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Clinical characteristics, genes identification and follow-up study of a patient with central venous thrombosis from a protein S deficiency pedigree

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Abstract. – OBJECTIVE: To explore the clinical and prognostic features of CVT caused by PROS1 gene mutations and to provide clinical experience for new oral anticoagulants, such as rivaroxaban, in the treatment of CVT with a high risk of thrombosis.

PATIENTS AND METHODS: The CVT patient's clinical symptoms were described, and the brain imaging and blood coagulation tests were performed to confirm the diagnosis of CVT. The patient's family members were recruited to receive blood coagulation tests and ultrasonic examination of lower limb vessels. Genetic analysis on the pedigree was carried out to identify the responsible gene for PS deficiency. We followed-up with this patient for 24 months to evaluate the clinical outcomes, laboratory results and imaging performances of CVT.

RESULTS: The patient presented with typical CVT symptoms, including headache and epilepsy. Brain CT showed hemorrhage in the bilateral frontal lobe and left occipital lobe, while MRV demonstrated that thrombus had occurred. It was reviewed that the patient and his mother had a history of bilateral leg deep vein thrombosis. Gene tests revealed that the patient and two family members carried a heterozygous mutation of PROS1 (c.751_752delAT, p.M251Vfs*17). During 24 months of follow-up study, the patient was treated with rivaroxaban continuously and recovered well, supported by an mRS score that remained below 2. Blood coagulation tests were within normal limits, and MRV revealed partial recanalization of the cerebral venous sinus.

CONCLUSIONS: The frame shift mutation in the PROS1 gene (c.751_752delAT) may greatly affect the function of protein S and lead to a severe phenotype of CVT. Rivaroxaban showed a satisfying therapeutic effect in this CVT patient with hereditary thrombophilia.

Key Words:
Cerebral venous thrombosis, Thrombophilia, Protein S deficiency, PROS1, Rivaroxaban.

Introduction

Cerebral venous thrombosis (CVT) is a rare cerebrovascular disease with variable clinical manifestations, including headache, epilepsy and coma[1,2]. With the development of magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) techniques, the diagnosis of CVT is not difficult. The majority of CVT patients can achieve a good prognosis if effective anticoagulant therapy is taken up in time[3-5]. Hereditary coagulation disorders, including protein S (PS) deficiency, are believed to be significant risk factors for CVT. However, only few cases with a clear correlation between CVT and PS deficiency have been reported[6,7]. For patients with hereditary thrombophilia, existing guidelines recommend Vitamin K antagonists (VKAs) as anticoagulation therapy for long-term treatment[8], while the use of new oral anticoagulants (NOAC) for the prevention of thrombotic events is still lacking clinical evidence[9-11].

Two years ago, we received a 32-year-old male patient presenting with headache and epilepsy as the main clinical symptoms, who was diagnosed with CVT by imaging techniques. Through receiving appropriate anticoagulation therapy, the patient recovered well. After reviewing that the patient had an 8-year history of bilateral leg

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deep vein thrombosis (BL-DVT), we traced the patient's family history and found that he came from a pedigree with hereditary thrombophilia. Utilizing gene sequencing analysis, we observed that the patient, along with his two relatives, suffered from PS deficiency. This patient was treated with rivaroxaban after being discharged, and we conducted a long term followed up examining the clinical outcomes, laboratory results and imaging performances.

Patients and Methods

Patients Conditions

A 32-year-old male was admitted to the hospital with a headache lasting for more than 10 days and epileptic seizures for 1 hour. We conducted brain computed tomography (CT), MRI and MRV, and performed blood coagulation tests such as prothrombin time, activated partial thromboplastin time and D-dimer to confirm the diagnosis of CVT. Then, the patient underwent anticoagulation and antiepileptic therapy. As a result, his symptoms gradually improved. All the abnormal results of blood coagulation were retested before he was discharged.

Pedigree Analysis

We traced the patient's possible risk factors of CVT and discovered that he was from a pedigree with thrombophilia. The patient's mother and son were recruited to receive blood coagulation tests and ultrasonic examination of the lower limb vessels, and we observed significant decreases on protein S activity in the blood samples of all three family members. Therefore, we performed genetic analysis on the pedigree and identified a frame shift mutation on the PROS1 gene, which caused a protein S deficiency.

Follow-Up Study

After being discharged, the patient visited Shanghai Ruijin Hospital and was treated with oral rivaroxaban 10 mg daily. We conducted a 24-month follow-up of this patient to evaluate the primary outcome with a CVT grading scale (CVT-GS) and modified Rankin Scale (mRS), as previously described[12]. Blood coagulation tests, lower limb vessels ultrasound and brain imaging were adopted to assess the recovery of CVT and other recurrent thrombotic events.

Results

Diagnosis and Treatment of CVT

The patient, a 32-year-old male, presented with headache due to fatigue and drinking 10 days ago. He complained of persistent, swelling pain in his forehead and fever 3 days later (the highest body temperature was 37.7°C), without vomiting or paralysis. The patient was treated with antibiotics (ceftriaxone 2 g/day) for 7 days; however, this treatment did not alleviate his symptoms. About 1 hour before admission, the patient suddenly suffered a loss of consciousness, convulsions of the limbs, upward rolling of the eyes and clenching of teeth, which lasted for about 3-4 minutes and repeated for three times. Brain CT was conducted urgently and showed a hyper intense clot in the left transverse sinus, as well as hemorrhage in bilateral frontal lobe and left occipital lobe (Figure 1A, B). Later, the patient's brain MRI revealed venous infarction with hemorrhage in the genu of the corpus callosum and bilateral thalamus (Figure 1C, D). MRV demonstrated thrombus in the superior sagittal sinus and straight sinus, along with complete occlusion of the left transverse sinus and sigmoid sinus, (Figure 1E, F). Blood tests, including prothrombin time, partially activated prothrombin time and D-dimer, were adopted to identify thrombophilia in the patient (Table I). We treated the patient with low molecular weight heparin (LMWH) and gradually transferred to VKA treatment as anticoagulant therapy in time. The international normalized ratio (INR) was maintained at approximately 2.6 (target 2.0-3.0). After 23 days of treatment in the hospital, the symptoms, including headache, were significantly relieved and no epileptic recurrence was observed during regular antiepileptic therapy of oral sodium valproate 500 mg twice a day. We re-examined the blood coagulation tests and noticed significant recoveries before the patient was discharged from the hospital (Table I).

Family Symptoms and Gene Analysis

We evaluated the risk factors of CVT for this patient and noticed that he had an 8-year history of BL-DVT. Moreover, his mother's history of BL-DVT was also remarkable. It was discovered that the patient's grandfather and aunt might also have symptoms of BL-DVT, such as skin discoloration of the lower extremities and intermittent claudication. The patient and his mother (55 years old) underwent ultrasonic examination, demonstrating multiple hypoechoic lesions in the lower

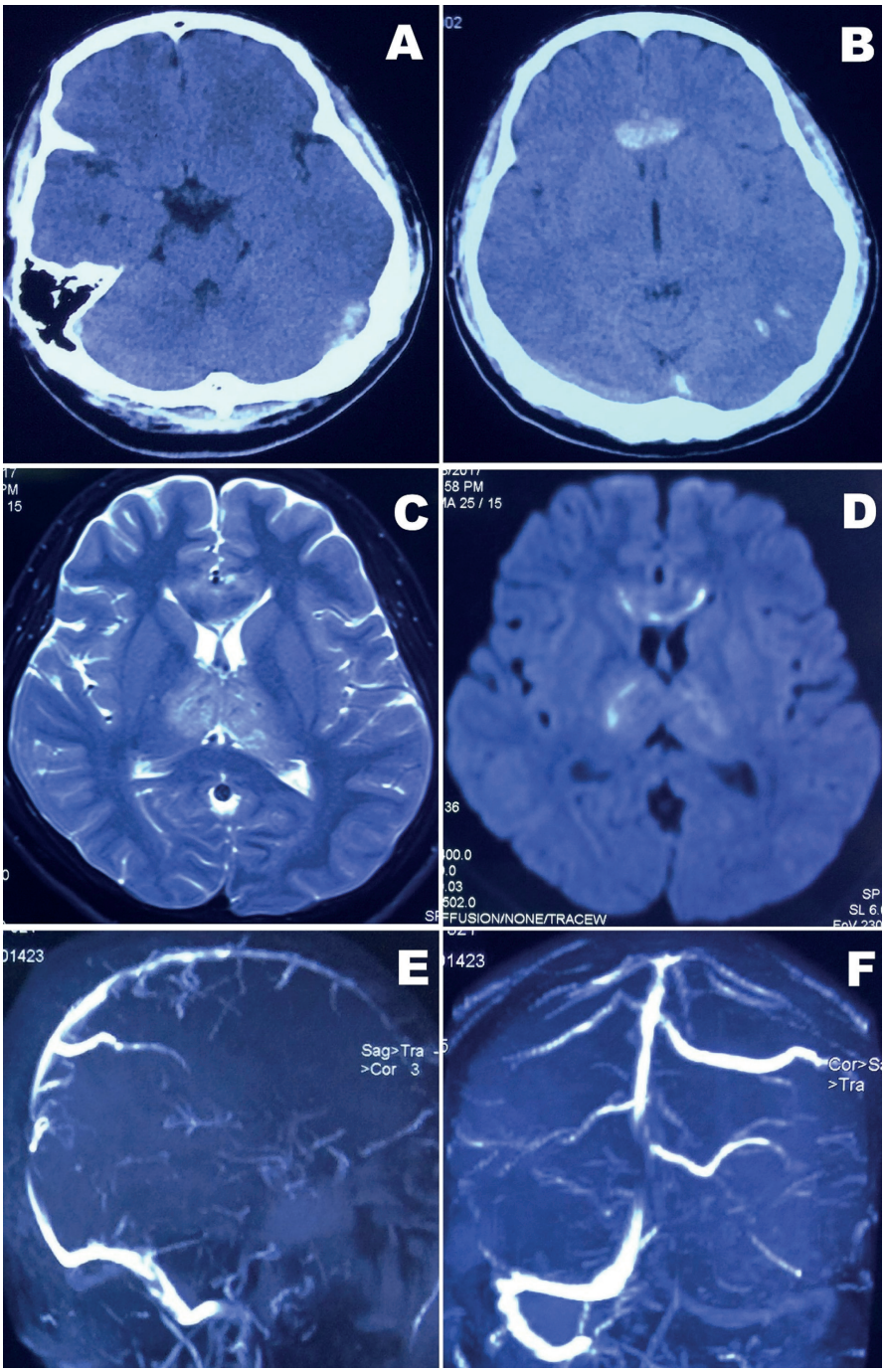

Figure 1. Brain images of the patient at admission. Brain CT demonstrated **(A)** hyperintense clot in the left transverse sinus and **(B)** hemorrhage in bilateral frontal lobe and left occipital lobe. Brain MRI revealed T2WI **(C)** and DWI **(D)** high signals in the genu of corpus callosum and bilateral thalamus, suggesting venous infarction with hemorrhage. MRV showed **(E)** the patency of superior sagittal sinus and straight sinus was compromised, and **(F)** occlusion of left transverse sinus and sigmoid sinus presented due to venous thrombosis.

Table I. Blood coagulation test results during hospitalization.

	PT-s	APTT-s	PT-INR	D-Di	FDP
At admission	13.2	39.9	1.03	17.59	52.98
At discharge	28.2	77.7	2.63	6.07	21.37

PT-s, prothrombin time (11-14.5 seconds). APTT-s, activated partial thromboplastin time (28-45 seconds). PT-INR, international normalized ratio (0.8-1.2). D-Di, D-dimer (<0.5 μg/ml). FDP, fibrinogen degradation products (<5 μg/ml).

limb vessels (Figure 2A), while the result of the patient's son (8 years) was normal. We carried out blood coagulation tests and found that D-dimer was significantly increased in the patient's mother and that protein S activities were significantly diminished in both his mother and son (Table II). Therefore, we employed sequence analysis on coagulation-related genes and revealed a heterozygous deletion mutation in the PROS1 gene (c.751_752delAT, M251Vfs*17), which existed in all three subjects, and which may greatly affect the function of protein S. Additionally, the patient and his son were found to carry another heterozygous mutation (c.577_579delAAG, K193del) in

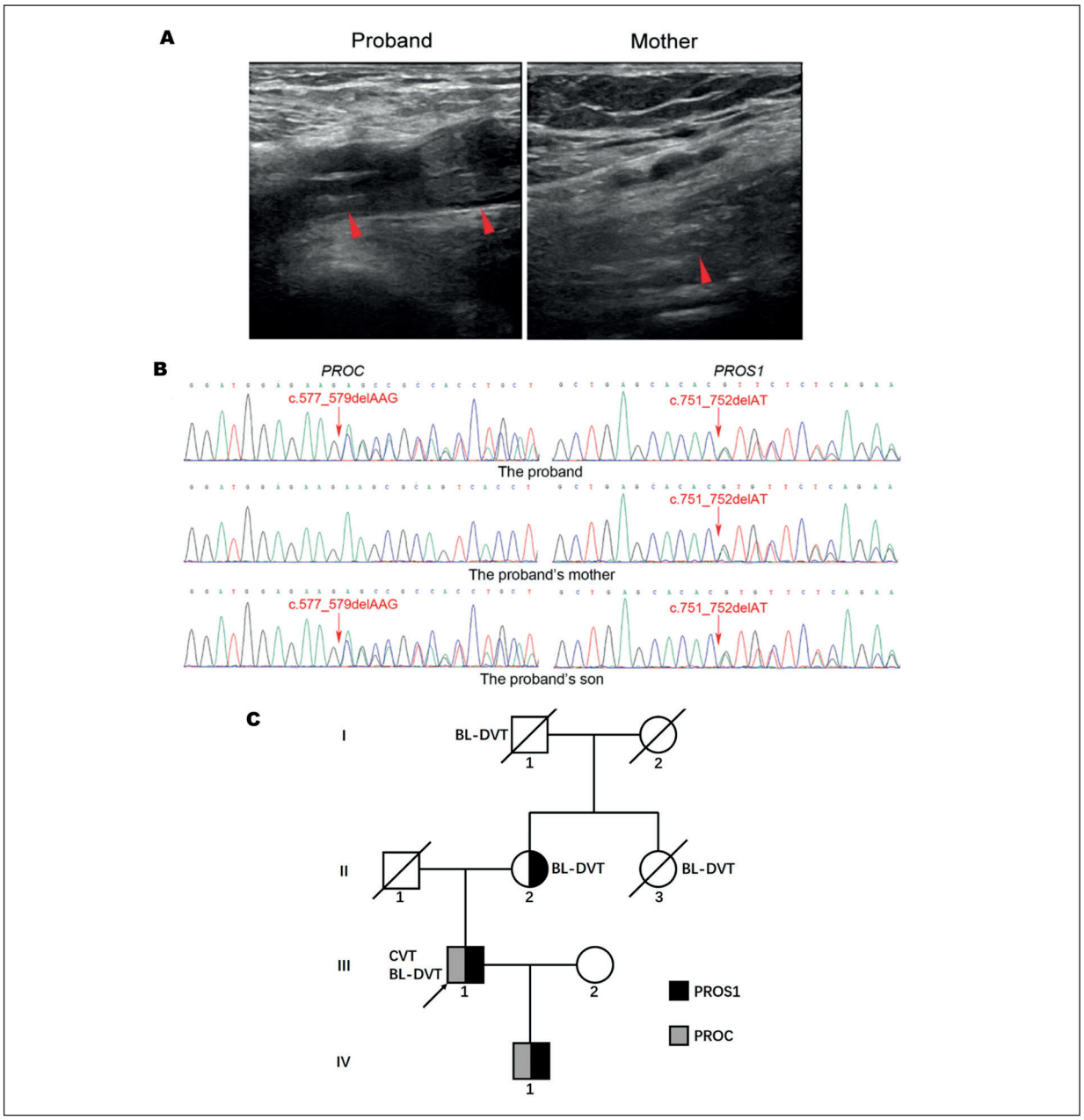

Figure 2. Ultrasound finding and gene identification of the patient's pedigree. **A,** Ultrasound showed thrombus developed in superficial femoral vein, common femoral vein, popliteal vein and posterior tibial veins of the patient, and popliteal vein of his mother as pointed by the arrows. **B,** Gene analysis demonstrated the patient (the proband) and his mother and son carried a heterozygous mutation of PROS1 (c.751_752delAT), whereas the mutation of PROC (c.577_579delAAG) was not detected in the mother, as red arrows emphasized. **C,** The family tree was drawn to reveal gene mutations and clinical symptoms of the patient's pedigree, arrow pointed the patient (III-1).

Table II. Blood coagulation tests results of the patient's family.

	PT-s	APTT-s	PT-INR	D-Di	FDP	PS (%)	PC (%)
Patient (using warfarin)	28.2	77.7	2.63	6.07	21.37	36.2	107
Mother	14.8	47.7	1.14	2.83	7.13	39.8	91
Son	14.7	39.4	1.13	0.72	3.30	43.2	103

PS (%), Protein S (60-130%). PC (%), Protein C (70-130%). Remaining abbreviations are listed in Table I. Other blood tests had been adopted to exclude coagulation factor disorders, antiphospholipid syndrome, systemic lupus erythematosus and hyperhomocysteinemia (data not show).

the PROC gene, which was not detected in the patient's mother (Figure 2B). This mutation may be associated with protein C deficiency, but the protein C activities of the subjects did not appear to be decreased (Table II). The coagulation-related gene mutations and clinical characteristics of the patient's pedigree are shown in Figure 2C.

Prognosis and Follow-up

The patient was prescribed rivaroxaban (10 mg/day) regularly after discharge. Since no seizures recurred, he was placed on sodium valproate 500 mg twice a day with gradual dose reduction and eventual suspension after 6 months. With a CVT-GS of 4 points (male and parenchymal hemorrhage), the severity of the patient was estimated to be moderate. During 24 months of follow-up, the patient occasionally had mild headaches, with no significant cognitive decline or disability. The outcome was classified according to the mRS, which revealed that the patient recovered well (Table III). The blood coagulation tests were within normal limits, and ultrasonic examinations were employed to evaluate the improvement of BL-DVT during treatment (Table III). The patient's brain MRI showed old hemorrhagic areas in the left parietal-occipital lobe, in the genu of corpus callosum and in the bilateral thalamus. MRV demonstrated local stenosis of the left transverse sinus, sigmoid sinus and interruption of the straight sinus (Figure 3). These results suggested that a partial recanalization of cerebral venous had been achieved in the patient.

Discussion

CVT is a rare cerebrovascular disease with serious clinical symptoms, which accounts for about 0.5%-1% of all strokes and mainly occurs in young patients[13]. Although blood tests and imaging examinations can provide evidence for the recognition of CVT, tracing the aetiology and risk factors for patients is crucial for both the diagnosis and the treatment. Risk factors can be divided into acquired factors (such as pregnancy, dehydration, infection, and substance abuse), and genetic risks (especially inherited thrombophilia)[14]. This patient had acquired factors, including fatigue and dehydration, which can lead to a disorder in blood viscosity. Moreover, hereditary PS deficiency may contribute to severe CVT. Through genetic identification, we discovered that the patient and his family members carried a heterozygous mutation in PROS1, which greatly impacted the function of PS. The patient's mother, who also had a history of BL-DVT, was found to have significantly decreased PS activity. The same findings were also discovered in the patient's son, therefore suggesting that this frame shift mutation in the PROS1 gene follows autosomal-dominant inheritance. PS is a vitamin K-dependent single-chain plasma glycoprotein, mainly synthesized in hepatocytes. As a cofactor of PC, PS enhances the affinity of activated PC with the phospholipid membrane, then accelerates the inactivation of factor Va (FVa) and factor VIIIa (FVIIIa) to inhibit the blood coagulation

Table III. Prognosis of the patient after discharge.

	mRS	D-Di	BL-DVT in ultrasound
3 months	1 (Headache)	1.82	SFV, CFV, PV, PTV, GSV
12 months	0	0.22	SFV, CFV, PV, PTV
24 months	0	0.27	CFV, PV, PTV

BL-DVT, bilateral leg deep vein thrombosis. SFV, superficial femoral vein. CFV, common femoral vein. PV, popliteal vein. PTV, posterior tibial veins. GSV, great saphenous vein.

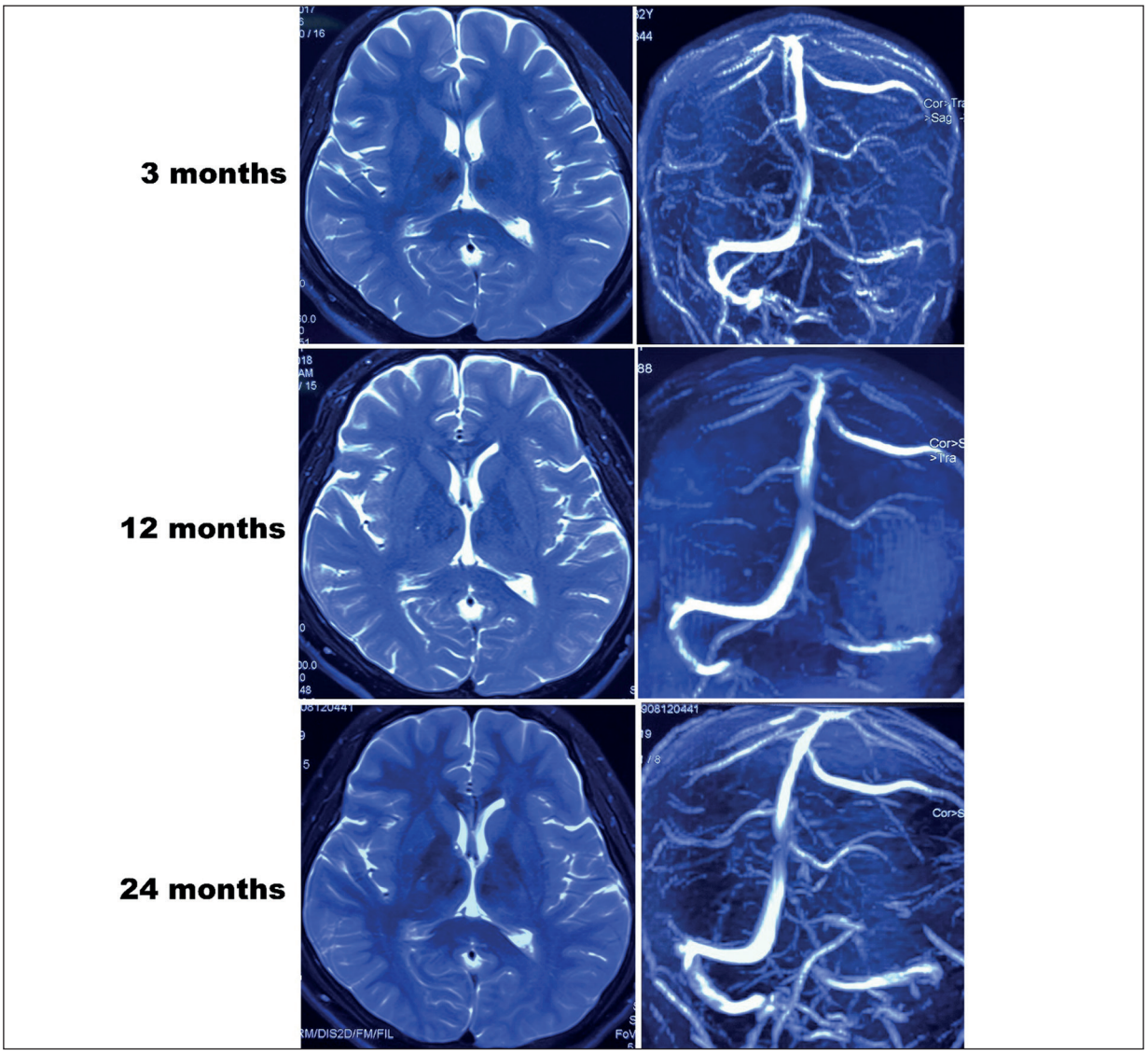

Figure 3. Brain MRI and MRV of the patient after discharge. MRI showed T2WI low-signals in the genu of corpus callosum and bilateral thalamus, suggesting old hemorrhagic areas. MRV revealed the left transverse sinus and sigmoid sinus achieved partial recanalization, whereas interruption of straight sinus was observed during the follow-up.

cascade[15,16]. Furthermore, PS also decreases blood coagulation by directly inhibiting the activity of FIXa-VIIIa complex and prothrombin (FXa-Va)[17]. Studies have demonstrated that PS deficiency is one of the major risk factors of venous thromboembolism (VTE) in Asian populations, increasing the risk of VTE by about 10-fold[18-20]. A certain correlation between PS deficiency and CVT has been confirmed. Two studies have analysed the horizontal comparison of 172 CVT patients with healthy control subjects and revealed that the combined odds ratio (OR) of CVT for PS deficiency was 12.5 (95% CI 1.45 to 107.29; p=0.03)[8,21,22]. A clinical and genetic analysis of 53 Chinese pedigrees with PS deficiency showed that about 7.5% (four cases) of patients developed CVT[23]. Therefore, it is crucial to examine PS activity and identify the underlying responsible genes in CVT patients with coagulation disorders.

We noticed that through genetic analysis, we discovered that both the patient and his son carried a heterozygous mutation on the PROC gene (c.577_579delAAG), which was not found in his mother and which was considered to be associated with PC deficiency[24]. Due to the lack of evidence regarding the genotype of the patient's paternal relatives, we cannot conclude whether this mutation was inherited from the patient's fa-

ther. In our study, the activities of PC in both the patient and his son were normal, indicating that this mutation may not greatly affect the function of PC in these individuals. Of note, during 24 months of follow-up, the son who carries both PROS1 and PROC gene mutations did not show any clinical symptoms without anticoagulation treatment. It has been reported that the levels of prothrombotic factors can be normal in children with inherited coagulation disorders, whereas endogenous fibrinolytic factors, such as PC and PS, may decrease with age[25,26]. It is necessary to monitor blood coagulation for the patient's family members and to carry out early interventions on thrombophilia in the future.

Currently, existing evidence from clinical data supports prompt and regular anticoagulation as a reasonable treatment for patients with CVT, regardless of the presence of intracerebral haemorrhage (ICH)[27-29]. In this study, the patient received LMWH in full anticoagulant doses followed by warfarin, and he recovered well, with an INR maintained at approximatively 2.6 at discharge, whereas ICH had been absorbed completely on CT. To reduce the recurrence of CVT, the ASA/AHA guideline recommends indefinite anticoagulation for patients with severe thrombophilia, including protein S deficiency, with a target INR of 2.0 to 3.0 using oral VKAs[8]. However, this patient chose rivaroxaban for his long-term anticoagulant therapy after discharge. Rivaroxaban is a specific factor Xa inhibitor approved for the treatment of VTE and stroke due to nonvalvular atrial fibrillation (AF). Because of their convenience and effectiveness, a variety of NOACs, including rivaroxaban, are being widely used for the prevention of thrombotic events[30]. We also observed that the clinical manifestation of BL-DVT in this patient was gradually improved during the follow-up, with treatment using rivaroxaban. At present, there is still a lack of evidence from large clinical trials to determine the role of rivaroxaban in the treatment of CVT and the prevention of recrudescence. In a series of follow-up studies on CVT patients who chose rivaroxaban over warfarin, rivaroxaban showed similar clinical benefits as VKAs, and no serious bleeding events were detected[31,32]. In one clinical study, seven CVT patients who received rivaroxaban were followed-up with MRV for at least 3 months. Rivaroxaban demonstrated non-inferiority to VKAs with regard to the long-term outcome as well as complete overall recanalization[33]. Another study followed twenty CVT patients treated with rivaroxaban. During the average 6 months of follow-up, complete recanalization was detected in twelve cases (60%) and partial recanalization was detected in eight cases (40%), while ICH was observed in eleven cases (55%)[34]. These results suggest that rivaroxaban might be a desirable treatment alternative to VKAs due to its effectiveness and metabolism benefits. In addition to recanalization, D-dimer was considered to be a significant element for evaluating the outcome of CVT. Studies demonstrated that D-dimer levels showed high sensitivity to determine the risk of recurrent VTE in patients with DVT or pulmonary embolism[35]. In another study, the concentration of D-dimer could be used as a factor for the prediction and identification of patients with CVT detection[36]. In this study, during the follow-up of nearly 24 months, the patient's venous sinus was partially recanalized, and D-dimer was maintained at a normal level. It can be inferred that our patient had a good prognosis with rivaroxaban for long-term anticoagulation.

Conclusions

In conclusion, we have developed a report of a CVT patient with a hereditary protein S deficiency that describes the clinical characteristics and identifies the defective gene of the pedigree, while following up on the patient's outcome. We demonstrated that a heterozygous mutation in the PROS1 gene (c.751_752delAT, p.M251Vfs*17) can lead to a significant decrease in protein S activity, which resulted in CVT and VTE in carriers. Our patient was prescribed rivaroxaban for long-term anticoagulation, which indicated that it was effective for the treatment of CVT and VTE. This study provides clinical experiences for the diagnosis and treatment of CVT patients with a hereditary protein S deficiency.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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