

Prothrombin G20210A and A19911G mutations in Turkish pediatric stroke patients

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ABSTRACT

Effects of PT A19911G polymorphism in Turkish pediatric stroke patients were investigated. The case-control study included 107 patients with cerebral infarct and 83 healthy unrelated controls. Distribution of PT A19911G and data on the combined effect of PT 19911G and PT 20210A alleles do not indicate that they constitute a risk in this group of patients.

Key Words: Pediatric stroke, PT A19911G, PT G20210A

ÖZET

Türk pediatrik inme hastalarında protrombin G20210A ve A19911G mutasyonları

Türk pediatrik inme hastalarında Protrombin G20210A ve A19911G mutasyonları ve PT A19911G polimorfizminin etkisi araştırıldı. Vaka-kontrol çalışmasına 107 serebral infarktli hasta ve 83 sağlıklı akraba olmayan kontrol grubu dahil edildi. Bu çalışma grubunda PT A19911G polimorfizminin dağılımı ve PT 19911G ile 20210A allellerinin etkisi birlikte değerlendirildiğinde bir risk oluşturmadıkları saptanmıştır.

Anahtar Sözcükler: Pediatrik inme, PT A19911G, PT G20210A

INTRODUCTION

The incidence of cerebral infarction in children has been reported to be 1.2 cases per 100,000 children per year. Although several causes or potential risk factors exist for the occurrence of stroke in children, in about one-third of these patients, no obvious cause or underlying disorder can be diagnosed ^[1]. Inherited gene defects related to the coagulation system were reported as risk factors for pediatric stroke ^[2-5].

Prothrombin (PT) G20210A alteration causes a “gain of function” in the coagulation system with an increase in PT levels associated with an increased potential to form thrombin ^[6]. Previous reports on PT 20210A revealed controversial data as to whether it is a risk factor for the occurrence of pediatric stroke ^[2-5].

Although numerous publications have indicated PT G20210A as a prothrombotic mutation, absence of an association with recurrent deep vein thrombosis (DVT), the identification of asymptomatic homozygotes, and the great clinical variability between carriers of this polymorphism have led some authors to suggest that this polymorphism could not be considered as a genetic risk factor for DVT ^[7-9].

Other genetic and/or environmental factors could influence and determine the prothrombotic role of the PT G20210A. Recently, another polymorphism located in the PT gene at A19911G and associated with slightly increased plasma PT levels was reported, which may modulate the risk of the PT 20210A allele in DVT but not in arterial thrombosis, as described in a limited number of adult samples ^[10-12].

We aimed to study the effect of the PT A19911G site in pediatric stroke patients.

MATERIALS and METHODS

This case-control study included 107 patients with cerebral infarct who were below the age of 18 years (range, 10 months to 18 years). All were clinically diagnosed and the infarction verified with magnetic resonance imaging (MRI) of the brain. Patients with venous thrombosis were excluded. Eighty-three healthy unrelated age- and sex-matched individuals from the same geographical area without any familial history of thrombosis or stroke were selected as a control group. A written consent was obtained from each individual and/or his/her parents. DNA

was extracted by conventional methods and PT G20210A, FV G1691A, and PT A19911G polymorphisms were analyzed according to previously described methods ^[6,11,13].

Mean values and standard deviations were calculated according to standard procedures. Differences between groups were analyzed with chi-square and Mann-Whitney U tests. Unmatched odds ratio (OR) and 95% confidence intervals (CI) as an estimate of the relative risk of the allele frequency were calculated in the entire study population. The 95% CIs were calculated from a conditional logistic-regression algorithm by the maximum likelihood method.

RESULTS

Distribution of PT A19911G and data on the combined effect of PT A19911G and PT G20210A alleles are given in Table 1. Thirteen (12.1%) of the 107 pediatric stroke patients had PT G20210A which brought a 2.7 fold risk (OR= 2.7, CI 95%= 0.8-8.7). This was 4.6% for the control group. The PT 19911G allele also did not constitute a risk in this group of patients (p= 0.7). When we search the combined effect of PT G20210A and PT A19911G, our data revealed no significant difference between the groups (p= 0.7).

Twenty-four (22.4%) of the pediatric patients carried the FV1691A allele, which was found to be a significant risk factor (OR: 4.5, CI 95%: 1.63-12.40) (p= 0.01). When we excluded FV 1691A- and/or PT 20210A-carrying patients from the main group, the PT19911G allele also did not reveal a significance (p= 0.23).

DISCUSSION

PT G20210A is the second most common cause of inherited thrombophilia. As the prothrombotic potential of this polymorphism is significantly milder, identification of asymptomatic homozygotes and the great clinical variability between carriers of this polymorphism have led some authors to suggest that this polymorphism could not be considered as a genetic risk factor for DVT ^[7-9]. Recently, another polymorphism located in the PT gene, A19911G, was found associated with slightly increased plasma PT levels, which modulate the risk of the PT 20210A allele in DVT but not in arterial thrombosis, as shown in a few adult cases ^[10-12]. In a recent study by von Ahsen and Oellerich ^[14] in a stable reporter gene assay system, they found that PT A19911G

Table 1. Distribution of PT A19911G and combined effect of PT G20210A and PT A19911G polymorphisms in pediatric stroke patients

PT1991G	AA	%	AG	%	GG	%	Frequency of G allele	P
Control (83)	14	16.8	48	57.8	21	25.3	54.2	0.72
Patients (107)	24	22.4	57	53.2	26	24.2	50.9	-

Genotypes	Control		Patient		p	OR	(CI 95%)
(PT20210/PT19911)	n	(%)	n	(%)	-	-	-
GG/AA	14	(16.8)	19	(17.7)	0.8	1	-
GG/AG	45	(54.2)	49	(45.7)	0.5	0.8	0.36-1.78
GG/GG	20	(24)	26	(24.2)	0.9	0.95	0.38-2.36
GA/AA	-	-	5	(4.6)	0.1	7.36	0.37-146.2
GA/AG	4	(4.8)	8	(7.4)	0.7	1.47	0.36-5.38

polymorphism influenced the splicing efficiency and modulated the effects of the G20210A polymorphism on mRNA amount and expression.

As most pediatric stroke patients have arterial thrombosis, we studied this polymorphic site in Turkish children with arterial strokes to determine whether it could influence the prothrombotic role of the PT G20210A. Our data re-

vealed that the PT A19911G polymorphism does not have any effect on PT G20210A in pediatric stroke, neither as an independent factor nor in combination with PT G20210A mutation.

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