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Factor V Q 506 Mutation in Children With Thrombosis

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The factor V Leiden mutation in 12-children with thrombosis and in 20 controls was investigated. Five heterozygous individuals and 1 homozygous individual among the cases with thrombosis and 1 heterozygous individual among controls were found. Central nervous system thromboses were increased in children with the factor V mutation, associated with protein S deficiency. © 1996 Wiley-Liss, Inc.

Key words: thrombosis, activated protein C resistance, factor V Q 506 mutation, factor V Leiden

INTRODUCTION

Recently, inherited resistance to the anticoagulant action of activated protein C (APC) was found to be one of the factors involved in thrombophilia [1]. APC resistance is associated with heterozygosity or homozygosity for a single point mutation in the factor V gene at nucleotide position 1691, G-A substitution (FV Leiden). This mutation results in the production of an FV molecule with a glutamine substitution for arginine at amino acid number 506 of the molecule (FV Q 506) [2,3].

Previous studies have revealed that most patients with the FV mutation associated with thrombosis are adults [3–5]. Here, we report on the factor V mutation associated with venous thrombosis in 6 children.

MATERIALS AND METHODS

Twelve children with thrombosis and 20 age-matched healthy controls at Hacettepe Children's Hospital were the subjects of this study. For confirmation of thrombosis in the patients, one or more of the following procedures were performed: color Doppler ultrasound, computed tomography, magnetic resonance imaging, and venogram. Laboratory procedures included the following assays in all patients: activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, protein C, protein S, antithrombin III (ATIII), anticardiolipin and antinuclear antibodies, and factor V mutation assay. Whole cellular DNA was isolated from peripheral blood, and DNA was analyzed for FV mutation in 12 patients with thrombosis and 20 controls. Factor V mutation (FV R 506 Q) was detected by amplification of the FV gene by PCR and by digestion of the fragment with *Mnl*I, as described by Bertina et al. [2].

RESULTS

Four children had central nervous system complication (1 transverse and sagittal sinus thrombosis, 1 cerebellar thrombosis, 1 hemorrhagic infarct of thalamus, and 1 cerebral infarct), and the remaining 2 children had deep venous thrombosis and purpura fulminans, respectively (Table I). Among 12 patients, we found 5 (42%) who were heterozygous and 1 (8%) who was homozygous for the factor V mutation. The other 6 patients did not carry the FV mutation. Among 20 controls, 1 (5%) was heterozygous and the other 19 were normal (Table I). Five children were evaluated for protein C deficiency, and 2 were found deficient. However, their parents had normal levels of proteins C and S and ATIII. These 2 children had presumptive acquired protein C deficiency as an end-result of thrombosis. Five children were evaluated for protein S deficiency. Three were found deficient, and each had central nervous system thrombosis or hemorrhagic infarct. Protein S deficiency was presumably genetically inherited in 2 of these 3 patients, because their parents had protein S deficiency as well. Protein S levels could not be determined in the family of case 4. Patient 5 was not evaluated for proteins C and S or antithrombin III.

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TABLE I. Data on Patients

Case	1	2	3	4	5	6
Age, sex	11 years, F	7 months, F	6 months, M	10 months, M	2 days, F	5 months, F
Protein C (N = 60–175%)	27[a]	38[a]	60	74		83
Protein S (N = 60–175%)	60	91	45[b]	38[c]		15[b]
ATIII (N = 18–28%)	20.7	25	22.5			132
Site of thrombosis	Deep-vein thrombosis	Purpura fulminans	Sinus thrombosis	Cerebral infarct	Cerebellar thrombosis	Cerebral infarct
Associated risk factor	Portal hypertension	Staphylococ. sepsis	Staphylococ. sepsis		Anoxic at birth	Fever
FV Q 506 mutation	Heterozygote	Heterozygote	Heterozygote	Homozygote	Heterozygote	Heterozygote
Outcome	Recurrence of DVT	Amputation of fingers	Alive	Alive	Dead	Alive

[a]Protein C was normal in parents.
[b]Protein S was low in parents.
[c]Protein S was not determined in parents.

Underlying precipitating events were present in 5 children. These included staphylococcal sepsis, portal hypertension, and anoxia at birth (Table I). Antinuclear antibodies and anticardiolipin antibodies were negative.

DISCUSSION

According to the literature, FV mutation is found in 20–50% of thrombotic patients and in 3–7% of healthy controls [3–5]. The frequency of the FV Q 506 mutation, in Greek and United Kingdom populations, has been estimated to be 15% and 8.8%, respectively [4]. This high frequency suggests that the factor V mutation could not be the sole cause of thrombosis, but may be a risk factor for thrombosis. Individuals with the heterozygous FV Q 506 mutation may often be asymptomatic, and thrombosis usually develops in adult life when additional risk factors such as surgery, obesity, trauma, or intake of oral contraceptives are present [3–5].

Recently, thrombotic events due to FV, mutations were described in a few children [6,7]. In this study, 5 of our patients with thrombosis were heterozygous for FV mutation, 4 of whom were under age 1 year. Sixty percent and 40% of our patients with the FV mutation were found to have an acquired or genetic deficiency of proteins S or C, respectively. Previously, it has been reported that the FV mutation was an additional risk factor for patients with protein C or S deficiency [8,9]. In addition to the above-mentioned factors, and the FVQ 506 mutation, there were predisposing events such as staphylococcal sepsis, portal hypertension, and anoxia at birth in our patients. In our study, the infant who had a life-threatening cerebellar thrombosis during the second day of life is interesting. Kodish et al. [6] reported a term infant with heterozygous FV mutation who had a life-threatening inferior venal caval thrombosis during the first 24 hr of life. They did not detect any additional risk factor. These observations suggest that the FV mutation itself may play a role in thrombosis in the neonatal period. We found one homozygous individual among 12 cases with thrombosis (Table I). This patient also happened to have congenital or acquired protein S deficiency. Homozygotes with the FV mutation usually have a risk for thrombosis that is 50–100 times increased compared to heterozygotes. We believe that the Coexistence of protein S deficiency with homozygosity for FV mutation in our patient may be responsible for an unusually early formation of hemorrhagic infarct.

In conclusion, our study shows that children with the FV mutation associated with protein S deficiency had an increased frequency of central nervous system thrombosis. The overall thrombogenicity of the FV Q 506 mutation seems to be aggravated by additional thrombogenic risk factors such as protein C and S deficiencies, staphylococcal infections, and anoxia at birth. Therefore, this mutation, along with protein C or S deficiency, should be studied in all children with thrombosis.

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