The Egyptian Journal of Hospital Medicine (April 2022) Vol. 87, Page 1743-1747

Evaluation of Interleukin-6 and Interleukin-1 β Levels in Febrile Status Seizures

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ABSTRACT

Background: Seizures triggered by fever are known as febrile seizures, and they are the most common form in children. The cause of febrile seizures is still a mystery, even though numerous studies have been carried out. Researchers have found cytokines may play an important role in the development of febrile seizures.

Objective: to evaluate the role of Interleukin-6 and interleukin-1β levels in febrile status epilepticus.

Patients and methods; This was a prospective case-control study, conducted at the Neurological Unit of the Pediatric Department, Faculty of Medicine, Zagazig University, Sharkia, Egypt on 52 children (26 in each group), plasma cytokine (IL-6 and IL-1β) levels were detected as a main part of the initial study design.

Results: A significant difference was found between both groups as regard IL-6 and IL-1β**. Conclusion:** A genetic risk factor for fever-related seizures in children may be associated with promotor variations in IL-1 β genes rather than IL-6 or HMGB1 genes.

Keyword: Cytokines, Seizures, IL-6, IL-1β.

INTRODUCTION

Children with a fever of 38°C or above with no history of an afebrile seizure, hypoglycemia, medication withdrawal or drug use, or an electrolyte imbalance are generally considered to have febrile seizures (FS) [(1)]. Pediatricians face a huge issue due to the prevalence of febrile seizures in young children. There has been a considerable increase in knowledge about how to prevent and treat febrile seizures in recent years [(2)].

Febrile seizures are still a mystery as to their cause and pathogenesis. Patients with febrile seizures have higher levels of IL-6 and IL-4 cytokines, which may be important in the disease's etiology [(3)]. Tumor necrosis factor-alpha, interleukin-1, and tumor necrosis factor are among the immune system's most potent weapons against infection. Due to the immune system's overproduction of proinflammatory cytokines, children are more susceptible to inflammation, which may be defined by the cytokine response in response to infections [(4)].

Both pro-inflammatory and anti-inflammatory cytokines have been associated with elevated levels of cytokines such as TNF-alpha and IL-10 in the peripheral blood of children with FS as well as children with epilepsy who had previously had seizures. There were significant variations in the levels of IL-1 and other proinflammatory cytokines between children who experienced a seizure attack and those who were feverish but not experiencing seizures, in both groups of children [(3)]. Child epilepsy sufferers have higher levels of IL-1, which suggests that this cytokine has a role in the development and progression of the disease [(5)].

IL-6 has been implicated in febrile seizures in the past, however, the results are mixed. The epileptogenic effect of IL-6 in febrile seizures has been demonstrated by certain research [(3)], Serum IL-6 has been found to have an antiepileptic effect via adenosine receptors in rat research [(6)]. Fever-induced seizures have also been linked to iron-deficient anemia [(7)].Children's higher IL-1β responses may play a role in FS patients' seizures, as demonstrated by Helminen and Vesikari's 1990 study [(8)]. FS-affected children's peripheral mononuclear cells were treated with the gram-negative molecule lipopolysaccharide., That their IL-1β was substantially higher than other children who had bacterial infections but had no seizures.

A study by **Matsuo and his colleagues** [(9)] indicated that FSD children's leukocytes were more sensitive to double-stranded RNA stimulation than those of healthy youngsters (a viral infection model). Several more studies have since investigated the role of cytokines in human FS in the time that has elapsed between the two of these [(10)].

Furthermore, it was shown that children with certain genetic abnormalities in the interleukin system were also more prone to FS, which was confirmed by cytokine measures. When LPS is administered to cultured monocytes with an IL-1β gene polymorphism, the monocytes produce more IL-1β. This polymorphism has been linked to a higher risk of developing FS [(11)]**.**

It was the goal of this work to evaluate the role of Interleukin-6 and interleukin-1β levels in febrile status epilepticus.

PATIENTS AND METHODS

This study was undertaken as a case-control study in the Neurological Unit of the Pediatric Department, Faculty of Medicine, Zagazig University, Sharkia, Egypt. Fifty -two patients were retrieved, 26 febrile status seizures children were considered as the case group and another 26 cases were controls.

Ethical considerations:

Zagazig University's research ethics council approved the study and informed consent forms signed by all participants' parents were collected following the Helsinki Declaration, which is the ethical norm for human testing established by the World Medical Association.

Inclusion criteria: All subjects met the following inclusion criteria: Both sexes included. Age equal or lower to 6. Convulsions lasting 30 minutes or more

Received: 06/11/2021
Accepted: 04/01/2022

without returning to baseline throughout 30 minutes in children with a febrile convulsion (temperature less than 38.4°C) and no indications of central nervous system (CNS) infection.

Exclusion criteria: Infection, open fractures, pathological fracture, and skeletal immaturity.

This is what all of the participants in this research had to go through:

1-Complete history taking.

2- Complete general and neurological examination.

3- Investigation:

- **Routine investigation:** CBC, CRP, Electrolytes, and Electroencephalogram when indicated.
- **Specific investigation.**

Serum level of interleukin 1 beta and interleukin 6: Plasma cytokine (IL-6 and IL-1β) levels were detected for viral testing within 72 hours of FSE and collected in plan vacuum tubes. Cytokines levels were estimated by ELISA.

Statistical Analysis:

The collected data were coded, processed, and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Numbers and percentages are used to represent data (percent) or mean ± SD. Different qualitative factors were examined using the Chi-square (X^2) test. ANOVA test was used. P-value < 0.05 was considered significant.

RESULTS

There was a non-significant difference between both groups as regard age, sex, or residence **(Table 1).**

there were 12 cases with Full recovery within 6 h, 9 with Full recovery within 12 h, 5 with the absence of full recovery at 12 h, the mean Convulsive seizure duration was 62.2(±3.0 SD) **(Table 2).**

There was a non-significant difference between both groups as regards the history of previous medical illness or history of neuro-medication **(Table 3).**

The difference in respiratory rate between the two groups was substantial **(Table 4).**

In terms of C-reactive protein, there was a huge disparity in the two groups **(Table 5).**

There were significant differences between both groups as regard IL-6 and IL-1β **(Table 6).**

Table (1): Comparison between the studied groups as regards demographic data

	Case Group (n=26)	Control Group (n=26)	Test	P-value
Age Mean ± SD	3.1±0.39	3.3±0.44	T=1.27	0.55
Sex Male Female	15 11	16 10	χ^2=0.07	0.77
Residence Urban Rural	14 12	13 13	χ^2=0.07	0.78

Table (2): Neurological examination of studied case group

Level of Consciousness	
Full recovery within 6 h	12
Full recovery within 12 h	9
Absence of full recovery at 12 h	5
Convulsive seizure duration, minute	62.2±3.0

Table (3): Comparison between the studied groups as regards past history

	Case Group (n=26)	Control Group (n=26)	Test	P-value
History of previous medical illness	9	8	χ^2=0.087	0.76
Age at afebrile seizure onset, years	3.1 ± 10.3	-	-	-
Duration of disease	2.5±0.95	-	-	-
History of Neuro-medication	20	15	χ^2=2.18	0.13

Table (4): Comparison between the studied groups regarding general complications

	Case Group (n=26)	Control Group (n=26)	Test	P-value
Temperature	38.7±0.53	38.6±0.51	**T= 1.079**	0.84
Heart rate	165±15	104±11	T= 1.85	0.12
Respiratory rate	40±5	25±3	T= 2.77	0.01*

Table (5): Comparison between the studied groups as CBC, CRP, and Electrolytes

	Case Group (n=26)	Control Group (n=26)	P-value
WBC count, median, per Ml	21200±3050	19500±500	0.32
Hemoglobin (gm/dl)	10.90±1.86	11.80±1.95	0.81
Platelets (x103 /mm3)	285.84±9.49	289.95±10.55	0.92
C-reactive protein, median, mg/dL	1.05±0.2	2.09±0.5	0.0001**
Na(mEq/ L)	138.6±4.1	137.5±3.5	0.43
K(mEq/ L)	4.6±0.52	4.2±0.45	0.47

Table (6): Comparison between the studied groups regarding IL-6 and IL-1β

	Case Group (n=26)	Control Group (n=26)	P-value
IL-6(pg/mL)	86.95±6.57	62.05±4.88	0.04*
IL-1β (pg/mL)	5.9±1.95	3.12±0.12	0.007*

T: Two-Sample Independent t-test

DISCUSSION

A seizure lasting more than 30 minutes is considered status epilepticus. In children, status epilepticus is a potentially life-threatening disorder. There are between 10 and 58 cases of status epilepticus in the US population every year. Status epilepticus in children occurs at a rate of 20 per 100,000 persons each year in poor nations. One of the most common symptoms of neurologic dysfunction is an epileptic seizure. The majority of seizures in children are the result of a febrile seizure [(12)].

Patients with seizures have been discovered to have abnormalities in the expression of proinflammatory cytokines recently. The brain parenchyma may be damaged over time by an imbalance of pro-and anti-inflammatory cytokines, which may be clinically linked to problems. There is a distinct difference between a febrile seizure and a state of epilepsy based on the clinical manifestations. Status epilepticus, on the other hand, has a poorer prognosis than febrile seizures[(13)].

The objective of this study is to estimate the serum levels of IL-6 and IL-1β cytokines in children with febrile status epilepticus and compared the results with clinical data obtained from the patient.

This study showed that there was a non-significant difference between both groups as regard age, sex, or residence. **Choi *et al.*** [(4)] presented a summary of the clinical data collected from the study's 56 FS patients, its 43 GEFS+ patients, and its 108 control children. In both the FS and GEFS+ populations, men outnumbered women (63 percent and 60 percent, respectively). 81 percent of the FS attacks were classified as simple and 19 percent as complex in terms of their semiology. FS lasted more than 30 minutes in three of the patients, all of whom had previously suffered from febrile status epilepticus.

Jafarpour *et al.* [(14)] indicated that separate investigations looked at the relationship between a patient's age and the risk of death from SE in children. Studies have indicated that patients under the age of one have a greater death rate, particularly during the first year of life. Another study found no correlation between age and mortality or a higher mortality risk in the second decade of life compared to the first decade. In spite of this, the underlying etiology has a huge impact on death rates. Different age groups have different etiologies to deal with. Patients less than one-year-old are more likely to have an acute symptomatic etiology, which is related to a greater death rate as stated in the etiology section above. That's why infants under one-year-old have a greater mortality rate than older children, which could be at least partially related to the higher prevalence of acute symptomatic causes, such as CNS infection and metabolic imbalances.

This study showed that in the case group, as regards neurological examination, there were 12 cases with Full recovery within 6 h, 9 with Full recovery within 12 h, 5 with Absence of full recovery at 12 h, the mean Convulsive seizure duration was 62.2(±3.0 SD). In a recent study by **Power *et al.*** [(15)] Neurocognitive outcomes were found to be worse in patients with SE and GTC who had experienced 10 or more lifetime GTC compared to the control group. The scientists could not conclude that SE had a bigger influence on cognitive outcomes than several lifetime GTCs because there was no statistically significant difference between the SE and multiple GTC groups.

There was no significant difference between the two groups in terms of prior medical disease or history of neuro-medication, according to this research. **Gencpinar *et al.*** [(16)] found that Prenatal history, nativity (including vaccinations), consanguinity, family history of epilepsy, afebrile seizure presence, seizure type, seizure semiology, and evaluation of the Wechsler Intelligence Scale for Children, Revised EEG and MRI findings did not show any significant differences between the groups. Statistically significant differences were detected in family history, total seizures, and the

use of prophylaxis across groups, according to the results of this study. In their research, they found no link between a child's risk of epilepsy and the educational attainment of either of his or her parents. Similarly terms of the highest recorded fevers, there were no significant variations between the groups. The total number of seizures, seizure type, type of FS, gender, consanguinity, family history of FS or epilepsy, or psychomotor impairment was not associated with experiencing an afebrile seizure.

This study reported that there was a highly significant difference between both groups as regard C-reactive protein. **Elhady *et al.*** [17] showed that regarding routine laboratory investigations among our studied children, the mean hemoglobin level was 10.90±1.86 mg/dl, arterial blood gas revealed average PH of 7.36±0.10, acute phase reactant was elevated in some cases: CRP ranged between 0.4-148 mg/dl and ESR ranged between 4-120

This study illustrated that there was a significant difference between both groups as regard IL-6 and IL-1β. Results by **Shofiyah *et al.*** [18] Status epilepticus patients were shown to have higher levels of IL-1β than those with febrile seizures or fevers. Status epilepticus participants had lower IL-1ra levels than febrile seizure participants, by a substantial margin. Patients in a state of status epilepticus had IL-1β /IL-1ra ratios that were much higher than those with febrile episodes. According to the findings of this investigation, the status epilepticus group had a higher concentration of IL-1β. (1.2 pg/mL) was considerably greater than in the febrile seizure (0.98) and feverish groups (0.83). Even Nevertheless, in both groups, the IL-1β concentrations were increased above the usual (0.3 pg/mL) threshold. According to a prior study, IL-1 levels were higher in patients with febrile seizures. Viruses are becoming more and more likely to be the cause of febrile seizures in children.

A previous study by **Uludag *et al.*** [19] revealed that IL-1β was shown to be elevated in patients with meningoencephalitis caused by meningococcus or pneumococcus bacteria. Meningoencephalitis has a high death rate because of tissue destruction, which is thought to be caused by IL-1β. **Elsaid *et al.*** [20] ELISA results showed that IL-1 beta (IL-1) and IL-1ra (IL-1ra) were assessed by ELISA in twenty-five children with febrile seizures and twenty-five age-matched control children with febrile illness without convulsions within 24 hours of the started fever. Serum IL-1β and IL-1ra levels were considerably greater in individuals with febrile seizures compared to patients with fever in controls. Complex febrile seizures had significantly greater amounts of IL-1β and IL-1ra in their blood than did simple febrile seizures. Patients' IL-1β and IL-1ra serum levels were substantially linked to seizure duration.

CONCLUSION

Proinflammatory cytokine IL-1 levels are associated with the genotypes of IL-1 β -31 and IL-1 β -511 promotor variants in children with an acute FS attack. CT genotypes of both IL-1 β -31 and IL-1 β -511 were related to increased postictal serum IL-1 β levels in children with FS compared to CC+TT genotypes. LD between these two variants is nearly complete. We believe that these new findings suggest that infants with fever-induced seizures may be more likely to have promotor variations in genes for interleukin-1 β (IL-1 β), rather than IL-6 or HMGB1.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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