



Letter

Treatment of an acute attack of type III hereditary angioedema with ecallantide

Hereditary angioedema (HAE) is a rare genetic condition characterized by recurrent attacks of nonpruritic, localized edema involving the face, extremities, gastrointestinal tract, and upper respiratory tract. Laryngeal attacks may be life-threatening. The 2 classic subtypes of HAE are caused by mutations in the C1 esterase inhibitor (C1-INH) gene, resulting in either a deficiency of C1-INH (type I HAE) or dysfunctional C1-INH (type II HAE).¹ Type III HAE is a newly identified and extremely rare subtype of HAE that is characterized by normal C1-INH antigenic and functional levels. It was initially reported in females but has now been observed in males as well.² Some patients with type III HAE have been shown to have a missense mutation in coagulation factor XII.³ The remainder have genetic defects that are not yet determined.⁴

C1-INH is a serine protease inhibitor that regulates the activity of the kallikrein-kinin, coagulation and complement cascades. In patients with type I and type II HAE, reduced activity of C1-INH results in overactivation of the kallikrein-kinin cascade. The large release of bradykinin that ensues is responsible for the vasodilation, edema, and pain characteristic of acute attacks.⁵ Patients with type III HAE have normal C1-INH activity, so they do not reliably respond to treatments that are effective in other types of HAE. Multiple therapies, including antifibrinolytics, androgen derivatives, and C1-INH replacement, have been attempted in patients with type III HAE with varying clinical responses.

Ecallantide is a plasma kallikrein inhibitor. Two phase 3 clinical trials of patients with type I and type II HAE showed efficacy of the drug in acute cutaneous, abdominal, and facial attacks.^{6,7} Because ecallantide affects the bradykinin pathway rather than the C1-INH pathway, it is promising for the treatment of patients with type III HAE. We describe a patient with type III HAE who experienced rapid, complete resolution of an acute attack with ecallantide.

The patient is a 14 year-old boy who first presented to us at 12 years of age with an 18-month history of severe, recurrent angioedema. His attacks last an average of 3 days each and typically involve his face and airway, and he has had multiple attacks requiring intubation. His attacks are never associated with urticaria or pruritus. Unlike patients with idiopathic angioedema, his symptoms do not respond to antihistamines, epinephrine, or corticosteroids. He is adopted, but he has a biological, paternal uncle with recurrent, non-medication-related facial swelling. His C4-INH and C1-INH antigenic and functional levels are all normal between and during attacks. His C1q level is also normal (Table 1).

The patient has attempted multiple therapies to prevent and treat HAE attacks. Oxandrolone prophylaxis has failed, and C1-INH treatment was not effective for acute attacks or prophylaxis. Fresh frozen plasma was minimally beneficial for acute episodes of swelling. He is currently receiving sulfasalazine prophylaxis, which has effectively reduced the frequency and severity of his attacks.

Recently published consensus guidelines categorize patients

Table 1

Results of the Patient's Laboratory Tests

Test	Patient value	Reference range
C1 esterase inhibitor, mg/dL	16, 14, 12	11–26
C1 esterase inhibitor function, %	>100	>68
C4, mg/dL		15–45
Baseline	23.3, 32.9, 19.5, 18.9	
During attack	30, 20.9	

with HAE according to clinical history but who have normal laboratory test results as having HAE with normal C1-INH, often referred to as type III HAE.⁴ The patient's normal laboratory test results and the failure of C1-INH, antihistamines, steroids, and epinephrine to treat or prevent episodes of angioedema are diagnostic of type III HAE.

Recently, the patient presented to the emergency department of a children's hospital with marked facial, tongue, and lip angioedema, which developed after mild facial trauma. He was not treated with antihistamines, steroids, or epinephrine. Forty-five minutes after subcutaneous administration of 30 mg of ecallantide, his angioedema had significantly improved, and by 90 minutes it had completely resolved.

Ecallantide ameliorated the patient's attack because it potently inhibited kallikrein and halted bradykinin production. His response to ecallantide proves that even though his laboratory test results are normal, his HAE is bradykinin mediated, similar to type I and type II HAE. Spontaneous resolution, although possible, is unlikely given the severity and duration of his prior episodes and the rapid resolution of symptoms after receiving ecallantide.

Although much progress has been made in diagnosing and treating HAE, there are still limited effective treatment options for patients with type III HAE. This case report describes a patient with type III HAE whose angioedema responded quickly and successfully to treatment with ecallantide, proving that his HAE attacks are due to overproduction of bradykinin. To our knowledge, this is the first documented report of efficacy of a plasma kallikrein inhibitor for treatment of an acute type III HAE attack. Further studies should be undertaken to explore the efficacy of kallikrein inhibitors for acute attacks in patients with type III HAE.

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Disclosures: Dr Maples is on the speaker's bureau for Teva Pharmaceuticals.

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