Pediatric Hereditary Angioedema as a Cause of Acute Compartment Syndrome of the Hand and Forearm: A Case Report

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Abstract

Background: Compartment syndrome of the upper extremity is a surgical emergency that, when left untreated, can have dire consequences. Its causes are numerous, one of which is the uncommon entity hereditary angioedema, an autosomal dominant disease resulting in edema in a variety of potential locations, including the extremities. This is only the second time hereditary angioedema has been mentioned in the literature as a cause of compartment syndrome. **Methods:** We present a case of hereditary angioedema leading to hand and forearm compartment syndrome in a 13-year-old pediatric patient. Diagnosis of hereditary angioedema was made by our Rheumatology colleagues with physical exam and a thorough history, and confirmed by laboratory studies. **Results:** Our patient presented with compartment syndrome of the hand and forearm and underwent hand and volar forearm fasciotomies. She was subsequently worked up for hereditary angioedema with laboratory results confirming the diagnosis. She was discharged after a 5-day hospitalization with prophylactic C1-inhibitor therapy. **Conclusions:** Hereditary angioedema is a rare but known cause of compartment syndrome of the upper extremity, and must be considered when patients present with compartment syndrome of unknown etiology. This disease can be diagnosed by laboratory studies and symptoms can be controlled with medical therapy.

Keywords: acute compartment syndrome, fasciotomy, plasma derived C1 inhibitor, icatibant, a selective beta 2 bradykinin receptor antagonist, hereditary angioedema

Introduction

Acute compartment syndrome (ACS) is a rare but potentially devastating condition of the upper extremity. Traumatic events resulting in fractures are the most common etiology; however, ACS can also be seen as the result of vascular or crush injuries. In the absence of trauma, ACS can be caused by infection, burns, snakebites, or by iatrogenic means, such as intravenous infiltration or tourniquet retention.^{3,5-7,11,12} The pathophysiology of ACS involves tissue swelling and edema, leading to elevated pressure within fascial compartments. As intracompartmental pressure continues to increase, tissue perfusion can become compromised with resultant ischemia and necrosis if left untreated.^{3,7,11,12} Early recognition is essential in minimizing long-term complications.^{3,5,12} ACS is largely a clinical diagnosis.¹¹ Classically described signs include the five Ps, pain, paresthesias, pallor, paralysis, and pulselessness, although most of these would be late findings. Pain associated with ACS is often described as being out of proportion to the apparent injury and elicited with passive stretch of involved muscle compartments. It may also be manifested by increasing analgesic requirements or swollen, tense compartments.^{3,5,7,11,12} The diagnosis may be more challenging in pediatric patients, who may

have difficulty communicating their symptoms or cooperating with examination.^{6,11,12} Once the diagnosis has been made, emergent intervention in the form of fasciotomy to release intracompartmental pressure is typically indicated.^{3,11} The purpose of this report is to describe a case of acute spontaneous compartment syndrome of the upper extremity due to hereditary angioedema (HAE) in a pediatric patient. To our knowledge, only one other case report exists in the literature regarding compartment syndrome caused by HAE, written by Malik and colleagues.⁹

Case Report

Our patient is a 13-year-old morbidly obese female who presented with a 1-day history of pain and swelling of her right hand and forearm. Upon waking the previous morning, she noticed swelling on the dorsum of her right hand,

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which gradually progressed to involve her digits and distal forearm over the course of the day. Her pain became progressively more severe and she was taken to an urgent care facility, where she was evaluated and discharged with instructions for hand elevation. Her symptoms persisted and she presented to an outside hospital emergency department, where she was evaluated and then transferred directly to our facility at Children's Hospital of Wisconsin. Thus, approximately 24 hours had passed from initial development of edema to consultation with our hand surgery team.

The patient's past medical history included a history of spontaneous left foot pain and swelling that had begun the year prior with a waxing and waning course. She was treated by a podiatrist who recommended compression garments and foot elevation. No formal diagnosis was given. She had also experienced recurrent bouts of diffuse abdominal pain with associated nausea, vomiting, and diarrhea, for which she underwent workup by her primary care physician. Ultrasound was obtained, which revealed fatty infiltration of her liver but no further etiology for her recurrent abdominal pain. In addition, she carries a diagnosis of asthma and has intermittent dyspnea. Family history was significant for multiple abdominal surgeries in our patient's father; however, given the estranged nature of her parents' relationship, further details were unknown. The patient's maternal grandmother was currently undergoing workup for rheumatoid arthritis, and her maternal great uncle had been diagnosed with rheumatoid arthritis.

On initial examination, the patient had diffuse edema of her right hand, which extended to her distal forearm (Figure 1). Her hand and forearm were both soft. She had discomfort with flexion but had full passive range of motion of her fingers with only minimal pain. Her sensation was intact and she had palpable radial and ulnar pulses and capillary refill less than 2 seconds. A solitary erythematous plaque was identified on her volar forearm (Figures 2 and 3).

Prior to evaluation by our hand surgery team, both general surgery and vascular surgery had been consulted, and decision was made to proceed with magnetic resonance angiography (MRA), which did not demonstrate any area of vascular obstruction or occlusion. Upon her return from MRA lab, the patient's exam had worsened with increased edema now extending to the proximal forearm, worsening pain and diffuse erythema of the volar and dorsal forearm with the hand held in intrinsic minus position (Figure 3). Due to concern for compartment syndrome, surgical intervention was recommended. It was discussed with the patient and her mother that we did not have a clear etiology for the compartment syndrome, but it was felt that her clinical picture necessitated emergent surgical intervention. Approximately 3 hours after our initial evaluation of the patient, she was taken to the operating room for fasciotomies.

Figure 1. Preoperative photograph of patient on initial assessment revealing diffuse hand swelling extending to the distal forearm.

Figure 2. Volar forearm plaque seen on initial assessment of patient raised our team's suspicion for a rheumatologic component to her presentation.

In the operating room compartment pressures were measured using a Stryker Intra-Compartmental Pressure Monitor (Stryker, Kalamazoo, Michigan). In the volar forearm, dorsal

Figure 3. Patient began to develop worsening edema with hand approaching intrinsic minus position on return from imaging and was subsequently taken to the operating room.

Figure 4. Intraoperative photograph revealing volar fasciotomy incision and carpal tunnel release.

Note. Significant improvement in volar edema is visualized.

forearm, and dorsal hand, the pressure measured in the 40s and 50s, confirming our suspicion of an ACS. Fasciotomy of the volar compartment of the forearm was performed first through a curvilinear incision (Figure 4). Due to the tense swelling and intrinsic-minus posturing of the hand, we also proceeded with fasciotomies to release the interosseous, thenar, hypothenar, and adductor compartments. The dorsal forearm compartment and mobile wad were not released, as they had become significantly softer once the volar compartments were released. At the time of surgery, there was significant edema in the subcutaneous tissues; however, the muscle compartments visualized appeared viable. The hand wounds were loosely closed with nylon sutures (Figure 5), and the

Figure 5. Intraoperative photograph of hand fasciotomy incisions, loosely closed.

Note. Significant improvement in clinical appearance of hand can be seen as compared with preoperative photographs.

volar forearm wound was dressed with a vacuum-assisted closure device (VAC). The hand and forearm were then placed in a protective splint.

Postoperatively she was managed collaboratively with the pediatric intensive care, rheumatology, and immunology services. Additional workup was undertaken to elucidate the cause of her compartment syndrome. Laboratory studies confirmed low C4 levels, C1 esterase functional activity in the equivocal range, and low C1 esterase quantitative levels consistent with a diagnosis of HAE.

Three days after her initial surgery, our patient returned to the operating room, where the volar forearm fasciotomy incision was closed without tension. On postoperative day 5, she was discharged to home following a largely unremarkable hospital course.

While in the hospital, she was started on a plasma-derived C1 inhibitor (C1-INH) used for acute attacks of angioedema. She was discharged with icatibant, a selective beta 2 bradykinin receptor antagonist in case of future attacks.

Eight days after discharge, she was re-admitted with swelling in her back. As a result, it was recommended that she receive home infusions of C1-INH typically used for prophylaxis as a control medication and arrangements were made for a central access port. She has been stable with this regimen, and on follow-up she has been found to have no long-term functional deficit following hand and forearm fasciotomies.

Discussion

HAE is a rare immune disorder characterized by recurrent episodes of swelling that have the potential of involving multiple different sites including submucosal and subcutaneous

tissues of the upper and lower extremities, chest, back and buttocks, small and large bowel, pharyngeal, laryngeal, and orofacial areas, as well as genitourinary tract.⁴ The vast majority of HAE patients experience their first attack prior to age 20 years. Early onset of symptoms, such as in prepubertal patients, portends a worse prognosis. Unfortunately, almost half of all HAE patients will experience an attack involving airway compromise by age 18 years.⁸ As Hofman et al reported in their 2014 study, many patients experience multi-location attacks simultaneously, and a single patient may have attacks involving up to 5 different anatomical locations at different times.⁴ Precipitating factors include trauma and stressful events. What is not clear is why attacks are self-limited, episodic, and occur at different anatomical locations. The unpredictable nature of this disease can significantly affect a patient's quality of life.

HAE is an autosomal dominant disease, though a small subset of patients develop the disease spontaneously and in the absence of a significant family history. The condition most often results from point mutations in C1-INH, a protease inhibitor imperative to normal function of the classical complement pathway as well as at multiple levels in the coagulation cascade and kinin systems.^{2,8}

Three types of HAE exist, types 1 and 2 being the most common and resulting from heterozygous mutations. Type 1 HAE most often involves decreased levels of C1-INH and Type 2 with normal or elevated but nonfunctional C1-INH.⁸ HAE with normal C1-INH, previously known as Type 3 HAE, is thought to be caused by a mutation in Hageman factor, resulting in enhanced bradykinin production.^{1,4,8,13}

When C1-INH comes into contact with the target protease it becomes cleaved, forming a covalent linkage and resulting in a conformational change which renders the target protease nonfunctional.^{2,8} Normally, factor XII facilitates the activation of prekallikrein to kallikrein. This results in the generation of bradykinin from high molecular weight kininogen. Bradykinin binds its B2 receptor on vascular endothelial cells, resulting in enhanced vascular permeability. Absent or poorly functioning C1-INH results in activation of factor XII and kallikrein at an accelerated rate, and thus increased bradykinin production. It is bradykinin that produces the massive edema response seen in HAE patients. Because C1-INH results in activation of the classical complement pathway, C2 and C4 become depleted.^{2,8}

The patient in this report presented with a constellation of symptoms which when considered together could be explained by episodic attacks of HAE. These included recurrent bouts of abdominal pain, nausea, vomiting, and diarrhea, and a history of unexplained swelling in the left foot, consistent with involvement of multiple organ systems as described by Hofman and colleagues.⁴ She had previously been given a diagnosis of asthma, but the intermittent dyspnea she was experiencing could also be another manifestation of HAE.

The episode detailed here is characterized by increasing swelling of the right hand and forearm. As the condition progressed, she had increasing pain with palpation of the hand and forearm, and with passive movement of her fingers. The hand also assumed an intrinsic minus position with the metacarpophalangeal joints being hyperextended and the proximal and distal interphalangeal joints held in flexion. These findings were all consistent with ACS. In their study on compartment syndromes of the hand, Ouellette and Kelly stated that a tense, swollen hand held in the intrinsic minus position was their most consistent clinical finding.¹⁰ The diagnosis of ACS was also confirmed by the use of intracompartmental pressure measurements. An absolute pressure measurement greater than 30 mm Hg (P) or a difference of less than 20 mm Hg between the intracompartmental pressure and the diastolic blood pressure or within 30 mm Hg of the mean arterial pressure (ΔP) is typically considered to be abnormally elevated.^{6,7,11} In our patient, compartment pressures measured in the 40s and 50s, while her diastolic blood pressure measured in the emergency room averaged in the low 60s. These values satisfy both the P and ΔP criteria for compartment syndrome. Also consistent with other reports, our patient demonstrated most significant involvement of the volar compartment in the forearm,¹¹ and with fasciotomy of the volar compartment, there was indirect decompression of the dorsal compartment precluding the need for fasciotomy.⁵

Diagnosis of HAE is made with the identification of low or nonfunctional C1-INH levels. This is done by testing C4 levels, which tend to be constitutively low in the majority of patients, and especially during an attack. If C4 levels do not correlate to suspicion of HAE, the recommendation is for C1-INH level to be checked, and then C1-INH function if necessary.⁸ In our patient, C4 and C1-INH levels were low, consistent with a diagnosis of HAE.

Treatment of HAE is multifactorial. Given the sudden onset of attacks and the potential to involve the upper airway and promote asphyxiation, the recommendation is for all patients with a diagnosis of HAE to have an emergency plan. Although typically used in patients with allergic reactions, epinephrine has not been confirmed as being therapeutic in acute airway attacks related to HAE, though it is not contraindicated. Often patients with HAE are initially and incorrectly treated with steroids and antihistamines, which are ineffective. The mainstays of treatment currently consist of plasma-purified C1-INH, which can be used to treat acute attacks or as long-term prophylaxis, such as Berinert (CSL Behring, King of Prussia, Pennsylvania) and Cinryze (Shire, Lexington, Massachusetts). Berinert has been found to be effective in treating acute facial, laryngeal, and abdominal attacks and can be self-administered.⁸ Cinryze has been studied for prevention of attacks in patients with severe HAE and demonstrated 50% decline in attack frequency, with decreased severity and duration of

attacks as well.⁸ Both medications are generally well tolerated and thus far have been found to have minimal side effects. Ecallantide, a kallikrein inhibitor, is also approved in the United States for treatment of HAE attacks.

In conclusion, the case described highlights HAE as a cause of ACS of the hand and forearm. Although this condition is rare, it could be considered in the differential diagnosis of an otherwise idiopathic compartment syndrome, especially in the presence of seemingly unrelated symptoms such as abdominal or respiratory complaints.

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Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

Informed consent was obtained from the individual whose case is described in this report.

Declaration of Conflicting Interests

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