CASE REPORTS

Angioedema in a Patient with C1 Esterase Inhibitor Deficiency

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ABSTRACT

Angioedema is characterized by recurrent, circumscribed, solitary or multiple subcutaneous and mucosal swelling, involving the extremities, face, larynx, bowel wall. Angioedema is due to hereditary or acquired varieties of C1 esterase inhibitor (C1INH) deficiency.

A case of atypical acquired angioedema in a 49-year old man, responding favourably to cinnarizine and alcohol abstinence, is presented in this article. Cinnarizine was prescribed due to presumed alcoholic liver disease.

The clinical significant amelioration was not associated with concomitant good laboratory result, which is a relatively common occurrence.

Keywords: Angioedema; Alcohols; Complement C1 inhibitor proteins; C1 esterase; Cinnarizine

INTRODUCTION

Angioedema, a rare potentially severe disease, is characterized by recurrent, circumscribed, solitary or multiple subcutaneous and mucosal swelling, involving the extremities, face, larynx and bowel wall.[1] Bradykinin appears to be the main mediator of the episodes.[2] Human complement C1 esterase inhibitor (C1INH) is a serine proteinase, a pivotal inhibitor of the inflammatory response proteins. C1INH inactivates the C1r and C1s components of the complement system and enzymes of the coagulation, fibrinolytic and kinin systems. Binding of the target proteinase to C1INH leads to the formation of a stable acyl-enzyme complex in which the proteinase is inhibited. C1INH irreversibly binds to activated C1, preventing the proteolytic cleavage of C4 and C2 by enzymatically active C1. Deficiency of C1INH permits C4 and C2 cleavage to go unchecked.

This highlights the involvement of the immune system in the pathogenesis of disorders characterized by the presence of dysfunctional response proteins.[3]

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Angioedema due to C1 esterase inhibitor deficiency (CINH) has two varieties, hereditary or acquired, each one comprising two types.[4]

In type 1 hereditary angioedema both C1INH protein level and function in plasma are decreased; whereas in type 2 hereditary angioedema the C1INH level is normal or elevated, but C1INH function is decreased due to synthesis of dysfunctional C1INH.[5] In type 1 acquired angioedema there is depressed functional C1INH activity, which is frequently associated with lymphoproliferative disorders,[6,7] whereas in type 2 acquired angioedema there is the presence of anti-C1INH autoantibodies, often monoclonal, but without proven associated malignant disease.[8,9] From the biological point of view the main difference between acquired and hereditary forms of angioedema is, the depressed level of C1 in addition to the low levels of C2 and C4 presents in the hereditary form.[10] The attacks are caused by several conditions: drugs and chemical additives, radiographic contrast medium, food and inhalant allergens, alcoholic beverages,[11] parasitic infections and physical stimuli induced by trauma.

The authors present a case of acquired C1INH deficiency, without associated lymphoproliferative disorder and no demonstration of anti-C1INH

autoantibody, success-fully treated with cinnarizine and alcohol abstinence. Cinnarizine was prescribed due to presumed alcoholic liver disease. The clinical significant amelioration, was however not associated with concomitant good laboratory result, which is a relatively common occurrence.[12]

CASE REPORT

A 49-year old man was admitted on JAN 03 with "spontaneous" angioedema of the face which did not resolve in the emergency ward with epinephrine, steroids and hydroxizin therapy, but ameliorated spontaneously within 48 hours. He had four other similar episodes of facial angioedema dating back to when he was 18 years old, three after tooth extraction and one after facial trauma and lip suture, the latter with difficulty in breathing due to edema of the glottis but again ameliorating spontaneously. After the first attack, more frequent episodes localized on hands, arms, toes and scrotum occurred after local trauma during professional activities. He denied any drug intake and also no family cases of angioedema in his father (already dead due to COPD at 79) and his wife and two sons. He confirmed heavy alcohol consumption and smoking habits, but no other diseases. Besides angioedema, moderate hepatomegaly was the only other abnormal physical sign detected. Blood tests revealed slight leukocytosis (12300/mm^3 with 92.4% neutrophils), slight hyper-uricemia (7.5 mg/dl), normal renal and liver function tests and lipid profile, and negative viral hepatitis B and C serology. Immunologic studies for common autoimmune diseases were negative and seric immunoglobulin G/A/M levels were normal. During the attack study of the complement pathway showed: C1 was not possible to study at that time; C2 by radial immunodiffusion = 1.5 mg/dl (0.4-2.4); C4 by nephelometry = 6.6 mg/dl, (10-34); C1INH protein by nephelometry = 10.7 mg/dl (21-39); C1INH function by ELISA 68%. The same study of complement levels on her mother and two sons were all normal. Abdominal ultrasonography with Doppler revealed diffuse liver steatosis and lower third esophagus varix. Chest x-Ray was normal. Due to probable alcoholic liver disease we decided to prescribe cinnarizine 50 mg daily. The patient decided to stop the therapy after 3 months. One month later and after a tooth extraction he again had facial angioedema. From then on he was taking the medicine again and he has had no more episodes. He was able not to drink alcoholic beverages again and substantially reduced the smoking habit.

One year after initiating the therapy with cinnarizine, and with the patient not having any other attack, another study of complement fractions and of C1INH function revealed: C1q 11.5 mg/dl (8-15); low C1r 5.4 mg/dl (7.5-10.5) by radial immunodiffusion in agarose; C2 1.04 mg/dl; C4 8.7 mg/dl; C1INH < 2.9 mg/dl; C1INH function 37.72%. Seric protein electrophoresis did not reveal monoclonal chains. By immune diffusion in agarose gel (the available test in our hospital) we were not able do detect the antibodies to C1INH. The same treatment was maintained and after another 6 months therapy the patient felts well and did not have any episodes of angioedema.

Although we were not able to demonstrate the antibodies to C1INH we think that this patient had the type 2 of acquired angioedema and not the type 1, because he had a long history of many years of episodes of angioedema, without development of any underlying disease. Also the late age occurrence of the first episode of angioedema, and the normal levels of the complement and protein and function of C1INH of both of his sons, are against a hereditary form of angioedema. Low C1r is also in favour of acquired angioedema. It is also interesting that some of the episodes of angioedema in our patient had some relation with heavy alcohol consumption.

DISCUSSION

From the therapeutic point of view, it is very important to define the exact type of C1INH deficiency, especially if the patients have a monoclonal gammapathy, to prevent in time a fatal outcome. Most of the times the angioedema attacks resolve spontaneously in two or three days. However in very severe cases of laryngeal asphyxia it can be necessary to resolve to a life-saving tracheotomy. Generally and after the diagnosis, the therapy shall be basically prophylactic. Most authors prescribe attenuated androgens, of which the more commonly used is danazol.[13-15] The efficacy of danazol is due to its capacity to increase the liver synthesis of C1INH. But if this drug has generally good results in both types of HAE and type 1 AAE, the efficacy in type 2

AAE is not proved or the disease becomes refractory to treatment during follow-up. The reason is probably the large excess of autoantibody able to neutralize any increased C1INH induced by the androgens. This could also explain the partial or complete resistance or even the exacerbation of angioedema attacks after the infusion of either fresh or frozen plasma or C1INH concentrate. Tranexamic acid is also sometimes utilized, but the results are not very satisfactory and there is some risk of venous thrombosis.[16] Some authors observed clinical improvement in these patients with type 2 AAE after plasmapheresis and cytotoxic therapy for treatment of the underlying diseases.[17,18]

Cinnarizine (acephyllin heptaminol) is a non-selective inhibitor of the slow calcium channels, belonging to the piperazine class of drugs, as flunarizine, normally used for the treatment of vertigo syndromes as well as an antiemetic drug. It works as an arteriolar vasodilator, also having an analeptic cardiovascular effect.[19] Cinnarizine is rarely referred as an option to the therapy of angioedema.[20] It works through the blocking of C4 activation.[21,22] Although other authors advise a lower dosage of cinnarizine (30 mg daily), we preferred a higher dosage due to previous serious episodes in our patient. The 50 mg daily dosage is commonly used in vertigo and cerebral circulatory disturbances. We decided not to prescribe androgens and utilize cinnarizine, because of the demonstration on ultrasonography of diffuse liver steatosis and lower third esophageal varix, on a patient with heavy alcohol consumption, due to the possibility of adverse effects of androgens in patients with liver disease. Until now, the drug was apparently efficacious. The patient had only one attack of facial angioedema due to a tooth extraction.

However this happened after the patient decided to stop the medication one month earlier after the first three months of therapy. From then on and taking again the medication, he had no more attacks. The future will define if the therapy will be efficacious permanently. Although the clinical result of therapy appears very good, there were no concomitant good laboratory results. However this point was already referred by other authors, the clinical and laboratory results can differ despite the therapy,[12] and the therapy shall be maintained. There are not many references about alcohol and angioedema in medical literature,[11] but we think that in our patient alcohol abstinence was also important on the result of the therapy.

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