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Case Series

Recurrent Angioedema: A Case Series of C1 Esterase Inhibitor Deficiency

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Abstract

We report a case series of recurrent angioedema, hereditary and acquired, diagnosed after a long period of time. The first and the second patient presented initially at the age of 13 years and were diagnosed finally at the age of 27 years and 18 years respectively. The third case is reported in an adult and was finally diagnosed as case of acquired angioedema. The patients were managed with danazol and tranexamic acid in absence of standard recommended drugs. The cases highlight the importance of diagnosing cases during childhood and emphasize the need of standard drugs in our scenario.

Introduction

Angioedema due to C1-inhibitor (C1-INH) deficiency can be hereditary (C1-INH-HAE) or acquired (C1-INH-AAE). The incidence of C1-INH-HAE is estimated at 1 in 67,000,[1] whereas C1-INH-AAE is about ten times less common.[2] Whereas C1-INH-AAE is about ten times less common.[2] Hereditary angioedema (HAE) and acquired angioedema due to C1 inhibitor deficiency (C1-INH-AAE) are characterized by recurrent non-urticarial angioedema, typically affecting the skin, respiratory, and gastrointestinal tracts.[3,4] Acquired angioedema typically affects individuals over 40 years old. In contrast, hereditary angioedema presents at an earlier age, often involves the gastrointestinal tract, and is associated with a positive family history of angioedema.[5] We, hereby, present two cases of hereditary angioedema and one case of acquired angioedema. The case-series illustrates the variability in how C1-INH deficiency presents across cases. A brief review of pathogenesis and treatment has also been done.

Case series

Case 1

A 27-year-old male presented with recurrent swelling of the limbs, sometimes associated with peri-orbital and lip swelling, as well as difficulty in breathing for last 15 years (Figure 1). The swelling was not associated with wheals or pruritus and used to resolve within three to five days and was triggered by minor blunt trauma. Initially, the swelling occurred one to two times a year, but later increased to more than three times per month. There was a similar history of recurrent attacks in his father and younger brother (who died at 19 years of age due to difficulty in breathing) and his daughter. On investigation, the observed serum C4 level was 3 mg / dl (Reference range: 10 - 40 mg / dl), and the C1 esterase inhibitor level was 0.03 g /

L (Reference range: 0.21 - 0.39 g / L). Based on these results, the diagnosis of C1-INH-HAE was made, and the patient was managed with oral danazol as a long-term prophylactic measure to prevent further attacks.

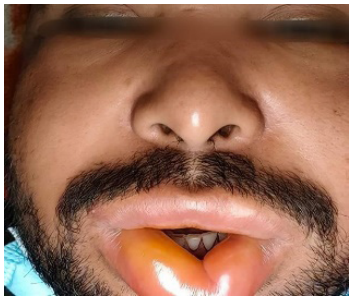

Figure 1: Progressive swelling during angioedema attack

Case 2

An 18-year-old-female presented with recurrent episodes of swelling of lips, face, and extremities (Figure 3) for last five years, mostly triggered by trauma, associated with abdominal pain, without any skin lesions or pruritus. The swelling used to resolve on its own in five to seven days and was unresponsive to corticosteroids and antihistamines. She was not under any medications for any systemic illness. The observed C1 esterase inhibitor level was 0.03 g / L (Reference range: 0.21 - 0.39 g / L). However, there was no family history of similar symptoms. She was managed with danazol as a long-term prophylactic measure and was well controlled at last follow-up at six months.

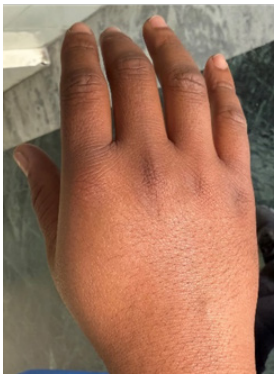

Figure 2: Swelling of right hand

Case 3

A 47 year old female presented with recurrent eyelids swelling, cheeks and lips for last three years (Figure 2) without wheals. The swelling was not linked to fever or any identifiable triggers. She had no family history of similar issues, no history of co-morbid conditions, and was not under any other medications. The observed serum C4 level was 2 mg / dl (Reference range: 10 - 40 mg / dl), and the C1 esterase inhibitor level was 0.0642 g / L (Reference range: 0.21 - 0.39 g / L). Based on the typical symptoms, minimal response to systemic corticosteroids and antihistamines, laboratory results, the age at presentation and lack of family history of similar symptoms, she was diagnosed as a case of acquired C1-INH deficiency. She was screened for possible underlying lymphoproliferative disorders and autoimmune diseases. No apparent associated disorders could be identified. She was managed with fresh frozen plasma and tranexamic acid with the desirable response.

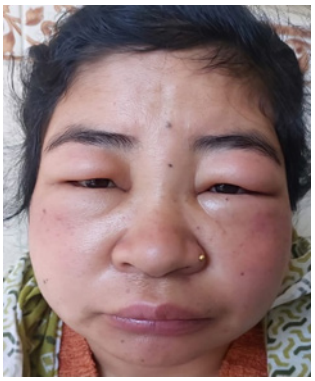

Figure 3: Swelling of lips, eyelids, and cheeks

Discussion

C1-inhibitor deficiency is hereditary or acquired conditions of low C1-inhibitor activity characterized by recurrent angioedema without urticaria commonly involving extremities, genitourinary tract, face, oropharynx, and larynx.[6,7] It is often inherited in autosomal dominant pattern, can occur spontaneously (in 25% of cases),[8]45 (32.8% or be acquired. The attacks of angioedema usually begin during childhood and worsen during the puberty in case of hereditary angioedema while acquired forms affect middle aged or older patients.[7] C1-INH-HAE results from genetic mutation of SERPING1 leading to disrupted C1 inhibitor protein secretion (HAE type I) or function (HAE type II) while C1-INH-AAE is due to increased catabolism of C1 inhibitor protein, usually related to underlying lymphoproliferative malignancy or C1 inhibitor autoantibodies in some cases.[7] A small proportion of patients have no detectable associated disorder, at least at the time of diagnosis. The most consistent clinical difference between hereditary and acquired C1-INH deficiency is the age of onset.[9] Among 77 patients with C1-INH-AAE, the earliest reported onset of angioedema was at 39 years of age. In contrast, over 90% of individuals with C1-INH-HAE develop their first symptoms before the age of 20 years.[10] In C1-INH-AAE, cutaneous angioedema tends to affect the face more frequently than the limbs, whereas in C1-INH-HAE, swelling of the extremities is more common, as seen in above cases. According to the International Consensus Algorithm for

diagnosis of C1-INH-HAE, diagnostic confirmation requires measurement of C4 level, C1 esterase inhibitor level and C1 inhibitor functional level if available.[6] Supporting family history with decreased C4 level and C1 inhibitor level is seen in C1-INH-HAE type I while low C4 level with normal C1 inhibitor level with decreased functional C1 inhibitor level is observed in C1-INH-HAE type II.[6] There are several FDA approved first line therapies for acute treatment of episodes of angioedema in C1-INH-HAE, including human plasma derived C1-INH concentrate, recombinant human C1-INH, icatibant (a synthetic bradykinin B2 receptor antagonist), ecallantide (a recombinant plasma kallikrein inhibitor).[7] All first-line therapies are expected to be effective if administered within the initial hours of an angioedema attacks. Only if none of the first-line therapies are available, fresh frozen plasma(FFP) can be considered.[6] Short term prophylaxis should be considered with plasma derived C1-INH, if patient is likely to be exposed to triggers or trauma (Dental and medical surgery).[6,7] In cases where acute treatments are not effective or > 1 severe attack per month, long term prophylaxis can be considered. The treatment options available are plasma derived C1-INH, lanadelumab (anti active-plasma kallikrein monoclonal antibody) and berotralstat (plasma kallikrein inhibitor).[6]

Conclusions

The diagnosis of C1 esterase inhibitor deficiency may be challenging. The case highlights the importance of timely diagnosis to reduce morbidity and mortality arising out of the disease.

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