Ischemic Stroke Due to Protein C Deficiency

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Plasma protein C exerts anticoagulatory effects by inactivating factors V and VIII. Hereditary protein C deficiency is transmitted as an autosomal dominant disorder. Homozygous individuals usually develop purpura fulminans as newborns; heterozygous protein C-deficient individuals are at increased risk for venous thrombosis and pulmonary embolism. However, arterial thrombosis has been only rarely observed. We describe a young patient with heterozygous protein C deficiency who experienced a severe stroke due to thrombotic occlusion of the left middle cerebral artery. (Stroke 1990;21:1077-1080)

Protein C is a plasma glycoprotein with a molecular weight of 62 kDa. Its synthesis by the liver depends on vitamin K. The inactive form of protein C is converted to the active protein C$\alpha$ by thrombin in the presence of Ca$^{2+}$. Combination of thrombin with the cofactor thrombomodulin on the surface of endothelial cells greatly accelerates the activation rate of protein C.$^1$ Protein C$\alpha$ acts as an anticoagulant by inactivating factors V$\alpha$ and VIII$\alpha$. Protein C$\alpha$ also exerts profibrinolytic properties by inactivating plasminogen activator inhibitor 1. Protein S, which is also a vitamin K-dependent plasma protein synthesized by the liver and the endothelium, enhances the activity of protein C$\alpha$.23 Protein C deficiency is inherited as an autosomal dominant trait with incomplete penetrance. Heterozygous individuals have an increased risk of venous thrombosis and thromboembolism at a young age.4 Homozygous protein C deficiency is rare and leads to a purpura fulminans-like syndrome in neonates. Homozygous individuals usually die within the first months of life unless treated with replacement of protein C during the acute phase, followed by lifelong anticoagulation.5,6 Two types of protein C deficiency are known. Most common is type I, in which both the absolute concentration of protein C and its functional activity are reduced. In type II protein C deficiency the activity is reduced whereas the concentration of protein C is normal.3

We describe a young patient with heterozygous protein C deficiency. Occlusion of the left middle cerebral artery led to a severe ischemic stroke.

Case Report

After suffering from a headache for several days, a 32-year-old mechanic acutely developed a brachiofacial hemiparesis of his right side and global aphasia. Cranial computed tomography showed an extensive ischemic infarct in the territory of the left middle cerebral artery (Figure 1). Occlusion of the left middle cerebral artery at its proximal stem was demonstrated by transtemporal Doppler sonography (Figure 2). Duplex scanning of the extracranial carotid arteries did not show arteriosclerotic lesions but revealed reduced blood flow velocities on the left. Since the Doppler sonographic data were unequivocal, cerebral angiography was not done.

The patient had been healthy until this event, and there were no obvious precipitants of thrombosis (i.e., no trauma, intoxication, or dehydration). His only apparent risk factor for vascular disease was the smoking of approximately 15 cigarettes/day. The patient had neither arterial hypertension nor diabetes. Cardiologic investigations including electrocardiography, Holter electrocardiographic monitoring, roentgenography of the chest, and two-dimensional echocardiography did not reveal any abnormality. There was also no evidence of an immunologic disease. Routine blood parameters and the hemostasiologic tests prothrombin and partial thromboplastin times, albumin, fibrinogen, factor VIII, and anti-thrombin III concentrations, platelet count, platelet aggregation, and bleeding time were normal. Protein C activity of the patient's plasma was measured in the Department of Internal Medicine using the Protein C Reagent Test (Behringwerke AG, Marburg, FRG); normal protein C activity was assumed to be in the range 60–160% of that in pooled normal plasma. The absolute concentration of protein C antigen was not determined. The patient's protein C functional activity was only 36% and 33% in two consecutive evaluations 5 days apart. The functional activity of anti
thrombin III and the concentrations of antiphospholipid antibodies and protein S were not measured at that time.

We treated the patient initially with 10% dextran until the diagnosis of a hypercoagulopathy due to protein C deficiency became probable; at that time long-term anticoagulation with 25,000 units/day heparin and 3 mg/day phenprocoumon was started. When adequate anticoagulation was achieved with phenprocoumon as shown by the prothrombin time, heparin was discontinued. There were no complications, particularly no coumarin necrosis.

The patient's hemiparesis improved during the following months, but his aphasia remained severe. One year after his stroke, the patient suffered two epileptic seizures, one beginning focally in the left hemisphere. He was thereafter treated with carbamazepine.

On reexamination 15 months after the stroke, the patient's left middle cerebral artery was recanalized according to Doppler sonographic criteria.

The family history was positive for thromboembolic disease; that is, the patient's father had died of pulmonary thromboembolism at age 49 years, and his paternal grandmother had died of ischemic stroke at age 64 years. Protein C activity was measured in plasma samples from several family members in the Department of Pediatrics with Thromboquant Protein C (Boehringer, Mannheim, FRG). The patient's mother and three of his siblings had normal protein C activity, whereas four of his sisters showed protein C deficiency (Figure 3). Furthermore, some children of the protein C-deficient sisters were found to be heterozygous for protein C deficiency also. None of these protein C-deficient relatives had suffered from thromboembolic disease. Protein S concentration was measured by the Electroimmuno diffusion Protein S Test (Boehringer) and was in the normal range in all relatives investigated.

Discussion

Cerebrovascular events in young and middle-aged persons can become a diagnostic problem since numerous disorders may lead to a stroke. In some cases, the cause remains unclear.7–9 Protein C deficiency has been known for some time to be a major risk factor for venous thrombosis. Its prevalence seems to be 6–8% in patients <40 years old with a history of venous thrombosis.4 Thrombosis of the cerebral veins, however, seems to be rare in heterozygous patients.10 There have been a few reports on cerebral hemorrhagic infarction caused by sinus thrombosis in homozygous protein C-deficient infants.11 However, a well-documented case of thrombosis of the cerebral arteries due to heterozygous protein C deficiency has not been reported yet. Dusser and coworkers12 described two children who had suffered from cerebral arterial thrombosis associated with a protein C deficiency that, however, was only temporary and probably not inherited. Smith and Ens13 discussed that protein C deficiency may cause amaurosis fugax. Israels and Seshia14 described a 17-month-old girl with protein C deficiency who presented with an acute hemiparesis; the computed tomogram was normal in this patient. Kemkes-Matthes15 examined a heterozygous protein C-deficient man who experienced the occlusion of a carotid artery 4 weeks after surgery for a nasal liquor fistula.

In our patient, occlusion of the left middle cerebral artery led to ischemic infarction with the clinical symptoms of right hemiparesis and persisting global aphasia. Embolic infarction from a cardiac source or arterioarterial embolism due to preexisting carotid artery sclerosis could largely be excluded as could immunologic diseases. The patient's protein C activity was significantly decreased in two tests before anticoagulation was started. Prior to his stroke, the patient had not experienced thromboembolic complications, but his father had died of pulmonary thromboembolism during middle age. The family study proved heterozygous protein C deficiency. Hypercoagulopathy due to inherited heterozygous protein C deficiency apparently caused the thrombosis of this patient's left middle cerebral artery. During anticoagulation therapy with phenprocoumon the occlusion was recanalized.

It could be argued that an ischemic stroke by itself could lower the protein C concentration by way of increased consumption and that our patient was falsely assumed to have an inherited protein C deficiency. However, this hypothesis would not explain his consistently low protein C activity some days after
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FIGURE 2. Transtemporal Doppler sonograms of 32-year-old man 1 day after stroke indicate occlusion of the left (L) middle cerebral artery (MCA). Intracranial carotid arteries (top) were examined with pulsed Doppler sonography (fo=2 MHz), and extracranial carotid arteries (bottom) were examined with continuous-wave Doppler sonography (fo=4 MHz). Positive Doppler shift corresponds to blood flow toward probe. There was little side-to-side difference in signals of internal and common carotid arteries (ICA and CCA). Signals of anterior cerebral artery (ACA) could be easily found on both sides, whereas there was no signal from left MCA. R, right.

FIGURE 3. Pedigree of 32-year-old man with heterozygous protein C deficiency who suffered severe ischemic stroke due to thrombotic occlusion of left middle cerebral artery. Numerals beneath each symbol indicate protein C activity in percent (normal range 60–160%).

the event. Moreover, protein C concentrations do not differ significantly between patients suffering from acute stroke and healthy controls. It remains unclear, however, why persons with heterozygous protein C deficiency do not present more often with arterial thromboembolic events. Smoking may have imposed an additional risk in our patient, but other still-unknown factors might also have contributed.

We conclude that protein C deficiency may cause cerebral artery thrombosis and ischemic cerebral infarction. Therefore, protein C activity should be evaluated in young persons presenting with ischemic stroke of unobvious cause.

References

KEY WORDS: arterial occlusive disease • cerebral ischemia • protein C
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