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Successful C1 esterase inhibitor therapy in a child with a novel type 3 hereditary angioedema-like syndrome

Hereditary angioedema (HAE) was first recognized as a distinct disorder in 1882, with a prevalence of approximately 1 in 50,000 people.¹ Episodes commonly present with laryngeal, abdominal, and subcutaneous edema.² The usual age of onset is 8 to 12 years. The typical delay from onset of symptoms to diagnosis is 13 to 21 years, resulting in up to 40% mortality, mostly due to upper airway obstruction.³ Laboratory evaluation reveals low C1 esterase inhibitor (C1-INH) levels (type 1) and/or function (type 2) with low C4 levels. Before the advent of more specific treatments for episodes of angioedema, therapy included attenuated androgens, antifibrinolytic agents, and fresh frozen plasma.⁴ Purified C1-INH has been used for treatment of attacks in Europe since the 1970s but was not licensed for use in the United States until 2008.⁵ Corticosteroids, antihistamines, and epinephrine are ineffective. In 2007, Bork et al⁶ described a new type of HAE (type 3) that also presents with angioedema with normal C1-INH levels and function and normal C4 levels and is not responsive to corticosteroids, antihistamines, and epinephrine; these patients have similarly affected family members. Treatment is not well defined for HAE type 3. We describe a young girl whose condition exemplifies HAE type 3 but who has no family history of angioedema and could have a novel angioedema syndrome; she has responded well to C1-INH for short-term treatment and preventive therapy.

Our patient was healthy except for a diagnosis of asthma and adenoidectomy in the first 2 years of life. Shortly after her second birthday, she started having frequent episodes of apparent abdominal pain, straightening of her legs, and fussing and crying that would last for a few minutes and gradually improve. Episodes would occur randomly, anywhere from 4 times weekly up to 4 times daily. At 29 months of age, a severe, prolonged episode of oropharyngeal swelling and respiratory obstruction resulted in an intensive care unit hospitalization. Epinephrine was administered, with minimal change noted. Subsequently, the patient was treated with 1 mg/kg/d of oral prednisone, which decreased the episodes to every 5 to 7 days. Multiple attempts to wean the corticosteroids resulted in increased frequency of lip swelling, respiratory difficulty, abdominal discomfort, and diarrhea. Antihistamines such as cyproheptadine were ineffective.

The results of skin tests for food allergies were negative. Laboratory evaluation findings at 29 months of age were normal for C1-INH antigen (54 mg/dL) and function (100%). Additional laboratory evaluation 2 months later again demonstrated normal C1-INH protein and function but revealed a low C4 level (9 mg/dL). Coagulation factor XII revealed 25% activity (reference range, 75%–150%). Subsequent testing for C4 and C1-INH protein and function before and during an episode of angioedema yielded normal results. No mutations were detected in the C1-INH (*SERPING1*) and factor XII

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(F12) genes, but a follow-up factor XII test revealed decreased activity (39%).

The patient began plasma-derived C1-INH (Berinert; CSL Behring, King of Prussia, Pennsylvania) replacement therapy for acute episodes of angioedema at 35 months of age. Initial doses of plasma-derived C1-INH (20 U/kg) were given, with the patient experiencing relief within 20 to 40 minutes of administration compared with 24 to 48 hours without treatment. Because of the frequency of the angioedema episodes, recurring every 3 days, preventive therapy (20 U/kg) via an indwelling venous catheter was initiated 3 times weekly, and she was weaned off corticosteroids. Attempts at decreasing the frequency of preventive treatment resulted in recurrence of the symptoms. During 20 months since the initiation of home-based preventive treatment, the patient has improved, with normal growth, development, and activity.

Our patient's presentation was similar to HAE type 3 in that she had normal C1-INH levels and was female. In contradistinction to the patients studied by Bork et al,⁶ however, our patient had symptoms at a very young age, had multisystem involvement, had minimal skin manifestations, and lacked any identifiable family history of similarly affected individuals. In addition, she had inconsistently low C4 levels and did not have an identifiable mutation in the factor XII gene that has been described in some patients with HAE type 3.⁷ Patients with HAE type 3 also tend to have more disease-free intervals than our patient and require less long-term treatment. A small subset of patients with HAE type 3 have received C1-INH for acute episodes; the therapy was effective in most patients.⁸

Thus, our patient had recurrent episodes of angioedema with findings distinct from known forms of angioedema. It could be that she has a previously undescribed form of angioedema whereby low factor XII levels relate to inadequate functional inhibition of C1-INH despite measured normal inhibition levels.

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Acute hemolysis secondary to high-dose intravenous immunoglobulin in a patient with Stevens-Johnson syndrome

Intravenous immunoglobulin (IVIG) is commonly used as replacement therapy in immunodeficiency disorders and in higher doses for certain autoimmune and inflammatory conditions.¹ Common side effects of IVIG include headache, flu-like symptoms, nausea, chills, rash, backache, and hypotension. Rare serious adverse events, including anaphylaxis, acute renal failure, aseptic meningitis, transfusion-related acute lung injury, and thrombo-embolic events, may occur.¹ A few scattered reports of hemolytic anemia associated with IVIG have appeared during the past 25 years, primarily in the hematology literature.^{2–8} We present a case of severe hemolysis following IVIG in a patient with Stevens-Johnson syndrome (SJS).

A 36-year-old African American woman was admitted to our hospital with a widespread rash that was worsening over a 2-week period. Her rash was preceded a few days earlier by fever, sore throat, and myalgia. She had taken Nyquil (acetaminophen/dextromethorphan/doxylamine), but no other medication. She had no history of autoimmune, hematologic, or other disorders. On admission, she had an extensive desquamating rash with significant conjunctival and oral mucositis, compatible with SJS, possibly secondary to medication or upper respiratory infection. She was treated with 3 consecutive doses of IVIG (Privigen; CSL Behring, King of Prussia, Pennsylvania) at 1 g/kg/day. Her hemoglobin was 11.4 g/dL on admission and dropped to 10.0 g/dL after the first IVIG dose, 9.2 g/dL after the second

dose, 8.7 g/dL after the third dose, and then 6.5 g/dL on hospital day 5, which was 1 day after the IVIG was discontinued (Fig 1). No evidence of bleeding was seen. After drawing blood for laboratory tests, 2 units of packed red blood cells (RBCs) were transfused, which resulted in an increase of hemoglobin to 8.7 g/dL.

The laboratory tests revealed abnormal values for lactate dehydrogenase (723 U/L; normal, 84–246 U/L), reticulocyte count (12.5; normal, 0.5–2.4%), total bilirubin (1.6 mg/dL; 0.2–1 mg/dL), and a haptoglobin less than 8 mg/dL (normal, 41–165 mg/dL); consistent with ongoing hemolysis. She had normal prothrombin time, partial thromboplastin time, C3, C4, and antinuclear antibodies. The patient's blood group was type A. A positive direct antiglobulin test demonstrated the presence of anti-A isohemagglutinins.

Four days after the first blood transfusion, her hemoglobin dropped to 6.8 g/dL, and haptoglobin was still not measurable. Two more units of PRBCs were transfused, which increased her hemoglobin to 9.6 g/dL but it gradually fell to a nadir of 7.8 g/dL and haptoglobin increased to 24 mg/dL on hospital day 15. By this time her rash had nearly resolved and the mucositis had improved. She was discharged for outpatient follow-up. Five days postdischarge her hemoglobin was 8.1 g/dL, and 6 days later it reached 11.9 g/dL with a haptoglobin of 102 mg/dL.

To the best of our knowledge, this is the first report of IVIG-related hemolysis in a patient with SJS. The underlying mechanism

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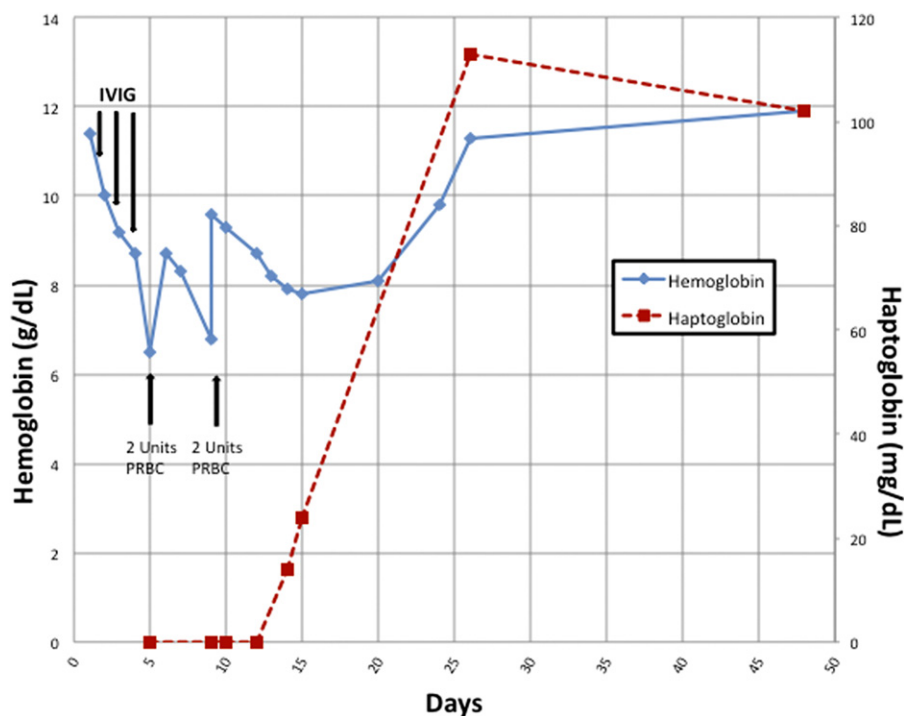


Fig. 1. Course of hemolysis related to IVIG therapy in a patient with Stevens-Johnson syndrome.