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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.

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 = <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 ± 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 ± standard deviation, or n (%).

Table 2
Comparison of birth outcomes and febrile seizure features between exposed and unexposed groups.

Variables	Exposed (n = 27)	Unexposed (n = 131)	P value
BW (kg)	3.01	3.24	0.024
Age of first FS (month)	4.91 ± 10.59	5.55 ± 12.48	0.65
Recurrent FS (%)	29	22	0.34
Type of seizure (%)	44 complex	16 complex	0.001
Seizure intensity	18.59	9.96	0.037

Seizure intensity = duration of seizure × number of seizures.

3.3. Effect of family history of seizures on FS

In the group with PFH, the recurrence of seizure was 39% and, in the group with NFH, it was 20%, which showed a significant difference between the two groups (Table 3, P = 0. 028, K^2). The risk of FS recurrence in the subjects with PFH was 3.36 times more than that among those with NFH (OR = 3.36, CI = 1.14–6.91) and the risk of complex seizure in the subjects with PFH was 2.71 times more than that among those with NFH (OR = 2.71, CI = 0. 78–3. 75).

3.4. Effect of child sex on stress-induced changes in FS

Type of FS (complex or simple) was compared between the male and female subjects by K^2 test. Although this comparison did not show any significant difference between the male or female subjects, the result (OR = 1.75, CI = 0.36–8.42) indicated that the risk of complex seizure in boys was 1.75 times higher than that among the girls in the exposed group.

3.5. Impact of stress during pregnancy on cortisol blood levels in the offspring

The normal range of cortisol blood level in children 1–24 months is 10–350 ng/mL [30]. In the current study, blood levels of cortisol differed by the sex of subjects. The levels of cortisol were significantly higher (P = 0. 049) in males than in females (Fig. 1). Cortisol blood levels in the male and female subjects were analyzed based on the score of maternal stress. Results showed that the cortisol levels in the females with lower stress were significantly lower than those with higher stress (two-way ANOVA, P = 0. 001). There was no significant difference between the male subjects with low and high stress scores (Fig. 2).

3.5.1. Correlations between different variables in the current study

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. There was a positive correlation between PSS and each of the seizure duration, seizure number, and cortisol levels (P < .001, P = 0.008, P = 0.008, respectively, Table 5).

4. Discussion

Findings of this study showed that high PSS and/or exposure to major stresses during pregnancy significantly increased seizure duration and seizure intensity; the complex FS was higher in prenatally stressed children than the unexposed ones; cortisol blood levels were higher in prenatally stressed subjects.

Table 3
Comparison of febrile-seizure criteria in positive and negative family history of seizure.

Variables	Negative history (n = 130)	Positive history (n = 28)	P value
Age of first seizures (month)	5.48 ± 12.64	10.57 ± 4.85	0.09
Seizure intensity	9.21 ± 5.8	12.94 ± 8.47	0.04
Recurrence of seizures (%)	20	39	0.028

Table 4
Comparison of seizure duration, seizure number, and cortisol level between children under 2 years old by different grouping factors.

Dependent variable	Grouping variable	Score or condition	Mean	SD	P-value
Seizure duration (min)	Perceived Stress Score (PSS)	PSS <15	5.61	1.61	0.002*
		PSS >15	7.12	4.07	
	Family history of seizure	Yes	6.08	3.04	0.496
		No	6.44	3.16	
	Abortion	Yes	6.42	3.12	0.882
		No	6.31	3.13	
	Major stress	Exposed	7.93	3.73	0.003*
		Not exposed	6	2.89	
	Delivery type	CS	6.83	3.74	0.72
		NVD	5.93	2.47	
	Child sex	Boy	6.42	3.17	0.722
		Girl	6.25	3.09	
	Child neurodevelopment	Normal	5.96	2.81	<0.001*
		Abnormal	9.60	3.86	
Seizure number	Perceived Stress Score	PSS <15	1.46	0.83	0.1
		PSS >15	1.71	1.06	
	Family history of seizure	Yes	1.76	1.08	0.99
		No	1.49	0.88	
	Abortion	Yes	1.33	0.64	0.176
		No	1.62	0.99	
	Major stress	Exposed	2	1.41	0.11
		Not exposed	1.49	0.81	
	Delivery type	CS	1.59	0.94	0.909
		NVD	1.57	0.96	
	Child sex	Boy	1.68	1.04	0.13
		Girl	1.45	0.83	
	Child neurodevelopment	Normal	1.46	0.84	<0.001*
		Abnormal	2.56	1.32	
Cortisol (ng/mL)	Perceived Stress Score	PSS <15	244.65	116.26	0.42
		PSS >15	260.88	90.68	
	Family history of seizure	Yes	255.63	107.86	0.779
		No	249.8	104.36	
	Abortion	Yes	216.41	93.06	0.105
		No	259.46	106.59	
	Major stress	Exposed	306.04	77.98	<0.001*
		Not exposed	212.98	93.95	
	Delivery type	CS	248.33	100.04	0.756
		NVD	254.69	109.55	
	Child sex	Boy	271.3	104.32	.042*
		Girl	230.54	103.06	
	Child neurodevelopment	Normal	249.26	103.15	0.328
		Abnormal	287.25	132.17	

* Indicates a significant difference between two conditions in each individual grouping variable.

4.1. Effect of prenatal stress on birth weight (BW) and features of FS

In this study, we found that mothers with more stress during pregnancy had given birth to newborns with lower BW, which was consistent with a previous report [31]. These findings have provided further

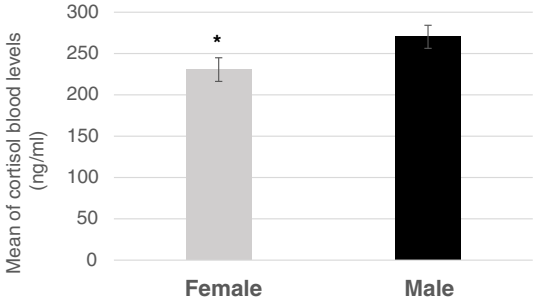

Fig. 1. Cortisol blood levels in male and female children under 2 years old; * indicates a significant difference with male subjects (P = 0.049).

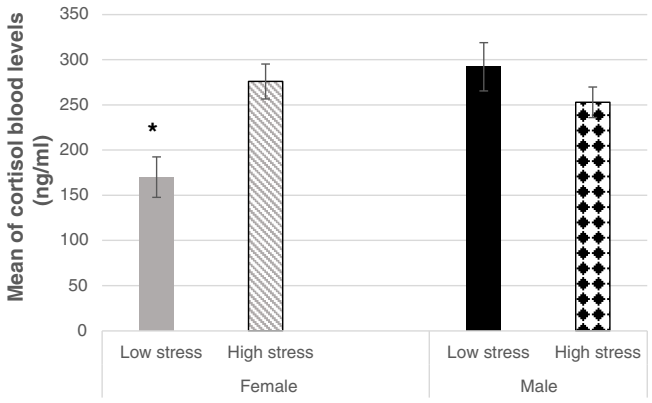

Fig. 2. Cortisol blood levels in children under 2 years old based on child sex and score of maternal stress; * indicates a significant difference with high stress female (P = 0.001).

evidence that prenatal stress exposure is negatively associated with fetal physical development [32,33]. Furthermore, stress during pregnancy not only is associated with low BW, but also causes preterm birth [33]. Wadhwa et al. showed that each unit of increase in prenatal life stressors was associated with a 55.03 g decrease in infant BW, a significant increase in the likelihood of low BW, and a 3-day decrease in gestational age at birth [34]. Our study indicated that, out of 158 children who had been admitted with FS, 19% had experienced FS for the second time and 5% referred more than twice with FS. In the individuals with PFH, seizure recurrence was higher than that with NFH, while no significant relationship existed between PSS. Berg et al. defined the risk and identified the predictors of single and multiple recurrent FS. Their studies on 428 children showed that 17.1% had only 1 recurrence, 8.9% had 2 recurrences, and 5.8% had 3 or more recurrences [35]. Although many factors have been raised about the risk factors for the recurrence of FS such as first time of FS, family history of seizure, type of seizure, degree of fever during seizure [35,36], and duration of fever [37], most of the emphasis is on the first time of FS and history of FS in the first-degree comparative [38–40]. In this study, we investigated seizure severity criteria in children with FS who had a history of seizure in the first-degree comparative (father, mother, brother, sister). In our study, 17% of children with FS had the history of seizures in the first-degree comparative compared to similar studies in which 18–25% of children had PFH [41,42]. The results of our study showed that PFH did not affect the age of the first FS but significantly increased the risk of recurrent seizures. It was reported that a first-degree PFH for seizure (parents or siblings affected by any kind of seizure) increased a child's two-year recurrence risk from 27 to 52%; however, the significant increase of recurrence risk for FS was not found in children with second-degree relatives. Most studies on FS are mainly focused on genetic factors, but the fact that the risk for FS increases with the reduction of BW and gestational age indicates that the environmental factors play a significant role although few prenatal environmental factors have been specified and studies have had conflicting results [43,44]. However, our results revealed that, in mothers with more stress during pregnancy or those facing major stressors, the duration of FS was significantly longer than that in the unstressed groups. Exposure to major stressors caused no significant difference in terms of the age of the first FS and recurrent seizures. Other results of the study showed that, although the children of the mothers who had higher PSS during pregnancy experienced more complex FS than those in the control subjects, this difference was not statistically significant. In contrast, those mothers who were faced with major stressors during pregnancy experienced significantly more complex FS in their offspring than the unexposed subjects so that the risk of complex FS in the exposed group was 4.96 times more than that in the unexposed one. The results of our study demonstrated that the possibility of complex seizure in the male offspring of exposed group was higher than that in the female one. Because of the difficulty of working on human subjects due to the immorality of applying stress and finding the control group, no study has to date examined this possibility prospectively using an independent stressor [45]. Animal studies have shown a relationship between stress during prenatal gestation and offspring seizure [10]. Some studies have suggested that prenatal stress influences male subjects more than females in rats [10,11,46], which may be due to the enzyme difference between male and female fetuses [47,48]; however, other researchers have not shown any sex differences in the influence of prenatal stress [49–52]. It has been reported that a certain part of the brain of female fetus has a different structure; stress experience early in pregnancy might contribute to male neurodevelopmental disorders through impacts on placental function and fetal development [53]. Less information is available about the effects of stress during pregnancy in human seizures. Vestergrad et al. observed that the children exposed to pre-eclampsia had the slightly increased risk of FS, but the association was apparently caused by shorter gestation in women with pre-eclampsia [54]. Li J et al. examined whether the exposure to prenatal stress following maternal

Table 5
Correlations (Pearson) between some variables in the current study.

	Seizure duration	Seizures number	cortisol	PSS	Mother age	Child age	Birth weight
Seizure duration	R = 1	.495[a]	−.015	.321[a]	−.041	−.057	−.084
		.000	.880	.000	.610	.475	.291
	N = 158	158	114	158	157	158	158
Seizure number	R = .495[a]	1	.105	.211[a]	.004	.120	−.006
	P < .001		.275	.008	.962	.135	.937
	N = 158	158	114	158	157	158	158
cortisol	R = −.015	.105	1	.249[a]	.045	−.124	−.015
	P = .880	.275		.008	.644	.199	.878
	N = 114	114	114	114	114	114	114
Perceived Stress Score (PSS)	R = .321[a]	.211[a]	.249[a]	1	.104	−.054	−.169[b]
	P < .001	.008	.008		.197	.500	.033
	N = 158	158	114	158	157	158	158
Mother age	R = −.041	.004	.045	.104	1	.017	−.068
	P = .610	.962	.644	.197		.831	.398
	N = 157	157	114	157	157	157	157
Child age	R = −.057	.120	−.124	−.054	.017	1	−.151
	P = .475	.135	.199	.500	.831		.058
	N = 158	158	114	158	157	158	158
Birth weight	R = −.084	−.006	−.015	−.169[b]	−.068	−.151	1
	P = .291	.937	.878	.033	.398	.058	
	N = 158	158	114	158	157	158	158

[a] Correlation is significant at the 0.01 level (2-tailed).
[b] Correlation is significant at the 0.05 level (2-tailed).

bereavement was associated with the increased risk of FS. Their study indicated that hazard ratio did not differ according to the nature in the exposed and unexposed newborns, so their study did not show any causal link between exposure to prenatal stress and FS in childhood [55]. Our studies have been focused on the criteria that determined the severity of seizures, not on the incidence of seizures, thus our study was different from Li and Vestergrad's works.

4.2. Effect of maternal PSS on offspring cortisol blood levels

Another finding of the current study indicated that cortisol blood levels were different between high PSS and low PSS subjects. Results showed that cortisol levels in female subjects from mothers with higher stress score during their gestation were significantly higher than those with lower stress score, while there was no significant difference between male subjects with low and high stress scores (Fig. 2). Also, our data indicated that there was a significant positive correlation between PSS and each of the seizure duration, seizure number, and cortisol levels (Table 5). A relationship between prenatal exposure to cortisol and infant HPA axis function was strongly proved by the animal result [56]; furthermore, previous studies have shown strong association between prenatal stress and seizure susceptibility as well as corticosterone blood levels in animal models [9–11]; however, interpreting the animal findings for human development has multiple difficulties, including the differential distribution of glucocorticoid receptors in the brain [57]. Besides, the rats, which are the target of much of the research on prenatal stress studies, are born much at an earlier stage than humans, confounding the conclusions about prenatal against postnatal effects. Furthermore, experimental animal work tendency is better for evaluating specific and precisely timed stressors in pregnancy, while it has limited application for humans where stresses are increasingly and typically chronic. In this study, a sex-dependent prenatal stress-induced elevation of cortisol blood levels was seen, but it was opposite to our previous findings in animal studies, in most of which it was indicated that male animals were affected more severely [6,10,11]. It is likely that lack of precise control in the current study could lead to this controversy, because the stress status of the mothers was asked from the mothers and the data were used as the fundamental of the current findings; in turn, it might have considerable inaccuracy.

5. Conclusion

The results of this study showed that prenatal stress might significantly increase the seizure intensity, potentiate many aspects of FS, and lead to long lasting rise in cortisol blood levels. The children appear most susceptible to FS development during the infancy. It is likely that prenatal stress may create a substrate for the later development of seizure disorders. Pregnant women might try to reduce their distress. Moreover, exogenous corticosteroids—used to promote lung development in the unborn offspring when there is a risk of preterm delivery—should be administered with caution.

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