

A Comparative Analysis of Serum Interleukin-6 Levels in Children with Febrile Seizures and Febrile Controls

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Abstract

Background Febrile seizures (FSs) are the common presentations of seizures in childhood. Activation of cytokine network plays a significant role in the genesis of FSs. Interleukin (IL)-6 is often considered as key cytokine in the generation of FSs.

Objectives To compare the serum IL-6 levels in children between simple febrile seizures (SFSs) and febrile controls (FCs).

Materials and Methods This hospital-based prospective cross-sectional study was conducted in JSS Hospital, Mysuru, during a period of 21 months. A total of 83 children were included in the study. Out of which, 38 were cases of SFSs and 45 were FCs without seizures. Serum IL-6 levels were estimated in both SFS and FC groups.

Results Serum IL-6 levels were increased among children with SFSs (mean = 608.15 pg/mL) when compared with FCs (mean = 342 pg/mL), but the results are not statistically significant ($p = 0.165$). In SFS and FC groups, percentage of subjects with IL-6 levels >50 pg/mL is 31.6 and 44.4%, respectively ($p = 0.16$).

Conclusion Serum IL-6 levels are higher in children with SFSs compared with FCs. However, this difference did not reach statistical significance.

Keywords

- ▶ simple febrile seizures
- ▶ cytokines
- ▶ IL-6

Introduction

Febrile seizures (FSs) are one of the most common clinical presentations in pediatric emergency department. FS commonly occurs in 5 to 14% of children between 6 months and 6 years of age in Asian countries.¹ FS is classified into simple febrile seizures (SFSs) and complex febrile seizures (CFSs) depending on the age, frequency, duration, and type of seizures.¹ SFS accounts for 70 to 75% of FS and CFS occurs in 9 to 35%.¹ Recurrent FS can cause behavioral cognitive impairment, language disability, and motor dysfunction.¹

The exact pathophysiology of FS is still elusive.² Cytokine cascade is the final pathway for development of fever in any infection. Tumor necrosis factor- α , interleukin (IL)-1 β , and IL-6 are the proinflammatory cytokines which cause fever, whereas IL-1 receptor antagonist and IL-10 are anti-inflammatory cytokines which have an inhibitory action over the febrile response.^{3–5} FSs may be triggered by proinflammatory cytokines.⁴ Intranasal administration of human IL-6 in rats increased the severity of seizures, indicating that there could be a proactive role of IL-6 in augmenting seizures.⁶ The balance between pro- and anti-inflammatory cytokines is

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known to be important in modulating fever and hence favors the argument of their role in genesis of FS.^{3,7} Advancement in molecular biology has led to increased interest in identifying the biomarkers for predicting or diagnosing FS.¹ IL-6 is often considered as key cytokine in the generation of FSs.⁵ However, the published scientific literature has often failed to support this view as the results of IL-6 role in FS is inconsistent among various studies across the world.^{1-4,7,8} Early prediction and intervention in FS is of great importance to reduce neurological sequelae in affected children. Therefore, this study was undertaken to compare the levels of serum IL-6 levels in children with FSs and febrile controls (FCs).

Materials and Methods

This hospital-based prospective cross-sectional study was conducted in JSS Hospital, Mysuru, from January 2019 to October 2020. The sample size was calculated based on the prevalence of FS of 4%,⁸ margin of error of 5%, alpha of 5%, and confidence interval of 95%. We needed minimum of 30 subjects in each group constituting a total sample size of 60 children. Children between 6 months to 5 years of age presenting with first episode of simple FSs formed the study group (FS = 38). Age- and gender-matched febrile children without seizures formed the control group (FC = 45). Children with a history of febrile convulsions, congenital anomalies, and developmental delay were excluded. Ethical committee clearance was taken from JSS University Ethical Committee. A written consent was taken from the parents of cases and controls. IL-6 levels were estimated by DIALsource IL-6-ELISA Kit (manufactured by DIALsource ImmunoAssays S.A., Belgium). Details of clinical features and investigations were entered in the pro forma. Statistical methods were done using SPSS 22.0 version for windows. Summary statistics were done by means of proportions for categorical/binary variables and mean, median, standard deviation, and interquartile range for continuous variables. Independent *t*-test was used to check for association between mean of different variables.

Results

The study included 83 children (38 cases and 45 controls). Age, gender, and etiological distribution of study group are shown in ►Table 1. The baseline parameters between FS and FC groups were comparable. Although serum IL-6 values are

Table 1 Demography of the study group

	Simple febrile seizures group, N = 38	Febrile control group, N = 45	p-Value
Age category (months)			
6-12	8 (21%)	11 (24.4%)	0.16
12-24	13 (34.2%)	10 (22.2%)	
24-36	10 (26.4%)	6 (13.3%)	
36-48	4 (10.5%)	8 (17.7%)	
48-60	3 (7.9%)	10 (22.2%)	
Gender			
Male	23 (60.5%)	29 (64.6%)	0.44
Female	15 (39.5%)	16 (35.6%)	
Etiology			
Acute respiratory infection	30	35	
Pneumonia	2	3	
Dengue fever	1	2	
Urinary tract infection	1	1	
Gastroenteritis	1	4	
Acute otitis media	3	0	

elevated in FS group (608.15 pg/mL) compared with FC group (342 pg/mL), the difference is not statistically significant with a *p*-value of 0.165 (►Table 2). In FS and FC groups, percentage of subjects with IL-6 levels > 50 pg/mL is 31.6 and 44.4%, respectively (*p* = 0.23; ►Table 2).

Discussion

Our study revealed that serum IL-6 levels are elevated in children with simple FSs when compared with FCs; however, it is not statistically significant (*p* = 0.165). Across the world, the difference between IL-6 levels in children with FSs and fever without seizures has shown conflicting results.^{1-4,7-9} Similar to our study, Choi et al observed that serum IL-6 levels in FSs were increased 1.8-fold

Table 2 Comparison of IL-6 levels between simple febrile seizure and febrile control groups

	Mean (pg/mL)	Standard deviation	Standard error mean	p-Value	IL-6 > 50 pg/mL	IL-6 < 50 pg/mL	p-Value
IL-6							
Simple febrile seizures (N = 38)	608.1579	1,004.22851	162.90738	0.165	12 (31.6%)	26 (68.4%)	0.23
Febrile controls (N = 45)	342.0000	777.79584	115.94696		20 (44.4%)	25 (55.6%)	

Abbreviation: IL, interleukin.

when compared with FCs, but it was not statistically significant ($p = 0.07$).⁴ Güven et al also found no significant difference ($p = 0.66$) in serum IL-6 levels between FS and FC groups which is similar to our study.⁷ In contrast to the results of earlier studies, some of the studies have shown the IL-6 to be significantly elevated in children with FSs.^{1-3,5,9} Contrary to earlier studies, one study from Northern India found significantly lower levels of serum IL-6 in children with FSs compared with FCs.^{8,9} They hypothesized that low serum IL-6 levels could be due to consumption of ILs in the genesis of FSs.⁸ Chen et al observed significantly higher levels of IL-6 in the FS group than in the FC and healthy control (HC) groups. However, there was no statistical difference between the FC and HC groups in the same study.¹ Study by Azab et al revealed significantly higher serum IL-6 levels in FS group than in the FC and HC groups.⁵ In CFS group, serum and CSF IL-6 levels were significantly higher when compared with the SFS group. They concluded that raised serum IL-6 levels can distinguish febrile children who are susceptible to develop seizure.⁵ Virta et al detected IL-6 in CSF in all 16 FS children. They suggest that in FS, elevated serum cytokine levels and detectable cytokine levels in CSF could be a cause for seizure, or they are produced as a consequence of seizure activity.^{3,5} However, CSF IL-6 was not done in our study. Inconsistencies among the various studies might be explained by the etiology of fever, ethnicity, geographic variations, age differences, timing of blood sampling, study design, or by gene-environmental interactions.⁸ Cytokine genes polymorphisms may have effect on the cytokine production and could influence the pathogenesis of FSs. Meta-analysis by Chen et al revealed that IL-6 polymorphisms (-572, -174, -597) were more susceptibility to FSs.¹⁰

An important factor that could explain the variations in the results of all the studies discussed could be due to lower half-life of IL-6. IL-6 half life is very short (20–60 minutes) and is rapidly cleared from plasma.² Therefore, time of blood sampling in children with FSs would have resulted in IL-6 levels variations seen in many studies.

Limitation

To establish the base values, IL-6 levels estimation was necessary after 14 days after the episode of FS.

Conclusion

Even though serum IL-6 levels were elevated among simple FSs children when compared with FCs, the results are statistically not significant. To reach robust conclusions, there is a need for high-quality clinical trials.

Authors' Contributions

G.K., H.C.K.K., and K.J.K. substantially contributed to the conception and design of the work, preparation and finalization of the draft, drafted the work, and revised it critically for important intellectual content. H.C.K.K., K.J.K., T.A., and M.V.G. substantially contributed to the acquisition, analysis, and interpretation of data for the work. G. K., H.C.K.K., K.J.K., T.A., and M.V.G. helped in the final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest

None declared.

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