



Letter

Hereditary angioedema presenting as compartment syndrome in a white girl

Hereditary angioedema (HAE) is a rare disease that presents as focal angioedema without wheals and has a prevalence of 1 in 50,000 people.¹ Episodes of HAE rarely cause musculoskeletal effects, resulting in significant morbidity. To our knowledge, this is the second reported case of HAE presenting with compartment syndrome and the first report of HAE type I.

A 13-year-old white girl with a 10-month history of recurrent leg swelling and abdominal pain presented to the emergency department with swelling and pain of the right arm. The patient denied recent trauma. Previous evaluations failed to determine a cause. The patient had a history of recurrent abdominal pain, which warranted ultrasonography and revealed an incidental finding of fatty liver that was not further evaluated. The maternal family history was unremarkable for contributing factors. Her estranged father reportedly had recurrent abdominal pain that required multiple exploratory laparoscopies without a definitive cause noted. Otherwise, there was no additional pertinent family history. She was afebrile with age-appropriate vital signs. Her weight was 88.6 kg, her height was 161 cm, and her body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 99%. Her right arm was edematous without erythema or tenderness. The edema was more prominent proximally, but she had normal perfusion and sensation distally. Pulses were intact, and no rashes were noted.

The differential diagnosis included thoracic outlet syndrome, deep venous thrombosis, necrotizing fasciitis, vasculitis, and trauma. Multiple imaging studies were performed, including right arm Doppler ultrasonography, right arm computed tomography–angiography, skeletal radiography, and chest magnetic resonance imaging. There was no evidence of fracture, deep venous thrombosis, vascular occlusion, lung mass, or tumor. The results of measurement of complete blood cell count, C-reactive protein, ferritin, and erythrocyte sedimentation rate were unremarkable. Cefotaxime and clindamycin were initiated empirically. She was admitted to the pediatric intensive care unit because of disease progression that required frequent neurovascular checks. After admission, the proximal arm edema worsened, leading to cyanosis of her distal arm and hand. She was evaluated by a plastic surgeon and taken to the operating room for emergency fasciotomy because of compartment syndrome (compartment pressure was >50 mm Hg higher than the normal²).

A surgical tissue sample and fluid sample were sent for bacterial and viral cultures. A vacuum-assisted closure drain was placed with only minimal clear drainage after the procedure. Her edema improved gradually. All culture results were negative. The results of further laboratory assessments, including antinuclear antibody,

Sjögren syndrome A, Sjögren syndrome B, and ribonucleoprotein, were all unremarkable. However, her C4 level was undetectable (<6 mg/dL; reference range, 13–44 mg/dL). On postoperative day 2, her right arm continued to improve; however, she began to develop edema of the left hand. Her recurrent angioedema, abdominal pain, and decreased C4 level raised the possibility of HAE. The allergy/immunology department was consulted, and qualitative and quantitative C1 inhibitor (C1-INH) activity was measured at 47% (reference range, >67%) and 7 mg/dL (reference range, 21–39 mg/L), respectively. These findings confirmed the presumptive diagnosis of HAE type 1. Human C1-INH, 2,000 U, was given to treat her left hand swelling, with improvement. A second dose of C1-INH (2,000 units) was given on postoperative day 3 before her fasciotomy closure.

HAE type I is an autosomal dominant disease.³ However, patients do not always have a positive family history.⁴ Approximately 25% of the patients with HAE have a de novo mutation in the C1-INH (*SERPING1*) gene.⁵ Although her father had a history of multiple operations for abdominal pain, it is only speculated that he may have had HAE.

The mechanism of angioedema is related to impaired bradykinin cascade with subsequent increased vascular permeability in the superficial tissues and gastrointestinal and respiratory mucosa. As opposed to superficial involvement, compartment syndrome is a perifascicular and intrafascicular edema in the deep closed osseofascial compartment. There is only 1 other case report of compartment syndrome resulting from HAE to date.⁶ In that report, a 13-year-old presented with a 5-day history of fever and progressive swelling of the left hand. Similarly, she subsequently developed compartment syndrome, requiring surgical intervention. Unlike our case, the only evidence of HAE in that report was a history of recurrent arm swelling. All other supportive data, including C1-INH level, C4 level, and family history, were unrevealing. The authors labeled that case as HAE type III, which is associated with mutations in factor XII, without further comment on genetic testing. That case report focused on surgical management and was devoid of further details of medical management.

The diagnosis of HAE is based on the clinical history in conjunction with laboratory test results. C4 is often the first screening test because it is low or undetectable in 95% of cases because of activation of the classic complement pathway in the setting of absence of its physiologic inhibitor C1-INH. C1-INH level and functional assays can further characterize the diagnosis because C1-INH levels (<50% normal value) are low in HAE type I and C1-INH functional assay (with a normal C1-INH level) is low in HAE type II. Although rarely some cases have normal C1-INH profiles,³ replacement of functional C1-INH and modulation of bradykinin pathway are the mainstay treatments for HAE.

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In addition to long-term prophylaxis with C1-INH inhibitor, short-term prophylaxis is recommended, especially in anticipation of triggering events such as operations.⁷

Our patient was given a second C1-INH dose before her fasciotomy closure, which successfully averted perioperative angioedema. Because our patient's swelling episodes were isolated and separated by several months, we did not start C1-INH replacement based on current expert consensus guidelines.^{7,8} The patient began taking rescue icatibant, a bradykinin B2 receptor antagonist.^{9,10} However, after discharge she experienced several episodes of icatibant-responsive angioedema within a short time frame. Because of increased frequency of the episodes, she was began taking twice-weekly home injections of human C1-INH as prophylaxis. This was escalated to every 3 days after an episode of abdominal pain that required multiple doses of icatibant. Overall, her angioedema has been better controlled with infusions of C1-INH.

We report a rare case of HAE that presented with compartment syndrome. To our knowledge, this is the first of HAE type I with detailed description of clinical, radiographic, and laboratory findings. We emphasize the importance of considering HAE in the differential diagnosis or cause of inflammatory musculoskeletal conditions, such as the compartment syndrome.

Wei-Liang Chen, MD^{*,†}

Joel Gallagher, MD^{*,†}

Heidi Zafra, MD^{*,†}

Rainer Gedeit, MD^{*,†}

^{*}Medical College of Wisconsin
Milwaukee, Wisconsin

[†]Children's Hospital of Wisconsin
Milwaukee, Wisconsin
rgedeit@mcw.edu

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