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Perioperative care of a patient with hereditary angioedema

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Key points

Hereditary angioedema (HAE) is a disorder charecterised by a deficiency or dysfunction of C1 inhibitor. It can manifest as severe angioedema during the preoperative period and can potentially cause fatal airway obstruction. Surgical trauma and airway manipulation are often precipitating factors for acute HAE in the perioperative period.

Abstract

Hereditary angioedema is a rare disorder caused by the congenital deficiency or dysfunction of C1 inhibitor. The deficiency results in recurrent episodes of angioedema, mainly involving the mucosa and skin. The most common clinical manifestations are the result of edema in the subcutaneous tissue, abdominal mucosa, and laryngeal tissue. Laryngeal involvement remains the most serious due to the risk of airway obstruction and fatal asphyxiation. Perioperative management should include maintenance of prophylactic treatment particularly for at risk procedures, early recognition of symptoms, and appropriate symptomatic management including early airway control with endotracheal intubation for signs of laryngeal involvement. Surgical trauma can be a precipitating factor of an acute attack. As such, perioperative prophylactic therapy aimed at preventing an acute episode of HAE may be indicated. We present a 15-year-old, 113 kg adolescent with a history of HAE scheduled for placement of a long term central intravenous access port under general anesthesia. The perioperative care of patients with HAE is discussed and options for prophylactic and pre-emptive therapy reviewed.

Keywords: angioedema; C1 inhibitor; perioperative care; airway management.

Introduction

Hereditary angioedema (HAE) is a rare genetic disorder resulting from the deficiency or dysfunction of C1 inhibitor. It follows Mendelian autosomal dominant inheritance with an estimated prevalence of 1 in 10,000 to 1 in 50,000. Clinical characteristics include recurrent episodes of angioedema, without urticarial or pruritus, which most often affect the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. The majority of patients will have an initial attack during childhood. It accounts for 2% of all clinical cases of angioedema.[2] Although angioedema of the larynx is rare (0.9% of all HAE attacks), it is a life-threatening manifestation of C1-inhibitor deficiency because of the risk of airway obstruction and respiratory failure. Laryngeal involvement generally occurs for the first time in patients in their mid-20s, afflicts approximately half of patients with HAE during their lifetime, and has

been reported as early as age 3. Surgical trauma is a well-recognized precipitating factor of an acute attack. As such, perioperative prophylactic therapy aimed at preventing an acute episode may be indicated. The perioperative care of patients with HAE is discussed and options for prophylactic and pre-emptive therapy reviewed.

Case report

At Nationwide Children's Hospital (Columbus, Ohio), Institutional Review Board approval is not required for presentation and reporting of an isolated case report. The patient was a 15-year-old, 113 kg adolescent with a history of HAE scheduled for placement of a long term central intravenous access port under general anesthesia. Her past medical history was significant for three prior episodes of acute angioedema in the last 12 months requiring emergency department admission and management. These episodes did not appear to have any provocative factor and presented as the spontaneous onset of tongue swelling. She was currently being treated with "on demand" prophylaxis with C1 esterase inhibitor replacement protein (C1INHRP, Berinert®, CSL Behring, Marburg, Germany) which was to be self-administered upon recognition of symptoms of an HAE attack. The replacement protein was administered through a peripherally inserted central intravenous catheter (PICC) line. There had not been a need for endotracheal intubation or other airway instrumentation during these attacks. The attacks were successfully treated with the replacement protein. Prior to placement of the PICC line, emergency department management was complicated by difficulty in placement of peripheral intravenous access. Her family history was significant for mother having C1-inhibitor deficiency and recurrent attacks. Mother had a tracheostomy and a permanent intravenous port for emergency management due to the severity of her attacks. Preoperative laboratory tests included a hemoglobin of 12.3 gm/dL, normal coagulation function (PT, INR, and PTT), INR-1.1, low normal levels of complement fraction C1 inhibitor, and normal levels of C4. The patient had been symptom-free for the past 6 months. She previously had general anesthesia and endotracheal intubation in the distant past for tonsillectomy for which she received preoperative intravenous C1INHRP as prophylaxis and no perioperative complications were reported. Airway evaluation revealed a modified Mallampatti classification of 2 and a normal thyromental distance. The remainder of her physical exam was unremarkable. She received intravenous C1INHRP 1500 units, 30 minutes prior to induction of anesthesia as prophylaxis. On arrival to the operating room, routine American Society of Anesthesiologists' monitors were placed. Pre-oxygenation with 100% oxygen was provided for 3 minutes via a face mask and anesthesia was induced with fentanyl 200 µg and propofol 200 mg. A laryngeal mask airway (LMA) was placed without difficulty. Anesthesia was maintained with isoflurane and pressure support ventilation was instituted to maintain normocarbia. The intraoperative course was uneventful and the LMA was successfully removed when the patient was awake and there was return of airway reflexes. C1INHRP was readily available in the post-anesthesia unit for on-demand treatment if required. The patient was observed in the post anesthesia care unit for 1 hour and was discharged to the inpatient ward. She was observed for a further 24 hours and was discharged home the next day. The remainder of her postoperative course was uncomplicated.

Discussion

In HAE, edema formation is related to reduction or dysfunction of C1 inhibitor, which results in the excessive release of bradykinin and C2-kinin mediators, which in turn enhance vascular permeability, leading to fluid extravasation and the development of angioedema.[3,4] In healthy individuals, C1-inhibitor blocks a number of physiological reactions in the plasma including the coactivation of coagulation factor XII and prekallikrein, the conversion of high-molecular-weight kinin into bradykinin, the breakdown of fibrin by

plasmin, and activation of the complement protein C4 by C1 esterase. Absence of the inhibitor results in the excessive formation of these vasoactive substances and the resultant clinical manifestations.

Three sub-types of HAE have been described. Type 1 HAE, which represents approximately 85% of the cases, is characterized by low levels of both C1-INH antigen levels and functional activity in the serum. Type 2 HAE (15% of cases), is characterized by normal levels of protein C1 inhibitor; however, the protein is abnormal thereby resulting in low functional levels of C1 inhibitor.[5] A third type of inherited angioedema (HAE with a normal C1-INH concentration) is exceedingly rare. It is associated with defects in the gene for coagulation factor XII and the kinin-generating pathways which interface with the coagulation (contact) system.

Clinical manifestations of angioedema include subcutaneous edema, abdominal edematous attacks, and laryngeal edema. Attacks are generally sporadic and unpredictable, but more likely to occur in association with minor trauma, dental procedures (which account for up to half of cases), infection as well as daily activities such as typing and stress. Patients with HAE do not respond to antihistamines, steroids, or epinephrine. The edema develops slowly over a period of up to 36 hours and resolves 1 to 3 days later.[6-8] The average HAE patient has approximately 20 attacks per year. Subcutaneous attacks can occur anywhere on the body, but show a predilection for the extremities, face, and genitalia.[9] Abdominal attacks involving the gastrointestinal tract, which are experienced by up to 93% of HAE patients, manifest as cramping pain, nausea, vomiting, and diarrhea.[7,10-12] The abdominal attacks may be extremely difficult to differentiate from an acute surgical abdomen. As a result, many patients present for anesthetic care during surgical interventions aimed at differentiating the cause of the abdominal pain.[13-16] However, the most dangerous manifestation of HAE is upper airway obstruction, which may occur at some point in the disease process in up to one-half to two-thirds of patients.[7,11,12]

The manifestations of HAE may begin during childhood with rare reports of attacks occurring during infancy.[7] Abdominal pain is the most common symptom in children, accounting for 40-80% of presentations. Respiratory attacks are less common in children, but when respiratory involvement occurs, the small airway diameters result in rapid progression of symptoms. As such, airway management may be more challenging, especially in the setting of acute upper airway obstruction. Diagnosis can be difficult in young children because C4 and C1-INH concentrations may not reach adult levels until 3 years of age. Young children with a high clinical suspicion of HAE should be treated with the assumption that they have the disease regardless of laboratory values.

HAE is diagnosed by the presence of specific abnormalities in complement levels, in the setting of a suggestive clinical history of episodic angioedema without urticaria. A family history of angioedema strongly supports the diagnosis, but it is not an absolute requirement. C4 (the natural substrate for C1 esterase), C1 inhibitor antigenic levels, and C1 inhibitor functional levels are recommended as initial screening tests. If C4, C1-INH antigenic, and C1-INH functional levels are all low, then the patient may have either type I HAE or acquired angioedema. If C4 is low, C1-INH antigenic levels are normal or elevated, and C1-INH function is normal, then the patient may have an autoimmune condition or an inherited deficiency of C4. If C4 is low, C1-INH antigenic levels are normal or elevated, and C1-INH function is low, then the patient has type II HAE. With this same combination of laboratory values (low C4, normal or high C1-INH antigenic level, low C1-INH function, and normal C1q), it is also possible that the patient has a rare variant of acquired C1 inhibitor deficiency. If C4, C1-INH antigenic and functional levels, and C1q are all normal and there is a suggestive clinical history, then C1-INH antigenic levels and C4

should be measured during an attack of angioedema. If these are also normal during attacks and there is a family history of angioedema, then the patient may have HAE with normal C1-INH (disorders caused by defects in factor XII or by an unknown mechanism). The diagnosis is confirmed either by demonstrating a factor XII mutation, or by demonstrating that symptoms are not improved by high-dose antihistamine therapy. In the absence of family history, angioedema caused by a medication or angioedema of undetermined cause (idiopathic angioedema) may be the primary diagnosis.

Once a diagnosis of HAE is confirmed, testing of immediate family members is strongly recommended. In children younger than one year of age, C1-INH levels are normally 30-50% lower than adult levels and thus C1-INH levels and function are difficult to interpret. Both false positives and false negatives may occur in infants.[17] C4 levels are also variable in this age group. Thus, the diagnosis in infants is confirmed either by repeating the studies after one year of age or occasionally by genetic typing.[3,18]

Education is the most important intervention for newly diagnosed patients. The affected individual and his/her family members should be involved. All first-degree relatives of the patient should be educated about the disease and offered diagnostic testing for HAE. Although the triggers vary among patients, measures such as avoidance of trauma, particularly to the face and upper respiratory tract, recognition and prompt treatment of oral and dental infections and avoidance of other triggers are extremely important management strategies. Specific medications known to trigger angioedema include estrogens and angiotensin-converting enzyme inhibitors. Patients should be equipped with a medical information bracelet or necklace identifying the condition, details of prophylaxis, and a written plan for treatment of acute attacks for use in emergency department care. Attacks of HAE with airway or laryngeal involvement are potentially life threatening. In contrast, gastrointestinal attacks can range from mild to severe, but usually resolve without serious complications.[19] Cutaneous attacks are not associated with substantial morbidity, although repeated episodes are painful and disruptive to a normal life-style.

Laryngeal involvement is the most serious manifestation of acute HAE and needs to be evaluated and managed in a timely manner with expertise in airway management readily available. Progression can rapidly lead to total airway obstruction while distortion of upper airway anatomy may preclude standard direct laryngoscopy and endotracheal intubation. In patients with impending respiratory failure, immediate transportation to the operating room with the involvement of the otolaryngology service is recommended. Laryngeal attacks, moderate to severe gastrointestinal attacks and severe cutaneous attacks should be treated with one of first line therapy medications which include Human plasma-derived C1 inhibitor concentrate (C1INHRP), icatibant (bradykinin B2 receptor antagonist) or ecallantide (kallikrein inhibitor).[20,21] In the absence of availability of these first line agents and based on the severity of the attack, the second line of management may include the administration of fresh frozen plasma. Less severe attacks, particularly those that do not involve the airway can be managed by supportive care, waiting for spontaneous resolution.

Pharmacological prophylaxis is used both for short term prophylaxis during anticipated procedures and periods of stress or long term prophylaxis for reduction of attack rates and severity. Short term prophylaxis is administered for high risk dental, medical and airway procedures (intubation and LMA placement) and for procedures that have known to trigger angioedema in the past. Commonly available options include androgens and/or C1 esterase inhibitor replacement protein (C1INHRP). C1NHRP is usually administered as an infusion as close to the procedure as possible, preferably within an hour as was done in our patient. Danocrine (Danazol®) is the androgen that is used most commonly.

It is often given as a premedication up to 5 days before and 5 days after the procedure. Both of these medications have an adverse effect profile that should to be addressed and individualized for every patient. Long-term prophylaxis may be given to decrease the overall number of attacks; however, with the availability of efficient on-demand therapies (C1 inhibitor, icatibant, or ecallantide), long-term prophylaxis is added for those patients whose disease is not satisfactorily controlled by on demand therapy alone or for whom access to on demand therapy is limited.[16] These options may include attenuated androgens administered regularly, tranexamic acid(TA) administered regularly or C1INHRP administered regularly, which is usually reserved for patients who are not experiencing adequate control with one of the other options or from on demand therapy.[16] There are limited data to prove the safety of the various modalities that are available for prophylaxis. Based on previous experience and the availability of newer first line drugs, androgens should be avoided for long term prophylaxis in prepubertal children. TA or regularly scheduled C1-INH infusions are safer options. In children especially, the availability of on-demand therapies for acute attacks has greatly reduced the requirement for long-term prophylaxis.

Conclusions

Anesthetic management for patients with HAE should include identifying risk factors for acute attacks, minimizing airway manipulation, and avoidance of endotracheal intubation if possible. An LMA may be less invasive and cause less edema than endotracheal intubation. Given this consideration and the type of surgical procedure, we chose to use an LMA in our patient. As surgical trauma and airway manipulation are recognized precipitating factors, some form of prophylactic therapy is generally suggested. The options for perioperative HAE prophylaxis are listed in table 1. It is extremely important to be aware of the patient's clinical presentation, successful treatment strategies in the past, and current management including prophylaxis. Based on this information it is important to device an acute angioedema treatment strategy including airway management and pharmacological treatment. Specific medications known to trigger angioedema include estrogens and angiotensin-converting enzyme inhibitors. Given the potential for an acute attack to develop postoperatively, ongoing monitoring of the patient's clinical status for up to 24 hours may be indicated.

Authors	*Patients number*	*Prophylaxis*	*Outcome details*
Grant JA et al[22]	41 (91 procedures)	C1 INHRP	Prevented acute of HAE in 98% of patients.
Farkas H et al[23]	12	Danazol	No reported cases of postoperative HAE.
Sheffer AL et al[24]	14	Tranexamic acid	No reported cases of postoperative HAE.

Table 1. Options for perioperative HAE prophylaxis

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