CASE REPORT

A Misleading Angioedema: Case Report

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Abstract

Hereditary angioedema is a rare clinical syndrome characterized by episodic nonpitting swelling of the subcutaneous and submucosal tissues due to a deficiency or lack of function of the C1 esterase inhibitor. It commonly affects nondependent areas, such as the tongue, lips, face, and upper airways. Potentially a life-threatening disease, it mostly resolves without complications. It is often unrecognized or misdiagnosed after the first episode. There are a number of triggers for hereditary angioedema, including medications, namely angiotensin-converting enzyme inhibitors. Their use is increasing in the pediatric age due to the higher prevalence of obesity and its comorbidities. Angioedema is a possible known side effect. We present a case report of a female teenager under angiotensin-converting enzyme inhibitor therapy who developed recurrent angioedema. The use of an angiotensin-converting enzyme inhibitor was a confounding factor for the diagnosis of hereditary angioedema.

Keywords: Adolescent; Angioedema/etiology; Hereditary/diagnosis; Angiotensin-Converting Enzyme Inhibitors/adverse effects

Keypoints

What is known:
- Hereditary angioedema misdiagnosis is still common, especially in the first episode of illness.
- In an angioedema episode, a particular focus on family history of angioedema and medication use is mandatory.

What is added:
- The use of an angiotensin-converting enzyme inhibitor is increasing in pediatric age.
- The use of an angiotensin-converting enzyme inhibitor can be a confounding factor for hereditary angioedema diagnosis.

Introduction

Angioedema is defined as an area of the deep dermis and subcutaneous tissue edema frequently caused by an acute mast cell-mediated allergic reaction.[1,2] Non-allergic causes of recurrent angioedema are related to the excess of bradykinin, being classified as hereditary angioedema and acquired angioedema (Table 1).[3,4]

Hereditary angioedema is a rare but potentially life-threatening disease due to a mutation in the C1 esterase inhibitor (C1-INH) *SERPING1* gene located on chromosome 11,[5] leading to a deficiency or dysfunction of C1 esterase inhibitor, a key enzyme inhibitor of the kallikrein-kinin cascade. The loss of functionality of C1 esterase inhibitor results in cascade activation, causing an increase in bradykinin production. Bradykinin binds to its receptor on vascular endothelial cells, which leads to vasodilation and increased endothelial permeability, inducing the classic symptoms of localized edema and inflammation, usually of the face, mouth, and upper airway.[6] Hereditary angioedema affects approximately one in 67 000 people, with no gender or ethnicity variation. The majority present their first symptoms within the first two decades of life.[7,8] Approximately, 75% have an autosomal dominant inheritance pattern.[9,10] Clinically, the edema is non-itching and not associated with urticaria, similar to angiotensin-converting enzyme (ACE) inhibitor angioedema, although erythematous rash may arise in some cases. It commonly affects nondependent areas, such as the tongue, lips, face, and upper airways. Episodes are usually self-limited, lasting from one to five days, with a variable intercritical period. Most of them are spontaneous and unexpected[7] although triggers have been described, such as trauma, surgery, infections (*eg Helicobacter pylori*), drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and estrogens), anxiety or stress, as well as menstrual cycle and pregnancy.[11] Those triggers

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apparently reduce the threshold for an exacerbation.[12] Angiotensin-converting enzyme inhibitors are widely used to treat hypertension. Its use in the pediatric age is increasing due to the higher prevalence of obesity and its comorbidities. Angiotensin-converting enzyme inhibitors may cause angioedema, up to five times greater in African descents.[13] There is no data in the literature regarding the incidence of this effect on children. The clinical features of ACE inhibitors angioedema derive from elevated levels of bradykinin, mostly present with facial, mouth, and upper airway edema. It might cause abdominal pain due to intestinal angioedema. Swelling develops over minutes to hours and resolves within 72 hours although complete resolution may take days. It can occur episodically with a long symptom-free period.

Case Report

A 15-year-old diabetic, hypertensive, African-descendent female admitted to a pediatric department for uncontrolled type 2 diabetes developed, on the fifth day of admission, labial and tongue edema (Fig. 1), followed by asymmetric periorbital involvement (Fig. 2). Pruritus, urticarial, or other systemic symptoms were not present. The patient reported a similar self-limited episode five months earlier. Family history was unremarkable for similar events. In addition to metformin, she was under lisinopril for the past year and denied the use of estrogens. Her menarche was at the age of 13.

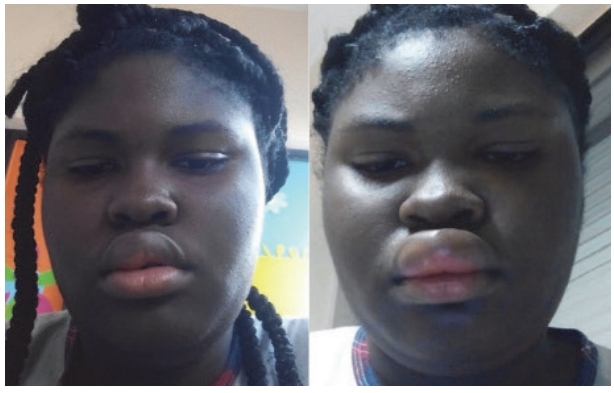

Figure 1. Labial angioedema.

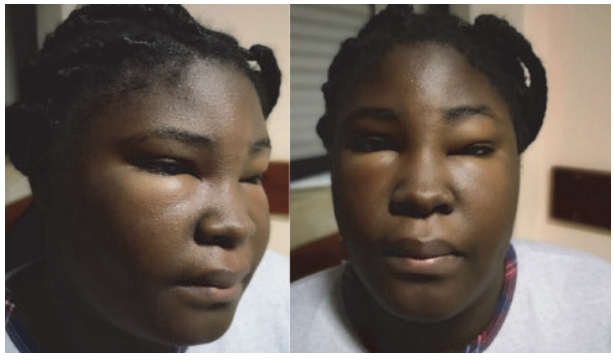

Figure 2. Periorbital angioedema.

Hydroxyzine was administered with no response. Lisinopril was replaced by a calcium channel blocker (amlodipine), and clinical manifestations gradually disappeared during the following days. A diagnosis of ACE inhibitor-induced angioedema was assumed. She had a relapse 18 months later. Family history was reassessed, and she revealed her mother used to have episodes of facial angioedema in her youth. The mother had all her children by caesarean section, and there was no history of other surgeries. Laboratory tests were performed and showed normal immunoglobulin (Ig) E levels to the most common inhalant allergens. An immunoenzymatic study revealed complement factor 4 (C4) 45 mg/dL (reference value 15-57 mg/dL), C1 esterase inhibitor 32 mg/dL (reference value 21-38 mg/dL), and functional C1-INH 25% (reference value > 68%), corroborating the diagnosis of type II hereditary angioedema. Given the low severity of the symptoms, she did not initiate any acute treatment or prophylaxis. At six months of clinical follow-up, she reported one additional periorbital edema episode that resolved spontaneously.

Discussion

After an angioedema episode, a complete medical and family history is mandatory, including a family history of angioedema, personal history of allergies, or medication use. Our patient reported a previous episode of angioedema, while on ACE inhibitor therapy, denying a family history of angioedema. The diagnosis of ACE inhibitor-induced angioedema is clinical.

After establishing the diagnosis, avoidance of ACE inhibitors is mandatory, and subsequent monitoring of symptoms resolution confirms the diagnosis. A misdiagnosis was made based on these premises. Delay in hereditary angioedema diagnosis has decreased in recent years.[14] However, a physician survey demonstrated that 65% of patients with hereditary angioedema in the United States of America received a previously misdiagnosis.[15] The angioedema etiology was reassessed after the recurrence, and new findings on the family history suggested hereditary angioedema. Lisinopril was the probable trigger for the first episodes of hereditary angioedema. Furthermore, hereditary angioedema diagnostic confirmation requires laboratory testing. Complement 4 plasma levels are low in the majority of cases.[16,17]

Table 1. Non-allergic recurrent angioedema

Angioedema due to the excess of bradykinin		
Hereditary angioedema	Deficiency of C1-INH	Quantitative and/or functional deficiency
	Normal C1-INH	Mutation of the *ANGPT1* gene
		Mutation of the *PLG* gene
		Mutation of the *FXII* gene
		(...)
Acquired angioedema	Deficiency of C1-INH	Autoimmune diseases
		Lymphoproliferative diseases
	Drugs	ACE inhibitors, glyptines, angiotensin I receptor blockers

ACE - angiotensin-converting enzyme; C1-INH - C1 esterase inhibitor.

However, up to 4% of patients have normal C4 levels as in our patient. C1 esterase inhibitor levels should be obtained, as well as C1-INH functional assay. In type I hereditary angioedema, C4, C1 esterase inhibitor levels, and C1-INH functional activity are low. In type II hereditary angioedema, C4 levels might be low or normal with normal C1 esterase inhibitor, but low C1-INH functional activity. In type III hereditary angioedema, C1 esterase inhibitor levels and function are normal, because the causative mutations are in the factor XII gene. Factor XII is part of the kallikrein-kinin system, and its activation leads to bradykinin release.[16]

Patient treatment should be individualized, considering episode history, its frequency, patient quality of life, and availability of healthcare resources. It should also be recognized that hereditary angioedema severity may wax and wane over time. Therefore, regular follow-up must be provided. The treatment of choice for acute episodes and short-term prophylaxis is plasma-derived C1 esterase inhibitor concentrate or recombinant C1 esterase inhibitor.[11] A recent option for acute therapy consists of icatibant, a synthetic molecule similar to bradykinin that acts as an antagonist to the bradykinin B2 receptor.[18] Regarding our patient, episodes were not severe. Accordingly, acute treatment was not needed. Recommendations for long-term prophylaxis are heterogeneous. The last recommendations for long-term prophylaxis include plasma-derived C1-inhibitor concentrate. However, recently published data showed recombinant C1 esterase inhibitor to be efficacious and well-tolerated as prophylactic therapy in individuals aged 13 years or older with angioedema due to C1 esterase inhibitor deficiency.[19]

In conclusion, angioedema without urticaria should trigger suspicion of hereditary angioedema, especially in patients with positive family history.[10,14,20] Even in the absence of family history, recurrence should prompt hereditary angioedema investigation. The use of an ACE inhibitor was a confounding factor for the diagnosis of hereditary angioedema.

Author Contributions

GV participated in the study conception or design. GV participated in acquisition of data. GV, MS, MSP, JE and PP participated in the analysis or interpretation of data. GV, MS, MSP, JE and PP participated in the drafting of the manuscript. GV, MS, MSP, JE and PP participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

Provenance and peer review

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Um Angiodema Enganador: Caso Clínico

Resumo:
O angioedema hereditário é uma síndrome clínica rara caracterizada por edema episódico não depressível dos tecidos subcutâneo e submucoso devido a deficiência ou ausência de função do inibidor de C1 esterase. Atinge habitualmente áreas não dependentes, como a língua, lábios, faces e vias aéreas superiores. Sendo uma doença que pode implicar risco de vida, resolve-se na maioria dos casos sem complicações. Frequentemente não é reconhecida ou diagnosticada após um primeiro episódio. Vários fatores podem desencadear o angioedema hereditário, incluindo medicamentos como os inibidores da enzima conversora de angiotensina. A utilização destes compostos na idade pediátrica tem vindo a aumentar devido à maior prevalência de obesidade e comorbidades associadas e o angioedema é um possível efeito colateral conhecido. Apresentamos o caso clínico de uma adolescente sob terapia com inibidor da enzima conversora de angiotensina que desenvolveu angioedema recorrente. O uso de inibidor da enzima conversora de angiotensina foi um fator confundidor para o diagnóstico de angioedema hereditário.

Palavras-Chave: Adolescente; Angioedema/etiologia; Angioedema Hereditário/diagnóstico; Inibidores da Enzima Conversora de Angiotensina/efeitos secundários