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ORIGINAL ARTICLE

Interleukin-1 receptor antagonist and interleukin-1β-511 gene polymorphisms among Egyptian children with febrile seizures

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Abstract Febrile seizures (FSs) are the most common form of childhood seizures. The higher levels of pro-inflammatory cytokines in children may induce seizures, and alternatively, higher levels of anti-inflammatory cytokines may act as a defense mechanism against seizures. We aimed to investigate whether interleukin (IL)-1β-511 C/T (pro-inflammatory cytokine) (rs16944) and IL-1 receptor antagonist (IL-1Ra) (an anti-inflammatory cytokine) gene polymorphisms could be used as markers for prediction of susceptibility to FSs. The current study included 22 patients with FSs and 22 normal control subjects. All patients were subjected to thorough history taking, full neurological examination, electroencephalography, and peripheral blood sampling for genotype analyses. Detection of IL-1Ra gene polymorphisms was done using polymerase chain reaction (PCR), while a restriction fragment length polymorphism analysis of the PCR products was used for the detection of IL-1β-511 C/T gene polymorphisms. The mean age of onset of first febrile seizures was 15.7 months. Eighteen (81.8 %) cases had the criteria of complex FSs. Frequencies of alleles C and T for IL-1β-511 were 26/44 and 18/44, respectively, in FS patients and 22/44 for both in the control subjects. The CC genotype was significantly more common in the FS patients than in the control group. The IL-1Ra-I homozygote was more frequent in patients with FSs than in healthy controls. The IL-1Ra homozygous I/I and IL-1β-511 CC gene polymorphisms are associated with a higher susceptibility to febrile seizures, which may be useful markers for predicting the development of febrile seizures.

Keywords Febrile seizures · Interleukin-1 receptor antagonist · Interleukin-1beta-511

Introduction

Febrile seizures (FSs) are the most common convulsive event in children before the age of 5 years, with both boys and girls being equally affected (Serdaroglu et al. 2009). FSs occur in 2 to 5 % of infants in Europe and North America and 6–9 % in Japan (Hauser 1994).

An FS is defined by the International League Against Epilepsy as a seizure in association with a febrile illness in the absence of a central nervous system infection, acute electrolyte imbalance, or any other acute neurological insults in children older than 6 months of age without prior afebrile seizures (Chou et al. 2010). The pathogenesis of febrile convulsions remains obscure. In fact, febrile seizures of children involve a complex interaction between the immune-inflammatory process, cytokine activation, and genetic factors (Tsai et al. 2002). Twin and family studies suggest that genetic factors may have an important effect on predisposition to febrile seizures. This underlying genetic predisposition, along with the association of fever with the seizures, suggests that some genes for the regulation of

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inflammatory processes and fever may play a role in the molecular pathogenesis of FSs (Tsuboi and Endo 1991; Berkovic et al. 1998; Haspolat et al. 2002). Cytokines are produced by peripheral monocytes and also by astrocytes and glial cells within the central nervous system (Tutuncuoglu et al. 2001). Interleukin 1 (IL-1) is the most important cytokine inducing fever. The action of endogenous IL-1 in the brain during fever is site-specific, with roles in the anterior hypothalamus, hypothalamic nucleus, and hippocampus. The genes of the IL-1 complex, which are located on chromosome 2q13, encode for three proteins: IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1Ra). Each of the genes is polymorphic, and there is evidence that certain alleles are associated with susceptibility to inflammation (Serdaroglu et al. 2009). A single nucleotide polymorphism has been identified at bp position −511 in the promoter region of the IL-1 β gene (Kira et al. 2005). The IL-1Ra gene has a penta-allelic polymorphic site in intron 2 containing variable numbers of an 86-bp tandem repeat sequence. IL-1RA binds to the IL-1 receptor that inhibits IL-1 α and IL-1 β binding. Because the effect of IL-1 β is countered by its endogenous antagonist IL-1RA, it is also considered to have an important role in inflammation (Serdaroglu et al. 2009). The underlying genetic predisposition and the association of fever with the seizures suggest that some genes responsible for the regulation of the inflammatory process and fever play a role in the molecular pathogenesis of FSs (Chou et al. 2010).

Aim

The aim of this study is to determine whether interleukin-1beta-511 promoter polymorphism (IL-1β-511 C/T) and IL-1Ra gene polymorphisms contribute to the susceptibility of FSs.

Subjects and methods

This study enrolled 22 Egyptian children (18 males and 4 females; age 2.62±1.15 years, mean±SD) diagnosed in the Pediatric Neurology subdivision of Fayoum University Teaching Hospital, from August 2010 till September 2011, as having febrile seizures. Twenty-two children, gender matched with cases, were assigned into the control group. They were recruited from outpatient clinic with negative history of any type of convulsions or any of the neurological disorders and living in Fayoum City, Egypt. The control subjects had no history of seizures or neurological disorders and were chosen from children older than 7 years of age, to lower the risk of febrile seizures during the study period. An informed consent was obtained from all parents of the patients and controls who donated their blood. The present study was approved by the Ethical Committee of Fayoum University Teaching Hospital.

Inclusion criteria were: patients aged 12 months to 6 years, the age of onset of the first febrile seizures ranged from 6 to 36 months, suffering from either simple (typical) febrile convulsion (fever with generalized tonic–clonic fit lasting less than 15 min and does not recur in the next 24 h), or complex (atypical) febrile convulsions (focal seizures lasting more than 15 min and recur in the same illness), and with complete normal neurological development. *Exclusion criteria* were: cases who had history of intracranial infections, cases diagnosed as cerebral palsy, cases with delayed motor or mental development, cases with previous attacks of afebrile seizures, and those who had FSs beyond 6 years which is known as febrile seizures plus.

All patients were subjected to thorough history taking focusing on the characteristics of FSs as regards the type, age of onset of seizures, duration, frequency, and a history of antiepileptic drug intake. The recruited patients were subjected to thorough general and full neurological examination and electroencephalography (EEG). All children underwent peripheral blood sampling for genotype detection.

Digital EEG

All patients were subjected to digital EEG at the Neuro-Pediatric Unit of Pediatric Department in Fayoum University Teaching Hospital. All EEGs were carried either under standard conditions or after sedative premedication as chloral hydrate in noncooperative children. The EEG machine parameters were adjusted before the record as follows: time constant 0.3 s; drawing speed 3.0 cm/s; and filter 75 Hz for EEG. The EEG tracing was analyzed as regards background activity and presence of generalized or focal epileptogenic discharges.

Genotyping

DNA purification All children underwent peripheral blood sampling for genotype analyses. Two milliliters of blood was collected in a tube containing ethylenediaminetetraacetate as an anticoagulant for DNA extraction and stored at −20 °C. Genomic DNA was isolated from peripheral blood leucocytes by means of a genomic DNA purification kit according to manufacturer's instructions (Fermentas Life Sciences, Lithuania).

IL-1Ra and IL-1β-511 C/T genotypes were determined as previously described (Zhang et al. 2007). Each polymerase chain reaction (PCR) reaction was carried out with 50 ng of genomic DNA, 20 pmol of each primer, 12.5 μl Master Mix (Dream Taq™, Green PCR Master Mix) (Fermentas Life Sciences, Lithuania) in a total volume of 25 μl. IL-1Ra genotyping was performed with the primer pair (forward, 5′-CTC AGC AAC ACT CCT AT-3′, and reverse, 5′-TCC TGG TCT GCA GGT AA-3′) (Bioneer, Korea) with initial denaturation at 94 °C for 4 min followed by 32 cycles of

94 °C for 1 min, 50 °C for 1 min, and 72 °C for 1 min with final extension at 72 °C for 10 min using a PCR Thermal Cycler (Thermo Hybaid, UK). PCR products were analyzed by electrophoresis on a 1.5 % agarose gel stained with ethidium bromide. Alleles 1–5 (IL1Ra 1–IL1Ra 5) were detected according to their sizes relative to a 100-bp DNA ladder: allele 1 (four repeats), 410 bp; allele 2 (two repeats), 240 bp; allele 3 (five repeats), 500 bp; allele 4 (three repeats), 325 bp; and allele 5 (six repeats), 595 bp (Fig. 1).

IL-1β-511 C/T genotyping was performed with the primer pair (forward, 5′-TGG CAT TGA TCT GGT TCA TC-3′, and reverse, 5′-GTT TAG GAA TCT TCC CAC TT-3′) (Bioneer, Korea) with initial denaturation at 95 °C for 1 min followed by 30 cycles of 95 °C for 30 s, 55 °C for 30 s, and 72 °C for 30 s with final extension at 70 °C for 7 min using a PCR Thermal Cycler (Thermo Hybaid, UK). PCR products were digested by restriction endonuclease Aval (Promega) and visualized by electrophoresis on a 3 % agarose gel stained with ethidium bromide. Alleles were coded as follows: T, 304 bp, and C, 190 and 114 bp (Fig. 2).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science version 17 (Chicago, USA). Data were subjected to Kolmogorov–Smirnov test to determine the distribution and method of analysis. Normally distributed quantitative variables are presented as mean±SD and the comparisons between groups were performed using Student's *t* test. Skewed data are expressed as median (range). Categorical variables are given as percentages. A chi-square test was used to compare the sex and gene polymorphism and each of consanguinity, frequency of seizures per year (more than five attacks per year), and positive family history of FSs. Genotype and allele distributions among cases and controls were compared using odds ratios and 95 % confidence interval. Allele frequencies were estimated by the gene counting method and expressed as a percentage of the total number of alleles. A p value of <0.05 was considered to represent statistical significance.

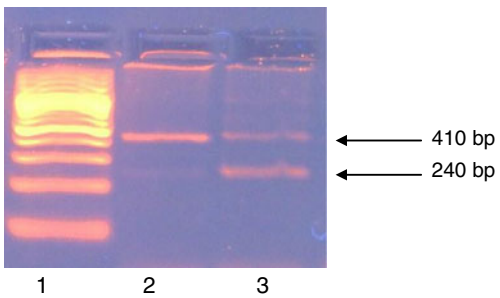

Fig. 1 Agarose gel electrophoresis of the IL-1Ra genotypes. *Lane1* 100 bp DNA marker. *Lane 2* IL-1Ra I/I (410 bp). *Lane 3* IL-1Ra I/II (410 and 240 bp)

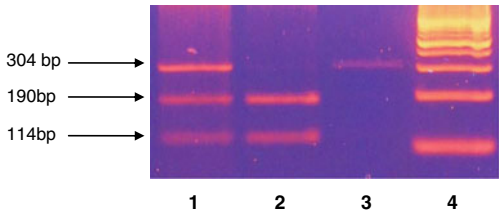

Fig. 2 Agarose gel electrophoresis of the IL-1β-511 genotypes. *Lane 1* CT genotype (304, 190, and 114 bp). *Lane 2* CC genotype (190 and 114 bp). *Lane 3* TT genotype (304 bp). *Lane 4* 100 bp DNA marker

Results

Twenty-two Egyptian children with FSs were recruited in the study. Clinical characteristics of the patient group are presented in Table 1.

The age of patients ranged from 12 months to 6 years, while the age of onset of first febrile seizures ranged from 6 and 36 months of age (mean±SD 15.7±7.6 months). The number of febrile seizures per year in the patient group ranged from 2 to 8 with mean±SD (4.9±2.1). Of the 22 FSs cases, eight cases (36.4 %) had more than two attacks of seizures in the same day. The average duration of the seizures was 6 min (3–20) (median; range).

Within normal EEG accounted for 14/22 (63.6 %), while 8/22 (36.4 %) had abnormal pattern in the form of either generalized slowing of postictal record or focal and multifocal epileptogenic activity. Regarding the medications, 17 FS cases (77.3 %) received antiepileptic therapy in the form of sodium valproate, while the remaining five cases (22.7 %) did not receive any treatment.

The distribution of the IL-Ra and IL-1β-511 promoter genotypes and allele frequencies in the patient group and control group are shown in Tables 2 and 3. Genotype proportions and allele frequencies for the IL-1Ra in both groups were significantly different between FS cases and the control group. The most common genotype for IL-1Ra gene in both groups was I/I. Allele I for IL-1Ra was associated with febrile seizures. The IL-1Ra I/I homozygote was more frequent in patients with FSs than in healthy controls (86.36 vs. 59.09 %, $p<0.05$). In addition, individuals homozygous for the IL-1 Ra I/I genotype were more than twice as likely to develop FSs as individuals heterozygous for the IL-1 Ra I/II genotype (odds ratio (OR), 4.385; 95 % confidence interval (CI), 0.993–19.356; $p<0.05$). IL-1Ra I/II genotype was significantly associated with resistance to febrile seizures (OR, 0.144; 95 % CI, 0.027–0.778; $p<0.05$).

There was no significant difference in the frequency of the IL-1β-511 TT genotype ($p>0.05$) between the FS patients and

Table 1 Clinical characteristics of febrile seizures patients and healthy control subjects

Characteristics	Febrile seizures (n=22)	Control subjects (n=22)
Age (years; mean±SD)	2.62±1.15	11.5±2.1
Gender		
Male, no. (%)	18 (81.82)	16 (72.73)
Female, no. (%)	4 (18.18)	6 (27.27)
Age of onset of first febrile seizure, months (mean±SD)	15.7±7.6	–
Age of presentation, months (mean±SD)	31.3±13.8	
Febrile seizure, number per year (mean±SD)	4.9±2.1	–
Duration of febrile seizures, minutes, median (range)	6 (3–20)	–
Family history of febrile seizures, no. (%)	6/22 (27.3)	–
Sporadic, no. (%)	16/22 (72.7)	
History of consanguinity, no. (%)	8/22 (36.4)	–
Simple febrile seizures, no. (%)	4/22(18.2)	–
Complex febrile seizures, no. (%)	18/22 (81.8)	–
Type of febrile seizures		
GTCs, no. (%)	19/22 (86.4)	
Focal, no. (%)	2/22 (9.1)	–
Atonic, no. (%)	1/22 (4.5)	
EEG findings		
Normal, no. (%)	14/22 (63.6)	
Abnormal, no. (%)	8/22 (36.4)	–
On treatment, no. (%)	17/22 (77.3)	–

GTCs generalized tonic–clonic seizures, *EEG* electroencephalography, *SD* standard deviation, *no*. number

controls. The percentage of CC genotype was more in the FS patients compared to the control group, while the percentage of the CT genotype was more in the control group compared

Table 2 Genotype and allele frequencies of IL-1Ra gene polymorphism in febrile seizure patients compared to the control group

	Febrile seizure cases (n=22)	Controls (n=22)	p value
IL-1Ra I/I genotype, no. (%)	19/22 (86.36 %)	13/22 (59.09 %)	<0.05
IL-1Ra I/II genotype, no. (%)	3/22 (13.64 %)	9/22 (40.91 %)	<0.05
I allele, no. (%)	41 (93.18 %)	35 (79.55 %)	<0.05
II allele, no. (%)	3 (6.82 %)	9 (20.45 %)	<0.05

p values for comparison of genotypes between cases and controls were calculated by means of a 2×2 contingency chi-square

no. number, *IL-1Ra* interleukin-1 receptor antagonist

Table 3 Genotype and allele frequencies of IL-1β-511 gene polymorphism in febrile seizure patients compared to the control group

	Febrile seizure cases (n=22)	Controls (n=22)	p value
CC genotype, no. (%)	8/22 36.36 %	2/22 9.09 %	<0.05
CT genotype, no. (%)	10/22 45.46 %	18/22 81.82 %	<0.05
TT genotype, no. (%)	4/22 18.18 %	2/22 9.09 %	>0.05
C allele, no. (%)	26 59.09 %	22 50 %	<0.001
T allele, no. (%)	18 40.91 %	22 50 %	<0.001

p values for comparison of genotypes between cases and controls were calculated by means of a 2×2 contingency chi-square

no. number, *IL-1β* interleukin 1-beta

to the FS patients. The IL-1β-511 CT and CC genotypes were associated with an odds ratio of 0.183 (95 % CI, 0.047–0.729) and 5.714 (95 % CI, 1.051–31.072), respectively, for FSs. FS patients with IL-1β-511 CC genotype were more than twice as likely to develop FSs. The presence of the C allele at IL-1β-511 increased the risk of FSs by more than twofold (odds ratio, 5.50; 95 % CI, 2.267–13.345).

There was a significant relationship between the CC and CT genotypes and the presence of positive consanguinity among the parents of our cases (p<0.001). And finally, we found a significant relationship between IL-1Ra I/I genotype and the frequency of seizures per year for those with more than five attacks per year (p<0.05; Table 4).

Discussion

Although an association between FSs and IL-1 β production has long been suspected, conflicting results have been reported (Tsai et al. 2002). In the present study, we investigated the role of IL-1β-511 C/T and IL-1Ra gene polymorphisms as risk factors for FSs.

The mean age at initial seizure was 15.7±7.6 months in the patient group, which is similar to age reported for simple FSs (19.7±11.2 months) in a previous study carried by Serdaroglu et al. (2009). A positive family history was found in 27.3 % of the FS children which agrees with Matsuo et al. (2006) who reported that a positive family history for FSs can be elicited in 25–40 % of patients with FSs.

Concerning the distribution of IL1Ra genotypes among our studied groups, the results of the present study show that the IL-1Ra allele I is associated with higher susceptibility to FSs and this is in agreement with the results of Tsai et al. (2002)

Table 4 Relationship between IL-1Ra and IL-1β-511 genotypes and each of positive consanguinity, positive family history of febrile seizures, frequency of seizures per day, frequency of seizure per year (more than five attacks per year), and duration of seizures among the febrile seizures subjects

	Positive consanguinity			Positive family history of FSs			Number of seizures/day			Number of seizures/year			Duration of seizures		
	Odds ratio	95 % CI	*p* value	Odds ratio	95 % CI	*p* value	Odds ratio	95 % CI	*p* value	Odds ratio	95 % CI	*p* value	Odds ratio	95 % CI	*p* value
IL-1Ra I/II genotype	1.86	0.10–34.44	NS (>0.05)	1.14	0.95–1.37	NS (>0.05)	1.18	0.94–1.49	NS (>0.05)	0.8	0.59–1.09	NS (>0.05)	1.86	0.1–34.44	NS (>0.05)
IL-1Ra I/I genotype	0.23	0.017–3.07	NS (>0.05)	0.71	0.05–9.7	NS (>0.05)	1.3	0.96–1.75	NS (>0.05)	0.70	0.47–1.05	<0.05	0.23	0.02–3.07	NS (>0.05)
IL-1β TT genotype	7.8	0.65–93.8	NS (>0.05)	0.87	0.07–10.42	NS (>0.05)	0.42	0.04–4.8	NS (>0.05)	1.5	1.00–2.24	<0.05	2	0.22–17.89	NS (>0.05)
IL-1β CT genotype	3.5	1.5–8.01	<0.001	2.2	0.32–14.97	NS (>0.05)	0.33	0.05–2.26	NS (>0.05)	3	0.49–18.17	NS (>0.05)	2.5	0.41–15.23	NS (>0.05)
IL-1β CC genotype	3.5	1.43–8.01	<0.001	0.5	0.07–3.5	NS (>0.05)	4.5	0.73–27.74	NS (>0.05)	1.4	0.26–7.6	NS (>0.05)	0.25	0.04–1.7	NS (>0.05)

p values for comparison of genotypes between cases and controls were calculated by means of a 2×2 contingency chi-square. Number of seizures per day: one attack and more than one attack. Frequency per year: less than five attacks per year and five or more than five attacks per year. Duration of seizures: less than 15 min and 15 or more than 15 min

IL-1Ra interleukin 1 receptor antagonist, *IL-1β* interleukin 1-beta, *95 % CI* 95 % confidence interval

and Chou et al. (2010). This is in contrast to the results of Serdaroglu et al. (2009) who reported that the frequency of both the IL1RaII/II genotype and the IL1RaII allele was significantly higher in the FS patient group than the controls.

Concerning the distribution of IL-1β-511 genotypes among our studied groups, our results show that the distribution of the IL-1β-511 TT genotype showed no significant difference between FS patients and controls. In agreement with the present findings, Tilgen et al. (2002), Haspolat et al. (2005), and Chou et al. (2010) reported no significant association between FSs in the studied German, Turkish, and Taiwanese populations, respectively, and IL-1β-511 polymorphism, indicating that it is not useful in predicting the susceptibility to FSs. In contrast to the present findings, Virta et al. (2002) and Serdaroglu et al. (2009) concluded that the distribution of IL-1β-511 genotypes and the allele frequency differed significantly between FS patients and the control group in the Finish and Turkish studied groups, respectively. They stated that the TT genotype was significantly more common in the patient group than in the control group. Virta et al. (2002) concluded that the T allele frequency was significantly higher in children with FSs. The inconsistent results may be attributed to different illness classification, ethnic variation, and local environmental factors. Interaction between environment and gene may play an important role and the inconsistent results may be due to the fact that not all studies listed the inclusion criteria of cases; in some studies, cases were matched to controls according to age, sex, ethnicity, and so on, but others were not (Wu et al. 2012).

Our results show that FS patients with IL-1β-511 CC genotype were more than twice as likely to develop FSs. Santtila et al. (1998) reported that IL1Ra allele II strongly increased in vitro production of IL1 β, regardless of the presence or absence of IL-1β-511. They stated that IL-1β-511 T allele had a slight but nonsignificant elevated capacity to produce IL-1β in vitro. The results of Tsai et al. (2002) suggested that the IL-1Ra allele *II* as well as the increased production of IL-1β might play a role in preventing febrile convulsions. Addas-Carvalho et al. (2004) stated that IL-1β-511 T polymorphism enhanced IL-1β production. From the present results, which showed that patients with IL-1Ra allele I and IL-1β-511 CC genotype were more than twice as likely to develop FSs, and those of previous studies, we can speculate that if IL1Ra allele II and IL-1β-511 T allele increase the IL-1β production, therefore increased IL-1β levels prevent febrile convulsions. In agreement, Matsou et al. (2006) had documented significantly increased IL-1Ra/IL-1 β ratios among FS patients.

Wen et al. (2006) concluded that IL-1β-511 SNP leads to an increased expression of the encoded protein as a result of enhanced gene transcription. However, this activity seems to be dependent on the haplotype context of the promoter

region of IL-1β. Chen et al. (2006) demonstrated that the IL-1β-511 T allele strongly enhanced the transcription of the IL-1β gene in the context of the IL-1β-31 C allele. These findings highlight the importance of understanding the haplotype structure of populations used for genetic studies (Kauffman et al. 2008).

Chou et al. (2010) suggested that the balance between IL-1β and IL-1Ra during seizures plays a significant role in altering neuronal network excitability, thus affecting the maintenance and spread of seizures. However, several studies speculated that IL-1β may play a role in FSs by direct action on ionic currents or indirectly by enhancing extracellular glutamate concentrations or reducing GABAA receptor function (Zeise et al. 1997; Kamikawa et al. 1998; Wang et al. 2000).

In the present study, there was no statistically significant relationship between IL-1Ra and IL-1β-511 genotypes and the presence of family history of FSs among the studied group of patients. On the other hand, there was a significant relationship between IL-1β-511 CC and CT genotypes and the presence of positive consanguinity among the parents of our patients that may suggest the presence of genetic factors. This is in contrast to the results that showed that the frequency of IL-1β-511 T allele was significantly increased in sporadic simple FS patients as compared with controls (Kira et al. 2010). We found a significant relationship between IL-1Ra I/I with the frequency of seizures per year for those with more than five attacks per year suggesting that the increased frequency may reveal the pivotal role of genetic factors. There was no significant association between IL-1Ra and IL-1β-511 genotypes and seizure duration and this is in agreement with the results of Serdaroglu et al. (2009).

Historical records show that the Egyptian population is one that has undergone genetic admixture and racial mixing, which created a heavily mixed population of modern Egyptians including several ethnic groups such as Bedouins, Peasants, Nubians, Berbers, and Urbanites (Shahin et al. 2011). Fayoum is a city in middle Egypt situated 130 km southwest of Cairo and all the participants were chosen from this town to allow for homogeneity. To our knowledge, this is the first study investigating the contribution of IL-1Ra and IL-1β-511 gene polymorphisms in the pathogenesis of FSs in a group of Egyptian children.

It is necessary to perform a large-scale, multicenter, case–control study before setting a final statement on the role of IL-1β and IL-1Ra gene polymorphisms in FSs. However, our present study provides evidence of association between the IL-1Ra I/I and IL-1β-511 CC genotypes and FSs pointing to the role of these loci in contribution to FS susceptibility in the studied group of Egyptian patients from Fayoum City.

Conclusion

In conclusion, our study suggests that IL-1Ra I/I and IL-1β-511 CC genotypes are positively associated with FSs. They may be used as useful markers for predicting susceptibility to FSs. In contrast, FSs are not associated with IL-1β-511 TT genotype. These data suggest that cytokine genes may act as enhancers or attenuators of FS susceptibility. If so, there may be a potential role for therapy targeting cytokines as a novel therapeutic strategy to prevent or limit FSs or subsequent epileptogenesis in the vulnerable, developing nervous system of children. Furthermore, the impact of other cytokine polymorphisms on the development of FSs merits further study.

Limitations of the study

We performed our study on a small sample of FS patients from Fayoum City. Indeed, the number of cases in almost all previous studies was also small. Thus, we recommend a large, multicenter, case–control study including thousands of cases to confirm the association between the IL-1Ra I/I and IL-1β-511 CC genotypes and FSs in the Egyptian population.

Conflict of interest The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

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