Case Reports

Cerebral Infarction Associated With Protein C Deficiency

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Background and Purpose: A deficiency of plasma protein C, both the hereditary and acquired types, is one cause of thromboembolic disease. Several antineoplastic agents have been reported to decrease the production of protein C in the liver by impairing either the absorption or metabolism of vitamin K, leading to acquired protein C deficiency.

Case Description: We treated a young woman with protein C deficiency, who had developed a cerebral infarction of the right parietal cortex of sudden onset. On admission, the antigenic level of plasma protein C was 38%. Serial cerebral angiography revealed occlusion of the right middle cerebral artery, which subsequently recanalized completely. This patient had taken fluorouracil derivatives orally for as long as 3 years following a left mastectomy for stage II breast cancer. Tests revealed that the patient's mother had only one-half the normal activity of plasma protein C despite a normal antigenic level.

Conclusions: We speculate that the etiology of the cerebral infarction in this patient might involve an embolic mechanism associated with protein C deficiency induced by an interaction between inherited and acquired factors. (Stroke 1992;23:108–111)

Recognizing the role of hematologic disorders in the etiology of cerebral infarction in young adults is growing, with special attention being paid to protein C deficiency. Since protein C deficiency was first reported by Mammen et al in 1960, detailed information about this disorder has been accumulating. Protein C is activated physiologically by thrombin, but also requires the coexistence of thrombomodulin and protein S. Activated protein C supposedly acquires its anticoagulant and fibrinolytic functions by inactivating coagulant factors Va or VIIIa or by countering the plasminogen activator inhibitor. As with ATIII deficiency, venous thrombosis is the most common clinical complication associated with protein C deficiency. Arterial thrombosis associated with these deficiencies has been reported in only a handful of cases. The clinicopathological type associated with protein C deficiency has not yet been fully identified. We evaluate the pathogenetic factors in the case of a 39-year-old woman with protein C deficiency who experienced a cerebral embolism.

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Case Report

A 39-year-old woman was admitted to the National Cardiovascular Center (Osaka, Japan) on October 29, 1990, because of sudden onset of neurological symptoms including left hemiparesis, a sensory disturbance, and dysarthria. Three years earlier she had undergone a left radical mastectomy following the diagnosis of stage II (scirrhous) breast cancer. She had been taking fluorouracil derivatives orally as adjuvant chemotherapy since that time. On admission, the patient was obese (height, 155 cm; weight, 68.3 kg); her blood pressure was 120/68 mm Hg, and her heart rate was 71, with no arrhythmia. Heart and respiratory sounds were clear, and no hepatosplenomegaly was observed. She appeared to have no risk factors for vascular disease. Her family history revealed that her father died after a third myocardial infarction and that her paternal uncle died suddenly of unknown cause. Neither her mother nor her siblings had experienced thrombotic episodes. The patient had never before experienced a vascular event.

Cranial computed tomography disclosed a fresh infarction in the right parietal lobe (Figure 1). Cerebral digital subtraction angiography showed the occlusion of the anterior branch of the right middle cerebral artery, with relatively good collateral circulation (Figure 2). Two-dimensional and color Doppler echocardiography did not reveal valvular disease,
thrombus formation, or intracardiac shunt pathway. Cervical echography did not demonstrate any abnormalities such as plaque formations at the bilateral carotid bifurcations. Other sources of embolism and venous thrombosis were not detected. Abdominal echography suggested only a fatty change without mass lesions. The laboratory findings, including antiphospholipid antibodies and lupus anticoagulant values, were essentially normal. The prothrombin time was slightly prolonged to 77% (international normalized ratio 1.17), and the protein C concentration was decreased to 38% (normal range, 75–125%).

FIGURE 1. Admission computed tomographic scan, 4 days after onset of symptoms. Low-density area localized in anterior parts of right parietal lobe is apparent. Scale, 50 mm.

FIGURE 2. Lateral view by cerebral digital subtraction angiography shows avascular area in anterior portion of right middle cerebral artery.
FIGURE 3. Lateral view by cerebral digital subtraction angiography clearly demonstrates reappearance of anterior branches of right middle cerebral artery.

with reproducibility on repeat testing. The patient’s mother had normal antigenic levels of protein C, but qualitative assays showed that the amidolytic activity based on plasma protein C activation by snake venom was less than half that of normal controls. Results of other hematology tests, such as active partial thromboplastin time, fibrinogen, antithrombin III, plasminogen, and fibrin degrading products, were within normal range.

We diagnosed a cerebral infarction caused by protein C deficiency. Since the fourth day in the hospital, the patient had received warfarin at a dose of 3 mg daily. On hospital day 29, recanalization of the right M2 occlusion was confirmed by follow-up angiography (Figure 3). The patient’s speech and left limb weakness gradually improved.

Discussion

Protein C deficiency has been described by some investigators as a cause-contributing factor in prothrombotic states. The hereditary or congenital type of protein C deficiency is transmitted mainly by autosomal-dominant regulation. Of the cases of venous thrombosis of unclear cause, 6–8% are believed to be associated with this abnormality. However, arterial thromboembolism associated with protein C deficiency is very rare, and very few such reports can be found. Protein C deficiency can be induced by certain conditions, particularly malignancies. Because protein C is a vitamin K-dependent protein (molecular weight, 62,000) produced in the liver, it is not surprising that acquired protein C deficiency is usually observed in patients receiving warfarin therapy. In addition, antineoplastic drugs are reported to reduce levels of protein C. The mechanism for this reduction is still unclear, but Seifert et al pointed out that antineoplastic drugs may impair either the absorption or metabolism of vitamin K. Barbui et al reported that L-asparaginase, an antineoplastic drug, reduced protein C antigen. Levine et al reported that chemotherapy itself contributed to thrombosis in a controlled study in patients with stage II breast cancer. Additionally, Rogers et al examined plasma levels of protein C and protein S during chemotherapy in patients with breast cancer and found that protein C levels decreased to <60% of normal in six of 15 patients. None of these patients, however, experienced a clinically apparent thrombotic event during a 1-month follow-up. The investigators warned, however, that it was possible for patients with low protein C levels before antineoplastic drug administration to develop thrombotic events after that.

In our case, the patient’s mother had 44% of the normal protein C activity without a decrease in antigenic levels (type II). Therefore, it is clear that there was a hereditary factor in the patient’s protein C deficiency. She had been taking fluorouracil derivatives for >3 years following a mastectomy, which may have impaired protein C production. We suspected a preexisting state of hypercoagulability in this patient because of these congenital and acquired protein C deficiencies. Clinically, cranial computed tomography revealed a cerebral infarction, partially
including the right parietal cortex. Serial cerebral angiography showed the recanalization of the occlusive site, which was similar to a cardiogenic cerebral embolism. In a case report by Kohler et al., an ischemic stroke due to protein C deficiency was described in which the recanalization of the occluded middle cerebral artery was documented by transtemporal Doppler ultrasonography on reexamination 15 months after the stroke. In our case, follow-up cerebral angiography was not done until day 25 after the stroke, and, of course, it is impossible to know when the recanalization occurred prior to that time. However, one would expect that decreased protein C activity might retard such recanalization.

References


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