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Delayed presentation of hereditary angioedema with ANGPT1 mutation: A case report

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Abstract

Background: Hereditary Angioedema (HAE) is a genetic disorder characterized by recurrent episodes of angioedema due to the deficiency or dysfunction of the C1-Inhibitor protein (C1-INH). This report presents a unique case of angioedema diagnosed later in life.

Case presentation: A Middle-aged female, presenting with newly noted episodes of angioedema, a few months preceding the diagnosis. Workup for both primary and acquired causes revealed low C1-INH levels and function, along with low C4 complement levels. Genetic studies ultimately revealed ANGPT1 mutation.

Conclusion: We present a case of angioedema with an abnormal C1-INH that presents later in life, with a mutation in the ANGPT1 gene, a mutation linked to HAE with normal C1-INH. This signifies the importance of understanding genetic associations for such rare diseases that have variable phenotypes.

Keywords: Hereditary angioedema; C1-INH; ANGTP1 gene; Late presentation; Treatment; Prophylaxis.

Abbreviations: HAE: Hereditary Angioedema; C1-INH: C1-Inhibitor Protein; ACEI: Angiotensin Converting Enzyme Inhibitor; SERPING 1: Serpin family G member 1 gene; HMWK: High Molecular Weight Kininogen; ANGPT1: Angiopoietin-1; KNG1: Kininogen-1; PLG: Plasminogen gene; MYOF: Myoferlin gene; HS3ST6: Heparan Sulfate-Glucosamine 3-Sulfotransferase 6 gene; VUS: Variant of Uncertain Significance; AAE: Acquired Angioedema; ANA: Antinuclear Antibody; PET: Positron Emission Tomography; FDA: Food and Drug Administration.

Introduction

Hereditary Angioedema (HAE) is a rare genetic disorder with an estimated prevalence of 1 in 50,000. Deficiency or dysfunction of the C1-Inhibitor protein (C1-INH) is the hallmark of this disorder. Hence, it is classified into three types based on the status of the C1-INH protein [1].

HAE due to C1-INH deficiency, previously classified as type I, accounts for approximately 85% of all

cases, making it the most prevalent form. The second most common variant is HAE with dysfunctional C1-INH, formerly known as type II, comprising the remaining 15%. The rarest form is HAE with normal C1-INH levels, formerly known as type III, which shows a higher prevalence among females. Patients present with recurrent episodes of angioedema that involve the skin, the respiratory tract, or the gastrointestinal tract. Cutaneous angioedema is characterized by non-pitting and non-pruritic swelling of the skin affecting the face or extremities. Gastrointestinal tract involvement usually presents with abdominal pain, nausea, or vomiting. Respiratory tract involvement with laryngeal edema is a life-threatening condition as it can lead to asphyxiation. Angioedema attacks tend to be recurrent, usually with no identifiable trigger. However, certain factors, such as local trauma, emotional stress, menstruation, and Angiotensin Converting Enzyme Inhibitor (ACEI), have been reported as possible triggering factors [2].

C1-INH is an essential protein that regulates different biological systems, including the complement system and bradykinin formation. Endothelial injury activates factor XII and prekallikrein, which is thought to be the initiating event in the pathogenesis of HAE. The activated Factor XII (XIIa) and kallikrein release bradykinin by breaking High Molecular Weight Kininogen (HMWK). Eventually, bradykinin binds to its receptors, causing vasodilation and vascular hyperpermeability.

C1-INH protein acts by inhibiting both kallikrein and factor XIIa, preventing the production of bradykinin. Therefore, when C1-INH is deficient or dysfunctional, unchecked production of bradykinin takes place. In addition, C1-INH inhibits the complement system. In case of deficiency or dysfunction, a non-controlled activation of the complement pathway leads to the consumption of the C4 complement [3,4].

Prompt testing for HAE should be considered among patients presenting with recurrent episodes of angioedema or who have a strong family history. Measuring serum C1-INH protein level and function, along with C4 complement level are used to diagnose HAE. In type I, both the level and function of C1-INH and C4 level will be low. In type II, the level of C1-INH will be normal, while the function and level of C4 will be low. On the other hand, type III will have normal values of the aforementioned laboratory tests [5,6].

Genetic testing plays a significant role in the diagnosis of HAE. Mutations in the Serpin Family G Member 1 gene (SERPING 1) are responsible for type I or type II HAE, and in most cases, the transmission is in an autosomal dominant fashion, while 25% of the cases are sporadic in nature. On the other hand, type III HAE has been linked to multiple other genetic mutations, including the F12 gene, Angiopoietin-1 (ANGPT1) gene, Kininogen-1 (KNG1) gene, Plasminogen Gene (PLG), Myoferlin Gene (MYOF), and heparan sulfate-glucosamine 3-sulfotransferase 6 (HS3ST6) gene mutations [7].

In this report, we present an exceptional case of HAE, diagnosed at a later age, found to have low levels and function of the C1-INH protein. Genetic testing revealed Sngiopoietin-1 (ANGPT1) mutation. A mutation that has been linked solely to HAE with normal C1-INH level and function.

Case Presentation

A 56-year-old female with a known history of hypertension on Amlodipine was referred to our

immunology clinic for evaluation of recurrent angioedema. Over six months, she experienced three distinct episodes:

- The first episode involved swelling of the forehead, periorbital region, and lips, without associated urticaria.
- The second episode presented with gastrointestinal symptoms, including abdominal cramps and bloating, suggestive of visceral angioedema.
- The third episode again involved facial swelling without urticaria, similar to the initial episode.

Treatment with oral antihistamines and corticosteroids during these episodes yielded no significant clinical improvement. The patient has ten siblings denied any family history of angioedema.

Initial laboratory evaluation revealed (Table 1):

- Low C1-INH level and function
- Low C4 complement level
- Normal C1q complement level.

Given the patient's late-onset presentation, Acquired Angioedema (AAE) was initially suspected. A full workup for secondary causes, including malignancy screening with protein electrophoresis, mammogram studies, colonoscopy, Positron Emission Tomography (PET) scan, and autoimmune screening with Antinuclear Antibody (ANA), all returned negative.

Genetic testing was pursued to clarify the etiology:

- Single-gene sequencing for the SERPING1 gene was negative.
- Whole-exome sequencing revealed ANGPT1 gene mutation: c.(297+1_298-1)_(575+1_576-1)dup. Exon 2 and 3 (of 9), Heterozygous. Classified as a Variant of Uncertain Significance (VUS).

The patient continued to have frequent emergency department visits for recurrent angioedema, primarily involving the face and gastrointestinal tract.

For the acute management, she was treated with intravenous plasma-derived C1-INH concentrate. Due to the increase in frequency of attacks to approximately once a month and the limited therapeutic options at our center, long-term prophylaxis with tranexamic acid was initiated. Despite this, angioedema episodes persisted.

Subsequently, Lanadelumab was requested and initiated at 300 milligrams subcutaneously every two weeks. Since its initiation four months ago, the patient has remained symptom-free with no further attacks.

Table 1: Laboratory result.

Test	Result	Reference range
C1-INH level	13 mg/dL	19-37 mg/dL
C1-INH function	<10%	Normal: >67% Equivocal: 41-67% Abnormal: <41%
C4 level	0.02 g/L	0.15-0.53 g/L
C3 level	1.23 g/L	0.91-2.41 g/L
Complement C1q level	18 mg/dL	12-22 mg/dL
Sequence analysis of SERPING1 gene	Negative	
Whole exome sequencing	ANGPT1	Description: c.(297+1_298-1)_(575+1_576-1)dup. Region: Exon 2 and 3 (of 9) Zygosity: Heterozygous Classification: VUS

Discussion

The ANGPT1 gene encodes angiopoietin-1, a key regulator of endothelial permeability and vascular stability. Mutations in ANGPT1 may disrupt vascular integrity, resulting in angioedema that is independent of both bradykinin and histamine-mediated pathways [8,9]. While the identified duplication is currently classified as a Variant of Uncertain Significance (VUS), its presence in a patient with a compatible clinical phenotype raises the possibility of a pathogenic role, particularly in the absence of SERPING1 mutation or identifiable secondary causes.

The management of HAE includes treatment of acute attacks and preventive measures for both short- and long-term care. For the acute attacks, there are four Food and Drug Administration (FDA) approved drugs: intravenous human plasma-derived C1-INH, intravenous recombinant C1-INH, subcutaneous plasma kallikrein inhibitor (Ecallantide), and a subcutaneous bradykinin B-2 receptor antagonist (Icatibant).

Long term prophylaxis aims to reduce the frequency and severity of the attacks, and it is prescribed for patients with frequent attacks not controlled by on-demand treatments. Options include intravenous or subcutaneous plasma-derived C1-INH, attenuated androgens such as Danazol, and antifibrinolytic such as Tranexamic acid. Recently, Lanadelumab; a subcutaneous monoclonal antibody against plasma kallikrein, has also been approved for the long-term prophylaxis. Short-term prophylaxis is used to prevent angioedema after surgical trauma, with intravenous plasma-derived C1-INH or danazol used for this purpose. Additionally, several medications are still under investigation, including anti-plasma kallikrein agents such as Berotralstat, IONIS-PKKRx, KVD900, and ATN-249, as well as factor XII inhibitors such as CSL312 and ALN-F12 [8,9].

Upon reviewing the literature, one published case of a three-generation Italian family, four of their members were diagnosed with HAE in their second decade of life. Their clinical presentation was characterized by recurrent episodes of angioedema of the face and gastrointestinal tract, comparable to our case, with the main difference being the age of presentation. Genetic testing of the family members showed a

heterozygous missense mutation in the ANGPT1 gene. Tranexamic acid was started as prophylactic therapy with well reported response [10].

This case has some limitations that should be acknowledged. Despite low C1-INH level and function alongside low C4 complement, the absence of SERPING1 mutations raises uncertainty about the precise genetic cause. Multiplex Ligation-dependent Probe Amplification (MLPA) or other methods to detect large deletions or rearrangements in SERPING1 were not performed, which may have provided additional insight. Furthermore, the identified ANGPT1 variant is classified as a Variant of Uncertain Significance (VUS), and its direct pathogenic role remains unconfirmed. The lack of family history and absence of genetic testing in relatives limit confirmation of hereditary transmission. Additionally, Acquired Angioedema (AAE) remains a differential diagnosis, especially considering the late age of presentation and absence of testing for anti-C1-INH autoantibodies. While C1q levels were normal, this does not exclude AAE.

Conclusion

This case report describes a late presentation of angioedema with reduced C1-INH level and function, in which genetic testing revealed a variant of uncertain significance in the ANGPT1 gene rather than mutations in the SERPING1 gene. While the pathogenicity of this ANGPT1 variant remains unclear, its presence alongside a compatible clinical phenotype and absence of other genetic or secondary causes could suggest a potential role in the disease. This case underscores the need for comprehensive genetic analysis and further research to better understand the genetic spectrum and mechanisms of HAE.

Declarations

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Consent: Informed consent was obtained from the patient. The consent form used was from our institution, “King Fahad Specialist Hospital, Dammam, Saudi Arabia.”

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