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A CASE OF STRESS INDUCED LOSS OF CONTROL OF HEREDITARY ANGIOEDEMA

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ABSTRACT

Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) is a rare, autosomal dominantly inherited disorder, characterized by episodes of oedema in different locations, triggered by various factors, including trauma, infections and stress. Therapy is addressed by treating or preventing acute attacks. We report the case of a patient with C1-INH-HAE on long-term prophylaxis with danazol, who over time, developed metabolic syndrome. Due to work stress both conditions deteriorated, with recurrent attacks or angioedema requiring increasing doses of androgens, and deterioration of the metabolic status. In order to stabilize the patient, long-term prophylaxis with C1 inhibitor was proposed. However, when the stressful conditions were discontinued (the patient stopped the work activity), the attacks became infrequent, danazol was discontinued and the need for medication for the metabolic syndrome decreased. A personalized approach to patients with HAE is essential to achieve good control of the disease and any comorbidities.

Hereditary angioedema (HAE) is a rare, autosomal dominantly inherited disorder, characterized by recurrent attacks of oedema in different locations, which may be peripheral or affect the intestinal wall, causing severe abdominal pain, and may even affect the face and airways with life-threatening asphyxia.[1] A number of mediators are involved in the pathophysiology of attacks of oedema, such as kallikrein and bradykinin, which cause vasodilatation and increased vascular permeability, and the complement fraction C1 inhibitor, whose deficiency has constituted a characteristic biomarker of the disease.[2] The characteristic clinical manifestations reduce the patient's physical and social functioning with a significant impact on their quality of life.[3] Attacks of oedema are triggered by various factors, including trauma, infections and stress.[4] The latter is related to both, the amount of attacks and a greater subjective perception of their severity.[5]

Therapy is addressed by treating or preventing acute attacks and the regimen should always be individualized. Acute attacks of angioedema are treated by the administration of bradykinin receptor blocking agents, kallikrein synthesis inhibitors or the administration of plasma-derived C1 inhibitor (pdC1-INH), which may also be administered on a short-term prophylactic basis 24 hours before surgical procedures, invasive examinations, etc.[1]

When attacks are frequent and from moderate to severe intensity, the administration of long-term prophylactic treatment is recommended. This treatment modality has been performed for years by the administration of anabolizing steroids, which stimulate synthesis of C1 inhibitor by the liver. However, use for prolonged periods has been associated with various side effects, including altered lipid metabolism[6,7] altered liver function[8] and even hepatocellular carcinoma.[9]

In this article, we present the case of a patient with C1-INH-HAE and metabolic syndrome whose condition worsened due to work related stress. The clinical status improved by cessation of the stressful work conditions. Long-term prophylaxis with attenuated androgens was withdrawn and the need for medication for the metabolic syndrome decreased.

CASE REPORT

A 58-year-old male diagnosed with C1-INH-HAE at age 21 after detecting below normal levels of C1 inhibitor: <5 mg/dl and C4: 5 mg/dl. C3: 85 mg/dl and C1Q 17 mg/dl were within normal levels. At that time the patient suffered recurrent attacks of peripheral angioedema (in hands, feet and occasionally knees) lasting 2-3 days. Attacks began with sweating and a sensation of warmth in the affected area. Hospital admission was sometimes required due to the severity of the symptoms.

The genetic history of C1-INH-HAE was confirmed in the patient and his two sisters by identification of a mutation in the C1 inhibitor gene (SERPING1), with substitution of a cytosine by a guanine in position 8823 (g.8823C>G), which leads to substitution of tyrosine 308 by a stop codon (Tyr308Stop).

Since diagnosis, long-term preventive treatment was initiated with tranexamic acid (250 mg/day) and danazol (200 mg/week). For several decades, attacks were treated

by doubling the dose of both drugs and pdC1-INH (Berinert®) when control was not achieved. Additional doses of pdC1-INH were given prophylactically on two occasions: prior to an exploratory colonoscopy for rectal bleeding and before cholecystectomy, with no incidents occurring during these procedures.

In 2005 hypercholesterolemia was detected and statins were added to treatment. The patient started metformin in 2010 for type 2 diabetes. Progressively, he developed central obesity.

Since 2012, in the context of outstanding work-related stress, the frequency and severity of angioedema attacks increased significantly, requiring an increase in the dose of attenuated androgens (up to 100 mg/day) as well as treatment with icatibant sulfate (Firazyr®) on three occasions, for extensive and troublesome peripheral attacks of angioedema. Laboratory assessments showed, hyperglucemia (147 mg/dl), hyperuricemia (8.1 mg/dl) and hyperlipidemia with triglycerides (201 mg/dl) and LDL cholesterol (171 mg/dl), C1 inhibitor: 9.9 mg/dl and C4: 14 mg/dl. Blood pressure was normal. Recommendations included diet, physical activity and allopurinol (100 mg/day).

As control of HAE attacks was not achieved, we proposed to initiate long-term prophylaxis with plasma-derived nanofiltered C1-esterase inhibitor (pdnfC1-INH), Cinryze®, aiming to discontinue danazol (which was probably contributing to metabolic destabilization). However, the patient preferred to stop his work activity. Soon thereafter, he had no more attacks and danazol was promptly discontinued as the metabolic syndrome improved (Figure 1). In the last two years, without long-term prophylaxis, he presented with a mild abdominal attack and two peripheral attacks. Due to the involvement of the hands and feet, one of the attacks was treated with icatibant sulfate (Firazyr®). Complement levels were C1 inhibitor: 8 mg/dl and C4: 9 mg/dl.

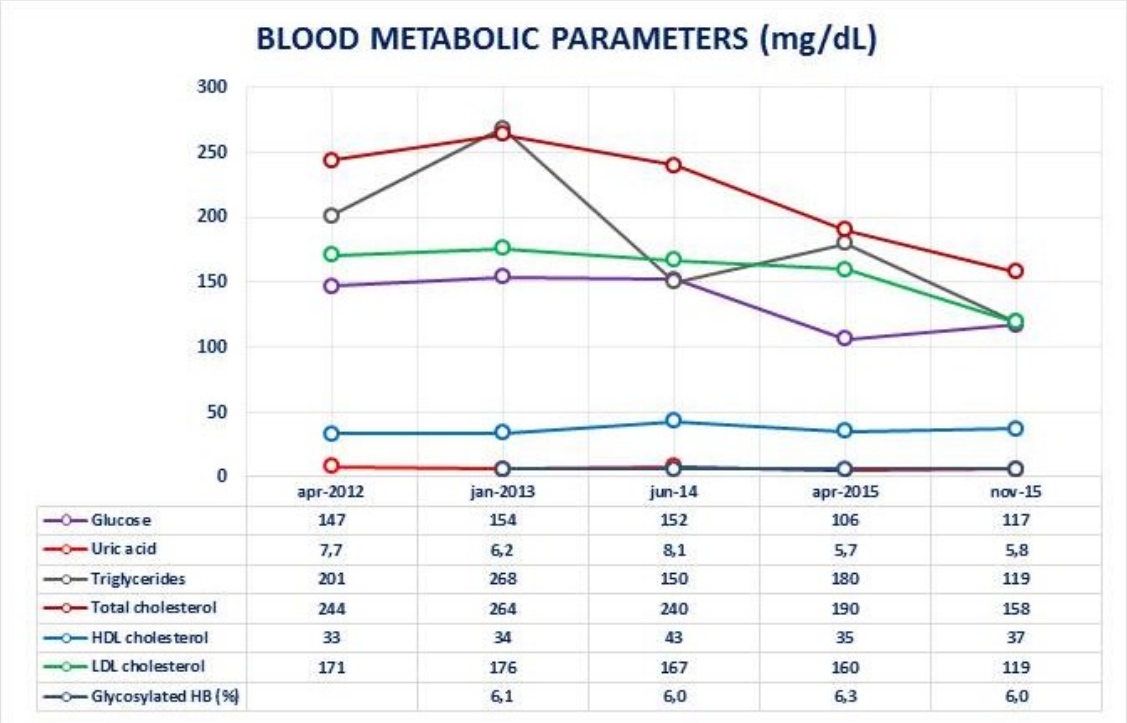
DISCUSSION

This case discusses a patient with HAE and metabolic syndrome who lost control of both conditions due to work stress. Increasing the dose of danazol and hypoglycemic, hypouricemic and lipid-lowering medications did not improve the situation. Control of both conditions was achieved when the patient stopped working, with less need of medication for the metabolic syndrome and no need of long-term prophylaxis for HAE.

In this case it is important to emphasize the great impact that stress has as a trigger of angioedema attacks. A relation has been shown between the number of HAE attacks and higher scores on the Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale.[10] Emotional stress was the most common trigger of angioedema attacks (54%), followed by trauma (39%) and infections (20.6%) in a large series of 306 patients with HAE.[4]

The administration of danazol is effective for long-term prophylaxis in patients with HAE. However, danazol may

Figure 1. Blood Metabolic Parameters



	apr-2012	jan-2013	jun-14	apr-2015	nov-15
Glucose	147	154	152	106	117
Uric acid	7,7	6,2	8,1	5,7	5,8
Triglycerides	201	268	150	180	119
Total cholesterol	244	264	240	190	158
HDL cholesterol	33	34	43	35	37
LDL cholesterol	171	176	167	160	119
Glycosylated HB (%)		6,1	6,0	6,3	6,0

potentially contribute to lipid profile alterations, as has been demonstrated in patients with endometriosis, although with higher doses (3-20 times higher than those for long-term prophylaxis of HAE), for shorter periods of time (2-6 months).[7] Antifibrinolytics such as tranexamic acid were initially used for prophylaxis, but their use was discontinued due to their low efficacy and potential risks.[11] Current guidelines recommend administration of pdC1-INH as long-term prophylactic treatment when C1-INH-HAE attacks are frequent, with moderate to severe intensity, to prevent side effects of attenuated androgens.[12] A retrospective analysis of two trials with nanofiltered pdC1INH showed it is effective for long-term prevention of HAE attacks even in patients who had previously been on anabolic androgens.[13]

In this case, long-term prophylaxis with pdnfC1-INH was proposed to avoid treatment with danazol which could potentially contribute to metabolic alterations. However, it was not necessary, as the stressful situation that caused lack of control of the HAE was resolved.

This case highlights the importance of providing a personalized approach to patients with HAE in order to achieve better control of the disease and the overall patient status.

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