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A Case of Antiphospholipid Syndrome and Protein C Deficiency due to PROC Gene Mutation

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Abstract
Patient with Antiphospholipid syndrome has a poor outcome. Though it has some special diagnostic criteria and therapeutic options, best treatment options are yet to specify. Inherited thrombophilias are also associated with adverse pregnancy outcomes, although the evidence is less compelling. Protein C is a vitamin K-dependent anticoagulant which plays a vital role in the regulation of coagulation. Deficiency of Protein C leads to thromboembolism. Protein C is an anticoagulant that is encoded by the PROC gene. Protein C deficiency is inherited in an autosomal dominant or recessive pattern. Autosomal dominant Protein C deficiency is caused by monoallelic mutations in PROC and often presents with venous thromboembolism. On the other hand, biallelic PROC mutations lead to autosomal recessive Protein C deficiency which is a more severe disease that typically presents in neonates as purpura fulminans. In this report, we describe an 65-year-old man who presented with intracranial venous thrombosis. After diagnosis of both antiphospholipid antibody and Protein C deficiency, he was treated with anti-vitamin K anticoagulant. Here we are focusing on pathogenesis and treatment aspect of the two conditions.

Keywords: Antiphospholipid Syndrome, Protein C Deficiency, Intracranial Venous Thrombosis

Introduction

The antiphospholipid syndrome (APS) is a prothrombotic condition characterized by venous or arterial thrombosis and/or pregnancy morbidity in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPLs). aPLs are autoantibodies that target phospholipid-bound proteins, notably β_2-glycoprotein I (β_2GPI). Although the presence of these antibodies is the defining feature of this syndrome, the mechanism by which aPLs result in a hypercoagulable state remains incompletely understood. APS is recognized to be a syndrome prone to recurrent thrombosis when anticoagulants are discontinued, although some patients develop recurrent events despite standard anticoagulant therapy. A subset of patients with APS have a severe variant known as catastrophic antiphospholipid syndrome (CAPS), which is characterized by thrombosis affecting multiple organs in a short period of time and histopathologic evidence of small vessel occlusion. Management of the thrombotic complications in these patients can be extremely challenging due to competing risks of bleeding and thrombosis. Understanding the thrombotic risk in this heterogeneous condition can assist clinicians in determining the optimal antithrombotic treatment. APS is one of the few clinical conditions in which patients can present with both venous and arterial thrombosis, with deep vein thrombosis of the lower extremity the most common presentation and stroke the most common arterial manifestation [1]. In 1999, international experts developed consensus criteria on the clinical and laboratory criteria for "definite APS" that became known as the Sapporo Criteria. These criteria were subsequently updated in 2006 at a meeting in Sydney, Australia and are now referred to as the updated Sapporo or Sydney Criteria [2], the clinical criteria include objectively confirmed venous, arterial or small vessel thrombosis, or pregnancy complications that may be attributed to placental insufficiency, including pregnancy loss or premature birth. The laboratory criteria require that a positive laboratory test for aPLs be found on 2 or more occasions at least 12 weeks apart. The aPLs recognized in the international criteria include lupus anticoagulant (LA) detected according to guidelines published by the International Society on Thrombosis and Haemostasis (ISTH) [3], anticardiolipin (aCL) antibody (IgG or IgM) exceeding 40 IgG or IgM phospholipid units, or anti-β2GPI antibody (IgG or IgM) at titers exceeding the 99th percentile. Protein C, a vitamin K-dependent factor synthesized in the liver, plays a significant role in regulating the coagulation cascade. It circulates as a zymogen and exerts its anticoagulant function after being activated on endothelial surfaces following binding to the endothelial protein C receptor. The inhibitory effect of

activated protein C is enhanced by protein S. Protein C primarily inactivates factors V and VIII, hence preventing thrombin generation and thrombosis formation. PROC, the gene encoding protein C, is located on chromosome 2q14.3 and contains 9 exons [4]. Similar to other inherited thrombophilias, a deficiency in protein C can predispose to thrombosis. Protein C deficiency (PCD) can be classified into type I, where there is a decrease in protein C concentration, and type II, where there is a decreased activity with normal level of protein C. Type I deficiency results from defective synthesis or secretion of the protein, whereas type II results from impaired binding to substrate, calcium, or receptor. Type I deficiency is the most common type, whereas type II accounts for 10–15% of cases [5]. PCD can be an autosomal dominant or recessive disease. Autosomal dominant PCD is caused by heterozygous (monoallelic) mutations in PROC and has an incidence of 1 in 200–500. Individuals with this form have a plasma protein C level around 50% of normal values. Affected individuals with autosomal dominant PCD are typically asymptomatic; however, some may develop venous thromboembolism during childhood or later as young adults [4]. Biallelic (homozygous or compound heterozygous) PROC mutations lead to the autosomal recessive PCD which occurs in 1 in 40,000-250,000 individuals. Autosomal recessive PCD, which is more severe than autosomal dominant PCD, is associated with very low level of protein C and typically presents in neonatal period with neonatal purpura fulminans [6]. Among the various proposed pathogenic theories to explain thrombotic APS, those involving the interaction between aPLs and the protein C system have gained much consensus. Indeed, robust data show an acquired activated protein C resistance (APC-R) in these patients. The role of aPLs in this impairment is clear, but the mechanism of action is uncertain, as the type of aPL and to what extent aPL are involved remains a gray area [7]. Here, we report case with two antiphospholipid syndrome and protein C deficiency coexistence.

Case Report

The 65-year-old male patient suddenly experienced seizures and weakness on the left side of the body. Upon admission, the patient was conscious, had good contact, regular heart rate, clear lungs, soft abdomen, and 4/5 muscle strength on the left side. His past history was that 10 years ago he had deep vein thrombosis.

Laboratory tests showed: Normal full blood count, elevated D-dimer 1140ng/ml (<500ng/ml). ANA-8-Profile and anti-ds DNA were negative; factor V Leiden was normal 2.86 (≥ 2.15), antithrombin III was 126% (83-128%), low protein C was 57 % (70-140%); protein S 76.6 % (74.1-146.1%); Lupus Anticoagulant Screen and confirm were positive, anti β2 glycoprotein I IgG was positive, anti cardiolipin IgG was grayzone. Brain MRI with contrast revealed the following findings: Venous infarction with scattered hemorrhage in the frontal region, adhering to the right and left sides. Venous sinus thrombosis above the superior sagittal sinus, sigmoid sinus, and bilateral cerebral veins (Figure 1). PROC gene sequencing identified a novel homozygous missense mutation, c.565C>T (p.Arg189Trp).

Ultrasound of the lower limb: Deep vein thrombosis of the left lower limb, scattered calcified atherosclerosis of the lower limb arterial system on both sides, deep vein valve insufficiency of the right lower limb. Carotid artery ultrasound showed scattered atherosclerosis of the carotid arteries on both sides, without causing significant obstruction. Echocardiogram was normal. Abdominal ultrasound only had large prostate gland.

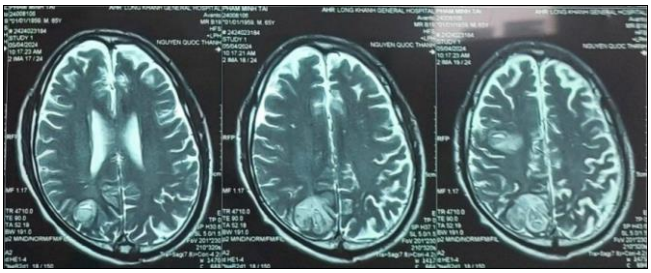

Fig 1: Brain MRI showed venous infarction with scattered hemorrhage in the frontal region, adhering to the right. Venous sinus thrombosis above the superior sagittal sinus, sigmoid sinus, and bilateral cerebral veins

We treated the patient with anticoagulation using subcutaneous low molecular weight heparin and his signs and symptoms gradually resolved over the next few days. On subsequent follow-up at one week, he remained well and asymptomatic and we change anti-vitamin K anticoagulant acenocoumarol.

Discussion

In the case presented, there is evidence of a deficiency of protein C and positive antiphospholipid syndrome. Although they alone generate a state of hypercoagulability, it is known that the activation of the pro-inflammatory cascade causes vascular endothelial injury, this being related to the triad of Virchow, increases the thrombotic phenomena. Acute phase cytokines promote an altered liver response, which in turn generates a deficiency in the production of proteins related to coagulation [8]. Regarding the antiphospholipid syndrome, it is defined as a systemic pathology with compromise of the immune system that conditions thrombotic or obstetric phenomena in the presence of a positive antiphospholipid antibody. It was described as a syndrome by Dr. Graham Hughes toward the year of 1983, in relation to the presence of antiphospholipid antibodies, thrombotic phenomena, and gestational losses [9], its diagnosis was developed over time through the holding of international workshops and symposia, the last documented in 1982 in Sapporo, Japan, where it was considered that the disease occurs if it meets clinical and laboratory criteria [10]. The development of the antiphospholipid syndrome increases oxidative stress which leads to an overexpression of the β2 glycoprotein, increasing its oxidation and its free expression in the circulation. Two hits are described to represent the pathophysiology, the first hit develops due to endothelial injury and the second hit is where the thrombus is established [11]. The relationship of protein C with the expression of glycoprotein β2 has been described as well as a subsequent activation of the coagulation cascade with the consequent result of thrombotic phenomena [2]. Lupus anticoagulant (LA) is often associated with APC-R, but antibodies generating LA comprise those directed to β2-glycoprotein I and antiphosphatidylserine/prothrombin. Moreover, the induction of APC-R by aPLs requires the presence of phospholipids and is suppressed by the presence of an excess of phospholipids. How phospholipids exposed on the cell membranes work in the system *in vivo* is unknown.

Interestingly, acquired APC-R due to aPLs might explain the clinical phenotypes of thrombotic APS. Indeed, the literature reports cases of both venous and arterial thromboembolism as well as skin necrosis, the latter observed in the severe form of protein C deficiency and in catastrophic APS [7].

Conclusion

Intracranial venous thrombosis is very rare. For patients with thrombosis in unusual locations, it is necessary to look for causes of hypercoagulability in the blood, including protein C deficiency and antiphospholipid syndrome. These two diseases can coexist in the same patient. Protein C deficiency can be caused by genetic mutations, patients need to be tested for genetic mutations. Attention should be paid to the long-term use of vitamin K antagonist anticoagulation in patients with antiphospholipid syndrome to avoid recurrence.

Conflict of interest

None.

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