

Hereditary hyperactivity of coagulation factor ix caused by a large fragment gene duplication as a rare etiology of cerebral venous sinus thrombosis

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Weihai Xu^a, Ming Yao^{a*}****ABSTRACT**

Background: Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease with a relatively high mortality and disability, which mainly affects young adults and children. Anticoagulation is currently the mainstay of treatment. Rapid diagnosis and prompt identification of the etiology of CVST are of great significance for the prognosis of this potentially life-threatening condition.

Case presentation: We presented a case of recurrent cerebral venous sinus thrombosis complicated with deep venous thrombosis (DVT) due to a large fragment duplication of the factor IX gene region on the X chromosome in a young adult. Long-term rivaroxaban anticoagulant treatment was suggested, and no thrombosis events occurred under regular follow-up.

Conclusion: Hereditary hyperactivity of coagulation factor IX is one of the relatively rare causes of hereditary hypercoagulability, which often causes venous thrombosis of lower limbs and rarely involves intracranial venous sinus, expanding the spectrum of etiology of this disorder and deserves attention.

KEYWORDS: Cerebral venous sinus thrombosis; Hereditary Hypercoagulability; Factor IX; Etiology; Treatment.

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease with a relatively high mortality and disability, which mainly affects young adults and children. Rapid diagnosis and prompt identification of the etiology of CVST are of great significance for the prognosis of this potentially life-threatening condition. We herein report a young male patient of recurrent cerebral venous sinus thrombosis complicated with deep venous thrombosis. A comprehensive investigation demonstrated a hereditary hypercoagulability due to a large fragment duplication in the coding region of the factor IX gene. Lifelong anticoagulation was thus suggested, the thrombotic event was not observed under regular follow-up.

CASE PRESENTATION

The patient was a male college student in his 20s who was admitted to Peking Union Medical College Hospital with a diagnosis of recurrent CSVT and DVT in 2020. He was first diagnosed with left CSVT (Fig. 1a-d) due to occipital pain and blurred vision in 2015. After

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interventional thrombectomy, anticoagulation by low-molecular-weight heparin (LMWH) was given for 1 month and followed by three years of oral warfarin treatment. A slight elevation of homocysteine was found simultaneously. All the symptoms gradually relieved post-thrombolysis except for an increased intracranial pressure. In November 2020, he was locally hospitalized again due to blurred vision and headache. A dural arteriovenous fistula secondary to new onset of CSVT was detected by Digital subtraction angiography (DSA) (Fig. 1e-g), therapeutic embolization of the dural arteriovenous

fistula was performed, followed by a short-term LMWH anticoagulation therapy. One month later, DVT was demonstrated in both lower limbs. Rivaroxaban was prescribed. Past medical history: The patient had less facial hair and was prone to acne after puberty. Deny a family history of venous thrombosis. Physical examination: body mass index (BMI) 27.8 kg/m², multiple acnes on the face, less body hair. Left eye abduction is limited, and diplopia can be reached when looking to the left side. Other neurological physical examinations showed no positive signs.

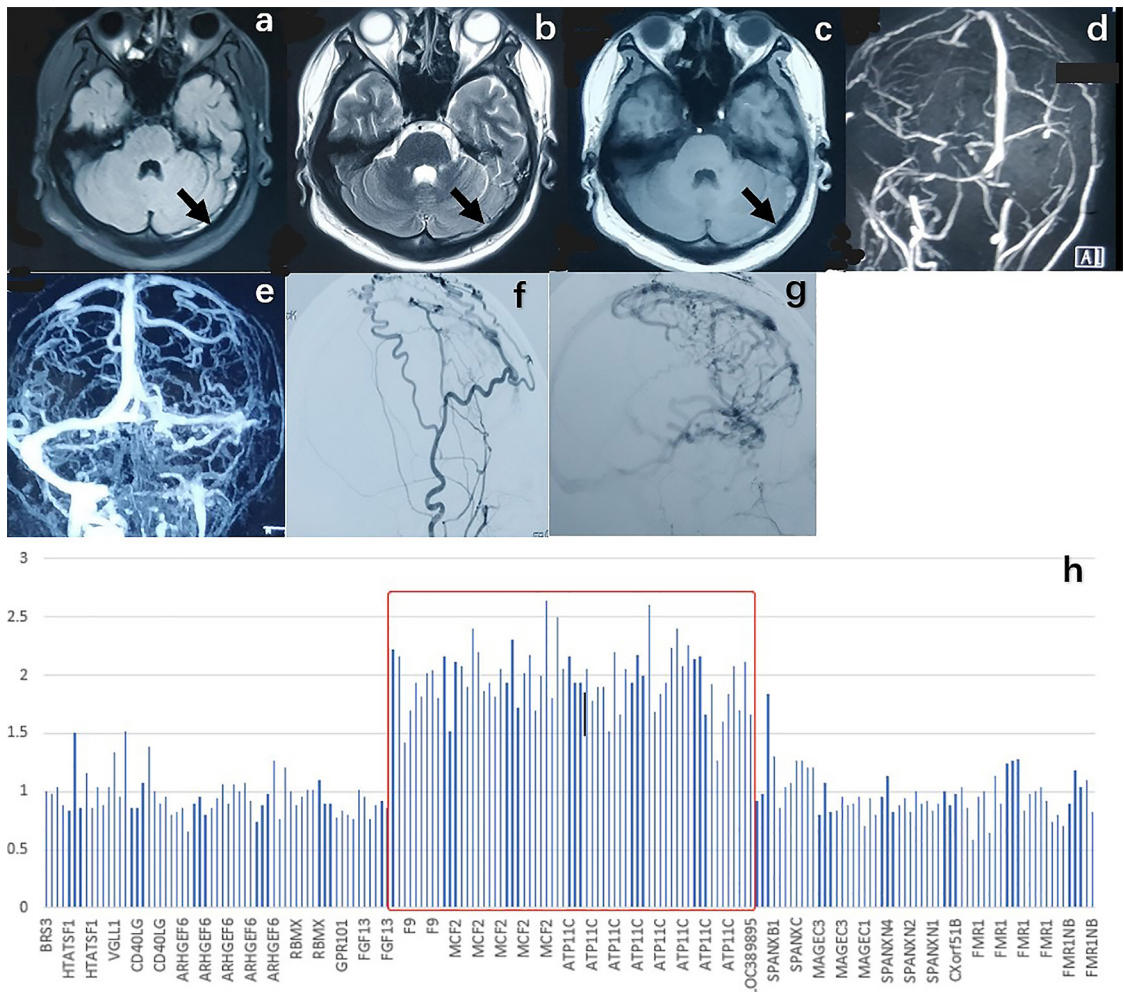


Figure 1. a-d: Cranial magnetic resonance imaging (MRI) showed hyperintensity on Flair and T1WI sequences in left transverse sinus and sigmoid sinus when the patient was first diagnosed with CVST in 2015. Cranial magnetic resonance venogram (MRV) showed left transverse sinus and sigmoid sinus occlusion. e-g: Cranial MRV showed the left transverse sinus is slender and the left sigmoid sinus occlusion when blurred vision and headache recurred in 2020. DSA showed the left superficial temporal artery and middle meningeal artery were anastomosed with cortical vein. Vein development was seen in the arterial stage. h: CNV verification found a novel de novo repeated variant in the X chromosome 138612907-139174763 region of the patient, among which eight genes are located including F9 (The meaning of y-axis is the copy number in CNV verification).

After admission, etiological screening was accomplished: serum prolactin and total cortisol slightly increased; Protein C, protein S, anti-thrombin and other screening for hypercoagulable thrombolysis and antibodies related to autoimmune diseases were all negative. Serum homocysteine (HCY) slightly increased (22.9 $\mu\text{mol/L}$), and MTHFR gene was detected as TT type on chromosome 1. To further clarify the underlying cause, genetic tests were conducted including second-generation sequencing of whole exon genes and copy number variations (CNV) verification. A novel de novo repeated variant (Fig. 1h) was found in the X chromosome 138612907-139174763 region of the patient, among which eight genes were located including F9. An obvious increased activity of factor IX [198.5% (65.0-150.0)] was then demonstrated, which was considered to be related to large duplicates of F9 gene in the X chromosome.

Based on the genetic findings, hyper-activity of factor IX was considered to be largely responsible for the recurrent venous thrombosis of the present patient. Life-long anticoagulation with rivaroxaban of 20mg once a day was thus suggested. No new onset of thrombotic event occurred during the one-year follow-up.

DISCUSSION

To our knowledge, this is the first reported case presenting with recurrent CVST due to a rare etiology of hereditary hyperactivity of coagulation factor IX. In the present case, a duplicated variation of the F9 gene was detected, resulting in increased activity of factor IX and thus a hyper-coagulating state. CVST is a heterogeneous disorder with a high mortality and disability. The predisposing factors and causes for CVST are quite extensive, generally classified as blood stasis, vascular wall injury and hypercoagulability^[1]. Prothrombotic conditions are the most common implicated predisposing factors. Coagulation factor IX is an important component of the endogenous coagulation activation system, which is encoded by the F9 gene located in X chromosome^[2]. Previous studies on factor IX were mostly related to hemorrhagic diseases due to factor IX deficiency caused by F9 gene mutation, such as X-linked recessive inheritance of type B hemophilia^[2]. Only limited studies have shown that an increased activity of factor IX was related to the risk of DVT^[3]. Findings from the Linden

Thrombophilia Study demonstrated that individuals with serum factor IX greater than 129IU/dL had 2-3 times increased risk of DVT compared to individuals with normal serum factor IX^[4]. However, the molecular basis for hyperactivity of factor IX remains unclear. Bezemer *et al.* verified that some mutation sites of F9 gene were associated with DVT. A substitution of leucine for arginine at position 338 in the factor IX gene was detected in a young patient with DVT. Although serum factor IX levels were normal, their activity was significantly higher than that of normal subjects without the mutation *in vitro*^[5]. Chang *et al.* investigated the activity of clot factor IX in which arginine is replaced by alanine (R338A), and suggested that the mechanism underlying the hyperactivity of clot factor IX is that the abnormal protein encoded by the mutation increases the binding of IXa to Xa, thus promoting thrombosis^[6].

It has been rarely reported that repeated mutations of genes lead to increased activity of the corresponding coagulation factor, further resulting in thrombotic events. Wang LL *et al.* reported a patient with acute myocardial infarction with a history of CVST and left ventricular thrombosis, whose activity of coagulation FVIII was shown to be a slight elevation. A duplicate chrX: 153991029-154348425 region was detected^[7]. In the present case, the patient's genetic test confirmed the existence of a repeated mutation near the upstream of F9 gene, which is located in the region chr X 138612907 to 139174763. The repeated mutation in this region has not been reported previously. Subsequent laboratory tests confirmed that the activity of clotting factor IX was significantly higher, which further supported that this repeated variation was responsible for the increased activity of factor IX. In addition, the patient had both CVST and DVT, which was also rare in previous cases of F9 gene-related venous thrombosis.

CONCLUSION

The present case highlights the necessity of hereditary screening to identify the underlying etiology of recurrent venous thrombosis in young adults. Hereditary hyperactivity of coagulation factor IX caused by duplicated variation of F9 gene was first reported as a rare etiology of CSVT, which expands the spectrum of etiology of this disorder and deserves attention.

Ethics Statement

The patient was enrolled in our prospective registration study entitled Clinical Cohort Study of Cerebral Venous System Diseases, which was approved by the Ethics Committee of Peking Union Medical College Hospital (ethics number: JS-1282). The corresponding written informed consent was received from the patient.

Findings

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Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Disclosures

The authors report no disclosures relevant to the manuscript.

Acknowledgments

Not applicable.

Abbreviations

CVST: cerebral venous sinus thrombosis; DVT: deep venous thrombosis; LMWH: low-molecular-weight heparin; DSA: digital subtraction angiography; BMI: body mass index; CNV: copy number variations; MRI: magnetic resonance imaging; MRV: magnetic resonance venogram.

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