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Association of TGFB, but not IL10, single nucleotide polymorphisms with febrile seizures

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ABSTRACT

Purpose: Febrile seizures (FS) are the most common convulsive event in children. Inflammatory elements and genetics seem to have major roles in their pathogenesis.
Methods: Seventy nine patients with FS were enrolled in this study and compared with 140 controls. Cytokine genotyping was performed, using polymerase chain reaction with sequence-specific primers. The allele and genotype frequency of three single nucleotide polymorphisms (SNPs) within the IL-10 gene at -1082, -819 and -592 positions (rs1800896, rs1800871, rs1800872), and two SNPs within the TGFB at codons 10 and 25 (rs1982037, rs1800471) were determined.
Results: No significant difference was detected in allelic frequency of IL-10 at -1082, -819 and -592 positions (rs1800896, rs1800871, rs1800872) and TGFB at codon 25 (rs1800471), between patients and controls. A significant negative association was observed at the codon 10/CT (rs1982037) in the patient group (OR, 0.5; 95%CI, 0.27–0.93; $p = 0.026$). Further, a negative association was detected in patients with simple FS at same position (OR, 0.41; 95%CI, 0.18–0.93; $p = 0.03$), thus revealing a protective effects in FS patients. There was no significant difference in allelic and genotype frequency between simple and complex FS samples. Furthermore, haplotype analysis revealed significant difference in frequency of TGFB/TC haplotype in comparison between complex FS patients and controls ($p = 0.048$).
Conclusion: Certain alleles, genotypes, and haplotypes in TGFB genes were over represented in patients with FS, which possibly could predispose individuals to this disease.

1. Introduction

Febrile seizure (FS) is the most common seizure in children with a prevalence of 2.5% [1]. The International League Against Epilepsy (ILAE) has defined FS as "elevated or rapidly rising fever of short duration associated with an uncomplicated seizure that does not predispose to epilepsy and is not accompanied by neurologic abnormalities, previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures in children between 6months and 5 years of age" [2]. Simple FSs are generalized tonic-colonic seizures lasting less than 15 min, only once in 24 h followed by a brief postictal period, whereas complex FS, lasting more than 15 min has focal features and multiple recurrences within 24 h and association with postictal neurological abnormalities, for example Todd paresis [3,4].

Many studies demonstrated that there is relevance between familial factors and occurrence of FSs; twin studies showed a higher occurrence rate in monozygotic with FS than dizygotic ones [5,1,6]. Several studies showed interaction between immune inflammatory system, cytokines and genetic factors, which are involved in FS [7–12].

IL-10 is a cytokine with multiple roles in inflammatory system. It is known to relay negative feedback signals that diminish the activated immune system after an inflammatory trigger [13]. Strausberg et al. reported that secretion of IL-10 was higher in the

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patients with history of convulsions [14]. Also, Nur et al. indicated that IL-10 production was increased in FS [15]. In a study of neonatal seizures, Youn et al. demonstrated that IL-10 was significantly elevated in plasma 48–72 h after seizure onset. They concluded the IL-10 levels surge 24–72 h after seizure onset may indicate the enhanced protective role of it as an anticonvulsant by suppressing proinflammatory cytokine production [16].

Transforming growth factor beta (TGFB) controls proliferation, cellular differentiation and many other functions in cells. Animal experiments showed TGFB up regulation as part of the inflammatory response in the brains of amygdala-kindled rats and the hippocampus of rats exposed to status epilepticus. These results indicate potential involvement of TGFB in epileptogenesis [17,18].

We studied IL-10 and TGFB SNPs in a number of diseases [19–26], but not FS. Meanwhile we have recently reported association of IL-4 and IL-6 SNPs with FS [8,27]. This study was conducted to find out the associations of allelic frequency of IL-10 at -1082, -819 and -592 positions (rs1800896, rs1800871, rs1800872) and TGFB at codons 10 and 25 (rs1982037, rs1800471) with FS in a group of Iranian patients.

2. Patients and methods

2.1. Participants

In this study, children with FS (simple and complex FS) who were referred to the Children's Medical Center Hospital, the Pediatrics Center of Excellence in Tehran, Iran, were enrolled. Informed consent was obtained from the parents of each individual before blood sampling, and the study was approved by the Ethics

Table 1
Comparison of allele and genotype frequency of IL-10 (-1082, -819, -592) polymorphisms between FS patients and controls.

Gene polymorphism	Alleles/genotypes	Patients $N=79$(%)	Controls $N=140$ (%)	Odds ratio (95% CI)	p-value
FS(simple and complex) and control					
-1082(rs1800896)	A	98 (63.6)	181 (64.6)	0.96 (0.62–1.47)	0.96
	G	56 (36.4)	99 (35.4)	1.04 (0.68–1.61)	1.04
	AA	27 (36)	53 (37.8)	0.92 (0.49–1.72)	0.92
	GA	42 (56)	75 (53.6)	1.1 (0.6–2.02)	1.1
	GG	6 (8)	12 (8.6)	0.93 (0.29–2.81)	0.93
-819(rs1800871)	C	113 (72.9)	199 (71.1)	1.1 (0.69–1.74)	1.1
	T	42 (27.1)	81 (28.9)	0.91 (0.58–1.45)	0.91
	CC	44 (57.9)	71 (50.7)	1.34 (0.73–2.44)	1.34
	CT	23 (30.3)	57 (40.7)	0.63 (0.33–1.19)	0.63
	TT	9 (11.8)	12 (8.6)	1.43 (0.52–3.88)	1.43
-592(rs1800872)	A	47 (31.8)	81 (28.9)	1.14 (0.73–1.8)	0.61
	C	101 (68.2)	199 (71.1)	0.87 (0.56–1.38)	0.61
	AA	9 (12.2)	12 (8.6)	1.45 (0.54–4)	0.55
	CA	29 (39.2)	57 (40.7)	0.94 (0.51–1.74)	0.94
	CC	36 (48.6)	71 (50.7)	0.92 (0.5–1.68)	0.88
Simple FS and control					
-1082(rs1800896)	A	46 (59)	181 (64.6)	0.79 (0.46–1.36)	0.43
	G	32 (41)	99 (35.4)	1.27 (0.74–2.19)	0.43
	AA	12 (32.4)	53 (37.8)	0.79 (0.34–1.81)	0.67
	GA	20 (54.1)	75 (53.6)	1.02 (0.46–2.24)	0.89
	GG	5 (13.5)	12 (8.6)	2.42 (0.67–8.45)	0.15
-819(rs1800871)	C	59 (74.7)	199 (71.1)	1.2 (0.66–2.2)	0.62
	T	20 (25.3)	81 (28.9)	0.83 (0.45–1.52)	0.62
	CC	24 (63.1)	71 (50.7)	1.67 (0.75–3.72)	0.23
	CT	9 (23.7)	57 (40.7)	0.45 (0.18–1.09)	0.08
	TT	5 (13.1)	12 (8.6)	1.62(0.46–5.43)	0.36
-592(rs1800872)	A	59 (74.7)	199 (71.1)	1.2 (0.66–2.2)	0.62
	C	20 (25.3)	81 (28.9)	0.83 (0.45–1.52)	0.62
	AA	24 (63.1)	71 (50.7)	1.67 (0.75–3.72)	0.23
	CA	9 (23.7)	57 (40.7)	0.45 (0.18–1.09)	0.08
	CC	5 (13.1)	12 (8.6)	1.62 (0.46–5.43)	0.36
Complex FS and controls					
-1082(rs1800896)	A	52 (68.4)	181 (64.6)	1.19 (0.67–2.11)	0.63
	G	24 (31.6)	99 (35.4)	1.84 (0.47–1.5)	0.63
	AA	15 (39.5)	53 (37.8)	1.07 (0.48–2.37)	0.99
	GA	22 (57.9)	75 (53.6)	1.19 (0.54–2.62)	0.77
	GG	1 (2.6)	12 (8.6)	0.29 (0.01–2.26)	0.3
-819(rs1800871)	C	54 (71.1)	199 (71.1)	1 (0.55–1.82)	0.89
	T	22 (28.9)	81 (28.9)	1 (0.55–1.81)	0.89
	CC	20 (52.6)	71 (50.7)	1.08 (0.5–2.35)	0.98
	CT	14 (36.8)	57 (40.7)	0.85 (0.38–1.89)	0.8
	TT	4 (10.5)	12 (8.6)	1.25 (0.32–4.57)	0.75
-592(rs1800872)	A	27 (36.5)	81 (28.9)	1.41 (0.79–2.5)	0.26
	C	47 (63.5)	199 (71.1)	0.71 (0.4–1.26)	0.26
	AA	5 (13.5)	12 (8.6)	1.67 (0.47–5.61)	0.35
	CA	17 (45.9)	57 (40.7)	1.24 (0.56–2.73)	0.7
	CC	15 (40.5)	71 (50.7)	0.66 (0.3–1.47)	0.36

*N, number of people in each group.