Ischemic Stroke in a Patient with Hetrozygous Factor V Leiden Mutation: An Uncommon Association

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Received: 18 January 2014 / Accepted: 5 April 2014 / Published online: 4 May 2014
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Introduction

Thrombosis is a major cause of morbidity and mortality in a wide range of arterial and venous diseases. It is a multicausal disease involving genetic and acquired risk factors like immobility, malignancy, pregnancy, oral contraceptive use and autoimmune disease [1]. The genetically determined increased likelihood of thrombosis is called thrombophilia. It is commonly due to activated protein C (APC) resistance due to factor V leiden mutation and prothrombin polymorphism. Other less common inherited causes are deficiencies of the protein C, protein S and anti thrombin, hyperhomocysteinemia and increased levels of factor VIII [2, 3]. Venous thrombosis or thromboembolism is most common manifestation of thrombophilia. Arterial thrombosis is present in only minority of cases especially with associated acquired risk factors [4]. We report a patient who developed ischemic stroke due to factor V leiden mutation which is quite rare first presentation.

Case Report

A 45 year old male presented with sudden onset of vertigo and slurring of speech for a duration of around 7–8 h. It was associated with numbness of left half of face and bilateral upper limbs without deviation of angle of mouth. There

was no associated weakness of any limb. There was no past history of similar episode, however, patient was treated for pulmonary tuberculosis in 1998. He had strong family history of early demise of his father due to myocardial infarction and early death of his brother.

On admission his vital parameters were: pulse 68/min regular, respiratory rate 16/min, BP 130/90 mm of Hg, temperature 98.6°F. Systemic examination was otherwise normal. Neurologically, the patient was conscious, alert and scored 30/30 on Folstein's minimal state examination (MMSE). The cranial nerves and sensory examination was normal. He had a power of 5/5, normal deep tendon reflexes, with flexor plantar response bilaterally.

Investigations revealed a normal hemogram, blood sugar, renal and liver function tests. Serum electrolytes including calcium and phosphorus were normal. His complete lipid profile showed slightly raised total cholesterol level 243 mg % and LDL level 167 mg %. Chest X ray, electrocardiogram, 2D echocardiogram and ultrasonography of abdomen were normal. Non contrast CT head was also normal. Bilateral carotid arteries on colour doppler showed normal intimal thickness with normal flow wave pattern. Evaluation of lupus anticoagulant by diluted Russell viper venom test and IgG, IgA anticardiolipin antibody by enzyme linked immunosorbent assay (ELISA) were negative. The serum homocysteine level was normal. The blood sample tested positive for heterozygous factor V leiden mutation by polymerised chain reaction (PCR) DNA sequencing. Estimated protein S activity and protein C activity were low, 29 % (77–143 %) and 65 % (67–195 %) respectively. His family members did not test their blood for factor V leiden mutation due to financial reasons.

He received low dose of aspirin 75 mg and clopidogrel 75 mg, along with atorvastatin 20 mg. Initially, he was given low molecular weight heparin 60 mg subcutaneously

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b.i.d. for 5 days, but long term anticoagulant was not prescribed, in view of arterial thromboembolism. However, the patient was advised to consult his treating doctor for start of anticoagulant in high risk situation like immobility due to trauma or major surgery.

Discussion

APC resistance caused by factor V leiden mutation and prothrombin polymorphism (G20210A) are two most common hereditary defects in patients presenting with venous thrombosis. Approximately 3 % of worldwide population is heterozygous for factor V leiden mutation [5]. It is found in up to 25 % of patients with recurrent deep vein thrombosis or pulmonary embolism [6]. The molecular basis for APC resistance arises as a result of G1691A alteration causing replacement of Arginine at 506 position by a Glutamine (Arg506Gln) [7]. This mutation conforms resistance on factor V_a for cleavage by APC. This lead to 5–10 times increased risk of thrombosis in patients heterozygous for factor V leiden mutation, whereas homozygosity increases the risk by a factor of 50–100 times [8].

A moderate association occurs between coronary artery disease and factor V leiden mutation, especially in young men and women, who also display other vascular risk factors [4]. Similarly, there is significant statistical association between ischemic stroke and factor V leiden mutation. This is especially increased in young women harbouring factor V leiden mutation who used oral contraceptives [9]. Haapaniemi et al. [10] reported in their observational study of 860 patients with ischemic stroke who were screened for factor V leiden mutation, out of which 48 patients were found positive. They found that half of these patients with factor V leiden mutation had family history with cardiovascular disease and multiple silent brain infarctions, whereas there were no such findings in control group of 144 (1:3) ischemic stroke patients without factor V leiden mutation. Thus, the factor V leiden mutation is one of the important cause of ischemic stroke in young patients.

The management of patients with factor V leiden mutation depends on recurrence of thromboembolic events, family history and associated risk factors i.e. use of oral contraceptive pills, smoking, obesity, etc. can guide for long term prophylaxis [11]. The oral anticoagulant, warfarin reduces the risk of recurrence by 90–95 %, but the annual risk of fatal haemorrhage is 0.25 % [12]. The prophylactic anticoagulant therapy is generally not indicated in patients who have not developed a thrombotic event, but these patients were found positive for heterozygous factor V leiden mutation due to family testing. The duration of

treatment depend on unprovoked or provoked reasons of thrombosis, site of thrombosis, family history, risk factors involved and type of thrombophilia, ranging from 6 months to indefinite [13, 14].

Conclusion

A patient with transient ischemic attack related to factor V leiden mutation is reported. There was strong family history of thromboembolic events and early deaths. Awareness of the condition and a high index of suspicion may be required to detect the inherited hypercoagulable state especially with strong family history and young unprovoked thrombotic events, arterial or venous both, so that long term complications can be prevented. The young patients found positive for factor V leiden mutation should be appropriately counselled for future risk modification and prophylaxis in high risk situations.

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