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## Thrombophilia Interpretation in Childhood Stroke: A Cautionary Tale

### ABSTRACT

Several authors have reported a link between childhood stroke and inherited thrombophilia in recent years. The impact of such a relationship on management and outcome is yet to be determined, as is the potential cost-benefit ratio associated with the performance of thrombophilic screening in children presenting with ischemic stroke. We present a case that highlights the need for clinical and radiologic examinations to remain the definitive criteria used to diagnose stroke in children. The diagnosis should not be influenced by the finding of a thrombophilic marker. (*J Child Neurol* 2004;19:218-219).

A number of studies have shown a relationship between childhood stroke and inherited thrombophilia.<sup>1,2</sup> The clinical significance of this relationship and the cost benefit of thrombophilic testing in children presenting with stroke remain uncertain. Additionally, the interpretation of thrombophilic markers in children is difficult, and age-appropriate reference intervals for thrombophilic markers must be used. We report a case that highlights the potential danger of overinterpretation of thrombophilic markers in children presenting with presumed stroke.

A previously well 5-year-old Arabic boy presented after being found pale, unresponsive, and aphasic and having been incontinent of urine. The symptoms and signs resolved over the following 12 hours. A postictal electroencephalogram (EEG) performed the following day identified left-sided slow-wave activity. A clinical diagnosis of a postictal state following a focal seizure was made. The patient recovered fully and was discharged. A magnetic resonance image performed 2 weeks later showed a low signal lesion in the left insula cortex (7 mm diameter), likely representing an old infarct (Figure 1). The lesion did not have the signal characteristics of cortical edema associated with a recent seizure. An extensive thrombophilia screen was performed, including protein C, protein S, antithrombin, lupus anticoagulant, anticardiolipin, and activated protein C ratio. All results were reported as normal, apart from reduced total protein S, 56% (laboratory reference

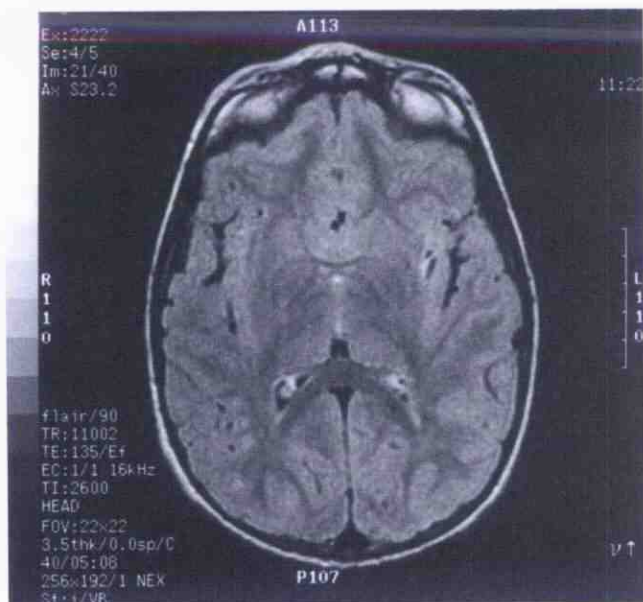


Figure 1. MRI demonstrating old infarct in left insular cortex.

range 77–130%), and free protein S, 44% (58–110%). Repeat protein S levels confirmed the initial results. Family studies (protein S) were normal.

The child again presented 11 months later with dysphasia, drooling, and unresponsiveness, followed by tonic-clonic activity with subsequent transient right face and arm weakness. Repeat imaging did not demonstrate any further lesions. Given his full neurologic recovery, the imaging evidence of previous cerebral infarction, and the impression of an inherited thrombophilia, a diagnosis of transient ischemic attacks complicated by seizures was made. The patient was heparinized and commenced on warfarin, maintaining an international normalized ratio of 2 to 3. The parents imposed significant restrictions regarding play and social contact based on their understanding of the bleeding risks associated with warfarin.

Two years later, the patient was reviewed in a recently established thrombosis clinic. The protein S result was reviewed using age-appropriate reference intervals<sup>3</sup> and was clearly within normal levels. A repeat interictal EEG showed focal epileptic activity in the left frontal region with features suggestive of idiopathic partial epilepsy. After considerable discussion with the parents, the diagnosis was changed to partial epilepsy, and the warfarin was ceased. Coincidentally, 5 weeks later, the patient presented with a prolonged and evolving complex partial seizure witnessed from the onset to the point of right-sided jerking and subsequent right-sided Todd's paresis. Carbamazepine was commenced, and the patient has now remained seizure free for 2 years. Repeat protein S measurements, after cessation of warfarin, confirmed normal levels for age.

The initial clinical diagnosis of focal seizure and transient postictal deficits in this patient was correct. Interictal focal epileptic activity might have been suppressed on the early postictal EEG. The finding of a very small old cerebral infarct was given too much

significance and led to a thrombophilia work-up. Seizures are not uncommon in the presentation of childhood stroke. A review of 98 episodes of childhood arterial ischemic stroke at this institution identified 36 episodes (36.7%) with seizures included as presenting symptoms (unpublished data, in press 2004). The results of the thrombophilic work-up were not interpreted with age-appropriate reference intervals, leading to the incorrect diagnosis and management of protein S deficiency. No significance was placed on the negative family studies. The case highlights the difficulties in the interpretation of thrombophilic markers in children.

A number of studies have reported that thrombophilic defects can be found in up to 20% of children presenting with stroke compared with an incidence of 4% in the general population.<sup>1,2</sup> "Silent" stroke can occur in up to 11% of adult patients, whereas the incidence in children is not known.<sup>4</sup> The diagnosis of clinically important stroke can only be made using appropriate clinical and radiologic criteria and should not be influenced by the finding of a thrombophilic marker. Given the current lack of data on the clinical relevance to prognosis and management of stroke in children, the cost-benefit ratio of a thrombophilic work-up remains to be determined.

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