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# A Case of Nephrotic Syndrome Associated with Protein S Deficiency and Cerebral Thrombosis

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***Protein S is found in two forms in plasma ; as free and functionally active protein S, and complexed to C4b-binding protein. Patients with nephrotic syndrome are at risk for arterial and venous thrombosis at various localizations, and acquired protein S deficiency due to the selective urinary loss of the free form may be a risk factor for the development of thromboembolic complications.***

***We report a case of cerebral arterial thrombosis associated with decreased level of free protein S antigen (44%) in a 39-year-old female patient with nephrotic syndrome.***

**Key Words :** *Protein S, Thrombosis , Nephrotic Syndrome.*

## INTRODUCTION

Thromboembolic events are well known complications in patients with nephrotic syndrome (Kendall et al., 1971), and both venous (Kanfer et al., 1970 ; Kauffmann et al., 1976) and arterial (Nitatori et al., 1987 ; Parag et al., 1990) thromboses have been noted, though the pathophysiologic mechanisms are not completely known.

Increased production of clotting factors (Vaziri et al., 1980), reduced fibrinolysis (Kanfer et al., 1970), and renal loss of regulatory proteins of the coagulation cascade such as antithrombin Ⅲ (Kauffmann et al., 1978) or protein S (Vigano-D'Angelo et al., 1987). Protein S circulates in a free form and in an inactive complex with C4b-binding protein, and only unbound or free protein S has functional activity as a cofactor for activated protein C in inhibiting factors Va and Ⅷa (Marlar et al., 1982). Herein we present a case of cerebral arterial thrombosis associated with a decreased level of free protein S antigen (44 %) and normal and elevated levels of antithrombin Ⅲ and protein C, respectively, in nephrotic syndrome.

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## CASE REPORT

A 39-year-old female had been diagnosed with membranoproliferative glomerulonephritis in April, 1990, and was admitted with 10 days history of dysarthria and weakness in the left extremities in October, 1992. The patient was found to have proteinuria and decreased serum albumin level, and diagnosis of nephrotic syndrome was made.

On admission, the patient was mentally clear. Her temperature was 36.5℃ and blood pressure was 140/80 mmHg. Neurological examinations disclosed sensory changes and motor weakness involving the left side of the face, and upper (grade 2) and lower (grade 3) extremities. A computerized tomogram brain study revealed multiple low density lesions from infarction on the periventricular area of the right frontal lobe (Fig. 1). Laboratory data revealed

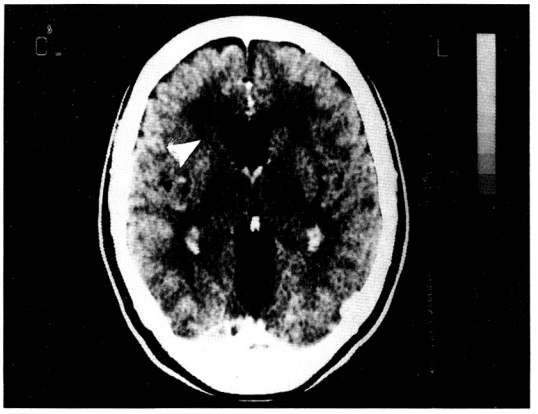

Fig. 1. Brain study of computerized tomogram revealed multiple low density lesions from infarction (arrow) on the periventricular area of right frontal lobe.

hemoglobin, 11.5 gm/dL ; hematocrit, 34.8% ; platelet count 276,000/ μL ; WBC count, 8,800/ μL, prothrombin time, 13.0 sec (normal, 12-14 sec) ; activated partial thromboplastin time, 25.2 sec(normal, 21-32 sec) ; fibrinogen, 384 mg/dL ; serum total protein 3.8 gm/dL ; albumin, 2.0 gm/dL ; total cholesterol, 235 mg/dL ; aspartate aminotransferase, 14 IU/L ; alanine aminotransferase, 9 IU/L ; and 24-hour urine protein, 3400 mg. Levels of coagulation factors Ⅴ, Ⅶ, Ⅷ, Ⅸ, and Ⅹ were within normal limits. Serological studies including VDRL, rheumatoid factor and antinuclear antibody were all nonreactive. The plasma antithrombin Ⅲ and protein C activity measured by chromogenic assay were 120 %(normal, 77-128%) and 121% (normal, 66-113%), respectively. Plasma antigen level of total protein S was 75% (normal, 84-101%) , and free protein S content was depressed to 40% (normal, 71-103%).

The patient was treated with coumadin and discharged on the 19th day after admission with clinical improvement.

## DISCUSSION

Nephrotic syndrome is characterized by profound changes in the turnover and concentrations of most plasma proteins, and those that take part in the coagulation cascades are not excepted (Cameron, 1984). Even though a clinical correlation or casual relationship between these changes and the subsequent development of thrombosis has not been clearly proven or established and the net effect of changes may cancel each other out, they seem to render the patient's blood somewhat hypercoagulable, which is likely to be an important factor in the high incidence of thromboembolic complications (Kendall et al., 1971).

Kauffmann et al. (1976) reported low plasma antithrombin Ⅲ concentrations in eight of nine patients studied, one of whom had renal venous thrombosis. This depletion of antithrombin Ⅲ in nephrotics has been confirmed and shown to be the result of urinary loss of this low molecular weight protein (Panicucci et al., 1983). However thromboembolic complications occurred in some patients with normal antithrombin Ⅲ levels, indicating that although antithrombin Ⅲ is a major determinant of plasma antithrombin activity in nephrotics, it is not the only one (Cameron, 1984) and other regulatory proteins of coagulation such as protein C or protein S may play a role. Protein S, a vitamin K-dependent plasma protein, serves as a cofactor for the anticoagulant activity of another vitamin K-dependent protein, activated protein C (APC) (Schwarz et al., 1985). Protein S increases the affinity of APC for negatively charged phospholipids by forming a 1 : 1 complex with APC, and consequently the proteolytic destruction of factor Va by APC is enhanced (Walker, 1984). Because it has been clearly established now that a hereditary deficiency in protein C is associated with an increased risk for the development of thromboembolic disease (Griffin et al., 1981 ; Pabinger-Fasching et al., 1983 ; Soria et al., 1985), an increased risk of thrombotic disease in isolated hereditary or acquired deficiency in protein S is not surprising (Schwarz et al., 1984 ; Comp et al., 1984 ; Comp and Esmon, 1984 ; Broekmans et al., 1985).

Acquired protein S deficiency can occur in a variety of clinical conditions including pregnancy (Comp et al., 1986), oral contraceptive use (Boerger et al., 1987), disseminated intravascular coagulation (D'Angelo et al., 1988), liver failure (D'Angelo et al., 1988), type 1 diabetes mellitus (Schwarz et al., 1987), autoimmune disease such as a systemic lupus erythematosus (Ruiz-Arguelles et al., 1991), and nephrotic syndrome (Vegano-D'Angelo et al., 1987). When compared with controls, patients with nephrotic syndrome had reduced functional levels of protein S despite having elevated levels of total PS antigen (Vigano-D'Angelo et al., 1987). Decreased PS activity was caused by significant re-

ductions in free (active) PS levels due to the selective urinary loss of free PS and elevation of C4b-binding protein levels that favors complex formation (Vigano-D'Angelo, 1987). Eventhough selective loss of the uncomplexed protein is a unique feature of nephrotic syndrome, plasma levels of antithrombin Ⅲ and protein C were normal and elevated, respectively in this case, suggesting that reduced free protein S could be related to the elevated level of C4b-binding protein without decrease of total protein S. Elevated protein C levels may represent a protective mechanism for the hypercoagulable state in patients with proteinuria and acquired protein S or antithrombin Ⅲ deficiency, inasmuch as the anticoagulant activities of antithrombin Ⅲ or protein S are probably complementary (Rosenberg and Rosenberg, 1984).

In all series where comparable data are available, arterial thrombosis is much less common than venous thrombosis and arterial thrombosis has been reported principally in children, involving the coronary, aortic, renal and femoral arteries (Kim et al., 1993). However, cerebral infarction in patients with nephrotic syndrome has also been reported (Marsh et al., 1991) and an occasional adult may suffer this complication (Kanfer et al., 1970). Though the incidence of arterial thrombosis in adult nephrotic syndrome, and the exact underlying mechanisms of the hypercoagulable state of the nephrotic syndrome remain unclear, acquired protein S deficiency should be considered as one of the contributary factors responsible for cerebrovascular accident in children or in young adults because of the high frequency (25%) of arterial thrombosis in protein S deficiency (Israels and Seshia, 1987 ; Wiesel et al., 1990).

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