Original Article

Clinical Features of Pediatric Hereditary Angioedema

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What is already known about this topic? Pediatric hereditary angioedema (HAE) is classically described as a disease with onset of symptoms in the teenage years; however, earlier onset of symptoms is often missed and contributes to a delay in diagnosis.

What does this article add to our knowledge? This study shows an earlier age of symptom onset of 5.7 years and age of diagnosis of 5.0 years; children without a family history experienced a 6-year delay in diagnosis.

How does this study impact current management guidelines? These findings emphasize the need to screen children suspected of having HAE at an earlier age and if positive then the need to develop an on-demand treatment plan for these children.

BACKGROUND: There is a paucity of data that describe the clinical course of hereditary angioedema (HAE) in children.
OBJECTIVE: The purpose of this study was to examine the clinical features of children with HAE.
METHODS: Electronic medical records from the past 10 years at Cincinnati Children's Hospital Medical Center and an outpatient allergy community practice were searched for ICD-9 code 277.6 (Other deficiencies of circulating enzyme). Exclusion criteria included laboratory data not supportive of type I or II HAE diagnosis or age at diagnosis greater than 18 years. Chart review was performed and missing data were collected by telephone interviews with patient families. Descriptive statistics were performed using SAS version 9.4.
RESULTS: Twenty-one children were identified. The median age was 13.2 years (interquartile range [IQR], 9.1-18.8), 71% were male, 86% had an HAE family history, and 95% were Caucasian. The median age of symptom onset and diagnosis was 5.7 (IQR, 5-9 years) and 5.0 (IQR, 4-8 years), respectively. Five children diagnosed were asymptomatic. Three children without a family history had a 6.0-year delay in diagnosis. The most common angioedema attack sites were abdominal, peripheral, and laryngeal, which occurred at least once in 93%, 73%, and 27%, respectively. Of the 15 children with onset of symptoms, only 6 children received on-demand therapy for an acute attack, whereas 13 children were administered either short-term or long-term prophylaxis therapy.
CONCLUSIONS: In this pediatric HAE population, symptom onset and diagnosis occurred at a median age of 5 years with a delay in diagnosis in those without a family history. Abdominal attacks were more common than peripheral attacks in this population. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

Key words: *Pediatric hereditary angioedema; Hereditary angioedema; Age onset*

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by episodic nonpitting edema of the face, neck, abdomen, extremities, and genitals.[1,2] Mutations in the C1 inhibitor (C1-INH) gene, *SERPING1*, lead to bradykinin overproduction and swelling attacks.[3,4] Although the defect is present at birth, presentation of clinical disease was initially reported to occur during the second decade of life. Bork et al reported in 209 HAE patients that the mean age of symptom onset was 11.2 years.[5] Another large study of 444 Spanish HAE patients reported a mean age of symptom onset of 12.6 years.[6] Although HAE is classically described as a disease with onset of symptoms in the teenage years, reports of symptoms in first decade of life are not uncommon.[7]

The failure to recognize onset of symptoms early in life can lead to a significant delay in diagnosis. Survey studies have reported that the average delay in diagnosis is between 11 and 20 years.[6,7] Factors

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Abbreviations used
C1-INH- C1 inhibitor
CCHMC- Cincinnati Children's Hospital Medical Center
EMR- Electronic medical records
ER- Emergency room
HAE- Hereditary angioedema
IQR- Interquartile range
pdC1INH- Plasma-derived C1 inhibitor

that lead to a delay in diagnosis include lack of recognition of symptoms, misdiagnosis, and absence of a family history as *de novo* mutations have been estimated to occur in up to 25% of patients.[8] There are few treatment options for children with HAE,[9,10] and in many cases parents often decide, possibly based on their personal experiences with the disease as a child, against having their child evaluated by a physician. This has also resulted in the paucity of epidemiologic information on this population.

Studies have found that the most common site of swelling episodes in adult and pediatric HAE populations was the peripheral extremities[11] followed closely by abdominal attacks and that an earlier age of disease onset was associated with more frequent attacks.[5,7] Although the location of swelling episodes have been well characterized in adults, less is known about the clinical presentation of HAE in children. Thus, we sought to better define the age and initial presenting symptoms in a pediatric HAE population under 18 years of age.

METHODS

Electronic medical records (EMR) from the past 10 years at Cincinnati Children's Hospital Medical Center (CCHMC) and paper charts from a community allergy practice were searched for the diagnosis of HAE defined as ICD-9 code 277.6 (Other deficiencies of circulating enzyme). Children with this diagnosis code were excluded if laboratory data did not support diagnosis of type I or II HAE or if the age was greater than 18 years at the time of physician diagnosis. Data was collected uniformly for each patient using a template which included the current age of the patient, gender, ethnicity, age at diagnosis, age at symptom onset, associated diseases, triggers for attacks, laboratory results (C1-INH, C1 inhibitor function, C1q, C2, C3, C4), treatment modalities for acute attacks after diagnosis, number of emergency room (ER) visits after diagnosis, number of hospitalizations and average number of days hospitalized, current medications, number of lifetime laryngeal attacks if applicable, and average number of attacks per year since diagnosis (divided into abdominal, peripheral, and laryngeal attacks). Children with missing information by the chart review were contacted by telephone for interview using a telephone script. If the child was under the age of 16 years, the parent was interviewed. If the child was 16 years or older, both the parent and child were interviewed. SAS 9.4 (SAS Institute, Cary, North Carolina) was used to perform descriptive analysis and to test the association of age of symptom onset and age of diagnosis with attack frequency, severity, and location using χ^2 and Fisher's exact tests. The survivor function using the proc lifetest was used to calculate the median age of symptom onset. This analysis was used because of the ability to censor observations of children who were asymptomatic at the time of analysis. All parents of children (or the child if older than 18 years) provided verbal informed consent or assent, and the Institutional Review Board at CCHMC approved this study with a waiver of written consent.

TABLE I. Demographic characteristics of the 21 children with hereditary angioedema

	n (%)
Gender	
Male	15 (71)
Female	6 (29)
Ethnicity	
White	20 (95)
Other	1 (5)
Family history of HAE	
Present	18 (86)
Absent	3 (14)
Comorbid diseases	
None	13 (65)
Atopy	3 (15)
Frequent infection	2 (10)
Asthma	1 (5)
Migraines	1 (5)
C1 inhibitor	Median (IQR)
Level (mg/dL)	6.0 (4.75-8.75)

HAE, hereditary angioedema; *IQR*, interquartile range.

RESULTS

There were 21 children with a diagnosis of type I or II HAE included in this study who were fairly evenly distributed between the 2 sites. One child had data limited to gender, ethnicity, family history, age at diagnosis, and laboratory tests. Of these 21 children, 15 (71%) were male, 20 (95%) were Caucasian, and 18 (86%) had a family history of HAE (Table I). At the time of the final phone interview in September 2013, the current median age was 13.2 years (interquartile range [IQR], 9.1-18.8).

The median age of symptom onset was 5.7 years (IQR, 5-9 years) in 21 children; using the survivor function analysis, 5 children without symptoms were censored observations and 1 was missing this information (Figure 1, Table II). The majority of these children had symptom onset in the first decade of life (n = 13 of the 15 children with symptom onset). One of the 2 children identified with symptom onset in the second decade of life had no family history of HAE.

The median age of diagnosis was 5.0 years (IQR, 4-8 years) in all 21 children, which was 0.7 years before the age of symptom onset (Table II). The majority of these children had a family history (n = 18); these children had a diagnosis made 0.9 years before symptom onset, whereas children without a family history (n = 3) had a median delay in diagnosis of 6.0 years (Table II).

Age of symptom onset (greater than 5 years) or age of diagnosis (greater than 5 years) was not significantly associated with family history, ER visits, hospitalizations, more frequent (greater than 6 per year) attacks, and peripheral (yes/no) or laryngeal attacks (yes/no). Age of symptom onset greater than 5 years was significantly associated with having abdominal attacks ($P = .04$).

Stress was the most commonly reported trigger for attacks, which was reported by 9 children (60%) (Table III). The mean numbers of lifetime hospitalizations and ER visits per year were 0.8 (0-6) and 1.4 (0-12), respectively, in 19 children; information was missing for 2 children. Most children (65%) reported no other underlying medical history. The most commonly reported concomitant disease was atopy (including eczema and/or allergic rhinitis) in 15% of children followed by self-reported