Cerebral Venous Thrombosis With Plasminogen Deficiency

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We describe a patient with inherited plasminogen deficiency who developed extensive cerebral venous thrombosis. Several other conditions that might have contributed to a hypercoagulable state, including mild thrombocytosis, thyrotoxicosis, and a chronic inflammatory lung disorder, were present. We also discuss the evidence linking plasminogen deficiency with a thrombophilic state. The diagnosis of cerebral venous thrombosis in this case was readily established by nuclear magnetic resonance imaging, a technique that is ideally suited for the evaluation and follow-up of patients with this condition. (Stroke 1991;22:401-405)

Cerebral venous thrombosis has been associated with diverse disease processes, and a number of risk factors have been identified. Kitchens and others have formulated the concept of thrombophilia or hypercoagulability to explain the increased tendency to intravascular thrombosis in a variety of circumstances. Thrombophilia may be congenital or acquired. The congenital hypercoagulable states are life-long conditions that may be clinically silent; thromboembolic episodes associated with congenital thrombophilic states are often precipitated by risk factors that promote thrombosis in "acquired" thrombophilia such as trauma, surgery, infection, or pregnancy.

The congenital disorders known to cause thrombophilia are deficiencies of antithrombin III, protein C, and protein S; certain types of dysfibrinogenemia; and homocystinuria. Deficiency of plasminogen, which in theory might predispose to thrombosis by slowing fibrinolysis, has been found in some patients with thrombosis. However, isolated plasminogen deficiency is not firmly established as a cause of thrombophilia. We report a patient with cerebral venous thrombosis and congenital hypoplasminogenemia.

Case Report

A 34-year-old man developed gradually increasing occipital headache accompanied by photophobia, nausea, and vomiting in October 1988; there was no history of thromboembolism. Neurological evaluation was normal except for slightly blurred disks and absent venous pulsations. The cerebrospinal fluid (CSF) opening pressure was 370 mm CSF, protein concentration was 35 mg%, and glucose concentration was 66 mg%, with 78 red blood cells (RBCs) and three white blood cells (WBCs) per milliliter. The headache subsided after lumbar puncture. A computed tomogram (CT scan) without intravenous contrast material performed on November 14, 1988, demonstrated generalized brain swelling with effacement of the cortical sulci. A magnetic resonance imaging (MRI) scan obtained on November 23, 1988, demonstrated complete thrombosis of the dural sinuses and internal jugular veins (Figure 1).

The patient was free from headache until the beginning of January 1989, when it recurred and gradually increased in severity. The patient was admitted to the University of Wisconsin Hospital on January 10, 1989. He was in obvious distress, complaining of a severe generalized headache. Physical examination was normal except for some blurring of the optic disk margins and the absence of venous pulsations. The CSF opening pressure was 210 mm CSF, with a normal cell count and normal protein and glucose concentrations. An MRI scan obtained on January 11, 1989, demonstrated partial recanalization of the sagittal sinus (Figure 2).

The patient has been maintained on warfarin since January 1989, with the prothrombin time being maintained at 1.2–1.4 times control. There has been no vomiting, but he still complains of intermittent headache, which is usually occipital and bitemporal. Magnetic resonance angiography performed on August 23, 1989, demonstrated patency of the middle and posterior portions of the sagittal sinus (Figure 3).
FIGURE 1. Brain magnetic resonance imaging scan performed November 23, 1988. Left: Sagittal T1-weighted image reveals high-signal-intensity thrombus (arrowheads) of sagittal sinus. Right: Axial T1-weighted image reveals high signal densities and thrombus within transverse and sigmoid sinuses, as well as jugular bulbs (arrows).

FIGURE 2. Brain magnetic resonance imaging scan performed January 11, 1989. T1-weighted sagittal image demonstrates partial recanalization of sagittal sinus (arrows).
FIGURE 3. Magnetic resonance angiogram performed August 23, 1989, demonstrates patency of middle and posterior portions of sagittal sinus and part of straight sinus.

In 1985 the patient suffered an industrial exposure to ammonia fumes, which resulted in a chronic inflammatory condition of the bronchial tree. This was treated with a steroid inhaler, a brief course of prednisone, and oral theophylline on a chronic basis. Hyperthyroidism associated with clinical evidence of thyrotoxicosis was diagnosed in August 1988 and treated with propylthiouracil at doses of up to 300 mg q.i.d. He was still biochemically hyperthyroid as of November 15, 1988 (T4 uptake by radioimmunoassay was 17.8, T3 uptake was 34.4, free thyroxine index was 6.1, and T3 uptake by radioimmunoassay was 143); by January 10, 1989, his thyroid function tests had returned to normal, and the propylthiouracil was discontinued. He remains euthyroid until the present.

Laboratory findings in January 1989 revealed that the SMA-12 and electrolyte concentrations were normal, the WBC count was 8,700/μl with a normal differential count, the hemoglobin concentration was 15.8 g/dl, the hematocrit was 48%, the platelet count was 422,000/μl, the prothrombin time was 11.5 seconds, the activated partial thromboplastin time was 24.8 seconds, and the fibrinogen concentration was 427 mg/ml. There was no evidence of a lupus anticoagulant, and the thrombin time was normal. A test for cryofibrinogen was slightly positive, suggesting the presence of fibrin in the circulation. Levels of protein C antigen and activity, protein S antigen, and antithrombin III activity were normal. The hematocrit and platelet count have been normal when measured subsequently.

Plasminogen activity (measured on a Du Pont ACA instrument [Wilmington, Del.] using a chromogenic substrate) was 58% of the activity in pooled normal plasma (normal range: 75–130%), and the plasminogen antigen concentration (by electroimmunoassay) was 50% of normal.

The patient's father had an abnormally low plasminogen activity of 51%, and his daughter, aged 5 years, also had a reduced plasminogen activity of 60% and a reduced plasminogen antigen concentration of 50%. Neither had a history of thromboembolic disease. The patient's mother's plasminogen activity was 106%.

These tests established that this patient has an inherited plasminogen deficiency due to reduced production of the protein rather than to synthesis of a functionally abnormal molecule.

Discussion

Although plasminogen deficiency has been found in other patients with pathological thrombosis,3–19 it has not previously been reported in a patient with documented cerebral venous thrombosis. A patient with a low plasminogen activity due to dysfunctional plasminogen developed intracranial hypertension,3 but the diagnosis of cerebral venous thrombosis
could not be confirmed “by extensive tests” short of MRI. The use of MRI in this case made the diagnosis easy and served as a useful tool for follow-up purposes (Figures 1–3).

There are a number of reports describing subnormal fibrinolytic activity in individuals and families with thrombophilia. Deficiency of plasminogen has also been proposed as a possible cause of congenital thrombophilia. An examination of the available evidence, however, suggests that plasminogen deficiency is not a strong risk factor for thrombosis. Including the patient described here, at least 17 individuals with both plasminogen deficiency and a thrombotic tendency have been reported.3–16 Nine of these had dysfunctional plasminogen (i.e., low activity with a normal antigen concentration), while eight (including our patient) had evidence of reduced plasminogen synthesis (low activity and a low antigen level). Including the father and daughter of our patient, 41 relatives with plasminogen deficiency have been identified, none of whom had a thrombotic tendency. This pattern is in sharp contrast to that found in thrombophilic families with inherited deficiencies of antithrombin III, protein C, or protein S, in which there is a strong association between the protein deficiency and a thrombotic tendency. Furthermore, while homozygous (complete) deficiency of either protein C28 or antithrombin III29 usually causes a severe thrombotic tendency beginning in infancy or early childhood, homozygous plasminogen deficiency has been found in a healthy 5-year-old girl.3 Approximately 3.6% of Japanese have a low plasminogen activity due to a nonfunctional plasminogen allele,30 but these individuals do not seem to have an increased incidence of thrombosis.31 It therefore seems unlikely that plasminogen deficiency alone is sufficient to cause abnormal thrombosis, but it is possible that plasminogen deficiency facilitates extension of small, subclinical thrombi in acquired thrombophilic states. In addition to hypoplasmogenemia, our patient had other risk factors for cerebral venous thrombosis, including thyroid disease,22 a high platelet count,33,34 and a chronic inflammatory condition. Any or all of these conditions, possibly acting in synergy with the plasminogen deficiency, may have contributed to abnormal thrombosis.

The risk of thrombosis in persons with plasminogen deficiency without a history of thromboembolic disease appears to be small, and prophylactic anticoagulation treatment does not seem warranted in such individuals. Options available for treating such patients who have had thromboembolic events include long-term anticoagulation with warfarin or short-term treatment with warfarin or low-dose heparin in circumstances in which the risk of thrombosis will be temporarily increased. Fibrinolytic activity can be enhanced by anabolic steroids such as stanozolol,35 which might also be considered for use in the prevention of thrombosis in these patients.

References

KEY WORDS • plasminogen • thrombosis
Cerebral venous thrombosis with plasminogen deficiency.
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*Stroke*. 1991;22:401-405
doi: 10.1161/01.STR.22.3.401

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/22/3/401

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