Hereditary Angioedema in Childhood: A Challenging Diagnosis You Cannot Afford to Miss

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Abstract: Hereditary angioedema (HAE) is a rare inherited disease that is often difficult to diagnose. We report a case of a 9-year-old boy with a spontaneous mutation causing HAE, diagnosed after a life-threatening episode of angioedema of the head and upper respiratory tract after a 5-year history of recurrent skin swellings and abdominal pain leading to several hospital admissions. The aim of this report is to direct focus on this rare disease, which can be treated effectively, to diminish morbidity and mortality of children suffering from undiagnosed HAE.

Hereditary angioedema (HAE) is a rare, potentially life-threatening disease inherited as an autosomal-dominant trait. A low concentration of C1 inhibitor (HAE type 1) or poorly functioning C1 inhibitor (HAE type 2) causes the condition (1). The disease manifests itself by attacks of swelling of the subcutaneous skin, the upper airway, the intestinal mucosa, or any combination of the three. Mechanical trauma, infection, or emotional stress often precipitate the attacks, which may be associated with a reticular erythematous eruption (2). The mean age of onset is between 5 and 11 years (3), and diagnosis is based on family history, clinical symptoms, and blood testing. We report a case of de novo mutation in the C1 inhibitor gene and emphasize the diagnostic challenge of HAE in patients without a family history.

REPORT OF CASE

A 9-year-old boy presented at the local emergency department with angioedema of his face (Fig. 1), stridor, and cyanosis. During the preceding 5 years, he had been seen at the hospital five times with a rash and edema of the trunk and extremities. During the same period, he had also had some attacks of abdominal pain. The differential diagnoses were viral rash, erythema multiforme, allergy, and juvenile arthritis. At the hospital, he was treated with intravenous glucocorticoids, antihistamines, and epinephrine, without effect. When he developed a life-threatening upper airway swelling with cyanosis, the suspicion of HAE was raised, and he was treated with fresh frozen plasma. After symptom relief, he was directed to the department of dermatology for allergy testing and follow-up. Blood testing showed C1 inhibitor concentration of 0.07 g/L (normal range 0.21–0.39 g/L) and a functional C1 inhibitor activity of 32% of normal values (normal range 70–130%), low C4, and low C1q, a pattern corresponding to HAE type 1. He received a multilingual emergency card explaining his disease and two vials of C1 inhibitor concentrate (each 500 U) for emergency treatment. The patient was a Boy Scout, and

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he was offered short-term prophylaxis with tranexamic acid 500 mg three times per day, before and during Scout camps, and no attacks were observed during these periods. Over 19 months of follow-up, he had two swelling episodes of his external genitalia and three painful abdominal attacks treated effectively using C1 inhibitor concentrate at the nearest hospital. Three minor attacks of abdominal pain were treated with tranexamic acid. He continued to have intermittent serpiginous erythematous rash (Fig. 2) accompanying swelling attacks but also seen as an isolated clinical finding. Molecular genetic testing was performed and showed a deletion of exon 7 and 8 in the C1 inhibitor gene (SERPING1). The parents’ genes were also analyzed, but no mutation was found, which meant that the patient had a spontaneous gene mutation.

DISCUSSION
This case shows how the diagnosis of HAE is often delayed for several years. The rare diagnoses are difficult for physicians in the emergency department, who often are the first to treat patients with HAE. Approximately 20% of patients lack a family history (4), which makes the diagnosis even more difficult.

Hereditary angioedema (HAE) attacks limited to the upper airways are easily mistaken for allergic angioedema and do not respond to corticosteroids or antihistamine. Epinephrine has only a transient and modest benefit (5). Abdominal HAE attacks with colicky pain and vomiting can mimic an acute abdominal catastrophe, and abdominal ultrasound or computed tomography scan may show ascites and intestinal wall edema (3). Consequently, some patients undergo several unnecessary abdominal surgeries. Differential diagnoses for HAE attacks limited to the skin include allergy, idiopathic angioedema, and angioedema induced by medications (e.g., angiotensin-converting enzyme inhibitor, acetylsalicylic acid), whereas the transient reticular and serpiginous erythematous eruption may be perceived as a sign of rheumatic fever (erythema marginatum) or urticaria. The difficulty of diagnosing HAE combined with a mortality rate of up to 25% to 30% in undiagnosed patients having severe attacks (3) emphasizes the importance of diagnosing this disease so that effective treatments can be used. The most established treatment for severe HAE attacks is C1 inhibitor concentrate, usually administered in the emergency department, although home therapy with intravenous C1 inhibitor concentrate is now well established also in children (6). The C1 inhibitor concentrate Berinert (CSL Behring GmbH, Marburg, Germany) is used in a dose of 20 U/kg administrated intravenously (5). C1 inhibitor concentrate is not available in all countries, and fresh frozen plasma may be used as an alternative treatment, although a few cases of worsening edema after treatment with fresh frozen plasma has been observed (7,8). Prophylaxis consists of avoiding precipitating factors such as physical trauma together with short- or long-term medical prophylaxis. Short-term prophylaxis with tranexamic acid, danazol, or C1 inhibitor concentrate is used before risky procedures such as surgery (3,5). Long-term prophylaxis is recommended if the patient has frequent or severe attacks, and the treatment of choice for children is tranexamic acid because of its safety profile. Attenuated androgens (danazol, stanozolol, or oxandrolone) can be used in fully grown patients. New drugs such as icatibant (a bradykinin B2-receptor antagonist) and ecallantide (a plasma kallikrein inhibitor) have been developed in recent years (5). They are favorable because they are administrated through subcutaneous injection, which makes treatment at home much easier for parents, who may have difficulties giving intravenous injections to...
their children (9). These drugs are not yet available in all countries and are not yet licensed for children (10). Ecallantide has received a boxed warning in the labeling stating that the drug should not be used as home therapy, because of possible hypersensitivity reactions including anaphylaxis.

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CONFLICT OF INTEREST

Anette Bygum has been involved in clinical research or educational events involving CSL Behring, Jerini/Shire, and Viropharma.

REFERENCES