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Letter

Resolution of an acute attack of idiopathic angioedema with ecallantide

Idiopathic angioedema is characterized by local edema involving the deeper dermis and subcutaneous tissue and triggered by the release of mediators that cause vasodilatation and increased capillary permeability.[1] Acute attacks most commonly occur in the periphery, but patients also may experience laryngeal or bowel angioedema. Idiopathic angioedema shares some clinical features with hereditary angioedema (HAE) types I and II and is physiologically distinct in that patients with idiopathic angioedema exhibit normal C4 and C1 esterase inhibitor levels and function.[2] Patients with type III HAE also exhibit normal C4 levels with normal quality and quantity of C1 esterase inhibitor; however, guidelines published by an international expert panel in 2012 on hereditary angioedema with normal C1 inhibitor function require that these patients have a family history significant for angioedema to establish a diagnosis of type III HAE.[3] A subpopulation of patients have a missense mutation in the factor XII gene,[4] which the 2012 consensus requires if family history is not present for the diagnosis of type III HAE. If no other causative factors are elucidated, patients with angioedema who do not qualify as HAE according to the 2012 Consensus guidelines are classified as having idiopathic angioedema.

Failure of treatment with high-dose anti-histamines indicates that idiopathic angioedema may not necessarily be mediated by histamines. One report of successful treatment of acute attacks secondary to idiopathic angioedema with icatibant, a bradykinin B-2 receptor antagonist, suggests that idiopathic angioedema may occur via the contact pathway.[5] Ecallantide, a member of the kallikrein inhibitor class approved for treatment of acute attacks in HAE, works by binding to kallikrein, preventing the conversion of kininogen to bradykinin.[6] This reduces vascular permeability and therefore the swelling associated with an acute attack. Administered subcutaneously, this medication affects the contact pathway but has no effect on the coagulation or complement pathways. Two phase 3 clinical trials of patients with type I and type II HAE showed efficacy of this drug in acute attacks.[7] One case report has been published suggesting this medication's efficacy in patients with type III HAE.[8] We describe a patient with an acute attack secondary to idiopathic nonhistaminergic angioedema who experienced rapid resolution of symptoms after administration of ecallantide.

An 8-year-old girl had a history of von Willebrand disease and recurrent angioedema without urticaria. At 4 years of age, she had 3 episodes of angioedema characterized by nausea and vomiting, tongue and uvular swelling, and difficulty swallowing. These events consistently occurred after dental procedures. Allergy testing for latex and topical anesthetics was negative. Although less severe, she had a similar episode at 7 years of age after a dental extraction. She began to have episodes of angioedema unrelated to trauma and infection. One episode affected her airway, for which she was admitted to the pediatric intensive care unit. Three other episodes of angioedema were manifested by swelling of her left foot, right shoulder, or right hand. Before an attack, the patient had experienced prodromal symptoms of tingling, with symptoms worsening in the first 24 to 36 hours and resolution by 48 hours. There is no family history of angioedema.

Laboratory evaluation at baseline and during an acute attack (Table 1) showed normal levels of C4, and normal quantity and function of C1 esterase inhibitor. Evaluation for single nucleotide polymorphisms in the factor XII gene was negative. This patient was brought to the emergency department or hospitalized for these episodes, and was unresponsive to treatment with epinephrine, antihistamines, and steroids. Off-label treatment with ecallantide, to be administered during acute attacks, was approved for this patient. Consent was provided by the patient's parents and approved for administration by the hospital pharmacy and medical staff in the emergency department. Recently, she presented to the emergency department with angioedema to her left lower extremity. She received 30 mg ecallantide subcutaneously within 4 hours of symptom onset. Decreased edema was noted at 2 hours, and complete resolution noted at 11 hours after administration of ecallantide. In comparison, a randomized double-blind, placebo-controlled trial showed that patients with HAE who received ecallantide for peripheral attacks showed significant overall improvement versus placebo at 24 hours.[9]

The resolution of her symptoms with ecallantide supports the hypothesis that angioedema in this patient is mediated through the contact pathway. To our knowledge, this is the only report of successful treatment of an acute attack due to idiopathic nonhistaminergic angioedema with ecallantide. Currently, ecallantide is approved for treatment of acute attacks secondary to HAE in patients older than 16 years of age, but data show that ecallantide is safe in patients as young as 10 years of age.[10] Additional studies should be performed to determine the efficacy and safety of plasma kallikrein inhibitors and bradykinin B-2 receptor antagonists for treatment of acute attacks and in pediatric patients.

Table 1
Results of laboratory evaluation

Test	Patient's value	Reference range
C4 component (mg/dL)		
Baseline	20	16–56
During acute attack	28	9–36
C1 esterase inhibitor, serum		
Baseline	1:8	1:4–1:16
During acute attack	26	21–39 mg/dL
C1 esterase inhibitor, function		
Baseline	—	
During acute attack	103%	

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Improvement in current strategies for evaluation and treatment of idiopathic angioedema should be pursued. Development of assays to measure bradykinin levels should be considered, because this would help stratify patients with idiopathic nonhistaminergic angioedema and may determine who would benefit from the medications available to treat acute attacks, which act at different points in the contact pathway. Our patient did not meet the criteria for type III HAE because of absence of family history; however, de novo mutations occur. Currently, the medications available for acute attacks of angioedema are approved for patients who are categorized as having HAE according to the 2012 consensus guidelines, thus making it difficult for patients with frequent, debilitating attacks attributable to nonhereditary bradykinin-mediated angioedema to qualify for treatment. Our patient's acute attack secondary to idiopathic nonhistaminergic angioedema was successfully treated with ecallantide, a medication currently approved for acute attacks secondary to HAE. This highlights the need for further studies to determine the effectiveness of these medications in nonhereditary angioedema.

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