Progressive Intracranial Occlusive Disease Associated With Deficiency of Protein S

Report of Two Cases

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Background and Purpose: Deficiency of the free fraction of protein S has been associated with arterial or venous stroke. The pathogenesis of vascular occlusion in patients with protein S deficiency is not known. We present two cases of cerebral infarction and deficiency of protein S in which the subjects had progressive intracranial occlusions.

Case Description: A 16-year-old girl was admitted because of left brain stem infarction and protein S deficiency. Cerebral angiography disclosed stenosis of the right intracranial vertebral artery and occlusion of the left posterior cerebral artery. A second angiogram performed 18 months later disclosed occlusion of the right vertebral intracranial artery. In the second case, a 17-year-old girl was admitted because of left hemispheric cerebral infarction and protein S deficiency. Cerebral angiography showed stenosis of the left anterior cerebral artery, left supraclinoid internal artery, and left middle cerebral artery. A second cerebral angiogram performed 5 months later disclosed occlusion of the left anterior cerebral artery and poor hemispheric perfusion through the left middle cerebral artery.

Conclusions: Based on our cases, we postulate that some patients with prothrombotic states may develop progressive intracranial arterial occlusions, possibly secondary to a permanent thrombogenic stimulus. We suggest routinely searching for prothrombotic states in young patients with intracranial occlusion, especially if the occlusion is progressive and other causes are not obvious. (Stroke. 1993;24:1752-1756.)

Key Words • arterial occlusive diseases • cerebral infarction • proteins

P rotein S is a cofactor of the anticoagulant action of activated protein C. Deficiency of the free fraction of this protein has been associated with arterial or venous cerebrovascular disease. The incidence and prevalence of free protein S deficiency are not known, and few cases of associated cerebral infarction have been reported. The pathogenesis of vascular occlusion in these patients is also not known.

In this article we present two cases of cerebral infarction due to progressive intracranial occlusive disease demonstrated by sequential cerebral angiography.

Case Reports

Case 1

A 16-year-old girl was admitted to the National Institute of Neurology and Neurosurgery, Mexico City, on December 20, 1989, because of vertigo and generalized, progressively severe headache. On admission she was drowsy and had conjugate deviation of the eyes to the right, bilateral ptosis, right central facial paresis, and was unable to protrude the tongue. She was tetraparetic and had bilateral Babinski's signs. Physical examination was otherwise normal. There was no previous or family history of vascular disease. The laboratory examination, including antiphospholipid antibodies, rheumatoid factor, lupus erythematosus preparation, antinuclear antibodies, erythrocyte sedimentation rate, and C3-C4 concentration, was normal. Results of electrocardiography and two-dimensional and transesophageal echocardiography were normal. Magnetic resonance imaging showed an infarction involving the basal and tectal portion of the pons and midbrain. A cerebral angiogram disclosed stenosis of the intracranial portion of the right vertebral artery with patent basilar artery and occlusion of the left posterior cerebral artery at its origin (Figs 1 and 2). Treatment with aspirin was started. In July 1992, a second cerebral angiogram showed occlusion of the right intracranial vertebral artery distal to the origin of the posterior inferior cerebellar artery, as well as persistence of the occlusion of the left posterior cerebral artery (Fig 3).

In August 1992, additional blood tests were performed, including quantification of antithrombin III (AT-III), protein C, plasminogen, plasminogen tissue activator, and the inhibitor of plasminogen activator by the chromogenic method (Kabi-Vitrum) and protein S by the Laurell method. The only abnormality noted was a deficiency of the free fraction of protein S at levels of 25% (normal levels for our laboratory, above 40%). Total protein S level was 42% (normal value, 60% to 150%).
The patient has been treated since that time with oral anticoagulant drugs and has had no recurrences for 24 months.

Case 2

A 17-year-old girl was admitted to the National Institute of Neurology and Neurosurgery on November 19, 1991, because of sudden right hemiparesis that evolved to hemiplegia and aphasia over 30 minutes. On admission she was conscious and was able to understand and obey orders. She had a nonfluent aphasia. Examination revealed right faciocorporal hemiplegia, hemihypoesthesia, and Babinski's sign but was otherwise normal. There was no family or personal history of previous vascular disease.

The laboratory examination, including antiphospholipid antibodies, rheumatoid factor, lupus erythematosus preparation, antinuclear antibodies, erythro sedimentation rate, and C3-C4 concentration, was normal. Results of electrocardiography and two-dimensional and transesophageal echocardiography were normal.

Magnetic resonance imaging showed a left frontoparietotemporal infarction with involvement of the internal capsule. Cerebral angiography revealed a reduction of the luminal diameter of the left supraclinoid internal carotid artery and irregularities of the lumen of the left anterior cerebral artery at its origin, as well as of the proximal segment of the superior division of the middle cerebral artery and its distal branches (Figs 4 and 5). Treatment with aspirin was started. In April 1992, another cerebral angiography showed occlusion of the left anterior cerebral artery and an intensification of the stenosis of the left supraclinoid carotid artery. Hemispheric perfusion was done through the inferior division of the left middle cerebral artery (Fig 6).

Blood tests done in June 1992 included quantification of AT-III, protein C, plasminogen, plasminogen tissue activator, and the inhibitor of plasminogen activator by the chromogenic method (Kabi-Vitrum) and protein S by the Laurell method. The only abnormality noted was a deficiency of the free fraction of protein S at levels of 16%, with total protein S level of 100%.

Since June 1992, the patient has been treated with oral anticoagulants.
Prothrombotic states are pathological conditions in which blood clotting, platelet function, or fibrinolysis has been altered in favor of thrombosis.5 Recently, hereditary or acquired protein S deficiency has been identified as a cause of cerebral infarcts of the arterial type in young subjects, although the pathogenesis remains unclear.6-13 One possible mechanism is a derailment in hemostatic balance, with intravascular thrombosis and occlusion of large or small vessels.14 Another explanation is an association between protein S deficiency and other primary structural arterial or cardiac abnormalities, which allows thromboembolic events to occur. Wallis and Godwin8 cite such an example in their report of a woman with cerebral ischemia associated with mitral valve prolapse, protein S deficiency, tobacco smoking, and the use of oral contraceptive agents. Recently, Matsushita et al15 reported a case of a woman with protein C deficiency and a cerebral infarction secondary to the occlusion of a cerebral artery that recanalized later, which suggests a possible embolic mechanism.

The frequency of arterial occlusion, as determined by cerebral angiography in patients with deficiency of natural anticoagulants, is not known. Few cases have been reported (Table). From 25 radiographically documented cases, including the two women studied by us, 13 had AT-III deficiency, 6 had protein C deficiency, and 6 protein S deficiency.9,11-13,15-18 In most the intracranial carotid territory was affected, and in only 2 was there involvement of the vertebrobasilar circulation.

To date, there is little knowledge regarding the natural evolution of such occlusions associated with prothrombotic states. In our two cases there was progression of the intracranial occlusive vascular lesion. In the second case we noted irregularities of the caliber of the blood vessels, similar to those observed in vasculitic processes. In both cases the diagnosis of protein S
deficiency was made after the second cerebral angiogram; for this reason, the patients had been treated exclusively with aspirin. Because anticoagulation has been postulated as the optimum treatment for this condition, our two cases could be considered examples of the possible natural evolution of arterial intracranial occlusion associated with protein S deficiency. Recently, Arima et al19 illustrated another case of progressive intracranial occlusive disease, documented by sequential cerebral angiography, associated with AT-III deficiency.

The combination of the very low free protein S level but a normal total protein S level in our second case is intriguing. Protein S exists in two distinct forms in human plasma. Approximately 40% occurs as free protein S, and the remainder is bound to C4b binding protein. During an inflammatory response the concentration of C4b binding protein concentration may be increased up to 400% of normal20; therefore, the concentration of free protein S in plasma may be reported as lower than normal.21 It is possible that blood contains other mechanisms (as yet unknown) that regulate the interaction between protein S and C4b binding protein. This case corresponds to a deficiency type I, in which the free fraction is decreased, but the total concentration of protein S is normal. Possibly this is not a quantitative deficiency but rather a disturbance in the complex protein S-C4b binding protein dissociation. The cause is unknown, but possible causes include autoimmune damage or an abnormality in the chemical structure.21

Green et al9 reported a case of protein S deficiency and major occlusion of the right internal carotid artery. Davous et al10 described a patient with familial protein S deficiency with distal occlusion of the temporal branch of the left middle cerebral artery in whom there was no evidence of a cardiac embolic source. The case described by Gómez-Aranda et al12 involved occlusion of one vertebral artery in its extracranial segment. In addition to these cases, other reports have documented cerebral vessel occlusion associated with deficiency of other natural anticoagulants (Table). Unfortunately, in the aforementioned reports serial cerebral angiography was not performed, and therefore it is not possible to report the outcome of these arterial occlusions.

Based on our cases and on that reported by Arima et al,19 we propose that a proportion of patients with prothrombotic states may develop progressive intracranial arterial occlusion that is possibly secondary to a permanent thrombogenic stimulus. This may justify the chronic use of anticoagulants as well as the routine search for prothrombotic states in young subjects with intracranial occlusion, especially if the occlusion is progressive and other causes are not obvious.

**References**

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