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RECURRENT EPISODES OF NONHISTAMINERGIC ANGIOEDEMA IN A POSTMENOPAUSAL WOMAN: A CLINICAL CASE

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Abstract: Nonhistaminergic angioedema (NH-AO) is a rare, heterogeneous condition characterized by recurrent episodes of tissue swelling due to a bradykinin-mediated or other nonmastocyte-mediated mechanism. Diagnosis of NH-AO remains challenging, particularly when the disease presents in adults without a family history or drug triggers. Hormonal changes during menopause may affect the kallikrein-kinin system and contribute to the clinical presentation; however, case reports are limited.

We present a 67-year-old postmenopausal woman with recurrent episodes of angioedema unresponsive to antihistamines and glucocorticosteroids. The patient had normal C1 inhibitor levels and functional activity, and no evidence of acquired or drug-induced causes. The clinical presentation was consistent with idiopathic nonhistaminergic angioedema. This case highlights the need to consider nonhistaminergic angioedema in middle-aged and older women with angioedema without urticaria. Possible hormonal mechanisms influencing vascular permeability and bradykinin metabolism require further study.

Keywords: nonhistaminergic angioedema; bradykinin; menopause; idiopathic angioedema; C1 inhibitor.

Introduction

Angioedema without urticaria can be histaminergic or nonhistaminergic in origin. Bradykinin-induced angioedema, including hereditary forms, acquired C1-inhibitor deficiency, and drug-induced variants, typically does not respond to antihistamines, glucocorticosteroids, and epinephrine. An accurate differential diagnosis is crucial, as misattributing symptoms to an allergic mechanism leads to delayed evaluation.

Menopause is accompanied by significant hormonal changes that can affect vascular permeability and the activity of the kallikrein-kinin system. Cases of increased or onset of angioedema associated with hormonal fluctuations have been described in the literature; however, data on postmenopausal patients are extremely limited. This article presents a clinical case of recurrent NG-AO in a postmenopausal woman.

Case Description

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A 67-year-old woman presented with recurring episodes of swelling of the lips, face, and upper extremities for two years. The swelling developed gradually over 6-12 hours, peaked within 24 hours, and resolved spontaneously within 48-72 hours. Hives, itching, difficulty breathing, or other signs of an allergic reaction were not observed.

The patient had been naturally postmenopausal for four years and was not receiving hormone replacement therapy. Her comorbidities included hypertension controlled with a calcium channel blocker and mild dyslipidemia. She denied taking ACE inhibitors, ARBs, or estrogen-containing medications. High doses of antihistamines and courses of oral glucocorticosteroids, previously prescribed, were ineffective. Laboratory testing outside of the attack revealed:

• normal C4 levels,

• normal C1 inhibitor antigen levels,

• normal C1 inhibitor functional activity,

• normal tryptase levels,

• negative ANA and C1q antibodies,

• absence of monoclonal gammopathy.

Given the absence of signs of mast cell activation, normal complement, and the absence of drug triggers, a diagnosis of idiopathic nonhistaminergic angioedema was established.

Discussion

This case demonstrates the diagnostic difficulties of recurrent angioedema in an adult with no family history or drug exposure.

Hormonal factors

Estrogens are involved in the regulation of endothelial permeability and bradykinin metabolism. Changes in estrogen levels may influence the activity of the contact junction system. Although such mechanisms are well described in hereditary angioedema, the impact of menopause on idiopathic NH-AO is poorly understood. Late onset of symptoms may reflect changes in hormonal regulation in postmenopause.

Diagnostic Aspects

Edema without urticaria, lack of response to antihistamines and corticosteroids, gradual development, and prolonged course are features characteristic of NH-AO. Normal C1-inhibitor levels ruled out types I and II of hereditary angioedema. The absence of estrogen-containing drugs made HAE with normal C1-inhibitor unlikely. After excluding secondary causes, a diagnosis of idiopathic angioedema was established.

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Clinical Significance

NH-AO is likely more common than diagnosed, especially in peri- and postmenopausal women. Understanding the clinical features helps avoid ineffective therapy and direct diagnostic efforts.

Conclusion

Recurrent nonhistaminergic angioedema may first occur in postmenopausal women. Hormonal changes can contribute to altered vascular response and activation of bradykinin mechanisms. Early differential diagnosis allows us to distinguish NG-AO from histaminergic forms and avoid ineffective interventions. Further research is needed to clarify the pathogenesis of NG-AO in postmenopause.

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