

# Superior Sagittal Sinus and Cerebral Cortical Venous Thrombosis Caused by Congenital Protein C Deficiency

## —Case Report—

Seikou KUWAHARA, Tomoki ABE\*, Shigetoshi UGA\*, and Koreaki MORI\*\*

Departments of Neurosurgery and \*Internal Medicine, Kouhoku National Health Insurance Hospital of Sakawa-cho, Kochi; \*\*Department of Neurosurgery, Kochi Medical School, Nankoku, Kochi

### Abstract

A 47-year-old male receiving anticoagulant therapy for thrombophlebitis in the left leg for several years presented with mild left hemiparesis and ipsilateral hypesthesia. The cause of the thrombophlebitis was still unknown. Magnetic resonance (MR) imaging showed subacute thrombosis of both the superior sagittal sinus (SSS) and a cortical vein in the right cerebral hemisphere. Fluid attenuation inversion recovery axial MR imaging demonstrated these lesions more obviously than conventional T<sub>2</sub>-weighted axial MR imaging. Right carotid angiography showed a partial SSS filling defect and occlusion of the cortical vein with collateral circulation. Coagulation studies revealed decreases in both protein C activity and antigen levels with normal levels of blood coagulation factors II, VII, IX, and X and protein S activity and antigen. The patient's mother had normal levels of both protein C activity and antigen, but his father had decreased levels. The diagnosis was SSS and cerebral cortical venous thrombosis caused by congenital protein C deficiency. The patient was treated conservatively, and his clinical course was uneventful. His neurological dysfunctions recovered within approximately 3 weeks after the onset. Ten months later, right carotid angiography showed recanalization of the SSS and partial filling of the cortical vein. Anticoagulant therapy has been continued, and no cerebral venous thrombosis has recurred during the 1.5 years after the onset.

Key words: cerebral venous thrombosis, superior sagittal sinus, protein C deficiency

### Introduction

Congenital protein C deficiency carries a high risk of venous thrombosis and embolism elsewhere in the body,<sup>1,3,8)</sup> and usually manifests as recurrent deep venous thromboses and/or pulmonary embolism occurring in younger people. We describe a rare case of superior sagittal sinus (SSS) and cerebral cortical vein thrombosis caused by congenital protein C deficiency.

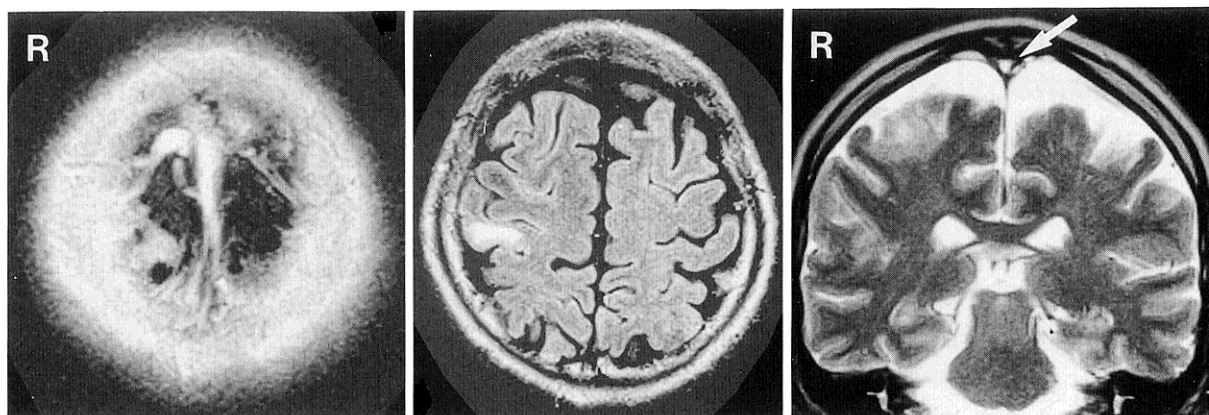
### Case Report

A 47-year-old male with a history of thrombophlebitis in the left leg developed mild left hemiparesis and ipsilateral hypesthesia 2 days prior to admission. He complained of headache but had no other signs of intracranial hypertension. The cause of the throm-

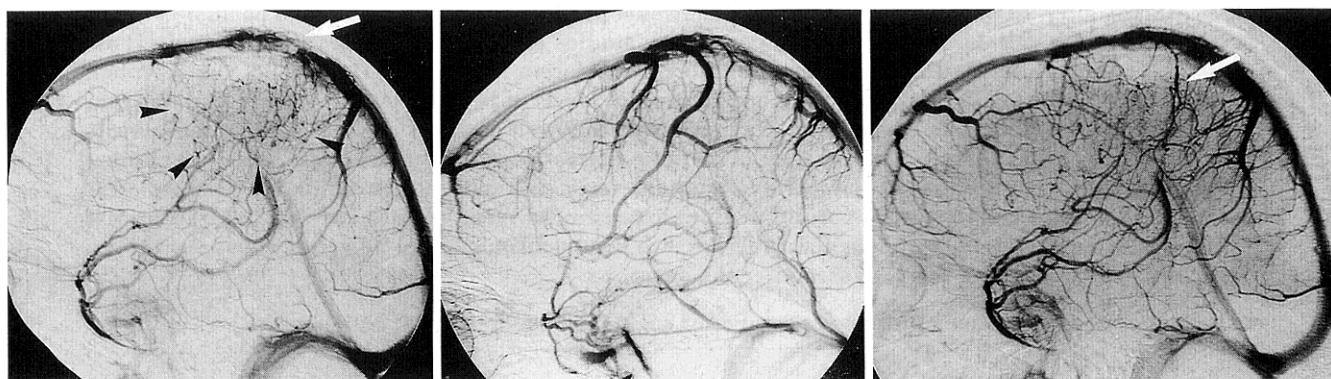
bophlebitis was still unknown but he had been receiving 1 mg of warfarin per day for several years.

Brain computed tomography showed no findings corresponding to the neurological dysfunctions. Fluid attenuation inversion recovery (FLAIR) (repetition time [TR]/echo time [TE]/inversion time = 6882/110/1700 msec) axial magnetic resonance (MR) imaging showed areas of homogeneous hyperintensity in both the SSS and a cortical vein in the right cerebral hemisphere (Fig. 1 left). FLAIR axial MR imaging also found a linear hyperintense area in the white matter of the right frontal lobe (Fig. 1 center). T<sub>2</sub>-weighted (TR/TE = 3630/110 msec) coronal MR imaging demonstrated a hyperintense spot in the SSS and swelling of the right frontal lobe (Fig. 1 right). These findings were strongly suggestive of subacute thrombosis in both the SSS and a cerebral cortical vein draining into the SSS.

Right carotid angiography showed no abnormalities in the arterial phase, but the lateral view during



**Fig. 1** Fluid attenuation inversion recovery (FLAIR) axial magnetic resonance (MR) image (*left*) showing hyperintense areas in both the superior sagittal sinus (SSS) and a cerebral cortical vein indicating subacute thrombosis. FLAIR axial MR image (*center*) showing a linear hyperintense area in the right frontal subcortex close to the thrombosed cortical vein. T<sub>2</sub>-weighted coronal MR image (*right*) showing hyperintense areas in the right frontal white matter and a hyperintense spot in the SSS (*arrow*).



**Fig. 2** Initial right carotid angiogram in the venous phase (*left*) showing a partial filling defect in the superior sagittal sinus (SSS) (*arrow*) and abnormal fine vessels with a corkscrew appearance (*arrowheads*) indicating venous collateral blood flow due to occlusion of a cortical vein (probably the right rolandic vein). Left carotid angiogram (*center*) showing normal venous flow in the same portion of the SSS. Follow-up right carotid angiogram (*right*) showing the normal SSS and partial recanalization of the occluded cortical vein (*arrow*) with reduction of the collateral vessels.

the venous phase demonstrated a partial filling defect of the SSS where the thrombosed cortical vein might have connected (Fig. 2 *left*). However, left carotid angiography of this portion of the SSS with the partial filling defect showed normal venous flow on the lateral view during the venous phase (Fig. 2 *center*). The occluded cerebral cortical vein was thought to be a rolandic vein, and the collateral vessels had a corkscrew appearance (Fig. 2 *left*). Left vertebral angiography showed no abnormalities in both the arterial and venous phases.

Measurement of blood coagulation parameters

showed a normal protein S total antigen level of 109% (normal: 65–135%) and activity of 66% (normal: 60–150%), but a decreased protein C activity of 34% (normal: 65–140%) and a decreased antigen level of 32% (normal: 70–150%). The levels of vitamin-K-dependent blood coagulation factors II, VII, IX, and X were 66%, 100%, 99%, and 76% of control (normal: more than 70%), respectively. Other results were normal. The patient's father also had a decreased protein C activity of 33% and a decreased antigen level of 43%. His mother had normal protein C activity and antigen levels (Table 1). The findings

**Table 1** Familial data of protein C and protein S levels

	Protein C (%)		Protein S (%)		
	Activity	Antigen	Activity	Free antigen	Total antigen
Normal range	65–140	70–150	60–150	60–150	65–135
Patient	34↓	32↓	66	95	109
Father	33↓	43↓	113	106	109
Mother	93	113	51↓	68	92

Protein C activity and antigen of both the patient and his father were below the normal level. His mother had values in the normal range.

of these neuroimaging and coagulation investigations confirmed the diagnosis of SSS and cerebral cortical venous thrombosis caused by congenital protein C deficiency.

The patient was treated conservatively because his neurological dysfunctions were mild and did not worsen in the acute phase. Administration of 1 mg per day of warfarin was continued, and intravenous infusion of 400 ml per day of 10% glycerol and 80 mg per day of sodium ozagrel was performed for 14 days. The clinical course was uneventful, and his neurological dysfunctions improved sufficiently to allow him to resume work within approximately 3 weeks after the onset. One month later, FLAIR axial MR imaging showed no sign of thrombi in the cortical vein, and T<sub>2</sub>-weighted MR imaging showed homogeneous hypointensity of the SSS indicating recanalization. Approximately 10 months later, right carotid angiography showed the SSS as normal, a partially recanalized cortical vein which might be occluded by thrombus, and reduction of the collateral vessels (Fig. 2 right).

In the outpatient clinic, oral anticoagulant therapy was continued to adjust the daily dose of warfarin to maintain the prothrombin time ratio according to the international normalization ratio of 1.5 to 2.5. No recurrent cerebral venous thrombosis has occurred during the past 1.5 years.

### Discussion

The present case of cerebral venous thrombosis is relatively rare, as the cause was congenital protein C deficiency. Only 11 cases, including the present case, of cerebral venous thrombosis caused by congenital protein C deficiency have been reported.<sup>2,5-7,12,15,16,18-20</sup> The clinical characteristics of the patients are as follows. There were four males and seven females, aged from 15 to 75 years, and nine patients were below the age of 50 years. There was an obvious congenital basis in eight patients, a history of venous thrombosis in six, and thrombotic

risk factors of pregnancy, oral contraceptives, and cigarette smoking in seven. Ten patients had thrombi of the SSS associated with or without thrombi in another intracranial venous system, such as the lateral sinus, straight sinus, inferior sagittal sinus, and cerebral cortical veins. There were hemorrhagic infarctions in five patients, brain edema or swelling in two, focal ischemia in one manifesting as parenchymal brain damage, and three patients had no abnormalities on brain MR imaging. Nine patients had a favorable outcome and only two died.

Cerebral venous thrombosis can be identified relatively easily by MR imaging within 15 days after occlusion of the dural sinus. However, the use of MR imaging requires knowledge of the different age of thrombi and pitfalls in the interpretation of the findings.<sup>9</sup> The present case was also confirmed without difficulty. FLAIR axial MR imaging was especially useful in confirming the signal of the intravenous thrombus and the ischemic lesion in the white matter adjacent to the brain surface, which could not be distinguished from that of cerebrospinal fluid on conventional T<sub>2</sub>-weighted MR images.

Our patient suffered from cerebral venous thrombosis at the age of 47 years, despite continuous anticoagulant therapy. Congenital protein C deficiency was verified after the onset. Therefore, congenital coagulation disorders are important to consider as potential causes of cerebral venous thrombosis in younger patients (less than 50 years), in particular those with episodes of venous thrombosis elsewhere in the body. In our case, the congenital protein C deficiency was identified after repeated measurements of serum protein C activity and antigen.

General considerations concerning protein C deficiency are as follows. Protein C is a vitamin-K-dependent plasma protein, and is probably one of the most important inhibitors of blood coagulation. Protein C is activated *in vivo* by thrombin coupled with the endothelial cofactor thrombomodulin to form the serine protease, activated protein C (PCa),

and is inactivated by a specific plasma protease inhibitor. PCa is a potent anticoagulant enzyme that also enhances blood clot lysis, and has at least three mechanisms of action: PCa inhibits thrombin formation by inactivating the coagulation factors Va and VIIIa; PCa inhibits binding of factor Xa to platelets, probably by inactivation of factor Va, the receptor for factor Xa; and PCa stimulates the release of plasminogen activator, thus promoting fibrinolysis.<sup>4,8,10,17)</sup> The mode of inheritance of congenital protein C deficiency is thought to be autosomal dominant.<sup>3,11)</sup> The heterozygous state is usually asymptomatic and the estimated prevalence is 1 in 200 to 300 according to a prospective study of 5422 normal adults.<sup>11)</sup> Diagnosis of protein C deficiency is made by repeated measurements of decreased levels of serum antigen and activity with a normal range of all other vitamin-K-dependent coagulation factors.<sup>3)</sup>

The present patient was successfully treated conservatively. However, if the patient's neurological condition deteriorates progressively, then prompt direct thrombolysis of the dural sinus should be performed, because recent developments in endovascular treatment can achieve satisfactory outcomes for acute dural sinus thrombosis.<sup>13,14)</sup> Whether direct thrombolysis of the dural sinus is performed or not, anticoagulant therapy should be started as soon as possible to prevent recurrent thromboembolic events. During the initial period of administration of warfarin, a high dose of heparin should be given concurrently, since the half life of protein C is shorter than that of the other vitamin-K-dependent coagulation factors, and the plasma concentration of protein C decreases more rapidly in response to warfarin leading to occurrence of thrombosis.<sup>4)</sup> Concurrent heparin administration must be maintained until warfarin reaches full effectiveness as determined by a prothrombin time ratio of international normalization ratio 2 to 3.<sup>5,6)</sup>

Thromboembolic diseases tend to occur during early adulthood when risk factors, such as a history of malignancy, cigarette smoking, oral contraceptive use, pregnancy, puerperium, trauma, or surgery, are present in patients with protein C deficiency.<sup>1,3)</sup> Therefore, lifelong anticoagulant therapy should be continued for patients with cerebral venous thrombosis caused by protein C deficiency and a history of thromboembolic diseases.

## References

- 1) Allaart CF, Poort SR, Rosendaal FR, Reitsma PH, Bertina RM, Briët E: Increased risk of venous thrombosis in carriers of hereditary protein C deficiency

- defect. *Lancet* 341: 134-138, 1993
- 2) Boulos P, Kouroukis C, Blake G: Superior sagittal sinus thrombosis occurring at high altitude associated with protein C deficiency. *Acta Haematol* 102: 104-106, 1999
- 3) Broekmans AW, Veltkamp JJ, Bertina RM: Congenital protein C deficiency and venous thromboembolism: a study of three Dutch families. *N Engl J Med* 309: 340-344, 1983
- 4) Clouse LH, Comp PC: The regulation of hemostasis: the protein C system. *N Engl J Med* 314: 1298-1304, 1986
- 5) Confavreux C, Brunet P, Petiot P, Berruyer M, Trillet M, Aimard G: Congenital protein C deficiency and superior sagittal sinus thrombosis causing isolated intracranial hypertension. *J Neurol Neurosurg Psychiatry* 57: 655-657, 1994
- 6) Enevoldson TP, Russell RW: Cerebral venous thrombosis: New causes for an old syndrome? *Q J Med* 77: 1255-1275, 1990
- 7) Éon B, Aknin P, Brun JP, Saux P, Gouin F: [Protein C deficiency and cerebral venous thrombosis in pregnancy]. *Ann Fr Anesth Reanim* 8: 137-139, 1989 (Fre, with Eng abstract)
- 8) Esmon CT: Protein-C: biochemistry, physiology, and clinical implications. *Blood* 62: 1155-1158, 1983
- 9) Isensee C, Reul J, Thron A: Magnetic resonance imaging of thrombosed dural sinuses. *Stroke* 25: 29-34, 1994
- 10) Marljar R, Kleiss AJ, Griffin JH: Mechanism of action of human activated protein C, a thrombin-dependent anticoagulant enzyme. *Blood* 59: 1067-1072, 1982
- 11) Miletich J, Sherman L, Broze G: Absence of thrombosis in subjects with heterozygous protein C deficiency. *N Engl J Med* 317: 991-996, 1987
- 12) Nishimura Y, Tanaka H: [Protein C deficiency associated with cerebral sinus thrombosis: case report]. *Kobe Shiritsu Byoin Kiyo* 34: 103-106, 1995 (Jpn, with Eng abstract)
- 13) Niwa J, Ohyama H, Matumura S, Maeda Y, Shimizu T: Treatment of acute superior sagittal sinus thrombosis by t-PA infusion via venography—Direct thrombolytic therapy in acute phase. *Surg Neurol* 49: 425-429, 1998
- 14) Philips MF, Bagley LJ, Sinson GP, Raps EC, Galetta SL, Zager EL, Hurst RW: Endovascular thrombolysis for symptomatic cerebral venous thrombosis. *J Neurosurg* 90: 65-71, 1999
- 15) Reidley PD, Ledingham SJM, Lennox SC, Burman JF, Chung HI, Sheffield EA, Talbot S, Bevan D: Protein C deficiency associated with massive cerebral thrombosis following open heart surgery. *J Cardiovasc Surg* 31: 249-251, 1990
- 16) Shimazaki H, Ogawa M, Takiyama Y, Nishizawa M, Yoshida M: [Cerebral sinus thrombosis in a young man with hereditary protein C deficiency]. *Rinsho Shinkeigaku* 33: 1083-1085, 1993 (Jpn, with Eng abstract)
- 17) Stenflo J: Structure and function of protein C. *Semin Thromb Hemost* 10: 109-121, 1984

- 18) Vieregge P, Schwieder G, Kömpf D: Cerebral venous thrombosis in hereditary protein C deficiency. *J Neurol Neurosurg Psychiatry* 52: 135-137, 1989
- 19) Vogt T, Besser R, Thoemke F, Hopf HC: [Therapy of sinus thrombosis in congenital protein C deficiency]. *Med Klin* 82: 801-803, 1987 (Ger)
- 20) Wintzen AR, Broekmans AW, Bertina RM, Briët E, Briët PE, Zecha A, Vielvoye GJ, Bots GTAM: Cerebral hemorrhagic infarction in young patients with hereditary protein C deficiency: evidence for

"spontaneous" cerebral venous thrombosis. *Br Med J* 290: 350-352, 1985

---

Address reprint requests to: S. Kuwahara, M.D., Department of Neurosurgery, Kouhoku National Health Insurance Hospital of Sakawa-cho, 1687 Sakawa-cho, Takaoka-gun, Kochi 789-1201, Japan.