Angioedema por deficiência de inibidor da esterase da fracção C1 do complemento – Revisão

Angioedema in C1 esterase inhibitor deficiency – A Review

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Abstract

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. Bradykinin appears to be the main mediator of episodes. Angioedema is due to hereditary or acquired varieties of C1 esterase inhibitor (C1INH) deficiency, each one comprising two types. 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. In type 1 acquired angioedema there is depressed functional C1INH activity, which is frequently associated with lymphoproliferative disorders, whereas in type 2 acquired angioedema there is the presence of anti-C1INH autoantibodies, often monoclonal, but without proven associated malignant disease. The attacks are caused by several conditions. Based on a case of atypical acquired angioedema in a 49-year old man, responding favourably to cinnarizine and alcohol abstinence, the authors provide a concise review of both types of angioedema, portending to pathogenic mechanisms, aetiology of attacks, clinical manifestations, differential diagnosis of both types of angioedema by quantification of the C1 complement fraction determination, and the available therapeutic possibilities. Cinnarizine was prescribed due to presumed alcoholic liver disease. The clinically significant improvement, was however not associated with concomitant good laboratory results, which is a relatively common occurrence.

Key words: Alcohol, Acquired/Hereditary Angioedema, C1INH Esterase Deficiency, Cinnarizine.

Resumo

O angioedema é uma síndroma potencialmente grave, caracterizada por edema recorrente, circunscrito, solitário ou múltiplo, do tecido subcutâneo e mucosas, envolvendo as extremidades, face, laringe e tubo digestivo. A bradicinina parece ser o principal mediador químico dos episódios de angioedema. O angioedema por deficiência do inibidor da esterase da fracção C1 do complemento (C1INH) classifica-se em dois tipos, hereditário e adquirido, por sua vez subdivididos em dois subtipos: O angioedema hereditário subtipo 1 – no qual tanto o nível plasmático do C1INH como a funcionalidade do mesmo no plasma estão diminuídos, enquanto no subtipo 2 – o nível plasmático do C1INH é normal ou elevado, mas a função do C1INH está diminuída, por virtude da síntese de C1INH disfuncional. No angioedema adquirido subtipo 1 – Existe diminuição funcional da actividade do C1INH, frequentemente associada a doenças linfoproliferativas, enquanto o angioedema adquirido subtipo 2 – caracteriza-se pela presença de autoanticorpos anti-C1INH, muitas vezes monoclonais, mas em que não se demonstra a associação a doença maligna. As crises de angioedema são desencadeadas por várias condições. Baseados num caso de angioedema muito provavelmente adquirido e de apresentação atípica num homem de 49 anos de idade, respondendo favoravelmente à terapêutica com cinarizina e abstinência alcoólica, os autores fazem uma revisão concisa de ambos os tipos de angioedema, referindo os mecanismos patogénicos, etiologia dos ataques, manifestações clínicas, diagnóstico diferencial entre ambos os tipos de angioedema pela quantificação do nível da fracção C1 do complemento, e modalidades terapêuticas possíveis. A cinarizina foi prescrita neste doente, devido à presumível doença hepática etanólica, pela possibilidade de risco de utilização de androgénios neste tipo de doença hepática. A franca melhoria clínica, imediata e mantida ao longo de 30 meses, não teve correlação ao nível de resultados laboratoriais, que é aliás uma situação de ocorrência relativamente comum.

Palavras chave: Angioedema adquirido, Angioedema hereditário, Deficiência do inibidor da esterase do C 1, Cinarizina, Álcool.

Introduction

Angioedema is a rare but potentially severe disease characterized by subcutaneous or mucosal swelling resulting from increased vascular permeability and extravasation of intravascular fluid and protein into

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subcutaneous and submucosal structures.[1] A variety of mediators may act independently or in conjunction to induce the phenomena, bradikynin being apparently the most important mediator.[2] Other apparently less important candidate mediators are a kinin-like peptide released from C2 during complement activation and thrombin, the final enzyme of the coagulation system.[3] Angioedema can be caused by a variety of conditions: allergies to drugs and chemical addictives, radiographic contrast medium, food and inhalant allergens; alcoholic beverages;[4] parasitic infections; systemic immunologic diseases; hereditary and acquired C1 esterase inhibitor (C1INH) deficiency;[5] physical stimuli; systemic capillary-leak syndrome and Gleich syndrome.[6]

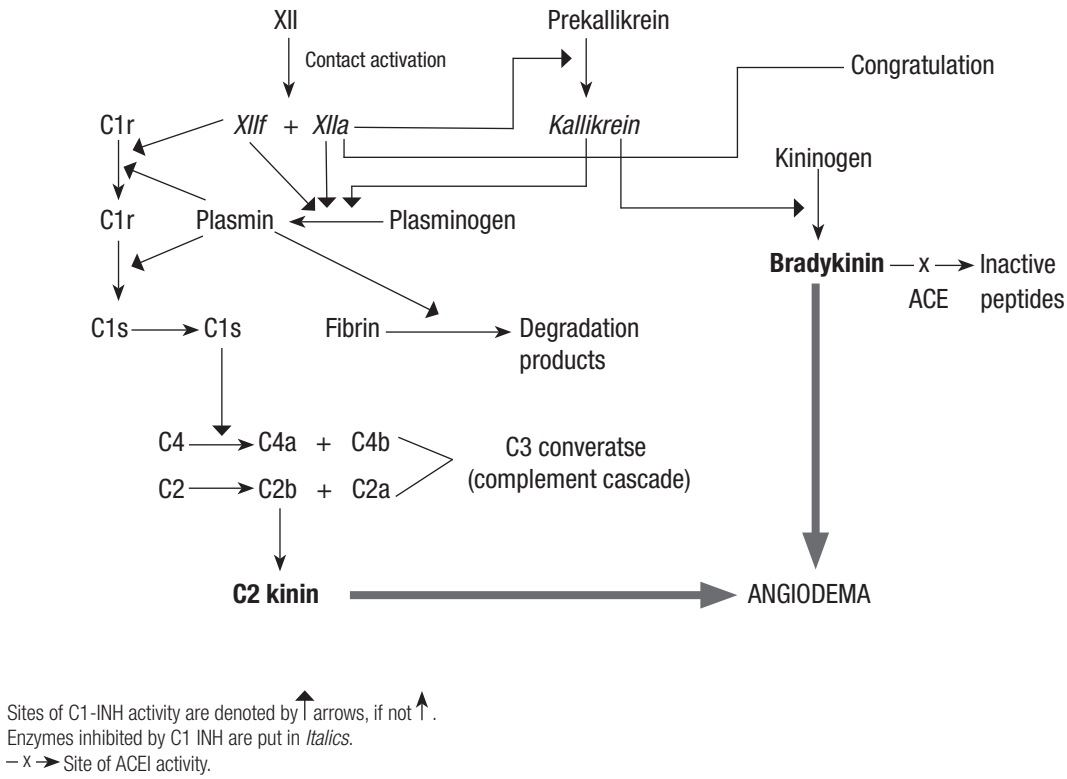
The classic pathway of complement is activated when C1 binds to the Fc fragment of IgM or IgG in immune complexes. The inactive C1 molecule has three subunits – C1q, C1r, and C1s – that are held together by ionic calcium. The C1q component binds to immunoglobulins in the immune complexes. With the binding of C1q, C1r undergoes enzymatic cleavage of its two subunits, exposing active proteolytic sites. The activated proteolytic site on C1r cleaves the C1s peptide, exposing its active enzymatic site. In turn, activated C1s acts as a protease for both C4 and C2. With the activation of C4 and C2 into C4b, 2a complex, C3 convertase enzyme is created *(Fig 1)*.[7]

Human complememt C1INH is a α_2-neuraminoglycoprotein synthesized most primarily by hepatocytes but also by peripheral monocytes, and is present in normal concentration of approximately 30 mg/dl. It is a serine proteinase inhibitor, a pivotal inhibitor of the inflammatory response proteins. C1INH inactivates the C1r and C1s components of the classic pathway of the complement system and enzymes of the coagulation (factors XIa, WIIa), fibrinolytic (plasmin) and kinin systems (kallikrein). Because there are two esterase sites in C1r and C1s, each molecule of C1 binds four molecules of C1INH. The 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.[8]

Hereditary or acquired C1INH deficiency have similar clinical manifestations of angioedema, including swelling of the skin or mucosa, with preferential involvement of the face, extremities and scrotum, gastrointestinal tract (presenting as functional intestinal occlusion),[9] and upper airway respiratory tract. Involvement of the laryngeal submucosa, the "edema glottidis", can be quickly fatal. Much more rarely there is involvement of the biliary and urinary tracts, and cerebral localization manifested by headaches, transitory aphasia and vertigo.[10,11]

Clinical report

A 49 year old white man was admitted on JAN 03 with "spontaneous" angioedema of the face that was not resolved on the emergency ward with epinephrine, steroids and hydroxizin therapy, but that ameliorated spontaneously in 48 hours. He referred four other similar episodes of facial angioedema, the first one dating back to when he was 18 years old, three after tooth extraction and one after facial trauma and lip suture, this one with difficult breathing due to edema of the glottis but also 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 at all any drug use and also no family cases of angioedema on his father (already dead due to COPD at age of 79 years) and his mother and two sons. Both sons were born after the patient began to have angioedema attacks He referred to usual 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 leucocytosis (12300/mm^3 with 92.4% neutrophils), slight hyperuricemia (7.5 mg/dl), normal renal and liver function tests and lipid profile, and negative viral hepatitis B/C serology. Immunologic studies for common autoimmune diseases were negative and seric immunoglobulin G/A/M levels normal. During the attack, study of the complement pathway showed: C1 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% of normal. Abdominal ultrasonography with Doppler revealed diffuse liver steatosis and lower third esophagus varices. Chest x-Ray was normal. Due to probable alcoholic liver disease we



Pathophysiology of angioedema due to C1INH deficiency (adapted from reference 4).

FIG. 1

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 had again facial angioedema. From then on he is taking the medicine again and he had no more episodes. He was able not to drink alcoholic beverages again and substantially reduced smoking habit.

One year after initiating 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% of normal. 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 antibodies to C1INH. The same treatment was maintained and after another 12 months of therapy the patient feels well and didn't have more episodes of angioedema. The same study of complement fractions and of C1INH serum levels on her mother and the two sons were all normal.

Although we were not able to demonstrate antibodies to C1INH we think that this patient can have an atypical form of type 2 of acquired angioedema and not the type 1, because he has a long history of many years of episodes of angioedema, without development of any underlying disease. Also the late occurrence of the first episode of angioedema in the patient and the absence of angioedema crisis and normal levels of the complement and of the protein and function of C1INH of their two sons, both of them born after the patient began to have angioedema crisis and already on the third decade of life, are against a hereditary form of angioedema. Low C1r is also in favor of acquired angioedema. It is also interesting that some of the episodes of angioedema in our patient were preceded by heavy alcohol ingestion.

Discussion

The primary biochemical defect in hereditary and acquired angioedema is a deficiency or abnormality of the C1INH.[12] On the cascade of the complement pathway C1 is converted to C1 esterase, and this acts on C4 and C2 to activate the rest of the classical complement pathway.[13] This pathway is a major effector mechanism of the antibody response. Regulation of the complement system depends in part on inhibitors in the serum, C1INH acting at the level of C1 esterase. Clinical attacks of angioedema, which are usually self-limiting, are attributed to activation of C1, consumption of C2 and C4, with release of vasoactive peptide fragments of C2 and C4 and several inflammatory mediators. Some attacks are spontaneous while others follow trauma that activates Hageman factor which in turn triggers the fibrinolytic pathway and release plasmin to activate C1 esterase, and also interfering with the coagulation system and kinin generation system.[14,15]

There are sporadic references to attacks of angioedema in patients with HAE in association with snoring,[16] celiac disease,[17] *Helicobacter pylori* infection,[18] Crohn's disease,[19] ulcerative colitis,[20] chronic hepatitis C.[21] It is advised not to prescribe some drugs to patients with known HAE because of the possibility of occurrence of severe attacks of angioedema. Most widely referred drugs are angiotensin converting-enzyme inhibitors (ACEI) and estrogen containing anticonceptives,[4] but there are some cases attributed to angiotensin II type 1 (AT1) receptor blockers and to alteplase.[22] The mechanism of angioedema due to ACEI appears to result from the partial inhibition of the inactivation of bradykinin, raising its effect.[23]

The HAE is the most common genetic deficiency state affecting complement factors. It occurs in a prevalence of 1/50.000,[4] and the transmission is through an autosomal dominant trait with variable penetrance, the disease occurring in heterozygous patients.[24] In these patients normal C1INH is synthesized from the normal gene, whereas there is little or no secreted product (HAE type 1) or a normal amount of dysfunctional C1INH (HAE type 2) from the abnormal gene. In HAE type 1, as the patients are heterozygous, theoretically, the serum level of C1INH should average 50% of normal. Instead, the mean serum level of C1INH is less than 30% of the normal values. High consumption of circulating C1INH protein remains the most likely explanation for the observation that the functional C1INH level can be approximately 15 to 25% of the normal value.[4] Half-normal levels of C1INH are not sufficient to maintain homeostasis and therefore allow excessive activation of the complement and contact systems with further decrease in C1INH levels. This occurs via complex formation with target proteases, followed by clearance via normal catabolic pathways.[3]

In both types of HAE there is insufficient normal C1INH in the plasma to meet homeostatic requirements and spontaneous activation of the classical pathway of complement and the Hageman factor-dependent pathways occurs. Serum levels of C1 are unchanged in HAE, in contrast to AAE, where the levels are usually depressed, due to the fast catabolism of C1INH, although a few reported cases of normal C1q levels will be referred later in this paper.[4] Natural occurring heparin produced by mast cells and basophils were proved to augment C1INH activity, and some authors suggested that inhaled heparin could be a safe and effective treatment of HAE.[25]

The C1 inhibitor gene maps to chromosome 11, p11.2-q13. An autosomal dominant gene defect of C1INH is the molecular base of HAE.[26] There are two types of HAE. In both of these C1INH deficiency states, a structural gene defect results in markedly diminished C1INH protein function, permitting unchecked complement activation, and the subsequent release of inflammatory mediators. Determination of C1INH protein level and function in plasma defines the two major forms of HAE. In HAE type 1 – both the C1INH protein and functional activity are generally decreased by 30-50% of normal by impaired biosynthesis and increased catabolic rate. HAE type 1 represents 75% of the cases of HAE and type 2 accounts for 25% of the cases. In HAE type 2 – the C1INH level is normal or elevated, but C1INH function is decreased due to synthesis of dysfunctional C1INH. The underlying molecular changes are of two types: mainly mutations in the reactive center (exon VII) and sometimes mutations outside it. This leads to abnormal folding of the C1INH so that the reactive center is not available for appropriate interactions with the target proteinase.[9]

De novo mutations made diagnosis difficult because of the lack of family history, and its frequency is reported to almost 25% in HAE.[27-29] Recently a variant of HAE was described, corresponding to 15% of HAE cases, characterized by normal quantitative

and qualitative values of C1 INH, only occurring in women, through a dominant transmission by chromosome X.[30]

In AAE there is functional deficiency of C1INH, which is characterized by adult-onset of angioedema and lack of evidence for inheritance of the disorder. From the biological point of view the main difference between AAE and HAE is, in the former, the depressed level of C1 in addiction to the low levels of C2 and C4 present in the latter. The hallmark of AAE is a low C1 titer, suggesting intense activation of the classical complement pathway.[31]

There are two types of AAE (7,32): In type 1 – there is depressed functional C1INH activity, resulting from its massive consumption secondary to complement classical pathway activation by either cryoglobulin or immune complexes of hematologic, autoimmune or infectious origins. This represents an accelerated catabolism of a normally synthesized C1INH.[33,34]

This type of AAE is commonly associated with lymphoproliferative or other malignant diseases: non-Hodgkin B-cell lymphoma, T-cell lymphoma, chronic lymphocytic leukemia, multiple myeloma,[31] Waldenstrom's macroglobulinemia, monoclonal gammapathy of undetermined significancy (MGUS), myelofibrosis, rectal carcinoma, signet ring cell gastric adenocarcinoma, mammary carcinoma.[35] In lymphomatous diseases the plasmatic or cellular complement-activating factors can be either monoclonal 7S IgM or anti-idiotype antibodies to their own monoclonal membrane or secreted Ig.[36]

Sometimes the association is with benign diseases: systemic lupus erythematosus (SLE),[37] Churg-Strauss vasculitis,[38] hepatitis B,[39] plane xanthomatosis,[40] *Echinococcus granulosus* infection.[41]

In AAE type 2 – there is the presence of both anti-C1INH autoantibodies often monoclonal (Ig G, IgM or IgA with k light chains),[42,43] and a circulating low molecular weight (95 kd) C1INH protein. The anti-C1INH antibody links to the normally synthesized C1INH and modifies the interactions with its target proteinases, converting the C1INH molecule from an inhibitor to a normal substrate of the proteinase, by destabilizing the enzyme-inhibitor complex leading to appearance of enzyme-cleaved functionally inactive 95 kd C1INH in patient's plasma. It is crucial to follow-up these patients, because there are references to later development of a monoclonal gammapathy[6,44] or malignant lymphoma.[45]

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 recur 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.[13,46,47] 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 AAE type 1, the efficacy in AAE type 2 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 episodes of venous thrombosis.[6] Some authors observed clinical improvement of patients with AAE type 2 after plasmapheresis and cytotoxic therapy for treatment of the underlying diseases.[14,48]

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.[49] Cinnarizine is rarely referred as an option to the therapy of angioedema.[50] It looks to work through the blocking of C4 activation.[51,52] 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 varices, 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 to be clinically 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,[53] and the therapy shall be maintained. There are not many references about alcohol and angioedema in medical literature,[4] but we think that in the case of our patient, perhaps alcohol abstinence may have been important on the result of the therapy.

A marked reduction of the C1q protein is considered as a hallmark of the acquired forms of angioedema and is thought to be constantly normal in the inherited forms. However D' Incan M[54] described a patient with repeatedly measured normal values of C1q levels, even during the angioedema crisis, due to a lately diagnosed monoclonal gammapathy (IgM). C1q was within normal values in only two other case reports, one only observed between angioedema crisis,[36] and in the other, the C1q value was only very slightly decreased.[8] In the absence of more extensive studies D' Incan M[54] suggests that a normal C1q level must no longer be considered a characteristic of the inherited forms of angioedema. We think that the case of our patient can be such an example as to be considered as an atypical form of acquired angioedema with a normal C1q level. Besides this normal level, we didn't find any other data to suggest an hereditary form of hereditary angioedema, and it is also interesting to correlate the possibility of an association of angioedema crisis with heavy alcohol consumption.

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