Protein C deficiency resulting from two mutations in *PROC* presenting with recurrent venous thromboembolism

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**ABSTRACT**

Hereditary protein C (PC) deficiency is an autosomal dominant disorder associated with a high risk of venous thromboembolism (VTE). Here we report a case of inherited PC deficiency associated with recurrent deep venous thrombosis. Two mutations were revealed in *PROC* (c.1152C>G, p.N384K and c.1207G>T, p.G403W) by genetic testing. Results from this case suggest that the inherited PC deficiency due to the *PROC* mutations may cause recurrent VTE. Long-term anticoagulant therapy may be appropriate for these patients with recurrent VTE and hereditary PC deficiency. (J Vasc Surg Cases and Innovative Techniques 2017;3:254-6.)

Protein C (PC) is a vitamin K-dependent plasma zymogen mainly produced in the liver.1 Activated PC plays an important role in anticoagulation by inactivating the blood coagulation factors Va and VIIIa.2 The gene encoding PC (*PROC*) is located on chromosome 2q13-q14 including nine exons.3 Hereditary PC deficiency is an autosomal dominant disorder associated with a high risk of venous thromboembolism (VTE).4 The prevalence of PC deficiency in the healthy Chinese population is about 0.29%.5 Whereas the prevalence of PC deficiency in VTE patients rises to about 14% to 19%, the rate of PC deficiency caused by missense mutation of *PROC* is about 55% in China.6,7 PC deficiency is diagnosed by laboratory tests for both antigen and activity, which can be considered to be type I quantitative disorder or type II molecular dysfunction, respectively.1,8 Here we report a case of PC deficiency resulting from *PROC* missense mutations presenting with recurrent deep venous thrombosis (DVT). Signed informed consent for publication was obtained.

**CASE REPORT**

A 45-year-old man with a past history of DVT presented to our hospital with recurrent left lower extremity pain for 2 months after the withdrawal of warfarin. The patient’s mother also had a history of DVT after cholecystectomy 2 months after the withdrawal of warfarin. The patient presented to the emergency department. The patient’s fibrinogen level was 2.88 g/L; hemoglobin level, 145 g/L; hematocrit, 42.1%; erythrocyte sedimentation rate, 4 mm/h; platelet count, 122 × 109/L; prothrombin time, 15.1 seconds; activated partial thromboplastin time, 39.2 seconds; and antithrombin III activity, 64%. DVT was identified in the left lower leg by color Doppler ultrasound.

Functional protein S (PS) activity of 93% and PC activity of 41% were measured using the StaClot (Diagnostica Stago Inc, Parsippany, NJ) PS and PC activity assay, which indicated a diagnosis of PC deficiency. There was also a mild decrease in antithrombin III activity at 64%. Sequencing of the *PROC* gene revealed two heterozygous nucleotide substitutions (Fig, B), resulting in the replacement of asparagine by lysine (c.1152 C>G, p.N384K) and glycine by tryptophan (c.1207G>T, p.G403W). Anticardiolipin antibodies were within normal limits, and results of DNA analysis for PS, PC receptor, factor V Leiden, and prothrombin G20210A were all normal.

To predict possible functional effects of sequence variation on the amino acid, we analyzed the variation by two prediction software programs, Polymorphism Phenotyping (PolyPhen; http://genetics.bwh.harvard.edu/pph2/) and Sort Intolerant from Tolerant (SIFT; http://sift.jcvi.org/). The N384K and G403W variants were both identified to be functioning as “probably damaging” by PolyPhen and “affect protein function” by the SIFT program.

**DISCUSSION**

Hereditary PC deficiency is an autosomal dominant disorder associated with an increased risk of recurrent thrombosis due to a failure to attenuate the coagulation cascade. Most individuals with single heterozygosity of a *PROC* mutation are at risk for superficial thrombophlebitis, DVT, and even pulmonary embolism.3,4 Severe PC deficiency is a rare autosomal dominant disorder caused by homozygosity or compound heterozygosity for the same spectrum of mutations; it is usually manifested with purpura fulminans and severe disseminated intravascular coagulation in the neonatal period combined with concomitant VTE, leading to death if it is not adequately treated.9 In this case, the patient developed...
recurrent DVT without any precipitating factors, indicating a deeper mechanism for anticoagulant abnormality. On the basis of our clinical experience, adolescent patients with recurrent VTE, especially with a family history of thrombosis and in the absence of precipitating factors, should undergo further examination for anticoagulant deficiencies, such as PC, PS, and antithrombin III deficiencies. Although PC deficiency can be easily detected, many factors influence the plasma PC level, such as vitamin K-based anticoagulant therapy as well as severe infections, liver disease, fresh thrombosis, oral contraceptive use, and presence of autoantibody, all of which had been excluded in this case. According to the patient’s clinical manifestations and laboratory examinations, we could tell the patient had a defect in both antigen levels and activity.

The heterozygous nucleotide substitution C>A in codon 1152 (p.N384K) had already been reported to be related to PC deficiency. To the best of our knowledge, the heterozygous nucleotide substitution G>T in codon 1207 has never been reported before; it results in the replacement of glycine by tryptophan (G403W), analyzed to be “probably damaging” by PolyPhen and “affect protein function” by the SIFT program. Previous researchers showed that genomic abnormalities would result in missense changes, aberrant polypeptide chains or premature termination codons, or abnormal splicing precluding DNA transcription. Molecular mechanisms underlying the single-nucleotide substitutions resulting in amino acid changes may be associated with impaired secretion and partial intracellular degradation of PC mutants, lower affinity for binding to the endothelial cell PC receptor, and impaired anticoagulant activity in the presence of PS. This is the first described case to show heterozygous quantitative and qualitative PC deficiency with the two mutations of PROC (c.1152C>G, p.N384K; c.1207G>T, p.G403W) and recurrent VTE.

Patients with low PC levels and the known mutation within PROC are at increased risk for recurrent thromboembolism events and need anticoagulation after the initial episode. This patient suffered left lower extremity pain 2 months after the first episode. Anticoagulant should be an option for this circumstance. As we know, there are numerous therapeutic alternatives for long-term management of hereditary PC deficiencies. For treating heterozygous PC deficiency, oral anticoagulation with a coumarin derivative or heparin remains standard therapy. Typical treatment of PC-deficient patients with oral anticoagulants for 6 months after the occurrence of the first thrombotic episode is recommended, but patients who experience subsequent thrombotic episodes need lifelong anticoagulation treatment to prevent a hypercoagulable state. Homozygous patients may be treated with fresh frozen plasma and PC concentrate or coumarin derivatives. Additional therapeutic options for the treatment of hereditary PC deficiency...
include low-molecular-weight heparin, steroids, and liver transplantation. However, liver transplantation still faces big challenges. Therefore, we suggest liver transplantation as an alternative therapy for patients with severe PC deficiency who have failed to respond to anticoagulant therapy. In cases of positive family history, including death from VTE among first-degree relatives, genetic counseling should be implemented, and appropriate thromboprophylaxis with high-risk status should be considered in asymptomatic carriers. The patient’s mother also had a history of DVT in our case, suggesting that genetic counseling is advised for his family members.

CONCLUSIONS

Genetic testing is suggested when PC deficiency is suspected. Genetic examination could be a valuable diagnostic tool to help identify PROC mutations for the PC-deficient patient. The described mutations in PROC (c.1152C>G, p.N384K and c.1207G>T, p.G403W) seem to have clinical relevance with functional PC deficiency. Therefore, the patient was advised to have a lifestyle change or to start extended prophylactic therapy.

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