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Case Report

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Protein S Deficiency and Arterial Thromboembolism: A Case Report and Review of the Literature

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Abstract

Protein S (PS) deficiency is associated with a well documented risk of venous thromboembolism. However, the relation between PS deficiency itself to arterial thrombotic events (ATEs) is not clearly established. In our case, we report an ATE in a patient with a documented novel *PROS1* mutation and a family history of PS deficiency. Other etiologies for arterial thrombosis were excluded. The role of precise diagnosis with levels of PS and documentation for mutational analysis are discussed. We highlight the problems with diagnosis in previously reported cases with arterial thrombotic events and discuss the potential for treatment with antiplatelet therapy in a subset of patients with PS deficiency.

Keywords: Protein S deficiency; Arterial thromboembolism; Thrombosis

Introduction

Protein S (PS) is a vitamin K dependent plasma glycoprotein that is synthesized by the liver, vascular endothelium, monocytes and megakaryocytes. PS serves as a cofactor for activated protein C (APC) and the degradation/deactivation of activated coagulation factor V (FVa) and activated coagulation factor VIII (FVIIIa), resulting in the restriction of thrombin generation. PS also inhibits the tissue factor pathway. PS deficiency is a thrombophilic condition inherited in an autosomal dominant fashion with mutations in the *PROS1* gene on chromosome 3 [1]. PS deficiency and the risk of venous thrombosis are well documented in literature [2]. This risk is compounded by other factors such as genetic thrombophilic deficiencies and acquired situations i.e. trauma, estrogens, pregnancy, HIV infection, age, immobilization, cancer, hypertension, diabetes, hyperlipidemia, smoking and others. However, the relation of PS deficiency itself to arterial events is not clearly established [3].

In this report we document the presentation of an arterial thrombotic event (ATE) in a patient with PS deficiency.

Case Report

A 78-year-old Caucasian female with a history of PS deficiency and on warfarin presented with sudden onset of right arm weakness. As the patient had hematuria 1 week prior to admission, warfarin was currently being withheld. Her past medical history included a diagnosis of PS deficiency for more than 25 years, aortic and mitral regurgitation, iron deficiency anemia secondary to chronic gastrointestinal blood loss, diverticulitis, and an open cholecystectomy. The patient had no history of diabetes, hypertension, dyslipidemia, or smoking. She had no previous thrombotic events and had multiple uneventful pregnancies. She has several family members (son, granddaughter, and grandson) with PS deficiency who had venous thrombotic episodes. Physical exam showed her fully alert and oriented, temperature was 37.0 °C, blood pressure was 112/80 mm Hg, heart rate was 65 beats per minute, respiratory rate was 10 breaths per minute, and oxygen saturation was normal. Cardiac examination showed regular sinus rhythm and a mild apical systolic murmur. Neck exam showed no carotid bruits or venous distension. Lungs were clear to auscultation. Abdomen was non-tender and no organomegaly was detected. Lymph nodes were not palpable. The legs were free of edema and there was no calf tenderness or erythema. Neurological exam revealed 3/5 strength in the right hand and forearm and mild ataxia on the right finger-to-nose test. The remainder of the neurologic exam was normal.

Complete blood count (CBC) revealed hemoglobin of 94 g/L (121 - 157 g/L), hematocrit of 31.5% (34.9 % - 46.1%), white cell count of 8.3 × 10^9/L (3.4 - 10.3 × 10^9/L), and a platelet count of 279 × 10^9/L (140 - 440 × 10^9/L). Electrolytes, glucose, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, creatine phosphokinase (CPK), troponin, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, bilirubin, and lipid profile were normal. Urinalysis revealed moderate occult blood and was positive for nitrites and leukocyte esterase. Urine microscopy revealed leukocytes and red blood cells. PS activity was 23% and free PS level was 40%, total PS was 51%. Protein C levels were not done as the patient was on warfarin. Genetic testing revealed the mutation to be *PROS1*, c.447G>T heterozygous (p.Trp149Cys). Factor V Leiden and

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prothrombin mutations were absent, and the antithrombin level was normal.

A non-contrast head computed tomography (CT) showed no acute abnormalities. Tissue plasminogen activator (tPA) was administered but was withdrawn because of repeated headaches. The magnetic resonance imaging (MRI) brain revealed bilateral small infarcts and one larger 1.5 cm cortical infarct in the left frontoparietal lobe; these findings were consistent with likely embolic phenomena. The magnetic resonance angiogram (MRA) of the head and neck showed no significant signs of focal stenosis, aneurysms, or vascular malformations. The carotid ultrasound, transthoracic echocardiogram, and transesophageal echocardiogram all were negative. Cardiac rhythm remained normal during her hospitalization.

Over the course of her hospital stay her arm strength began to improve.

Discussion

In our patient the level of PS, family history, and *PROS1* mutation confirmed the diagnosis of PS deficiency. This mutation has been previously described [4, 5]. Other than age, the patient has no major risk factors for stroke, including diabetes, hypertension, hyperlipidemia, coronary artery disease, smoking, or known cardiac arrhythmias. The complete work up for ATE was negative including cardiac causes, atherosclerotic changes, and other acquired and congenital thrombophilias. But, as congenital thrombophilia is quite prevalent with an incidence of about 5.07-10.09% in the general population (factor V Leiden 3-7%, prothrombin mutation 0.7-4%, protein C deficiency 0.2%, protein S deficiency 0.03-0.13% and antithrombin deficiency 0.02%) [6], the association in about one out of 10 patients with ATE can be purely coincidental. Nevertheless, it is important to recognize that PS deficiency, or a subset of patients with PS deficiency, could be associated with ATE because it would change medical management of such patients.

PROS1 mutations are studied in some patients with PS deficiency, but not all [3]. There have been more than 200 genetic mutations associated with PS deficiency [7]. Gross deletions/duplications in *PROS1* are relatively common in point-mutation-negative hereditary PS deficiency. *PROS1* mutations are reported with type I and III PS deficiency. There seems to be no correlation between genotype and phenotypes of *PROS1*. A recent report with Arg 451 mutation suggests that venous thromboembolism with this mutation is associated only with trauma, surgery or neoplasm [8]. In reported cases of PS deficiency and ATE, the levels of PS are variable suggesting that different mutations could exist, which exhibit a stronger thrombotic effect. *PROS1* mutations are not seen when the levels of PS are higher than 55%. Associating PS deficiency with ATE is difficult as the diagnosis requires either the *PROS1* mutational analysis to confirm the deficiency and/or family history with diagnostic levels of PS [9]. Additionally all known causes of acquired thrombophilias need to be ruled out. If a specific *PROS1* mutation is identified in ATE cases, the association could be more definitive.

In a 2010 meta-analysis, neonates and children showed no clear, significant relationship with PS levels and ATE or cerebral sinovenous thrombosis [9, 10]. Most of the studies in which this relation of thrombophilia and ischemic stroke is looked at, do not find supportive evidence to attribute the ischemic events purely to PS deficiency [9]; however, should the relationship exist, the treatment of patients with warfarin would be drawn into question. Prophylactic warfarin and other agents have been used in inherited thrombophilic patients in high risk situations such as pregnancy and recurrent thrombotic events but if the relationship of PS deficiency and arterial ischemic or thrombotic events is firmly established, the role of antiplatelet therapy for prophylaxis may have more benefit than with warfarin. If more cases of patients with specific *PROS1* mutations and arterial thrombotic events are identified, we may elucidate a relationship between the two and justify therapy with antiplatelet agents in a subset of patients with PS deficiency. It is quite clear and supported by the literature that currently the definitive evidence to relate arterial events to PS deficiency is not scientifically convincing.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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