RECURRENT CEREBRAL THROMBOSIS ASSOCIATED WITH PROTEIN S DEFICIENCY IN A CHINESE FEMALE

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ABSTRACT

A 52-year-old Chinese female with recurrent cerebral thrombosis associated with hereditary protein S deficiency is described. The need to consider clotting disorders in young patients with no known risk factors for stroke is emphasized.

Keywords : Cerebral thrombosis, protein S deficiency

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INTRODUCTION

In 1977, Di Scipio et al in Seattle first purified a new glycoprotein from human plasma which was named protein S in reference to its isolation and characterization in Seattle[1]. Protein S has an important role in blood coagulation and fibrinolysis. Hereditary protein S deficiency associated with venous thrombosis has been well reported[2-4] but it is only recently that a relationship between protein S deficiency and arterial thrombosis is noted[5-8].

We report on a Chinese female with protein S deficiency who presented with recurrent cerebral thrombosis.

CASE REPORT

A 52-year-old Chinese housewife presented with progressive weakness over the left upper and lower limbs over one day. Two years ago, she was admitted for left hemiparesis which was successfully rehabilitated with good recovery and she was able to walk with a quadstick. She did not complain of any sensory symptoms and there was no cognitive deficit. There was no history of diabetes mellitus, hyperlipidemia, hypertension or ischaemic heart disease. She did not smoke or drink any alcohol. Since the first stroke she was started on Aspirin 600 mg bid.

On admission, she was alert and rational with a blood pressure of 130/90 mmHg and a regular pulse rate of 70 beats per min. No carotid bruit was heard and there was no evidence of peripheral vascular disease. Auscultation of the heart revealed no murmur. She had left hemiparesis which was associated with increased tone but no cranial nerve or sensory deficit was noted.

Investigations

Haemoglobin level 14.4g/dl, total white cell count 9.2 x 10^9/l, platelet count of 230,000/ml, random sugar level 5.2 mmol/l, fasting cholesterol level at 5.02 mmol/l and triglyceride level at 0.84 mmol/l, erythrocyte sedimentation rate of 10 mm/hr, non reactive VDRL test result, absence of both antinuclear factor and anticardiolipin antibodies, prothrombin time 12s (control 13s) and partial thromboplastin time 27s (control 38s), antithrombin III level 114% which is normal, protein C level 86% (normal range 70 to 140%), protein S levels done on 2 occasions one week apart 55% and 54% (normal range 70 to 140%), liver function test was normal, transoesophageal echocardiography was normal, ultrasound of the carotid arteries was normal, CT scan of the head showed multiple small infarcts over the right internal capsule with periventricular ischaemia.

Laboratory Diagnosis of Protein S Deficiency

The total protein S antigen was determined by Laurell rocket electrophoresis with antisera supplied by Behring. The ASSERA PLATE PROTEIN S test method is described on page 434 to 435 in the Diagnostica Stago manual. The criteria for the laboratory diagnosis of protein S deficiency were the following:

1. The plasma concentration of total protein S antigen should be lower than the lower limit of the range as established for healthy blood donors (that is less than 70%).
2. The plasma of 30 normal blood donors of both sexes was used to establish the normal range (70 to 140%).

DISCUSSION

Since protein S was discovered in 1977, much work has been done to elucidate its significance in coagulation. Its role as a cofactor of activated protein C was reported by Walker[9] who observed that plasma deficient in protein S was not effectively anticoagulated by activated protein C. In plasma, protein S exists in two forms[10], namely as a free protein and as a bound protein, complexed to C4b binding protein (an inhibitor of the complement system). Only the free protein S is active functionally[11]. Specifically, protein S facilitates the binding of activated protein C to the surface of bovine platelets[12] and is also required for activated protein C to inactivate factor Va[13] and factor VIIIa[14]. This degradation of V and VIII results in the inhibition of the clotting cascade.

Protein S deficiency can occur as a hereditary disease[2-4] or as an acquired disorder in various clinical conditions eg pregnancy[15], liver failure[16] and type I diabetes mellitus[17]. Thus, to diagnose hereditary protein S deficiency, the possible

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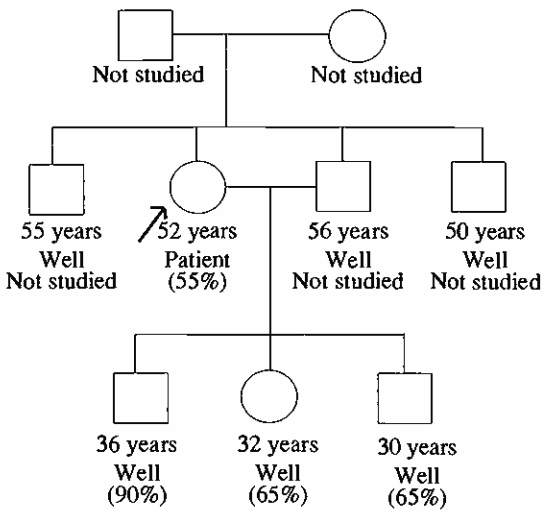
acquired causes need to be excluded and the screening of family members for the deficiency is necessary.

After its discovery, the association of protein S deficiency and thromboembolic disease was subsequently reported in several families by Comp, Broekmans and Batard[3,4]. These patients often presented with thrombotic complications at a young age. Initial reports highlighted its association with venous thrombosis, but recently more investigators have reported the presence of protein S deficiency in patients with arterial thrombosis[5-8]. The mode of inheritance is autosomal dominant[2,4] and the prevalence of hereditary protein S deficiency in the general population is presently unknown. However, in patients with spontaneous venous thrombosis it is reported to be between 2 to 8%[18].

We describe a Chinese woman with recurrent cerebral thrombosis at 52 years of age with associated protein S deficiency. She had no other risk factors (hypertension, hyperlipidemia, diabetes mellitus or smoking) which predisposed her to arterial thrombosis. She did not have any liver disease and never receive any anticoagulation. Two of her three children also had low levels of protein S at 65% (refer to Fig 1), although none of them was symptomatic. This patient illustrated the importance of considering clotting disorders in the etiology of cerebrovascular occlusion especially in young patients without the common predisposing risk factors. In a study reported by Sacco, the frequency of free protein S deficiency is higher in patients with acute stroke than in the general population. Out of 103 patients with cerebrovascular disease, he reported that 21 had free protein S deficiency[19].

Fig 1
Family Pedigree



The proposita is indicated by the arrow.

( ) denotes level of protein S antigen as % of normal

With regards to treatment, the institution of well monitored oral anticoagulation seems to be effective in preventing venous thrombosis in hereditary protein S deficiency[20]. However, little evidence is presently available to support a similar approach in patients with protein S deficiency and stroke. In a case report by Girolami[8], a 44-year-old woman with protein S deficiency and severe arterial cerebral thrombosis was treated with Aspirin and Dipyridamole with no further relapses. Similarly, our patient was treated with Ticlopidine 250 mg bid and to date, 6 months later, she did not have any new complaints.

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