

Two Cases of Recurrent Vascular Events Due to Protein C Deficiency

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Abstract

Protein C deficiency is a rare autosomal dominant disorder with a characteristic of hypercoagulation state and recurrent venous thrombosis in clinics. It is one important cause for youth vascular ischaemic events including cerebral stroke. However, less attention was focused on the disorder of protein C deficiency so that misdiagnosis is very common. Here, we reported two cases of recurrent vascular ischaemic events due to protein C deficiency. They accepted warfarin and fresh frozen plasma respectively and fully recovered. Our report suggest the importance of early recognition of protein C deficiency in youth with recurrent vascular thrombosis and personalized management should be emphasized.

Keywords Protein C deficiency; Thrombosis; Anticoagulation; Fresh frozen plasma

Introduction

Protein C (PC) deficiency induces hypercoagulation state and subsequently makes individuals at high risk of thromboembolism. It is usually a common cause for youth venous ischaemic events such as deep venous thrombosis and is an uncommon one for arterial thrombosis like cerebral stroke, eventually contributing to the detrimental impact on the health of the young [1,2].

PC is a vitamin K-dependent plasma glycoprotein that exerts a critical role in the regulation of coagulation [3-5]. PC is produced in hepatocytes, which circulates in an inactive form. As thrombin binds to the membrane protein thrombomodulin, PC can be activated on the endothelial cells and consequently acts as an anticoagulant via inactivating the procoagulation factors, factors V (FV) and VIII (FVIII). Therefore, PC deficiency leads to coagulation disorders as the form of Thrombophilia.

PC deficiency is inherited as an autosomal dominant disorder with a morbidity of 0.02-0.5% [6], and is identified when the PC concentration or activity is below 60-70% of the normal value (normal concentration, 4-5 mg/L; normal activity, 70-140%) [7]. Clinical presentation of PC deficiency varies. Mild PC deficiency is often asymptomatic but may involve venous thrombosis because of imbalances between procoagulant and anticoagulant pathways. While moderate-severe PC deficiency would lead to deep venous thrombosis, pulmonary embolism, parenchymal thrombi and DIC [7] in adolescents and adults and purpura fulminans in neonate [8]. One feature of this disease is the repeated occurrence of vascular thrombosis in diverse parts or organs of bodies. In particular, arterial thrombosis involved in several parts related with PC deficiency is rarely reported [2]. Currently, there are no guidelines for treatment of PC deficiency. Most patients with PC deficiency do not need treatment. Patients who have venous clots, recurrent thromboembolic events or at high risk of further episodes may be considered for anticoagulation involving low-

molecular-weight heparins and warfarin [7]. Fresh frozen plasma or PC concentrates is recommended, when patients have the risk of death from thrombosis [9].

Here, we report two cases of PC deficiency patients who experienced recurrent vascular ischaemic events, with the aim to highlight the importance of early recognition or diagnosis of PC deficiency and personalized management in young patients with recurrent vascular events.

Case presentation

Patient 1

A 33-year-old male was admitted to our hospital with a sudden onset of left-sided hemiparesis on Sep. 23, 2014. Recurrent epileptic seizures of left side limbs occurred before his admission. In 2009, the patient experienced deep vein thrombosis in his lower limbs. On Apr. 12, 2014, he developed a mesenteric venous thrombosis and portal venous thrombosis. He was a 27-year-old male in good health when he developed deep vein thrombosis. The patient had neither hypertension nor diabetes, and there were no obvious precipitants of thrombosis. He also denied habits of smoking and drinking. The family history about vascular events of the patient was unremarkable.

His general physical examination was normal. Neurological examination showed slightly hypoesthesia of the left limbs and trunk. He had Medical Research Council grade 4/5 muscle power over the left limbs. Laboratory tests including routine blood parameters, blood biochemistry, erythrocyte sedimentation rate, hyperhomocysteinemia, platelet count, platelet aggregation, prothrombin and partial thromboplastin times, factor VIII, antithrombin III activity, and protein S were within normal limits. Fibrinogen was slightly lower than the normal value. Tests of HIV, RPR and TPPA, syphilis and hepatitis were negative. However, functional activity of plasma protein C was just 23.1% (normal, 70-140%) (Table 1). The cerebrospinal fluid (CSF) opening pressure was 190 mmH₂O without any other abnormality. Cardiologic investigations including electrocardiography,

Holter electrocardiographic monitoring, and two-dimensional echocardiography did not suggest any abnormality. Double carotid chromatic ultrasonic (DCCU) did not show arteriosclerotic lesions in bilateral carotid. Brain magnetic resonance imaging (MRI) showed an ischaemic lesion on the right frontal lobe (Figure 1).

	Patient 1		Patient 2	
	Pre	Post	Pre	Post
PC (70-140%)	23.1	8.2	8.2	12.2
PS (60-130%)	95.1	72.0	122.2	94.1
PT (10.7-14.4 s)	11.9	30.3	11.6	12.9
APTT (23.5-35.0 s)	25.9	43.0	26.9	30.0
FBG (2.0-4.0 g/l)	1.62	2.28	2.31	3.49
D-II (0-0.55 ng/l)	4.72	0.08	-	2.86
INR	1.08	2.02	1.02	2.05

Table 1: Coagulation parameters and PC alteration of the two patients before and after treatment. Pre: Pre-treatment; Post: Post-treatment; PC: Protein C; PS: Protein S; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; INR: International Normalized Ratio.

According to clinical feature and laboratory and imageological findings, this patient was diagnosed as acute ischaemic stroke caused by PC deficiency. Then he was administrated with long-term anticoagulation with warfarin at the dose of 3 mg/day following initial anticoagulation with low molecular weight heparin 25,000 units/day for 10 days. No complications especially coumarin necrosis were observed during his treatment course, while fine response to this therapy with improvement in hemiparesis was observed. One month after the anticoagulation therapy, he was totally asymptomatic with improved brain MRI (Figure 2). Currently, this patient is in good condition with regularly monthly monitoring of prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR) (Table 1).

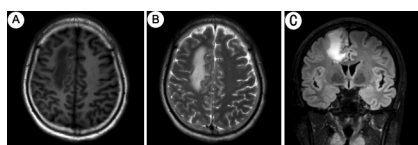


Figure 1: T1WI (A), T2WI (B) and FLAIR (C) of Patient 1 brain MRI showed the infarct lesion on the right frontal lobe at the time of onset.

Patient 2

On Jan. 25, 2014, a 26-year-old male was admitted to our hospital with complaints of repeated painful swelling of his lower limbs for 10 years. He had neither hypertension nor diabetes, and there were no obvious precipitants of thrombosis. He also denied the habits of smoking and drinking. His family history about vascular events was unremarkable. Laboratory tests including routine blood parameters, blood biochemistry, hyperhomocysteinemia, platelet count, platelet

aggregation, prothrombin and partial thromboplastin times, factor VIII, antithrombin III activity, fibrinogen and antithrombin III concentrations, and protein S were within normal limits. Tests of HIV, RPR and TPPA, syphilis and hepatitis were negative. However, functional activity of plasma PC was only 8.2% (Table 1). Vascular Ultrasound confirmed deep venous thrombosis in lower limbs. Finally, Patient 2 was diagnosed as PC deficiency as well and accepted anticoagulation treatment with warfarin similar to Patient 1. Unfortunately, the clinical manifestation of Patient 2 was not relieved. Then he was treated with fresh frozen plasma at the dose of 2 units/day for successive three days. On Day 4, the painful swelling of his lower limbs dramatically alleviated. He was kept on anticoagulation therapy with warfarin and regularly monitored with PT, APTT and INR. At present, he is under our constant observation and does not show any deterioration.

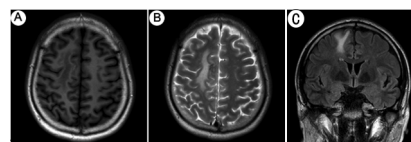


Figure 2: T1WI (A) T2WI (B) and FLAIR (C) of Patient 1 brain MRI showed the reduced infarct lesion located at the right frontal lobe one month later after anticoagulation therapy.

Discussion

The natural profibrinolytic system consists of protein C, protein S and thrombomodulin [10]. PC exerts its anticoagulant function through regulation of activities of FVIIIa and FVa. PC deficiency encompasses two subtypes, type I and type II [11,12]. Type I is more common than type II. Both concentration and functional activity of PC are equally reduced in type I while Low PC activity but normal concentration observed in type II. The capacity of anticoagulation in PC deficiency is reduced so as not to effectively counteract procoagulation of thrombin generated by FVa and FVIIIa, finally leading to recurrent attacks of thromboembolisms. The prevention of recurrent thrombosis is critical. Medical treatment of this condition includes administration of heparin, warfarin, fresh frozen plasma and PC replacement [7].

Although there are many important diagnostic laboratory and imaging technologies, the cause and risk factors for young adult stroke are often rare or undetermined [13].

Most stroke cases do not require evaluation of coagulation, but hypercoagulability is a significant reason for unexplained strokes, especially for youth strokes. A study of young Indians revealed that PC deficiency alone or in combination with PS deficiency is significantly associated with ischaemic stroke in young adults [14,15]. However, the impact of PC deficiency on recurrent vascular ischaemic risk is less well defined and needs to be further investigated [16].

Patient 1 experienced several dangerous vascular events including deep vein thrombosis of low limbs, mesenteric venous thrombosis and portal venous thrombosis. He was not correctly diagnosed and suffered from recurrent thrombosis until the acute ischaemic stroke. It implied that this disorder is not well recognized in clinics and more attention should be paid. Pleasantly, treatment with heparin and long-term warfarin was gratifying. Patient 2 has been unluckily

misdiagnosed for 10 years and furthermore, anticoagulation therapy didn't receive good response. However, Patient 2 were finely responded to treatment with fresh frozen plasma and symptoms of his lower limbs remarkably alleviated. This is probably due to that warfarin sensitivity depends on factors such as age, diet, drug interactions, smoking status, concomitant diseases and genetic variability [17,18]. It is reported that CYP4F2 is able to influence warfarin pharmacokinetics and pharmacodynamics via reduction of vitamin K metabolism [19].

In conclusion, more attention to protein C deficiency should be paid for early diagnosis when patients manifested as recurrent vascular thrombosis in youth and personalized management should be emphasized.

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