

Increased Post-Seizure ACTH Peak May Have a Role in the Benign Characteristics of Febrile Seizures

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Introduction:

Febrile seizures (FS) are the most common seizures in childhood (1,2). There is substantial evidence about the role of inflammation in the pathogenesis of FS. It is thought that the cytokine network is active in FS and may have a role in the pathogenesis (3). Other molecular mechanisms that may affect inflammation have not been studied well.

Objective:

We aimed to elucidate the role of some molecular mechanisms other than cytokines in the inflammatory process in FS.

Materials and methods:

The study comprised patients aged six months to six years old with FS (n=29), afebrile seizures (AS group, n=17), and fever without seizures (F group, n=30). Total leukocyte count, and serum CRP, fibrinogen, complement-C3, -C4, intercellular and vascular adhesion molecules (ICAM1, VCAM1), ACTH and cortisol levels were measured at arrival or after seizure, in all groups; and also, at 24th hour in the FS and AS groups.

Statistical analysis: Kolmogorov-Smirnov test was used to determine whether the distribution of data was normal. In the comparison of the two groups, Student-T test was used in case of normal distribution and Mann-Whitney U test was used in case of non-normal distribution. In the comparison of the three groups, ANOVA test was used in case of normal distribution and Kruskal Wallis test was used in case of non-normal distribution.

Results:

Age and gender distribution were similar between groups (Table 1). In terms of cortisol and ACTH levels showing circadian rhythm, blood collection times were divided into 3 groups according to diurnal change: 03:00 – 12:00, 12:00 – 20:00, 20:00 – 03:00. Blood collection times did not differ significantly between the groups (p>0.05). Initially, the FS group's ACTH and cortisol levels were higher than the F and AS groups, (p=0.001, p=0.032, respectively). In contrast, at the 24th hour, ACTH level was significantly lower in the FS group (p=0.009, Table 2, Figure 1). In comparison of the levels at initial and 24th hour, VCAM1 increased in the FS (p=0.001) and ICAM1 increased in the AS groups (p=0.035) (Table 3). The post-seizure leukocyte counts were higher in both FS and AS groups than the levels at 24th hour (p=0.000, p=0.023). In the FS group, there was a negative correlation between complement-C4 level and age of first FS [r= -0.548, p=0.003 (for post-seizure C4 value); r= -0.431, p=0.025 (for C4 level at 24th hour), Spearman analysis)] (Figure 2).

Variable (mean±SD or n/total)	FS group	AS group	F group	p value
n	29	17	30	
Female gender	16/29	9/17	12/30	>0.05
Age (years)	2.3±1.2	2.1±1.7	2.8±1.5	>0.05
CRP (mg/dL)	15.6±20.6, median 10.15	0.94±0.67, median 0.85	21.2±32.06, median 14.9	0.000
Leukocytes (x10 ³ /µL)	12.19±6.01	9.57±3.09	10.71±5.15	>0.05
Fibrinogen (mg/dL)	331.9±91.1	285.6±132.6	326.2±107.3	>0.05
C3 (mg/dL)	1.07±0.17	1.08±0.27	1.05±0.22	>0.05
C4 (mg/dL)	0.25±0.11	0.34±0.47	0.22±0.07	>0.05
ACTH (pg/mL)	157.1±155.2, median 76.1	79.2±89.4, median 60.3	94.1±279.3, median 17.05	0.001
Cortisol (µg/dL)	25.8±11.9	16.3±10.7	19.4±13.3	0.032
ICAM-1 (pg/mL)	1102.3±867.2	996.8±716.5	1415.1±795.3	>0.05
VCAM-1 (ng/mL)	28.56±9.33	31.3±10.07	31.14±7.53	>0.05

Table 1. Comparison of demographic characteristics and laboratory values at admission in patients with febrile seizure (FS), afebrile seizure (AS), and febrile (F) without seizures.

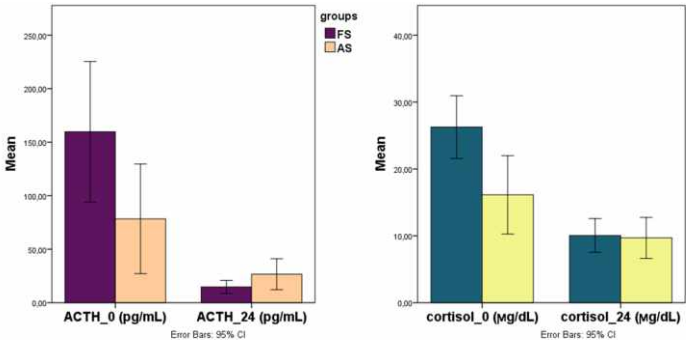


Figure 1. An ACTH peak was observed in the febrile seizure (FS) group at post-seizure period. While ACTH level was the highest in the FS group at early post-seizure period (p=0.001), it was significantly lower in the FS group at 24th hour, in comparison with the afebrile seizure (AS) group (p=0.009). While post-seizure cortisol level was higher in the FS group (p=0.032), there was no difference between the groups at the 24th hour (p>0.05). When the levels at the post-seizure period were compared with the levels at 24th hour, while ACTH and cortisol levels significantly decreased in the FS group (p<0.001), there was no significant change in both values in the AS group (p>0.05).

Variable (mean±SD)	FS group	AS group	p value
Cortisol (µg/dL)	9.8±6.38	9.69±5.76	>0.05
CRP (mg/dL)	33.6±35.3, median 14.5	1.56±1.66, median 0.9	0.000
Fibrinogen (mg/dL)	346.3±95.9, median 326.6	238.4±53.8, median 245.3	0.000
ACTH (pg/mL)	14.18±14.4, median 10.6	25.4±25.7, median 16.7	0.009
Leukocytes (x10 ³ /µL)	8.89±3.64	7.82±2.03	>0.05
C3 (mg/dL)	1.01±0.18	0.99±0.22	>0.05
C4 (mg/dL)	0.24±0.05	0.22±0.07	>0.05
ICAM-1 (pg/mL)	1589.9±1109.2	1894.8±1616.5	>0.05
VCAM-1 (ng/mL)	34.32±9.83	31.59±11.21	>0.05

Table 2. Comparison of data at 24th hour in FS and AS groups.

Variable (mean±SD)	FS group			AS group		
	Post-seizure	At 24 th hour	p value	Post-seizure	At 24 th hour	p value
VCAM-1 (ng/mL)	28.56±9.3	34.32±9.8	0.001	31.3±10.1	31.6±11.2	>0.05
C3 (mg/dL)	1.07±0.17	1±0.18	0.048	1.08±0.27	0.99±0.22	>0.05
Leukocytes (x10 ³ /µL)	12.19±6	8.9±3.6	0.000	9.57±3.09	7.82±2.03	0.023
Cortisol (µg/dL)	25.8±11.9	9.8±6.4	0.000	16.13±10.99	5.76±1.44	0.057
CRP (mg/dL)	15.6±20.6	33.6±35.3	0.000	0.94±0.67	1.56±1.65	>0.05
ACTH (pg/mL)	157.1±155.2	14.18±14.4	0.000	79.2±89.4, median 60.3	25.4±25.7, median 16.7	>0.05
ICAM-1 (pg/mL)	1102.3±867.2	1589.9±1109.2	>0.05	996.8±716.5	1894.8±1616.5	0.035
Fibrinogen (mg/dL)	331.9±91.1	346.3±95.9	>0.05	285.6±132.6	238.4±53.8	>0.05

Table 3. Comparison of data at 24th hour in FS and AS groups.

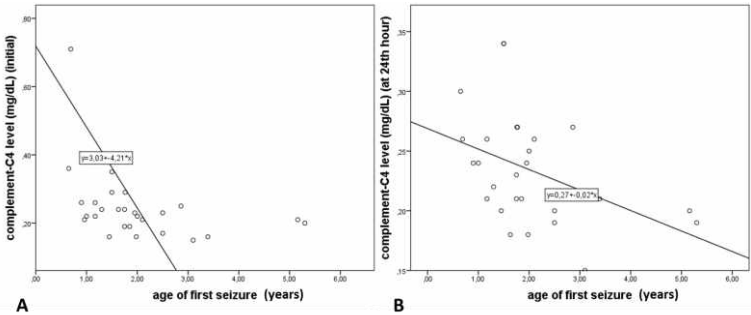


Figure 2. In the FS group, age at first seizure was negatively correlated with the complement-C4 levels at early post-seizure period (a) and at 24th hour (b). [a] r= -0.548, p=0.003, b) r= -0.431, p=0.025]

References:

1.Singhi PD, Jayshree K. Indian Pediatr 1995;32(5):564–72. 2.Reuber M, et al. Seizure. 2004;13(2):129–35. 3.Virta M, et al. Epilepsia. 2002;43(8):920–3. 4.Fabene PF, et al. NatMed 2008;14(12):1377–1383. 5.Kallmann BA, et al. Brain. 2000;123(4):687–97. 6.Dougherty D, et al. Pediatrics. 2008;121(6):1281–6.

Conclusions:

In the FS group, the higher ACTH peak following seizure, considering its protective effects on blood-brain permeability and its role in the anti-inflammatory response, may be a reason for the self-limiting character of simple FS. To our knowledge, the present study is the first report of the evaluation of ACTH and cortisol levels in FS.

Seizure-related differences in VCAM1 or ICAM1 levels within 24 h were observed in both the FS and AS groups. IL-1β, which is thought to have a role in the pathogenesis of FS, is a potent inducer of endothelial adhesion molecules (4). Adhesion molecules are involved in the processes of leukocyte attachment and transmigration through the endothelium to the area of inflammation (5).

A statistically significant, negative correlation was found between the complement C4 level and the age at first FS in our study. This finding may be important since the onset of the first FS before the age of one may increase the risk of epilepsy (6). To the best of our knowledge, our study is the first to evaluate complement levels in FS patients.

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