Almalky *et al.*
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RESEARCH

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Clinical and laboratory spectrum of hereditary angioedema in a group of Egyptian children: a cross sectional study

Mohamed Almalky[1], Reham M. El Shabrawy[2], Najeeb Ali Mohammed Gheetah[3], Hossam Moustafa Elkady[4], Naglaa S. Osman[5], Walaa Shoman[6] and Eman Gamal Baz[1*]

Abstract

Background Hereditary angioedema (HAE) is a hereditary illness represented by repeated bouts of submucosal or subcutaneous edema. Types of HAE includes; HAE with deficient C1-inhibitor (type 1), HAE with dysfunctional C1-inhibitor (type 2), and HAE with normal C1-inhibitor. Data on the epidemiology of HAE in Egypt are limited. Therefore, we aimed to characterize HAE in Egyptian children, identify the morbidity, and clarify HAE's different clinical and laboratory presentations.

Methods In this cross-sectional study, we enrolled pediatric patients diagnosed with HAE according to the international hereditary angioedema WAO/EAACI guidelines. We gathered laboratory data on patients' mean serum C1 esterase inhibitor (C1-INH) level and activity, C4, and IgE levels.

Results We included 18 HAE patients (14 females and 4 males). They were between the ages of 6 and 18 years. The mean age upon confirmation of diagnosis was 8.4 ± 2.4 years. The mean time required to correctly diagnose HAE was 3.2 ± 1.8 years. We detected type I in 15 cases and type II in three cases. Eleven patients had a family member with HAE. In terms of previous misdiagnoses, 50% of patients were diagnosed with allergic angioedema. The median annual frequency of episodes was 17. The mean HAE attack time was 2.9 ± 1.5 days. Edema was most typically found in the face and abdomen. Trauma was the main triggering factor. We detected a significant direct relationship between severity of attack and C1-INH activity level.

Conclusions This research adds a considerable clinical information about children with HAE. According to current results, there is a considerable underdiagnosis of HAE in Egypt. The detection and management of HAE can be improved by screening the relatives of HAE patients.

Keywords Hereditary angioedema, Children, Clinical presentations, Laboratory presentations, Egypt

*Correspondence:
Eman Gamal Baz
eman_albaz@yahoo.com
Full list of author information is available at the end of the article

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Background

The clinical manifestations of hereditary angioedema (HAE) range from asymptomatic patients to life-threatening episodes. It is a hereditary condition distinguished by repeated attacks of submucosal or subcutaneous edema. Types I and II are caused by autosomal dominant mutations in the region of the gene that encodes for the C1 inhibitor (C1-INH), leading to either a deficit (type I) or an inactive form (type II) [1].

HAE is caused by variations in the SERPING1 gene linked to C1-INH dysfunction. When C1-INH function is impaired, the circulating kallikrein-kinin system (KKS) is not sufficiently regulated. As a result, prekallikrein is transformed into plasma kallikrein and BK, a vasoactive peptide that activates the B2 BK receptor to promote vascular permeability, is synthesized. KKS, complement, and fibrinolysis all have numerous inflammatory properties and are controlled by C1-INH; these effects are all mediated by the vascular system [2].

The number of patients with C1 inhibitor hereditary angioedema (C1-INH-HAE) is unknown. The approximate global incidence described in the research ranges from one in every 10,000 to one in every 150,000 individuals, with no ethnic or sex disparities [3].

Edema in HAE is nonpitting and nonpruritic. It involves three primary regions: subcutaneous tissue, the upper airway, and the gastrointestinal tract. The regions with the greatest incidence of edema are the skin, abdomen, and larynx (100%, 97%, and 54%, respectively), however, any of these sites may be implicated alone or in combination [4].

A lack of suspicion for C1-INH-HAE, especially in clinicians who are unaware of this disease, might lead to inaccurate diagnosis. There are many erroneous diagnoses, including hypersensitivity reactions to autoimmune disorders, involving a wide range of medications that might be harmful and have little clinical benefit. Delays in establishing an accurate diagnosis in individuals with HAE might have serious consequences, especially if the oedema involves the upper airway, leading to asphyxia [5].

As in other countries, the data on the epidemiology of HAE in Egypt are limited. In this study, we aimed to characterize HAE in Egyptian children, identify the morbidity, and clarify the different clinical and laboratory presentations of HAE in children.

Methods

The design of the study

This is a cross-sectional study held between January 2022 and January 2023 at Zagazig University Children's Hospital in Egypt. We enrolled patients diagnosed with HAE according to the international World Allergy Organization (WAO) in collaboration with the European Academy of Allergy and Clinical Immunology (EAACI) (WAO/EAACI) guidelines.

Inclusion and exclusion criteria

Types of HAE includes; HAE with deficient C1-inhibitor (type 1), HAE with dysfunctional C1-inhibitor (type 2), and HAE with normal C1-inhibitor. According to the worldwide hereditary angioedema WAO/EAACI standards, HAE-1/2 was considered when an individual developed repeated angioedema episodes. This assumption was more established if patients described, firstly, a family history of the condition (although this illness could only be found in only one-fourth of patients), secondly, the beginning of manifestations in childhood or adolescence, thirdly, repeated painful gastrointestinal complaints, fourth, the development of edema in the airways, fifth, the inability to respond to treatment with antiallergic medications, sixth, the existence of early manifestations prior to swellings, and/or seventh, the lack of wheals. The possible existence of HAE-1/2 culminated in testing procedures to confirm the diagnosis [6].

We excluded any patient with angioedema who did not meet the diagnostic criteria for hereditary angioedema, including acquired angioedema, chronic urticaria, contact urticaria syndrome, drug eruptions, and pressure urticaria.

Severity score criteria for HAE

Severe type: serious edema attacks and/or six or more bouts in the previous six-month period using the preventative medication and/or continued treatment utilizing plasma-derived C1-INH and/or more than 12 episodes in the previous six-month period without preventive therapy. Moderate: No serious bouts in the past six-month period with preventive medication (apart from ongoing treatment with C1-INH) or > 4–12 attacks in the previous 6 months without preventive therapy. Mild: no severe attacks, no preventive medication, and three episodes in the previous six- months. Asymptomatic: no clinical manifestations nor preventive medications [7].

Data collection

Clinical information about patients included the age of diagnosis, onset of symptoms, diagnostic lag, history of HAE in the family members, the rate of episodes, and episode triggers, emergency room visits, intensive care unit (ICU) admission site of edema, severity score, previous diagnosis, and drug history. Regarding the laboratory investigations, we collected data about the quantitative determination of complement 4 (C4), blood levels and activity (%) of C1 inhibitor (C1-INH), and IgE.

Statistical analysis

Statistical evaluation was performed on the clinical and laboratory data of HAE patients using IBM SPSS (Statistical Package for the Social Sciences) for Windows, version 23.0. The qualitative findings are displayed as percentages (%) and numbers (N), while the quantitative findings are shown as the mean, standard deviation, median, and range. Using the chi-square test, percentages of category variables were compared. To evaluate the association between different research variables, Spearman's correlation coefficient was determined. A p-value below 0.05 indicates statistical significance, whereas a p-value above or equal to 0.05 indicates statistical insignificance.

Results

Primary aspects of the study's population

Table 1 shows that we included 18 HAE patients (14 females and 4 males). They were between the ages of 6 and 18 years. In the patients under study, the mean age upon confirmation of diagnosis was 8.4 ± 2.4 years. The mean time that required to correctly diagnose HAE was 3.2 ± 1.8 years, while the age at which symptoms first appeared was between 2 to 10 years. Previous diagnoses (misdiagnoses) were 50% allergic reactions, 27.8% familial Mediterranean Fever (FMF), and 22.2% with no specific diagnosis. The patients were categorized into two groups: 83.3% (15 patients) with HAE type 1 based on C1-INH deficiency (quantity) and 16.7% (3 patients) with type 2 HAE, as determined by adequate values and a decline in C1-INH activity. Eleven patients (61.1%) had a familial history of hereditary angioedema.

Table 1 General characteristics of the studied population

Variables	Mean ± SD	median(range)	
Age (years)	11.9 ± 3.6	12 (6–18)	
Age at diagnosis (years)	8.4 ± 2.4	8 (4–13)	
Onset of symptoms (years)	5.1 ± 1.96	5 (2–10)	
Diagnostic lag (years)	3.2 ± 1.8	3 (0–7)	
Variables		n. (18)	%
Gender	females	14	77.8
	males	4	22.2
Types of angioedema	Type 1	15	83.3
	Type 2	3	16.7
Family history of angioedema	No	7	38.9
	Yes	11	61.1
degree of relation	First degree relative	10	55.6
	Second degree relative	1	5.6
previous diagnoses	Allergic reaction	9	50.0
	FMF	5	27.8
	No	4	22.2

Clinical features and treatment modalities of the studied patients

Table 2 shows that the median (IQR) annual frequency of episodes was 17(4–48). Angioedema attacks have been reported to last between 2 and 7 days, with a mean of 2.9 ± 1.5 days. Facial edema was found in 14 patients (77.8%), laryngeal angioedema in 8 patients (44.4%), and eyes, lips, feet, and hands in 4 patients (22.2%). We reported HAE with abdominal attacks in 14 patients (77.8%). The main trigger of HAE attack was trauma in 15 patients (83.3%). Spontaneous angioedema was detected in 14 patients (77.8%). Regarding disease severity, we reported 11 patients (61.1%) with severe angioedema attacks, 4 patients (22.2%) with moderate attacks, and 3 patients (16.7%) with mild attacks. Regarding the treatment modalities in our study, the main treatment during the attack was antihistamines in 17 patients (94.4%), steroids in 15 patients (83.3%), and epinephrine and plasma in certain situations. In four cases (22.2%), fresh frozen plasma was given as temporary prevention. Danazol was used for permanent prevention in seven cases (38.9%), and in one case, danazol was combined with a human C1-esterase inhibitor.

Hereditary angioedema testing results

Table 3 shows the quantitative amounts of C1-INH and its activity, as well as the C4 and IgE levels. Table 4 shows that there was no statistically significant association between the severity of the attack and age, diagnostic delay, the number of attacks, duration of the attack, C4 level, C1 esterase inhibitor level, or total immunoglobulin E. The degree of C1 esterase inhibitor activity had a significant and direct relationship with the severity of the attack.

Discussion

HAE is an uncommon and potentially fatal inherited immunological disorder. The clinical pattern of this disorder in pediatric patients is little understood. The exact number of HAE pediatric patients in Egypt remains unknown. In the current study, we aimed to characterize HAE in Egyptian children, identify the morbidity, and clarify different clinical and laboratory presentations of HAE in children and adolescents to gain more detailed insights into the existence of the disease. We included 18 HAE patients (14 females and 4 males). They were between the ages of 6 and 18 years.

The median age during which symptoms occurred in the current research was five years, that is in accordance with earlier researches on pediatric HAE in the United States and Hungary [8, 9]. However, the median age of HAE onset was lower in the Danish and Swedish studies (4 years) [10, 11] and higher in a US study (7 years)

Table 2 Clinical characteristics and treatment modalities of hereditary angioedema in the studied patients

Variables		n. (18)	%
Site of oedema	Face	14	77.8
	Laryngeal	8	44.4
	Eyes	4	22.2
	Lips	4	22.2
	Feet	4	22.2
	Hand	4	22.2
The attacks associated with abdominal symptoms	yes	14	77.8
	no	4	22.2
Trigger of the attack	Trauma	15	83.3
	Spontaneous	14	77.8
	Menstruation	4	22.2
	stress	1	5.6
Severity Score	Mild	3	16.7
	Moderate	4	22.2
	Severe	11	61.1
Variable	Mean ± SD	median(range)	
Number of attacks per year	23.7 ± 15.3	17(4–48)	
Duration of angioedema attack (days)	2.9 ± 1.5	2 (2–7)	
Variables (treatment modalities)		n. (18)	%
Treatment during the attack	Antihistamine	17	94.4
	steroid	15	83.3
	adrenaline	1	5.6
	Plasma	1	5.6
Short-term prophylaxis	fresh frozen plasma	4	22.2
Long-term prophylaxis	Danazol	7	38.9
	Danazol/(human C1 esterase inhibitor)	1	5.6

Table 3 Laboratory Findings in Patients with Hereditary Angioedema

Variables ($n = 18$)	Mean ± SD	median(range)
C4 level [mg/dl] (normal: 15–45 mg/dl)	7 ± 3.9	7.5 (2–18)
C1-INH level [g/l] (normal: 0.15–0.35)	0.12 ± 0.14	0.061 (0.02–0.05)
C1-INH activity (%) (normal: 70–130)	18.5 ± 10.3	16.4 (12.7–58.8)
Total immunoglobulin E	105.8 ± 89.8	67.5(51–341)

compared to our study results [12]. The symptoms of HAE usually appear between the ages of 5 and 11 years, despite C1-INH deficiency being present since birth, according to Campos et al [5].

The age of the HAE diagnosis in our studied patients ranged from 4 to 18 years. The median time lag for an accurate HAE diagnosis was 3 years, consistent with Aabom et al., who found that the median diagnostic delay was 2.8 years in Danish children [10]. A USA study by Nada et al. showed a longer diagnostic delay of 6 years in HAE patients [12].

Table 4 Correlation between the severity of HAE attacks and multiple variables of the studied patients

Variables	Severity of the attack	
	r	p
Severity score	1	
Age of patient (years)	0.09	0.713
Age at diagnosis (years)	0.016	0.95
Age at onset of symptoms (years)	-0.13	0.61
Diagnostic lag time (years)	0.013	0.96
Frequency of attack per year	0.348	0.171
Duration of attack (days)	-0.348	0.157
C4 level [mg/dl]	-.152	0.546
C1-INH level [g/l] normal (0.15–0.35)	0.29	0.24
C1-INH activity level (%)	**0.535***	**0.022**
Total immunoglobulin E	0.458	0.056

(r) Correlation coefficient; it has significance at 0.05

Initial manifestations of C1-INH-HAE occur during childhood, yet identifying this condition can take up to 8.5 years because it is an uncommon illness that is typically misinterpreted as a hypersensitivity [5]. Given the disease's infrequent and unclear symptoms, a general practitioner's early suspicion is the most significant obstacle to diagnosis. Prolonged diagnostic delays can be exacerbated by inappropriate surgical treatments, psychiatric illness, or potentially fatal laryngeal angioedema [13].

Type I was found in 83.3% of our patients, almost fourfold greater than type II (16.7%), as reported in other previous studies by Bowen et al. and Lang et al. [14, 15], while F. Kargarsharif et al. found that type I HAE was diagnosed in 63.3% of Iranian patients, which is approximately 2 times more than type II (36.7%) [16].

Regarding the familial history of HAE in the present study, eleven patients (61.1%) had a familial history of HAE; ten patients were first-degree relatives, and one patient was a second-degree relative. Our findings are consistent with those of Kargarsharif F et al., who found that 75% of cases had a family member with HAE [16]. Nanda et al. reported that 86% of patients had an HAE family history [12]. Araújo-Simões et al. reported that 84% of patients had a family member with HAE [17]. A positive family history was found in more than half of our studied patients, which may explain the shorter diagnosis delay, emphasizing early diagnosis of HAE in patients' relatives if they have any clinical features suggestive of an HAE diagnosis.

The current study revealed that patients with HAE are frequently misdiagnosed: nine of our patients were misdiagnosed as having allergic angioedema, five were managed as familial Mediterranean fever, and four had no specific diagnosis, which is consistent with Zanichelli A. et al., who observed that 66.0% of the participants in their research had provided data on misdiagnosis, with allergic edema (55.7%) and appendicitis (27.0%) being the most common diagnoses [5].

The considerable risk of incorrect diagnosis can be due to the scarcity of HAE, the variety of individual features, and the clinical presentations that coincide with those of common diseases. Additionally, there are other forms of angioedema, including acquired and idiopathic histaminergic forms. So, it makes sense that awareness of C1-INH-HAE can be very low, especially among medical practitioners who are inexperienced with the condition or its treatment [5].

According to our results, the face was the prevalent location for oedema in 14 patients (77.8%), then the larynx in 8 patients (44.4%), followed by oedema of the eyes in 4 patients (22.2%), oedema of the mouth in 4 patients (22.2%), oedema of the hands in 4 patients (22.2%) and oedema of the feet in 4 patients (22.2%). We reported HAE with abdominal attacks in 14 patients (77.8%). Araujo-Simoes J et al. reported that most HAE patients had edema of limbs, 66.3% of patients had abdominal pain, and upper airway edema in 10% of patients [17]. Laryngeal, peripheral, and abdominal angioedema occurred at least once in 27%, 73%, and 93% of patients, respectively, according to Nanda et al [12]. During major retrospective research conducted by Henao et al., 80–90% of all HAE patients experienced skin swelling episodes on the face and extremities [13].

We found that abdominal attacks were more common in our patients, consistent with findings from previous surveys [18–20]. However, Farkas reported that peripheral attacks were more common [21]. Because both locations (the abdomen or extremities) are very common in HAE patients, the predominant presentations may vary slightly depending on the cross-sectional population analyzed. The majority of HAE episodes manifest as cutaneous angioedema. As Gastrointestinal discomfort usually occurs in children, so gastrointestinal episodes are frequently misdiagnosed. Owing to the narrow width of the airways, children with HAE of the airways might develop hypoxia rapidly [6]. Families remember abdominal attacks more commonly than minor swellings in their children's peripheral limbs because these abdominal episodes tend to be apprehensive for pediatric patients and require emergency care. As a result, the number of documented episodes is susceptible to memory bias because no objective data have been obtained to validate every attack as an HAE episode [12].

In our study, the median (IQR) frequency of episodes was 17 (4–48) per year. Araujo-Simoes J et al. found that the frequency of attacks was less than one/month in 26.25%, once a month in 45%, 1–6 episodes/month in 25%, and > 6 episodes/month in 3.75% of patients [17]. The duration of the attack in our patients was 2–7 days, which is similar to the findings of the Kargarsharif F et al. study [16].

In terms of disease severity, we reported 11 patients (61.1%) with severe HAE attacks, 4 (22.2%) with moderate attacks, and 3 (16.7%) with mild attacks. However, Araujo-Simoes J et al. reported that 37.5% of patients had a mild or moderate clinical presentation, 30% had a moderate clinical presentation, and 27.5% had a severe clinical presentation [17].

In our patients, trauma was the main trigger of HAE episodes in 15 patients (83.3%), followed by spontaneous angioedema in 14 patients (77.8%), then menses in 4 female patients (22.2%), and only one patient reported stress as a trigger. According to Kargarsharif and his colleagues, the greatest prevalent trigger was trauma (75%), then stress (64.6%), then food (39.5%) [16].

Araujo-Simoes J et al. identified trauma (25%), stress (12.5%), infection (6.2%), exercise (3.7%), and menstruation (2.5%) as triggering factors in HAE patients [17].

Although an identified trigger does not precede most attacks, local trauma, infection, and emotional stress can trigger episodes of angioedema in patients with HAE. Many HAE patients suffer from psychological symptoms such as depression and anxiety, which can worsen the consequences [13].

Regarding the treatment modalities in our study, the main treatment during the attack was antihistamines in 17 patients (94.4%), steroids in 15 patients (83.3%), and epinephrine and plasma in certain situations. In four cases (22.2%), fresh frozen plasma was given as temporary prevention. Danazol was used for permanent prevention in seven cases (38.9%), and in one case, danazol was combined with a human C1-esterase inhibitor. All consequences of HAE attacks, such as asphyxia (airway obstruction), abdominal pain, and functional limitations (extremity edema), may be reduced by using therapy when needed. HAE episodes have an ambiguous clinical pattern. Because laryngeal type might result in death, laryngeal episodes should be treated as life-threatening conditions [6].

To avoid acute episodes, prophylactic medications were used. Prophylactic treatments include intravenous C1 inhibitors derived from plasma or recombinant technologies, inhibitors of Kallikrein, and antagonists of bradykinin receptors. Unfortunately, the previously mentioned drugs are only available to some patients worldwide [22]. These medications are not available for most of the recruited patients in the current study.

Antihistaminic and steroids have little effect on episodes of HAE because histamine does not serve as the primary modulator of episodes [23]. However, we found elevated IgE levels in our HAE patients, which can be partially explained by concomitant allergic diseases. Furthermore, Ferrara AL et al. discovered that 102 HAE patients with remission showed greater histamine levels than 64 healthy controls, supporting the hypothesis that HAE patients had higher histamine concentrations during their remission [24].

We found a significant and direct relationship between attack severity and activity level, which may be attributed to physiological reasons causing a greater variability in C1-INH function values, the wide range of the C1-INH function normal reference value (70–130%), and the influence of the blood collection conditions before the measurement may contribute to this correlation [25].

This study examined patients with HAE in a tertiary referral hospital and showed variable clinical presentations. As more HAE patients were identified, different HAE phenotypes emerged. This study can provide information about different clinical phenotypes of HAE, which can be helpful in developing best practice guidelines and ensuring quality patient care. A comprehensive medical history, thorough physical examination, and laboratory tests including C1-esterase inhibitor level and activity in a child with recurrent attacks of edema involving various body parts should enable a knowledgeable physician to distinguish between HAE and diseases with overlapping presentations. There are some limitations to this study, including a relatively small number of participants and memory bias. We tried to reduce these biases and increase the sample size by collecting data from medical records and recruiting patients from multiple tertiary hospitals.

Conclusions

In conclusion, this research reveals valuable new clinical information on HAE pediatric patients. The HAE starts to manifest during the first ten years of life. It is significantly unidentified in Egypt. The recognition and management of HAE can be improved by screening individuals with recurring bouts of intense unexplainable gastrointestinal pain, those with repeated angioedema, as well as relatives of HAE patients. Prompt illness detection may facilitate the implementation of a personalized therapeutic regimen that assists in avoiding and managing the episodes. Failures in recognition persist as physicians did not consider HAE as a possible cause of gastrointestinal pain or limb and facial edema. As a result, individuals frequently remain untreated or receive inaccurate diagnoses for many years until receiving an HAE evaluation. To successfully identify, avoid and manage subsequent manifestations, physicians need to identify HAE's physical manifestations and screen patients. This study is essential for the development of an international HAE registry. Children in low- and middle-income countries should have access to effective HAE medications. Future collaborative international studies should be encouraged to obtain more detailed epidemiological and clinical data on HAE in children and the required treatment plans.

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Authors' contributions

MA conceived the study, participated in designing the study, assisted in data collection, and participated in the checking, analysis and interpretation of the data and drafting the manuscript. RME conceived the study, participated in designing the study and in the checking, analyzing, and interpreting of the data. NAG collected the data, analysis and interpretation of the data and drafting the manuscript. HME assisted in data collection, and participated in the checking, analysis and interpretation of the data and drafting the manuscript. NSO participated in collecting and checking of the data and had input in the drafting of the manuscript. WS conceived the study, participated in designing the study, assisted in data collection, analyzed, and interpreted the laboratory measurements and drafted the manuscript. EGB conceived the study, participated in designing the study, assisted in data collection, and participated in

the checking, analysis and interpretation of the data and drafting the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials
The dataset used and/or analyzed during this study is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The Institutional Review Board approved the research protocol (ZU-IRB#9432/2022). Written informed consent was obtained from the parents of enrolled patients before being included in this study.

Consent for publication
Informed assent and written informed consent were obtained from all participants and their care givers.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Pediatrics, Faculty of Medicine, Zagazig University, Zagazig, Egypt. [2]Department of Allergy and Immunology, Microbiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt. [3]Department of Pediatrics, Aljmil Hospital, Aljmil, Libya. [4]Department of Internal Medicine, Allergy and Clinical Immunology, Faculty of Medicine, Ain Shams University, Cairo, Egypt. [5]Department of Pediatrics, Faculty of Medicine, Assiut University, Assiut, Egypt. [6]Department of Pediatrics, Faculty of Medicine, Alexandria University, Alexandria, Egypt.

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