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The Role of CYP2C19 and GABRG2 Genes in Febrile Convulsion

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Abstract

Introduction: Although the pathogenesis for febrile convulsions (FC) is not completely understood, genetic susceptibility is at the forefront. The main purpose of the study is to determine the role of mutations in CYP2C19 and GABRG2 genes and the effect of these mutations on EEG abnormality and prophylactic treatment indication of febrile convulsions.

Materials and Methods: In this prospective conducted study, patients aged between 6 - 12 years old were recruited from the clinics of paediatric neurology, the paediatric emergency, and the paediatrics, which were diagnosed with FC by the paediatric neurologist and treated and/or followed up between the dates of August 2015 and January 2017. The study group comprised of 102 patients, and the control group included 96 children who met the above-mentioned criteria. The patients were subjected to detailed history and clinical examination, including for genetic (and) dysmorphic features to exclude other causes for FC, and were evaluated for EEG (electroencephalography) and whether they were on medication, as well.

Results: According to our findings; (i) the presence of FC in the patient history was significant high compared to control group (p = 0.001), (ii) the incidence of FC was higher in boys (1,56/1), (iii) the majority of patients were subjected to EEG procedures (92%; 92/100) and in more than half of the cases, abnormal EEG findings were present (56%), (iv) the drug use rate was higher in patients with abnormal EEG findings (37/56, 66,7%, p = 0,001), (v) the distribution of GABRG2 (R43Q) mutation and CYP2C19 (*2 and *3) polymorphisms were found to be similar in FC patients and the control group, (vi) EEG anomaly and drug use were found to be significant in the study group as regards clinical effects of GABRG2 mutation (p = 0,032 and p = 0,021, respectively), and (vi) all of the patients with homozygous R43Q mutation had abnormal EEG findings as well as higher rates of drug use (5/6, 83,3%).

Conclusion: Even though the distribution of R434Q mutation and CYP2C19 polymorphism were found to be similar in FC patients and the control group, the presence of R43Q mutation in the patient group had a negative contribution to abnormal EEG findings and lowered the necessity for drug use, which may indicate the prognostic importance of the presence of R43Q mutation in FC patients.

Keywords: *Febrile Convulsion; GABRG2; R43Q; CYP2C19; *2, *3, Mutation; Polymorphism; Anticonvulsant*

Abbreviations

CYP: Cytochrome p450 Gene; CYP2C19: Cytochrome P450 Family 2 Subfamily C Member 19 Gene; GABRG2: GABA-A Receptor 2 Subunit Gene; GABA-A: Gamma-Aminobutyric Acid; FC: Febrile Convulsion; EEG: Electroencephalogram; ILAE: International League against Epilepsy

Introduction

Febrile convulsions (FC) are the most common seizure disorders of childhood, are acute symptomatic and occur in an age-specific manner. FS are triggered by fever, which is common between 6 months and 6 years [1,2]. Febrile seizures are seizures that occur in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of a febrile seizure. Febrile seizures are subdivided into 2 categories: simple and complex. Simple febrile seizures last for less than 15 minutes, are generalized (without a focal component), and occur once in a 24-hour period, whereas complex febrile seizures are prolonged (> 15 minutes), are focal, or occur more than once in 24 hours [3]. Pathogenesis of FC is not completely understood, but it is thought that multiple factors play a role in pathogenesis. Among these, genetic susceptibility is at the forefront in recent studies. In recent years, mutations in nicotinic receptor, cholinergic receptor and gamma-aminobutyric acid (GABA-A) genes like GABRG2 related to voltage-dependent ion channels and ligand-dependent ion channels [4-6] have been identified in the etiology of FC. In particular, mutations in the GABRG2 gene are thought to be related to FC [6].

GABA-A is ligand-gated ion channel and has many subunits (α1-α6, β1-β3, ɣ1-ɣ6, π, £). GABA-A is the major inhibitor neurotransmitter of the central nervous system. There are few studies suggesting that the R43Q (rs211037) mutation in the ɣ 2 subunit of the GABA-A receptor may be associated with epilepsy and FC [7-11]. However, the relationship between FC and R43Q has not been fully elucidated [9]. Complete clarification of the association of the R43Q mutation with FC will contribute to the development of more effective follow-up and treatment protocols for these patients [9]. Also, the cytochrome P450 (CYP450) system is an enzyme system that plays an important role in drug metabolism and is responsible for the metabolism of antiepileptic drugs. CYP2C9 and CYP2C19 polymorphisms related to CYP450 system play an important role in determining response to antiepileptic drug therapy, and also provide information on the behavior of the seizure activity, but there are not enough studies evaluating its relationship with FC [12,13].

Thus, we aimed to determine the association of GABRG2 R43Q mutation and CYP2C19 *2 and *3 polymorphisms with FC frequency, type, EEG findings and prophylactic treatment need.

Materials and Methods

Patients who were admitted to the pediatric neurology, pediatric emergency and child health clinic between August 2015 and January 2017 and who were diagnosed with FC by pediatric neurologist according to ILAE criteria [14] were prospectively included in the study. Children aged between 6 - 12 years old without any febrile/afebrile seizure history and having normal neurological examinations were enrolled in the control group. Informed consent forms were received from the families. Ethical approval was obtained from Abant Izzet Baysal University Ethics Committee (Ethics Committee No: 2015/51).

In the study, demographic informations, clinical history of convulsion(s) including age of first convulsion, type of convulsion, recurrence of convulsion were recorded for all participants. Patients who were diagnosed as FC were continued to followed up after acute treatments. EEG was performed after DeRoss ST., *et al* [15]. The first EEG recordings after sleep-deprivation were performed 10 days after FC. Abnormal EEGs were repeated two times one month apart. All abnormalities (focal asymmetry, focal or generalized slow waves, abnormal theta rhythms and asymmetric backgrounds) except epileptiform activities (spikes, sharp waves, or spike-wave complexes) were evaluated as abnormal EEGs. Prophylactic treatment was initiated to patients according to ILAE criteria [14].

Genetic Analysis

Peripheral vein blood samples were taken from 102 individuals with FC and 96 control individuals. Samples were collected and stored at 4°C until genomic DNA extraction from peripheral blood leukocytes according to standard methods (High Pure PCR Template Preparation Kit-Roche). After DNA concentrations were checked, real time PCR (lightCycler480 II), (Roche Diagnostics, Mannheim, Germany) with Light SNIPs (single nucleotide polymorphism) were performed to detect all individuals' genotypes for the GABRG2 R43Q mutation and the CYP2C19 (*2 and *3) polymorphism, with different protocols in different runs for each (Light SNP prob kits suppl. by TIB MOLBIOL

GmbH, Berlin, Germany). Samples were studied using SNPs with rs211037 for R43Q CYP2C19*2 rs4244285 and CYP2C19*3 rs4986893 for CYP2C19. A high-throughput assay for both loci genotyping was used for the SNPs. For each SNP a single hybridization-based method was established on a high-resolution platform, the 96-well Roche LightCycler® 480 (LC480) instrument. Melting curve peaks were evaluated, so genotyping could be possible.

Genotyping

R43Q gene analysis: Homozygote (CC), wild-type homozygote (TT), and heterozygote (CT) genotypes.

CYP2C19 Polymorphisms: CYP2C19*2; CYP2C19*3: *1/*1, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3.

Statistical Analysis

Descriptive analysis were expressed as percentages for categorical variables and mean ± standard deviation for continuous variables. Categorical variables were compared by means of the Chi-square test and continuous variables were compared with Student-T test with the help of SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The data of the genotype analysis were calculated by using the Epi info 3.5.3 statistical program. P values lower than 0.05 was considered as significant.

Results

102 patients with febrile convulsions and 96 control patients were included in the study. Two patients with FC were developed epilepsy at follow-up (1 and 3 months) and they were excluded from the study. The mean age of the patients with FC was 33.0 ± 17.2 months old and 61% were male. The first seizure age in patients with FC were mostly at the age of 1 - 3 years (58/100, 58%). Within the FC group, 73% of seizures were simple FC (SFC) and 27% were complex FC (CFC). 38.2% of the patients had single seizures and 16% had four or more seizures. Fifty six of 100 patients had abnormal EEG findings, and prophylactic treatment was started in half of them. When the EEG findings were examined according to seizure subtypes (SFC and CFC), the frequency of EEG abnormality were similar between two groups (70,1% and 66,1%, p = 0,196). The demographic and clinical characteristics of patients with febrile convulsions are shown in table 1.

Age (month), (median ± SD)	33,0 ± 17,2
Sex, male, n (%)	61 (61%)
Age at first FC episode (month) (median ± SD)	20,0 ± 11,8
< 1 years old, n (%)	30 (30%)
1 - 3 years old, n (%)	58 (58%)
> 3 years old, n (%)	12 (12%)
Febrile convulsion type n (%)	
Simple	73 (73%)
Complex	27 (27%)
Number of febrile convulsion	
1 convulsion, n (%)	38 (38%)
2 convulsion, n (%)	33 (33%)
3 convulsion, n (%)	13 (13%)
≥ 4 convulsion, n (%)	16 (16%)
EEG n (%)	
Normal	36 (36%)
Abnormal	56 (56%)
Not done	8 (8%)
Anti-convulsion prophylaxis, yes, n (%)	50 (50%)

Table 1: *Demographic and clinical characteristics of patients with febrile convulsion.*
EEG: Electroencephalography; SD: Standard Deviation

When the FC and control groups were compared in terms of family story of FC, the presence of family history was significantly higher in the patient group (p < 0.001). Demographic characteristics of the study and control groups are given in table 2.

Variables	Patient N	Control N	P value
Age, month, median ± SD	33,0 ± 17,2	112,9 ± 19,7	< 0.001
Sex, male, n (%)	61 (61%)	50 (52,1%)	0.249
Family history of FC, n (%)	33 (33%)	11 (11,5%)	< 0.001
Consanguinity, n (%)	18 (18%)	20 (20,8%)	0.718
R43Q mutation, n (%)			
Wild type	58 (58%)	54 (56,3%)	0.927
Heterozygote	36 (36%)	35 (36,5%)	
Homozygote	6 (6%)	7 (7,3%)	
CYP2C19 Polymorphism			
Fast metabolizers	77 (77%)	77 (80,2%)	0.393
Intermediate metabolizers	22 (22%)	16 (16,7%)	
Poor metabolizers	1 (1%)	3 (3,1%)	

Table 2: *Comparison of patients and control group according to demographic and genetic analysis.*
SD: Standard Deviation

When the R43Q mutation distribution was evaluated, there was no statistically significant difference between FC group and control group (Table 2, p = 0,927). When the clinical effect of the R43Q mutation was examined in the FC group, there was no statistically significant difference in sex, first FC age, number of seizures, seizure type, family history, and consanguinity, while EEG abnormalities and prophylactic treatment ratio were statistically significantly different (Table 3, p = 0.032, p = 0.021, respectively). All patients with R43Q homozygous mutation had EEG abnormality and the rate of drug use was higher (5/6, 83.3%) (Table 3).

		CC (Wild type)	CT (Heterozygote)	TT (Homozygote)	p value
Sex n (%)	Female	20 (34,5%)	14 (38,9%)	5 (83,3%)	0,065
	Male	38 (65,5%)	22 (61,1%)	1 (16,7%)	
Age of first FC n (%)	< 1 years	20 (34,5%)	9 (25%)	1 (16,7%)	0,136
	1 - 3 years	34 (58,6%)	19 (52,8%)	5 (83,3%)	
	> 3 years	4 (6,9%)	8 (22,2%)	0 (0%)	
Type of seizure n (%)	Simple	41 (70,7%)	28 (77,8%)	4 (66,7%)	0,706
	Complex	17 (29,3%)	8 (22,2%)	2 (33,3%)	
Times of seizure n (%)	1	17 (29,3%)	20 (55,6%)	1 (16,7%)	0,170
	2	23 (39,7%)	7 (19,4%)	3 (50%)	
	3	9 (15,5%)	3 (8,3%)	1 (16,7%)	
	≥ 4	9 (15,5%)	6 (16,7%)	1 (16,7%)	
Family history n (%)	Yes	20 (34,5%)	11 (30,6%)	2 (33,3%)	0,925
	No	38 (65,5%)	25 (69,4%)	4 (66,7%)	
Consanguinity n (%)	Yes	10 (17,2%)	6 (16,7%)	2 (33,3%)	0,6
	No	48 (82,8%)	30 (83,3%)	4 (66,7%)	
EEG n (%)	No	3 (5,2%)	5 (13,9%)	0 (0%)	0,032
	Normal	19 (32,8%)	17 (47,2%)	0 (0%)	
	Abnormal	36 (62,1%)	14 (38,9%)	6 (100%)	
Drug use n (%)	Yes	33 (56,9%)	12 (33,3%)	5 (83,3%)	0,021
	No	25 (43,1%)	24 (66,7%)	1 (16,7%)	

Table 3: *Comparison of patients R43Q gene mutations and clinical findings.*

When the FC and control group were compared in terms of CYP2C19 polymorphism, there was no statistically significant difference between the two groups (P = 0.393) (Table 2). In our study, fast metabolizer frequency was found 77%, intermediate metabolizer frequency was 22%, slow metabolizer frequency was 1% in the FC group. In the control group, fast metabolizer frequency was found to be 80.2%, intermediate metabolizer frequency was 16.7%, slow metabolizer frequency was 3% (p = 0.393). When the clinical effect of CYP2C19 polymorphism was examined in the FC group; there was no statistically significance by means of gender, first FC age, number of seizures, type of seizure, family history, consanguinity, EEG abnormality and prophylactic treatment (Table 4).

		Fast metabolizer	Medium metabolizer	Slow metabolizer	p value
Sex n (%)	Female	30 (39%)	8 (36,4%)	1 (100%)	0,443
	Male	47 (61%)	14 (63,6%)	0 (0%)	
Age of first FC n (%)	< 1 years	26 (33,4%)	4 (18,2%)	0 (0%)	0,649
	1 - 3 years	42 (55,5%)	15 (68,2%)	1 (100%)	
	> 3 years	9 (11,6%)	3 (13,6%)	0 (0%)	
Type of seizure n (%)	Simple	54 (70,1%)	18 (81,8%)	1 (100%)	0,718
	Complex	23 (29,9%)	4 (18,2%)	0 (0%)	
Times of seizure n (%)	1	32 (41,5%)	6 (27,3%)	0 (0%)	0,464
	2	24 (31,2%)	8 (36,3%)	1 (100%)	
	3	11 (14,3%)	2 (9,1%)	0 (0%)	
	≥4	10 (13%)	6 (27,3%)	0 (0%)	
Family history n (%)	Yes	25 (32,5%)	8 (36,4%)	0 (0%)	0,735
	No	52 (67,5%)	14 (63,6%)	1 (100%)	
Consanguinity n (%)	Yes	11 (14,3%)	7 (31,8%)	0 (0%)	0,151
	No	66 (85,7%)	15 (68,2%)	1 (100%)	
EEG n (%)	No	5 (6,5%)	3 (13,6%)	0 (0%)	0,685
	Normal	27(35%)	9 (40,9%)	0 (0%)	
	Abnormal	45(58,5%)	10 (45,5%)	1 (100%)	
Drug use n (%)	Yes	38 (49,3%)	12 (54,5%)	0 (0%)	0,401
	No	39 (49,7%)	10(45,5%)	1 (100%)	

Table 4: *Comparison of patients CYP2C19 polymorphisms and clinical findings.*

When we look at the FC patients who were not performed EEG (N = 8), a significant proportion of the patients had SFC (7/8, 87.5%), and their genetic results and need for prophylactic treatment were similar with EEG performed FC patients (p > 0.05) (Data not shown).

Discussion and Conclusion

Although FC is the most common type of seizure in childhood; the etiopathogenesis is still unclear. Since the pedigrees of patients with FC show familial clustering with no distinct Mendelian inheritance pattern, genetic factors have begun to be considered in pathogenesis [16-18]. Recent genetic studies have shown that mutations in ion channels may play a role in the development of FC and epilepsy [4-6]. However, none of these studies investigated the association between R43Q mutation and CYP2C19 polymorphisms and clinical and EEG findings of FC. In our study, we tried to determine the role of CYP2C19 polymorphisms and R43Q mutation in FC; besides, the effect of these two genetic analyzes on EEG abnormality and prophylactic treatment indication was also investigated. In this respect, our study may be considered as the first study in the literature.

Febrile convulsion is more common in boys than in girls. In a study conducted by Okumura., *et al.* [19] on 203 patients, male to female was 1.3/1, while it was 1,4/1 in Knudsen's [20] study, and 1.42/1 in Tsuboi's study [21,22]. In our study, this ratio was found to be almost similar to the literature data (1.56/1). This suggests that, male gender may have an important role in FC pathogenesis.

Febrile convulsion is mostly seen between 3 months to 5 years of age, and infectious disease that can cause fever also common in this age group. In a study conducted by Okumura., *et al.* [19], the age range was 7 - 69 months (mean 25 months), whereas the age range was found to be 1 - 77 months in another study [23]. Kölfen., *et al*. reported that 25% of the first FC was below one year of age, 46% between 1-2 years of age, and 29% of the was over 2 years of age. In our study, although similar results were obtained with the literature, it was determined that most of them occurred at 1 - 3 years of age. Approximately 30 to 40% of children who experienced one FC will have a recurrence, and within this group nearly half of them will have a third FC. Nine percent of children will have more than three FC after an initial FC [24,25]. In our study, recurrence (62%) was higher than literature. Our study population may be genetically predisposed to FC compared to previous studies and this may have a role in this high recurrence rate. Besides, our clinic is a tertiary center serving a wide area and with close patient follow-up we aimed to prevent data loss.

Non-specific abnormalities can be seen temporarily in the EEG (bioccipital theta slowing, focal sharp waves, generalized spike-wave discharges, multifocal spikes) in the first week after FC. However, there are no studies on the follow-up of these disorders in EEG. In our study, all patients with EEG anomalies were also subjected to 2nd and 3rd EEG recording. Thus, the persistent abnormalities were accepted as "abnormal EEG". In literature, the EEG is 60% normal in simple FC. In contrary to this finding, in some studies, the frequency of EEG abnormality ranges between 2 to 86% in FC [26]. In our study, 56% of the EEGs were abnormal. We performed EEG to 92% of our patients which is high when compared with the literature. This is mostly related to our concern that these patients might have epilepsy in the future. This is because we had considerable amount of patients presented with FC and developed different epileptic disorders in follow-up. The rate of prophylactic treatment among patients with EEG abnormalities was also high (37/56, 66.7%, p = 0.01). The rate of EEG abnormality in patients with complex FC was higher than the patients with simple FC (70.1% versus 66.1%), and prophylactic treatment rate was also higher in complex FC group (81.5% versus 60.2%). This data may show the importance of EEG and its importance in prophylactic treatment decision in patients with FC, especially in patients with complex FC.

One of the most debated topics in children with FC is the antiepileptic drug prophylaxis. In previous studies, prophylaxis was widely suggested due to the thought that FC could progress to epilepsy [27]. However, in recent epidemiological studies, it has been reported that FCs do not lead to structural and cognitive disturbances in the central nervous system, and that the risk of developing epilepsy is very low [28,29]. In our study, the rate of prophylactic treatment was higher than the literature (50%). The most important reason for this is the ongoing EEG abnormalities, but sociocultural and geographical factor may also have a role in this finding.

The influence of ion channels in the etiopathogenesis of FC has been emphasized in recent years. GABA is the major inhibitor neurotransmitter of central nervous system (CNS). There are three different GABA receptors; GABA-A, GABA-B, GABA-C. Frugier., *et al*. [6] have associated several GABA-A receptor mutations with epileptic syndromes. It has been shown that R43Q mutation in the GABA-A receptor γ2 subunit may be associated with childhood absent epilepsy and FC [7,8,30]. It was shown that GABRG2 R43Q mutation did not affect GABA-associated synaptic events, but it was found to be related with reduced surface expression of the γ2 subunit, decreased synaptic aggregation, and decreased tonic flow of GABA. Wallace., *et al*. detected a heterozygous R43Q mutation in a large family with epilepsy (mainly childhood absence epilepsy and FC) [8]. Hancili., *et al*. showed that heterozygous R43Q mutation was higher in patients with FC (n = 44) than heathy controls (n = 49), but homozygous mutation rates were similar in both groups [9]. In our study, we did not find any significant difference between patients and controls according to the presence of heterozygous or homozygous R43Q mutation. This finding suggests that FC is a multifactorial disorder and cannot be explained by a single mutation. When the clinical effect of the R43Q mutation was examined in the FC group, there was no statistically significant difference in sex, first FC age, number of seizures, seizure type, family history, and consanguinity. However, all patients with R43Q homozygous mutation had EEG abnormality and the rate of pa-

tients without prophylaxis was high. Besides, none of the patients with normal EEG had a homozygous R43Q mutation. This may indicate that homozygous R43Q mutation may have adverse effect on EEG and prophylaxis need in patients with FC. However, more comprehensive studies are required to help establish the link between R43Q mutation and FC.

CYP2C19 is one of the enzymes that plays an important role in drug metabolism and metabolizing rate differs with genetic polymorphism. In the second step of our study, we examined the frequency of CYP2C19 polymorphisms and its possible association with clinical features of FC and prognosis. There are several studies carried on the frequency of CYP2C19 polymorphism in Turkish population, and frequency of slow metabolizers varies between 0.94 - 1.2% [31-33]. In our study, the frequency of moderate and slow metabolizers were similar between controls and patients. When we evaluated the relationship between CYP2C19 polymorphism and clinical findings, we found that CYP2C19 polymorphism was not related with sex, type of seizure and first FC age, number of seizures, family history, EEG findings and prophylactic treatment. These findings suggest that CYP2C19 polymorphisms do not provide an effective contribution to the pathogenesis of FC. But our results might be related to the low number of patients, because there was only one slow metabolizer patient in our study. Therefore, prospective studies are needed to establish the relation between CYP2C19 polymorphisms and FC.

In conclusion, even though the distribution of GABRG2 R434Q mutation and CYP2C19 *2 and *3 polymorphisms were found to be similar in FC patients and the control group, the presence of R43Q mutation in the patient group had a negative contribution to abnormal EEG findings and the necessity for drug use, which may indicate the prognostic importance of the presence of R43Q mutation in FC patients. In addition, in contrast to the general acceptance, a significant portion of patients with FC persisted with an EEG anomaly, which needs to be confirmed by large-scale prospective studies.

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Volume 10 Issue 9 September 2018