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Association of SNP (rs1360780) in *FKBP5* Gene and Plasma 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 gene polymorphisms rather than the disorder itself. We aimed to investigate the rs1360780 polymorphism in the *FK506 binding protein 5* (*FKBP5*) gene and its relation to ASD and cortisol levels. Eighty-nine children with ASD ranging in age from two to fifteen years were selected for the study group, and eighty-six healthy children were selected for the control group. Blood samples were collected between 10 and 12 am in the morning. Enzyme linked immunosorbent assay and polymerase chain reaction were used to assay serum cortisol levels and genotyping, respectively. The mean cortisol levels for the study and the control groups were 8.5±3.6 µg/dL and 6.1±3.5 µg/dL, respectively. Cortisol levels were significantly higher in the study group compared to the control group ($p<0.001$). There was no statistically significant difference in terms of allele and genotype frequencies between the groups ($p>0.05$). Carrying the C allele was found possibly to increase the cortisol levels in the study group. This is the first clinical study to evaluate the association between rs1360780 polymorphism in the *FKBP5* gene and serum cortisol levels in children with ASD compared to those of healthy participants. Since the prevalence of ASD is gradually increasing in recent years, possible endocrine and related genetic factors should be borne in mind while examining this population.

Keywords: Autism, cortisol, *FKBP5* gene, rs1360780 polymorphism

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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.

Highlights

- This is the first clinical study to evaluate the association between rs1360780 polymorphism in the *FKBP5* gene and serum cortisol levels in children with autism spectrum disorder (ASD) compared to those of healthy controls.
- Cortisol levels were found to be significantly higher in children with ASD than in their healthy peers.
- No significant allele and genotype differences were found between the groups, and no genotype effect on cortisol levels was observed between children with ASD and healthy controls.
- Since the prevalence of ASD is gradually increasing in recent years, possible endocrine and related genetic factors should be born in mind while examining this population.
- More research is also needed to further explore the relationship between ASD and these factors.

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, higher functioning children with ASD have been reported to have a normal secretion pattern of cortisol[2-5]. The rhythm tends to be much more variable from day to day compared to that of typically developing (TD) children, especially in terms of morning values[3,6]. Evening values have been found to be higher and are also associated with increased stress related to a poor response to changes throughout the day[6,7]. However, almost all studies suggest greater circadian dysregulation 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 FKBP5 was associated with glucocorticoid resistance and high cortisol levels, suggesting an involvement of 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 and 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 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 gene polymorphisms rather than the disorder itself. Therefore, we aimed to investigate the rs1360780 polymorphism in the *FKBP5* gene and its relation to ASD and cortisol levels compared to those of healthy participants.

Materials and 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 were referred to the 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, with diagnosis of ASD based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. Subjects with any genetic syndrome (e.g., Down syndrome, Fragile X, Rett syndrome), any medical disorder (e.g., epilepsy, clinically active infection, Cushing syndrome, hypothyroidism, vitamin deficiencies, and morbid obesity), or 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), without any neurological disorder or clinically active infection, and without a history of past or current cortisol therapy or vitamin use were selected as the healthy control group. The study protocol was approved by the Non-invasive Clinical Research Ethics Committee of Gaziosmanpaşa University (approval number: 15-KAEK-226, date: 05.01.2016), and written informed consent was obtained from both parents before starting any study-related procedure.

Measures

Autism Behavior Checklist

Autism behavior checklist (ABC) was developed by Krug et al.[15] It has been used to evaluate the severity of autism symptoms. ABC consists of five subscales with 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 postprandial, between 10 and 12 a.m. 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 the enzyme linked immunosorbent assay (ELISA) method (Shanghai LZ Biotech Co., Ltd, China, catalogue number 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 that are pre-coated with monoclonal antibody, and incubated. Then, antibodies labeled with biotin were added and combined with Streptavidin-HRP to form an immune complex. Incubation and washing steps were then carried out. Then the chromogen solutions were added to the wells, and the yellow color was finally observed under the effect of the stop solution. We measured the optical density (OD) of each well at a wavelength of 450 nm within 10 minutes after adding 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

A whole blood sample (200 µL) was taken into ethylenediaminetetraacetic acid-treated tubes, and genomic DNA was isolated using a commercially available kit according to the 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 polymerase chain reaction (PCR) system (ThermoFisher Scientific, MA, USA). PCR conditions were 60 ºC for 30 seconds, 95 ºC for 10 min, followed by 40 cycles of 15 seconds at 95 ºC and 1 minute at 60 ºC. Lastly, a temperature of 60 °C was applied for 30 seconds during the 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 diagnostic 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 between 10 am and 12 noon 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 the log base 10 of the values. The effects of age, gender, ABC scores, and genotypes on cortisol levels were evaluated using two-way ANOVA and ANCOVA tests. Pearson's test was used to evaluate correlation coefficients and the 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. We have compared the genotype distribution and allele frequencies of 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 was 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% in the control group had consanguineous marriages. There was no significant difference between the groups regarding mean age of the participants, number of siblings, and the rates of consanguineous marriage ($p>0.05$). A significant difference was found between the groups for gender ($p<0.05$).

The mean cortisol level for the study group was 8.5±3.6 µg/dL, while the mean cortisol level for the control group was 6.1±3.5 µg/dL. 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 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 ($p<0.05$).

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 (µg/dL)	8.5±3.6	6.1±3.5	4.195	**<0.001**

Two-way analyses of variance (ANOVA or ANCOVA) were 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.

The *FKBP5* genotype distribution between the study and control groups is shown in **Table 2**. The frequencies of the C and the T alleles in the study group were 72.5% and 27.5%, respectively, while the control group they were 68% and 32%, respectively. *FKBP5* rs1360780 genotype frequencies were CC=46; CT=37; TT=6 for the study group and CC=42; CT=33; TT=11 for the control group. There was no statistically significant difference in terms of allele and genotype frequencies between the groups (p>0.05). Under the recessive model, the mean cortisol levels in the participants of the study group with the CC and CT genotypes were found to be significantly higher than those of the control group with the same genotypes (p<0.001), while there was no statistically significant difference in terms of mean cortisol levels between the study and control groups with the TT genotypes (p>0.05). Under the dominant model, homozygous and heterozygous subjects for the T allele were combined in our analysis, a significant difference between the study and control groups was also found for cortisol levels (p<0.05). The mean cortisol levels were compared between genotypes under the additive, recessive, and dominant models in both the study and control groups separately. No significant difference was found between genotypes in the level of cortisol. **Table 3** displays the comparison of mean cortisol levels based on the genotype models between the groups, and **Figure 1** demonstrates the mean cortisol levels according to genotypes within the groups.

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 peers. The study also shows no genotype effect on cortisol levels in children with ASD.

Children with ASD often experience poor adaptation to change and exhibit marked stress responses in novel and social situations compared to their typically developed peers. Additionally, sensory hypersensitivity in ASD contributes to the influence of external and internal factors that alter the regulatory system, which in turn leads to greater diurnal variability. Since cortisol secretion is known to be associated with markedly

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)		

OR; Odds ratio, CI; Confidence interval

Table 3.
Mean cortisol levels based on the genotype models between the groups

		Mean cortisol level (± standard deviation)		
Model	**Genotype**	**Study**	**Control**	**p**
Additive	CC	8.2 (±3.3)	6.3 (±3.9)	**0.02**
	CT	9.2 (±3.8)	6.0 (±3.2)	**0.001**
	TT	8.7 (±4.2)	6.0 (±3.9)	0.21
Recessive	CC+CT	8.6 (±3.6)	6.2 (±3.6)	**0.00**
	TT	8.7 (±4.2)	5.9 (±3.9)	0.21
Dominant	CC	8.2 (±3.3)	6.3 (±3.9)	**0.02**
	CT+TT	9.1 (±3.8)	6.0 (±3.4)	**0.00**

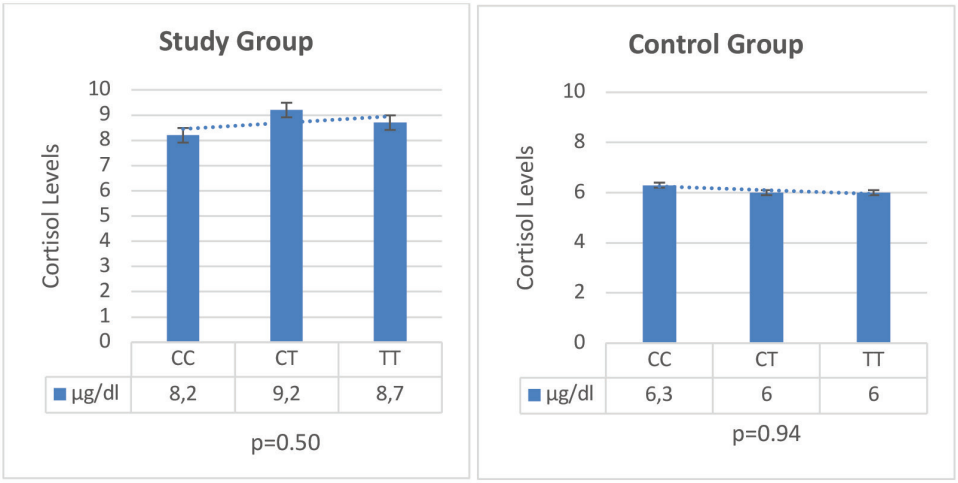

Figure 1. Mean cortisol levels based on the genotypes within the groups

increase in response to stress and greater sensory sensitivity, cortisol levels are more likely to be higher in children with ASD which is in accordance with 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, as in our study. In contrast to our findings, Curin et al.[18] and Hamza et al.[19], using plasma cortisol collected in the morning hours, found lower cortisol levels in children with ASD relative to TD controls. However, no difference has been reported in cortisol levels between the ASD group and the TD controls in other studies using the same method[20,21]. Despite the inconsistent results, most of the studies suggest greater circadian dysregulation 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 both younger children with ASD and their TD peers during play[22,23]. The negative correlation between age and cortisol levels in the present study is probably due to the cortisol sampling method, since we did not measure the serum levels in response to a social interaction or a stressful event. Also, no association was 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 was reported between autism severity based on the autism diagnostic observation schedule, IQ and cortisol levels, similar to the findings of the present study. However, Hamza et al.[19] reported that autism severity, based on the childhood autism rating scale score, was significantly and negatively correlated with basal and stimulated cortisol levels. In line with this study, Gabriels et al.[25] 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. 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 the HPA axis.

The *FKBP5* protein plays a crucial role in determining sensitivity to glucocorticoid negative feedback, a key mechanism for terminating the HPA axis response to a stressful event. Alterations in the expression or function of FKBP5 could increase cortisol burden and contribute to the allostatic shift in cortisol regulation (Lee et al., 2011). Common SNPs in FKBP5 have been associated with increased FKBP5 protein expression as well as variation in the correlation between plasma cortisol levels and peripheral blood FKBP5 mRNA expression (Binder et al., 2004). The alleles of these polymorphisms are associated with a differential induction of FKBP5 by GR activation and should also be linked to differences in GR sensitivity. In light of this, FKBP5 is considered a promising genetic candidate for vulnerability particularly to stress-related disorders. The rs1360780 polymorphism is among the most common SNPs of FKBP5 that have functional effects. Therefore, 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 personality traits and ASD has been demonstrated in several studies[26,27]. Higher harm avoidance and lower cooperativeness were found in individuals with ASD measured by temperament and character

inventory (TCI)[27]. In this context, Shibuya et al.[28] suggested that the T allele of rs1360780 polymorphism in the *FKBP5* gene was associated with higher scores of harm avoidance, and lower scores of cooperativeness, in healthy subjects using TCI. Based on these findings, the personality traits rather than the core features of ASD might be related to *FKBP5* gene polymorphisms. On the other hand, a cohort study using the Neonatal Intensive Care Unit Network Neurobehavioral Scales (NNNS) for evaluating infant neurobehavioral outcomes demonstrated that infants with higher FKBP5 methylation were at increased risk of exhibiting high NNNS arousal scores[29]. The study also found that infants with the TT genotype rs1360780 were more likely to exhibit high NNNS stress response. Since neurobehavioral profiles derived through NNNS have been previously shown to predict neurodevelopmental and cognitive performance in childhood, SNPs in the *FKBP5* gene could serve as biomarkers of neurobehavioral risk, facilitating early screening for neurodevelopmental disorders like ASD. Some forms of SNPs in the *FKBP5* gene were also found to be associated with attention deficit hyperactivity disorder, another neurodevelopmental disorder of childhood, while some forms were not reported to be associated, as observed the present study[30].

We observed significantly higher cortisol levels in the study group with the CC and CT genotypes than in the control group. However, no significant difference was found in terms of mean cortisol levels between the study and control groups among those with the TT genotypes. This finding of the present study is most probably due to the small number of the cases homozygous for the T allele. Carrying the C allele of FKBP5, seems to increase cortisol levels contrary to literature findings. Previous research showed an association of the T allele of the FKBP5 rs1360780 polymorphism with hypercortisolism in the HPA axis[8]. In addition, we compared the cortisol levels among 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 in 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 the 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.

Study Limitations

Our study has several limitations that should be addressed. The first limitation 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, and 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 accurate 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. Not only do cortisol levels affect the circadian rhythm, but other hormones like melatonin, thyroid-stimulating hormone, and prolactin also play a crucial role in the diurnal rhythm. Evaluating these hormones along with cortisol could provide more information about the circadian dysregulation of ASD. Additionally, not measuring body mass index is a limitation because body weight influences morning cortisol levels.

Conclusion

Despite these limitations, this is the first clinical study to evaluate the association between rs1360780 polymorphism in the *FKBP5* gene and serum cortisol levels in children with ASD compared to those of healthy participants. 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, possible endocrine and related genetic factors should be born in mind while examining this population. However, more research is needed to further explore the relationship between ASD and these factors.

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We would like to thank all the children and parents who took part in this research for giving us their time.

Ethics

Ethics Committee Approval: The study protocol was approved by the Non-invasive Clinical Research Ethics Committee of Gaziosmanpaşa University (approval number: 15-KAEK-226, date: 05.01.2016).

Footnotes

Informed Consent: Written informed consent was obtained from both parents before starting any study-related procedure.

Author Contributions: Bozkurt H: Concept, Design, Writing; Haktan A: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation; Şimşek Ş: Concept, Literature Search, Writing; Şahin S: Data Collection or Processing, Analysis or Interpretation, Literature Search; Coşkun S: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation.

Conflict of Interest: The authors declare no conflicts of interest.

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