Early Identification of Protein S K196E Mutation in a Patient With Cerebral Venous Thrombosis: A Case Report

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Background: Mutation of protein S K196E (PS K196E) is a genetic risk factor for venous thromboembolism; however, there are few reports on cerebral venous thrombosis (CVT) with this mutation. We report a case of CVT that was diagnosed as having PS K196E mutation at the initial thrombotic event. *Methods:* A 54-year-old man suddenly developed generalized seizures after headache and nausea. Brain magnetic resonance imaging showed cerebral edema, and angiography revealed CVT. Blood examination revealed that protein S activity was low (44%) despite normal free protein S antigen levels (81%). Sequence analysis revealed a heterozygous PS K196E mutation. We treated him with warfarin with the international normalized ratio maintained at 2.0-3.0. After 1 month, he was discharged without any neurological sequelae. *Results:* Early identification of the causes of thrombophilia is important for the long-term management of CVT. However, detection of PS K196E mutation is difficult because its only feature is a moderate decrease in the activity of protein S, which is influenced by environmental factors. *Conclusions:* The possibility of PS K196E mutation should be considered if other causes of CVT are ruled out and if protein S activity is decreased.

Key Words: Cerebral venous thrombosis—protein S activity—protein S K196E mutation—genetic analysis

Case Report

A 54-year-old man with a history of hypertension, dyslipidemia, and hyperuricemia experienced progressive headache and nausea. He had never taken routine medication and had no history of thrombotic events. His father had developed ischemic stroke at 70 years of age. Seven days after symptom onset, he suddenly developed generalized seizures and visited our emergency room. On arrival, he was clear and showed weakness in his right arm.

Emergent brain magnetic resonance imaging showed vasogenic edema in the left frontal lobe (Fig 1, A-C) and prominent cortical veins on T2*-weighted images (Fig 1, D). Cerebral angiography showed cerebral venous thrombosis (CVT) in superior sagittal sinus and left transverse sinus (Fig 1, E, F). Heparin, glycerin, and oral levetiracetam were started for this patient.

On blood examination, protein S (PS) activity was low (44%) despite a normal free PS antigen level (81%). Hereditary PS deficiency was suspected because the possible causes of CVT including infection, connective tissue disease, cancer, trauma, and other thrombophilia were excluded. After written informed consent was obtained from the patient, sequence analysis was performed, which revealed a heterozygous protein S K196E (PS K196E) mutation. Heparin was switched to warfarin with the

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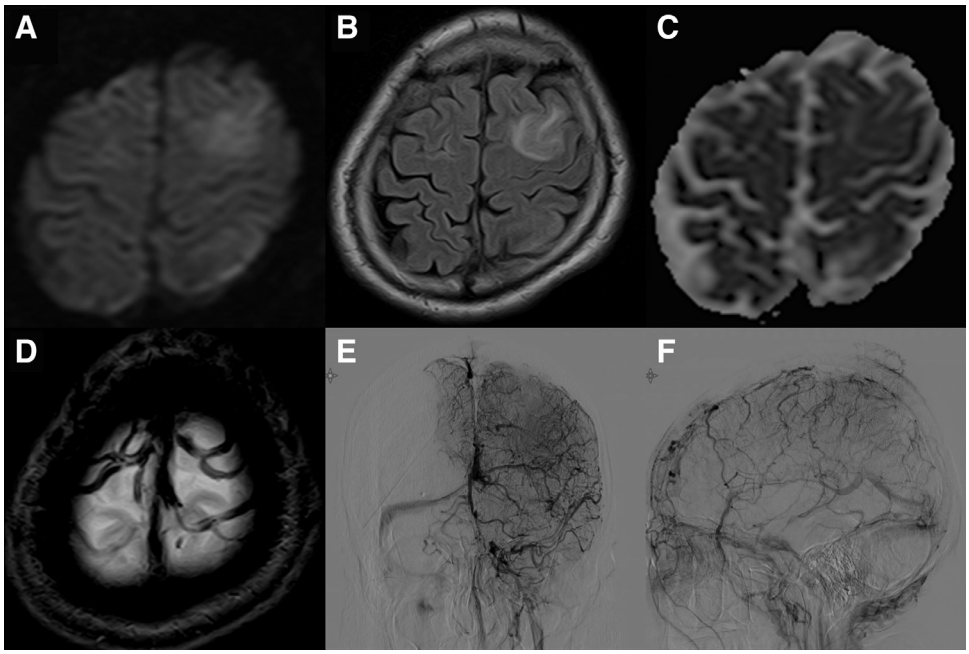

Figure 1. *Brain magnetic resonance imaging shows a hyperintense area in the left frontal lobe on diffusion-weighted imaging (A) and fluid-attenuated inversion recovery imaging (B). This area shows isointensity on the apparent diffusion coefficient map (C). T2*-weighted image shows hypointense lesions, suggesting prominent cortical veins, in the bilateral cerebral hemispheres (D). Cerebral angiography shows occlusion in the superior sagittal sinus and the left transverse sinus (E and F).*

international normalized ratio maintained at 2.0-3.0. After 1 month, the patient was discharged without any neurological sequelae.

Discussion

PS K196E mutation is a genetic risk factor for venous thromboembolism specific to the Japanese populations[1] with an odds ratio ranging 3.74-8.56.[2-4] It is estimated that approximately 1 in every 55 Japanese persons is heterozygous for this mutation.[5] however, there are few reports on CVT with PS K196E mutation. In the only reported case of CVT with PS K196E mutation, the mutation was detected after recurrent thrombotic events.[6]

Earlier identification of the causes of thrombophilia can be beneficial for long-term management of CVT.[7,8] However, the detection of PS K196E mutation is difficult because the only feature of this mutation is the moderate decrease in PS activity, which is influenced by environmental factors.[9] Thus, genetic analysis is useful for early definite diagnosis. On the other hand, it should be noted that genetic analysis is not always feasible at all hospitals and ethical considerations are necessary. Thus, as in the present patient, if there are no other abnormalities causing CVT and the PS activity is decreased, the possibility of the PS K196E mutation should be considered, especially in Japanese populations.

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