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The role of oxidative stress levels and S100B levels in children with functional neurological disorder

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The study was approved by the Dicle University ethics committee with decision number 276 dated October 17, 2018.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Although stressors and traumatic life events are known to be predisposing factors for developing functional neurological disorder (FND), the etiology of the disorder has not been fully elucidated. In this study, oxidative stress parameters and serum levels of S100B protein were investigated in pediatric patients with functional neurological disorder. The association of these parameters with stress factors and traumatic life events was investigated.

Methods: This case-control study included a control group of 35 patients aged 8-18 years and 32 healthy subjects diagnosed with functional neurological disorder. The Childhood Trauma Scale and Dissociative Experiences Scale were applied to both groups. Serum levels of the patient and control groups were compared by blood sampling: total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), and S100B.

Results: It was found that the Childhood Trauma Scale total score, emotional neglect, emotional abuse, physical neglect and the Dissociative Experiences Scale were statistically significantly higher in the FND group than in the control group ($P<0.001$, $P<0.001$, $P=0.013$, $P=0.017$, $P<0.001$). Stressors were found to be statistically significantly higher in the FND group than in the control group ($P=0.020$). There was no statistical difference between the FND group and control groups regarding the TAS, TOS, OSI, and S100B levels ($P=0.965$, $P=0.228$, $P=0.268$, $P=0.517$, respectively).

Conclusion: Our study is the first to investigate TOS, TAS, OSI and S100B in children with FND. In our study, although stressors and traumatic experiences were significantly higher in the functional neurological disorder group compared to the control group according to the stress susceptibility model, contrary to expectations, there was no significant difference in oxidative stress parameters and serum S100B levels. It was thought that the interaction between FND, which is characterized by biopsychosocial interaction and can manifest itself with various clinical symptoms, and stress may not be linear as initially thought, and the interaction between genetic predisposition and environmental factors may play a more complex role. The absence of significant differences observed in oxidative stress parameters and serum S100B levels may suggest that we should focus on different pathways and different potential biomarkers that need to be investigated in the future to understand the etiology and diagnosis of FND. However, the limitations noted above may affect the generalizability of the study findings.

Keywords: pediatric, functional neurological disorder, oxidative stress, S100B

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Introduction

Functional neurological disorders refer to clinical presentations characterized by neurological symptoms such as voluntary or motor issues in the body, despite the absence of any identifiable physical or physiological problems [1]. In adults, the prevalence of the disorder is two to ten times higher among females compared to males, while in children it is more common among girls. The condition usually first appears in adolescents and young adults, often between the ages of 10 and 35 [2]. The incidence of functional neurological disorder is estimated to be 2% to 5% per year in large-scale population-based studies. Studies have found that early childhood trauma, emotional life stress, and conflict are associated with functional neurological disorder symptoms [3,4].

Chung et al. reported irregularities in the hypothalamus-pituitary-adrenal (HPA) axis in children and adolescents with functional neurological disorders. They observed a weakened or inverted cortisol awakening response, which is typically associated with chronic stress [5]. Additionally, one adult study found a decreased cortisol awakening response in FND patients using a transdiagnostic approach. This findings suggests that the previously activated system exhibits a more chronic stress or disorder pattern. Therefore, the flow effect can be more complex than a simple activation [6]. Additionally, the irregularities in the HPA axis can be triggered by glucocorticoids, and it can disrupt the oxidant-antioxidant balance [7]. In aerobic organisms, oxidant and antioxidant systems are actually in balance. Although oxidants in trace amounts are known to play a role in signal transduction and immune responses in the cell, in cases where the antioxidant balance is disturbed, excess oxidants damage membrane lipids, enzymes, structural proteins, and DNA by oxidation and play a role in the development of neurodegenerative and neuropsychiatric conditions [8-10]. The brain is particularly sensitive to stress due to its physiological and structural properties and high metabolic rate [11]. Some studies have shown that serum oxidant levels are elevated in mood disorders, depressive disorders, and neurodevelopmental disorders [12-14].

S100B is produced and released by astrocytes, contributing to the modulation of calcium ion signaling, maintenance of internal balance, protein phosphorylation, cellular growth, genetic transcription, cellular differentiation, enzymatic function, and internal cellular processes [15]. While nanomolar concentrations of S100B are a neurotrophic factor that reduces stress-induced damage and stimulates neuronal and astrocyte growth and differentiation, recent observations show that micromolar concentrations of S100B trigger apoptotic cell death by causing an increase in reactive oxygen species, the release of cytochrome C, and activation of the caspase cascade [16,17]. Studies have shown that serum S100B levels increase in psychosis, depression, and other mood disorders and revert with treatment in some disorders [18-21].

No study in the literature has examined the levels of oxidative stress and S100B that could contribute to the etiology of functional neurological disorder in childhood. It has already been mentioned that stressors and traumatic life events are predisposing factors for the development of functional neurological disorders. We aimed to look at the etiology of functional neurological disorder from a neuroinflammatory standpoint by examining oxidative stress parameters and serum levels of S100B protein in pediatric patients with functional neurological disorder and investigating the association between these parameters and predisposing factors.

Materials and methods

Study design

This case-control study was carried out by the Dicle University Faculty of Medicine, Department of Child and Adolescent Mental Health and Diseases. This study was approved by the Dicle University Ethics Committee with decision number 276 dated 17.10.2018. Study reporting was done following the STROBE guidelines [22]. The data were collected between October 30, 2018 and May 30, 2019.

Evaluation of functional neurological disorder groups

Thirty-seven patients (6 boys, 29 girls) aged 8-18 years and diagnosed with functional neurological disorder were enrolled in the study. The diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) were used to diagnose functional neurological disorder, and the patients were evaluated by two different psychiatrists. To meet the criteria, one or more changes in voluntary motor or sensory function had to be present. Based on DSM-5 criteria, clinical findings should demonstrate evidence of inconsistency or incompatibility between the symptom in question and known neurological or general medical conditions. The symptom or deficit should be better explained by another physical or mental health condition. Furthermore, the symptom or deficit should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrant medical evaluation.

According to the diagnostic criteria, acute functional neurological disorder (FND) is defined as the presence of symptoms for fewer than six months, while persistent FND is defined when symptoms have been present for six months or longer [1]. In our study, the mean time between the onset of symptoms and the first visit to a psychiatry outpatient clinic was 6.41 (10.9) months, and patients with persistent FND were included in the study. In our study, we found that 21.6% of the FND group initially visited the psychiatry clinic, which is consistent with the literature, but 78.4% came to our unit after referral. It was observed that, prior to seeking psychiatry admission, 45.7% of the patients visited pediatric neurology, 22.9% visited pediatrics, 22.9% visited emergency services, and 8.6% visited related clinics for their symptoms. Consequently, the time between the onset of symptoms and admission to psychiatry was prolonged. When the subtypes were examined according to the symptoms in the FND group, it was found that 21 (60.0%) patients came mainly with seizures or seizure attacks. In the other subtypes, there was one patient (2.9%) with weakness or paralysis, three (8.6%) with unusual movements, one (2.9%) with difficulty swallowing, and one (2.9%) with speech signs *(aphonia),* anesthesia, or sensory loss. It was observed that there was one (2.9%) patient with sensory loss,

three (8.6%) patients with specific sensory symptoms, and four (11.4%) patients with mixed symptoms.

Evaluation of control groups

At the Dicle University Faculty of Medicine, Department of Child and Adolescent Mental Health and Diseases where our study was conducted, there is a pediatric outpatient clinic that provides services for healthy children, including growth development, vaccinations, puberty issues and other follow-ups. We invited eligible children and their families to participate in this study at our clinic. Those who agreed underwent a psychiatric evaluation conducted by two different psychiatrists and met the exclusion criteria before being included in the control group. In our study, 32 healthy volunteers were included in the control group.

Exclusion criteria

For the patients and control groups, exclusion criteria included severe neurological or chronic medical illness, head injury, acute infection or inflammation, mental retardation, psychotic disorders, bipolar disorder, moderate psychiatric disorders, alcohol and substance use disorders, use of psychotropic drugs, a diet high in oxidants and antioxidants, intake of antioxidants such as vitamin E and C, and obesity in their past and/or present lives.

Participant selection

Prior to commencing, the necessary sample size was determined employing the G Power 3.1 analytical software. Through power analysis, a sample size of 34 patients was computed, considering a significance level (α) of 0.05, a statistical power (1-β) of 80%, and a medium effect size. The recruitment was concluded upon reaching an adequate number of participants within the stipulated timeframe. Subsequently, three individuals from the control group were excluded from the analysis due to their expressed intention to withdraw from the study.

Data collection

The Childhood Traumas and Dissociative Experiences Scale was completed in the FND and control groups. After 12 hours of fasting, blood samples were drawn from the antecubital vein into a biochemistry tube containing EDTA for the patient and control groups. It was centrifuged at 3500 rpm for five minutes (NF 048, NUVE). The sera obtained were stored at -80 C°.

Measurement of total antioxidant status (TAS)

The total antioxidant capacity (TAS) of serum samples was measured by the automated measurement method developed by Erel using an autoanalyzer (Architect C16000, Abbott). In this method, the characteristic color of ABTS* $^{+}$' is bleached by the antioxidants present in the sample. This reaction can be monitored spectrophotometrically, and the rate of bleaching is inversely proportional to the TAS of the sample. The reaction rate is calibrated with Trolox, widely used as a conventional standard for TAS measurement assays, and the appraisal results are expressed in mmol Trolox equivalent/L. The assay has a sensitivity of less than 3% [23].

Measurement of total oxidant status (TOS)

In the method developed by Erel, the oxidants present in the sample oxidize the ferrous ion-*o*-dianisidine complex to ferric ions. The oxidation reaction with glycerol molecules is accelerated and increased up to threefold. The iron (III) ion forms a colored complex with xylenol in an acidic environment. The color intensity, which can be measured spectrophotometrically, is related to the sample's total amount of oxidant molecules. The assay is calibrated with hydrogen peroxide, and the results are determined in micromolar hydrogen peroxide equivalents per liter (expressed in μmol H_2O_2 Equiv./L) [24].

Calculation of oxidative stress index (OSI)

After aligning the measurement units, the oxidative stress index (OSI) was calculated by dividing the total oxidant content (TOS)/by the total antioxidant content (TAS) [24].

Measurement of S100B level in serum

The serum level of human S100B (Sunred Biological Technology, catalog number: 201-12-4851 Shanghai, China) was determined by the enzyme-linked immunosorbent assay (ELISA) method with commercially available kits following the kit procedures.

Childhood Trauma Questionnaire

This assessment instrument, developed by Bernstein et al., consists of 28 questions. The scale determines a total score of five subscores related to childhood sexual abuse, physical abuse, emotional abuse, and emotional and physical neglect [25]. The Turkish validity and reliability study of the Childhood Trauma Scale was conducted in 2012 by Şar et al. [26].

Dissociative Experiences Scale

This is a 28-question self-report scale developed by Bernstein and Putnam in 1986 that measures the frequency of various dissociative experiences. Subjects give a score between 0 and 100 for each item, and the result is obtained by calculating the average of the total score obtained [27]. The Dissociative Experiences Scale was translated into Turkish by Şar et al. [28] in 1997, and a validity and reliability study of the Turkish version of the scale was conducted.

Statistical analysis

Statistical analysis was performed using the package program SPSS 21.0 for Windows (SPSS, Inc.; Chicago, USA). Descriptive values are expressed as number (n), percent (%), mean (mean), standard deviation (SD), and median (median). Pearson's chi-square and Fisher's exact test were used to compare categorical variables. Continuous variables were compared with parametric tests (independent samples t-test) if they conformed to the normal distribution determined by the Kolmogorov-Smirnov and Shapiro-Wilk tests, If they did not conform to the normal distribution, a nonparametric test (Mann-Whitney U test) was used. The relationship between variables was assessed with the Spearman correlation test. The significance level was accepted as *P*-value <0.05.

Results

The functional neurological disorder group (FND) consisted of 35 participants (29 [82.9%] female, 6 [17.1%]) male with a mean age of 14.20 (2.33) years. The mean age of the 32 participants (27 [84.4%] female, 5 [15.6%]) male in the control group was 14.22 (2.29) years. The mean educational level in the FND and control groups was nine years. There was no statistically significant difference between the groups regarding age and gender (*P*=0.974, *P*=0.867). It was found that in the

FND group, from the onset of symptoms to admission to psychiatry was, on average, 6.41 (10.9) months.

When evaluating the results of the Childhood Trauma Scale and the Dissociative Experiences Scale, it was found that the total scores of the Trauma Scale, emotional neglect, emotional abuse, physical neglect, and Dissociative Experiences Scale were statistically significantly higher in the FND group than those in the control group (P<0.001, P<0.001, P=0.013, P=0.017, P<0.001) (Table 1).

Table 1: Childhood trauma scale and dissociative experiences scale results between groups

Groups	Parameter	n	mean (SD)	DF	*t*	*P*-value
FND group	Emotional abuse	35	7.75 (3.54)	65	0.192	0.013
Control group		32	6.37 (2.21)			
FND group	Physical abuse	35	5.94 (2.37)	65	0.589	0.081
Control group		32	5.51 (1.55)			
FND group	Physical neglect	35	7.46 (3.09)	65	1.950	0.017
Control group		32	6.19 (1.71)			
FND group	Emotional neglect	35	12.54 (6.02)	65	4.052	<0.001
Control group		32	7.04 (2.86)			
FND group	Sexual abuse	35	5.40 (1.09)	65	0.570	0.084
Control group		32	5,08 (0.27)			
FND group	CTQ Total	35	40.11 (12.75)	65	3.132	<0.001
Control group		32	31.57 (5.48)			
FND group	DES Total	35	28.77 (22.70)	65	2.481	<0.001
Control group		32	21.87 (13.66)			

FND: functional neurological disorder, CTQ: Childhood Trauma Questionnaire, DES: Dissociative Experiences Scale, n: number, SD: Standard deviation, DF: Degree of freedom, *t*: Independent t-test value

There was no statistical difference between the FND and control groups regarding TAS level and OSI (P=0.965, P=0.268). TOS and S100B levels were slightly higher in the FND group, and there was no significant difference between the two groups (P=0.228, P=0.517) (Table 2 and 3). There was no significant relationship between the total score of the Childhood Trauma Scale, the Trauma Scale subgroups and the Dissociative Experiences Scale score, and the TAS, TOS, S100B, and OSI (Table 4).

Table 2: TAS, TOS, OSI INDEX scores between groups

Groups	Parameter	n	mean (SD)	DF	*t*	*P*-value
FND group	TAS, mmol Trolox equiv/L	35	1.53 (0.18)	65	0.200	0.911
Control group		32	1.53 (0.18)			
FND group	TOS, μmol H_2O_2 equiv/L	35	25.80 (10.93)	65	1.252	0.596
Control group		32	22.66 (9.45)			
FND group	OSI	35	1.71 (0.82)	65	1.296	0.540
Control group		32	1.47 (0.64)			

FND: functional neurological disorder, n: number, SD: Standard deviation, DF: Degree of freedom, *t*: Independent t test value

Table 3: S100B values of the between groups

Groups	Parameter	n	Median	Mean Rank	U	*P*-value
FND group	S100B, ng/L	35	333.35	34.48	544.500	0.846
Control group		32	322.71	33.56		

FND: functional neurological disorder, n: Number, Median: Median value, Mean Rank: Mean Ranks, U: Mann Whitney U test value

Table 4: Correlation of childhood trauma scale and dissociative experiences scale scores with parameters measured in blood

FND group		TAS mmol Trolox equiv/L	TOS μmol H_2O_2 equiv/L	S100B ng/L	OSI
Emotional abuse	r_o	0.113	0.190	0.033	-0.114
	p	0.253	0.130	0.423	0.251
Physical abuse	r_o	0.001	-0.205	-0.136	0.239
	p	0.498	0.112	0.211	0.077
Physical neglect	r_o	-0.002	-0.156	0.026	0.181
	p	0.496	0.179	0.439	0.141
Emotional neglect	r_o	-0.132	-0.035	-0.035	0.000
	p	0.219	0.419	0.419	0.499
Sexual abuse	r_o	-0.099	-0.163	-0.064	0.174
	p	0.280	0.167	0.362	0.152
CTQ Total	r_o	-0.046	-0.030	0.024	0.036
	p	0.393	0.429	0.444	0.416
DES Total	r_o	0.054	-0.030	-0.030	-0.002
	p	0.376	0.429	0.433	0.494

FND: functional neurological disorder, CTQ: Childhood Trauma Questionnaire, DES: Dissociative Experiences Scale, p: Spearman correlation significance value (*P*-value), r_o : Spearman Correlation Number

When asked about stressors, 8 subjects (22.9%) reported family stressors, 9 subjects (25.7%) reported school problems, 6 subjects (17.1%) reported social relationship issues, and 12 subjects (34.1%) reported no stressors in the functional neurological disorder group. In the control group, 3 individuals (9.4%) reported family stressors, 2 individuals (6.3%) reported school problems, 1 individual (3.1%) reported social relationship issues, and 26 individuals (81.3%) reported no stressors. It was found that stressors were statistically significant more frequently in the FND group (P=0.020). In the FND group, when the stressors (65.9%) and those who did not have stressors (34.1%) were considered separately, there was no statistically significant difference in serum levels of TAS, TOS, OSI and S100B (P=0.185, P=0.286, P=0.098, P=0.710).

Discussion

Our study investigated the relationship between stressors and adverse childhood experiences, which are considered predisposing factors for the development of functional neurological disorder, oxidative stress parameters, and serum levels of S100B protein. One of our important findings is that stressors and traumatic life events were more prevalent in the functional neurological disorder group, as expected. Another important finding is that measurements of oxidative stress indicators and S100B concentrations exhibited no notable distinctions among pediatric patients with functional neurological disorder when compared to the control group. There was no significant correlation between the extent of adverse childhood experiences and oxidative stress parameters and S100B levels.

If we consider stress from a psychoneuroimmunological perspective, studies have shown that psychological stress induces a cascading effect of hypothalamic-pituitary-adrenal axis dysregulation that activates both the immune system and oxidative stress [29,30]. According to the stress diathesis model of Keynejad et al. [31], the interaction of different combinations, such as a low or high genetic load of the individual and the severity and frequency of traumatic experiences in childhood, result in the individual having a different risk of developing functional neurological disorder. Monocytes and glial cells are activated following emotional trauma, which triggers the inflammatory system. Although the link between traumatic experiences in childhood and S100B is unknown, it is thought to affect the transition of S100B into the serum by producing cytokines and disrupting the blood-brain barrier [32].

Falcone et al. described adverse childhood experiences and showed that serum S100B levels were higher in pediatric patients hospitalized with a diagnosis of mood disorder and psychotic disorder compared with the control group [33]. However, in our study, no significant difference was found between serum S100B levels in the functional neurological disorder group with high adverse childhood experiences compared with the control group. Adverse childhood experiences can explain the stress diathesis model, and stressors cause mental disorders other than childhood functional neurological disorder. However, the differences in serum S100B protein levels according to the type of psychiatric disorder suggested that the disorder may have caused varying degrees of changes in the

different brain regions specifically affected by the condition. This indicates that imaging and neuroinflammatory studies might provide clearer results.

In an examination carried out by Büyükaslan et al. [34] involving 25 adult female and 12 male patients with conversion disorder, between 18 and 60 years, it was observed that the functional neurological disorder group exhibited notably elevated levels of total oxidative status, oxidative stress index, and S100B compared to the control group. Furthermore, a significant reduction in total antioxidant status was also identified in the same functional neurological disorder group. Our study found that the TAS, TOS, and OSI scores did not differ significantly between the pediatric functional neurological disorder and control groups. Studies show the effects of childhood traumatic experiences on oxidative stress in the brain [35,36]. Research has indicated that glial cells, which possess immunological memory within the brain and contribute significantly to the brain's reaction to stress, might be involved in either safeguarding or disturbing the stress equilibrium. Additionally, microglial neuroimmunity is believed to have a crucial impact on alterations in experience-dependent plasticity among individuals with functional neurological disorders [5,37-39]. Recent neuroimaging studies have shown that different brain regions are affected in children and adolescents with functional neurological disorder more than in adults. These neuroplastic changes in children with short disease duration may not correspond to those in adult patients with chronic disease duration [40-42]. Therefore, long-term follow-up of patients with childhood functional neurological disorder and investigation of the effects of oxidative stress and neuroinflammatory changes may provide more important information for understanding the condition.

In our study, oxidative stress parameters were studied in total. Özdemir et al. [ref#?] did not find a significant difference in total oxidant and antioxidant parameters in their study with adults with post-traumatic stress disorder; however, a significant difference in lipid peroxidation markers and prolidase among sub-parameters was found in other studies [43-45]. These data led us to understand the functional neurological disorder better, and assessing oxidative stress sub-parameters might be more useful before the deterioration of oxidative capacity affects total antioxidant capacity.

Limitations

The results of our study could be limited due to the small number of participants, the absence of long-term follow-ups, the lack of research on how these parameters respond to treatment, and the long time elapsed until the patients presented to our psychiatry clinic. Furthermore, given that S100B can be released extracranially, certain investigations have suggested the importance of assessing S100B within cerebrospinal fluid (CSF), coupled with the calculation of a serum/CSF ratio [46-48]. FND encompasses a wide variety of clinical presentations and often requires multiple-site evaluation before initiating psychiatric treatment. These assessments may include specialists from neurology, pediatrics, or other related disciplines. Due to the nature of FND, patients typically do not seek emergency psychiatric care in the acute phase of the disorder [49]. This situation led us to believe that our results might have been compromised due to the inability to obtain blood samples in the acute phase and also the examination of serum S100B levels instead of CSF. Furthermore, because there is no standardized measurement method for functional neurological disorder severity, the effect of disease severity on oxidative stress and S100B parameters was not examined. Begue et al. [50] noted that creating standardized measurement tools to classify the FND by demographics, duration of disease severity, symptoms, comorbidities, and functionality for neurobiological studies in functional neurological disorder would increase the biological specificity of the studies.

Conclusion

Our study is the first to investigate TOS, TAS, OSI and S100B in children with FND. In our study, although stressors and traumatic experiences were significantly higher in the functional neurological disorder group compared to the control group according to the stress susceptibility model, contrary to expectations, there was no significant difference in oxidative stress parameters and serum S100B levels. It was thought that the interaction between FND, which is characterized by biopsychosocial interaction and can manifest itself with various clinical symptoms, and stress may not be linear as initially thought, and the interaction between genetic predisposition and environmental factors may play a more complex role. The absence of significant differences observed in oxidative stress parameters and serum S100B levels may suggest that we should focus on different pathways and different potential biomarkers that need to be investigated in the future to understand the etiology and diagnosis of FND. However, the limitations noted above may affect the generalizability of the study’s findings.

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