Review Article

Hereditary Angioedema in Pediatric Age: An Overview

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Abstract

Introduction : Hereditary angioedema is an autosomal dominant inherited disease that leads to either dysfunction or low level of a circulating inhibitory protein called C1 esterase inhibitor. This condition is characterized by the localized swelling of parts of the body and can be life-threatening if it affects the larynx. **Objectives :** We aimed to review the recent literature on hereditary angioedema, along with its latest management. **Methodology:** PubMed database was used for articles selection, papers on were obtained and reviewed. PubMed database was used for articles selection, and the following keys terms: Hereditary angioedema, Bradykinin-mediated angioedema, C1 esterase inhibitor, and emergent therapy. **Conclusion:** Hereditary angioedema is a self-limited, localized swelling of the dermis, subcutaneous tissues. Or it is a submucosal tissue that is caused by fluid which leaks into the interstitial tissue. It is mediated by the vasoactive substance bradykinin and can be classified into three types depending on the pathophysiology. Patients usually present with swelling of the eyelids, lips, and tongue. However, immediate airway protection is required because life-threatening laryngeal edema may occur. If applicable, aggressive supportive care and avoidance of triggers are in the treatment process. In acute cases, hereditary angioedema is treated with C1 inhibitor (C1-INH) concentrate, bradykinin-B_2-receptor antagonists, or kallikrein inhibitors.

Keywords: Hereditary angioedema, Bradykinin-mediated angioedema, C1 esterase inhibitor, factor XII, kal-likrein, C1-INH

Introduction

Hereditary angioedema (HAE) is a condition characterized by recurrent episodic attacks of edema without urticaria or pruritus. Although self-limiting, it can lead to dangerous consequences. For instance, laryngeal edema can result in asphyxiation, and abdominal angioedema attacks can lead to unnecessary procedures and narcotic dependence due to severe pain. Also, a disfiguring and disabling factor is the cutaneous attacks. [1, 2] Low levels of the plasma protein C1 inhibitor (C1-INH) can cause an autosomal dominant disease which, including the bradykinin, leads to the unchecked activation of the classic complement pathway and other biochemical systems system. It affects 1 in 60,000 individuals, males and females equally. HAE leads to around 15,000–30,000 ER visits per year in the US. [1, 3] In this review, we will talk about the pathophysiology, types, epidemiology, clinical features, diagnosis, and management of this condition.

Methodology

PubMed database was used for articles selection, and the following keywords used in the search: Hereditary angioedema, Bradykinin-mediated angioedema, C1 esterase inhibitor. Regarding the inclusion criteria, the articles were selected based on the inclusion of one of the following topics; hereditary angioedema, pathophysiology, diagnosis, clinical features, or treatment. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Review

Hereditary angioedema can be classified into three types as seen in (Table 1). Low plasma levels of a normal C1 inhibitor (C1-INH) protein characterizes Type I HAE, which means that one allele gene of the protein has an abnormality. Type II HAE is defined by the presence of normal or elevated levels of a dysfunctional C1-INH, reflecting that one of the gene alleles is abnormal in the sense that it produces a defective

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protein, unlike the first type. Type III HAE was identified as an estrogen-dependent form of angioedema which occurs mainly in women that have, whose levels of C1-INH are normal, functional, and quantitative. No clear pathophysiological mechanism has been described for the latter type. [4, 5]

Table 1: Hereditary Angioedema Types

	Type I	Type II	Type III
C1-INH level	↓	Normal	Normal
C1-INH function	↓	↓	Normal
C4 level	↓ (During the attack)	↓ (During the attack)	Normal
C1q level	Normal	Normal	Normal

Pathophysiology

The swelling that occurs in HAE results from excessive production of bradykinin, a potent vasodilatory mediator and it enhances vascular permeability. During an acute episode, plasma levels of bradykinin can be as high as seven times the normal levels. Unlike other types of angioedema, histamine and mast cells mediators are not involved, which explains the lack of response to antihistamines. The drastic increase in bradykinin level is linked to the reduction, either in number or function, of C1-INH proteins. [4, 6] C1-INH is an acute-phase reactant and a member of the serine protease inhibitors family (serpin family). Through the inhibition of kallikrein and FXIIa, C1-INH efficiently controls bradykinin generation. [3, 5] It regulates many plasmatic cascade systems, such as the classical pathway of complement, fibrinolysis, and the intrinsic coagulation system.

Moreover, the initial molecular events in the genesis of an attack are not entirely understood. It is largely thought that the local activation of factor XII and plasma prekallikrein on endothelial cell surfaces is important in initiation. The activation of factor XII, possibly by phospholipids released from damaged cells, is believed to be a leading mechanism, possibly via heat shock protein 90 that is generated during cell stress. Factor XIIa and kallikrein catalyze the cleavage of high molecular weight kininogen (HMWK) by kallikrein, with the release of bradykinin. C1-INH normally plays a role in limiting bradykinin production by inhibiting both kallikrein and factor XIIa. In HAE, due to C1-INH being either deficient or dysfunctional, bradykinin production is relatively unchecked. [4, 5, 7]

During the attack, it can be noted that the levels of C4 protein are reduced. C1-INH protein is a potent inhibitor of the function of C1 protein in the classical pathway of the complement system. Normally, C1 protein cleaves C4 protein as a part of the classical pathway. While it is thought that low C4 levels are not related to the pathogenesis of HAE, it can be used as a sensitive test for the screening of HAE during attacks. [2, 6]

Triggers

Patients suffering from HAE report a variety of triggers for the episodes. Mental and physical stress and dental procedures are the most common. However, many patients may not report any event preceding the attack. Physical triggers include all traumas, ranging from mild to severe. These include, but are not limited to, dental procedures, piercings, sexual intercourse, and even bicycle riding. Adding to that, infections have also been known to be frequent triggering factors. Gastrointestinal attacks have been linked to *H. pylori* infections and its eradication has been proven to lower the frequency of attacks. [1, 7, 8] Additionally, estrogen-containing medications and ACE inhibitors can precipitate the attacks, but not ARBs. [2, 7]

Clinical Manifestations

Patients with HAE, during childhood, they have some episodic attacks that begin and become more severe as the patient ages are reported. Approximately 40 percent of patients experience their first HAE attack before age 5, and 75 percent, by age 15. In childhood, attacks usually are mild, infrequent, and they commonly manifest in an abdominal form. In family history, HAE is usually found, but it is not necessary as spontaneous mutations may occur. [1, 2]

Attacks most often affect the skin, manifesting as non-pitting edema of the face, hands, feet, legs, or buttocks without urticaria and pruritus; GIT, manifesting as diarrhea, vomiting, and a colicky abdominal pain that may mimic an acute abdomen; and the upper airway that may result in upper airway obstruction, a true emergency. Many episodes involve only one region. However, multiple regions and systems can be involved in a single episode. The attacks are usually self-limited, resolving within 2-5 days from the onset. Attacks are often preceded by a tingling sensation in the area that will swell 1-2 hours before the swelling starts. [7, 9]

HAE's physical symptoms are overt, noninflammatory swelling of the skin, and mucous membranes. The edema can localize under the skin at any site and so, typical involvement includes the hands, face, legs, arms, genitalia, and also, the buttocks. Tension vesicles or bullae may develop in some patients that have severe edema. If the only active problem of the patients is HAE, it should not make the patients febrile. Most abdominal attacks are not associated with peritoneal signs or an elevated white blood cell count. However, during a severe abdominal attack, a rise in neutrophils has been reported. [1, 7, 9]

Associated Conditions

Although most Individuals suffering from HAE are otherwise healthy, they are at increased risk of developing depression, pancreatitis, celiac disease, and other autoimmune disorders. Associated autoimmune diseases include thyroiditis, SLE,

Sjögren's syndrome, inflammatory bowel disease, glomerulonephritis, and non-rheumatoid arthritis of the hips and wrists. [3, 6] Healthy lifestyle patterns are considered one of the health-related practices that affect the performance and the future health of the youth. [10-14]

Evaluation and Diagnosis

Patients that have or pruritus, which lasts from two to five days without any form of treatment, or recurrent episodes of angioedema without urticaria are suspected to have HAE. In diagnosis, unexplained recurrent episodes of self-limited, colicky, abdominal pain, or laryngeal edema are shown. Angioedema episodes in the absence of ACE inhibitors, NSAIDs, or history to suggest an allergic cause, but a family history of angioedema would be more likely in HAE patients. [4, 5, 7] The diagnosis of HAE is not straightforward, especially if it is the first presentation. This is evident by the fact that there is a significant delay (up to 16 years) between the first symptoms and the final diagnosis. [4] The diagnosis is largely based on the suggestive history and physical findings during episodes, combined with consistent results from at least two sets of complement studies. A family history of angioedema strongly supports the diagnosis, but it is not required. Genetic testing is not required to confirm the diagnosis of HAE. Once a diagnosis of HAE has been made, testing of the patient's family is strongly recommended. The recommended studies are the same as those used for screening: C4, C1-INH antigenic levels, and C1-INH functional levels. [4, 5]

During the gastrointestinal attacks, there is no need for imaging studies for patients already known to have HAE with no alarming signs. If there are alarming signs (peritoneal irritation, fever) it is advised to do acute abdominal series and ultrasonographic studies to rule out other causes of acute abdomen. The same rule applies to patients who are not known to have HAE. [3, 6]

Approach to Management

Treatment of HAE consists of the management of acute attacks and prophylactic therapy. The treatment of acute attacks aims to reduce the severity and duration of the episode. In contrast, prophylactic therapy targets to prevent the occurrence or reduce the frequency and severity of attacks and to prevent attacks during anticipated stress situations. The goal of all the therapies is to reduce and restore the regulation of bradykinin levels. [15]

Because of its rarity, as soon as a patient has been diagnosed with HAE, a plan for emergency care should be put in place, with particular focus on how the patient should seek care in the event of a laryngeal attack. Patients should be educated that any swelling involving the airway is life-threatening and should be treated in the ER. Patients should also be equipped with forms that summarize the treatment for acute attacks of HAE, since clinicians in the emergency setting may not be familiar with the condition or its treatment. [9, 15]

Acute Management

During the acute attack, four medications are considered as first-line therapy for HAE. These include plasma-derived C1-INH, recombinant human C1-INH, icatibant (a synthetic bradykinin B_2-receptor antagonist), and ecallantide (a plasma kallikrein inhibitor). These medications should be administered within the first few hours of the attack. It is advisable to give one of these drugs to patients for self-administration. However, this should be done on an individual basis, such as those who may not be able to receive proper treatment for a few hours after the attack. It is of note that the usual drugs of anaphylaxis, which is on top of the differential diagnosis for HAE, will not work at all. So, always consider the possibility of HAE when patients present with signs and symptoms of anaphylaxis but do not respond to the usual treatment. [4]

When there is suspicion of laryngeal attacks, prompt assessment of the airway is crucial for the patient's survival. Intubation must be attempted immediately if there are signs of threatening airway collapse or difficult intubation, i.e. stridor or signs of respiratory arrest. If endotracheal intubation cannot be achieved and the patient is arresting, summon a clinician that is experienced in attempting tracheostomy. Once patients are intubated and the airway is secure, proceed to the first-line therapy and transfer the patient to the ICU. [9]

Since most gastrointestinal attacks mimic an episode of an acute abdomen, clinicians must always ascertain whether the patient has HAE or not. If the patient has a history of HAE, then the focus should be on whether this episode is due to HAE or an actual cause of an acute abdomen. The most useful signs are peritoneal signs and fever. If these are present, it is more likely to be a case of an acute abdomen. When in suspicion, imaging (acute abdominal series, US) might help determine the diagnosis. Monitor the hydration status of the patient, and restore fluids when seems fit. For the pain, it is usually not relieved by over-the-counter medications, and opioids should be administered to relieve the pain. [15] Cutaneous attacks are not life-threatening, but they result in great physical dysfunction. Patients may, therefore, miss a few days of work or school because of them. Prompt treatment is required as to not impede the patient's life any longer. [2]

Prophylactic Treatment

As aforementioned, the goal of prophylactic treatment is to reduce the frequency and severity of attacks in the future. After the diagnosis is established, family testing should be sought after. Education about the possible triggers is of paramount importance, as the patient is required to take prophylactic measures, for example, before dental procedures. Since most patients' conditions are not severe nor frequent, prophylactic drugs should be given on an individual level. It is far more important to educate the patients on their possible triggers and provide them with the first-line therapy to be used during acute attacks. [16, 17]

Furthermore, there are three options for prophylactic treatment in those whose condition is severe or frequent. These are plasma-derived C1-INH (pdC1-INH) concentrate, attenuated androgens, and anti-fibrinolytic agents. Regular injections of pdC1-INH are safe and effective. Lanadelumab, a monoclonal antibody to kallikrein, is a novel drug that could replace the regular injections of pdC1-INH. Both of them run into the issues of injection-induced lipohypertrophy. An effective therapy for prophylaxis which is an attenuated androgen is Danazol. However, it runs with the issues of long-term androgen administration and may lead to significant side effects, such as acne, hoarseness, breast size decrease in females and increase in males, and rarely, liver cancer. Antifibrinolytic agents include tranexamic acid and epsilon aminocaproic acid. These agents are less effective, but tranexamic acid can be used safely in pregnancy in the absence of pdC1-INH or in cases where it is not tolerable. [4, 7, 16] As it has been stated earlier, infections are potent triggers. In the case of *H. pylori*, the eradication of this infection will possibly eliminate the gastrointestinal attacks or, at the very least, reduce the frequencies. Always be on the lookout for possible triggers and eliminate them. [7]

Conclusion

In the past, patients with hereditary angioedema often had anxiety, depression, and disruption of work, school, and daily life. The improvement of our understanding of the pathophysiology of hereditary angioedema and classification leads to the investigation of new and targeted therapies. On-demand, first-line treatments have incrementally enhanced patients' safety and quality of life. Effective and safe prophylactic treatments now provide a pathway toward a normal life. It can be safely assumed that a further increase in our understanding of the pathogenesis of angioedema formation and the link to precipitating events may further improve the treatment of the next generation that is suffering from this condition.

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