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RESEARCH ARTICLE

T102C polymorphism of the serotonin (5-HT) 2A receptor gene in Turkish children with cerebral infarct

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ABSTRACT

Platelet-dependent thromboembolism is an underlying mechanism in the pathogenesis of stroke. 5-HT2A receptor gene is expressed in human platelet, coronary artery (blood vessels) and brain. A polymorphism T102C at the 5-HT2A receptor gene was found that may possibly affect the 5-HT2A receptor function. As there is no existing data on T102C variant of 5-HT2A receptor gene in pediatric stroke, we aimed to study in this case-control study whether there is a association between this polymorphism and pediatric stroke. 111 patients (10 months-18 years old) with cerebral infarct and 79 healthy control was included to our study. Polymerase chain reaction (PCR) of the T102C alteration at the 5-HT 2A receptor gene was performed. Our data revealed that, 5-HT (2A) receptor T102C polymo phism was not associated with pediatric stroke in our population either alone or in combination with underlying pro thrombotic factors. However, this needs to be clarified with further studies.

Key Words: Pediatric stroke, 5-HT 2A receptor gene, T102C polymorphism

ÖZET

Serebral infarktlı Türk çocuklarında seratonin (5-HT) 2A reseptör genindeki T102C polimorfizmi

5-HT2A reseptör genindeki T102C polimorfizmi muhtemelen bu reseptörün fonksiyonlarını etkilemektedir. Pediatrik inmede 5-HT2A reseptör genindeki T102C varyantı ile ilgili mevcut bilgi olmadığı için çalışmamızda; bu polimorfizm ile pediatrik inme arasında ilişki olup olmadığını araştırmayı amaçladık. Serebral inme öyküsü olan 111 çocuk (10 ay-18 yaş) ve 79 sağlıklı kontrol çalışmaya dâhil edildi. 5-HT2A reseptör genindeki T102C değişimi PCR tekniği ile çalışıldı. Sonuç olarak; bu polimorfizm ne tek başına ne de diğer altta yatan protrombotik faktörlerle birlikte değerlendirildiğinde pediatrik inme ile ilişkili bulunmadı, ne var ki bu bilgi daha sonraki çalışmalarla da aydınlatılmalıdır.

Anahtan Sözcükler: Pediatrik inme, 5-HT 2A reseptör geni, T102C polimorfizmi

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 [1-3]. Inherited gene defects related to the coagulation system were reported as risk factors for stroke [4-6].

The most common cause of thrombophilia is the G-A substitution at the nucleotide 1691 of Factor V gene leading to a single amino acid alteration in one of the three cleavage sites, i.e. Arg instead of Gln at position 506. This common mutation causes activated protein C resistance [7]. Another common mutation is prothrombin 20210 G-A alteration, which causes a "gain of function" in the coagulation system with an increase of prothrombin levels associated with an increased potential to form thrombin [8]. The prevalences of FV1691A and PT20210A varies among populations; they were reported between 7-10% and 2.6% in a healthy Turkish population [9,10]. Although most of the case reports and series have suggested FV1691A as a risk factor in childhood stroke, reports on PT20210A have revealed contradictory data for pediatric stroke. The reason could be other genetic and/or environmental factors which may influence and determine the prothrombotic role of the FV1691 G-A and PT20210 G-A mutations [4-6,11-14].

Platelet-dependent thromboembolism is an underlying mechanism in the pathogenesis of stroke. The formation of thrombus is initiated by platelet adhesion and aggregation. During platelet aggregation, several substances such as serotonin [5-hydroxytryptamine (5-HT)], thromboxane A2 and adenine nucleotides (ADP, ATP) are released [15]. 5-HT2A receptor gene is expressed in human platelets, coronary artery (blood vessels) and brain [16-18]. Furthermore, a polymorphism T102C at the 5-HT2A receptor gene was found that may possibly affect the 5-HT2A receptor function [19,20].

Two previous reports presented controversial data on the 5-HT2A receptor gene [15,21]. Yamada *et al.* [15] reported that 5-HT with respect to the 102T allele may play an important role in the pathogenesis of acute myocardial infarction through 5-HT2A receptor activation in the Japanese. On the other hand, Coto *et al.* [21] reported no association with myocardial infarction at any age in the Spanish population.

As there is no existing data on the T102C variant of the 5-HT2A receptor gene in pediatric stroke, we aimed in this case-control study to investigate whether there is an association between this polymorphism and pediatric stroke.

MATERIALS and METHODS

This case-control, consecutive study included 111 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 cranial imaging (hypodensity on computed cranial tomographic scan or hyposignal on T1-weighted and hypersignal on T2-weighted magnetic resonance imaging-MRI) and MRI of the brain. Patients with venous thrombosis were excluded. Seventy-nine 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 polymerase chain reaction (PCR) of the T102C alteration at the 5-HT2A receptor gene (GenBank, ACCESSION S71229) was performed by using two primers, 5' TCTGCTACAAGTTCTGGCTT 3' and 5' CTGCAGCTTTTTCTCTAGGG 3', which was reported previously. PCR product restricted with Msp I (Fermentas, Lithuania) was used to determine the mutation [21]. FV1691 G-A and

Table 1. Distribution of T102C of the serotonin (5-HT) 2A receptor gene in Turkish children with cerebral infarct

	N	*TT*		*TC*		*CC*		*C%*	*T%*
		n	%	*N*	%	*N*	%		
CONTROL	79	21	26.6	43	54.4	15	19.0	46.2	53.8
Patients	111	26	23.4	58	52.3	27	24.3	50.5	49.5
p	-	-	-	-	-	-	-	0.6	0.6

Table 2. Combined effect of T102C of the serotonin (5-HT) 2A receptor gene and FV1691 G-A

FV 1691 G-A	*5-HT 2A T102C*	*CONTROL*	*Patients*	*OR*	*95%CI*
GG	TT	20	24	1	-
GG	TC	39	47	1	0.4-2.0
GG	CC	9 12	19	1.3	0.5-3.3
GA	TT	1	1	0.8	0.04-14.0
GA	TC	4	11	2.2	0.6-8.3
GA	CC	0 3	8	2.2	0.5-9.5
AA	TT	-	1	1.6	0.05-52.0

Table 3. Combined effect of T102C of the serotonin (5-HT) 2A receptor gene and PT20210 G-A

PT20210A	*5-HT 2A T102C*	*CONTROL*	*Patients*	*OR*	*95%CI*
GG	TT	18	24	1	-
GG	TC	43	50	0.8	0.4-1.8
GG	CC	14	25	1.3	0.5-3.2
GA	TT	3	2	0.5	0.07-3.3
GA	TC	-	8	12.0	0.6-222
GA	CC	1	2	1.5	0.11-17.8

PT20210 G-A mutations were analyzed according to previously described techniques [8,22].

Differences between groups were analyzed with chi-square and Mann-Whitney U test. Unmatched odds ratio and 95% confidence intervals as an estimate of the relative risk of the allele frequency were calculated in the entire study population. The 95% confidence intervals were calculated from a conditional logistic-regression algorithm by the maximum likelihood method.

RESULTS

Distributions of T102C of the serotonin (5-HT) 2A receptor gene in Turkish children with cerebral infarct are given in Table 1. From our data, it was apparent that FV1691A and prothrombin 20210 A were associated with a risk in pediatric stroke. Data on the combined effect of T102C of the serotonin (5-HT) 2A receptor gene with FV1691 G-A and PT20210 G-A did not show an association with a risk in pediatric stroke (Tables 2 and 3). When FV1691 G-A and PT20210 G-A carriers were excluded, 5-HT2A receptor T102C polymorphism was also not associated with pediatric stroke in our population.

DISCUSSION

Thrombosis is a rare disorder in the pediatric age range and will occur when a sufficient number of risk factors are present simultaneously. Of all thrombotic patients, one-third manifest as stroke. Stroke has certain differences between pediatric patients and adults. First, it is common in adults; second, vascular occlusive strokes in adults are mostly secondary to arteriosclerosis, which is not the case in pediatric patients; third, there are special properties of the hemostatic system during infancy and childhood; and fourth, there are several developmental differences in the cerebrovascular and neurologic systems. 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. Numerous clinical and environmental conditions leading to a prothrombotic state were reported [1-3].

Various prothrombotic disorders particularly affecting the physiological anticoagulant systems have attributable risk for stroke including common mutations FV1691 G-A and PT20210 G-A.

Platelet-dependent thromboembolism is an underlying mechanism in the pathogenesis of stroke.

During platelet aggregation, several substances such as serotonin [5-hydroxytryptamine (5-HT], thromboxane A2 and adenine nucleotides (ADP, ATP) are released [15]. 5-HT2A receptor gene is expressed in human platelets, coronary artery (blood vessels) and brain [16-18]. Furthermore, a polymorphism, T102C at the 5-HT2A receptor gene, was found that may possibly affect the 5-HT2A receptor function [20]. Two previous reports presented controversial data on 5-HT2A receptor gene in the pathogenesis of acute myocardial infarction in Japanese and Spanish populations [15,21]. It is interesting that controversial data exist in two populations. As our patient group is in the pediatric age group, a different result from the above-mentioned adult groups is somewhat logical. However, this needs to be clarified with further studies.

Our study is the first report on the T102C variant of the 5-HT2A receptor gene in pediatric stroke. Our data revealed that 5-HT2A receptor T102C polymorphism was not associated with pediatric stroke in our population either alone or in combination with underlying prothrombotic factors.

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