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Congenital Antithrombin III Abnormality and Cerebral Arterial Thrombosis

To the Editor:

A recent review by Hart and Kanter¹ pointed out that a congenital abnormality of antithrombin III can be associated with both venous and arterial intracranial thrombosis. They indicated that antithrombin III abnormalities with cerebral arterial thrombosis preceded systemic venous thrombosis, with only one reported exception.² We report here another such exception.

A 23-year-old woman who had no previous heart disease, venous or arterial thrombosis, migraine, or contraceptive use developed sudden severe headache preceded by symptoms of an upper respiratory infection. It subsided in some minutes, followed by blurring of her left visual field. When examined 6 hours after onset, she had no heart murmur, irregular pulse, or signs of systemic venous thrombosis. Neurological and neuropsychological examinations revealed left homonymous hemianopsia, left unilateral spatial neglect, defective route finding, and prosopagnosia. No other motor, sensory, or cranial nerve signs were present. Routine laboratory findings were normal.

On the second hospital day, computed tomography of the head showed posterior medial temporal and medial occipital infarctions of the right hemisphere. Subsequently, angiogram revealed an occluded branch of the right posterior cerebral artery, but there were no angiographic signs of atherosclerotic change or intracranial venous thrombosis. Neurological signs rapidly improved and, 2 weeks after onset, only the visual defect at the periphery of the left homonymous field could be detected. Survey of her heart, including electrocardiogram, Holter monitoring, and echocardiogram, was normal. Blood cell count, liver and renal functions, prothrombin and activated partial prothrombin times, plasminogen and protein C activities, and fibrin degradation products were all within normal ranges. The antigen concentration of antithrombin III measured by single radial immunodiffusion method was 30.7 mg/dl (normals 21.0-34.0 mg/dl). However, antithrombin III activity, estimated as heparin cofactor antithrombin activity of her plasma measured with Coatest Antithrombin (Kabi, Stockholm,

Sweden), was 55% (normals 75-126%), with increased fibrinopeptide A to 22.1 ng/ml (normals 0.5-2.0 ng/ml).

These findings suggested excessive production of active thrombin due to low antithrombin III activity and prompted us to begin oral coumarin therapy. Two months after onset, the fibrinopeptide A was reduced to 7.7 ng/ml, but repeated analysis of antithrombin III showed constantly reduced heparin cofactor activity (49%), with normal antithrombin III antigen concentration (30.3 mg/dl). Progressive antithrombin activity of her plasma in the absence of heparin measured by the reported method³ was 115% (normals 80-120%). She continued oral coumarin and had no recurrence of arterial or venous thrombosis for 3 years, but heparin cofactor activity did not normalize (65% at 3 years after onset). We could not evaluate other members of her family because she was an orphan and had no children.

The reduced heparin cofactor activity of her plasma is attributed to abnormal antithrombin III. Dysfunction of heparin cofactor II, the second major thrombin inhibitor of human plasma, cannot explain the degree of reduction found in this patient because of its relative activity⁴ and antigen concentration.⁵ This sustained hypocoactivity without reduction of progressive antithrombin activity and antigen concentration, together with the normal liver and renal functions, suggests the heterozygous type III form of congenital antithrombin III abnormality,^{1,6} although her family history is uncertain. The homozygous form of this type is predominant in patients complicated by cerebral arterial thrombosis.¹ The cerebral arterial thrombosis was the only manifestation of her antithrombin III abnormality, which we emphasize as the rare but probable etiology of intracranial arterial occlusive disease in young adults, even if they have no past history of venous thrombosis.

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