

Case Studies

Recurrent Hemorrhagic Venous Infarctions Caused by Thrombosis of a Pontine Developmental Venous Anomaly and Protein S Mutation

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A 34-year-old man presented with an acute onset of upbeat nystagmus, slurred speech, and limb and truncal ataxias. The patient had a history of limb ataxia and gait disturbance previously treated as brainstem encephalitis with corticosteroids 3 years previously. Brain magnetic resonance imaging showed pontine developmental venous anomaly (DVA) and hemorrhagic infarction within the drainage territory of the DVA. Three months later, the patient exhibited recurrent limb ataxia, double vision, and numbness of the left side of the body. The brain magnetic resonance imaging revealed recurrent hemorrhagic venous infarction within the same territory of the pontine DVA. Laboratory tests disclosed a hypercoagulable state owing to a decrease of protein S activity despite the normal antigen level. Genetic testing indicated that the patient was a homozygous carrier of protein S Tokushima. The patient's severe disability remained unchanged in spite of treatment with anticoagulation therapy using warfarin. We propose that further research on hereditary coagulopathy be carried out in patients with recurrent episodes of DVA-related infarction. **Key Words:** Recurrent cerebral venous infarction—hemorrhagic cerebral venous infarction—developmental venous anomaly—protein S deficiency—protein S Tokushima.

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Case Report

A 34-year-old man was referred to our hospital by ambulance because of dysarthria and gait disturbance. Neurological examination on admission revealed upbeat nystagmus, dysarthria, and limb and truncal ataxias. Brain magnetic resonance imaging showed a developmental venous anomaly (DVA) (Fig 1, A) and pontine hemorrhagic infarction within the drainage territory of the DVA (Fig 1, B,C). Three months later, the patient exhibited recurrent limb ataxia, double vision, and numbness of the left side of his body. The T2* sequence revealed a new pontine hemorrhagic infarction. The digital subtraction angiography demonstrated a dilated transpontine DVA draining into the left inferior petrosal sinus (Fig 1, D,E). Laboratory examinations disclosed a hypercoagulable

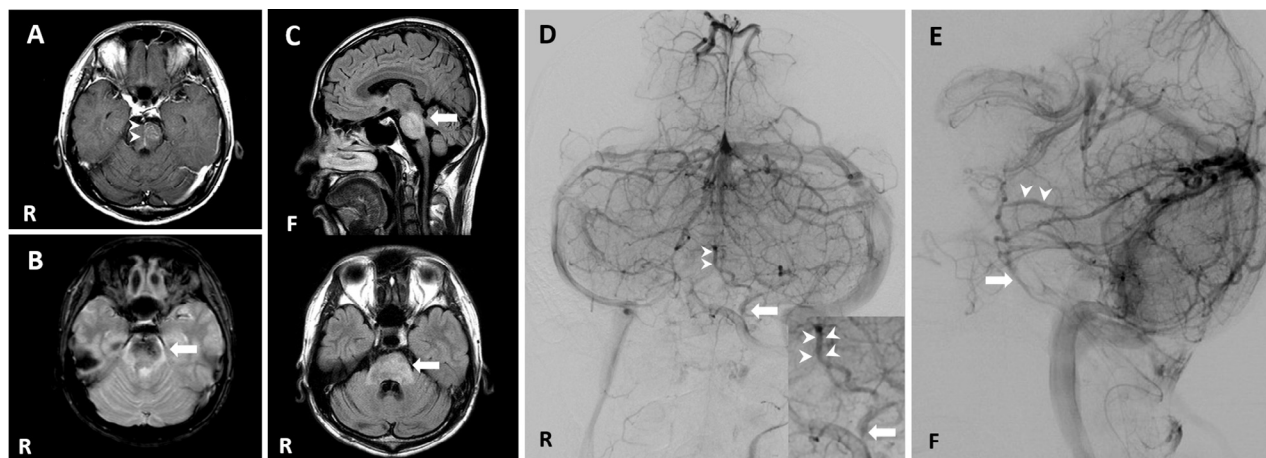


Figure 1. (A) An axial gadolinium-enhanced T1-weighted image at the first admission indicates a developmental venous anomaly (white arrowhead). (B) An axial T2*-weighted image at the first admission shows pontine hemorrhagic infarction (white arrow). (C) Sagittal and axial magnetic resonance imaging fluid-attenuated inversion recovery images at the first admission in our hospital. The brainstem edema is spread in the pons (white arrows). (D) Digital subtraction angiography at the second admission (venous phase, anteroposterior projection) demonstrates a dilated anterior transpontine vein (white arrowheads), draining into the left inferior petrosal sinus (white arrow). (E) Digital subtraction angiography at the second admission (venous phase, lateral projection) demonstrates a dilated anterior transpontine vein (white arrowheads), draining into the left inferior petrosal sinus (white arrow). Abbreviations: F, front; R, right.

state (D-dimer, 5.4 mg/mL; fibrin/fibrinogen degradation products, 10.9 $\mu\text{g/mL}$). Protein S activity was decreased (36%; normal range: 73%-121%) despite its normal antigen level (110%; normal range: 65%-135%). Genetic testing indicated that the patient was a homozygous carrier of protein S Tokushima. The patient's protein C level was normal. Lupus anticoagulant and anticardiolipin antibodies were negative. Therefore, we concluded that thrombotic occlusion of DVA was accelerated by protein S deficiency, resulting in recurrent pontine hemorrhagic infarctions. The patient had been treated with warfarin for 4 years with only 1 recurrence.

Discussion

To our knowledge, this is the first case of recurrent hemorrhagic pontine infarction developed in association with DVA and protein S mutation. DVA is considered a common cerebrovascular variation of the parenchymal venous angioarchitecture.^{1,2} Although DVA is usually asymptomatic,² hemorrhagic and/or ischemic infarction can occur unexpectedly as a result of acute thrombosis of DVA.³ DVA may be a vulnerable anatomic architecture, microscopically showing degenerative changes, including thickened and hyalinized vessel walls.⁴ Hereditary thrombophilia is an important risk factor for cerebral venous thrombosis.⁵ Protein S Tokushima has 1 missense mutation (927A>G), resulting in 1 amino acid substitution from Lys-155 to Glu (K155E), which causes decreased protein C cofactor activity despite normal protein S antigen levels.⁶ Deep vein thrombosis is usually caused by a combination of hypercoagulability, stasis of venous

blood, and injury to the venous wall intima.⁷ The recurrent hemorrhagic venous infarction in our case might have been caused by microscopic damage to vessel walls accelerated by the hypercoagulability state owing to protein S deficiency. Anticoagulation can be used in patients with symptomatic DVA who have hereditary thrombophilia. Our case suggests the importance of further research on hereditary coagulopathy in patients with recurrent episodes of DVA-related infarction.

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