ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Hereditary angioedema with C1 inhibitor deficiency: traps in the diagnosis, treatment, and understanding

Angioedema hereditário com deficiência do Inibidor de C1 – Armadilhas no diagnóstico, tratamento e compreensão

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ABSTRACT

Hereditary angioedema (HAE) is a rare, underdiagnosed condition with high morbidity and mortality due to the characteristics of its clinical presentation. HAE differs from histaminergic angioedema by not responding to antihistamines, corticosteroids, or epinephrine. Therefore, early diagnose is crucial to initiate adequate therapy. HAE is suspected in patients with a clinical history of unpredictable and recurrent episodes of edema. When laryngeal edema occurs, it can lead to death from asphyxiation if not treated properly. We report the case of an 18-year-old patient previously diagnosed with HAE type 1 who sought emergency care during an angioedema attack. However, the patient was not taking any specific medication and did not have an action plan to manage attacks. This case highlights the importance of increasing awareness about the disease, educating patients and their families about the disease and potential attacks, and ensuring access to medications.

Keywords: Emergency care, angioedema, hereditary angioedema, hereditary angioedema types I and II, respiratory failure.

RESUMO

Angioedema hereditário (AEH) é uma condição rara, subdiagnosticada e de elevada morbimortalidade, devido ao caráter de suas manifestações clínicas. O AEH se diferencia do angioedema histaminérgico por não responder aos anti-histamínicos, corticosteroides ou epinefrina. Por esse motivo, é extremamente importante o diagnóstico dessa situação, a fim de instituir a terapia adequada. Tal afecção deve ser suspeitada a partir da história clínica de episódios imprevisíveis e recorrentes de edema que quando se manifesta sob a forma de edema laríngeo, pode levar a óbito por asfixia, se não for adequadamente tratado. Relatamos o caso de uma paciente de 18 anos que, apesar de previamente diagnosticada com AEH tipo 1, ao procurar um serviço de emergência devido a crise de angioedema, não dispunha de medicação específica nem apresentou plano de ação com as opções possíveis para crises. Este caso reforça a necessidade de maior divulgação da doença, além da conscientização de pacientes e familiares sobre a doença e eventuais crises, assim como o acesso as medicações.

Descritores: Emergência, angioedema, angioedemas hereditário, angioedema hereditário tipos I e II, insuficiência respiratória.

Introduction

Hereditary angioedema (HAE) with C1-INH deficiency is an autosomal dominant genetic disease that affects around 1:67,000 people.1 There is excessive activation of the contact (kinin–kallikrein), coagulation, and fibrinolysis system, with consequent increase in bradykinin (BRA), which is the main mediator.[1,2]

Clinical manifestations may have onset during the first or second decade of life. Patients present with recurrent and transitory angioedema (duration

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2- 5 days), without hives, involving the mucosa or submucosa of any part of the body, but primarily the extremities, face, genitalia, and digestive and respiratory tracts.[1,3] Episodes typically do not respond to treatment with antihistamines, corticosteroids, and epinephrine.[4] The most common reasons for seeking at emergency departments include angioedema of intestinal loops, which presents with strong abdominal pains and can lead to unnecessary exploratory laparotomies as a result of the difficulty in establishing diferencial diagnosis in order to rull out other causes of surgical acute abdomen,[5] and laryngeal edema, which is the most serious event, because of the possibility of progression to asphyxia and death if not promptly reversed.[6,7]

Laryngeal edema crises demand particular attention and rapid access to an emergency unit must be guaranteed, to enable early treatment. Laryngeal angioedema must not be mistaken with other causes of angioedema often seen at emergency services, which are mediated by histamine.[4,7] Warning signs that indicate the need for immediate intervention include feelings of a tight chest, discomfort in the oropharynx, and/or difficulty swallowing.[6]

Despite advances in understanding of the disease in recent years, significant delays in diagnosis are still described, confirming that this condition remains unknown to many health professionals.[8,9] Lack of knowledge about the disease has been linked to unnecessary invasive procedures and incorrect treatments, worsening patient quality of life and increasing morbidity related to the disease.[9]

Case report

The patient was an 18-year-old, Black, unmarried female with recurrent angioedema involving limbs and genitalia from 2 years of age that later progressed to include recurrent abdominal pains. Episodes receded spontaneously in 3 to 5 days. The crises increased in frequency after menarche, at 11 years, and were associated with emotional stress. There was a family history of HAE; both her father and a brother had a history of recurrent angioedema and the brother had died from laryngeal edema at the age of 23. When the patient was 13 years old, laboratory investigation identified reduced C4 and C1-INH levels and she was diagnosed with HAE with quantitative C1-INH deficiency.

Long term prophylaxis was initiated with antifibrinolytics, but satisfactory control of symptoms was not achieved, and they were withdrawn and replaced with attenuated androgens, despite the patient's age. The patient was also prescribed plasma derived C1 inhibitor specifically for the crises, but she was unable to obtain access to it. She was also instructed to avoid possible trigger factors, such as taking estrogens (oral contraceptives), trauma, and, as far as possible, emotional stress. An action plan for HAE crises was provided and she was instructed to seek emergency medical care in the event of crises.

At the age of 18 years, the patient was using long-term prophylaxis irregularly and during a period of considerable emotional stress she suffered a sudden episode of oropharyngeal discomfort with dyspnea and was taken to emergency by family members. Based on a clinical suspicion of laryngeal edema and not having been told about the crisis action plan, the care team administered antihistamines and intravenous corticosteroid and told her to stay for observation. Despite this recommendation, the patient left the emergency service and later developed acute respiratory failure, followed by convulsive crisis, and was taken back to emergency. She was subjected to oral endotracheal intubation (OEI) to try and provide ventilatory support. At this point, the local team contacted the specialists and were informed of the diagnosis of HAE. The hospital did not have especific crisis drugs available or even fresh frozen plasma. Despite the local team's efforts, the patient died.

Discussion

Hereditary angioedema is a complex condition that has a considerable impact on the quality of life of patients and their families. This disease should always be considered in patients with a history of recurrent edema without hives, especially if there is a family history of similar crises. It can present with sudden episodes of angioedema involving any part of the body.[1,2] It is estimated that approximately half of HAE patients will have at least one episode of laryngeal edema in life.[6] As seen in the case presented here, airway compromise is the most important medical emergency, with the potential to cause death and requiring early intervention.[4,7] In this scenario, faced with involvement of the upper airways, uvula, or tongue, the first step is to guarantee airway patency. Patients at imminent risk of asphyxia must immediately undergo OEI.[1,4,7]

In a case of suspected HAE crisis, particularly if there is involvement of the face and abdomen, patients

should always be encouraged to seek an emergency service.[7] It should be pointed out that during hospital admission, it is not uncommon for diagnostic confusion to occur with other conditions that also present with angioedema, such as those caused by histamine-mediated anaphylactic reactions. Unlike histaminergic angioedema, HAE does not respond to antihistamines, corticosteroids, and adrenaline.[4,7] This failure to respond to conventional treatment and a lack of knowledge of the treatment options available for HAE and how to access them underscore the need for better dissemination, particularly among emergency professionals.[4,9,10] Once HAE has been diagnosed, an action plan should be prepared and given to the patient, attempting to significantly reduce the extent to which the disease interferes in the daily activities of patients and their families, in addition to facilitating dealing with crises.[11] Against medical advice, the patient did not comply with the recommended regular use of medication and did not have her action plan with her on the day she had the crisis. Unlike what actually happened in this case, the action plan should be shown to the emergency care team.[11] As a result, the patient was given drugs that are not indicated for management of an HAE crisis.

The crisis action plan is prepared by the health professionals involved in caring for the patient with HAE and is designed to help the emergency team make treatment decisions.[2,11] The majority of crises are spontaneous, but some triggers have been described and so to prevent them patients are instructed about individual conditions that they should pay particular attention to for management of the disease, such as surgical and dental procedures, pregnancy, avoiding use of antihypertensive medications, certain oral hypoglycemics (gliptins), and medications containing estrogen, as part of a process known as "shared decision making".[1,12] Assessment of the frequency and severity of crises is intended to identify any need for long term prophylaxis to prevent recurrence, and continuous monitoring of these patients is necessary.[1,2,12]

Hereditary angioedema significantly compromises patients' quality of life and these measures are intended to reduce the significant morbidity and mortality associated with HAE, since a strategy based on careful treatment of crises and crisis prevention is essential for adequate management of patients.[11]

One recent study found that digital action plans help to reduce care delays in emergency situations and enable administration of appropriate treatment. Moreover, having a specialist available to communicate with the patient and the emergency team during crisis episodes helps with treatment adherence and facilitates management of this condition that is still unknown to many health professionals.[12,13] In the case described, even though a specialist and an action plan were available, because the patient and her family did not show the action plan to the emergency team, there was inadequate communication at the initial point of care, delaying knowledge of the diagnosis and measures essential to reverse the situation.

In addition to all of the aspects already mentioned, the unpredictability of crises has been linked to significant psychosomatic harm to HAE patients.[14] Despite all the family's efforts to avoid conditions that caused the patient emotional discomfort or stress, she reported considerable emotional stress, which is a known trigger factor for HAE crises. Living with a rare disease that is still unknown to many people, compounded by the difficulties of accessing crisis medications are the greatest challenge faced by these patients.[9,11]

Several studies have assessed the impact of emotional disorders on the population with HAE.[14,15] One of them, conducted in several countries, reported that anxiety and depression were described in 38% and 17.4% of patients respectively.[15]

Savarese et al. also linked emotional disorders and lack of knowledge to poor adherence to treatment.[16] According to Graffigna et al., when a patient is given an important diagnosis, he or she may not be as actively engaged in their treatment because of the emotional instability inherent to the process.[17]

The psychological processes associated with HAE are extremely important because they can act as triggers of crises and interfere in disease management by affecting patients' quality of life. Depression and anxiety have not only been described as frequent comorbidities caused by the disease, but are also listed as important crisis trigger factors.[17] A growing body of research has linked depression to angioedema via common neurobiological factors.[18]

Stress is described as the principal trigger and also appears to modify disease activity.[19] According to Felger et al., chronic exposure to inflammatory cytokines can lead to persistent changes to neurotransmitters and consequently to psychiatric disorders, such as depression.[20] Additionally, psychic stress alters the functional activity of the

complement cascade, intensifying the inflammatory process. Increased production of bradykinin in stressful situations may explain the correlation between dysfunctions of the autonomic nervous system and activation of the contact/complement system.[21] Metabolites of bradykinin, such as des-arg-9-bradykinin and IL1beta, which are responsible for increased vascular permeability, have also been associated with depression in experimental models.[18] Therefore, it is essential to study the interface between immunopathological disorders such as angioedema and these emotional disorders.[18]

Another disorder being studied currently is alexithymia, or augmented stress perception, which is more frequent among children and young adults with HAE. People with alexithymia have difficulties coping with stress and with recognizing and regulating emotions. One study reported that alexithymia affects 84% of children with HAE-C1-INH, and may also be associated with severity of the disease.[22] However, these data were not confirmed in adults, according to Savarese et al.[16]

These findings demonstrate how important managing psychological wellbeing is for the course of HAE. Its interference in the disease should be assessed individually, and it is very important to conduct periodic assessments of the frequency and severity of symptoms and of the efficacy of prophylactic treatment, when this is prescribed. A quality-of-life questionnaire such as the Hereditary Angioedema Quality of Life Questionnaire (HAE-QoL) is routinely administered, to achieve early identification of disease control and of the impacts of the disease on patients' daily lives and any possible associated psychiatric disorders.[11,23]

Furthermore, with this objective, specialist centers in several countries have set up non-profit support groups for patients with HAE, with the objective of providing support and representing patients' interests, in order to reduce morbidity and potential deaths, when not treated adequately. In Brazil, the Brazilian Hereditary Angioedema Association (Abranghe - Associação Brasileira de Angioedema Hereditário) represents this group of patients, working with education about recognition of the disease and crisis triggers, screening of family members, and lobbying for public policies, since access to expensive medications is a challenge that is faced constantly.[11]

Access to/availability of medications such as plasma derived C1 inhibitor or B2 bradykinin receptor inhibitor is essential for adequate management of an HAE crisis.[2,4,7,11] However, when these are not available, fresh frozen plasma replacement is recommended (2-4 units).[2,4,7,11] In the case described here, when the emergency team communicated with the assisting physician, they were informed of the ideal treatment options for management of the crisis, but the unit did not have these options available and so OEI was indicated. When crisis medications are not available, invasive ventilatory support should be provided immediately, to prevent rapid progression to asphyxia.[4,7,11] The procedure should preferably be performed by a qualified medical professional, since any mechanical manipulation of these patients' airways could provoke exacerbation of the edema, and the airway is generally difficult to access.[7,24] In some cases, tracheostomy or cricothyroidotomy can be attempted to speed up ventilatory support in order to stabilize the patient.[7,24]

According to current guidelines, it is recommended that patients should keep at least two doses of medication at home in case of crises.[2,11,25] All of the medications approved for crises in Brazil permit home self-administration and are of fundamental importance for early treatment of crises and prevention of fatal events, avoiding exposing patients to health care services that are still substandard in our country. However, because of their high cost, a large proportion of patients in Brazil cannot access these drugs and continue using inadequate treatments, both for prophylaxis and to treat crises.[11] In this scenario, it is important that public policies be adopted to improve access to especific medications by including them on the Ministry of Health's therapeutic guidelines clinical protocol. In the absence of these drugs, the emergency physician must be aware of the option of treating crises with fresh frozen plasma, in addition to being well trained in airway management. However, in some regions of Brazil, access to transfusion of plasma is not available, as in the case described. Therefore, we highlight the need to make specific, effective, and self-administrable treatments available.[11] Moreover, patients should be educated about possible trigger factors, regular use of prophylactic medication, when appropriate, when to seek emergency care to treat crises, and the importance of showing the emergency physician the action plan with treatment guidelines and the specialist's contact.[2,4,11,15]

Hereditary angioedema is a rare condition that causes considerable morbidity and can be fatal. Although it is better publicized and better known among specialists, a lack of knowledge among

pediatricians, general practitioners, and emergency physicians and underdiagnosis are still obstacles that need to be overcome.[9,10] Hereditary angioedema is a treatable disease and so we hope that over the coming years knowledge about it will spread, both among health professionals and patients and their families, so that more positive outcomes can be achieved.

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