



## Hereditary Angioedema with Normal C1 Inhibitor Response to Progesterone Therapy: A Case Report and Review of the Literature.

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### ABSTRACT

This article presents a case of hereditary angioedema (HAE) with a normal C1 inhibitor (C1-INH) level. HAE with normal C1-INH, previously termed HAE type III, is diagnosed when a patient has recurrent angioedema in the absence of hives, but has normal C4 and C1-INH levels and normal C1-INH function, and either a factor XII mutation or a positive family history and a failure to respond to high-dose antihistamines. The diagnosis of HAE with normal C1-INH is primarily clinical, as less than a third of patients have any defined mutations. The function of C1-INH is to inhibit factor XIIa, factor XII fragment, kallikrein, and plasmin. When C1-INH is absent or dysfunctional, there is marked activation of the bradykinin-forming cascade, resulting in increased vascular permeability with symptoms of swelling. Treatment involves avoidance of triggering factors, control of acute symptoms, and, in some cases, prophylactic therapy. In the present case, the patient responded to on-demand therapies developed for patients with HAE types I and II, as well as prophylactic therapy with a progesterone-only oral contraceptive. A brief review of the epidemiology, clinical presentation, diagnostic criteria, pathophysiology, genetic mutations, and treatment of HAE with normal C1-INH is presented.

### INTRODUCTION

Hereditary angioedema (HAE) affects all ethnic groups equally, and its global prevalence is estimated to be between 1 in 10,000 and 1 in 100,000.<sup>1-4</sup> HAE is a rare autosomal dominant disease characterized by recurrent attacks of subcutaneous or submucosal swelling that usually affects the face, respiratory tract, extremities, gastrointestinal tract, or genitalia.<sup>1,5</sup> Unlike allergic (histamine mediated) causes of angioedema, HAE swelling episodes do not respond to antihistamines, corticosteroids, or epinephrine, and typically last for >24 hours.<sup>1</sup> The genetic mutation that causes HAE encodes the C1 inhibitor (C1-INH) of the complement system and either leads to a reduction in its synthesis (HAE type I) or to the formation of a dysfunctional protein (HAE type II).<sup>1</sup> These defects induce activation of factor XIIa, factor XII fragment, kallikrein, and plasmin, which causes marked activation of the bradykinin-forming cascade, resulting in increased vascular permeability and manifesting as angioedema.<sup>6</sup>

In 2000, clinicians diagnosed a new subtype of HAE with normal level and function of C1-INH but a clinical and family history of recurrent angioedema not responsive to antihistamines.<sup>7,8</sup> This form of HAE was initially termed HAE type III but is now referred to as HAE with normal C1-INH.<sup>9</sup> HAE with normal C1-INH occurs predominantly in women, affects mainly the face or oral mucosa, and has a verifiable association with states of increased levels of estrogen, such as pregnancy or oral contraceptive (OC) use, and disease flares.<sup>9,10</sup> The objective of this article is to describe a case of HAE with normal C1-INH and briefly review the existing literature on the pathophysiology, clinical features, genetic alterations, diagnosis, and treatment of this disorder.

### CASE PRESENTATION

A 26-year-old woman was transferred from an outside hospital with recurrent episodes of tongue swelling and concern for airway compromise in the summer of 2013. From 2006 to 2011, the patient reported intermittent episodes of tongue swelling and less-frequent episodes of extremity and abdominal swelling. Urticaria was not present with these episodes, and the swelling would typically persist for >24 hours. She was seen by an allergist who diagnosed her with HAE with normal C1-INH, and on-demand therapy with ecallantide, a kallikrein inhibitor, was initiated after high-dose prophylactic antihistamines failed to alleviate her symptoms. She had 3 episodes of swelling over an 18-month time period, all of which responded to on-demand ecallantide therapy. She was not using prophylactic therapy during this time. In the 2 years (2011-2013) prior to her presentation, she was either pregnant or breast feeding and had no swelling episodes.

When she started weaning her infant in 2013, she presented with recurrent tongue swelling to her outpatient allergist. She was given ecallantide at the allergist's office and initially experienced improvement in her swelling. However, when the tongue swelling recurred 1 hour later, she was sent to a local hospital and later transferred to our institution's intensive care unit. At time of arrival at our institution, the differential diagnosis included angioedema (including both allergic and nonallergic causes), capillary leak syndrome, superior vena cava syndrome, Melkersson-Rosenthal syndrome, amyloidosis, tumor, or lymphedema. Family history revealed her mother also had a history of swelling episodes. There were no medications, including angiotensin-converting enzyme



(ACE) inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs), associated with the angioedema episodes. A physical examination was notable only for an enlarged tongue (Figure 1). Laboratory investigation showed normal levels of tryptase, C2, C4, C1q, and C1-INH [level](#) and function during her swelling episode.



**Figure 1.** Tongue swelling in a 26-year-old woman with hereditary angioedema with a normal C1 inhibitor level.

Laboratory tests, including a complete blood count with differential, comprehensive metabolic panel, erythrocyte sedimentation rate, antinuclear antibodies, thyroid function, thyroid autoantibodies, quantitative immunoglobulins, and serum protein electrophoresis were performed and were within normal limits. During day 1 of hospitalization, she was treated with 2 doses of icatibant, a selective bradykinin B2 receptor antagonist, for progressive tongue swelling. Over hospital days 2, 3, 4, 5, and 6, she was treated with another 6 doses of icatibant and 2 doses of Cinryze<sup>®</sup> (C1 esterase inhibitor; Shire) because of recurrent tongue swelling with concern for airway compromise. Administration of these medications reduced her swelling acutely, and her tongue returned to baseline within a few hours. However, the swelling would return an indeterminate number of hours later, progressing and persisting until antibradykinin therapy was repeated.

A tongue biopsy was then performed to exclude an alternative cause of her tongue swelling, but this too was normal. On the same day as her biopsy, the patient was started on a progesterone-only OC. Over the next 3 days, she was treated with only 1 dose of icatibant and was discharged after she had no further swelling episodes for 48 hours. The patient declined factor XII genetic testing because of cost concerns.

Given the patient's clinical history, family history, failure to respond to antihistamines, and laboratory evaluation, she received a diagnosis of HAE with normal C1-INH. Since

discharge, the patient has continued on the progesterone-only OC and has used 5 doses of on-demand icatibant therapy over a 9-month period for 5 orofacial and abdominal attacks without concomitant urticaria. Her swelling episodes have all responded to icatibant treatment on demand, and she has not needed to repeat hospitalization because of HAE.

## DISCUSSION

The 3 types of HAE are distinguished by the level and activity of plasma complement-1 esterase inhibitor. HAE type I is defined by a lack of plasma C1-INH and is the most prevalent form, affecting 85% of patients with HAE.<sup>11</sup> HAE type II affects 15% of patients with HAE and is characterized by dysfunctional C1-INH.<sup>11</sup> HAE with normal C1-INH (formerly HAE type III), a relatively newer diagnosis (first described in 2000) affecting an unknown percentage of the population, is defined by (1) recurrent angioedema in the absence of hives, (2) normal C1-INH level and function, (3) and either a factor XII mutation or positive family history and lack of response to antihistamines.<sup>7-9</sup>

HAE with normal C1-INH shares similarities to HAE types I and II, mainly in signs and symptoms of an HAE attack. Differences are seen in mean age of onset (26.8 vs 11.7 years), distribution of swelling episodes (more likely to affect tongue, uvula, and face, and less likely to affect the gastrointestinal tract), female predominance and disease severity, decreased disease intensity and activity, cutaneous findings (easy bruising and skin swelling seen in HAE with normal C1-INH), and lower penetrance.<sup>9,10,12,13</sup> Unlike HAE types I and II, in which bradykinin has been proven to cause swelling, the mediator or mediators responsible for swelling in HAE with normal C1-INH have not been identified.<sup>6</sup> Additionally, the underlying molecular defect for most patients with HAE with normal C1-INH are unknown, but its familial pattern of transmission supports an autosomal dominant inheritance.<sup>8,10,14</sup> Investigators presume that mutations leading to activation of the kinin system are also critical to HAE with normal C1-INH. Supporting this hypothesis, mutations in coagulation factor XII (Hageman factor) have been identified but are only present in approximately 20% to 30% of patients.<sup>10,15</sup>

There are 2 subtypes of HAE with normal C1-INH recognized: HAE with normal C1-INH and a factor XII mutation, and HAE with normal C1-INH of unknown cause.<sup>9</sup> These 2 subtypes are clinically indistinguishable from one another and their treatment is similar. Factor XII is a protease in the plasma contact system that generates bradykinin. A mutation in factor XII, such as those observed in patients with HAE with normal C1-INH, can lead to increased bradykinin production, which makes affected patients more prone to swelling episodes. The incidence of asphyxia and death is equal between all 3 types of HAE. Estrogen's effect in patients with HAE with

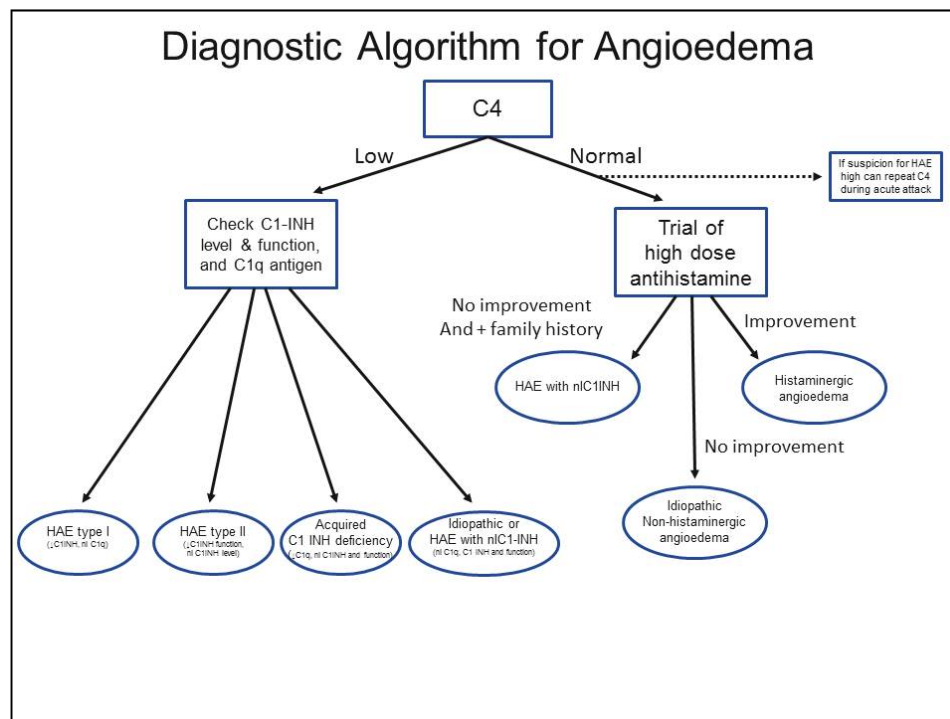


normal C1-INH is variable. In an early description of the disease, women only experienced angioedema attacks during pregnancy or when exposed to exogenous estrogen.<sup>8</sup> Since this first associative publication, additional patients with estrogen-triggered angioedema have been described.<sup>16-18</sup> Nonetheless, some women with HAE with normal C1-INH can tolerate high levels of estrogen with no exacerbation in HAE attacks.<sup>16,19</sup> There is speculation that estrogen may affect expression of transcriptional factors important in the synthesis and degradation of bradykinin. Along this line, high estrogen levels reportedly reduce plasma C1-INH levels, increase transcription of factor XII, increase plasma prekallikrein levels, and reduce expression of ACE, which leads to increased bradykinin production or persistence.<sup>20,21</sup> Lastly, estrogen may contribute to HAE flares by increasing the expression of bradykinin type 2 receptors.<sup>22</sup> Estrogen's effect on swelling episodes is not limited to patients with HAE with normal C1-INH, as it is a well-established trigger in some females with HAE types I and II.<sup>23</sup>

A diagnosis of HAE with normal C1-INH is based on the presence of recurrent angioedema in the absence of hives; absence of relevant medication exposures (ACE inhibitors, NSAIDs); normal C4 and C1-INH levels and C1-INH function; and either a factor XII mutation or a positive family history and a failure to respond to high-dose antihistamines.<sup>9</sup> Suspicion for HAE should be raised in a patient with recurrent angioedema without urticaria or

pruritus, recurrent episodes of abdominal pain, laryngeal edema, and a family history of angioedema. Given that HAE with normal C1-INH is a subtype of idiopathic angioedema, it is important to exclude histaminergic idiopathic angioedema before arriving at a diagnosis of HAE with normal C1-INH. To accomplish this, a trial of antihistamine therapy is an important diagnostic step. Initial regimens include daily cetirizine (10 mg), fexofenadine (180 mg), or loratadine (10 mg). If patients continue to have swelling episodes despite these medications, regimens in which these doses are doubled or even quadrupled for 1 to 3 months should be pursued to definitively exclude idiopathic histaminergic angioedema.<sup>9</sup> Some clinicians also advocate that patients should take on-demand diphenhydramine (25-50 mg) and prednisone (40 mg) at the first signs of an attack to further exclude idiopathic histaminergic angioedema. A patient failing to respond to high-dose antihistamine therapy and on-demand treatment may have HAE with normal C1-INH (Figure 2).

Treatment for HAE with normal C1-INH is similar to HAE types I and II and is divided into on-demand attack management and prophylactic therapy.<sup>24</sup> However, whereas treatment for HAE types I and II has been evaluated in placebo-controlled clinical trials, the data regarding treatment of patients with HAE with normal C1-INH are limited to small uncontrolled trials and case reports. Treatment for HAE attacks begins with



**Figure 2.** Diagnostic algorithm for angioedema.

C1-INH, C1 inhibitor; HAE, hereditary angioedema; nl,





assessment and protection of the upper airway, as these patients are at risk for fatal asphyxiation. After initial assessment and the patient is either intubated or deemed stable, other therapies can be considered. Icatibant and ecallantide have been reported to be effective in treating patients with HAE with normal C1-INH.<sup>25-27</sup> C1-INH concentrate has also been used in some cases,<sup>15</sup> including with our patient as described here. Prophylactic treatment in patients with HAE with normal C1-INH is given to decrease the overall number of attacks. With patients experiencing >1 severe event per month, who have laryngeal attacks, or whose quality of life is affected >5 days per month, prophylactic therapy should be discussed.<sup>28</sup> Androgens, tranexamic acid, C1-INH infusions, and progesterone-only OCs have shown variable success in reducing HAE attacks.<sup>5,7,14,29-33</sup> Danazol, an attenuated androgen, works by increasing the levels of C1-INH and can lead to remission in some patients; it is the most frequently used drug for prophylaxis.<sup>10,34</sup> Adverse effects of danazol, although rare, include hepatotoxicity and virilization, limiting its use.<sup>34</sup> Tranexamic acid, an antifibrinolytic agent used for prophylaxis of HAE types I and II, acts by preventing the activation of factor XII and was effective in preventing attacks in patients with idiopathic angioedema.<sup>24,35</sup> Progesterone therapy for HAE with normal C1-INH was used for 1 to 6 years in 8 patients with factor XII mutations, and all remained attack free during therapy.<sup>15</sup>

## SUMMARY/CONCLUSIONS

HAE with normal C1-INH is a rare genetic disease for which a diagnosis is made based on a history of recurrent angioedema (1) in the absence of hives, (2) with normal C4 and C1-INH levels and C1-INH function, and (3) either a factor XII mutation or a positive family history and a failure to respond to high dose antihistamines.<sup>9</sup> Our case illustrates a patient with HAE with normal C1-INH who responded to on-demand therapies developed for HAE types I and II and prophylactic treatment with progesterone. Suspicion for HAE should be raised in a patient with recurrent angioedema without urticaria or pruritus, recurrent episodes of abdominal pain, laryngeal edema, and a family history of angioedema. After a thorough evaluation for causes and exclusion of idiopathic histaminergic angioedema, on-demand and prophylactic therapies used to treat conventional HAE (types I and II) should be considered.

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