

Original Research Article

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## Tumor Necrosis Factor-Alpha and Interleukin-1 Beta in Febrile Seizures

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### ABSTRACT

Febrile seizures happening between 6 months and 5 years are considered the most prevalent form of childhood seizures. It is defined as seizures occurring during fever in children without central nervous system infection. Pro-inflammatory cytokines released during infection play an essential role in the mechanism of febrile seizures. Studies try to clear the responsibility of these pro-inflammatory cytokines in the pathogenesis of febrile seizures. Among these cytokines, interleukin-1beta (IL-1 $\beta$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ ) have important roles in the pathogenesis of febrile seizures with contradictory results. In our study we aimed to identify the relation between serum TNF- $\alpha$ , IL-1 $\beta$  and febrile seizures. The study included ninety patients, with an age range between 6 months and 5 years, who were taken consecutively from the out-patient clinic and emergency department of Mansoura University Children Hospital "MUCH" between June 2015 and August 2016. Forty children presented with febrile seizures, 30 children presented with fever without seizures and 20 patients with seizures without fever. Blood sample was taken from patients with febrile seizures and also from those with afebrile seizures within half hour of the time of the convulsion, then we measured serum TNF- $\alpha$  and IL-1 $\beta$  levels by ELISA technique. Also, samples were taken from patients with fever but without seizures then they were similarly studied. Serum IL-1 $\beta$  and TNF- $\alpha$  level were higher in children with febrile seizure than in those with fever only (significant P value < 0.05). Their serum levels were also higher in afebrile seizure children than those with febrile illness only and lower than febrile seizure patients with no significant P value. Our study supports that the increased production of TNF- $\alpha$  and IL-1 $\beta$  is positively concomitant with the occurrence of febrile seizures.

#### Keywords

Febrile seizures,  
Interleukin-1beta  
and Tumor necrosis  
factor-alpha.

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### Introduction

Febrile seizure (FS) is considered the most common form of convulsive disease during infancy and young childhood (Stafstrom, 2002). Febrile seizure has been defined by the American Academy of Pediatrics (AAP) as a seizure which occurs between the ages of 6 months and 5 years in febrile children do not suffer from intracranial infection, metabolic

abnormality, or history of afebrile seizure (American Academy of pediatrics, 2008).

The prevalence of febrile seizures varies between 2% and 5% of children aged from 6 months to 5 years. It decreases after 4 years of age and rarely reported after 7 years (American Academy of pediatrics, 2008) and

(Sugai, 2010). There is a 15 -70% chance after a single attack of febrile seizures to develop another one (Graves *et al.*, 2012).

Febrile seizures can be classified into simple and complex types. Simple febrile seizures last for less than 10 minutes, are generalized tonic-clonic convulsions and occur only once within a twenty four hours period. They are not associated with any focal lesion and they clear spontaneously. However, complex febrile seizures are prolonged (last for more than ten-fifteen minutes), relapse many times within 24 -hour period and characterized by focal, or multiple *lesions* (Baumann, 1999), (Shinnar and O'Dell, 2003) and (Waruiru and Appleton, 2004).

Febrile seizures have many risk factors include delay in development, neonatal nursery stay for more than 30 days, viral infections, genetic predisposition of febrile seizures, certain types of vaccines, and electrolytes deficiency as zinc and iron (Berg *et al.*, 1995; Chung and Wong, 2007; Hartfield *et al.*, 2009; Laina *et al.*, 2010).

Many factors have been described in the febrile seizures pathophysiology as viral and bacterial infections (Millichap and Millichap, 2006), immature brain susceptibility to temperature (Holtzman *et al.*, 1981), association with interleukins (Tsai *et al.*, 2002), circulating toxins (Virta *et al.*, 2002), deficiency of trace element (Amiri *et al.*, 2010) and deficiency of iron (Kumari *et al.*, 2011).

One of the most important factors which play a role in the mechanism of febrile seizures is cytokines (Virta *et al.*, 2002). They are immunological mediators involved in many immunological diseases and infectious diseases. Studies show promising role to understand the role of pro-inflammatory cytokines in the pathogenesis of febrile convulsions (Haspolat *et al.*, 2002).

So TNF- $\alpha$  and IL-1 $\beta$  are considered the most important. They have direct and also indirect effects on neurons and neurotransmitters which are secreted during stress and fever in children (Tomoum *et al.*, 2007).

In this study we aimed to evaluate the relation between febrile seizures and serum TNF- $\alpha$  and IL-1 $\beta$ .

## **Materials and Methods**

Our study design was case control study. It included ninety patients, with an age range between 6 months and 5 years, who were taken consecutively from the out-patient clinic and emergency department of Mansoura University Children Hospital "MUCH" between June 2015 and August 2016. Forty children presented with febrile seizures, 30 children presented with fever without seizures and 20 patients with seizures without fever. Children with febrile seizures were classified into two types: simple febrile seizure (seizure with duration less than fifteen minutes and only occur once within twenty four hours); and complex febrile seizure (seizure lasting for more than 15 minutes, or recurred within 24 hours).

Patient inclusion criteria include: age between 6 months and 5 years, body temperature higher than 38°C without recognized cause of the seizure in febrile seizure patients. Children with neurological disabilities, electrolyte imbalance, metabolic disorders, intracranial infection and co-morbidity of different disorders which can change leucocytes count, were excluded.

Written full informed consent was taken from the parents of each patient after discussion of our study with them with approval of our institutional IRB. All patients underwent history taken and full general and neurological assessment.

Blood samples were obtained within half an hour after the episode of seizure in both groups with seizures either febrile or afebrile, then serum samples were separated and frozen for cytokine assay later on.

IL-1 $\beta$  and TNF- $\alpha$  were measured using commercially available, enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's procedure (for IL-1 $\beta$ , TNF- $\alpha$ , Panomics Inc., Redwood City, CA, USA).

CRP was done using turbidometric kits (Spinreact, USA), in which the CRP binds with specific antibody producing insoluble immune complexes causing turbidity which were be measured spectrophotometrically.

### **Statistical analysis**

It was considered that P value was significant if less than 0.05 and if less than 0.001 it was considered highly significant. This was done using the Statistical Package for Social scientists (SPSS) (SPSS Inc., Chicago, IL, USA).

### **Results and Discussion**

Table 1 shows the number, age, temperature, WBC, and CRP in the studied groups. There was no significant difference in the CRP level between the febrile seizures and febrile control group (P value: 0.27).

Table 2 shows that serum IL-1 $\beta$  and TNF- $\alpha$  level were significantly higher in febrile seizure patients than in those with fever only (P value < 0.05).

Their serum levels were also higher in afebrile seizure patients than patients with fever only and lower than febrile seizure patients with no significant P value.

Table 3 shows that serum CRP, IL-1 $\beta$  and TNF- $\alpha$  level were not significantly differing between simple and complex febrile seizures (P value > 0.05).

Many studies have been done to determine the mechanism of childhood febrile seizures, but the definite mechanism of this condition has not yet been discovered (French, 2012). A little number of studies pointed to that certain cytokines may play a role in febrile seizures (Matsuo *et al.*, 2006). Of these cytokines, TNF- $\alpha$  and IL-1 $\beta$ , play a major role in the pathogenesis of the disease with contradictory results in many studies (Hopkins, 2003).

In our study, serum levels of IL-1 $\beta$  were higher in our patients with febrile seizures than those with fever but without seizures with a significant P value. This agree with Yuhás *et al.*, (1999) who noted that IL-1 $\beta$  have pro-convulsing action in experimental animals. Also, Watkins *et al.*, (1995) study reported that glutamate release is increased through the role of IL-1 $\beta$  in increasing the production of TNF- $\alpha$ , resulting in increased levels of glutamate in extracellular spaces and also hyper-excitability.

In addition, IL-6 production is stimulated by IL-1 $\beta$  (Muñoz-Fernandez *et al.*, 1998). This agree with Tomoum *et al.*, (2007) who reported that TNF- $\alpha$  and IL-1 $\beta$  which are released during inflammation play a role on the secretion of neurotoxic neurotransmitters.

Several studies which described the roles of TNF- $\alpha$  and IL-1 $\beta$  in the development of febrile seizures reported contradictory results (Haspolat *et al.*, 2002). It is found by Tutuncuoglu *et al.*, (2001) that production of IL-1 $\beta$  increased in association with convulsions in febrile children. But Tomoum *et al.*, (2007) recorded that IL-1 $\beta$  does not increase in association with febrile seizures.

**Table.1** Descriptive data of the studied groups

|                                  | Febrile seizures | Febrile control | Afebrile seizures |
|----------------------------------|------------------|-----------------|-------------------|
| <b>Number</b>                    | 40               | 30              | 20                |
| <b>Age Mean (months)</b>         | 19.1             | 18.7            | 18.2              |
| <b>Male/ Female</b>              | 21/19            | 18/12           | 11/9              |
| <b>Temperature at admission</b>  | 38.7             | 38.8            | 37.0              |
| <b>WBC count /mm<sup>3</sup></b> | 11.800           | 12.100          | 7.200             |
| <b>CRP</b>                       | 7.1              | 6.7             | 2.8               |

**Table.2** Comparison of TNF- $\alpha$  and IL-1 $\beta$  between febrile seizures, febrile control and afebrile seizures subgroups

|                          | IL-1 $\beta$ (pg/ml) | TNF- $\alpha$ (pg/ml) |
|--------------------------|----------------------|-----------------------|
| <b>Febrile seizures</b>  | 12.6 $\pm$ 5.7       | 8.9 $\pm$ 3.2         |
| <b>Febrile control</b>   | 4.1 $\pm$ 2.6        | 3.2 $\pm$ 1.6         |
| <b>Afebrile seizures</b> | 8.2 $\pm$ 3.5        | 7.0 $\pm$ 4.5         |

**Table.3** Comparison between simple febrile seizures and complex febrile seizures

|  | Simple febrile seizures | Complex febrile seizures |
|--|-------------------------|--------------------------|
| <b>Number</b>                          | 31                      | 9                        |
| <b>IL-1<math>\beta</math> (pg/ml)</b>  | 12.1                    | 13.4                     |
| <b>TNF-<math>\alpha</math> (pg/ml)</b> | 8.6                     | 9.1                      |
| <b>CRP</b>                             | 7.5                     | 6.6                      |

Dube *et al.*, (2005) found that IL-1 $\beta$  plays a role in increasing N-methyl-D-aspartate secretion on an experimental animal, so it has a role in the development of febrile convulsions. Other studies agree with Dube, in that cytokines play a major role in the mechanism of febrile seizures. These studies demonstrated that immune cells such as B cells, macrophages and T cells are stimulated during viral infections, especially upper respiratory tract infection and they release IL-6, TNF- $\alpha$ , and IL-1 $\beta$  (Yuhas *et al.*, 1999).

It is recorded by Lahat *et al.*, (1997) that children with febrile seizures had no significant difference in levels of TNF- $\alpha$  in their cerebrospinal fluid and also in plasma IL-1 $\beta$  levels in comparison to a control child group. And also Mahyar *et al.*, (2014) found different results from us which do not support the hypothesis that increased TNF- $\alpha$  and IL-1 $\beta$

production is included in febrile seizures pathogenesis.

Other studies reported that there were no significant difference in the serum levels of TNF- $\alpha$  and IL-1 $\beta$  between children with febrile seizures and the control group.

However, levels of IL-1 $\beta$  in cerebrospinal fluid were higher in patients with febrile seizures in comparison to the control children with significant P value (Haspolat *et al.*, 2002; Virta *et al.*, 2002; Tomoum *et al.*, 2007).

Ichiyama *et al.*, (1998) recorded that a significant higher plasma concentration of IL-1 $\beta$  in patients with febrile convulsions and those with encephalitis or meningitis.

Contradictory findings of previous studies can be explained by variability in the sample time,

temperature degree, fever duration, and infection type (Roth *et al.*, 1993). Several studies reported that levels of IL-6 may be increased also in epileptic patients (Liimatainen *et al.*, 2009; Lehtimäki *et al.*, 2011).

In our study TNF- $\alpha$  and IL-1 $\beta$  levels were not significantly differing between simple and complex febrile seizures. Also, there is high CRP as a result of underlying infection in both groups with febrile seizures and those with fever only without significant difference P value. This agree with Biyani *et al.*, study in 2017.

Our study supports that the increased production of TNF- $\alpha$  and IL-1 $\beta$  is positively concomitant with the occurrence of febrile seizures.

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