Association between the rs1360780 polymorphism in *FKBP5* gene and serum cortisol levels in children with autism spectrum disorder

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Abstract

The inconsistent results about cortisol levels in individuals with autism spectrum disorder (ASD) may be suggestive of other factors like gen polymorphisms rather than the disorder itself. So we aimed to investigate the rs1360780 polymorphism in FK506 binding protein 5 (*FKBP5)* gene and its relation to ASD and cortisol levels comparing with that of healthy participants. We have included two main groups as study and control groups in the present study. Eighty nine children with ASD ranging in age from 2 to 15 years were selected for the study group and age-matched 86 healthy children were selected for the control group. Cortisol levels were found to be significantly higher in the study group. However there was no statistically significant difference in terms of allele and genotype frequencies between the groups. Carrying the C allele of *FKBP5* seems to increase the cortisol levels in the study group. This is the first clinical study to evaluate the association between rs1360780 polymorphism in *FKBP5* gene and serum cortisol levels in children with ASD. Since the prevalence of ASD is gradually increasing in recent years, several endocrine and related genetic factors should be born in mind while examining this population.

Introduction

Autism spectrum disorder (ASD) is a phenotypically heterogeneous group of neurodevelopmental syndromes, with polygenic heritability, characterized by a wide range of impairments in social interaction, communication, and stereotypic behaviors [1]. Because individuals with ASD often experience poor adaptation to change, examination of the hypothalamic-pituitary-adrenal (HPA) axis via cortisol has been a growing area of research interest.

The majority of the studies concerning the HPA axis reactivity and diurnal fluctuations in ASD have been conducted on children. While lower functioning children with ASD have been shown to exhibit atypical diurnal regulation of the HPA axis [2], higher functioning children with ASD have been reported to have a normal secretion pattern of cortisol [3-5]. The rhythm tends to be much more variable from day-to-day compared to that of typically developing (TD) children, especially the morning values [3,6]. Evening values have been also found to be higher and associated with increased stress related to poor response to changes throughout the day [6,7]. However almost all studies suggest greater circadian dysregularity in ASD groups relative to age-matched TD controls.

The FK506 binding protein 5 (*FKBP5*), encoded by the *FKBP5* gene, is a co-chaperone of heat-shock protein 90 which regulates glucocorticoid receptor (GR) sensitivity [8]. It has been reported that overexpression of the *FKBP5* was associated with glucocorticoid resistance and high cortisol levels, suggesting an involvement of the *FKBP5* in the HPA axis as a determinant of the negative feedback regulation [8-10]. Single nucleotide polymorphisms (SNPs) within the *FKBP5* gene are known to influence GR sensitivity and thus HPA axis regulation, which has been discussed as a key endocrine marker for several psychiatric disorders such as major depression or posttraumatic stress disorder [11,12]. The most consistent findings have been reported for rs1360780, a SNP located in the second intron of the *FKBP5* gene; the T allele of this SNP forms a putative transcription start site [13].

A recent study reported higher messenger RNA (mRNA) levels of FKBP5 protein in the postmortem middle frontal gyrus tissues of ASD subjects [14]. To the best of our knowledge, no previous study has directly examined the association between *FKBP5* gene polymorphisms and ASD. The inconsistent results about cortisol levels in individuals with ASD may be suggestive of other factors like gen polymorphisms rather than the disorder itself. So we aimed to investigate the rs1360780 polymorphism in *FKBP5* gene and its relation to ASD and cortisol levels comparing with that of healthy participants.

Methods

Participants

We have included two main groups as study and control groups in the present study. Subjects in the study group were recruited among children and adolescents who referred to Department of Child and Adolescent Psychiatry in two centers during a period of one year. Eighty nine children with ASD ranging in age from 2 to 15 years were selected for the study group and diagnosis of ASD was based on DSM-V criteria. Subjects with any genetic syndrome (e.g., Down syndrome, Fragile X, Rett syndrome) and any medical disorder (e.g., epilepsy, clinically active infection, Cushing syndrome, and morbid obesity) and with a history of past or current cortisol therapy or vitamins were excluded from the study group. Healthy children without any neurodevelopmental disorder (e.g., ASD, intellectual disability, communication disorders) and any neurological disorder or clinically active infection and without a history of past or current cortisol therapy or vitamins were selected as healthy control group. Written informed consent was obtained from parents and the faculty ethical committee approved the study.

Measures

Autism Behaviour Checklist (ABC)

ABC was developed by Krug et al. [15]. It has been used to evaluate the severity of autism symptoms. ABC consists of five subscales which have a 57-item scale including sensory, relationship building, the use of the body and objects, language skills, social and self-care skills. The lowest score of the scale is 0 and the highest score is 159. The scale has been adapted to Turkish by Irmak et al. [16].

Biochemical analysis

Peripheral venous blood samples were collected in the morning, postprandial, between 10 and 12 am. The samples were stored at room temperature for 15 minutes for coagulation. Then, blood samples were centrifuged to separate serum from clot at 1000 g for 10 minutes. The sera were stored at -80 °C until the time of analysis. The sera of the study and control groups were measured together using the same plate. Serum cortisol levels were determined with ELISA method (Shanghai LZ Biotech Co., Ltd, China, catalogue numbers is YHB0851Hu), according to the manufacturer's instructions. These kits include a double-antibody sandwich ELISA to assay the level of cortisol in samples. Briefly, samples were added to wells which are pre-coated with monoclonal antibody and incubated. Then, antibodies labeled with biotin

were added, and combined with Streptavidin-HRP to form immune complex; then incubation and washing steps were carried out. Then chromogen solutions were added to the wells, and under the effect of stop solution, the yellow color was observed finally. We measured the optical density (OD) of each well under 450 nm wavelength within 10 minutes after having added stop solution. According to standard concentrations and corresponding OD values, we calculated the linear regression equation of the standard curve, and we determined the cortisol concentration of the samples.

DNA Isolation and Genotyping

Whole blood sample (200 µl) was taken into ethylenediaminetetraacetic acid-treated tubes, and genomic DNA was isolated using a commercially available kit according to manufacturer's instructions (QIAamp DNA Mini Kit, Qiagen, Hilden, Germany). The SNP rs1360780 was genotyped using the TaqMan 5'-exonuclease allelic discrimination assay (assay ID: C___8852038_10) and StepOnePlus Real-Time PCR system (ThermoFisher Scientific, MA, USA). PCR conditions were 60ºC for 30 seconds, 95ºC for 10 min, followed by 40 cycles of 15 seconds at 95ºC for and 1 minute at 60ºC. Lastly, 60ºC for 30 seconds was applied for Post-PCR reading. The fluorescent signal was detected at pre-PCR, amplification (at the end of each cycle) and post-PCR reading steps.

Procedure

Firstly the diagnosis process of ASD was conducted in referred subjects. The severity of autistic symptoms was assessed with the ABC scale. Hearing tests were applied to all participants. Blood samples for detecting cortisol levels were collected in the morning, postprandial, between 10 and 12 am once a day. ELISA and PCR were used to assay serum cortisol levels and genotyping, respectively.

Statistical Analysis

The student's t-test was used to compare normally distributed variables in independent groups, and the Mann-Whitney U test was used to compare nonparametric or ordinal variables. The cortisol levels were not normally distributed. For this reason the data were transformed to Log(10) of the values. The effects of age, gender, ABC scores, and genotypes on cortisol levels were evaluated using a two-way ANOVA and ANCOVA tests. Pearson's test was used to evaluate correlation coefficients and statistical significance of normally distributed variables, and Spearman's test was used to evaluate non-normally distributed variables. The values were given as mean ± standard deviation (SD). We have compared the genotype distribution and allele frequencies of the rs1360780 between the study and control groups using Chi-square or Fisher's exact tests. A value of $p<0.05$ was considered statistically significant.

Results

The study group consisted of 89 children (76 males, 13 females) with a mean age of 43.9±25.7 months and the control group consisted of 86 healthy children (61 males, 25 females) with a mean age of 47.7±14.2 months. Mean number of siblings in the study and control groups were 2.7±1.2 and 3.0±1.5,

respectively. 26.9% of parents in the study group were found to have consanguineous marriages while 26.7% of parents in the control group had consanguineous marriages. There was no significant difference between the groups in terms of mean age of the participants, number of siblings and the rates of consanguineous marriage ($p>0.05$). Significant difference was found between the groups for gender ($p<0.05$).

The mean cortisol level for the study group was 85.5±36.8 ng/ml while the mean cortisol level for the control group was 61.9±35.8 ng/ml. Cortisol levels were significantly higher in the study group compared to the control group ($p<0.001$). Table 1 shows the socio-demographic attributes and cortisol levels in the study and control groups.

The mean total ABC score was 79.5±21.4 in the study group. The ABC subscale scores were found to be 9.5±3.9 for sensory, 20.1±5.6 for relating, 17.9±5.8 for body and object use, 18.5±5.5 for language, and 12.6±3.6 for social and self-help. Regressive type of autism was observed in 23.6% of the subjects with ASD (n=21). The total ABC scores and language, social and self-help subscale scores were significantly higher in subjects with regressive autism than those without regression ($p<.05$).

Two-way analysis of variance (ANOVA and ANCOVA) was conducted in order to assess the contribution of age, gender, ABC total and subscale scores, and regressive type of autism on cortisol levels of the study group. There was a statistically significant negative correlation between age and cortisol levels in the study group ($r=-0.360$, $p=0.001$). Gender, ABC total and subscale scores, and the regressive type of autism had no significant effect on cortisol levels.

Discussion

The present study investigated the association between *FKBP5* rs1360780 polymorphism and serum cortisol levels in children with ASD. The results suggest that there was no significant difference in terms of allele and genotype frequencies between children with ASD and their healthy peers; however, cortisol levels were significantly higher in children with ASD than their healthy controls. The study also shows no genotype effect on cortisol levels in children with ASD.

The children with ASD demonstrated significantly higher cortisol levels than healthy children in the present study. The normal circadian pattern of cortisol is a sharp increase in the morning hours, with a gradual decline throughout the day until it reaches its nadir during nighttime sleep; deviation from this pattern is suggestive of HPA-axis dysregulation [17]. Some studies have focused on specific aspects of this pattern (e.g., cortisol awakening response, daily decline, variability) while others examined cortisol levels once a day like our study. Using plasma cortisol collected in the morning hours, Curin et al. and Hamza et al. found lower cortisol levels in children with ASD relative to TD controls in contrast to our findings [18,19]. However no difference has been reported in cortisol levels between ASD group and TD controls in other studies using the same method [20,21]. Despite the inconsistent results, most of the studies suggest greater circadian dysregularity of cortisol in ASD groups relative to age-matched TD controls [6,7].

It has been shown that age is a critical moderating factor in the activation of the HPA axis in children with ASD. We found a statistically significant negative correlation between age and cortisol levels in the study group. Studies have demonstrated an interaction between diagnosis and age resulting in significantly higher stress responses in older school age youth that engage in play with peers. For example, older children with ASD show higher levels of cortisol compared to younger children with ASD as well as their typically developing peers during play [22,23]. Negative correlation between age and cortisol levels in the present study is probably due to cortisol sampling method since we did not measure the serum levels in response to a social interaction or a stressful event. No association was also shown between cortisol levels and age in other related studies [18,24].

Furthermore, cortisol levels were not significantly associated with ABC total and subscale scores, and the regressive type of autism in our study. In an earlier study conducted by Tordjman et al. [24], no significant relationship has been reported between autism severity based on the autism diagnostic observation schedule (ADOS), IQ and cortisol levels, like the present study. However, Hamza et al. reported that autism severity, based on the Childhood Autism Rating Scale (CARS) score, was significantly and negatively correlated with basal and stimulated cortisol levels [19]. In line with this study, Gabriels et al. also reported that children with ASD and high occurrence of repetitive behaviors showed lower diurnal salivary cortisol levels than children with ASD and low occurrence of repetitive behaviors [25]. The authors suggest that repetitive behaviors may serve to mitigate distress or that the glucocorticoid system has been down regulated in association with prolonged distress in the children with repetitive behaviors. Further studies are warranted to clarify the inconsistent results regarding the association between autism severity and HPA axis.

FKBP5 is considered as a promising genetic candidate for vulnerability particularly to stress-related disorders. The rs1360780 polymorphism is among the most common SNPs of *FKBP5* that has functional effects. So we focused on this functional polymorphism in the current study. However no statistically significant difference was found related to *FKBP5* rs1360780 polymorphism between the study and control groups. To the best of our knowledge, there is no study investigating the *FKBP5* associated SNPs in individuals with ASD in the literature. The link between the personality traits and ASD has been demonstrated in several studies [26,27]. Higher harm avoidance and lower cooperativeness was found in individuals with ASD measured by temperament and character inventory (TCI) [27]. In this context, Shibuya et al. suggested that the T allele of rs1360780 polymorphism in *FKBP5* gene was associated with higher scores of harm avoidance and lower scores of cooperativeness in healthy subjects using TCI [28]. The personality traits rather than the core features of ASD might be related to *FKBP5* gene polymorphisms based on these findings. On the other hand, a cohort study using the Neonatal Intensive Care Unit (NICU) Network Neurobehavioral Scales (NNNS) for evaluating infant neurobehavioral outcomes demonstrated that infants with higher *FKBP5* methylation were at increased risk of exhibiting high arousal of NNNS scores [29]. The study also found that infants with TT genotype of rs1360780 were more likely to exhibit high NNNS stress abstinence. Since neurobehavioral profiles derived through NNNS have previously shown to predict neurodevelopmental and cognitive performance in childhood, SNPs in *FKBP5* gene could serve as biomarkers of neurobehavioral risk facilitating early screening for

neurodevelopmental disorders like ASD. Some forms of SNPs in *FKBP5* gene were also found to be associated with attention deficit hyperactivity disorder (ADHD), another neurodevelopmental disorder of childhood while some forms were not reported to be associated, like the present study [30].

We observed significantly higher cortisol levels in the study group with the CC and CT genotypes than in that of the control group. However, no significant difference was found in terms of mean cortisol levels between the study and control groups with the TT genotypes. This finding of the present study is most probably due to small number of the cases homozygous for the T allele. Carrying the C allele of *FKBP5* seems to increase the cortisol levels in contrast to literature findings. Previous research showed that the T allele of the *FKBP5* rs1360780 polymorphism was found to be associated with hypercortisolism in the HPA axis [8]. In addition, we compared the cortisol levels within the participants of the study group for the effect of the T allele in the HPA axis. However we found no significant difference between T allele carriers and non-T allele carriers among the participants in the study group for cortisol levels. Several recent studies also reported no difference for cortisol secretion between the two genotype groups (CC vs CT/TT) in line with the present study. Fujii et al. [31] indicated no significant difference in any cortisol response value to dexamethasone suppression test between T allele and non-T allele carriers in young healthy participants while Höhne et al. [32] suggested that the TT genotype of the *FKBP5* rs1360780 polymorphism had no effect on cortisol increase in patients with remitted depression compared to healthy controls.

Our study has several limitations that should be addressed. First is the cortisol sampling method since we collected plasma cortisol once a day and the second is that we did not measure the serum levels in response to a social interaction or a stressful event because social impairment is the most critical symptom in children with ASD. Measuring cortisol levels more than once a day in response to a social or stressful trigger could provide exact cortisol levels. Another limitation is that we investigated only the common functional *FKBP5* variant (rs1360780). The effect of other genotype variants on cortisol levels should be analyzed.

Despite these limitations, this is the first clinical study to evaluate the association between rs1360780 polymorphism in *FKBP5* gene and serum cortisol levels in children with ASD comparing with that of health controls. No significant allele and genotype differences were found between the groups and no genotype effect on cortisol levels between children with ASD and healthy controls. Since the prevalence of ASD is gradually increasing in recent years, several endocrine and related genetic factors should be born in mind while examining this population. However more research is also needed to further explore the relationship between ASD and these factors.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Non-invasive Clinical Research Ethics Committee of Gaziosmanpasa University and meets the ethical guidelines of the

Declaration of Helsinki. Written informed consent was obtained from both parents before starting any study-related procedure.

Consent for publication: All authors have approved the manuscript and consented to publish the data before submitting to the journal.

Availability of data and materials: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ŞŞ, AÇ, SC and HB. The manuscript was written by HB and SŞ contributed to writing the manuscript. All authors read and approved the final manuscript.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest: The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals: All procedures performed in the study involving human participants were in accordance with the ethical standards of the institution at which the study was conducted.

Informed consent: Not applicable

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Tables

Table 1

Socio-demographic variables and cortisol levels in the study and control groups.

	Study group (n = 89)	Control group (n = 86)	t	p
Age (months)	43.9 ± 25.7	47.7 ± 14.2	-1.195	0.23
Gender (Male/Female)	76/13	61/25		0.03
Number of siblings	2.7 ± 1.2	3.0 ± 1.5	-1.267	0.20
Consanguineous marriage (yes/no)	24/65	23/63		1.00
Cortisol (ng/ml)	85.5 ± 36.8	61.9 ± 35.8	4.195	< 0.001

Table 2

Genotype distribution and allele frequencies in the study and control groups.

Polymorphism		Study group n (%)	Control group n (%)	p	ORs (95%CIs)
rs1360780	Genotype			0.52	
	CC	46 (51.7)	42 (48.9)		
	CT	37 (41.6)	33 (38.3)		
	TT	6 (6.7)	11 (12.8)		
	Allele frequency			0.46	1.23 (0.76–1.98)
	C	129 (72.5)	117 (68)		
	T	49 (27.5)	55 (32)		
	Recessive			0.23	1.88 (0.65–5.46)
	CC + CT	83 (93.3)	75 (87.2)		
	TT	6 (6.7)	11 (12.8)		
	Dominant			0.69	1.13 (0.61–2.1)
	CC	46 (51.7)	42 (48.8)		
	CT + TT	43 (48.3)	44 (51.2)		

Table 3

Mean cortisol levels based on the genotypes of rs1360780 polymorphism in FKBP5 gene.

	Mean Cortisol Level (± SD)									
	Additive				Recessive			Dominant		
	CC	CT	TT	p	CC + CT	TT	p	CC	CT + TT	p
Study	82.5 (± 33.7)	92.3 (± 38.6)	87 (± 42.7)	0.50	86.8 (± 36)	87 (± 42.7)	0.99	82.5 (± 33.7)	91.5 (± 38.7)	0.26
Control	63.2 (± 39.1)	60.6 (± 32.8)	60 (± 39.9)	0.94	62 (± 36.2)	59.7 (± 39.9)	0.85	63.2 (± 39.1)	60.4 (± 34.1)	0.74