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Reduced cerebrospinal fluid levels of interleukin-10 in children with febrile seizures

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ABSTRACT

Purpose: The exact etiology of febrile seizures (FS) is still unclear. However, it is thought that cytokine network activation may have a causative role. Therefore, this study aimed to evaluate the levels of interleukin-12 (IL-12) as a proinflammatory cytokine, interleukin-10 (IL-10) as an anti-inflammatory cytokine, and interferon-β (IFN-β), a marker of toll-like receptor-3 activation as a host response to viruses. These cytokine levels were analyzed in the cerebrospinal fluid (CSF) of children after a FS.

Methods: With the approval of the Human Research Ethics Committee, 76 patients with FS, who underwent lumbar puncture (LP) for the exclusion of central nervous system (CNS) infection, and who didn't have CSF pleocytosis, were included in the study. The control group consisted of 10 patients with similar ages, with an acute febrile illness and who required LP to exclude CNS infection. The analyses were made by the enzyme-linked immunoassay method.

Results: Age, gender distribution and CSF IL-12 and IFN- β levels did not differ, but CSF IL-10 levels were significantly lower in the FS group as compared to the control group (0.78 ± 4.5 pg/ml, versus 27 ± 29 pg/ml, $p < 0.0001$).

Conclusion: The low-level of CSF IL-10, considering its anti-inflammatory properties, may play a role in the etiopathogenesis of FS.

1. Introduction

Febrile seizures (FS) are the most common seizures in childhood [1,2]. The incidence of FS is 2–5% in children under five years of age [3]. There are a lot of reports about the contribution of the pro-inflammatory cytokine interleukin-1β (IL-1 β), which is involved in the host defense during the infections, in patients with FS [4–6]. Therefore, cytokine network activation is mostly considered in FS pathogenesis [7]. Various other immunological parameters are also different in patients with FS. In a study by Montelli et al. [8], an increase in CD8 + count, a low helper/supresor T lymphocytes ratio and a defective proliferative response to phytohemagglutinin in lymphocytes were detected in patients with FS. Based on literature data, some authors suggested that the balance between proinflammatory and anti-inflammatory cytokines might have a role in the pathogenesis of FS [4]. In the present study, it was hypothesized that this deterioration of the cytokine balance in FS may be due to the increase in pro-inflammatory cytokines, as well as the decrease in anti-inflammatory cytokines. Therefore, this study aimed to evaluate the levels of interleukin-12 (IL-12), a pro-inflammatory cytokine, interleukin-10 (IL-10), an anti-inflammatory cytokine, and interferon-β (IFN-β), a marker of toll-like receptor-3 (TLR3) activation as a host response to viruses. These cytokines were analyzed after a FS, in the cerebrospinal fluid (CSF) of children.

2. Methods

2.1. Patient selection

The study protocol was approved by the Human Research Ethics Committee of Istanbul University Cerrahpaşa Faculty of Medicine (approval number: 9102). FSs were defined as seizures that occurred with a

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fever higher than 38 ° Celsius (ºC) and without central nervous system (CNS) infection [4]. Complex FSs were defined as more than one seizure within 24 h or seizures that lasted longer than 15 min or focal seizures. Lumbar puncture (LP) was decided and performed by the emergency unit team who followed patients clinically. Patients with FS, between the ages of 6 months and 7 years, who underwent LP for the exclusion of CNS infection, and who didn't have CSF pleocytosis (number of CSF cells less than 5/mm3), were included in the study. Patients with CSF pleocytosis and an a febrile seizure history were excluded from the study. Informed consents were obtained from the parents of the patients who met the study criteria after CSF examinations. The control group consisted of patients with similar ages, with an acute febrile illness, who required LP to exclude CNS infection and who didn't have CSF pleocytosis. All CSF samples were taken within the first 24 h following a FS. Simultaneous CSF and serum samples were stored at -80 °C before the analysis. In all patients, neurological examinations were repeated within the first month after LP to exclude other possible neurological conditions.

2.2. Data selection and laboratory tests

The age and gender of the patients, characteristics of the seizures and whether or not the anticonvulsant was administered, the duration of the FS and duration of the febrile period preceding the seizure, the medication used before the seizure, number of the previous FSs, the first seizure age, the neuromotor development, the family histories for FS and epilepsy were recorded.

CSF cytokine levels were assayed by the enzyme-linked immunoassay (ELISA) method in accordance with the instructions. Human ELISA kits were used for IL-10 (AssayPro; St. Charles, MO, USA), IL-12p70 + p40 (Biosource; the USA) and IFN-β (Fujirebio, TFB Inc.; Tokyo, Japan). Immunoglobulin G (IgG) and the albumin levels in CSF and serum were studied by the nephelometric method using human immunoglobulin and albumin antibodies (Dade Behring; Marburg, Germany).

The CSF/serum albumin ratio and also IgG index of the patients were calculated to assess the blood brain barrier permeability and intrathecal antibody production, respectively. The IgG index was defined as [(CSF IgG level / serum IgG level) / (CSF albumin level/serum albumin level)] [9]. In this study, the upper limit of the [CSF albumin/serum albumin] ratio was accepted as 1/230 [10]. In the IgG index, values less than 0.7 were considered normal [11].

2.3. Statistical analysis

The Kolmogorov Smirnov test was used to assess whether the data of the FS and control groups were in a normal distribution. The Mann-Whitney *U* test was used for comparison of the cytokine levels and IgG index in FS and control groups. Fisher's exact test was used to compare the gender distribution in the groups. The correlation between cytokine levels and the IL-10 level and also the degree of fever was assessed by Spearman's correlation analysis. The statistical significance level was accepted as $p < 0.01$ (0.05/5) with a Bonferroni procedure [12].

3. Results

3.1. Patient characteristics

The FS group consisted of 76 patients (31 girls and 45 boys). The clinical and demographic characteristics of the patients are shown in Table 1. There was no significant difference between the FS and control groups in terms of age and gender distribution (Table 2). The male/female ratio was 1.45 in the FS group and 1.5 in the control group.

In the FS group, 63.1% (n = 48) were under 2 years of age, 19.7% (n = 15) were between 2–4 years old and 17.1% (n = 13) were over 4 years of age. In the control group, 80% (n = 8) were under 2 years of age and 20% (n = 2) were over 4 years of age.

Table 1
Clinical and demographic characteristics of the patients with febrile seizures.

Parameters	Number of patients	
	n	%
Gender		
Male	45	59.2
Female	31	40.8
Febrile seizure type		
Simple	64	84.2
Complex	12	15.8
Seizure type		
Generalized	71	93.4
Focal	5	6.6
Number of seizures		
First	59	77.6
> 1	17	22.4
Grade of fever (ºC)		
< 38.5	12	15.8
38.5-39.5	30	39.5
> 39.5	34	44.7
Family history of FS		
yes	29	38.2
no	47	61.8
Family history of epilepsy		
yes	6	7.9
no	70	92.1

Table 2
Comparison of CSF cytokine levels in febrile seizure and control groups.

	Age *(years)*	CSF IFN-β *(IU/ml)*	CSF IL-12 *(pg./ml)*	CSF IL-10 *(pg./ml)*	IgG index
FS group					
n	76	76	76	76	74
mean	2.15	0.27	3.7	0.78	0.4
SEM	0.19	0.14	0.83	0.52	0.03
SD	1.7	1.2	7.25	4.5	0.25
median	1.5	0.0	2.5	0.0	0.37
Control group					
n	10	10	10	10	10
Mean	2.34	0.3	3.5	27	0.4
SEM	1.1	0.08	0.6	9.2	0.036
SD	3.5	0.26	1.8	29	0.11
median	1.0	0.3	3.5	25.6	0.36
p-value	> 0.05	> 0.05	> 0.05	< **0.0001**	> 0.05

CSF, cerebrospinal fluid; FS, febrile seizures; IFN, interferon; IgG, immunoglobulin G; IL, interleukin; n, number; SD, standard deviation; SEM, standard error of the mean.

3.2. Results related with CSF cytokine levels and IgG index

In the comparison of the FS and control groups, the CSF levels of IFN-β, IL-12, CSF/serum albumin ratio and the IgG index levels were not statistically different ($p > 0.05$, Table 2). However, the CSF IL-10 level in the FS group was significantly lower ($p < 0.0001$, Table 2). In the FS group, the CSF IL-10 levels were negatively correlated with the grade of fever ($r = -0.255$, $p = 0.028$). In addition, CSF IL-10 levels were positively correlated with IgG index ($r = 0.299$, $p = 0.01$) and IFN-β levels ($r = 0.349$, $p = 0.002$) (Fig. 1).

The history related with infection was reliable in 66 FS patients. In 38 of those patients, the CSF sample was taken within the first 24 h after the onset of fever, but at least 24 h later in 28 of the patients. In the comparison of those two groups, CSF cytokine levels did not show a statistically significant difference ($p > 0.05$, Table 3).

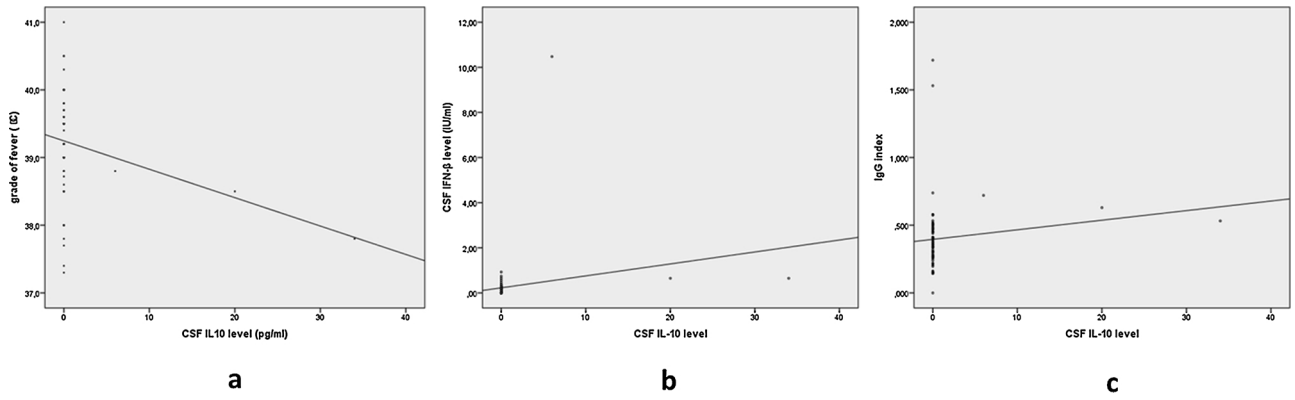

Fig. 1. Correlations between CSF IL-10 level and grade of fever **(a)**, IFN-β level **(b)** and IgG index **(c)**. Spearman's correlation analysis: **a.** r = - 0.255, p = 0.028; **b.** r = 0.349, p = 0.002; **c.** r = 0.299, p = 0.01. CSF, cerebrospinal fluid; IFN, interferon; IgG, immunoglobulin G; IL, interleukin.

Table 3
Comparison of CSF cytokine levels between the patients who underwent lumbar puncture within or after 24 h following infection onset.

Parameters (mean ± SEM)	The time between infection onset and CSF examination		p-value
	≤ 24 h	> 24 h	
n	38	28	
Age (years ± SD)	2.09 ± 1.55	2,19 ± 1.19	0.873
CSF IFN-β (IU/ml)	0.14 ± 0.04	0.5 ± 0.37	0.245
CSF IL-12 (pg./ml)	2.82 ± 0.26	5.36 ± 2.2	0.403
CSF IL-10 (pg./ml)	1.42 ± 1	0.2 ± 0.2	0.719
IgG index	0.44 ± 0.05	0.36 ± 0.03	0.545

CSF, cerebrospinal fluid; IFN, interferon; IgG, immunoglobulin G; IL, interleukin; n, number; SD, standard deviation; SEM, standard error of the mean.

In the FS group, the ratio of CSF/serum albumin was normal in all patients, suggesting that the blood-brain barrier permeability was normal. The IgG index was higher in only one patient in the FS group, who was an 11-month-old girl with a first simple FS. Her seizure was within the first 24 h from the beginning of febrile disease. There was a history of FS in her family.

4. Discussion

In this study, CSF IL-10 levels were significantly lower in patients with FS compared to those in the control group. In addition, there was a negative correlation between the CSF IL-10 levels and grade of fever. These findings conform to the studies suggesting that IL-10, an anti-inflammatory cytokine, has an antipyretic effect and plays a role in the resistance to FS [3,4,13]. In rats treated with IL-10, the threshold of fever for seizure was significantly higher compared to that in the control group [4]. The antipyretic effect of IL-10 is thought to be due to the inhibition of IL-1 and IL-6 production [3]. IL-10 inhibits the production of pro-inflammatory cytokines and mediators, especially IL-1, IL-6, IL-12, and tumor necrosis factor (TNF), in macrophages and dendritic cells [14]. Some authors suggested that IL-10 is a regulatory cytokine rather than a type-2 helper cytokine in humans [15,16].

There are several studies evaluating the CSF IL-10 levels in patients with FS. It has been reported that in 12 patients with complex FS the CSF IL-10 levels in addition to CSF IL-6, IL-1β, and TNF-α levels were significantly lower than in patients with acute encephalopathy [17]. However, in comparison of the patients with only FS and FS with encephalopathy, accompanied with influenza virus infection, there was no difference in the CSF IL-10 levels [18]. In patients with FS associated with human herpesvirus-6 (HHV-6) infection, significant differences in serum and CSF IL-10 levels compared with the control group were not reported [19]. In the CSF cytokine kinetics in patients with aseptic meningitis, there was an increase in proinflammatory cytokines within 24 h, whereas the IL-10 peak levels were in the 2nd or 3rd day after the onset of the disease. Therefore, the IL-10 level increase has been thought to be a response to the inflammatory process [20]. However, in the present study, levels of IL-10, IL-12, and IFN-β did not differ in the CSF samples taken within or after the first 24 h of febrile disease (Table 3).

It was generally reported that in FS patients, higher serum IL-10 levels [18,21,22], and higher IL-10 response in their peripheral blood mononuclear cells [3,23] were present. The higher IL-10 levels in serum have been thought to be associated with the defensive mechanism that emerges secondarily to the increase in proinflammatory cytokines [3,18,21]. Additionally, the IL-10 levels were higher in serum compared to CSF [22]. However, Virta et al.[7] reported that the serum IL-10 levels in patients with FS did not differ from those of the control group.

In this study, a positive correlation between CSF IL-10 level and IgG index was found (Fig. 1). Similarly, it has been reported that the CSF IL-10 levels in patients with multiple sclerosis significantly correlated with IgG index [24]. This finding may be due to the fact that IL-10 is one of the potent differentiation factors that induce the production of immunoglobulins by human B-cells [24,25]. IL-10 activates naive B cells to produce immunoglobulins, particularly high levels of IgG1 and IgG3 [25].

In the present study, the CSF levels of IFN-β, one of the type-1 interferons, did not differ between the FS and control groups. Type-1 interferons are cytokines secreted as a response by the virus-infected cells [26]. IFN-β is the primer product in TLR3 activation. The TLR family plays an important role in innate immunity with their pathogen recognition ability [27]. In children with a history of FS, the induction of leukocytes by a TLR3 activating viral factor resulted in a significant increase in IL-1β production, in comparison with the control group [6]. The present study also indicated a statistically significant positive correlation between IFN-β and IL-10 levels. We suggest that the IFN-β response, associated with TLR3 activation, may also be inducing IL-10 production. In support of this, it has been reported that the treatment of mononuclear cells, obtained from multiple sclerosis patients, with recombinant IFN-β, stimulated IL-10 secretion in a time- and dose-dependent manner [28]. In the present study, the CSF IL-12 levels of children with FS did not differ significantly from the control group. Although there are a lot of reports on the relationship between FS and IL-1β [3,4], which is another pro-inflammatory cytokine, no other studies that evaluated the IL-12 levels in FS were found. IL-12 is one of the earliest synthesized proinflammatory cytokines during the infections [15,29].

Based on the results of this study that indicate normal CSF/serum albumin ratios, it can be said that FS does not cause any deterioration of the blood-brain barrier. The IgG index elevation, which may indicate

intrathecal IgG synthesis, was detected in 1/76 (1.3%) of the patients in this study. On the other hand, taking into account the synthesis of IgG, IgA and IgM, Eeg-Olofsson et al. [30] found that the intrathecal synthesis of one or more immunoglobulins were present in 42% of 64 FS patients in the post-seizure period. Additionally, this ratio was reported as 25% in 28 patients evaluated at 3–4 weeks after FS [30].

There are some limiting factors in the present study. One of these factors was the small number of the patients in the control group. Very few patients who met the study criteria were found as very few met the criteria of not having seizure and CSF pleocytosis, despite the suspicion of CNS infection. However, the CSF IL-10 levels in the FS group of this study seem lower also in consideration of the CSF IL-10 levels in children with noninflammatory neurological disease in another study by Pranzatelli et al.[31]. In the present study, the inclusion of FS patients who underwent LP due to their clinical needs, and the lack of CSF examinations in other FS patients was another limiting factor. This was due to ethical reasons. Another limiting factor was that serum cytokine levels were not analyzed. It was reported in previous studies that serum and CSF cytokine levels were different [22]. However, the present study aimed to especially evaluate the CNS-induced cytokine level differences considering the evidence of the presence of intrathecal cytokine production associated with seizures in patients with epilepsy [32]. Experimental studies also indicated increased cytokine production in brain tissue, even if this was not detected in serum and CSF, associated with seizures [33]. However, cytokines measured in CSF may be peripheral blood or intrathecal origin [32]. Therefore in this study, the CSF/serum albumin ratios were also evaluated and found normal in all patients, suggesting intact BBB.

5. Conclusion

In conclusion, this study indicates lower CSF IL-10 levels in children with FS. We suggest that inadequate IL-10 production in response to the inflammatory conditions might have a role in the pathogenesis of FS, in consideration of its anti-inflammatory effects [34], regulatory function [15,16] and its suppressor effects on proinflammatory cytokine production [4]. In this study, the negative correlation between CSF IL-10 levels and the grade of fever confirmed that IL-10 has an antipyretic effect as in previous studies and also indicated that this antipyretic effect is also present in children with FS. It is possible that IL-10 may be involved in the pathogenesis of FS by a decreased suppression of the fever response, thus increasing susceptibility to FS [4,13]. It can be said that the possible defects related with the IL-10 response in FS may be related with a delay in maturation because FS involves a certain age group. However, it may be useful to consider the probability of similar low IL-10 levels in other seizures and epilepsies, involved in pro-inflammatory conditions.

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Conflict of interest

There is no conflict of interest.

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