CASE REPORT

Critical upper airway obstruction in sporadic angioedema responding to C1-esterase inhibitor

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SUMMARY

We describe a case of recurrent oropharyngeal angioedema in a 16-year-old boy with a history of sickle cell disease and thrombocytopenia and with no family history of angioedema. Emergency treatment of angioedema with C1-esterase inhibitor (C1-INH) provided immediate relief, avoiding the placement of a surgical airway. Further evaluation has shown C1-INH to be normal in quantity and function, with normal complement studies during acute attacks. Genetic testing revealed no abnormality in the factor XII gene. Our case exemplifies that even in cases of sporadic angioedema, treatment with C1-INH may be an effective and life-saving management strategy.

BACKGROUND

Angioedema presents with oedema of the skin, gastrointestinal tract or other organs, and can be allergic or non-allergic. Non-allergic angioedema can be classified as hereditary (HAE), acquired or sporadic. All forms of non-allergic angioedema result from local transient and episodic increases in bradykinin. Triggers such as trauma or infection may activate the contact-kinin pathway and result in increased bradykinin levels. Bradykinin increases vascular permeability leading to soft tissue swelling. Angioedema of the oropharynx may lead to potentially life-threatening airway obstruction. C1-INH acts as an inhibitor of the classical complement pathway and the contact-kinin pathway. In the latter, it directly inhibits activated Factor XII and kallikrein. With insufficient or dysfunctional C1-INH, there is an uncontrolled synthesis of bradykinin leading to oedema.¹ Given the substantial risk associated with episodic oedema, such cases must be diagnosed and treated promptly. However, laboratory diagnostic tests are not possible in the acute setting and thus empiric treatment with exogenous C1-INH in patients with severe angioedema may be life saving. We describe a case of angioedema of the oropharynx that illustrates these diagnostic and management challenges.

CASE PRESENTATION

A 16-year-old boy with known sickle cell disease (HbSC) and associated thrombocytopenia presented to the emergency room (ER) at 4:15, having awoken from sleep at 2:30 with lip and tongue swelling associated with dysphagia, dyspnoea and dysphonia. The patient was in his usual state of health, with no sick contacts or unusual exposures (drugs, foods, animals, insects or plants). He had been to the orthodontist the previous day for a

minor intervention. His history revealed similar episodes of lip and tongue swelling albeit to a lesser degree during the last 6 months. These episodes occurred every 1–2 weeks and would persist 1–4 h before resolving without treatment. He had not previously sought medical attention for these episodes and they had not been associated with respiratory distress, dysphonia or dysphagia. There was no history of similarly affected family members.

His sickle cell disease was characterised as HbSC and crises were distinct from the episodic angioedema.

In the ER, the patient was in apparent respiratory distress although he maintained an oxygen saturation of 100% in room air. Physical examination was notable for the left-sided facial swelling. Visualisation of the upper airway by laryngoscopy revealed significant swelling of the uvula (figure 1). He was initially treated with 100 mg of solumedrol (intravenously) at 7:35 then 0.5 mg of epinephrine (intramuscularly) at 8:00 without significant effect. He developed worsening respiratory distress and preparations were made for an urgent cricothyroidectomy. On the advice of the Allergy and Immunology service empiric treatment of C1-INH concentrate, Berinert, 500 units, intravenously was

Figure 1 Prior to treatment with Berinert, there is a marked oedema of the tongue and soft tissues of the oropharynx.

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Figure 2 After treatment with Berinert, the oedema has resolved.

given. There was a marked improvement in symptoms within 20 min of treatment avoiding the need for placement of a surgical airway. Re-examination by laryngoscopy 3 h later showed a marked improvement with only residual swelling of the epiglottis (figure 2). He was admitted to the hospital and monitored for 24 h with no recurrence of symptoms.

INVESTIGATIONS

The evaluation of complement pathways, including C3, C4, classical, alternative and MBL pathways and tryptase levels, was normal when studied during the severe presentation as well as on two separate subsequent minor episodes of angioedema. Quantitative and functional assays of C1 esterase inhibitor were also within normal limits. Genetic analysis of gene F12 of coagulation factor XII revealed no mutations or sequence variations.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for episodic angioedema includes allergic angioedema caused by insects, food, drugs (usually associated with the presence of hives) or non-allergic angioedema. Non-allergic angioedema can be acquired secondary to the use of ACE inhibitors or angiotensin-II receptor blockers, infections, autoimmune or malignant processes and hereditary (types I, II and III) and sporadic, where no identifiable cause is present.²

The patient was not taking any medications and there was no urticaria during the attacks, suggesting that allergic angioedema was unlikely given the frequency of the attacks and the lack of an identifiable exposure. There was no family history of HAE. Further, the quantitative and functional assays of C1-INH were normal, eliminating HAE types I and II. In addition, HAE type III is highly unlikely given a lack of mutations in the gene for factor XII.

TREATMENT

Treatment of acute attacks of HAE includes C1-INH, a replacement therapy given intravenously. Two newer subcutaneous

treatment options are ecallantide and icatibant, which target the kallikrein and bradykinin signalling pathways, respectively. Ecallantide administration has been associated with hypersensitivity reactions including anaphylaxis, and as such must be done in a setting where complications can be managed appropriately. Icatibant can be self-administered subcutaneously. Prophylactic treatment options include anabolic androgens such as danazol and stanozolol, the fibrinolytic agent tranexamic acid and in some cases C1-INH.³

OUTCOME AND FOLLOW-UP

The patient subsequently has had two further episodes associated with milder lip and tongue swelling, persisting for approximately 3 h before resolving without treatment. He has had no episodes during the last 3 months. He has been instructed to present to ER if he develops worsening symptoms and to have the immunology service contacted for assistance in medical management. He has been counselled to wear a medic-alert bracelet.

DISCUSSION

Hereditary angioedema has been classified as a quantitative (type I) or functional (type II) deficiency of C1-INH. More recently, a third type of HAE has been described in patients with normal C1-INH antigenic protein level, function and normal C4 levels during attack.⁴ Type III HAE can be further subclassified into cases related to factor XII mutation as well as cases with an unknown genetic mutation.⁵ The clinical manifestations of type III HAE are extremely variable. It was first described in women and was associated with estrogen levels; however, the cases of affected men have been described within several families with multiple affected members.² With acute attacks, corticosteroids, antihistamines and adrenalin are generally not effective, while C1-INH concentrate, icatibant (a bradykinin B2 receptor antagonist), plasma kallikrein inhibitor and fresh frozen plasma have provided relief in some patients.^{6 7} Options for prophylactic treatment include attenuated androgens such as danazol, antifibrinolytics such as tranexamic acid and a plasma-derived C1-INH concentrate (Berinert).⁶ The diagnosis of HAE in this case is unlikely given the absence of family history, normal quantitative levels and function of C1-INH and lack of factor XII mutations. Hence, this patient's angioedema is best described as sporadic. Similar to our case, Rasmussen *et al* described a girl with clinical findings consistent with HAE type III without a family history. Following admission to intensive care unit for oropharyngeal swelling and respiratory distress, she was started on corticosteroids which did not attenuate symptom recurrence. She began treatment with plasma-derived C1-INH concentrate at the onset of acute episodes of angioedema with prompt resolution of symptoms. Given her response, she was treated with Berinert prophylactically three times weekly and has stopped corticosteroids. A reduction in the frequency of Berinert treatment has resulted in the recurrence of symptoms.⁸

In our case, the clinical response to C1-INH concentrate suggests an impairment in the bradykinin pathway that can be rectified with the use of exogenous C1-INH. This case exemplifies that C1-INH may be life saving and should be considered in severe cases of angioedema regardless of the aetiology.

Learning points

- ▶ Overproduction of bradykinin in the contact system pathway is the primary pathological mechanism responsible for episodes of hereditary and sporadic angioedema.
- ▶ Angioedema may be life threatening and can present without a suggestive family history with normal C1-INH and C4 levels.
- ▶ Treatment with C1-INH may be life saving in sporadic angioedema.

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Competing interests None.

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