

Stroke in a Child with Heterozygous Factor V Leiden Mutation

[Heterozigot Faktör V Leiden Mutasyonu olan İnmeli Bir Çocuk]

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ABSTRACT

Although thrombosis is seldom seen in children, reports of young patients with thrombosis are becoming more frequent with time. Activated protein C resistance, caused by a point mutation factor V gene was described in last decade. This article highlights a case of a 9 year-old-boy who admitted to Başkent University Hospital with right- sided hemiplegia. He was diagnosed as heterozygous for the FVL mutation and with stroke due to arterial thrombus in the left middle cerebral arterial territory. We suggest that thrombophilic mutations should be considered in the etiology of acute stroke in pediatric patients.

Key Words: Stroke, heterozygous factor V leiden mutation, activated protein C resistance

ÖZET

Tromboz, çocuklarda nadiren görülmekle birlikte, son yıllarda trombozlu çocuk hasta daha sıklıkla bildirilmeye başlanmıştır. Aktive olmuş protein C rezistansı, son 10 yılda tanımlanmış olup faktör V genindeki nokta mutasyonu sonucunda gelişen bir bozukluktur. Bu çalışmada, Başkent Üniversitesi Hastanesine sağ tarafta hemipleji nedeniyle başvuran 9 yaşındaki erkek hasta sunulmaktadır. Sol orta serebral arterin kanlandığı bölgede arteriyel trombus sonucu gelişen felç tanısı konulan hastanın FVL mutasyonu için heterozigot olduğu saptanmıştır. Pediatrik hastalarda gelişen akut felç durumunda, trombofilik mutasyonların etiolojisinin de dikkate alınması gerektiğini düşünmekteyiz.

Anahtar Kelimeler: inme, heterozigot faktör V leiden mutasyonu, aktive olmuş protein C direnci

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INTRODUCTION

Thrombosis is seldom seen in children. The incidence of venous thrombosis in pediatric age group is approximately 0.07 per 10,000, whereas the rate in adults is 2.5-5% (1). The reported annual incidence of cerebral infarction in children is 1.2 cases per 100,000, and approximately one-third of these events are spontaneous (2,3) Activated protein C resistance resulting from a point mutation in the gene for factor V (factor V Leiden, or FVL) is a relatively common risk factor for thromboembolism in several countries. The incidence of this mutation is high in Turkey, where the estimated rate of heterozygosity was detected as 7% (4). Mutant factor V causes resistance to activated protein C, which normally inhibits coagulation by cleaving factor V. Typically, the FVL mutation facilitates clot formation in the presence of other risk factors, such as immobilization, trauma, or surgery. However, spontaneous thromboembolic events may also occur in affected population. Here we report a 9-year-old boy with acute stroke who was heterozygous for FVL mutation.

Patient

A 9-year-old boy admitted to our hospital with right-sided hemiplegia. He had developed sudden-onset right-sided weakness and loss of speech while at school. There was no recent history of infection or trauma. The patient's medical history included a febrile seizure at 3 months of age, but he exhibited normal motor and mental development. Except for second-degree consanguinity of the parents, there was nothing in the family history related to thrombosis. However, two of the boy's paternal uncles had died of leukemia. On work-up at a local hospital, cranial computerized tomography had revealed no abnormalities and MRI had shown a large subacute infarct involving the left middle cerebral artery territory.

General physical status of the patient was normal. The neurological examination revealed expressive aphasia, right-sided central facial palsy, right-sided deep hemiplegia, and decreased sensitivity to pain, temperature, and touch on the same side. The deep tendon reflexes in the right upper and lower extremities were weak, and there was a positive Babinski's sign on the right side. Diffusion MRI showed a subacute infarct in the left middle cerebral arterial territory. MR angiography revealed irregularity of the vessel wall in the supraclinoid segment of the left internal carotid artery, and this was interpreted as a possible resolving thrombus and/or vasculitis. ANA testing was negative, and the levels of anti-dsDNA, C3, C4, pANCA, and cANCA were within normal limits. The cerebrospinal fluid (CSF) was acellular and contained normal concentrations of glucose, protein, and lactate. Analyses for myelin basic protein and oligoclonal bands were found to be negative. Viral serologic data of the CSF examinations for cytomegalovirus, Epstein-Barr virus, mumps, rubella, measles, parvovirus-B19, varicella, and herpes simplex virus type-1 were all negative. The results of electroencephalography, echocardiography, and thyroid function tests were found to be normal. Abdominal USG revealed coincidental left renal agenesis. The diagnosis was stroke due to arterial

thrombus or vasculitis. The patient was started on 1-mg/kg subcutaneous enoxaparine twice daily and 3-mg/kg/d oral acetylsalicylic acid. Following the one month's period of this regimen, oral warfarin treatment was initiated and the dose was adjusted to achieve an INR of 2-3. After an acute period of therapy, the patient was put on an intensive physical therapy program. He was able to walk without assistance at the end of the third month and had only a slight limp behind. His aphasia and central facial palsy disappeared.

Coagulation test results of the patient were within normal ranges for the values of PT, aPTT, protein C and S, fibrinogen, anti-thrombin, factor VIII, homocysteine, and lipoprotein (a) during the both acute and chronic phases of the disease. Tests for PPD, hepatitis B,C, and HIV were all negative. Molecular studies revealed that this boy was heterozygous for the FVL mutation. No mutation obtained in prothrombin G20210 and methylenetetrahydrofolate reductase (MTHFR) C677T genes.

Methods

The FVL, prothrombin G20210A (Pt 20210), and MTHFR C677T mutations were detected by polymerase chain reaction methodology and restriction enzyme digestion, as previously described (5-6). All the coagulation testing (PT, aPTT, protein C and S activities, and anti-thrombin and d-dimer levels) was done in a coagulometer (Diagnostico Stago, Asnieres, France) using commercial kits from the same manufacturer.

DISCUSSION

In a recent report, McColl et al. investigated the prevalence of the FVL, Pt20210, and MTHFR mutations in the etiology of stroke in 50 children at two centers (7). Excluding the 11 neonatal cases, the median age at which stroke occurred was 51 months (range, 10-168 months). Most of the patients had hemiparesis, and had no family history of cerebrovascular disease at a young age. Of the 50 cases, only 37 were evaluated for the detailed analysis. The authors found that 2 children were heterozygous for the FVL mutation, One patient was heterozygous for the Pt20210 mutation, 7 patients were homozygous for the MTHFR gene mutation, and 13 patients were heterozygous for this alteration. Compared to the findings in random, unselected, cord-blood controls, the patients who carried one of these mutations did not have a significantly higher odds ratio for stroke. The authors concluded that thrombophilia did not appear to play a significant role in the etiology of stroke in children. In contrast to the reports demonstrated that thrombophilia might be an important contributor to this condition. Zenz et al.(8) detected that 5 of 33 children as heterozygous for the FVL mutation. One of them was reported as homozygous whereas the other one was found to be heterozygous for the Pt20210 mutation Although they found no significant difference between the prevalence of Pt20210 mutation in the study group and that in the general population of Austria, the data identified FVL mutation as a possible risk factor for acute stroke after the neonatal period. Nowak-Göttl et al. (9) compared the findings in 148 children aged 0.5-16 years who had suffered spontaneous ischemic

stroke to findings in 296 age-matched controls and identified elevated lipoprotein (a) level, FVL, Pt20210 and MTHFR mutations as important risk factors for spontaneous ischemic stroke in childhood. The odds ratios for the FVL and the Pt20210 mutations were reported as 6 and 4.7, respectively. However, the authors noted that the presence of an additional risk factor increased the odds ratio significantly. The patient's history did not

reveale a previous infection as a risk factor. In addition, there were no underlying issues such as cardiac disorder, intracardiac thrombus, or vasculitic disease. We suggest that the thrombosis in our patient was a spontaneous event that was facilitated by FVL. We also conclude that thrombophilic mutations should be kept in mind in the etiology of acute stroke.

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