Case Report

Recurrent Venous Thrombosis with Factor V Leiden Mutation

S Meenakshi-Sundaram, Rohini Sridhar*, JJ Jithendrian**, RN Durai***, MJ Arunkumar, Bharathi Sundar

Abstract

A patient who presented with recurrent venous thrombosis is reported. Following an episode of spontaneous deep vein thrombosis of the lower limb he was started on oral anticoagulant therapy, which he discontinued. He presented with cerebral venous thrombosis and improved partially with anticoagulant therapy. Evaluation for hypercoagulable states revealed factor V Leiden mutation by polymerized chain reaction method. Long-term anticoagulation has been planned. Evaluation for factor V Leiden mutation is always warranted in patients presenting with spontaneous thrombosis, especially if there is recurrent thrombosis.

INTRODUCTION

Thrombus formation requires an alteration in either the vessel wall or flow of blood or in the coagulability of blood. Alteration in coagulability resulting in hypercoagulable state is an important contributing factor for venous thrombosis. While the role of several secondary hypercoagulable states which are often multiple, heterogeneous, multifactorial and acquired are well recognized, the significance of several primary hypercoagulable states as predisposing factors to hyperthrombotic states are only now being increasingly recognized. These are often the result of single gene mutations and resistance to activated protein C and the factor V Leiden mutation is now recognized as the single most common cause of hereditary thrombophilia.1 We report a patient, who developed both deep venous thrombosis of the lower limb and cerebral venous thrombosis, was evaluated for a hypercoagulable state and was detected to have factor V Leiden mutation.

CASE REPORT

A 42-year-old man presented with severe aching headache, non-projectile vomiting and right motor seizures with secondary generalization since a week. Three days later he developed weakness of right-sided limbs and on the day of admission he reported weakness of left sided limbs. There was no history of loss of consciousness, facial or bulbar weakness, visual, sensory or cerebellar disturbances. There was no history of fever, cough, ear discharge, head injury, abdominal pain or diarrhea. There was no history of arthralgias, rash or recurrent orogenital ulcerations. Eight months ago he had been diagnosed to have thrombosis of the deep venous system of the left lower limb. He had been started on acenocoumarol (Acitrom 3 mg / day), which he took for 7 months but subsequently switched over to native medicines. He did not smoke or consume alcohol and there was no history of drug abuse. There was no history of similar illness in the family.

On admission his vital parameters were: pulse 108/minute, regular; respiratory rate 28/minute, BP 140/90 mm Hg and temperature 98.4°F. The left lower limb was diffusely swollen with hyperpigmentation of the dorsum of the foot. There was no pallor or lymphadenopathy. There were no arthralgias, rash or recurrent orogenital ulcerations. Eight months ago he had been diagnosed to have thrombosis of the deep venous system of the left lower limb. He had been started on acenocoumarol (Acitrom 3 mg / day), which he took for 7 months but subsequently switched over to native medicines. He did not smoke or consume alcohol and there was no history of drug abuse. There was no history of similar illness in the family.

On admission his vital parameters were: pulse 108/minute, regular; respiratory rate 28/minute, BP 140/90 mm Hg and temperature 98.4°F. The left lower limb was diffusely swollen with hyperpigmentation of the dorsum of the foot. There was no pallor or lymphadenopathy. Systemic examination was otherwise normal. Neurologically he was conscious, alert and scored 30/30 on Folstein’s mini mental state examination (MMSE). There was quadriplegia (motor power 0/5 in all four limbs on MRC scale). Muscle stretch reflexes were bilaterally sluggis over the upper limbs, knee jerk was normal and ankle jerk was brisk on both sides. Plantar responses were extensors bilaterally. There were no other deficits.

Investigations revealed a normal blood sugar, renal and liver function tests. Serum electrolytes including potassium and calcium were normal. Hemogram, urinalysis, chest skiagram, electrocardiogram, 2D echocardiogram and ultrasonogram of the abdomen were normal. Cranial CT scan revealed hyperdense (cord sign) superior sagittal sinus and few adjacent cortical sulci on the right side on plain scan. On contrast enhanced study, there was diffuse enhancement of the
cortical sulci and a filling defect in the right transverse sinus. MR imaging of the brain revealed loss of flow voids in the right transverse and sigmoid sinuses, entire superior sagittal sinus and in the parasagittal parietal cortical veins of the cerebral hemispheres. These involved veins appeared hyperintense on all spin-echo pulse sequences and showed absence of signals on MR venogram. Both parietal lobes revealed infarcts with a small area of hemorrhage on the right side. These were suggestive of dural sinus and cortical venous thrombosis (Fig. 1). Evaluation of lupus anticoagulant by diluted Russel viper venom test and IgG, IgA anticardiolipin antibody by enzyme linked immunosorbent assay (ELISA) were negative. The serum tested positive for Factor V Leiden mutation by polymerized chain reaction (PCR) method. Estimation of protein C, protein S and antithrombin III levels were not done. His family members did not consent to test their serum for factor V Leiden mutation.

He received acenocoumarol (Acitrom) with maintenance of INR between 2.5 – 3.5, physiotherapy and supportive care. He gradually improved with recovery of upper limbs after 25 days and lower limbs after 35 days of onset of illness. Presently he has residual weakness at ankle (dorsiflexors 1/5 and plantar flexors 3/5) and mild weakness of the intrinsic muscles of the feet.

**DISCUSSION**

This is the first report of a well-documented case of factor V Leiden mutation from south India although it has been recognized as the commonest inherited thrombophilic disorder worldwide. This patient who had a peripheral venous system thrombosis as the first manifestation, was treated with anticoagulant therapy initially although the etiology of the thrombosis was not established. Venous thromboembolism associated with factor V Leiden mutation can be protean and may range from a simple lower limb deep venous thrombosis to the Budd-Chiari syndrome. Cerebral venous sinus thrombosis is well known to occur in patients with factor V Leiden mutation. In a case control study of 55 patients with cerebral venous thrombosis evaluated for factor V Leiden mutation, eight (14.5%) were detected to have the same compared with 17 of 272 controls (6.25%). It was also noted in this study that the recurrences of venous thromboembolic events were more frequent in patients with the mutation (5 of 8 patients, 62.5%) than in those without (8 of 47 patients, 17%; p < 0.005). Other neurological syndromes known to be associated with factor V Leiden mutation include childhood ischemic stroke and central retinal vein occlusion.

The mechanism by which factor V Leiden mutation confers the risk of thrombosis deserves mention. Activated partial thromboplastin time of normal plasma is prolonged by addition of activated protein C (APC) that inhibits factors Va and VIIIa thus preventing the efficient generation of thrombin. Dahlback and colleagues showed that in patients with recurrent thromboembolism, addition of APC produced a much shorter prolongation of the clotting time. Thus these individuals were supposed to have resistance to the action of APC or APC resistance. This abnormal response to APC could be corrected in vitro by the addition of normal plasma and this capacity of the normal plasma to correct the APC resistance phenotype was identified to be a property of factor V thus suggesting that this factor was resistant to the APC cleavage. The molecular basis for APC resistance arises as a result of single G A mutation at nucleotide 1765 (CGA CAA) within the factor V gene. This mutation results in the replacement of the normal arginine at position 506 by a glutamine (Arg506Gln). This mutation confers resistance on factor Va for cleavage by APC. This APC resistant, dysfunctional factor V molecule is known as factor V Leiden.

This mutation has an uneven prevalence: the gene frequency is as high as 5–10% in Europe while it is virtually absent in others such as the Japanese. Population data in India is sparse. Studies from Northern and Western parts of India looking at the prevalence of this mutation in patients with deep venous thrombosis show a striking variation. Saxena et al found factor V Leiden mutation in 39.2% of their patients from North India presenting with deep venous thrombosis of lower limbs before the age of 42. Ghosh et al detected the mutation in only 3% of similar patient population from western India. No data are as yet available from other parts of India, especially the south from where this
patient is being reported.

Implications regarding recurrence of thromboembolic events need to be considered in weighing the management options of patients with factor V Leiden mutation. Thrombosis incidence is increased 7-fold in heterozygotes and 80-fold in homozygotes compared to incidence in people without the mutation. The risk is still higher when clinical or environmental risk conditions are also present. In addition, the risk of recurrent thrombotic events is significantly higher in carriers of the factor V mutation than in patients without this abnormality. The duration of anticoagulation in patients with heterozygous Factor V Leiden mutation is considered the same as those without. While guidelines exist for a single event life-threatening or otherwise, or a second event which is either an ipsilateral or contralateral deep venous thrombosis or pulmonary embolism, no definitive guidelines exist for a patient with a deep venous thrombosis once and a life-threatening event such as cerebral venous thrombosis subsequently. Lifelong anticoagulation has been suggested for this patient although such a recommendation remains controversial.

In conclusion, a patient with recurrent thrombotic events related to factor V Leiden mutation is reported. Deep venous thrombosis in the lower limb was followed by cerebral venous thrombosis resulting in quadriplegia. Awareness of the condition and a high index of suspicion may be required to detect the complications arising from the same and thus avert life-threatening complications. It is recommended that all patients less than 50 years of age presenting with spontaneous lower limb deep venous thrombosis are screened for factor V Leiden mutation and appropriately counselled and managed when the same is detected.

Acknowledgement

We thank Dr. Sanjib Sinha, Assistant Professor, Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India for reviewing our manuscript and giving his valuable suggestions.

REFERENCES