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Interleukin-1β-511 and interleukin-6 gene polymorphisms in Egyptian children with febrile seizures

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Abstract: Purpose: to determine whether interleukin-1β-511 promoter polymorphism (IL-1β-511 C/T) and Interleukin-6 gene polymorphism (_597) (IL-6), contribute to the susceptibility of Febrile Seizures (FS). **Method:** A case-control study was conducted on 91 children. It included 49 patients with FS and 42 healthy control subjects. They were subjected to full medical history, general and neurological examination and E.E.G. IL-1β (_511) polymorphism and IL-6 (_597) polymorphism genotyping by RFLP (Restriction fragment length polymorphism) were done for all participants. **Results:** Twenty-six patients (53.1%) had complex FS. IL-1β (_511) gene polymorphism and IL-6 (_597) gene polymorphism were more statistically significant in FS. IL-1β (_511) gene polymorphism was more sensitive specific and accurate in FS than IL-6 (_597) gene polymorphism. **Conclusions:** Our data support the contention that interleukin-6 and Interleukin-1β single-nucleotide polymorphisms play a role in the etiopathogenesis of febrile seizures. Neither Interleukin-1β (_511) gene polymorphism nor interleukin-6 (_597) gene polymorphism is affected by type of FS (whether simple or complex).
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1. Introduction

The most frequent form of childhood seizures happening in 2%-5% of children younger than 6 years old is febrile seizures. Regarding prevalence there are no geographical, racial, or ethnic differences. [1]

The etiopathogenesis of febrile seizure is unidentified. The main risk factor is family history of febrile seizure, and the risk is greater when more relatives are affected. [2] Actually, febrile seizures of children involve a composite collaboration between genetic factors, immune-inflammatory process and cytokine activation. [3] Proinflammatory and anti-inflammatory cytokines (interleukin-1, interleukin-6, and tumor necrosis factor) have significant role in the regulation of febrile responses. [4]

In patients with febrile seizures, Plasma interleukin-1 receptor antagonist/interleukin-1β ratio and plasma interleukin-6 levels were significantly higher. [5] [6]

The production of cytokines is changed by polymorphisms in side genes coding inflammatory cytokines. [5]

Thus, the association between these polymorphisms and febrile seizures in Egyptian children can be revealed by the study of different polymorphic regions of the interleukin -1-β or interleukin-6 gene.

Aim of the work

The aim of this study is to determine whether interleukin-1β-511 promoter polymorphism (IL-1β-511 C/T) and IL-6 gene polymorphism (_597 G>A) donate to the susceptibility of FSs.

2. Materials and methods:

Patients:

The study was conducted in neuro-pediatric clinic at Fayoum University hospital. It included 49 patients with history of febrile seizures who were subdivided into two groups:

a) Twenty two patients with simple (typical) febrile convulsion (fever with generalized tonic–clonic fit lasting less than 15 min and does not recur in the next 24 hours).

b) Twenty two patients with complex (atypical) febrile convulsions (focal seizures lasting more than 15 min and recur in the same illness).

c) Five patients were excluded due to failure of genotyping.

Forty four children, gender and geographic location of origin matched with cases, were assigned into the control group. They were recruited from

outpatient clinic and pediatric department at Fayoum university hospital with negative history of any type of seizures or any of the neurological disorders.

The control patients were chosen from children older than 7 years of age, to lower the risk of febrile seizures during the study period. The study was conducted from Jan 2017 till December 2017.

Inclusion criteria:

The age of onset of the first febrile seizures ranged from 6 months up to 5 years with complete normal neurological development.

Exclusion criteria:

Patients who had history of intracranial infections, cases diagnosed as cerebral palsy, cases with delayed motor or mental development and cases with previous attacks of a febrile seizures.

Study design:

The study design is a case-control study.

The Patients were subjected to full history taking, full general examination and thorough regional examination (cardiac, chest, abdominal and neurological examination).

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 (quick-gDNA™ MiniPrep catalog No. D3024kit).

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 (MyTaq™ Red Mix Kits (Catalog No. BIO-25044)) (Fermentas Life Sciences, Lithuania) in a total volume of 25 µl.

IL-1β-511 C/T genotyping was performed with the primer pair (forward, 5′-TGG CAT TGATCT GGT TCATC-3′, and reverse, 5′-GTT TAG GAATCT TCC CAC TT-3′) (Bioneer, Korea) with initial denaturation at 95 °C for 1min 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 (ThermoHybaid, 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.

IL-6-597 A/G genotyping was performed with the primer pair Primer pair (forward, 5′-GGGGCTGCGATGGAGTCAGAG and reverse, 5′-TCCCTCACACAGGGCTCGAC). (fermentas). The computerized thermocycler was programmed for the following conditions:

Thirty-five cycles of amplification were performed (30 seconds at 95°C, 45 seconds at 59°C, and 60 seconds at 72°C). The products of the polymerase chain reaction were then digested FokI (NewEngland Biolabs) for _597 at 37°C for 3 hours. PCR products were digested by restriction endonuclease FokI (NewEngland Biolabs) and visualized by electrophoresis on a 3 % agarose gel stained with ethidium bromide. Alleles were coded as follows: in the presence of a G allele, digestion with FokI results in no digestion (162 base pairs), whereas the prescence of a C allele results in fragments of 47 bp and 115 bp.

Electroencephalography (EEG):was done for all patients: All EEG were carried either under standard conditions or after sedative premedication as chloral hydrate in non-cooperative children. The EEG machine parameters were adjusted before the record as follows; time constant 0.3 seconds; drawing speed 3.0 cm / seconds; filter 75 Hz for EEG. Bipolar as well as referential montages were applied. The EEG tracing was analyzed as regards; background activity, presence of generalized or focal epileptogenic discharges.

Statistical analysis of data:

The collected data were organized, tabulated and statistically analyzed using SPSS software statistical computer package version 18 (SPSS Inc, USA). For quantitative data, the **mean, median, standard deviation (SD)**, and **inter-quartile range (IQR)** were calculated. **Kolmogorov-Smirnov test (KS)** test was performed as a test of normality; age of children was not a normally distributed variable, so **Mann-Whitney-U test** was used as a test of significance to compare between study groups as regard age.

Qualitative data were presented as **number** and **percentages**, **chi square (χ^2)** was used as a test of significance.

Sensitivity, specificity & total accuracy measures of genotypes in differentiating cases from control were presented as % with (95% CI) and calculated using OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01.

For interpretation of results of tests of significance, significance was adopted at **$P \leq 0.05$**.

Ethical Consideration:

This study was reviewed by the Faculty of Medicine Research Ethical Committee. The researcher was informed the participants about the objectives of the study, examination, investigation that were done. Also, we explained the confidentiality of their information and their right not to participate in the study. Written consents were taken from all patients.

3. Results:

The study included 49 children with history of febrile seizures, 27 boys (55.1%) and 22 girls (44.9%) with mean age 3.3 years + SD 1.6. 34.7% patients had positive consanguinity with statistically significant association with febrile seizures. (P value < 0.0001) History of febrile seizures in the family was reported in 28.6% of patients with statistically significant association with febrile seizures. (P value < 0.0001) 40.8% of our patients had age of onset between the ages of 1-2 years of old. The characteristics of febrile seizures were demonstrated in table (1) regarding frequency, duration of fit, description of fit, consciousness during fit, recurrence during the same illness and type of FS.

Twenty six of our patients had characteristic of complex febrile seizures. Four of them were excluded due to failure of genotyping. Ten patients (45.4%) had recurrent seizures during the same illness. Two of them (9.09%) had focal seizures. Ten patients (45.4%) had prolonged febrile seizures (more than 15 minutes).

Forty one (83.7%) patients had normal EEG, 2 patients (4.1%) had epileptogenic activity and 6 patients (12.2%) had generalized slowing. The characteristics of seizures among the case group are demonstrated in Table 1.

In Group I (Febrile seizures): 17 (34.7%) patients had positive consanguinity. Fourteen patients (28.6%) had family history of febrile seizues. In group II (control group): No one had positive consanguinity nor family history of febrile seizures. There was significant association between consanguinity and history of febrile seizures among Group I (febrile seizures).

The frequency of IL-1 β 511 genotype was significantly different in the CT allele between cases and controls. (P value 0.001). Also, there was significant difference in the AG allele between cases and controls in the frequency of IL-6 (_597) genotype. (P value 0.004) as presented in table 2.

Table (1): The characteristics of seizures among the case group.

Variable	N	%
Frequency:		
Within 1 month	**9**	**18.4**
1-3 months	**14**	**28.6**
3-6 months	**12**	**24.5**
> 6 months	**14**	**28.6**
Duration of fit:		
< 5 minutes	**16**	**32.7**
5-15 minutes	**14**	**28.6**
> 15 minutes	**19**	**38.8**
Description:		
GTC*	**46**	**93.9**
Other	**3**	**6.1**
Conciosness during fit:		
Disturbed conscious level	**46**	**93.9**
Normal conciousness	**3**	**6.1**
Group:		
Simple	**23**	**46.9**
Complex	**26**	**53.1**
Recurrence during the same illness:		
Not recurrent	**30**	**61.2**
Recurrent	**19**	**38.8**

Table (2):Distribution of genotype frequencies among the studied groups

Variable	Cases (N=45)	Controls (N=41)	P-value#
	N (%)		
IL-1 β 511:			
CC	**9 (20.0)**	**24 (58.5)**	0.001*
CT	**27 (60.0)**	**11 (26.8)**	
TT	**9 (20.0)**	**6 (14.6)**	
IL-6_597:			
GG	**13 (28.9)**	**5 (12.2)**	0.004*
AG	**23 (51.1)**	**14 (34.1)**	
AA	**9 (20.0)**	**22 (53.7)**	

It's noticed that sensitivity of IL-1 β 511 was 60% and specifity was 73.2% with total accuracy 66.3%. While in IL-6_597, sensitivity was 51.1% and specifity was 65.9% with total accuracy 58.1%. So according to table 3, IL-1 β 511 is more sensitive, specific and accurate than IL-6_597.

Table (3): Accuracy of genotypes

	Sensitivity % (95% CI)	Specificity % (95% CI)	Total accuracy % (95% CI)
IL-1 β 511	**60.0 (45.5-72.9)**	**73.2 (58.1-84.3)**	**66.3 (55.8-75.4)**
IL-6_597	**51.1 (37.0-65.0)**	**65.9 (50.6-78.4)**	**58.1 (47.6-68.0)**

The allele frequencies of IL-1 β (_511) gene polymorphism and IL-6 (_597) gene polymorphism were statistically significant in cases than controls with P value (0.003, 0.001 respectively) as shown in table 4.

Table (4):Genotype and allele frequencies of IL-1β (_511) gene polymorphism and IL-6 (_597) gene polymorphism in febrile seizure patients compared to the control group:

Variable	Cases (N=45)	Controls (N=41)	OR (95% CI)	P-value#
	N (%)			
IL1β 511:				
T	**45 (50.0)**	**23 (28.0)**	2.565 (1.360-4.839)	0.003*
C	**45 (50.0)**	**59 (72.0)**		
IL6 597:				
G	**49 (54.4)**	**24 (29.3)**	2.888 (1.536-5.429)	0.001*
A	**41 (45.6)**	**58 (70.7)**		

There was no significant difference between sex, consanguinity or positive family history and age of onset of febrile seizures of case group and genotypes (IL-1 β 511 and IL-6 (_597) gene polymorphisms).

There was no significant difference between frequency, duration of fit, type of seizures (simple or complex) or recurrence during the same illness in the case group and IL-1 β 511 and IL-6 (_597) gene polymorphisms. However, there is significant difference between focal seizures and IL-1 β 511 gene polymorphism (CC pattern) (P value 0.015) but no significant relation with IL-6 (_597) genotype. There was significant association between high fever (>39^{o}C) and IL-6_597 gene polymorphism (GG and AG patterns). (P value 0.015) but there was no association with IL-1 β 511 genotype.

There was no relation between patients receiving antiepileptic treatment and IL-1 β 511 gene polymorphism and IL-6 (_597) genotype. There was no statistical significance between EEG findings and IL-1 β 511 gene polymorphism and IL-6 (_597) genotype.

There was statistical significance between the characteristics of complex seizures and IL-1β 511 gene polymorphism. (P value 0.037) However, No statistical significance was detected with IL-6 (_597) genotype.

The results of IL-1β 511 gene polymorphismis shown in figure 1.

4. Discussion

In this study, 34.7% patients had positive consanguinity with statistically significant association with febrile seizures. This percentage was higher than ***Dalbem et al. in 2015***[7] who stated that all his FS patients had negative consanguinity. Also higher than ***Renda et al. in 2017*** [8] who reported that 25.8% positive consanguinity. That's may be attributed to traditional thoughts in our region about consanguineous marriage.

History of febrile seizures in the family was reported in 28.6% of patients with statistically significant association with febrile seizures. That was slightly higher than ***Sadlier and Scheffer 2007*** [9] However, it was lower than ***Eseigbe findings in 2012***[10] ***and Hwang et al. 2015.*** [11]

Twenty six (53.1%) of our patients had complex febrile seizures. Only 9% had focal seizures, 45% had prolonged fits more than 15 minutes and 45% had recurrent convulsions during the same illness. ***Abdel Rasol et al. 2012***[12] reported that 86.4% of their patients had GTC, 9.1 % had focal convulsions and only 4.5% had atonic convulsions.

This was not similar to ***Sadlier and Scheffer*** in ***2007***[9] who reported prolonged FS in only 9%. It did not agree with ***Behmanesh et al. in 2012***[13] who listed that patients with seizures longer than 15 minutes was 6.6% and complex seizures in only 20%.

Forty one (83.7%) of our patients had normal EEG, 4.1% showed epileptogenic activity while 12.2% had generalized slowing. In contrast to ***Kanemura et al. 2012***[14] who reported paroxysmal abnormality on EEG in 21.8% of his patients. And ***Abdel Rasol et al. 2012***[12] who listed that 63.3 % of their patients have normal EEG and 36.4% had abnormal EEG.

LI et al 2017[15] stated that EEG abnormalities were detected in 35 children (68.6%), including 8 children (15.7%) with epileptiform abnormalities and 27 children (52.9%) with nonspecific abnormalities.

In our study, there was significant difference between patients and controls in the frequency of CT alleles of IL-1 β 511 genotype (60% vs 26.8%). In contrast to us, ***Abdel Rasol et al. 2012***[12] found that there was no significant difference in the frequency of the IL-1β-511 TT genotype (p>0.05) between the FS patients and controls and that 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 to the FS patients.

In contrast to the present findings, ***Tilgen et al. in (2002)*** [16], ***Haspolat et al. in (2005)*** [17]**,** ***Chou et al. in (2010)*** [18]***and Abdel Rasol et al. in 2012*** [12]reported no significant association between FSs in the studied German, Turkish, Taiwanese and Egyptian populations, respectively, and IL-1β (_511) polymorphism, indicating that it is not useful in predicting the susceptibility to FSs. However, other studies concluded that the distribution of IL-1β-511 genotypes and the allele frequency differed significantly between FS patients and the control group. ***(Virta et al., 2002)*** [6] ***(Serdaroğlu et al., 2009)*** [19] ***(Al Morshedy et al., 2017)*** [20]. They stated that the TT genotype was significantly more common in the patient group than in the control group. ***Virta et al. (2002)*** [6] concluded that the T allele frequency was significantly higher in children with FSs.

In this work, allele frequencies of IL-1 β (_511) gene polymorphism was 50% for C allele and 50% for T allele, showing odd ratio 2.565 and that was statistically significant in cases group. That was in agreement with ***Abdel Rasol et al. 2012.*** [12] In contrast to us ***Al Morshedy et al. 2017***[20] reported no statistical difference.

The inconsistent results may be attributed to ethnic variation, local environmental factors and different illness classification. Interface between environmental and genetic factors might play an important role and the varying results may be due to the fact that not all studies registered 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)*** [21]

In our study, there was no significant relation between IL-1β (_511) gene polymorphism and positive consanguinity. In contrast to ***Abdel Rasol et al. in 2012***[12] who found highly significant relation.

In this work, there was significant relation between IL-1β (_511) gene polymorphism and description of seizure (CT and TT with GTC with p value 0.015). However, other studies reported no relation. (***Dalbem et al. in 2015)*** [7] (***Abdel Rasol et al. in 2012)*** [12].

No significant relation was found between IL-1β (_511) gene polymorphism and seizure duration, type of seizure (simple or complex) and history of febrile seizures in the family among patients which was consistent with other studies. ***(Virta et al., 2002)*** [6] ***(Dalbem et al. in 2015)*** [7] ***(Abdel Rasol et al. in 2012)*** [12] ***(Haspolat et al., 2005)*** [17] ***(Chou et al., 2010)*** [18] ***(Serdaroğlu et al., 2009)*** [19]

In our study, there was significant difference between patients and controls in the frequency of AG alleles (patients 51.1% Vs34.1%). In agreement with ***Nur et al. 2012***[5] ***and Azab et al. 2016.*** [22] However, ***Chou et al. 2010***[18] did not detect any association between interleukin-6 promoter gene polymorphism and febrile seizures in Taiwanese population.

In this study, allele frequencies of IL-1 6 (_597) gene polymorphism was 54.4% for G allele and 45.6% for T allele, showing odd ratio 2.888 and that was statistically significant in cases group. That was in agreement with ***Nur et al. in (2012)*** [5] On the other hand ***Azab et al. 2016***[22] ***reported*** no significant difference.

No significant association was evident between IL6 (_597) genotype and positive family history of febrile seizures or positive consanguinity among studied patients. This was matched with ***Azab et al. 2016.*** [22]

Also, there was no association between IL-6 (_597) genotype and complex FS or duration of seizure. This was concordant with ***Nur et al. 2012***[5] and ***Azab et al. 2016.*** [22]On the other hand they reported significant association between this genotype and complex FS.

Differences in age; geographic/ethnicity, study design or by gene-gene or gene-environmental interactions may explain the differences between our study and previously published studies. Several variants in multiple gene loci play an important role in the genetic predisposition to febrile seizures.

In the present study, we found that IL-1β (_511) gene polymorphism is more sensitive, specific and accurate than IL-6 (_597) gene polymorphism in diagnosing and predicting FS.

It's worth mentioning that only few studies had focused over the association between IL-6 genotypes and FS. Only our study compared IL1-β (_511) genotype and IL-6 (_597) genotype in the Egyptian children.

However, more studies are needed regarding cytokine profiles and genotypes of children with febrile seizures for a definite conclusion.

However, one of the limitations of this study is the small sample sizeso, we recommend that multicenter approaches may be necessary to obtain larger sample size.

Conclusions:

Interleukin-1β (_511) gene polymorphism and interleukin-6 (_597) gene polymorphism play a role in the etiopathogenesis of febrile seizures.

Interleukin-1β (_511) gene polymorphism is more sensitive, specific and accurate for diagnosis and prediction of febrile seizures.

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