



Prenatal stress potentiates febrile seizure and leads to long-lasting increase in cortisol blood levels in children under 2 years old☆



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ABSTRACT

Neurological disorders can be exacerbated in an offspring that is exposed to stress prenatally. This study is aimed to investigate the severity of febrile seizures (FS) in the offspring under 2 years old that were prenatally stressed. In this study, 158 children below 2 years old with FS were selected. Information about convulsion including seizure lasting, recurrence of seizure, age of the first seizure and type of FS was gathered. Blood samples were obtained from the offspring to measure the cortisol blood levels. Questionnaire was filled in to evaluate the perceived stress and exposure or non-exposure to major stresses during pregnancy. Results of this study showed that both high Perceived Stress Scores (PSS) during pregnancy and exposure to major stresses during pregnancy significantly increased seizure duration and seizure intensity. Also, the appearance of complex FS was significantly higher in prenatally stressed children than the unexposed ones. Further, cortisol blood levels were significantly higher in prenatally stressed subjects. It can be concluded that both higher PSS and/or exposure to major stresses during pregnancy potentiate FS parameters and lead to long lasting increase in cortisol blood levels in the offspring.

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1. Introduction

A febrile seizure (FS) refers to the seizure that occurs during a febrile episode. It is a common condition, affecting 2–5% of children aged 3 months to 5 years [1]. Febrile seizures are divided into the following three distinct categories: simple febrile seizure, complex febrile seizure, and febrile status epilepticus. A simple febrile seizure is one that is generalized, occurs once in a 24-h period and lasts less than 15 min. Among children with febrile seizures, 70–75% have simple febrile seizures. A febrile seizure is considered complex if it is focal or localized to a specific part of the body, duration longer than 15 min but less than 30 min, or involves recurrence of seizures in a 24-h period; 20–25% of febrile seizures are complex. Febrile status epilepticus is prolonged lasting longer than 30 min. Recently a 4th category has emerged describing a subset of

complex febrile seizures called febrile seizure plus. It includes simple febrile seizures that have occurred more than once in a 24-h period [2].

Simple FSs are considered benign, while complex seizures can be later developed into more severe conditions such as temporal lobe epilepsy [3]. It is believed that both genetic and early environmental factors play a role in the etiology of the disease [4,5] and several studies have suggested that prenatal factors might influence the risk of any kind of seizures including FS [5–11]. Prenatal stress is the exposure of an expectant mother to distress and can lead to neurological disorders in the offspring [11,12]. It has been suggested that prenatal stress can have programming effects on the brain development [13,14], which may underlie the relationship between prenatal factors and some neurological disorders in childhood [15]. Stress hormones, such as glucocorticoids and corticotrophin releasing hormone (CRH), are related to alterations in the fetal central nervous systems [16]. Both endogenous and synthetic glucocorticoid exposure may modify the neurotransmitter systems and transcriptional machinery influencing the brain morphology [5,17]. Experimental animal findings have shown that severe stress may cause structural changes in the hippocampus and the function of the hypothalamic–pituitary–adrenal (HPA) axis in the offspring, which decreases the seizure threshold [18]. The extension of these findings to human development is not yet clear [19]. Repetitive activation of the HPA axis during the frequent bouts of stress often results in the

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elevated concentrations of glucocorticoids in both peripheral and central circulation [20]. Abnormally high levels of glucocorticoids have been shown to be toxic to the regions of the nervous system that are easily excitable such as the pyramidal cells of the hippocampus [21]. These regions may therefore be intimately involved in the development of seizure activity [22]. We hypothesized that stress hormones in pregnant mothers could cross the placenta and enter the fetal circulation [23], which may program the brain development in fetus [4] and increase the susceptibility to seizure [6,7,9,11]. Therefore, this study was designed to investigate the severity of febrile seizures in the offspring under 2 years old that were prenatally stressed.

2. Materials and methods

2.1. Study design and participants

This work is a population-based historical cohort study performed on 158 children aging less than 2 years (range:3–24, mean: 13.92 ± 5.8 months) whose mothers had referred to Health Care Center (Mottahari Hospital) of Urmia City in 2014. All the experimental procedures had been approved by Ethics Research Committee of Urmia University of Medical Science and the written informed consent was obtained from the mothers participating in the study. We collected information on FS by using a Perceived Stress Score (PSS) questionnaire. The maternal PSS was determined by the European Spanish Version PSS that demonstrated adequate reliability, validity (concurrent), and sensitivity [24]. In this research, 10-item version of the questionnaire was used. The items are rated on a 5-point Likert scale ranging from “Almost Never” to “Almost Always”. In studies conducted by Ghorbani et al. Cronbach's alpha for American and Iranian population was calculated as 0.86 and 0.81, respectively [25]. Construct validity of the questionnaire was determined as 0.63 that is significant in alpha level of $p < 0.05$ [26]. All the potential FSs were checked through the diagnostic review of medical records. The inclusion criteria related to the mother and child included maternal weight, maternal age, history of illness, birth score, maternal education, delivery type, delivery status, family history of seizures, and information on FS severity. The exclusion criteria included child age of over 2 years old, history of seizure without fever during 2 years, children with sign of brain infections, congenital malformation in children, neonate seizures on the first day of parturition, and mother's inability to cooperate in the survey. Type of seizures was also assessed as simple or complex; a seizure was considered as complex if it: 1. Was focal or localized to a specific part of the body; 2. Lasted for more than 15 min but less than 30 min; and 3. Was repeated more than once over a period of fever. The remaining seizures were regarded as simple except those lasted more than 30 min [2,27]. Here, we used seizure intensity criteria defined as the multiplication of the duration of seizure and number of seizures. These criteria were similar to the criteria that we used in a previous animal study [28]. The maternal PSS was determined and then they were divided into two groups: mothers who had high score of stress ($PSS > 15$) and mothers with lower score ($PSS \leq 15$). Although, there is no clear cutoff point for PSS, a study has reported 14.95 ± 5.29 for normal subjects and higher values for more stressed ones [29]. In analyzing the data, we categorized children as exposed to bereavement during prenatal life if their mothers had lost a child, husband, sibling, and a parent during the prenatal period or the mother had an exposure to an uncommon stressful event during gestation. The remaining children were considered as unexposed subjects. Also in analyzing the data, the participants were divided into two groups based on positive or negative family history (PFH or NFH). PFH was considered if at least one of the siblings or close relatives had history of any kind of seizure.

2.2. Assay of infants' cortisol blood levels

Blood samples were obtained from the participants in the morning at 8:00 and 10:00 and, then, the cortisol blood levels (ng/mL) were

analyzed using commercially available ELISA assay kit (Abcam, MA, USA).

2.3. Data processing and statistical analysis

For descriptive information on qualitative variables, the absolute and relative frequencies were calculated and, for the quantitative variables, the mean and standard deviation were calculated using SPSS (ver.21) software. To compare two groups who had normally distributed data, t-Student test was used. In the case of data without normal distribution, non-parametric tests were used. Type of FS (complex or simple) and the recurrence of seizure were compared between subjects by K^2 test. In addition, Pearson Correlation test was run to test whether there is a relationship between PSS, cortisol levels, seizure parameters and other relevant variables in mother and babies. The results were presented as mean $\pm$ SD and the differences were considered significant if $P < 0.05$.

3. Results

3.1. Neonatal birth weight and features of febrile seizure in high PSS and low PSS groups

Birth weight (BW), age of first FS, recurrent FS, type of seizure, and duration of seizure were compared between the high PSS and low PSS groups (based on maternal PSS). In the low PSS group, 83 women had full-term offspring with the BW of 3.33 kg, first FS age of 5.17 ± 12.00 months, recurrent FS of 19%, type of seizure (69 simple and 14 complex), and seizure duration of 5.61 min. In the high PSS group, 75 women had full-term children with the BW of 3.09 kg, age of first FS of 5.77 ± 13.30 months, recurrent FS of 28%, type of seizure (55 simple and 20 complex), and seizure duration of 7.12 min. Children in the high PSS group had lower BW and higher duration of FS ($P = 0.018$ and $P = 0.03$, respectively; **Tables 1 and 4**). Recurrent FS and type of FS differences were not significant between low and high PSS groups.

3.2. Neonatal birth weight and febrile seizure in exposed and unexposed groups

We also compared BW, age of first FS, recurrent FS, type of seizure, duration of seizure, and seizure intensity scores between exposed (exposure of mother to a major and uncommon event during the gestation) and unexposed groups. In the unexposed group, 131 women had the offspring with the BW of 3.24 kg, age of first FS of 5.55 ± 12.48 months, recurrent FS of 22%, complex seizure type of 16%, seizure duration of 6 min, and seizure intensity score of 9.96. In the exposed group, 27 women had children with the BW of 3.01 kg, age of first FS of 4.91 ± 10.50 months, recurrent FS of 29%, complex seizure type of 44%, seizure duration of 7.93 min, and seizure intensity score of 18.59. Children in the exposed group had lower BW, higher duration of seizure, higher incidence of complex seizure, and higher seizure intensity ($P = 0.024$, $P = 0.016$, $p = 0.001$, $P = 0.037$, respectively; **Tables 2 and 4**). There were no significant differences between the two groups in terms of recurrent FS.

Table 1

Comparison of birth outcomes and febrile seizure based on maternal PSS (high PSS and Low PSS).

Variables	High PSS (n = 75)	Low PSS (n = 83)	P value
BW (kg)	3.09	3.33	0.018
Age of first FS (month)	5.77 ± 13.30	5.17 ± 12.00	0.26
Recurrent FS (%)	28	19	0.15
Type of seizure (%)	26.66 complex	16.87 complex	0.09
Duration of seizure (min)	7.12	5.61	0.03

FS = febrile seizure; BW = birth weight; data presented as mean $\pm$ standard deviation, or n (%).

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