Case Reports

Arterial Ischemic Stroke with Protein S Deficiency in Pakistan

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ABSTRACT

Protein S deficiency is a disorder with increased risk of venous and rarely arterial thrombosis. We report three cases of arterial ischemic stroke secondary to protein S deficiency. All patients were young and presented with focal neurological deficit, seizures or both, had markedly reduced serum protein S levels and all improved with anticoagulation. (Rawal Med J 2007;32:205-207).

Key words: Arterial ischemic stroke, Protein S deficiency.

INTRODUCTION

Protein S is a vitamin K-dependant plasma protein involved in the regulation of Protein C anticoagulant pathway. Protein S deficiency (PSD) is a disorder with increased risk of thrombosis. Activated protein C inactivates factor Va and VIIIa in the presence of free protein S and phospholipids, thereby inhibiting the generation of thrombin. Free protein S itself has an anticoagulant effect: it inhibits the prothrombinase complex (factor Xa, Va and phospholipids) that converts prothrombin to thrombin and the tenase complex (factor IXa, VIIIa and phospholipids)**,** which convert factor X to Xa. The reduced activity of protein C and protein S diminishes the control of thrombin generation. Both these

mechanisms increase susceptibility to venous thrombosis[1] and rarely arterial thrombosis. We report three cases with arterial thrombosis secondary to protein S deficiency.

CASE REPORTS

Case 1. A 27-year-old female presented on the third post- partum day with hypertension and fits onset two hours post partum and a day history of altered mentation. She had a past medical history of miscarriage one-year back, at six-month gestation. Her general examination was unremarkable apart from vitiligo. Neurological examination showed abnormal signs (Table 1). CT of brain without contrast showed small hypodense areas in bilateral occipital lobes. MRI brain with MRA showed cerebral arterial infarction (fig 1) secondary to hypercoagulable state. She was given phenytoin 15mg/kg body weight loading dose IV, ceftriaxone1 gram Q 12 hour I/V, enoxaparin 40mg s/c Q 12 hour and dexamethasone 4mg Q 8 hour IV. Her GCS improved to 15/15 the next day. Her coagulation profile was done [Table 1]. Over the next two days she became alert and had no abnormal neurological signs. She was discharged home on oral warfarin and aspirin and was advised a target INR between 2.0 and 3.0. She has been coming for regular During follow up she is asymptomatic and an MRI brain with MRA, three months later showed complete resolution of the infarcts (Fig 2).

Case 2. This 32-year old female was brought to the emergency department with a two-day history of an episode of dizziness and fall after which she developed weakness in left half of her body. She was suffering from hypertension for the last one year and was non-compliant in taking her medication. She was married for last eight years and had no children. There was no history of stroke in the family.

Table 1. Clinical data and laboratory data

	Patient 1	Patient 2	Patient 3
Age	27 years	32 years	17 years
Gender	Female	Female	Male
HMF	Drowsy	Conscious	Conscious
Speech	Incomprehensible	Normal	Normal
Cranial nerve	Normal	Left UMN VII	Normal
Power	Normal	Decreased	Normal
Upper limb		Left MRC 2/5	
Lower limb		Left MRC 3/5	
Planters	Bilaterally flexor	Bilaterally flexor	Bilaterally flexor
CT/MRI scan	Arterial ischemic infarct	Arterial ischemic infarct	Arterial ischemic Infarct
ANA	Negative	Negative	Not done
ASMA	Negative	Not done	Not done
P-ANCA	Negative	Not done	Not done
C-ANCA	Negative	Not done	Not done
Anti Thrombin III	Negative	Negative	Negative
Homocysteine	Not done	Negative	Negative
Protein C	Normal range	Normal range	Normal range
Protein S	**25.3%** (55-130%)	**19.7%** (55-130%)	**17.9%** (55-130%)

On arrival she had a BP of 140/100mmHg. She was conscious and alert and walked with support. Abnormal neurological signs are listed in table 1. CT scan brain without contrast showed findings consistent with acute infarct in right basal ganglia. She refused admission to hospital. Aspirin 150mg once daily, clopidogrel 75mg once daily and atorvastatin 20mg at night daily were precribed along with home physiotherapy program. She improved over the next few days with motor power of 4/5 in both upper and lower limbs on the left side. Her routine investigations and coagulation profile is shown in table 1. Warfarin dose was adjusted according to the recommended INR value between 2-3. A diagnosis of cerebral arterial infarction secondary to protein S deficiency was made. The patient was last seen in July 2006 and had improved but she had mild gait difficulty.

Case 3. This 17-year old male presented in the out patient neurology clinic for seizures. He was being treated for epilepsy for the past 3 years. Three years prior to presentation he had a fall, frothing from the mouth and loss of consciousness, for which he was

prescribed carbamazepine but was non-compliant and the frequency of seizures had increased to one seizure daily. At the time of presentation his vital signs were stable. His systemic and neurological examination was normal (Table 1).

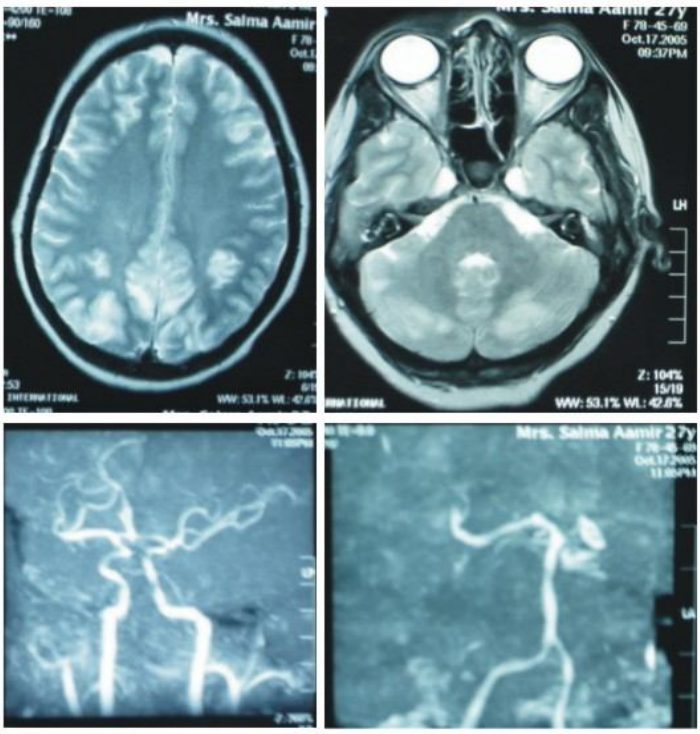

Figure 1 MRI brain with MRA showing multiple arterial infarcts in temporo-parietal cortex and cerebellum.

A CT scan done one year back showed left frontal infarct. He was diagnosed to have secondary seizures. He was given tablet sodium valproate 750mg twice daily. He was diagnosed to have arterial cerebral infarct secondary to protein S deficiency. Warfarin 5mg daily to maintain an INR between 2.0 and 3.0 was prescribed. He was lost to follow up.

DISCUSSION

Protein S deficiency may be hereditary or acquired, the later due to hepatic disease or vitamin K deficiency. PSD manifest as an autosomal dominant trait. Recent studies have

indicated a high prevalence in the Japanese population**.** The deficiency is rare in the Caucasians at approximately 0.03%, [2] with no male-female difference.

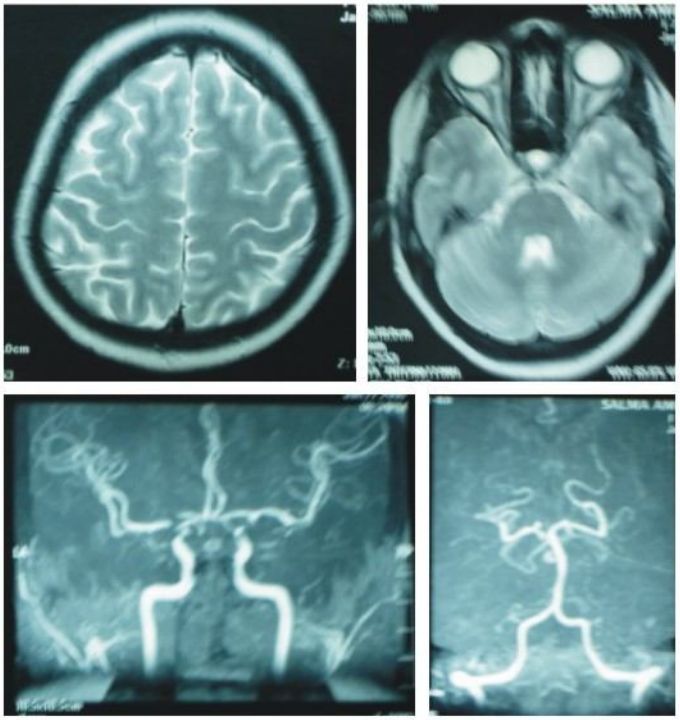

Figure 2 Follow up MRI after three months showing complete resolution of infarcts and MRA showing a substantial interval improvement in stenosis

A report of 10 adults younger than 45 years with cerebral arterial thrombosis due to deficiencies in coagulant inhibitor protein C, protein S and antithrombin III has been published**.**[3] In all 10 patients the cerebral infarct involved the carotid territory. A case of protein S deficiency resulting in cerebral infarction of arterial origin has been reported.[4] A similar case of a 44-year old woman with severe cerebral arterial thrombosis who reportedly had a moderately reduced level of total and markedly reduced level of free protein S has been reported.[5] In another report of 33 patients with cerebral arterial thrombosis with a mean age of 31-years, 9 patients had a decreased level of free and total protein S and 4 had only the free protein S deficiency.[6] Contrary to the previous idea it is now perceived that patients with protein S deficiency exhibited a surprisingly high tendency to arterial thrombosis.[7] It is now indicated that for patients with ischemic stroke

and under the age of 50, additional coagulation profile including protein S should be done.[7,8]

PSD is also associated with fetal loss in women, in the absence of VTE,[2] and this has been validated by a meta-analysis.[9] Our first patient also had a late 6-month gestation fetal loss in her previous pregnancy, which was non-recurrent. In another study of 57 patients with a history of unexplained abortion, 12 were found with protein S deficiency.[10] Patients with inherited thrombophilia who present with venous thromboembolism should be treated with a standard regimen of heparin overlapped with warfarin until an international normalized ratio (INR) of 2.0 to 3.0 is obtained on two consecutive days.[1] The potential benefit of chronic anticoagulation therapy for the primary or secondary prevention of stroke in patients with prothrombotic states has not been addressed in controlled clinical trials.[8] In conclusion, patients with young arterial stroke should have work-up for inherited thrombophilia including protein S deficiency. Anticoagulation may reverse the damage and prevent recurrence of stroke. Recommendations for arterial ischemic stroke secondary to protein S deficiency need to be developed.

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