

## ORIGINAL ARTICLE

Iran J Allergy Asthma Immunol

August 2020; 19(4):409-415.

Doi: 10.18502/ijaai.v19i4.4115

# Investigating the Relationship between Serum Levels of Interleukin-22 and Interleukin-1 Beta with Febrile Seizure

Ahmad Talebian<sup>1</sup>, Farzaneh Hassani<sup>1</sup>, Hassan Nikouejad<sup>2</sup>, and Hossein Akbari<sup>3</sup>

<sup>1</sup> Department of Pediatric Neurology, Kashan University of Medical Sciences, Kashan, Iran

<sup>2</sup> Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

<sup>3</sup> Department of Biostatistics and Public Health, Faculty of Health, Kashan University of Medical Sciences, Kashan, Iran

Received: 2 March 2020; Received in revised form: 25 June 2020; Accepted: 1 July 2020

## ABSTRACT

A febrile seizure is the most common type of seizure in young kids, which is not fully known. Inflammatory mediators can affect the pathogenesis of the disease. Considering the controversy about the impacts of interleukin 1 beta (IL-1 $\beta$ ) and the lack of a study on interleukin 22 (IL-22), the purpose of the present study was to investigate the relationship between IL-22 and IL-1 $\beta$  serum levels with febrile seizure in young kids.

Our case-control study has been conducted on 120 young kids aged 6-60 months with the sign of the fever. Rectal temperature was measured for all cases. Patients with febrile seizure (n=60) and patients with fever and without a seizure (n=60) were investigated as case and control groups, respectively. Serum levels of IL-22 and IL-1 $\beta$  were measured in all participants through the ELISA method.

The serum level of IL-1 $\beta$  was significantly higher in the case group compared to the control group ( $p < 0.001$ ), while there were no significant differences between the two groups in terms of IL-22 ( $p = 0.92$ ). Unlike IL-1 $\beta$  ( $p \leq 0.021$ ), IL-22 showed no difference between two groups according to some demographic and clinical features like gender, age group, family history of febrile seizure, family history of epilepsy, and evolutionary status ( $p > 0.22$ ). Logistic multiple regression analysis showed that, unlike IL-1 $\beta$  ( $p < 0.001$ ), IL-22 does not change the chance of febrile seizure in the study groups ( $p = 0.737$ ).

The findings of this study indicated that, unlike IL-1 $\beta$ , IL-22 has not any changes/effects in the febrile seizure.

**Keywords:** Febrile seizure; Interleukin-1 beta; Interleukin-22

## INTRODUCTION

A febrile seizure is the most common type of

Seizure (3-4 percent) in young kids under the age of 6 years<sup>1</sup> and occurs due to fever at different infections<sup>1,2</sup> as well as vaccines.<sup>3,4</sup> There is usually a positive family

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**Corresponding Author:** Hassan Nikouejad, MD, PhD;  
Nephrology and Urology Research Center, Baqiyatallah University of  
Medical Sciences, Baqiyatallah Hospital, P.o.Box: 19395-5487,

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Tehran, Iran. Tel: (+98 913) 1615 530, Fax: (+98 21) 8126 2073,  
E-mail: hnikouejad@yahoo.com

history in one of the members of the kid's family in the term of febrile seizure. In other words, genetic predisposition is involved in this problem.<sup>5,6</sup> Seizures usually occur during the first hours of fever as a sudden loss of consciousness, clenching of the jaw, blurred lips, uncontrollable muscle spasms of the entire body, and jerking movements of arms and legs.<sup>1,7</sup> Seizure is usually short-lived and resolves within 1-2 minutes (less than 15 minutes);<sup>8</sup> however, it can also be a sign of a serious illness that will promise to be well-proven if its cause be found out and treated.<sup>8,9</sup>

Different opinions have been suggested about the pathophysiology of febrile seizures, including the activity of genetic and environmental factors. Some new studies have proposed that the activation of pro- and anti-inflammatory networks can contribute to febrile seizures.<sup>10</sup> The newly-identified subtype of CD4+T cell, namely T helper 22 (Th22), which is induced by tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) as well as TGF- $\beta$  cytokines, may also be important to play some role in such immune-pathogenesis<sup>11</sup> through the secretion of well-identified cytokines of IL-1 $\beta$ , tumor necrosis factor- $\alpha$ , Interleukin-10, and its signature cytokine, interleukin-22 (IL-22).<sup>12</sup> Th22 plays both inflammatory and anti-inflammatory paradoxical roles. Considering pro- and anti-inflammatory properties of cytokines that induce and/or produce from Th22 cells may define such dual uncertain roles. Evidence indicates that IL-22 affects epithelial homeostasis, tissue repairing, and inflammatory processes.<sup>13</sup> Having suggested that inflammation, as a pyrogenic response, is involved in the generation of febrile seizures;<sup>14</sup> we considered a potential role of IL-22 in neuro-inflammatory process of febrile seizure. The convincing reason for such consideration is that IL-22 compromises the blood-brain barrier integrity and, in this way, enables lymphocytes to enter into the brain.<sup>15</sup> However, IL-22 may paradoxically ameliorate the inflammatory process of febrile seizures and provide neuroprotective effects by different pathways.<sup>16</sup> It is obvious that even if we show increased IL-22 levels associated with febrile seizure, it would not have been able to indicate the causality of such inflammation.

Although no study has ever been conducted on possible effects of IL-22 in febrile seizures, several studies conducted on the role of other inflammatory cytokines in the neuronal system. For example, IL-1 $\beta$  and TNF- $\alpha$  are both potent febrile agents that can cause fever and consequently seizure.<sup>14</sup> In their study, Yu et

al stated that a small imbalance of IL-1 $\beta$  can cause febrile seizures; and the severity of such imbalance can lead to complex febrile seizures and persistent seizures with fever.<sup>17</sup> Paradoxically, another study showed no effect of IL-1 $\beta$  and TNF- $\alpha$  on the pathogenesis of febrile seizure;<sup>18</sup> and there were also no changes of IL-6, Leptin, and Adiponectin in patients with febrile seizure.<sup>19</sup>

Considering 1) the above-mentioned controversies on the effects of IL-1 $\beta$  and 2) lack of studies on the effects of IL-22 on febrile seizure, we conducted the present study to investigate the relationship between serum levels of IL-22 and IL-1 $\beta$  with febrile seizure in young kids to provide some un-recognized aspects of the disease from the point of the changes of the mentioned cytokines.

## MATERIALS AND METHODS

### Study Design

A present case-control study has been conducted on 120 young kids aged 6-60 months admitted in 2019. All parents of young kids participating in the study were informed about the bases and objectives of the study. The study protocol was approved by the research ethics committee of Kashan University of Medical Sciences (KAUMS) (no: IR.KAUMS.NUHEPM.REC.1397.31). Written informed consent was taken from each participant's parent/guardian. The inclusion criterion was considered the body temperature greater/equal to 38 degrees Celsius. Exclusion criteria were considered as dietary supplement consumption, previous febrile seizure, brain inflammation and neurological defects, any kind of systemic diseases, liver failure, allergies, malignancy, diabetes, thyroid disorders, electrolyte imbalance, metabolic disorders and parental dissatisfaction for entering the study. Patients were divided into two groups of 60 patients with febrile seizures as the case group and 60 febrile patients without seizure as the control group.

### Study Protocol

Body temperature was measured; using a rectal mercuric thermometer. The fever was defined as a central body temperature greater than or equal to 38°C. Diagnosis of febrile seizure was confirmed by a pediatric neurology subspecialist in the form of a generalized seizure with a duration of fewer than 15 minutes and no recurrence within 24 hours later. 4 cc of

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venous blood was taken from all patients. In the case group, sampling was carried out up to 5 hours after a febrile seizure. Sandwich Elisa method was used to measure the serum levels of IL-1 $\beta$  (China; with a sensitivity of 2.56 pg/mL) and IL-22 (Diaclone, France; with a sensitivity of 6.5 pg/ml) according to manufacturer instructions.

### Statistical Analysis

The obtained data were entered into SPSS-16 software and analyzed through descriptive and analytical statistics of Chi-square and independent T-tests. We also used multiple binary logistic regression analyses for evaluating the relationship between both IL-1 $\beta$  and IL-22 cytokines with febrile seizures by removing the effect of confounding variables.

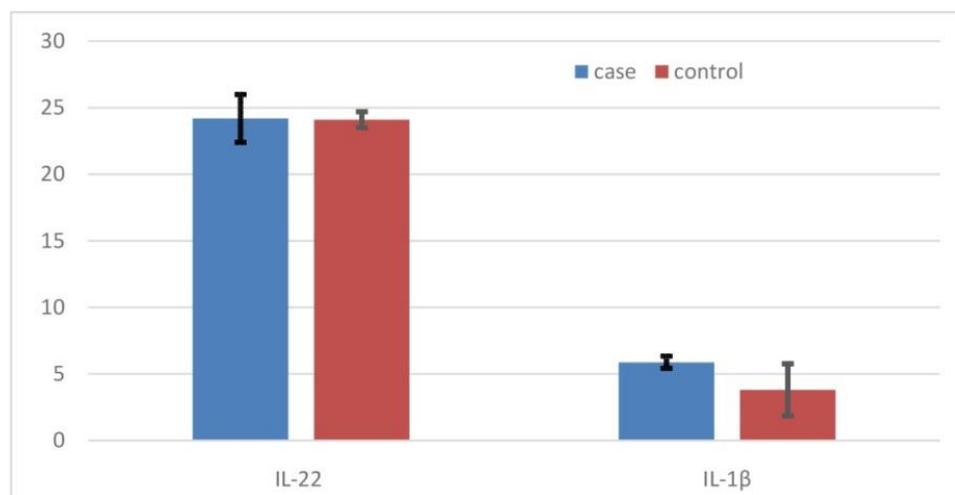
## RESULTS

Demographic, clinical, and laboratory findings are summarized in table 1. According to the table, the serum levels of IL-1 $\beta$  ( $p < 0.001$ ) and the frequency of kids with a positive family history of epilepsy ( $p = 0.008$ ) in the case group were significantly higher

compared to the control group (Figure 1). However, there was no significant difference in the frequency distribution of two groups in the case of sex, age, body temperature at admission time, family history of febrile seizure, and IL-22.

The mean and standard deviation of serum levels of IL-22 and IL-1 $\beta$  in both groups were examined based on gender, age group, family history of febrile seizure, family history of epilepsy, and evolutionary status. Unlike IL-1 $\beta$ , IL-22 showed no difference between the two groups according to each above-mentioned variables ( $p > 0.22$ ) (Table 2).

Logistic multiple regression analysis showed that both groups are not statistically different according to serum changes of IL-22 ( $p = 0.737$ ). It means that IL-22 does not affect the study groups. However, IL-1 $\beta$  showed significant effects on study groups in such a way that every-unit increase in the serum level of IL-1 $\beta$  raised the chance of febrile seizure to 80% (Adjusted OR=1.8). Other variables including gender, age, family history of febrile seizure, family history of epilepsy, and evolutionary status of the patients didn't show any significant effect on study groups (Table 3).



**Figure 1.** Mean and confidence interval of serum levels of interleukin-22 (IL-22) and interleukin 1 beta (IL-1 $\beta$ ) in two groups of febrile kids with (n=60) and without (n=60) seizure ( $p$  values of 0.92 and  $< 0.001$ , respectively)

**Table 1. Demographic and clinical characteristics of two groups of febrile kids with (case) and without (control) seizure**

| Variable                              |          | Case      | Control   | <i>p</i>          |
|---------------------------------------|----------|-----------|-----------|-------------------|
| Age (months)                          |          | 22.6±13.3 | 25.1±9.4  | 0.24*             |
| Sex male/female                       |          | 38/22     | 36/24     | 0.707**           |
| Body temperature (°c)                 |          | 38.7±0.53 | 38.6±0.55 | 0.37*             |
| Family history of febrile seizure (%) | Yes      | 45(75)    | 37(61.7)  | 0.116**           |
|                                       | No       | 15(25)    | 23(38.3)  |                   |
| Family history of epilepsy (%)        | Yes      | 53(88.3)  | 41(68.3)  | <b>0.008**</b>    |
|                                       | No       | 7(11.7)   | 19(31.7)  |                   |
| Evolutionary status (%)               | Normal   | 54(90)    | 57(95)    | 0.298**           |
|                                       | Abnormal | 6(10)     | 3(5)      |                   |
| IL-22 serum levels (pg/mL)            |          | 24.2±7.1  | 24.1±9.15 | 0.92*             |
| IL-1β serum levels (pg/mL)            |          | 5.88±1.81 | 3.81±1.96 | <b>&lt;0.001*</b> |

\* Independent T test

\*\* Chi square test

Statistical analysis method and *p*<0.05 as significant data should be shown under the tables**Table 2. Mean and standard deviation of serum levels of interleukin-22 (IL-22) and interleukin 1 beta (IL-1β) in two groups were examined based on demographic and clinical characteristics**

| Variable            | Group                             | Case            | Control          | <i>p</i> * |        |
|---------------------|-----------------------------------|-----------------|------------------|------------|--------|
|                     |                                   | Mean ± Std. dev | Mean<br>Std. dev |            |        |
| IL-22               | Gender                            | Male            | 23.26±6.14       | 24.18±9.16 | 0.617  |
|                     |                                   | Female          | 25.88±8.33       | 23.94±9.32 | 0.461  |
|                     | Age group (months)                | ≤18             | 24.24±8.22       | 24.75±9.13 | 0.851  |
|                     |                                   | >18             | 24.2±5.74        | 23.9±9.25  | 0.845  |
|                     | Family history of febrile seizure | Yes             | 23.9±7.65        | 22.67±8.57 | 0.486  |
|                     |                                   | No              | 25.24±5.09       | 26.36±9.77 | 0.616  |
|                     | Family history of epilepsy        | Yes             | 23.89±7.37       | 24.52±9.94 | 0.723  |
|                     |                                   | No              | 26.78±3.56       | 23.14±7.31 | 0.222  |
| Evolutionary status | Normal                            | 24.57±7.24      | 24.18±9.29       | 0.804      |        |
|                     | Abnormal                          | 21.08±4.6       | 22.25±6.76       | 0.765      |        |
| IL-1β               | Gender                            | Male            | 5.65±1.81        | 3.95±1.93  | <0.001 |
|                     |                                   | Female          | 6.28±1.77        | 3.61±2.04  | <0.001 |
|                     | Age group                         | ≤18             | 5.53±1.71        | 4.43±2.39  | 0.049  |
|                     |                                   | >18             | 6.26±1.86        | 3.61±1.78  | <0.001 |
|                     | Family history of febrile seizure | Yes             | 5.86±1.84        | 3.56±1.93  | <0.001 |
|                     |                                   | No              | 5.97±1.75        | 4.22±1.99  | 0.009  |
|                     | Family history of epilepsy        | Yes             | 6±1.84           | 4.1±1.95   | <0.001 |
|                     |                                   | No              | 4.99±1.3         | 3.2±1.9    | 0.03   |
| Evolutionary status | Normal                            | 5.85±1.81       | 3.88±1.98        | <0.001     |        |
|                     | Abnormal                          | 6.16±1.92       | 2.62±0.97        | 0.021      |        |

\* Independent T test

Statistical analysis method between which groups and *p*<0.05 as significant data should be shown under the tables

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**Table 3. Binary logistic multiple regression analysis evaluating the effects of different factors on febrile seizure**

| variables                         | B      | S.E.   | Wald   | df | <i>p</i> * | Adjusted OR |
|-----------------------------------|--------|--------|--------|----|------------|-------------|
| IL-22                             | 0.009  | 0.027  | 0.113  | 1  | 0.737      | 1.009       |
| IL-1 $\beta$                      | 0.587  | 0.129  | 20.688 | 1  | 0.000      | 1.799       |
| Sex                               | 0.573  | 0.483  | 1.407  | 1  | 0.236      | 1.773       |
| Body temperature ( $^{\circ}$ c)  | 0.150  | 0.435  | 0.119  | 1  | 0.730      | 1.162       |
| Age                               | -0.027 | 0.020  | 1.851  | 1  | 0.174      | 0.974       |
| Family history of febrile seizure | 0.803  | 0.510  | 2.480  | 1  | 0.115      | 2.232       |
| Family history of epilepsy        | 0.483  | 0.568  | 0.722  | 1  | 0.395      | 1.621       |
| Evolutionary status               | -0.854 | 0.944  | 0.819  | 1  | 0.365      | 0.426       |
| Constant                          | -8.732 | 16.918 | 0.266  | 1  | 0.606      | 0.000       |

\* Adjusted *p*.value by logistic regression model

Statistical analysis method between which groups and  $p < 0.05$  as significant data should be shown under the tables

### DISCUSSION

The present study was conducted to investigate the relationship between serum levels of IL-22 and IL-1 $\beta$  with febrile seizures in young kids. There was a significant relationship between IL-1 $\beta$  serum levels and febrile seizures. However, such a difference was not found between IL-22 serum levels and febrile seizures. Importantly; we showed that not only IL-22 has no effect on the study groups, but also no variable (including in our study) can induce febrile seizures through some effect on IL-22. Such findings were completely different in the case of IL-1 $\beta$ .

We didn't find any other studies investigating the relationship between IL-22 and febrile seizures. However, in the case of IL-1 $\beta$ , our study is in accordance with the results of some other studies which support the pre-seizure role of IL-1 $\beta$  in febrile seizures.<sup>20-23</sup> Although low levels of IL-1 $\beta$  show neuroprotective effects, its high concentrations can lead to neurotoxicity at certain pathological conditions like seizure and epilepsy syndrome.<sup>24</sup> The mechanisms of such effect are that 1) causing excessive excitability of neuron directly through its effect on ionic flow and indirectly through inhibiting the function of GABA receptors, 2) increasing the level of extracellular glutamate, 3) increasing nitric oxide formation which increases seizure readiness.<sup>25</sup> In animal models, IL-1 $\beta$  could worsen and prolong their electrical and behavioral activities, while its depletion could depress and stop their activity.<sup>26</sup> Such models have also shown that systemic inflammation can increase the probability of seizure through stimulating inflammatory cytokines of TNF- $\alpha$  and IL-1 $\beta$  inside hippocampus and cortex.<sup>27</sup>

Blocking this process through neutralizing antibodies as well as inhibiting activation of microglia has prevented further progress in the preparation of long-term seizures.<sup>28</sup> Considering that IL-1 $\beta$  is a pro-inflammatory cytokine that appears in the host's response, we may assume that it induces both fever<sup>29</sup> and seizure. In addition, it seems that peripheral inflammation strengthens seizures as synergistic and increases the production of s caused by seizure and microglia activation.<sup>30</sup> However, several studies in contradiction with the present study have shown no significant difference in plasma IL-1 $\beta$  levels with febrile seizure.<sup>31-33</sup> A recent study using an animal model of seizure caused by increased temperature showed an increase in IL-1 $\beta$  levels in the hippocampus within 1 to 3 hours after the seizure. Surprisingly, such elevation promoted the seizure susceptibility in adulthood.<sup>34</sup> Cytokine levels have been reported to increase only after a sudden seizure attack.<sup>35,36</sup> It is important to note that cytokine levels in our study have been obtained after febrile seizures. The differences in two groups of the present study can indicate the different nature of febrile seizure and an inflammatory factor may not necessarily be its cause.

In summary, not finding a strong correlation between IL-22 and the occurrence of febrile seizure after adjusting the effects of other confounding factors, we showed that, unlike IL-1 $\beta$ , IL-22 is not a predictor of seizure after fever in kids. According to our knowledge, this study is the first one in this regard. However, functional assays that provide supplementary information on possible immunoregulatory mechanisms of Th22 cells expressing IL-22 were not performed.

According to the results of the present study, we

showed no changes in serum levels of IL-22 in the occurrence of febrile seizures in young kids. It is necessary to conduct further studies on the possible role of the Th22 system and related cytokines in the development of febrile seizures in humans.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### ACKNOWLEDGEMENTS

This study funded and supported by Deputy of Research, Kashan University of Medical Sciences (KAUMS), and Grant No. 9781

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