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Hereditary angioedema with normal C1-inhibitor levels: a rare case report

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RESUMO

Hereditary angioedema (HAE) is a rare, hereditary disease and its manifestations may be life-threatening. It differs from histaminergic angioedema since it shows different underlying mechanisms and, therefore, does not respond to antihistamine or adrenaline treatment. The authors present a case of hereditary angioedema to highlight the importance of prompt referral to the allergy and clinical immunology for further evaluation and correct diagnosis in case of suspicion of this entity.

Keywords: Hereditary angioedema; Normal C1-inhibitor; FXII gene.

INTRODUCTION

Hereditary angioedema (HAE) is a rare and possibly life-threatening disease characterized by recurrent episodes of deep dermal/subcutaneous or submucosal tissue swelling that results from localized increased permeability of blood vessels.[1] These crises typically do not respond to antihistamines, corticosteroids, or adrenaline treatment, and tend to disappear spontaneously within 72 hours.

Different forms of hereditary angioedema (HAE) are currently recognized and include HAE due to C1-INH deficiency (type 1 HAE), HAE due to C1-INH dysfunction (Type 2 HAE), and HAE with normal C1-INH. The last is a very rare form of HAE, showing clinical manifestations similar to classical type 1 and type 2 HAE but without the typical mutations detected in the SERPING1 gene. It was first reported in families of women and showed to be related to high oestrogen levels such as the use of oral contraceptives or pregnancy.[2-3] Mutations in F12, plasminogen (PLG), and angiopoietin (ANGPT1) genes were described for HAE with normal C1-INH, however, the full pathophysiology for this condition is not yet well established.[2,4] Mutations in these genes lead to increased bradykinin 2 receptor-mediated signalling via increased production of bradykinin.[5] The authors describe a case of hereditary angioedema to highlight that hereditary angioedema is a familiar entity, may be life-threatening and its diagnosis requires high clinical suspicion, so clinicians need to be aware of this entity when managing patients who present to the clinic with a history of angioedema.

CASE DESCRIPTION

A 60-year-old female patient referred by the general practitioner to the allergy and immunology clinic with a history, since childhood, of skin swelling of hands, feet, and lips. She denied laryngeal swelling. Attacks occurred nearly every 2-3 months and were largely unpredictable, resolving spontaneously for two to five days. The agudizations were not associated with urticaria or pruritus, respiratory symptoms, gastrointestinal symptoms, nor with the intake of food or any medication, including ACE inhibitors or oral contraceptives. The patient had no history of infection. A lack of efficacy in chronic high-dose antihistamine therapy was reported after a three-month trial. The crisis incapacitated the patient from her socio-labour activities due to an alteration in facial aesthetics. The last episode occurred in 2020. The patient's father and her two daughters had similar episodes of angioedema, but in the last five years, they did not have any attacks.

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Laboratory findings did not show changes in blood count, leukocyte formula, or platelets. Kidney, liver, and thyroid function were normal, as were sedimentation rate and C-reactive protein. Protein electrophoresis and immunoglobulin assay showed no alterations. The autoimmunity study was negative as well. The immunological study showed normal levels of C1q (20.5 mg/dL; normal range 12.2-20.8), C3 (105.5 mg/dl; normal range 81.0-167.0), C4 (20.3 mg/dL; normal range 11.0-42.0), C1-INH–quantification (31.5 mg/dL; normal range 15.0--35.0) and C1-INH function. All other labs for infection, allergic, and autoimmune diseases were normal.

Given that the patient had no medical history of autoimmune diseases and laboratory workouts showed normal C4, C1-INH, and C1q levels, acquired angioedema was excluded. She was not taking ACE inhibitors, and therefore the diagnosis of ACE inhibitor angioedema was also excluded. Since the episodes were not associated with concomitant urticaria and were not responsive to high-dose antihistamine therapy, histaminergic angioedema was also excluded. A genetic analysis was then performed and detected Exon 9 missense heterozygous variant p.Thr328Arg in the FXII gene, making the diagnosis of HAE with normal C1-INH. Currently, since the condition remains in remission, the patient shows no criteria for long-term treatment and maintains follow-up at our clinic. The patient has as an HAE/rare disease identification card and instructions on how to manage if an HAE attack occurs. She also has access to therapeutic drugs if an acute HAE attack occurs.

COMMENTS

HAE is a rare disease. It is bradykinin-mediated and does not involve histamine. The onset of HAE symptoms may begin during paediatric age and exacerbate at puberty but sometimes begin in adulthood. The latter is considerably higher in patients with HAE type III. Diagnosis of HAE type III is based on the clinical history, family history, and in some cases, there an association with oestrogen may be seen. The underlying mechanisms linking HAE with oestrogen are not yet fully understood.

Nowadays, there is a wide range of treatment options available, which may go unnoticed in our daily clinical practice. The authors highlight the need for recognition of this disease as well as the prompt referral to the allergy and immunology clinic when it is suspected. Correct diagnosis allows for effective treatment measures with a major improvement in the quality of life of these patients, as it is noticed that angioedema causes immense social and physical discomfort.[8]

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AUTHORS CONTRIBUTION

Conceptualization, FS; methodology, FS, IF, and LC; resources, FS; writing – original draft preparation, FS; writing – review and editing, FS, IF, and LC; supervision, LC. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ABSTRACT

ANGIOEDEMA HEREDITÁRIO COM C1-INIBIDOR NORMAL: UM CASO CLÍNICO RARO

O angioedema hereditário (AEH) é uma doença hereditária rara e as suas manifestações podem ser fatais. Difere do angioedema histaminérgico, pois apresenta diferentes mecanismos subjacentes e, portanto, não responde ao tratamento com anti-histamínicos nem com adrenalina. Os autores apresentam um caso de angioedema hereditário para destacar a importância da referenciação de imediato à especialidade de imunoalergologia para posterior avaliação e diagnóstico correto em caso de suspeita desta entidade.

Palavras-chave: Angioedema hereditário; C1-inibidor normal; Gene FXII.