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Case Series

Hereditary Angioedema with Varied Clinical Presentations: A Case Series

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Abstract

Introduction

Hereditary angioedema (HAE) is a rare, potentially life-threatening condition caused by deficiency or dysfunction of C1 esterase inhibitor (C1-INH). It is often misdiagnosed because it clinically resembles other causes of angioedema, such as allergic or acquired forms.

Case Series presentation

This paper highlights two cases of adolescent boys with recurrent, non-pruritic angioedema, without associated urticaria. The first patient experienced mild facial edema without identifiable triggers, along with allergic rhinitis. The second patient presented with swelling of the face, lips, and hands, triggered by trauma, and also affecting the airways and abdomen. Family history was significant for a death due to laryngeal edema. Laboratory investigations revealed severely reduced C4 and C1-INH levels in both patients, confirming Type I HAE.

Discussion

These cases demonstrate the variable presentation of HAE, ranging from mild peripheral swelling to abdominal and potentially life-threatening airway involvement. Coexisting allergic disease may lead to confusion with allergic angioedema, while an initially normal C1-INH result may delay diagnosis. Repeat testing and family screening are therefore important when clinical suspicion remains high. Limited access to functional C1-INH testing and targeted therapies remains a major challenge in resource-limited settings.

Conclusion

These cases show that HAE may present with mild or severe symptoms and may be overlooked when allergic features are present or when an initial C1-INH result is normal. In resource-limited settings, repeat testing, family screening, and early recognition are important to support diagnosis and prevent serious complications.

Keywords: Hereditary angioedema; C1 esterase inhibitor; Complement C4; Type I HAE; Type II HAE; Diagnostic challenges

1. Introduction

Hereditary angioedema (HAE) is a rare but severe condition characterized by recurrent episodes of non-pitting, painless edema affecting the skin, gastrointestinal tract, and upper airways [1]. Unlike histamine-mediated angioedema, which responds to antihistamines and corticosteroids, HAE is a bradykinin-mediated disorder that increases vascular permeability [2]. Several therapies for HAE have been approved, and additional agents to further improve management are under investigation. Early recognition and diagnosis of HAE are crucial for implementing appropriate management strategies [3].

Most cases are caused by deficiency or dysfunction of C1 esterase inhibitor (C1-INH). Type I HAE is associated with reduced C1-INH antigen levels, while Type II HAE is associated with normal or raised antigen levels but reduced function [3]. Clinical

severity can vary widely, from mild swelling to severe abdominal or laryngeal attacks [3–5].
In Pakistan, limited access to C1-INH antigen testing, functional C1-INH assays, and targeted HAE therapies can delay diagnosis and restrict treatment choices. As a result, patients may be misdiagnosed, undergo repeated investigations, or continue to experience preventable attacks before the condition is recognized. These gaps also make family screening and long-term disease monitoring more difficult [6].
In this case series, we describe two adolescent boys with different clinical presentations of hereditary angioedema. These cases highlight the challenges of recognizing and confirming HAE in Pakistan, where functional C1-INH testing and targeted treatments are not readily available. They also show the importance of repeat laboratory testing and family screening when clinical suspicion remains high.

2. Case Presentation

2.1. Case 1

2.1.1. History and Initial Presentation

A 14-year-old boy, a known case of Immune Thrombocytopenic Purpura (ITP), presented with recurrent episodes of swelling primarily affecting the facial region, including the areas around the eyes and mouth, over three years, with a total of eight documented episodes. One episode involved scrotal swelling, and another affected both feet. The swellings occurred spontaneously, without identifiable triggers such as food, medications, insect bites, or trauma, and were non-pitting and non-pruritic. Each episode lasted from several hours to a few days and resolved spontaneously without treatment. Notably, during these episodes, there were no accompanying signs of pruritus, rash, abdominal discomfort, nausea, vomiting, or fever. Additionally, the child has a long history of nocturnal enuresis and has never had a dry night. He was diagnosed with primary monosymptomatic nocturnal enuresis by the pediatric urology department.
Upon further questioning, the patient also reported symptoms consistent with allergic rhinitis, including rhinorrhea, sneezing, nasal congestion, and excessive lacrimation.
His family history is notable for an older brother with recurrent respiratory infections, a sibling who died in early childhood due to a respiratory illness, and two paternal aunts with asthma. He also has one sister who is alive and healthy.

2.1.2. Diagnostic workup

On physical examination, the patient was vitally stable with no evidence of active swelling. There was no tenderness or guarding on abdominal palpation, and no signs of urticaria or cutaneous rashes. No scrotal or genitourinary swelling was noted during the examination. Growth parameters, including height and weight, were within normal age-appropriate ranges.
The patient's laboratory parameters were evaluated. His complete blood count was normal, and the urine analysis showed no abnormalities. Complement component 3 (C3) concentration was 1.21 g/L (Laboratory reference range: 0.81–1.57 g/L), while complement component 4 (C4) was abnormally low at 0.042 g/L (Laboratory reference range: 0.13–0.39 g/L). A repeat test for C4 confirmed the low level (0.073 g/L). The thyroid-stimulating hormone (TSH) levels were normal for his age. His antinuclear antibody (ANA) test was positive, showing a fine speckled pattern, but the anti-extractable nuclear antigen (ENA) panel was negative. C1 esterase inhibitor (C1-INH) levels were severely reduced at 0.01 mg/dL (Laboratory reference range: 4–70 mg/dL; method: Radial Immunodiffusion).
Given the patient's symptoms of allergic rhinitis, relevant testing was conducted. Serum total immunoglobulin E (IgE) levels were elevated at 574 IU/mL. Food allergen testing revealed no sensitivities. Serum allergen-specific IgE testing for inhalational allergens showed class 5 sensitivity to Dermatophagoides pteronyssinus and Dermatophagoides farinae, and class 1 sensitivity to sheep. Skin prick testing (SPT) identified sensitivity to house dust, acacia, and raw cotton.
The clinical presentation, low C4 levels, and markedly reduced C1-INH antigen level were strongly consistent with Type I hereditary angioedema. However, C1-INH functional testing was not available, which remained a limitation of the diagnostic workup.

2.1.3. Treatment

Treatment for HAE included danazol 200 mg twice daily, along with cetirizine 10 mg twice daily for the management of his allergic rhinitis. For acute attacks, the patient was counseled to receive Fresh Frozen Plasma (FFP) based on his body weight. Recombinant C1 esterase inhibitor (C1-INH) and icatibant were not available.

2.1.4. Follow-up

The patient had significant clinical improvement following treatment. The patient was reviewed at 1, 3, 6, and 12 months after starting treatment. No further attacks were reported during this period.
Table 2 summarizes all clinical features, laboratory findings, management, and outcomes of Case 1.

2.2. Case 2

2.2.1. History and Initial Presentation

A 16-year-old male presented with a history of recurrent episodes of swelling affecting the face, lips, throat, and hands, which began at approximately two years of age. The swellings were non-pruritic and not associated with urticaria. The episodes typically occurred after minor trauma, such as a blow to the face or something dropping onto his face. Figure 1 illustrates the swollen lips during an acute attack.

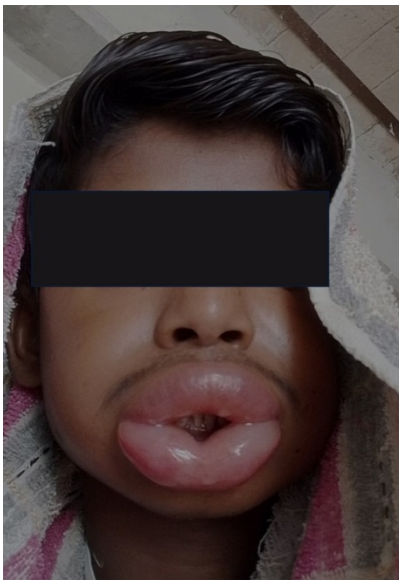

Figure 1: *Clinical photograph of Case 2 demonstrating marked swelling of the lips (labial edema) during an acute episode. No identifiable facial features are visible. Informed consent was obtained for publication of the image.*

These attacks were frequently accompanied by difficulty in breathing. Additionally, the patient reported occasional abdominal pain with cramps, though it was not associated with vomiting or diarrhea. The episodes occurred spontaneously, persisted for a few hours, and resolved over time without intervention. No identifiable triggers were noted, and the patient remained asymptomatic between episodes.

The patient had three siblings, two of whom also experienced similar episodes of swelling. There was a notable family history of the death of an elderly sister due to laryngeal edema. He was born to non-consanguineous parents. The patient had no known history of food or drug allergies, asthma, eczema, or allergic rhinitis.

2.2.2. Diagnostic workup

Upon physical examination, the patient was vitally stable with no evidence of active swelling. There was no tenderness or guarding on abdominal palpation, and no signs of urticaria, rash, or other cutaneous lesions. No swelling was noted in the genital area. Growth parameters, including height and weight, were within normal age-appropriate ranges.

Laboratory investigations revealed that the complete blood count was within normal limits. Complement component 3 (C3) levels were normal at 1.01 g/L (Laboratory reference range: 0.81–1.57 g/L), while complement component 4 (C4) levels were significantly low at less than 0.006 g/L (Laboratory reference range: 0.13–0.39 g/L). Thyroid-stimulating hormone (TSH) levels were within normal limits at 3.919 mIU/L. All C1-INH samples were collected while the patient was asymptomatic and between angioedema attacks. There was no evidence of acute infection or inflammation at the time of sample collection. Initial C1 esterase inhibitor (C1-INH) levels were normal at 14.9 mg/dL (Laboratory reference range: 8–44 mg/dL, method: Immunonephlometry on Optilite). Given strong clinical suspicion, levels were repeated at another laboratory using a different method. On repeat testing (twice), C1INH levels were low (<0.207 mg/dL) (Laboratory reference range: 4–70 mg/dL; method: Radial Immunodiffusion), confirming deficiency (Table 1).

Recurrent angioedema, markedly low C4 levels, low C1-INH antigen levels on repeat testing, and a positive family history were strongly consistent with Type I hereditary angioedema. However, C1-INH functional testing was not available, which remained a limitation of the diagnostic workup

Table 1: C1-INH antigen results in Case 2 using different laboratory methods

Test	Laboratory method	Result	Reference range	Interpretation
Initial C1-INH antigen	Immunonephelometry on Optilite	14.9 mg/dL	8–44 mg/dL	Within the method-specific reference range
First repeat C1-INH antigen	Radial immunodiffusion	<0.207 mg/dL	4–70 mg/dL	Low
Second repeat C1-INH antigen	Radial immunodiffusion	<0.207 mg/dL	4–70 mg/dL	Low

Family screening was performed. His mother, who was asymptomatic, and two sisters, who had similar clinical symptoms, were found to have low serum C4 and C1-INH levels, consistent with Type I hereditary angioedema. One brother, who had no symptoms, had normal levels of both C4 and C1-INH. This pattern is consistent with the autosomal dominant inheritance typically observed in HAE Type I.

2.2.3. Treatment

The patient was prescribed danazol 200 mg twice daily. Because recombinant C1 esterase inhibitor (C1-INH) and icatibant were unavailable, he was advised to receive Fresh Frozen Plasma (FFP) during acute attacks, based on his body weight.

2.2.4. Follow-up

The patient responded well to treatment, with a reduced frequency of attacks. At the 6-month follow-up visit, the patient reported one episode of facial swelling without respiratory involvement.

2.3. Emergency advice for both patients

Both patients and their families were advised to seek immediate emergency care if throat swelling, voice change, difficulty swallowing, or breathing difficulty developed. They were also advised to inform the treating team before dental procedures, surgery, or other procedures involving the airway so that short-term prophylaxis and emergency treatment could be arranged Table 2 summarizes the main clinical features, laboratory findings, treatment, and follow-up outcomes of both patients.

Table 2: Comparison of the clinical features, laboratory findings, management, and outcomes of both patients

Feature	Case 1	Case 2
Age	14 years	16 years
Age at onset	11 years	2 years
Main sites of swelling	Face, scrotum, and feet	Face, lips, throat, and hands
Trigger	No clear trigger	Minor trauma
Severity	Mild; no airway involvement	Severe; airway and abdominal involvement
Family history	No confirmed family history of HAE	Two affected siblings; sister died from laryngeal edema
C4	Low (0.042 g/L; repeat 0.073 g/L)	Very low (<0.006 g/L)
C1-INH antigen	Low (0.01 mg/dL by radial immunodiffusion)	Initial normal (14.9 mg/dL by nephelometry); repeat low (twice <0.207 mg/dL by radial immunodiffusion)
C1-INH functional assay	Not available	Not available
Long-term prophylaxis	Danazol 200 mg twice daily	Danazol 200 mg twice daily
Acute attack plan	Fresh Frozen Plasma (FFP) advised	Fresh Frozen Plasma (FFP) advised
Follow-up	Reviewed at 1, 3, 6, and 12 months; no further attacks were reported	At the 6-month follow-up visit, the patient reported one episode of facial swelling without respiratory involvement

3. Discussion

Hereditary angioedema is a bradykinin-mediated disorder caused by deficiency or dysfunction of C1-INH. It should be suspected in patients with recurrent, non-pruritic swelling without urticaria, particularly when attacks involve the abdomen or upper airway. Epidemiologically, HAE is rare, affecting an estimated 1 in 50,000 individuals. [1–3]. However, underdiagnosis remains a significant concern, with the median time between symptom onset and accurate diagnosis reported to be between 3.7 and 10.5 years [5].

In Pakistan, HAE cases are mostly limited to case-based reports and family-screening studies rather than population prevalence estimates. A recent cascade-screening study there identified 16 confirmed and 24 probable cases among relatives of 10 index patients and noted limited diagnostic access and absence of a national registry [6].

Both of our patients had type 1 HAE; however, they presented with varying clinical findings. The first patient appears to have a mild and atypical presentation of HAE, with unprovoked attacks that do not involve airway obstruction and occur alongside allergic rhinitis. Elevated immunoglobulin E levels and allergen sensitization in this patient may have contributed to an initial misdiagnosis of allergic angioedema. Coexisting allergic disease, including allergic rhinitis, and raised IgE have also been reported in children with HAE [7]. ITP and ANA positivity were also noted, as autoimmune diseases may occur more often in patients with C1-INH deficiency [8], although no unifying autoimmune diagnosis was identified. Primary monosymptomatic nocturnal enuresis was considered a separate comorbidity.

In contrast, the second patient presents with the classic and severe form of HAE, characterized by early onset of symptoms, attacks triggered by minor physical trauma, recurrent abdominal episodes, and potentially life-threatening airway involvement. The notable family history, including a fatal case of laryngeal edema, further underscores the hereditary nature of the disease. Airway obstruction is the most serious complication of HAE [9, 10]. In one study, 32.7% of deceased patients with HAE had died from asphyxiation during a laryngeal attack, and most of these deaths occurred before the disease had been diagnosed [10]. Laboratory testing showed low levels of complement component 4 and C1-INH in both cases. C1-INH has been proven to be a critical diagnostic marker in the diagnosis of HAE [11]. A low C4 value is also of paramount importance; however, a normal C4 value does not rule out HAE [12, 13].

In the second case, the initial C1-INH antigen measurement, performed on the Optilite nephelometry system, was normal, whereas two subsequent radial immunodiffusion measurements were low. Causes of a falsely normal C1-INH value merit discussion since they may result in a diagnosis of type II HAE. A literature search revealed an Optilite validation study in which Tange and colleagues found 100% agreement between radial immunodiffusion and the Optilite turbidimetric immunoassay for C1-INH protein concentration below or above the lower limit of the respective reference ranges. All Type I HAE samples in that study were low by both methods [14].

C1-INH is considered an acute-phase reactant, and elevation during acute inflammation could result in falsely normal levels in a patient with HAE who otherwise has low C1-INH levels. However, a study of HAE patients that assessed C4, C1-INH, CRP, and ferritin at baseline and during acute infections reported no significant change in C1-INH levels [15].

Unlike C4, testing outside an attack also does not explain the falsely normal C1-INH levels, as low antigenic C1-INH is usually persistent rather than attack-dependent in Type I HAE [16].

Laboratory factors remain a likely cause for the unexpected normal C1INH result in the second patient. Early diagnostic evaluations have shown that measurement of C1INH and related serological markers can vary in routine practice, suggesting inherent variability in common assays and the need for careful sample handling [11]. Although most studies focus on functional C1INH assays, they consistently highlight that time delays, temperature fluctuations, sample transport, and processing conditions significantly influence measured C1INH values [17]. Complementing this, broader surveys of complement diagnostic methods stress that prompt serum/plasma separation, storage, and standardized laboratory protocols are critical to minimize error, not only for functional testing but also for reliable antigen determination.[18]

Family screening is essential in an autosomal dominant disorder, because first-degree relatives often remain undiagnosed until specifically tested, and both international and Pakistani data show a high yield from cascade screening [6, 19].

The management of HAE has improved considerably with the introduction of therapies such as C1 esterase inhibitor concentrates, bradykinin receptor antagonists, and kallikrein inhibitors [2, 3]. However, in resource-limited settings like Pakistan, treatment options are largely restricted to attenuated androgens, such as danazol, and the use of fresh frozen plasma during acute attacks. Both patients in this report were treated with danazol, counseled on the use of fresh frozen plasma during acute attacks, and demonstrated satisfactory clinical responses on follow-up. Danazol was started at 200 mg twice daily for long-term prophylaxis because the preferred targeted treatments, including C1-INH concentrate, lanadelumab, and berotralstat, were not available in our setting. Tranexamic acid was not used because its benefit in preventing HAE attacks is limited, and current guidelines do not recommend it as a preferred option for long-term prophylaxis [3]. As both patients were adolescents, they were monitored for possible adverse effects of danazol through regular complete blood counts, liver function tests, abdominal ultrasound, and assessment of pubertal development [20]. The patients were started on this dose, with a plan to review their response during follow-up visits and reduce treatment to the lowest effective maintenance dose once adequate control of attacks was achieved, per guidelines [3, 20].

As targeted on-demand treatments, including plasma-derived C1-INH concentrate, icatibant, and ecallantide, were unavailable, fresh frozen plasma was advised as an alternative for acute attacks. However, the families were counseled that FFP may

cause transfusion reactions and fluid overload. It may also theoretically worsen an attack because it contains proteins that can contribute to bradykinin formation, although published evidence has not consistently shown clinical worsening [21, 22]. Despite these limitations, FFP remains an important option where specific HAE treatments are unavailable [3, 21].

The main importance of these cases lies in the practical challenges of diagnosing and managing HAE in Pakistan. In Case 1, allergic symptoms and raised IgE could have led to the swelling being mistaken for allergic angioedema. In Case 2, the first C1-INH result was normal, and the diagnosis became clearer only after repeat testing and family screening. These cases show that HAE should still be considered when the clinical history is strongly suggestive, even if allergic features are present or the initial laboratory result is inconsistent. They also highlight the effect of limited access to functional C1-INH testing and targeted treatments.

This report has several limitations. It includes only two patients, which restricts the generalizability of the findings. Laboratory measurements of C1-INH showed variability between the Optilite nephelometry and radial immunodiffusion methods, highlighting potential assay-related differences that could affect diagnostic accuracy. Functional C1-INH assays were not available for a complete workup. Patient follow-up was limited, particularly for Case 2, which restricted assessment of long-term treatment effectiveness and safety. Finally, restricted access to newer therapies means that treatment outcomes may differ from what could be achieved in better-resourced settings.

4. Conclusion

These cases show that HAE may present with either mild or severe symptoms and can be missed when allergic features are present or when an initial C1-INH result is normal. In settings where functional testing and targeted treatment are not easily available, repeat testing, family screening, and early clinical recognition are especially important. Greater physician awareness, improved access to diagnostic and treatment options, and the development of national registries may help reduce delayed diagnosis and prevent avoidable complications.

5. Declarations

Ethics Approval and Consent to Participate

Ethical approval and written informed consent were obtained from the patient for participation and publication of this case report.

Consent for Publication

Written informed consent was obtained for publication of the patient's clinical information and the clinical photograph.

Data Availability Statement

Not applicable

Conflicts of Interest

The authors declare no conflicts of interest.

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Author Contributions

SA and HH contributed to the conceptualization, methodology, and investigation. MA prepared the original draft. SA and HH reviewed and edited the manuscript. SA supervised the work. All authors read and approved the final manuscript.

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AI Declaration

The authors confirm that no content in this manuscript was generated using artificial intelligence (AI) tools, and the authors take full responsibility for the accuracy and integrity of the work.

6. Abbreviations

The following abbreviations are used in this manuscript:

ANA	Antinuclear antibody
C1-INH	C1 esterase inhibitor
C3	Complement component 3
C4	Complement component 4
ENA	Extractable Nuclear Antigen
FFP	Fresh Frozen Plasma
HAE	Hereditary Angioedema
IgE	Immunoglobulin E
SPT	Skin prick testing
TSH	Thyroid-stimulating hormone

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