.^{20,21} Fortunately, angiotensin-converting enzyme inhibitors are infrequently prescribed for use in children. However, hormonal therapy is frequently used for birth control and acne control in adolescents.

Although the true physical, emotional, and economic burden of this disease is relatively difficult to quantify, it has recently been noted that the vast majority of patients with HAE experience unwanted alterations in their daily activities and experience significant anxiety and depression about future HAE exacerbations.²² It has been estimated that average total annual costs are \$42,000 per patient with HAE; with an incidence as high as 1 in 10,000 persons, this disease burden is substantial.²³

Despite an increasing amount of data related to HAE in the adult population, there is a relative paucity of information for children diagnosed with HAE. To the best of our knowledge, no significant series of confirmed cases of HAE in children in the United States have been described in the pediatric medical literature.

To develop a clinical picture of children with HAE, the goals of this article are to describe patients' gender, age at initial diagnosis, and presenting complaint (including airway involvement); history of atopic comorbidities, family history of HAE, and initial patient encounter settings as compared with previously published international data.

METHODS

Institutional review board approval was obtained for this retrospective chart review study of a database of children diagnosed using International Statistical Classification of Diseases and Related Health Problems code 277.6: deficiencies of circulating enzymes. Of the seventy

Table 2. HAE patient demographic data

	Airway Involvement	Atopic History	Family History of HAE	HAE Type 1
Yes	16%	44%	84%	100%
No	72%	40%	8%	0%
Unknown	16%	16%	8%	0%

HAE = hereditary angioedema.

pediatric patient files examined, 25 children had a confirmed diagnosis of HAE. Inclusion criteria for diagnosis required screening demonstration of low levels of C4 (less than 14 mg/dL) with low levels of C1-INH protein levels (less than 11 mg/dL) and/or function (less than 40%). Positive family history was defined as a first-degree relative diagnosed with HAE. The patients presented, in most instances, to the emergency department for evaluation and management of edematous episodes involving various parts of the body. Some patients were referred by emergency department, primary care, or other physician specialists for suspicion of HAE.

Patient chart reviews were conducted, including documentation of patient demographics (age, gender), patient history (including medications administered, atopic comorbidities, and family history of HAE), and presenting complaint (including airway involvement).

RESULTS

Twenty-five pediatric patients, ranging in age from 1 to 18 years, were identified with the diagnosis of HAE based on the aforementioned inclusion protocol. Of the patients encountered in our study, 13 patients were female and 12 male (Table 2). All patients were diagnosed with type 1 HAE. The median age at initial presentation was seven years and mean age was 7.7 years. Average age at initial presentation for females was 6.8 years and 8.8 years in males. The average at diagnosis was 7.2 years for those with a known positive family history and 9.5 years for those patients with no known/unknown previous family history of HAE. The most common presenting symptom was swelling of the upper extremity (n = 10), followed by abdominal pain (n = 9), facial swelling (n = 8), lower extremity swelling (n = 4), and scrotal swelling

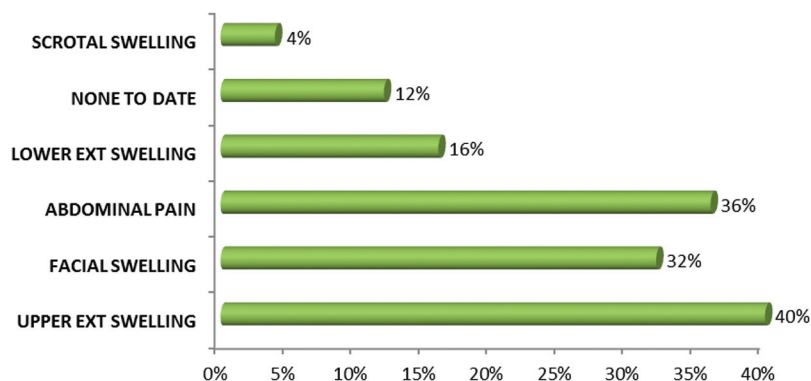


Figure 1. Presenting complaint at diagnosis of HAE (multiple sites reported; total, >100%).

($n = 1$) (Fig. 1). Many patients presented with symptoms at multiple sites. Three patients reported no previous symptoms and were diagnosed due to a family history of HAE with confirmatory laboratory testing. Four patients reported airway involvement, including wheezing, a sensation of swelling, and/or failure to control oral secretions.

Over half (60%) of the patients had a documented history of receiving plasma-derived C1-INH at or after diagnosis; 28% had a documented history of receiving a bradykinin B2 receptor antagonist at or after diagnosis.

The majority of patients (84%) reported a family history of HAE. Almost half of the patients (44%) reported a concomitant atopic disease history (consisting of atopic dermatitis, asthma, and/or allergic rhinitis). Most patients (96%) were diagnosed as an outpatient. Only two patients were diagnosed during an inpatient hospitalization. No fatalities were documented for the current study population.

DISCUSSION

Although there has been no previous demographic case series of laboratory-confirmed HAE in children in the United States, the current cohort data are similar to previously published international studies. A 2010 study of Hungarian children revealed a median age at first attack between 3 and 6 years, with ages ranging between 4 and 11 years.²⁴ A study of Danish children in 2011 revealed a median age of nine years for the onset of a first swelling episode.²⁵ Additionally, a study of German children in 2006 revealed a mean age of 11.2 years for patients diagnosed with HAE.² The only American study, published by Donaldson and Rosen in 1966,⁸ reported on surveys of pediatric patients experiencing swelling episodes attributed to angioneurotic edema. Donaldson noted a median age between 5 and 10 years for first swelling attacks,⁸ which is consistent with our data. There have been no documented fatal episodes in our pediatric HAE population, similar to international data suggesting an incidence as low as 1.5%.²⁶

The majority of pediatric patients were treated with either a plasma-derived C1-INH or bradykinin B2 receptor antagonist at or after diagnosis of HAE. Despite this, 24% of patients did not have documentation of FDA-approved therapies prescribed at or after this diagnosis. This lack of access to therapy is secondary to zero FDA-approved therapies for children under 12 years of age. This poses a quandary for practitioners, because health insurers often disallow the prescription of non-FDA-approved therapies for children. It is important to note that appropriate therapy should be prescribed at the time of diagnosis so that the patient is adequately prepared to treat the first HAE attack. The lack of therapies for children under 12 years of age is a critical issue, and the FDA and pharmaceutical companies should work toward approval of treatments for children and define the safety and efficacy in very young children.

Limitations of the present study include its small sample size ($n = 25$ patients) obtained from a single source (a large quaternary care medical center from 2001 to 2011), the requirement of confirmed laboratory diagnoses of HAE types 1 and 2, a patient sample obtained based on a single International Statistical Classification of Diseases and Related Health Problems code nonexclusive to HAE, and the use of retrospective data restricted to the contents of a clinical chart. In particular, the clinical chart did not include data pertaining to duration of symptoms before diagnosis or provide a comprehensive history detailing medications used, given, or prescribed for HAE episodes or as prophylaxis for future exacerbations.

Despite limitations, our results suggest similar median ages of children with HAE at seven years of age. This affirms that diagnosis should be confirmed early in life with therapy prescribed so the patient, family, and physician are prepared to treat the first attack. As recognized and expected, 84% of our patients reported a positive family history for HAE. All siblings and children of persons with HAE should be tested as long as they are over the age of one year so that diagnosis can be confirmed and appropriate therapy prescribed. In young children with previous negative HAE testing but a high suspicion

for HAE, retesting is recommended. Females did present with symptoms earlier than males, which may be correlated with earlier onset of puberty in females.²⁷ Similar to previous reports, there is no associated gender predilection based on our case series data. Common areas affected with swelling attacks included the face, extremities, gastrointestinal tract, and urogenital areas of the body. Although relatively uncommon, those patients reporting airway symptoms are at a greater risk of serious adverse outcomes.^{28,29} Due to this, therapy should be available for all ages, because the first attack may result in significant morbidity and possible mortality. Despite the need to be prepared for an airway attack, these data reinforce a low mortality documented early in life.²⁶

CONCLUSIONS

Future directions for research on HAE in children include further patient demographic information, including (but not limited to) documentation of duration of patient symptoms before diagnosis; medications used, given, and/or prescribed to date; number of emergency department visits or hospitalizations related to symptoms; and frequency of attacks, quality of life, and burden of disease analyses.

HAE is a serious, life-threatening condition requiring accurate and timely diagnosis and treatment due to its early presentation in life. With prompt diagnosis of HAE and the availability of targeted medications, therapy should be prescribed at the time of diagnosis so that the patient is adequately prepared to treat HAE attacks. Promising new therapies are available to prevent and control HAE exacerbations, with continued research and development toward novel therapies. An understanding of HAE allows medical practitioners to adequately treat and prevent future edema attacks safely and effectively in children. However, present therapies are limited, especially for those under 12 years of age. FDA-approved therapies for patients under 12 years remains a priority to improve the quality of life for children with HAE.

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