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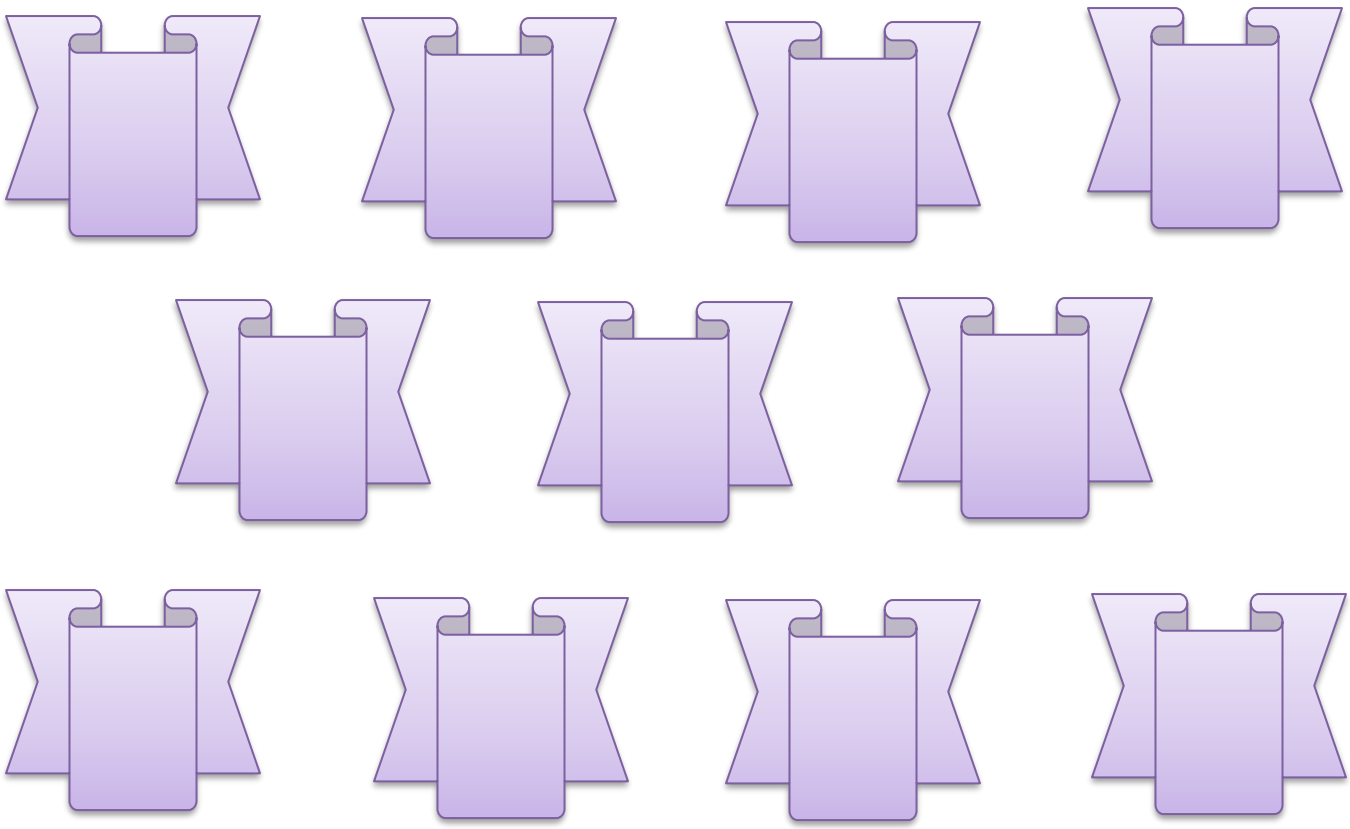

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Original Article

Serum Level of Interleukin 6 in Children with Febrile Seizures

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ABSTRACT

Background: Febrile seizures [FSs] are frequently observed seizure occurrences during childhood, making them the most prevalent form of seizures in this age group. The activation of the cytokine network is known to play a substantial role in the development of febrile seizures. It is hypothesized that the activation and subsequent release of Interleukin [IL]-6 may be responsible for the induction of fever in individuals experiencing febrile seizures. Interleukin-6 [IL-6] is widely recognized as a pivotal cytokine in the pathogenesis of febrile seizures.

The Aim of the work: This study aims to assess the value of serum interleukin-6 [IL-6] in children with febrile seizures [simple or complex].

Patients and Methods: This cross-sectional controlled study was conducted on 100 children, 50 formed the febrile seizure group [35 patients had a simple febrile seizure and 15 had a complex febrile seizure] aged 6 months to 6 years and 50 matched febrile children formed the control group. The patients of both groups were selected in the period from February to September 2022.

Results: We compared the serum IL-6 between the studied groups. The mean level of IL-6 in simple febrile seizure [SFS] was 44.04 ± 39.4, in complex febrile seizure [CFS] was 124.4 ± 95.69 and in the control group, it was 16.98 ± 14.4. Serum IL-6 was significantly higher in complex febrile seizure than in simple febrile seizure and the control group.

Conclusion: Inflammatory cytokines especially IL-6 play an important role in the genesis of febrile seizures.

Keywords: Febrile Seizures, Interleukin-6, Simple febrile seizure, Complex febrile seizure.

INTRODUCTION

Febrile seizures are prevalent convulsive disorders that occur during childhood, with a reported incidence rate of 2-5% among children [1]. A febrile seizure [FS] is characterized by the occurrence of a seizure in a child between the ages of 6 and 60 months, which is accompanied by a fever. This seizure occurs in the absence of any central nervous system infection or any other identifiable cause of acute seizures. Furthermore, the child experiencing the febrile seizure has no previous history of seizures unrelated to fever [2].

The etiology and pathogenesis of febrile seizures remain unknown. The most significant risk factor for febrile seizure is a familial history, with a higher number of affected relatives correlating with an increased risk [3].

Individuals who are susceptible to febrile seizures may experience seizures as a result of a sudden increase in body temperature, commonly referred to as fever, during an infectious disease [4]. There exists a possibility of recurrence in children who experience a simple febrile seizure, and it has been observed that approximately 2-7% of these children may develop epilepsy during their adolescence [5].

The pathogenesis of febrile seizures involves an intricate interplay between immune-inflammatory processes, activation of cytokines, and genetic factors [6]. The regulation of febrile responses is significantly influenced by cytokines with proinflammatory and anti-inflammatory properties, such as interleukin-1, interleukin-6, and tumor necrosis factor [7].

Research has indicated that there are changes in the levels of pro-inflammatory cytokines such as IL-6 and anti-inflammatory cytokines such as IL-4 in individuals experiencing febrile seizures. These alterations potentially contribute significantly to the development and progression of febrile seizures [8].

Interleukin-6 [IL-6] is a proinflammatory cytokine that exhibits biological activity in the context of inflammation and is linked to the occurrence of fever during the acute stage of febrile seizures. Previous studies have reported on the correlation between the levels of IL-6 in both plasma and cerebrospinal fluid and the occurrence of febrile seizures over an extended period of time. The induction and subsequent liberation of interleukin-6 [IL-6] are hypothesized to be responsible for the occurrence of fever in individuals experiencing febrile seizure [9, 10].

So, this study aims to assess the value of serum interleukin-6 [IL-6] in children with febrile seizures [simple or complex].

PATIENTS AND METHODS

This cross-sectional-controlled was conducted on 100 children, 50 formed the febrile seizure group [35 patients had simple febrile seizure and 15 had complex febrile seizure] aged 6 months to 6 years and 50 matched febrile children formed the control group. The patients of both groups were selected from the pediatric outpatient clinic of Bab-Elsharyia University Hospital, Egypt in the period from February to September 2022. The study was approved ethically by the faculty of medicine [Al-Azhar University]. Patients were recruited after taking informed written consent according to the following criteria:

The inclusion criteria: For the febrile seizure group [50 children]; 1] 6 months to 6 years old diagnosed as febrile seizures [by history, clinical examination, fever > 38 °c]. 2] Included simple seizures [lasting less than 15 minutes, have no focal features and do not recur within 24 hours] and complex seizures [lasting more than 15 minutes, have focal features and recurred within 24 hours] [11].

For the control group [50 children]: full-matched patients attended outpatient clinics with acute febrile illnesses without a present or past history of seizures.

The exclusion criteria are: Known patients with neurological diseases e.g. CP. 5] Congenital anomalies. 6] Inborn error of metabolism. 7] Patients with severe chronic diseases e.g., liver disease, renal disease, and diabetes mellitus.

Data collection

The patients of the study were subdivided into 3 groups: Group [1]: patients had a simple seizure 35 [70%]. Group [2]: patients had a complex seizure 15 [30]. Group [3]: 50 matched children. All patients were subjected to the following: Full history taking which included personal history including [age and sex], detailed seizures history, first attack or

recurrent, degree of fever, duration of the attack and description of fit including focal or generalized, degree of consciousness, post-ictal stupor and treatment of fit], Developmental history, and family history for similar condition or consanguinity. General, local examinations and complete neurological assessments were also done for every child. Laboratory investigations including Complete blood count [CBC], ESR, C- reactive protein [CRP], Ca+ Mg+, and blood glucose level were done immediately after recruitment. Serum IL-6 assay was done as the following; Venous blood samples were obtained from patients within 30 min of the time of seizure, centrifuged, and stored at -20 C till the time of assay. The IL6 concentrations in the stored specimens were determined through the utilization of a double antibody sandwich ELISA technique. The Elecsys IL-6 kit [Ref:05109442] was employed for this purpose, following the manufacturer's instructions and employing a standard curve.

Statistical analysis: The data underwent analysis using the statistical software package for social sciences, version 20.0 [SPSS Inc., Chicago, Illinois, USA]. The quantitative data were represented as the mean value ± the standard deviation [SD]. The qualitative data were represented using frequency and percentage. The independent-sample t-test was employed to assess the significance of differences between the two quantitative normally distributed means. The chi-square [$\chi 2$] test of significance was employed to assess the differences in proportions between two qualitative variables. A P-value $\leq$ 0.05 is considered significant.

RESULTS

Table 1 showed the demographic data for each group, including age, gender, consanguinity, and positive family history of febrile seizure. The mean age in the group [1] was 34.5 ± 17.3 months, 37.1 ± 15.2 months in group [2], 36.06 ± 16.46 months in group [3]. Males made up 57% of the patients in group [1], 46% of the patients in group [2], and 42% of the patients in group [3]. Only [18%] of the febrile seizure patients have positive consanguinity history and 15 [30%] of Febrile cases have a positive family history.

In Table 2 the pattern of febrile seizures was compared between group [1] and group [2], the history of recurrence of the attack was positive in 45% of group [1] and 40% in group [2] with no significant difference between them.

According to the causes of the fever, there were no significant differences in the etiology of fever between the cases and the control group. [Table 3].

Table 4 showed the hematological data between the three groups, there were no significant differences regarding Hb and ESR. However, CRP and PLT were significantly Lower in group [3] than group [1] and group [2]. Moreover, WBCs was significantly higher in group [2] than group [1] and group [3].

In table 5 the serum electrolytes, we measured serum Mg, serum Ca and RBG. there were no significant differences between the studied group as regard the serum electrolytes measured. Table 6 showed the serum IL-6 between the studied groups. The mean level of IL-6 in group [1] was 44.04 ± 95.6, 124.54 ± 39.4 in group [2], and 16.98 ± 14.4. in group [3]. Serum IL-6 was significantly higher in group [2] than group [1] and group [3] with a p-value < 0.001.

Table [1]: Demographic data of the studied cases

		Group [1] N= 35	Group [2] n= 15	Group [3] N = 50	P value
Age [years] [mean ± SD]		34.5 ±17.3	37.1 ± 15.2	36.06 ± 16.46	0.860
Sex	Female	15 [42.8%]	8 [53.3%]	29 [58%]	
	Male	20 [57.1%]	7 [46.6%]	21 [42%]	0.499
Consanguinity		2 [5.7%]	7 [46.6%]	-	0.577
Positive family history		11 [31.4%]	4 [26.6%]	-	0.736

Table [2]: Types of febrile seizures among the studied cases

Seizure pattern	Group [1] [n= 35]	Group [2] [n=15]	Group [3] [n=50]	P value
First attack	19 [54.2%]	9 [60%]	–	0.717
Recurrent attack	16 [45.7%]	6 [40%]		

Table [3]: Etiology of the acute febrile illness

Etiology	Group [1] [n= 35]	Group [2] [n=15]	Group [3] [n=50]	P value
Pharyngitis	10 [28.5%]	5 [33.3%]	18 [36%]	0.391
Tonsillitis	6 [17.14%]	3 [20 %]	11 [22%]	0.446
Otitis media	2 [5.7%]	2 [13.3%]	5 [10%]	0.728
Lower respiratory infection	7 [20%]	2 [13.3%]	5 [10%]	0.604
Gastroenteritis	7 [20%]	3 [20%]	9 [18%]	0.799
Urinary tract infection	3 [8.5%]	0 [0%]	2 [4%]	0.242

Table [4]: Hematological findings of the studied cases

	Group [1] [n= 35]	Group [2] [n=15]	Group [3] [n=50]	P value
Hemoglobin [mean ± SD]	11.07 ± 0.576	11.30 ± 0.535	11.21 ± 0.742	0.618
WBCs [mean ± SD]	18.5±1.56	19.4 ± 1.29	17.9 ± 1.504	0.009**
PLT [mean ± SD]	249.14± 78.13	310.33 ± 108.9	235.16 ± 46.91	0.04*
CRP [mean ± SD]	33.91±2.24	38.16 ± 6.64	32.58 ± 6.41	0.001**
ESR [mean ± SD]	10.97 ± 2.50	10.33 ± 2.32	7.79 ± 1.79	0.055

Table [5]: Serum electrolytes of the studied cases

	Group [1] [n= 35]	Group [2] [n=15]	Group [3] [n=50]	P value
Serum Ca+	8.83 ± 1.39	9.60 ± 1.09	9.08 ± 1.22	0.171
Serum Mg+	1.63 ± 0.170	1.65 ± 0.191	1.59 ± 0.203	0.392
RBG	82.93 ± 12.5	87.49 ± 14.6	85.52 ± 12.25	0.541

Table [6]: Serum levels of IL-6 of the studied groups

	Group [1]	Group [2]	Group [3]	P value
IL-6 [pg/ml)	44.04 ± 95.6	124.54 ± 39.4	16.98 ± 14.4	<0.001 *

DISCUSSION

As regards measures the demographic data for each group, including age, gender, consanguinity, and positive family history of febrile seizure. The mean age in the group [1] was 34.5 ± 17.3 months, the mean age in group [2] was 37.1 ± 15.2 months and the mean age in group [3] was 36.06 ± 16.46 months. Males made up 57% of the patients in group [1], 46% of the patients in group [2], and 42% of the patients in group [3]. Only [18%] of the febrile seizures' patients have positive consanguinity history and 15 [30%] of febrile cases have a positive family history, all groups were equivalent in terms of demographic data with no statistically significant difference in age, gender, consanguinity, and positive family history.

The result is similar to previous studies, in **Azab *et al.*** [9] study the patients with simple febrile seizure and 35 patients with complex febrile seizure, their ages ranged from 6 to 72 months [mean 31 months], 51 males and 49 females. In the study done by **Fadl *et al.*** [12], the mean age in the Febrile seizure group was 3.1±0.39 years old, and 57% of them were males. **Gupta *et al.*** [13], the mean age of cases was [12.8] months, 61.2% of them were males.

The causes of acute febrile illness among the studied cases were so similar between the three groups, the pharyngitis was the most common cause that was found in 28.5% of the group [1], 33.3% in group [2] and 36.6% in group [3]. Those are similar to **El-said *et al.*** [14], result; in his study, the most common cause is respiratory tract infection and pharyngitis. Also, in **Kumar *et al.*** [15], study Acute respiratory tract was the main cause of the fever.

Regarding the type of seizure among the studied cases simple seizure was the dominant, it presented in 70% of patients and there was a positive history of previous attack in 56% of the cases, in **El-said *et al.*** [14], report, [60%] of the patients had a simple seizure, positive family history was found in [44%] of the patients. In **Gupta *et al.*** [13], report [31.2%] had complex febrile seizure.

The results of the study showed that regarding to routine blood work there was an elevation of WBCs, CRP, PLT in group [2] than group [1] and group [3] and a slight reduction of RBG. Hb, ESR, Ca and Mg were within the normal ranges. Whether blood indices can help predict the prognosis of febrile seizures is worthy of further study. Deferent parameters were measured in each study, these differences may due to the different presentation of the cases of different inclusion criteria. In **chen *et al.*** [10], study of clinical and laboratory findings of patients showed that Hb, platelet counts, and blood sodium levels were significantly lower in the febrile seizure group than those in the febrile complex and control groups.

The study further evaluated the difference of these findings between simple and complex seizures, and there were no significant differences found. There was a statistical difference in WBCs, PLT and CRP they were higher in the complex seizure's group in comparison to the control group.

In **Azab *et al.*** [9], study WBCs and CRP levels were significantly higher in the complex group. However, in **Chen *et al.*** [10], results, the platelet count of the complex febrile group was significantly lower than that of the simple febrile group, and there were no significant differences between the two group in other clinical data and laboratory findings.

IL-6 is a pleiotropic proinflammatory cytokine with a wide range of biological activities in immune regulation, hematopoiesis, inflammation, and neoplasia and interleukin-6 demonstrates a strong correlation with fever [9].

A dual role of IL-6 in seizures has been demonstrated in febrile seizure experimental models. **Fakuda *et al.*** [16], reported that interleukin-6 plays an anticonvulsive role in experimental hyperthermia-induced seizures which might suggest similar properties of this cytokine in children with febrile seizures.

These data releveled the mean value of serum IL-6 was 76.6 pg/ml, which is significantly high according to its baseline level [7 pg/ml]. Moreover, the study compared the IL-6 level between the three studied groups and it was significantly higher in the complex group than the other two groups. In simple seizures [group 1] the mean level of IL6 was [44.04 ± 95.6], while in complex seizures [group 2] the mean level was [124.54 ± 39.4] and control group [group 3] the mean level was [16.98 ± 14.4].

These findings are consistent with the study conducted by **Azab *et al.*** [9], in which they examined the levels of adiponectin, serum leptin, and serum IL-6. **Azab *et al.*** reported that patients with simple febrile seizures exhibited similar levels of adiponectin in both serum and cerebrospinal fluid [CSF] compared to those with complex febrile seizures. However, they found that serum leptin levels were significantly lower in patients with complex febrile seizures compared to the group with simple febrile seizures. Additionally, **Azab *et al.*** observed significantly higher levels of serum and CSF IL-6 in patients with complex febrile seizures compared to those with simple febrile seizures. However, in **Chen *et al.*** [10] result, there was no significant difference found in IL-6 between Simple and complex seizers groups.

The levels of IL-6 may exhibit variability in relation to the timing of fever and seizures, thus obtaining serial measurements would have provided more informative data. In certain instances, the levels of cytokines after the stimulation of lymphocytes may exhibit a stronger correlation with the association or etiology of febrile seizures.

Conclusion: Serum IL-6 plays an important role in the genesis of febrile seizure which may cause subsequent epilepsy.

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