

SHORT REPORT

Protein S deficiency in HIV associated ischaemic stroke: an epiphenomenon of HIV infection

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The purpose of the study was to determine the relevance of protein S deficiency in HIV infected patients with ischaemic stroke. In total, 33 HIV positive patients with ischaemic stroke, previously described by us, were prospectively compared with control groups for occurrence of protein S deficiency. The control groups comprised an equal number of consecutive matched HIV positive and negative patients without and with stroke respectively. Data were analysed in contingency tables using Fisher's exact test. Protein S deficiency occurred significantly more frequently in HIV positive compared with HIV negative stroke patients ($p < 0.001$). However, by including HIV positive patients without stroke as a control group and comparing this group with the HIV positive stroke group we found that protein S deficiency is statistically related to HIV infection and not stroke occurrence. Our data indicate that the presence of protein S deficiency in HIV positive patients with stroke is an epiphenomenon of HIV infection.

Stroke in patients with HIV infection has been ascribed to vascular abnormalities, coagulation disorders (in particular, protein S deficiency) and cardioembolic disease in several clinical and pathological studies.^{1–5}

Protein S deficiency in HIV infection is thought to result from autoantibodies and the release of tumour necrosis factor alpha.^{6–9} The relationship between protein S deficiency and the occurrence of stroke is unclear. A retrospective case control study demonstrated a significant correlation between protein S deficiency and the occurrence of stroke in HIV positive compared with HIV negative patients.² In a prospective case series that we undertook, 17 of 33 HIV positive patients with cerebral infarctions had a coagulopathy, and 11 of these patients had protein S deficiency.³ We did not have HIV negative stroke controls in that study.

We therefore undertook a prospective study of protein S deficiency in comparative control groups to our HIV positive stroke cohort described previously.³

PATIENTS AND METHODS

The study design was a case control study to determine the relevance of protein S deficiency in HIV associated stroke. Approval for the study was obtained from the institutional ethics review board.

We had previously studied and reported 35 adult (age >18 years) HIV infected patients presenting with stroke, of whom 33 patients had cerebral infarctions and 11 of these patients had protein S deficiency (33%).³

This study was prospectively expanded to include two control groups: (a) 33 consecutively identified HIV negative patients with cerebral infarction matched for age and sex, and (b) 33 consecutively identified HIV positive patients without cerebral infarction, matched for age, sex, and CD4 count. Thus, the total number of patients was 99, with 33 in

each group. Mean age was 32.1 years (range 20–61 years), and female to male ratio was 1.5:1. The patients were inpatients of the medical wards at the Chris Hani Baragwanath Hospital (CHBH), Soweto, South Africa.

In the stroke patients, the presence of cerebral infarction had to be confirmed on computed tomography (CT) scan. Protein S activity in both control groups was determined using the same functional assay measuring free protein S activity as in the previously described cohort of HIV positive stroke patients. The method used was as described by the manufacturer (Ilex Automated Coagulation Analyzer; Ilex Medical Ltd, Israel). The assay was repeated in the stroke patients at 3 months. Abnormalities that persisted were then interpreted as relevant.¹⁰ The control group of HIV negative stroke patients had protein S assays as part of standard investigations. The control group of HIV positive patients without stroke had protein S assays as part of the study protocol but not for any clinical indication.

RESULTS

Group 1: HIV positive patients with stroke (previously reported)³

Eight patients (24%) had meningitis (3 tuberculous, 1 pyogenic and 4 viral), 3 (9%) had a potential cardioembolic source (HIV related dilated cardiomyopathy, postpartum cardiomyopathy and mitral valve prolapse respectively), 2 had hypertension (6%), and 17 (51%) had a coagulopathy. Of these 17 patients, protein S deficiency occurred in 11, protein C deficiency in 1, and antiphospholipid antibodies were found in 5. The protein S deficiency was found at both measurements—that is, on admission and at repeat testing 3 months later, in all 11 patients. A vasculopathy/vasculitis occurred in four patients (12%). In these 17 patients, more than one underlying cause was found in 10 patients, one cause was identified in 2 patients, while no potential cause was identified in 5 patients (15%).

Group 2: HIV negative patients with stroke

Four patients had a potential cardioembolic source (12%), 4 had hypertension (12%), 4 had carotid artery dissection (12%), 3 had vasculitis (9%), 3 had meningitis (9%), 2 had eclampsia (7%), 1 had fibromuscular dysplasia (3%), and 12 had no identified cause (36%).

Group 3: HIV positive patients without stroke

Fifteen patients had pulmonary tuberculosis (45%), 8 had bronchopneumonia (24%), 7 had community acquired lobar pneumonia (21%), 2 had Guillain-Barré syndrome (7%), and 1 had bilateral Bell's palsy (3%).

CD4 counts

The CD4 counts of the groups 1 and 3 were measured at the time of admission: eight patients (23%) were CDC category 1, 13 (37%) were category 2, and 14 (40%) were category 3 in each group.¹¹

Protein S deficiency

Protein S deficiency was found in 11 of 33 patients in group 1 (HIV positive patients with stroke), none of the 33 patients in group 2 (HIV negative patients with stroke) and in 12 of 33 in group 3 (HIV positive patients without stroke).

Analysis of the protein S data in relation to stroke in HIV positive and negative patients, and in relation to HIV infection in the absence of stroke was performed using a contingency table. By Fisher's exact test, groups 1 and 3 did not differ, but both were significantly different from group 2 ($p < 0.001$). The data show a significant association between HIV infection and protein S deficiency, but not between stroke and protein S deficiency.

DISCUSSION

The data we have obtained here concur with the literature that HIV infection is significantly ($p < 0.001$) associated with protein S deficiency.¹²⁻¹⁷ With respect to HIV infection and ischaemic stroke, the retrospective case control study from the USA showed that the association is statistically significant.² Similarly, we also found that protein S deficiency occurred significantly more frequently in HIV positive than in HIV negative stroke patients ($p < 0.001$).

Furthermore, by including HIV positive patients without stroke as a control group and comparing this group with the HIV positive stroke group we found that protein S deficiency is statistically related to the HIV infection rather than the stroke occurrence ($p < 0.001$). Of the 33 HIV positive stroke patients, 11 had protein S deficiency, and 12 of the 33 HIV positive control patients without stroke had protein S deficiency.

The role of hereditary or acquired protein S deficiency in the aetiopathogenesis of stroke remains poorly understood.¹⁸ Familial protein S deficiency has been linked to a hypercoagulable state that may present clinically with recurrent venous thrombosis but rarely with arterial cerebral infarction.¹⁸ With acquired protein S deficiency there is no consensus on its relationship to ischaemic stroke.¹⁸⁻²¹ In terms of HIV infection our data support the concept that its occurrence is an epiphenomenon of the HIV infection itself.

The limitations of our study include the relatively small numbers of patients and the comparison of prospectively defined control groups with a previously reported cohort; however, this may be justified by the fact that the patients are all from the same region and hospital and that the control groups were appropriately matched.

CONCLUSION

Protein S deficiency in HIV positive patients with stroke is an epiphenomenon of the HIV infection.

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