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Original Article

From Febrile Seizures to Epilepsy: *IL-1β (-511)* and *IL-10 (-1082)* Gene Polymorphisms

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ABSTRACT

Aim: The etiology of febrile seizures (FS) is multifactorial, including genetic, immunological, and inflammatory components. The primary objective of this research was to assess the relationship between *IL-1β* (*-511*) and *IL-10* (*-1082*) gene polymorphisms and the likelihood of recurrent FS and subsequent epilepsy in pediatric patients.

Materials and Methods: In this study, we retrospectively reviewed data from 44 patients diagnosed with FS. We employed restriction fragment length polymorphism-polymerase chain reaction (PCR) and amplification refractory mutation system-PCR techniques in order to detect genetic variations in the IL-1β (-511) and IL-10 (-1082) loci. The study population underwent long-term follow-up for an average of 13±5 years to evaluate the correlations between these polymorphisms and clinical prognoses, specifically FS recurrence and the onset of epilepsy.

Results: In the IL-1β (-511) region, no significant association was found between G/A, A/A, or G/G polymorphisms and FS recurrence (p=0.131) or epilepsy development (p=0.407). Likewise, the G allele at the IL-10 (-1082) position showed no meaningful correlation with epilepsy risk (p=0.378). However, the presence of the A allele at the locus in question was found to be significantly associated with the development of epilepsy (p=0.002). Carriers of the A allele exhibited a 10.8-fold increased risk of epilepsy compared to non-carriers (odds ratio=10.8; 95% confidence interval: 2.04-57).

Conclusion: Our data indicate that the IL-10 (-1082) A allele serves as a significant predictor for epilepsy susceptibility after FS. These results highlight the potential role of cytokine gene variations, especially IL-10, in determining the long-term neurological prognosis of children with FS.

Keywords: Febrile seizures, genetic polymorphism, interleukin-1 beta, interleukin-10

Introduction

Febrile seizures (FS) constitute a common pediatric neurological emergency with a male predominance; although typically benign, their underlying pathogenesis remains incompletely understood (1,2). FS are generalized seizures which occur with a fever (>38 °C) in children between 6 months and 5 years of age and are not caused by central nervous system (CNS) infection or metabolic imbalance (3). Approximately half of children with FS manifest their initial episode between 12-30 months of age, whereas only 6-15% experience seizure onset beyond four years of age. Typical symptoms include altered consciousness, limb movements and ocular signs (4).

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FS are among the most prevalent neurological disorders in childhood, with an incidence ranging from 2% to 5% (3,5). FS are the most common convulsive disorder of childhood, with a recurrence probability of 33% (6). High recurrence rates and incidence are commonly associated with early age of onset, prolonged seizure duration, positive family history, and convulsions occurring at lower body temperatures (6,7). Furthermore, several factors such as a family history of FS and early age at onset have been identified as significant risk factors for recurrence in the Turkish pediatric population (6). Moreover, studies have indicated a familial predisposition to FS, with 20-33% of patients reporting a family history of the condition (8). Reported recurrence rates after the first seizure range widely from 15% to 70%, whereas approximately 5.4% of these children eventually develop epilepsy (9). FS evaluation primarily consists of the characterization of its type (either simple FS or complex FS) (10).

A prolonged FS (more than 5 minutes) may eventually lead to febrile status epilepticus (FSE). FSE accounts for 25-52% of pediatric status epilepticus (11). Securing intravenous access represents an essential intervention during prolonged FS in order to facilitate the administration of rescue anticonvulsants and maintain adequate hydration status (3). Multiple factors confer elevated risk for epileptogenesis in children, including atypical seizure semiology, persistent electroencephalographic abnormalities, neurodevelopmental impairment, and positive familial epilepsy burden (5). Brief FS rarely induce neuronal injury, with prolonged events showing minimal neuropathological correlation in most pediatric cases. Core prevention relies on timely fever mitigation (10).

The pathogenesis of FS involves a complex interaction of genetic, immune, and inflammatory factors (12,13) Inflammatory processes are primarily triggered by fever, where pro-inflammatory cytokines such as interleukin-1 beta (*IL-1β*), IL-6, and tumor necrosis factor-alpha are produced within the brain and play a central role in seizure generation (12). These cytokines stimulate prostaglandin E2 synthesis in the hypothalamus, elevating the thermal set-point. Crucially, the susceptibility to FS is determined by the balance between these pro-inflammatory mediators and anti-inflammatory cytokines, including *IL-10* and IL-1 receptor antagonists (*IL-1Ra*) (13). Genetic variations in these cytokine genes may alter an individual's inflammatory response to infection, thereby influencing the neuronal excitability threshold (13). Furthermore, biochemical alterations such as decreased serum zinc levels during febrile episodes have been proposed as contributing to the underlying mechanisms of convulsions (12). Additionally, ion channel variations and the resulting neuronal hyperexcitability further complicate the etiopathogenesis of FS (14).

This study aimed to investigate the associations between cytokine gene polymorphisms and the risk of recurrence of FS and epilepsy development in those patients with FS who presented with *IL-1β* (*-511*) and *IL-10* (*-1082*) gene polymorphisms.

Materials and Methods

Ethical approval for this research was granted by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 749, date: 31.10.2018), and this study was performed in compliance with the STROBE statement. Written informed consent was obtained from the parents or legal guardians of all of the pediatric participants included in this study. All procedures were conducted in accordance with the principles of the Declaration of Helsinki, ensuring data privacy and confidentiality throughout the 13-year follow-up period.

This cohort study is based on an article published in 2012 by Nur et al. (15). This retrospective analysis included 92 pediatric cases presenting with their initial FS episode at the Pediatric Emergency Service and Pediatric Neurology Outpatient Clinic of Akdeniz University Faculty of Medicine Hospital. For genetic evaluation, the IL-1β (-511) polymorphism was identified via restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR), while the IL-10 (-1082) region was analyzed using the amplification refractory mutation system-PCR technique. A new study was created from the original study which stemmed from the previous study by Nur et al. (15) The new cohort included 44 pediatric patients selected retrospectively from electronic medical records, all of whom had been diagnosed with FS and who carried *IL-1β* (*-511*) and *IL-10* (*-1082*) gene polymorphisms.

Participants were included in this study if they met the following criteria:

(1) they had experienced one or more FS and had received a diagnosis of FS,

(2) they had undergone genotyping for IL-1β (-511) and IL-10 (-1082) variants,

(3) they had been followed up for at least three years, and

(4) they had experienced their first FS episode between 6 and 60 months of age.

Patients who met any of the following criteria were not included in this study.

(1) the presence of other neurological disorders which could cause seizures, such as CNS infections, intoxication, or acute electrolyte imbalances;

(2) inadequate clinical or genetic data in the electronic medical records;

(3) a follow-up duration of less than three years; or

(4) a lack of genetic analysis for *IL-1β* (*-511*) and *IL-10* (*-1082*) gene polymorphisms.

Statistical Analysis

Statistical processing was conducted using IBM SPSS Statistics for Windows, version 23.0 (SPSS Inc., Chicago, IL, United States). The normality of data distribution was assessed via the Kolmogorov-Smirnov test, while Levene's test was utilized to verify the homogeneity of variances. Continuous variables following a normal distribution are expressed as mean ± standard deviation, whereas non-normally distributed data are presented as medians (minimum-maximum). Categorical variables are reported as frequencies and percentages (n, %). In order to examine differences between independent groups, the Student's t-test was used for data meeting parametric assumptions, while the Mann-Whitney U test was applied for data not meeting these assumptions. Categorical data were compared using either the Pearson chi-square test or Fisher's exact test. Relationships between variables were assessed with Pearson or Spearman correlation analyses, according to the distribution characteristics. Statistical significance was set at $p<0.05$.

The distribution of IL-1β (-511) and IL-10 (-1082) genotypes was tested for Hardy-Weinberg equilibrium using the chi-square test in order to ensure the representativeness of the study population.

Results

A total of 44 patients with FS were evaluated for this study. Table I summarizes the demographic and clinical findings of the cases.

In the whole cohort, for the IL-1β (-511) region, G/A polymorphism was detected in 31 patients (70%), A/A polymorphism in 6 (14%), and G/G polymorphism in 7 (16%). In the IL-10 (-1082) region, G/A polymorphism was identified in 22 patients (50%), A/A polymorphism in 6 (14%), and G/G polymorphism in 16 (36%).

In the group with recurrent FS, in the IL-1β (-511) region, polymorphism frequencies were 77% for G/A, 9% for A/A, and 15% for G/G. In the G/A region, FS recurrence occurred in 84% of those patients with G/A polymorphism, 50% of those with A/A polymorphism, and 71% of patients with G/G polymorphism. However, there was no statistically significant difference between FS recurrence and the presence of polymorphisms in the IL-1β (-511) region (p=0.131).

In the subgroup analysis of those patients with recurrent FS, the distribution of genotypes in the IL-10 (-1082) region was as follows: 56% carried the G/A genotype, 15% carried the A/A genotype, and 29% carried the G/G genotype. Statistical analysis revealed no significant correlation between the occurrence of FS recurrence and the presence of these specific polymorphisms at the IL-10 (-1082) locus (p=0.219).

A statistically significant difference was identified between epilepsy risk and IL-10 (-1082) polymorphisms (G/A, A/A, and G/G). Bonferroni correction indicated that G/A and A/A polymorphisms yielded a higher probability of developing epilepsy compared to G/G polymorphism (Table II).

The associations between genetic polymorphisms in the IL-1β (-511) and IL-10 (-1082) regions and the development of epilepsy following FS are detailed in Table II.

Table I. Demographic and clinical characteristics of patients with FS (n=44)

Characteristic	**n (%)**
Total cases	44 (100)
Age	
≤18 months	25 (57)
>18 months	19 (43)
Male	25 (57)
Female	19 (43)
Term	40 (90)
Preterm	2 (5)
No data (gestational age)	2 (5)
Family history of FS	13 (30)
Family history of epilepsy	7 (16)
Consanguineous marriage	
Yes	3 (7)
No	16 (36)
Unknown	25 (57)
Simple FS	32 (73)
Complicated FS	8 (18)
Unknown FS type	4 (9)
One-time FS	10 (23)
Recurrent FS	32 (73)
Unknown recurrence	2 (4)
Neurodevelopmental delay	4 (8)

FS: Febrile seizures

Table II. The comparison of the groups with epilepsy versus no-epilepsy in follow-up with respect to IL-10 (-1082) and IL-1β (-511) genetic polymorphisms

Polymorphism (Position)	Epilepsy status	Genotype	n (%)	p value
IL-1β (-511)	Epilepsy (+) n=19	G/A A/A G/G	15 (48) 1 (17) 3 (43)	p=0.407
	Epilepsy (−) n=25	G/A A/A G/G	16 (52) 5 (83) 4 (57)	
	Generalized Epilepsy n=8	G/A A/A G/G	7 (47) 1 (100) 0 (0)	p=0.228
	Focal Epilepsy n=11	G/A A/A G/G	8 (53) 0 (0) 3 (100)	
IL-10 (-1082)	Epilepsy (+) n=19	G/A A/A G/G	13[a] (59) 4[a] (67) 2[b] (13)	***p=0.006**
	Epilepsy (−) n=25	G/A A/A G/G	9 (41) 2 (33) 14 (87)	
	Generalized Epilepsy n=8	G/A A/A G/G	7 (54) 1 (25) 0 (0)	p=0.478
	Focal Epilepsy n=11	G/A A/A G/G	6 (46) 3 (75) 2 (100)	

*Chi-square test result with Bonferroni correction indicates significant differences, marked by different letters

No statistically significant association was found between carrying the A allele genotype in the IL-1β (-511) region and the development of epilepsy after FS (χ^2=0.62; p=1.00; Table III).

No statistically significant association was found between carrying the G allele genotype in the IL-10 (-1082) region and the development of epilepsy after FS (χ^2=2.16; p=0.378; Table III). Patients without the G allele genotype in this region showed a higher likelihood of epilepsy predisposition compared to those with the G allele genotype.

A statistically significant association was found between carrying the A allele genotype in the IL-10 (-1082) region and the development of epilepsy after FS (χ^2=2.84; p=0.002; Table III). Patients with the A allele genotype in the IL-10 (-1082) region were found to have a 10.8 times higher likelihood of epilepsy predisposition compared to those without the A allele genotype [Odds ratio (OR)=10.8; 95% confidence interval (CI): 2.04-57].

Table III. Relationship between the alleles identified for the IL-10 (-1082) and IL-1β (-511) regions and the development of epilepsy following FS

Region	Allele	Epilepsy (+) n (%)	Epilepsy (−) n (%)	χ^2; p value
IL-1β (-511)	G A	18 (47) 16 (43)	20 (53) 21 (57)	χ^2=0.012 p=0.213 χ^2=0.62 p=1.00
IL-10 (-1082)	G A	15 (40) 17 (61)	23 (60) 11 (39)	χ^2=2.16 p=0.378 χ^2=2.84 **p=0.002**

*Chi-square test result with Bonferroni correction indicates significant differences, marked by different letters
FS: Febrile seizures

Discussion

Analysis revealed a significant correlation between the IL-10 (-1082) polymorphism and the risk of developing epilepsy following FS (p=0.006). Polymorphism in the IL-10 (-1082) region manifested a statistically significant difference in epilepsy susceptibility among the G/A, A/A, and G/G genotypes.

Previous studies have examined cytokine levels and gene polymorphisms in FS (7,16). However, a research gap exists in investigating the prevalence and risk factors for long-term FS recurrence and epilepsy development in those patients with cytokine gene polymorphisms. Han et al. (14) argued against the routine application of genetic testing for all FS cases, instead emphasizing the need for close clinical monitoring. They suggested that genetic evaluations should be specifically reserved for those children who manifest complex FS, develop subsequent a FS, or suffer from accompanying neurodevelopmental disorders (14).

A study conducted by Haspolat et al. (17) using the enzyme linked immunosorbent assay (ELISA) method revealed a significant increase in cerebrospinal fluid IL-1β and nitrite levels in children with FS. In another study by Virta et al. (18) conducted in Finland using the RFLP-PCR method, FS patients exhibited an increased prevalence of the second allele of IL-1β (-511). Additionally, in a study conducted by Al Morshedy et al. (19) in Egypt using the RFLP-PCR and ELISA methods, the presence of the T allele or TT genotype in the IL-1β (-511) promoter region and the IL-1RA II/III genotype in FS patients were identified as risk factors. However, in a study conducted by Chou et al. (20) in Taiwan using the RFLP-PCR method, no significant difference was observed in IL-1β promoter, exon 5 regions, and *IL-10* gene polymorphism between an FS group and a control group.

For the IL-10 cytokine, in a study conducted by Virta et al. (18) using the ELISA method, while there was no significant increase in plasma IL-10 levels in those patients with FS compared to the control group, a noteworthy increase in the plasma IL-1RA/IL-1β ratio was observed (20). Research by Nur et al. (21), using the RFLP-PCR and ELISA methods, demonstrated an increased prevalence of the IL-10 (-1082) G allele genotype in FS patients. Children with previous FS manifested a significantly enhanced peripheral blood IL-1β and IL-10 synthesis; however, no statistical relationship was observed between the increased cytokine synthesis and IL-1β (-511) and IL-10 (-1082) genotypes (21).

Although the association between the IL-10 (-1082) A allele and epilepsy risk was statistically significant (OR=10.8), its clinical application should be interpreted with caution due to the small sample size and retrospective design of this study. These findings suggest that genetic screening could potentially aid in identifying high-risk children for closer neurological monitoring; however, larger prospective multi-center trials are necessary in order to validate these markers before routine clinical implementation.

Study Limitations

The present study had several limitations. First, the sample size was relatively small (n=44), which constrained the feasibility of a robust formal power analysis and may have limited the statistical power to detect weaker associations, particularly regarding IL-1β polymorphisms. The wide confidence interval observed for the risk of epilepsy associated with the IL-10 allele (95% CI: 2.04-57) reflects an imprecision in the effect estimate, which is a direct consequence of the limited cohort size. Second, this study was conducted at a single tertiary center, which may restrict the generalizability of our findings to other populations with different genetic backgrounds. Third, the retrospective design relies on the accuracy of medical records, which inherently carries the risk of missing data or recall bias regarding specific seizure details or family histories. Additionally, while the long-term follow-up (average 13±5 years) is a significant strength of this study, the inclusion of cases with a minimum follow-up of only three years might be a relatively short window for observing all potential cases of late-onset epileptogenesis. Finally, our genetic evaluation focused specifically on IL-1β and IL-10 polymorphisms; however, the pathogenesis of FS and epilepsy involves a complex network of numerous other cytokines and ion channels which were not evaluated in this research.

Conclusion

This study highlights a significant association between the IL-10 (-1082) A allele and the risk of epilepsy following FS, suggesting a potential genetic marker for potential epilepsy development related to FS. In contrast, IL-1β (-511) polymorphisms showed no clear link to seizure recurrence or epilepsy development. These findings underscore the role of certain cytokines gene variations in epileptogenesis and warrant further investigation in larger cohorts.

Ethics

Ethics Committee Approval: Ethical approval for this research was granted by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 749, date: 31.10.2018).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of all of the pediatric participants included in this study.

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Footnotes

Authorship Contributions

Concept: A.A., S.A., B.N., Ş.H., Design: A.A., S.A., B.N., Ş.H., Data Collection or Processing: A.A., S.A., Ş.H., Analysis or Interpretation: B.N., Ş.H., Literature Search: A.A., S.A., B.N., Ş.H., Writing: A.A., S.A., Ş.H.

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