

## Case Report

# Protein S Deficiency Associated with Progressive Loss of Vision and Intracranial Venous Sinus Thrombosis

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### Key Words

increased intracranial pressure;  
intracranial venous sinus thrombosis;  
protein S deficiency

**P**rotein S (PS) is 1 of the vitamin K-dependent natural anticoagulants and serves as a cofactor for activated protein C (APC) for inactivating factors Va and VIIIa.<sup>1</sup> Deficiency of PS, therefore, is associated with increased thromboembolic risk in the venous and arterial systems.<sup>2,3</sup> However, the association of PS deficiency and intracranial venous sinus thrombosis (VST) is quite uncommon.<sup>12</sup> We describe the occurrence of chronic intracranial VST despite anticoagulation therapy in a 27-year-old male patient with PS deficiency.

### CASE REPORT

A 27 year-old male suffered from a generalized seizure in June of 1999, which was controlled with oral phenytoin. He discontinued phenytoin after remaining

We report a 27-year-old male who presented with headache and rapid visual impairment. He had been diagnosed with venous sinus thrombosis 3 months earlier, when he had diffuse headache, nausea and vomiting, which subsided after incomplete thrombolytic therapy. Warfarin was then prescribed without screening for coagulopathy. Ophthalmic examination revealed bilateral papilloedema, splinter hemorrhage and lipid exudates. Neuroradiological studies including magnetic resonance imaging and cerebral angiography revealed chronic partial thrombosis over superior sagittal sinus, left side transverse sinus, right side transverse and venous confluence with engorged cortical veins and secondary dural arteriovenous malformation (AVM) and reversed flow over bilateral superior orbital veins, and thrombolytic therapy was considered not feasible. Clot-assay protein S activity was decreased (25%, normal range: 65-140%). No underlying connective tissue diseases or other coagulopathies were noted. The patient's vision failed to respond to aggressive medical treatment, and he received lumboperitoneal shunt in another hospital. His vision was improved. For young patients with occlusive cerebrovascular disorder, extensive hematological investigation for coagulopathy is strongly recommended.

seizure free for 6 months. He remained healthy for another 14 months before suffering from diffuse headache, nausea, vomiting, photophobia and phonophobia. Cerebral angiography performed at another hospital showed intracranial VST (superior and inferior sagittal sinus, bilateral transverse sinus and right sigmoid sinus) and thrombolytic therapy over bilateral jugular veins was performed. However, the thrombus was too hard such that the catheter could not be placed in bilateral sigmoid sinuses despite urokinase infusion. His symptoms gradually improved but diplopia developed subsequently, which remitted in 1 month. Warfarin 5 mg per day had been used since then without hematological screening for coagulopathy. The patient later visited another hospital for chronic otitis media, where cholesteatoma on the left side was diagnosed, and he was referred to our otology department 3 months after the onset of his symptoms. Meanwhile he noted rapid

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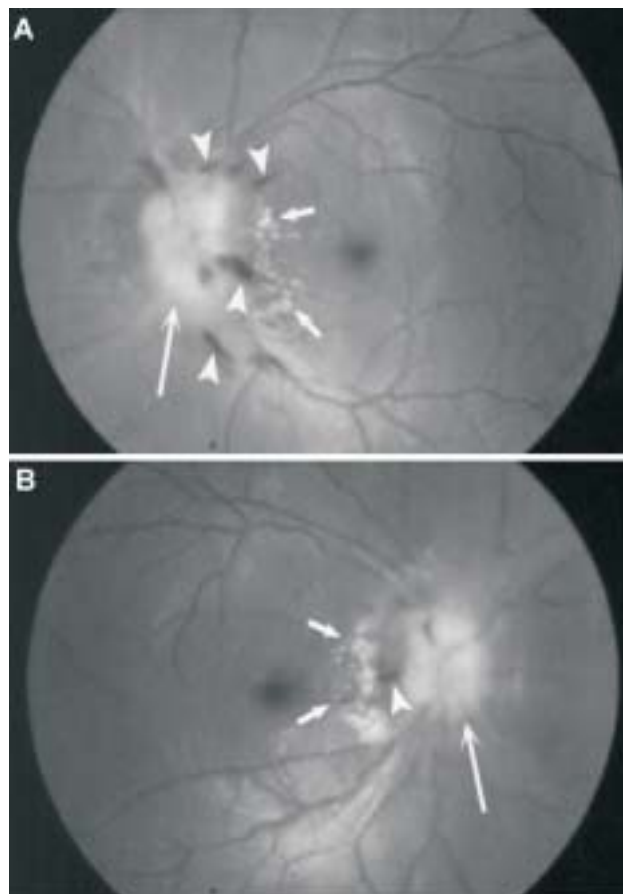
worsening of vision, especially on the right side, and bilateral papilledema with impaired visual acuity (VA) (6/7.5, OD and 6/15, OS) was noted. In addition, he was advised to see a hematologist for possible coagulopathy, and warfarin was discontinued for 1 week before hematologic screening.

The patient was admitted to the otology ward for presurgical evaluation of cholesteatoma in January of 2002. Color-coded Duplex study of cervical and orbital arteries and veins revealed reversed flow of bilateral superior orbital veins. Ophthalmological evaluation showed bilateral severe papilledema and impaired VA (6/8.6, OD and 6/6, OS). Poor vision due to poor orbital venous drainage was considered. The patient's brain magnetic resonance imaging (MRI) studies were reviewed, and disclosed thrombosis of superior and inferior sagittal sinus and bilateral transverse sinuses and thrombosis with partial venous return of right sigmoid sinus, without brain edema. Computed tomography (CT) scan of temporal bone showed patent left sigmoid sinus and cholesteatoma on the left side without bony dehiscence. The otologist therefore concluded that the cholesteatoma was not related to the intracranial VST. He was then admitted to the neurology ward 4 months after the onset of symptoms under the impression of chronic VST with increased intracranial pressure (IICP).

The patient had past history of fracture of the right forearm with successful open reduction in 1994 and was allergic to contrast medium. He denied other medical diseases except seizure disorder in 1999 and use of warfarin 5 mg per day since VST was diagnosed. There was no family history of thromboembolic diseases including deep vein thrombosis, pulmonary embolism and coronary or cerebral occlusive diseases.

On examination, he was conscious and robust, weighted 81 kg and 171 cm tall. General physical examination was unremarkable. Ophthalmologic examination revealed bilateral papilledema, splinter hemorrhage and right side lipid exudates (Fig. 1). Visual acuity was finger counting on the right side and normal on the left. Hearing was impaired on the left side. Bilateral pupils were isocoric and light reflex was preserved. Generalized brisk tendon reflexes and bilateral non-sustained ankle clonus without Babinski sign were

noted. Neurologic examination was otherwise normal, including extraocular eye movement, accommodation

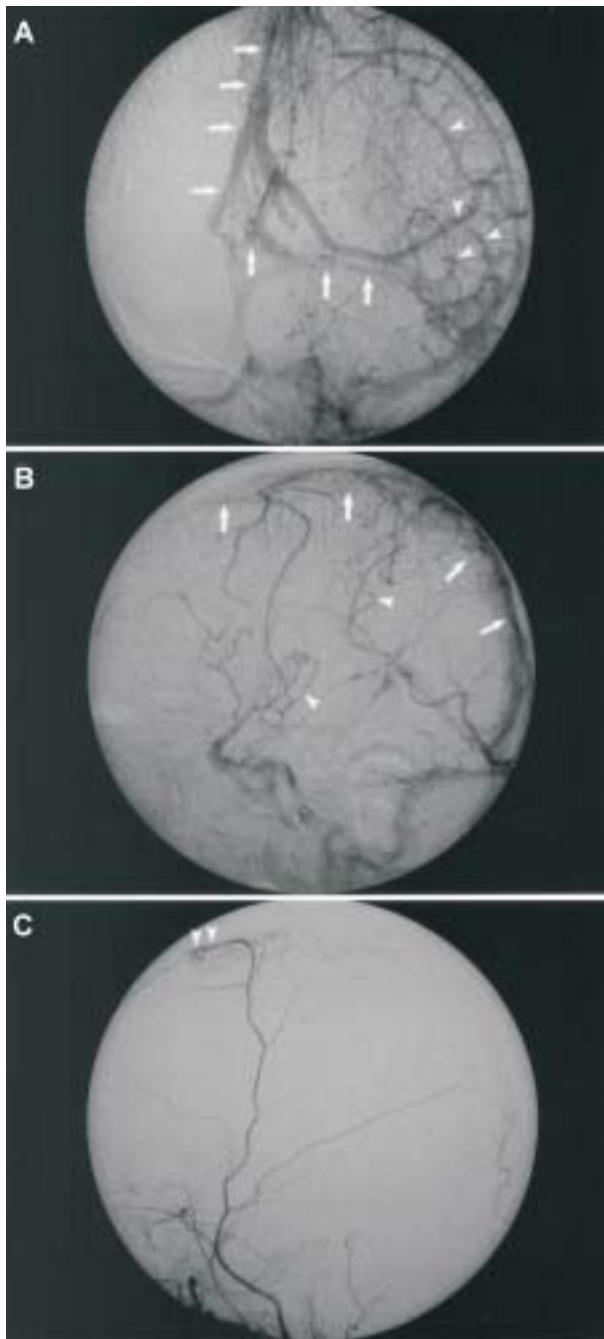


**Fig. 1.** Bilateral eye fundi show papilledema (long arrow), splinter hemorrhage (arrowheads) and lipid exudates (short arrows). (A: OS; B: OD).



**Fig. 2.** Brain magnetic resonance imaging (MRI) (T1 WI) shows loss of flow void of superior sagittal sinus (short arrows).

and other cranial nerves, muscle strength and tone, coordination and sensory system.



**Fig. 3.** Left carotid angiography. **A:** A-P view, **B:** Lateral view. Chronic partial thrombosis of superior sagittal sinus, left transverse sinus and venous confluence (short arrows) with engorged cortical veins (arrowheads). There was still some contrast media flow to the left sigmoid sinus. **C:** Left external carotid artery angiography, lateral view: engorged cortical veins and secondary dural arteriovenous malformation (arrowheads).

After admission, heparin was used and brain MRI study was repeated, which revealed chronic VST (Fig. 2), and thrombolytic therapy was considered not feasible. Cerebral angiography disclosed chronic partial thrombosis over superior sagittal sinus, left side transverse sinus, right side transverse and venous confluence with engorged cortical veins and secondary dural arteriovenous malformation (AVM) (Fig. 3). Heparin therapy was later shifted to warfarin therapy.

The patient's coagulation profile, including protein C, PS, antithrombin III, prothrombin time (PT), activated partial thrombin time (APTT), bleeding time, thrombin time, fibrinogen, protamine sulfate test (PST), fibrinogen degradation product (FDP), platelet aggregation test, and D-D dimer previously evaluated at our hematologic clinic after discontinuation of warfarin for 1 week, was otherwise normal except for decreased clot-assay PS activity (25%, normal range: 65%-140%). The results of immunologic studies including lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), C3c, C4 and antinuclear antibodies (ANA) were within normal ranges. Follow-up PS activity (rechecked 18 days after the first study) was 18% when warfarin had been used for 2 days. Prothrombin time (PT INR) was evaluated another 4 times during these 18 days; except 1 measurement of 1.13, the results were below 1, even after warfarin use. Lumbar puncture study revealed increased ICP (opening pressure was 240 mm H<sub>2</sub>O and closing pressure 170 mm H<sub>2</sub>O) but additional CSF study, including cell counts, protein and sugar, was normal.

Retinal fluorescent angiography showed dye staining of bilateral optic discs, compatible with bilateral papilledema. His VA continued to deteriorate despite medical treatment with prednisolone, acetazolamide, heparin and warfarin. His VA on the second day of hospitalization was 20/50, od and 20/25, os. His VA on the sixth day of hospitalization was 6/6.8, od and 6/5, os, and on the sixteenth day of hospitalization was 6/12, ou. Bilateral papilledema persisted. Lumbar-peritoneal (LP) shunt or optic nerve fenestration was suggested. He decided to have LP shunt at another hospital and was discharged. We contacted his family 10 months later and learned that the patient's vision improved after LP shunt with VA of 20/25, od, and 20/20, os. He was

not able to return for follow-up because of migration abroad.

## DISCUSSION

PS deficiency has been found in 1.5% to 7% of different groups of patients with thrombophilia.<sup>1</sup> Inherited prothrombotic tendencies such as PS deficiency, protein C deficiency, and antithrombin III deficiency, account for about 10-15% of intracranial VST. In patients younger than 45 years with unexplained venous thrombosis (systemic and intracranial), the incidence of PS deficiency was 10% or greater.<sup>5</sup> The prevalence of PS deficiency in the general population is unknown. There were only a few case reports of PS deficiency and cerebral venous sinus thrombosis.<sup>12,14</sup> The risk of thrombotic diseases was 2.4-fold higher in those with PS deficiency.<sup>6</sup>

PS deficiency may be acquired or hereditary. PS levels can be influenced by several factors, including warfarin therapy, disseminated intravascular coagulation, primary thrombocytopenia, severe liver disease, diabetes mellitus, nephrotic syndrome, oral contraceptives, hormone replacement therapy, L-asparaginase therapy for leukemia, pregnancy and postpartum stage and gender.<sup>7</sup> Age has no independent effect on PS levels.<sup>8</sup> In this patient, free PS activities (clot-assay) were significantly lower than the expected ranges and other factors associated with acquired PS deficiency were not present. This strongly suggests that the cause of PS deficiency in this patient may not be acquired.

Hereditary PS deficiency is an autosomal dominant genetic disease, in which active PS gene (PROS1 gene) defects are the underlying causes.<sup>2,9</sup> Genetic survey for PROS1 gene defects and assay of free or total PS antigen levels were not available in the hematology laboratory of our hospital, so we were not able to definitely diagnose and classify this patient as hereditary PS deficiency, though it was highly suspected. In addition, APC resistance cannot be completely excluded in this patient based on the PS level. It is extremely rare in Taiwan, and is very unlikely for this patient.<sup>23,24</sup>

The association of hereditary PS deficiency and intracranial VST is very uncommon.<sup>12</sup> The clinical mani-

festations of cerebral VST with or without PS deficiency include intracranial hypertension, hemiplegia, seizures, cranial nerve dysfunction, optic atrophy and unconsciousness.<sup>11,13</sup> In the long-term evolution of dural fistulas or intracranial VST, symptoms of IICP often worsen such that impaired vision may progress to complete blindness and chronic or acute tonsillar herniation may be lethal.<sup>13</sup> Therefore, VST-associated IICP may have caused the progressive visual deterioration in this patient. Some may have VST and IICP without visual loss. One 38-year-old woman whose diagnosis of hereditary PS deficiency was established by demonstrating decreased PS levels (free and total) in her family members had clinical presentation of generalized tonic-clonic seizures, severe frontal headache, nausea and vomiting.<sup>12</sup> Intracranial VST was diagnosed by angiography.<sup>12</sup> She responded well to heparin and showed no recurrence of VST with chronic warfarin prophylaxis. There have been reports of dural arteriovenous fistula (DAVF) associated with cerebral VST.<sup>14</sup> One 12-month-old infant with cerebral VST and low free protein S level, similar to our patient, also had DAVF revealed by cerebral angiography and refractory to medical treatment.<sup>14</sup> He failed to respond to chronic anticoagulation therapy and succumbed 1 year later.

The chronological relation in terms of cause and effect between VST and DAVF is very difficult to prove.<sup>15</sup> Most authors consider that DAVF arises from VST,<sup>13,14</sup> but VST can be secondary to a DAVF that results in external and internal hydrocephalus and brain atrophy.<sup>15,16</sup> In this patient, absence of severe brain atrophy and hydrocephalus would suggest that DAVF was secondary to VST.

To date, there are no randomized therapeutic trials in patients with inherited hypercoagulable states including PS deficiency. Long-term use of warfarin or even low-molecular-weight heparin may be recommended for patients with thrombotic disease secondary to persistent risk factors (*e.g.* hereditary PS deficiency).<sup>17,18</sup> Unfortunately, in this patient with PS deficiency, intracranial VST had progressed despite continuous prophylactic use of warfarin. In addition, his IICP also failed to respond to warfarin, heparin and other medications.

Thrombolytic therapy, angioplasty or venous sinus stenting was considered not feasible for our patient due to

chronic VST. Some reports revealed recanalization after successful angioplasty and/or venous sinus stenting.<sup>19,21,22</sup> Angioplasty may fail because of elastic recoil of the sinus wall after removal of the balloon or reocclusion of the venous sinus.<sup>21,22</sup> The long-term effectiveness of sinus stenting in intracranial VST still remains to be established. For patients with IICP due to intracranial VST who are refractory to anticoagulant or thrombolytic therapy and/or medical treatment to control IICP, CSF diversion procedures (lumbar puncture or lumbar-peritoneal shunt) are recommended but may be associated with substantial morbidity, such as acute tonsillar herniation, especially in patients with DVA, and often are only partly effective.<sup>13,21</sup> Nevertheless, the satisfactory response of our patient to such surgical procedure would suggest its feasibility to control IICP secondary to intracranial VST.

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