

Hemiconvulsion, Hemiplegia, Epilepsy Syndrome and Inherited Protein S Deficiency

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Abstract. A nine-year-old Nepalese girl developed hemiconvulsion, hemiplegia, epilepsy syndrome (HHE syndrome) after an episode of right-sided focal status epilepticus following acute gastroenteritis. She had left middle cerebral artery (MCA) territory infarcts due to inherited protein S deficiency. [*Indian J Pediatr* 2006; 73 (2) : 157-159]
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Prolonged focal status epilepticus may be followed by permanent hemiplegia, the hemiconvulsion, hemiplegia, epilepsy syndrome (HHE syndrome) in some children¹. The HHE syndrome is usually associated with atrophy of involved cerebral hemisphere.² The pathogenesis of HHE syndrome is likely to be due to histotoxic epileptic brain damage following prolonged focal convulsion due to any cerebral insult.³ One case of HHE syndrome due to factor V Leiden mutation thrombophilia has been described from Quebec.⁴ Protein S is a cofactor and in association with protein C is required for hemostatic homeostasis.⁵ To the best of our knowledge there has been no case of HHE syndrome associated with inherited protein S deficiency alone reported in medical literature. Here is presented a case of HHE syndrome associated with inherited protein S deficiency.

CASE REPORT

A nine-yr-old Nepalese girl was referred from Sikkim to our institution, complaining of weakness in the right side of the body for the last 4 months. The patient developed this problem suddenly following unilateral status epilepticus which lasted for hours. She also had an ongoing acute gastroenteritis. This child was born out of a non-consanguineous marriage without any history of similar illness in family. Her neonatal period and developmental history were essentially normal. On examination, the child had a height of 118 cm (89% of

expected), weight of 26kg (92% of expected), and head circumference of 50cm (expected 51cm). Her central nervous system (CNS) examination revealed right-sided complete hemiparesis. Her other system examination was within normal limit.

She was investigated to look for the etiology of childhood hemiplegia. Investigations revealed hemoglobin of 12gm/dL, total leukocyte count of 9700/cmm, differential count of polymorphs 68%, lymphocyte 30%, eosinophil 2%, and platelet count of 3.02 lakhs with erythrocyte sedimentation rate of 38mm (1st hour). Her liver function tests and kidney function tests were essentially normal. Urine routine examination was normal. Her chest X-ray and Mantoux test were also normal. Echocardiogram with Doppler study revealed trivial pulmonary and tricuspid regurgitation. Antinuclear antibody was negative. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were within normal limits. Antiphospholipid antibody IgG [5.75Gpl u/ml (<10.00)] and antiphospholipid antibody IgM [4.37 MPL u/ml (<10.00)] were within normal limit. Her lipid profile showed cholesterol 164 mg/dl (150-200), triglycerides 68mg/dl (<150.00), high density lipoprotein (HDL)-cholesterol 51.00mg/dL (45-70), low density lipoprotein (LDL)-cholesterol 80mg/dl (<100), very low density lipoprotein (VLDL)-cholesterol 33mg/dL (<40) and cholesterol HDL ratio of 3.22. Homocysteine level was 8.84 μ mol/L (3.36-20.44). Activated protein C resistance or factor V Leiden mutation was within normal limit. Antithrombin III was 139% of normal. Protein C estimation was 130% of normal but protein S activity was <70% of normal (reference range 75%-106%). Carotid Doppler study was showing normal flow in the carotid artery. Magnetic resonance (MR) study revealed left cerebral hemisphere small in size in comparison to right side with mark widening of cortical sulci and sylvian

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fissure suggestive of left-sided cerebral hemiatrophy (Fig 1).

Subsequent magnetic resonance (MR) angiography study showed paucity of distal vessels in left middle cerebral artery segment possibly due to thrombotic occlusion causing ischemia (Fig. 2). Electroencephalogram was consistent with focal epilepsy.

Protein S activity (functional) of parents could not be done due to financial constraints. The child was managed with anticonvulsant therapy and physiotherapy. She was put on warfarin to maintain international normalized ratio (INR) of 1.5. She was advised to be attended immediately if the paresis worsens and avoid conditions

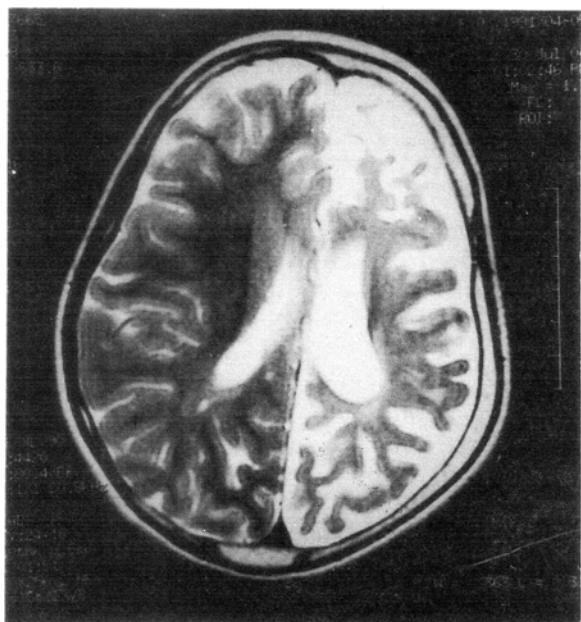


Fig. 1. Magnetic resonance (MR) study showing atrophy of left cerebral hemisphere and prominent left lateral ventricle.

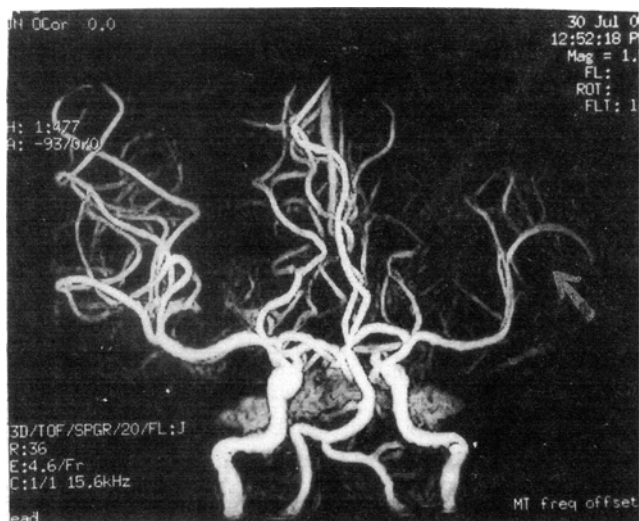


Fig. 2. MR angiography showing paucity of distal vessels in left middle cerebral artery (indicated by arrow) suggestive of left middle cerebral artery (MCA) territory infarct.

such as dehydration that can precipitate thrombosis in the presence of hypercoagulable state.

DISCUSSION

HHE syndrome is characterized by hemiconvulsive seizure, hemiplegia and epilepsy syndrome in sequence.^{6,7} This syndrome has been categorized into two varieties: type I and type II.⁸ Type I is called symptomatic and commonly follows symptomatic febrile seizures after acute cerebral disorders such as meningitis, encephalitis, subdural hematoma and vascular lesion.⁴ Generalized epilepsies follow it as a sequel. Type II is known as idiopathic status epilepticus precipitated by simple hyperthermia due to non-specific infection.⁴ Subsequently, temporal lobe type of epilepsy may follow.⁹

Epilepsy syndrome usually develops after a variable interval of one to three years.¹⁰ The electroencephalogram (EEG) shows spike or spike-wave discharge over the involved-side and may have reflection on the contra lateral side.¹¹ Interestingly, this patient belongs to type I as investigation shows evidence of vascular pathology though there was no clinical evidence of acute cerebral involvement initially besides convulsion.

We hypothesized that, possibly, deficiency of protein S led to a hypercoagulable state, and presence of ongoing acute gastroenteritis (GE), like illness precipitated the thrombotic stroke. Studies have documented that half of the childhood thromboembolism are due to hypercoagulable state such as deficiencies of protein C, protein S, antithrombin III and mutation of factor V Leiden.^{12,13} To the best of our knowledge there has been no documented case report of protein S deficiency associated with HHE syndrome in medical literature.

Due to lack of randomized controlled-trials of anticoagulant therapy in children, modified adult guidelines remain the primary source of recommendation in childhood thromboembolic disease.¹⁴ Treatment of thromboembolic CNS disease primarily includes heparin or low molecular weight heparin and replacement of the deficient inherited factor during acute episode and long-term anticoagulation with warfarin in selected cases to prevent recurrence.¹⁵

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