Role of SCN1A, GABRA1, and GABRA2 in pathogenesis of febrile convulsions

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Aim

The commonest seizure disorder in childhood are febrile seizures (FS). The aim of the study was to show the role of some genes (SCN1A, GABRA1, and GABRA2) in pathogenesis of the development of febrile convulsions.

Patients and methods

In total, 20 children from 6 to 60 months with FSs and 20 cross-matched healthy controls (regarding sex and age) were included in this study. Digital electroencephalogram was performed. The SCN1A (rs3812718 A/G), GABRA1 (rs2290732 A/G), and GABRA2 (rs 2298771 A/G) polymorphisms were analyzed by allelic discrimination Taqman assay.

Results and conclusion

Most of the patients developed FS at the age of 6 months–2 years (55%). About 40% of the patients had positive family history of FS. We did not find a significant difference between patients and controls in the three studied genes. Larger studies with a larger number of patients are needed to study these genes.

Keywords:
febrile seizures, children, genetic

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Introduction

Febrile seizures (FS) are convulsions associated with a rise in temperature during childhood that could result from affection of the immature brain by fever. FS occur in all ethnic populations. The definition of FS according to the American Academy of Pediatrics is seizure occurring in children with fever between 6 and 60 months without disturbance in metabolism, infection in the central nervous system, or history of seizures without fever [1].

FS occur in childhood classically from 6 to 60 months of age in association with fever that is usually more than 38°C (or ≥100.4 F) [2,3]. Head injury, infection, epilepsy, and metabolic abnormalities, for example, hypoglycemia, hyponatremia or hypernatremia, hypocalcemia, hypomagnesemia, and drug intoxication or withdrawal must be excluded before the diagnosis of FS. Also, no history of seizures without fever should be present [4–7].

FS is believed to occur due to the susceptibility of either the developing or immature brain to be affected by fever in association with genetic and environmental factors [8]. Boosted neuronal impulsiveness to fever during brain maturation process may make the seizure threshold lower and induces FS [9].

Studies showed that family history was positive in approximately one-third of children. With an affected sibling, the chance for febrile convulsion in a child is about 20%, while with an affected parent, the chance is about 33% [5,10]. The genetic predisposition to FSs can be mediated either through autosomal-dominant inheritance with reduced penetrance or multifactorial/polygenic factors [5,11–13].

The possibility of having FSs in monozygotic and dizygotic twins has been 35–69 and 14–20%, respectively [5,14]. The most commonly involved genes are SCNIA, IL-1β, CHRNA4, and GABRG2 [12]. There are several genetic loci responsible for increased risk of febrile convulsion and they include 1q31, 2q23–34, 3p24, 3q26, 5q14–15, 5q34, 6q22–24, 8q13–21, 18p11, 19p13, 19q, and 21q22 [5,11–16]. No causative gene was identified in most patients with FS.

About 80% of febrile convulsions occur with viral infection [8,13,17,18]. Other causes include otitis media, pharyngitis, and dysentery due to Shigella species [19,20]. Postvaccination fever such as diphtheria–tetanus–pertussis is another cause of FS [21].

Besides prenatal acquaintance to nicotine and alcohol [22], prematurity, intrauterine growth retardation, and postnatal treatment with corticosteroids are associated with high chance of having FS [23,24]. Either perinatal or prenatal exposure to stress and deficiency of iron, zinc, selenium, calcium, magnesium, folic acid, and vitamin B12 may have an effect on febrile convulsions owing to lowered seizure threshold [24–27]. Other contributory factors for FS include a past history of FS, first-degree relatives with a history of seizures, staying in a neonatal unit for more than 4 weeks, neurodevelopmental delay, and attending a daycare nursery [28,29].

FS can be classified as simple (80–85%) and (15–20%) complex [28]. A simple FS occurs with generalized tonic–clonic convulsion typically lasting for less than 5 min followed by postictal drowsiness of a minimal duration with no further attacks occurring within 24 h [5,7,30]. A complex febrile convulsion generally persists for more than 10 min, usually focal in nature (movement involved to a side of the body), and might reappear within 24 h with a longer duration of postictal drowsiness [5,30,31].

Aim

The aim of the study was to show the role of some genes [SCN1A (rs3812718 A/G), GABRA1 (rs2290732 A/G), and GABRA2 (rs 2298771 A/G)] in pathogenesis of development of febrile convulsions.

Patients and methods

The study included 20 children aging 6 months–5 years with generalized convulsions that occurred during 24 h of the onset of fever with no previous neurologic problems, intracranial infection, or metabolic disturbance. The control group, consisting of 20 cross-matched healthy individuals (regarding sex and age) with no history of epilepsy, neurological problems, intracranial infection, or metabolic disturbance, was collected from nonneurological clinic outpatients. Digital electroencephalogram (EEG) was performed.

Genomic DNA extraction from venous blood was done by a pure linked kit and the procedure recommended by the manufacturer (Vivantis Technologies Sdn Bhd, Revongen Corporation Centre, Setia Alam, Seksyen U13, Selangor Darul Ehsan, Malaysia). Extracted DNA was quantified using Nanodrop analyzer (ND-1OOO) spectrophotometer (Nanodrop Technologies Inc., Ortenberg, Germany). The SCN1A (rs3812718 A/G), GABRA1 (rs2290732 A/G), and GABRA2 (rs 2298771 A/G) polymorphisms were analyzed by allelic discrimination Taqman assay according to the manufacturer's protocol (850 Lincoln Centre Drive Foster City, CA 94404 USA). Genotyping were performed using real-time PCR with thermal profile (60°C for 30 s, 95°C for 10 min, 95°C for 15 s, and 60°C for 90 s).

Ethical considerations

The Committee of Medical Ethics, Faculty of Medicine, Assiut University, has reviewed and approved this study.

IRB no: 17200505.

Results

Table 1 shows demographic data among febrile convulsion patients and controls.

Fig. 1 shows birth-data season in studied patients' febrile convulsion.

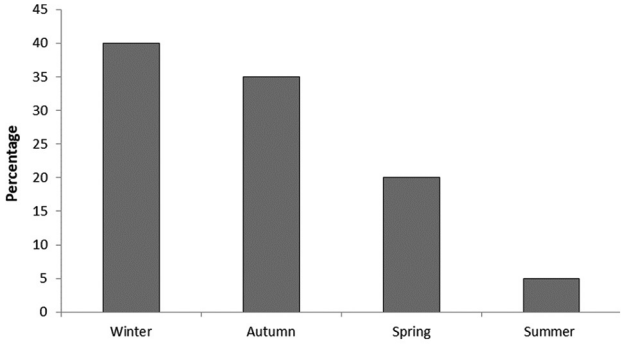
It was found that eight (40%) patients had positive family history of febrile convulsion, while positive consanguinity was presented in only one patient. Regarding obstetric history of the studied patients, all studied patients had normal pregnancy, neonatal

Table 1 Demographic data among febrile convulsion patients and controls

	Patients (*n*=20)	Control (*n*=20)	*P*
Age group			
6 months-1 year	5 (25)	4 (20)	0.25
1-2 years	6 (30)	5 (25)	
2-3 years	2 (10)	5 (25)	
3-4 years	2 (10)	5 (25)	
4-5 years	5 (25)	1 (5)	
Sex			
Male	14 (70)	14 (70)	0.63
Female	6 (30)	6 (30)	

Data expressed as *n* (%). *P* value was significant if less than 0.05.

Figure 1



Birth-data season in studied patients' febrile convulsion.

period, and mental and physical development. All patients were full term, and born at the hospital. The first cry was delayed in only one patient. In total, 14 (70%) patients were born with cesarean section, while six (30%) patients were born by vaginal delivery. The majority (95%) of patients were fed with breast feeding and bottle feeding.

Table 2 shows the characteristics of convulsion in studied the patients with febrile convulsion.

Table 3 shows genetic studies in the studied groups.

Discussion

One of the commonest causes for emergency hospital admission for 0 day is FS [32]. In this study, 70% of both groups were males. Several studies showed that the incidence of FS is higher in males than females [33–35]. As regards age in our study group, 25, 30, and 25% patients were 6-months–1-year, 1–2-year, and 4–5-year old, respectively.

Our results agree with Aliabadi *et al.* [36] who studied 600 children, among them 21 had FS with incidence of about 3.5%. In total, 13 (61.9%) patients had the first FS during the first year of life, while eight (38.1%) patients had the first FS after the first year of life.

Our results also agree with many other studies, such as Sartori *et al.* [37], who studied 108 children (57 males, 51 females) presented by first convulsive seizure; 90.7% were 6-months–6-years old (median age 1 year 10 months, mean 2 years 7 months).

About 2.2–5% of all children develop at least one FS under the age of 5 years according to studies in the United States, Western Europe, and South America, and the incidence of FS is higher in other populations, for example, 7% in Japan, 14% in Guam [38].

In our study, we found that eight (40%) patients had positive family history of febrile convulsion, while positive consanguinity was presented in only one patient. Aliabadi *et al.* [36] found that family history

Table 2 Characteristics of convulsion in studied patients with febrile convulsion

		Febrile convulsion (*n*=20)
Grade of fever	High grade	8 (40)
	Low grade	12 (60)
Duration of fever before convulsion	>1 h	7 (35)
	<1 h	13 (65)
Type of convulsion	Partial with secondary generalization	5 (25)
	Tonic-clonic	15 (75)
Postictal state	0	
Recurrence	0	
Red-flag signs	0	
EEG	Normal	8 (40)
	Generalized spike waves	8 (40)
	Focal spike waves	2 (10)
Drug therapy	Sodium valproate	15 (75)
	Carbamazepine	2 (10)
	None	3 (15)

Data expressed as *n* (%). EEG, electroencephalogram.

Table 3 Genetic studies in the studied groups

	Febrile convulsion (*n*=20)	Control group (*n*=20)	*P*
SCN1A			
Homogeneous (CC, wild type)	3 (15)	5 (25)	0.60
Homogeneous (TT, mutant type)	4 (20)	5 (25)	
Heterogeneous (CT, carrier)	13 (65)	10 (50)	
GABRA1			
Homogeneous (CC, wild type)	5 (25)	6 (30)	0.62
Homogeneous (TT, mutant type)	5 (25)	7 (35)	
Heterogeneous (CT, carrier)	10 (50)	7 (35)	
GABRA2			
Homogeneous (CC, wild type)	4 (20)	0	0.09
Homogeneous (TT, mutant type)	7 (35)	7 (35)	
Heterogeneous (CT, carrier)	9 (45)	13 (65)	

Data expressed as *n* (%). *P* value was significant if less than 0.05.

of convulsions was positive in two (9.5%) out of 21 patients.

In our study, 40% of patients had high-grade fever and 60% had low-grade fever. This is in agreement with Jeong *et al.* [39] who found no association between the degree of fever and FS. Another study showed that higher incidence of FS was found in children with body temperature less than 39°C [33].

EEG was normal in eight (40%) patients, while generalized and focal spike presented in eight (40%) and two (10%) patients, respectively. Fung *et al.* [40] showed that 19 (65%) patients out of 29 had normal EEG. Generalized slowing was found in five EEGs and focal slowing was found in three EEGs. Two EEGs only showed epileptiform discharge and only one patient was diagnosed to have epilepsy and started antiepileptics. Cappellari *et al.* [41] found that the independent risk factor for FS recurrence may include pseudo-petit maldischarge pattern and when EEG is abnormal.

There was no significant difference between patients and controls regarding SCN1A. FS appear to be isolated and infrequent but they occur most often in a family setting. Kamoun *et al.* [42] collected 107 individuals with febrile with or without afebrile seizures. FS phenotype was found in 18 (60%) families, GEFS+ in seven (23.33%), and idiopathic generalized epilepsy in five (16.66%). Sequencing analyses of SCN1A found a known SCN1A mutation in GEFS + family.

Ma *et al.* [43] studied the frequencies of genotypes of CC, CT, and TT in SCN1A, a significant difference was found in the TT genotype frequency between the GEFS+ and the control group ($P < 0.05$). Also, a significant difference was found in the T-allele frequency between the two groups ($P < 0.05$).

In a large Hungarian study, Till *et al.* [44] represented the first genetic testing of the SCN1A gene in patients with GEFS+. Among the 63 patients with GEFS+, pathogen alterations of the SCN1A gene were found in 33 (52.4%) patients and in five asymptomatic relatives. In total, 12 previously described mutations were detected in 18 individuals and 15 novel mutations were detected in 17 participants.

Regarding GABRA1 gene, we did not find a significant difference between patients and controls. Many studies showed that either mild or severe generalized epilepsy may result from GABRA1 subunit loss of function through the regulation of the inhibitory neuronal network and early brain development [45–47]. Mutations in GABRA1 subunit may make an important contribution to the genetic cause of many epilepsy syndromes (either benign or severe) and FS [48].

Also, we did not find a significant difference between patients and controls regarding GABRG2 gene. In an Egyptian study, Salam *et al.* [49] suggested that the GABRG2 allele may be a genetic indicator for susceptibility to simple FS.

In a meta-analysis of eight studies (published between 2002 and 2011) on Asian, Europian, and American populations, the GABRG2 rs211037 genotype distribution in patients with epilepsy, FS, and healthy populations was assessed. The meta-analysis showed that rs211037 alone may be a risk factor for FS, partial seizure, and symptomatic epilepsy, and in linkage disequilibrium with rs210987 can contribute to FS and symptomatic epilepsy in Asians, particularly in Chinese [50].

Li *et al.* [51] found that deletion of GABRG2 is associated with genetic epilepsy with FSs and affects the GABAA receptor subunit expression.

The present study showed no agreement with previous studies due to different sample size and different gene expression. More studies are needed to show the association between single-nucleotide polymorphisms within the SCNA1, GABRG1, GABRG2 gene and FS, and the genotype–phenotype relationship in children with FS.

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Conflicts of interest
There are no conflicts of interest.

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