Arterial strokes associated with factor V Leiden mutation

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Various coagulopathies have been increasingly recognized as causing stroke in the young. Factor V Leiden mutation is well known to cause venous thromboses. However, its role in arterial disease is controversial. This article describes two patients with this defect who presented with arterial stroke and gives a review of the literature.

DISCUSSION

Stroke is not a rare event in young adults and presents a major challenge because of its psychosocial impact and associated diagnostic problems. Most strokes in young patients are of ischaemic origin, and the major causes are atherosclerosis, non-atherosclerotic arteriopathies, cardioembolism, migraine stroke and haematological disorders (including systemic lupus erythematosis and antiphospholipid antibody syndrome) (Asherson et al, 1989). Activated protein C resistance has been found to be a major cause of venous thrombosis. This paper has described two patients with activated protein C resistance who presented with cerebral arterial strokes. In both patients, the diagnosis was confirmed by polymerase chain reaction, and they are now being treated with warfarin.

WHAT IS FACTOR V LEIDEN MUTATION?

Activated protein C is a serine protease formed from an inactive precursor. The protein C system normally inhibits coagulation by inactivating procoagulant factors Va and VIIIa. In younger populations with venous thrombosis, there is a high prevalence of resistance to activated protein C, and this is inherited as an autosomal dominant trait. Dahlback described the condition first when in an activated partial thromboplastin time assay the addition of activated protein C did not result in the expected anticoagulant response (Dahlback et al, 1993).

A single point mutation in the factor V gene at nucleotide position 1691codes for a mutant factor V where glutamine (Q) replaces arginine (R) at position 506, and this factor is now referred to as factor V:Q506, factor V:R506Q or factor V Leiden (FVL). Normally factor V is cleared by activated protein C at arginine 306, 506 and 679. However, factor V:Q506 is not cleared at position 506 and is relatively resistant to degradation by protein C.

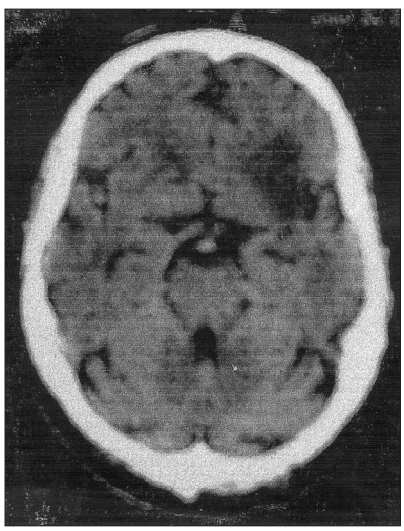
CASE REPORT 1

A 41-year-old Caucasian woman was admitted with right hemiparesis and blurred vision. There was no history of hypertension, diabetes, ischaemic heart disease, previous stroke, oral contraceptive use or miscarriages nor any family history of stroke. She was a non-smoker. Clinical examination confirmed the presence of right-sided weakness. There were no carotid bruits and her fundi were normal. Computed tomography scan of the brain confirmed the presence of a large infarct in the right middle cerebral artery territory (*Figure 1*). Full blood count, urea, creatinine, glucose and cholesterol levels were normal. Autoimmune profile, including antinuclear antibody, antineutrophil cytoplasmic antibody and anticardiolipin antibody, were negative. Other thrombophilia tests, including lupus anticoagulant, antithrombin III, plasminogen and protein S levels, were normal. Her electrocardiogram, chest X-ray, echocardiogram and a carotid Doppler study were unremarkable. A thrombophilia screen revealed markedly decreased activated protein C activity at 1.32 (normal ratio 2.25–2.63) when tested with factor V deficient plasma suggestive of factor V Leiden mutation.

CASE REPORT 2

A 44-year-old Caucasian woman was admitted with sudden dysarthria and vertigo associated with headache and vomiting. She had been a smoker in the past. There was no positive family history of stroke. Clinical examination confirmed the presence of a posterior circulation stroke with dysarthria, ataxia and dysdiadochokinesia. Computed tomography scan confirmed the presence of a left cerebellar infarct. Routine blood tests were normal and autoantibodies negative. Her cholesterol level was elevated at 6.2 mmol/litre. Her electrocardiogram, chest X-ray and carotid Doppler study were normal. An echocardiogram revealed mild septal hypertrophy. A thrombophilia screen revealed decreased activated protein C activity (1.26) when tested with factor V deficient plasma suggestive of factor V Leiden defect.

Figure 1. Computed tomography scan of head showing infarct in the left middle cerebral artery territory.



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Up to 7% of Caucasians are heterozygous for FVL, and it is very rare in Afro-Caribbeans and Orientals. The mutation is of variable penetrance. In patients with recurrent deep venous thromboses and pulmonary emboli, the prevalence may be 10–25%. Homozygotes have a 20-fold risk of thromboembolism. The risk increases with age, oral contraceptive use and pregnancy (Handin, 1998). Sometimes FVL coexists with other defects like antiphospholipid antibody syndrome, antithrombin III deficiency or homocysteinaemia. In antiphospholipid syndrome, FVL may contribute to hypercoagulability of a small albeit significant proportion of antiphospholipid subjects.

ROLE IN ARTERIAL DISEASE

The role of FVL in arterial disease remains controversial. A direct relationship has not been clearly established (Dunn et al, 1998; Ganesan et al, 1998). In children with arterial stroke, the prevalence of the mutation was 12% in the patients and 5% in controls, the difference not being statistically significant (Ganesan et al, 1998). While some workers did not find a significant association of FVL with myocardial infarction or stroke, others have estimated the risk of ischaemic stroke at 2.5 in the general population; the risk in women is 3.9 suggesting an interaction with female hormones (Margaglione et al, 1999). The prevalence of FVL is significantly high in patients with myocardial infarction without coronary artery stenosis (Mansourati et al, 2000). Smoking carriers of FVL have a 32-fold increased risk of myocardial infarction, and the difference is most pronounced in young women (Siscovick et al, 1997).

In the first patient described in this article, no other risk factor for stroke was identified. In the other patient, hypertension, a previous smoking habit and high cholesterol levels were noted. Interestingly, FVL may be associated with migraine and angiographic changes among patients with cerebrovascular disease raising the possibility of an association with vasospastic cerebrovascular disease. Retinal artery occlusion associated with the FVL and positive rheumatoid factor has been described (Dhar-Munshi et al, 1999).

Young patients with stroke should be thoroughly evaluated for coagulation disorders including FVL. However, some workers have shown a statistically significant correlation between FVL and myocardial infarction in the elderly. This makes the situation complex since most physicians do not routinely test for FVL in the elderly (Baranovskaya et al, 1998).

THE FUTURE

Whether FVL is a primary risk factor for arterial stroke remains to be seen, but it seems to play at least some role in certain individuals. It certainly appears that heterozygosity, along with other coexisting prothrombotic states, such as ingestion of oral contraceptives, pregnancy, concomitant primary thrombotic states and metabolic risk factors for atherosclerosis, increases the risk considerably. Further data are needed to establish this. **HM**

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