

## Serum Interleukin-6 Levels in Children with Febrile Seizures

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**Objectives:** To compare levels of Interleukin-6 (IL-6) in children with febrile seizures and febrile controls. **Methods:** Study conducted in a tertiary-care hospital in Northern India from November 2013 to April 2015, enrolling 160 children (80 each with febrile seizures and febrile controls), aged 6 – 60 months. Serum IL-6 estimated by ELISA method. Iron study done as per standard technique. All the cases of febrile seizure were followed up at 1 week, 3 months and 6 months for recurrence of seizures. **Results:** The mean serum IL-6 levels in children with febrile seizures was 62.0 (63.9) pg/mL and febrile controls was 86.9 (70.6) pg/mL ( $P=0.025$ ). **Conclusion:** Serum IL-6 levels were significantly lower in children with febrile seizures as compared to febrile controls.

**Keywords:** Cytokines, Inflammation, Iron profile.

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The exact etiology and pathogenesis of febrile seizures is not known [1]. Studies have shown alterations in levels of pro-inflammatory cytokines like IL-6 and anti-inflammatory cytokines like IL-4 in febrile seizures, which may play an important role in its pathogenesis [2-4]. Previous studies have shown a conflicting role of IL-6 in febrile seizures. Some studies have shown the epileptogenic role of IL-6 in febrile seizures [3,4], a study on mice has shown antiepileptic role of serum IL-6 via adenosine receptors [5]. Iron deficiency anemia has also been found to be associated with febrile seizures [6,7].

These studies have not been carried out in Indian population and they have variable results; hence, this study was planned to measure and compare the levels of serum IL-6 levels in children with febrile seizures as compared to febrile controls, and to correlate IL-6 levels with iron indices.

### METHODS

This study was conducted in a tertiary-care hospital in Northern India from November 2013 to April 2015. Sample size of 80 in each group was calculated based on previous study by Choi, *et al.* [4], to detect a difference of 20 pg/mL in IL-6 levels with a power of 80% and alpha of 0.05. Ethical clearance was obtained from IEC of our institute. Written informed consent was obtained from the guardian of the child.

Children diagnosed as febrile seizure were enrolled

from the emergency department, within 24 hours of a seizure. Eighty children with temperature  $>38$  °C of duration  $\leq 2$  days with minor febrile illness without present or past history of seizures were enrolled as controls from out-patient department. These children were sex- and age- matched. We excluded children with previous history of any seizure disorder, congenital anomalies and developmental delay and/or any chronic illness. Clinical examination and blood samples for complete blood picture, iron profile, blood culture/sensitivity and serum IL-6 were done in all children.

Serum IL-6 was estimated by ELISA Diaclone human IL-6 Elisa kit. Children with iron-deficiency anemia were treated with iron supplementation and dietary advise upto 3 months of correction of anemia. All the cases of febrile seizure were followed up at 1 week, 3 months and 6 months after enrolment for the recurrence of seizure.

**Statistical analysis:** Statistical analysis was performed using SPSS for Windows, version 20.0. The clinical characteristics and hematological parameters were compared using *t* test for quantitative data and chi-square test for qualitative data. Serum IL-6 levels were compared between the study subjects using Mann Whiney U test. Spearman rho test was used to find the correlation of serum IL-6 levels with clinical and hematological parameters.

### RESULTS

All the children with febrile seizures belonged to 6

months to 5 years of age (61.2% males), out of which 41 (51%) presented in the first two years of life. Mean age of cases was 25.1 (12.8) months, and 25 (31.2%) had complex febrile seizure. Generalized seizures were seen in 78 cases, whereas only 2 cases had partial seizure. Seizure occurrence within first 24 hours of fever was seen in 20% cases, and 21% had multiple seizures in the first 24 hours of fever.

Mean serum IL-6 levels in children with febrile seizure were 62.0 (63.9) pg/mL vs 86.9 (70.57) pg/mL in controls ( $P=0.025$ ). There was no statistically significant difference in hematological parameters between the two study groups (**Table I**).

There was a significant negative correlation between serum IL-6 with serum iron and transferrin saturation in children with febrile seizures (**Fig. 1**). On long term follow up, recurrence of febrile seizures was seen in 19 (24%) cases. Serum IL-6 levels did not vary significantly with recurrence of febrile seizure in 6 months follow up ( $P=0.7$ ).

**DISCUSSION**

In this cross-sectional study with a comparator group, the mean serum IL-6 levels in children with febrile seizures were significantly lower than age- and sex-matched febrile controls. Our results are in contrast with previous studies [2-4], that have shown higher levels of pro-inflammatory cytokines in children with febrile seizures as compared to febrile controls. Wide variation in levels of serum IL-6 has been seen in previous studies, that may be due to the difference in time of sampling, cause of fever, genetics or geographical variation. The variation in

**TABLE I** STUDY PARAMETERS IN CHILDREN WITH FEBRILE SEIZURES AND FEBRILE CONTROLS

Parameters	Febrile seizures (n=80)	Febrile Controls (n=80)
*Serum IL-6 (pg/mL)	62.05 (63.88)	86.95 (70.57)
Hemoglobin (g/dL)	9.8 (1.41)	9.6 (1.75)
Serum iron (µg/dL)	40.1 (18.78)	44.3 (24.38)
Serum ferritin (pg/mL)	17.4 (16.58)	26.9 (43.06)
TIBC (µg/dL)	386.5 (56.69)	400.4 (317.66)
Transferring saturation (%)	12.0 (8.64)	13.9 (15.89)

$P=0.025$ , Rest all  $P>0.05$ ; TIBC: Total iron binding capacity.

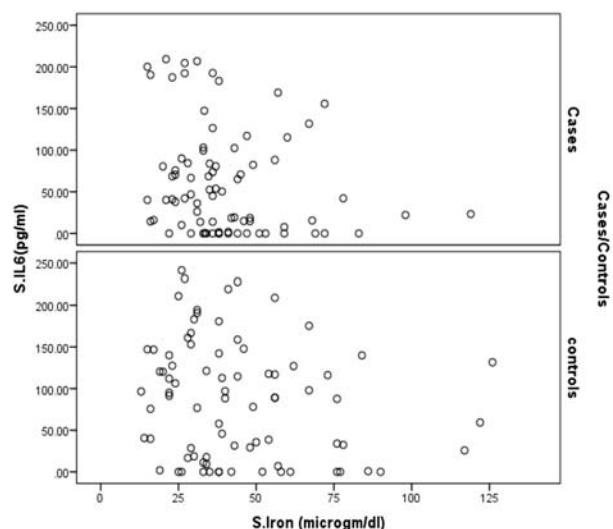
mean serum IL-6 levels between the two groups was less in our study as compared to previous studies.

No previous human study revealed lower levels of cytokines in febrile seizures compared to febrile controls. None of the previous studies were in Indian settings. The cause of fever may be different in different clinical setting and different geographical areas. Another reason for low serum IL-6 levels in children with febrile seizures in present study could be the possibility of consumption of cytokines in the genesis of febrile seizures.

There have been conflicting reports on influence of IL-6 on febrile seizures in recent years. In a study on developing rats [5], IL-6 had anticonvulsive effect by acting *via* adenosine receptors. On the other hand, IL-6 in adult rats was shown to exacerbate the severity of seizures [8]. Some of the animal studies demonstrated that IL-6 deficient mice had higher aspartate levels, whereas some had deficient GABA-mediated neuro-transmission, both leading to increased epileptogenesis [9,10].

The level of serum cytokines may vary with the time gap between the fever onset and collection of serum sample. Straussberg, *et al.* [3] studied LPS-stimulated polymorphs to estimate the production of IL-6 in children with febrile seizures as compared to the febrile controls. They estimated the pro-inflammatory cytokine IL-6 levels after two weeks of the febrile event, as it was presumed that the patient will be in a steady state after two weeks. We estimated the serum IL-6 levels within 72 hours of fever onset. This could have led to the contrasting results of our study with the previous studies.

No significant difference was found in the hematological parameters between those with febrile seizure and febrile controls. Similar results were observed by Choudhury, *et al.* [11]. However, our results are in contrast with others [6,7] who have shown that iron deficiency anemia is a risk factor for febrile seizures.



**FIG. 1** Correlation of Serum IL-6 and serum iron.

**WHAT THIS STUDY ADDS?**

- Serum IL-6 levels were lower than febrile controls in Indian in children with febrile seizures.

We observed a negative correlation between the levels of serum IL-6, and serum iron level and transferrin saturation in the cases of febrile seizure. No previous study has correlated serum IL-6 levels with the hematological parameters.

IL-6 levels may vary with time of onset of fever and seizures, hence serial levels would have been more informative. At times levels of cytokines after stimulation of lymphocytes may correlate better with association or etiology of febrile seizures. Estimation of other cytokines may also give an insight in actual etio-pathogenesis of febrile seizures. Genetic association has been studied previously, by Salam, *et al.* [12] in frequency of CC genotype of *GABRG2* gene and febrile seizures. Therefore further studies are required to link the cytokine gene polymorphisms and febrile seizures.

Further studies are required to elucidate the role of IL-6 in febrile seizures. If we are able to elucidate the definite role of IL-6 in febrile seizures, then with the use of anti-cytokine drugs, febrile seizures can be prevented in high-risk patients.

*Contributors:* SG,AA,MMA,SD,GR,MK: planned the study. All the authors were involved in data interpretation and analysis, literature search and drafting of manuscript. SG: recruited the patients; SG,GR,SD: estimated and analyzed Serum IL-6 levels. SG,MK: estimated and analyzed the Iron profile .

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