Is inherited thrombophilia a risk factor for arterial stroke?

The term thrombophilia describes an increased tendency to clinical thrombosis associated with laboratory evidence of abnormal haemostasis. Causes include inherited deficiencies of natural anticoagulants (antithrombin, protein C, and protein S), polymorphisms causing resistance to activated protein C (factor V Leiden mutation) or disturbing the normal procoagulant or anticoagulant balance (prothrombin G20210A mutation), and disorders which are polygenic or interact with dietary and environmental factors (high factor VIII and hyperhomocysteinaemia). Inherited thrombophilias, most commonly factor V Leiden and high VIII, are risk factors in most cases of venous thromboembolism under the age of 40. It is therefore tempting to assume that a similar relation will be found in arterial thrombosis, especially as stroke in young people often remains unexplained even after extensive investigation of other possible causes. In the previous issue of this journal, pp 508–511 Ganesan et al described a prospective case-control study of 60 children with arterial ischaemic stroke which failed to show any significant association between inherited thrombophilia and stroke. Haemostatic abnormalities were initially found in 24% of the patients, but only 12% (eight children) were confirmed when the tests were repeated 3 months later, after the acute phase. Two children had thrombophilia in association with moyamoya disease (protein S deficiency, V Leiden) which is consistent with previous findings in this entity. One child had activated protein C resistance without factor V Leiden, a combination sometimes seen with high VIII status. Ganesan et al did not report VIII concentrations or the prothrombin G20210A mutation. The remaining six children (12%) were found to have the factor V Leiden mutation. This was not significantly different from the control group of Ganesan et al, in whom the prevalence of V Leiden was 5%, but because ethnic origin strongly determines the frequency of this predominantly white polymorphism, the ethnic composition of study and control groups (not given by Ganesan et al) should have been carefully matched.

It can be concluded that inherited thrombophilia does not seem to be a major cause of stroke in children, except perhaps in the category of moyamoya disease. It remains possible that there would have been a significant association between thrombophilia and stroke if a larger series of ethnically matched children had been available for study, especially as the odds ratio for the incidence of stroke associated with V Leiden was more than doubled. Although there have been anecdotal reports of arterial stroke associated with thrombophilia, a large study failed to confirm any significant association in adults. By contrast, there is a striking association between both V Leiden and prothrombin G20210A mutations and cerebral venous thrombosis.

What is the relevance of these findings for clinical practice? It seems reasonable to continue to screen patients younger than 50 presenting with ischaemic stroke for thrombophilia, recognising that positive results have to be interpreted with caution. Firstly, inherited abnormalities of this type are found in a significant proportion of the normal population, often without any history of thrombosis. Secondly, concentrations of protein C, protein S, and antithrombin are depressed after stroke. The blood tests should be repeated at least 3 months after the acute event before concluding that inherited deficiency is present. Coumarins lower protein C and S, so if the patient is on warfarin interpretation is unreliable; interrupting anticoagulation to confirm thrombophilia may be appropriate. The finding of inherited thrombophilia in a patient with stroke should always raise the possibility that an infarct that may seem arterial has in fact resulted from cerebral venous thrombosis or paradoxical embolism, because of the stronger association of thrombophilia with venous thrombosis. We do not know if finding inherited thrombophilia in a patient with stroke indicates an increased risk of recurrent stroke. In general, it seems reasonable to ignore the association if other strong risk factors for stroke are found, but in patients in whom no other cause is established, lifelong anticoagulation should be considered. The decision should be made in consultation with an experienced coagulation specialist. In some patients, particularly those with the factor V Leiden mutation, it may be more appropriate to anticoagulate only patients with recurrent thrombosis.

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