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Prenatal androgens and autistic, attention deficit hyperactivity disorder, and disruptive behavior disorders traits

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ABSTRACT

Objective: *Androgen exposure is hypothesized to play a role in the development of autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and disruptive behavior disorders/DBDs (oppositional defiant disorder/ODD and conduct disorder/CD). The aim of this cross-sectional study was to investigate ASD, ADHD, and DBD (ODD and CD) traits in children and adolescents with congenital adrenal hyperplasia (CAH), a natural cause of prenatal androgen excess in females.* ***Methods:*** *Forty-five children and adolescents (27 girls, mean age 11.1±3; 18 boys, mean age 10.8±3.6) with CAH and their unaffected siblings (16 girls, mean age 11.4±3.9; 14 boys, mean age 12.6±4.2) were included in the study. Parents completed the Social Communication Questionnaire, to measure ASD symptoms; and the Turgay DSM-IV-Based Child and Adolescent Disruptive Behavioral Disorders Screening and Rating Scale to assess ADHD and DBD traits.* ***Results:*** *In this study, boys but not girls with CAH showed higher autistic traits. There was no significant difference between either girls or boys with CAH and their unaffected counterparts with respect to inattention or hyperactivity symptoms. Boys with CAH showed more ODD symptoms than the unaffected boys. There was a trend for boys to have more CD symptoms compared to unaffected boys.* ***Conclusions:*** *Our study does not support the hypothesis that prenatal androgen exposure is associated with ASD, ADHD or DBDs. Postnatal/circulating androgen levels, higher testosterone/cortisol ratio, lower basal cortisol or dysregulation in HPA axis might be related to higher autistic traits or increased DBDs symptoms found in boys with CAH. Further investigations with larger groups are needed to clarify these associations.* ***(Anatolian Journal of Psychiatry 2020; 21(4):435-442)***

Keywords: *Autism spectrum disorder, attention deficit hyperactivity disorder, disruptive behavior disorders, congenital adrenal hyperplasia*

Prenatal androjenler ve otizm spektrum bozukluğu, dikkat eksikliği hiperaktivite bozukluğu, yıkıcı davranış bozuklukları belirtileri

ÖZ

Amaç: *Yapılan araştırmalar sonucunda, prenatal androjen maruziyetinin otizm spektrum bozukluğu (OSB), dikkat eksikliği hiperaktivite bozukluğu (DEHB), yıkıcı davranış bozuklukları/YDB (karşıt olma karşı gelme bozukluğu/ KOKG ve davranım bozukluğu/DB) ve bunların subklinik belirtilerinin gelişmesinde rolü olduğu düşünülmektedir. Bu*

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araştırmanın amacı kız çocuklarda prenatal dönemde aşırı androjen maruziyetine yol açan konjenital adrenal hiperplazi (KAH) tanısı almış çocuk ve ergenlerde otizm spektrum bozukluğu özellikleri, DEHB ve YDB (KOKG ve DB) belirtilerinin sıklığının araştırılmasıdır. ***Yöntem:*** *KAH tanısı konmuş 45 çocuk ve ergen olgu (27 kız, ortalama yaş: 11.1±3; 18 erkek, ortalama yaş: 10.8±3.6) ve bu olguların etkilenmemiş akrabaları (16 kız, ortalama yaş: 11.4±3.9; 14 erkek, otalama yaş: 12.6±4.2) çalışmaya alınmıştır. Sosyal İletişim Ölçeği ve Turgay Yıkıcı Davranım Bozuklukları için DSM-IV'e Dayalı Tarama ve Değerlendirme Ölçeği (T-DSM-IV-S), sırasıyla otizm spektrum bozukluğu özellikleri, DEHB ve YDB (KOKG ve DB) belirtilerinin sıklığını değerlendirmek üzere ebeveynler tarafından doldurulmuştur.* ***Bulgular:*** *Bu araştırmanın sonucunda KAH tanısı konan erkek olgularda OSB özelliklerinin görülme sıklığının etkilenmemiş erkek akrabalarla karşılaştırıldığında artmış olduğu gösterilmiştir. KAH tanısı konan ve etkilenmemiş kız olgular arasında OSB özellikleri sıklığı açısından bir fark bulunmamıştır. KAH tanısı konmuş kız ve erkek olgularla bu olguların etkilenmemiş kız ve erkek akrabaları arasında dikkat eksikliği ve hiperaktivite belirtilerinin sıklığı açısından bir fark bulunmamıştır. KAH tanısı konan erkek olgularda KOKG belirtileri sıklığı etkilenmemiş erkek akrabalara göre artmıştır. KAH tanısı konan erkek olgularda DB belirtileri sıklığının etkilenmemiş erkek akrabalara göre artış eğilimi gösterdiği belirlenmiştir.* ***Sonuç:*** *Araştırmamız prenatal androjen maruziyetinin OSB, DEHB ve YDB ile ilişkili olduğu hipotezini desteklememektedir. KAH tanısı konan erkek çocuklarda artmış YDB belirtileri sıklığı postnatal androjen düzeyleri, yüksek testosterone/kortizol oranı, düşük bazal kortizol düzeyi veya hipotalomopitiüter aks disregülasyonu ile ilişkili olabilir. Daha geniş bir örneklemle yapılacak olan araştırmaların sözü geçen bağlantıları değerlendirmek üzere yararlı olacağı düşünülmektedir.* ***(Anadolu Psikiyatri Derg 2020; 21(4):435-442)***

Anahtar sözcükler: *otizm spektrum bozukluğu, dikkat eksikliği hiperaktivite bozukluğu, yıkıcı davranış bozuklukları, konjenital adrenal hiperplazi*

INTRODUCTION

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are both neurodevelopmental conditions.[1] ASD is characterized by deficits in social communication and interactions, stereotypic behaviors, and restricted interests. Attention-deficit/hyperactivity disorder (ADHD) is defined by developmentally inappropriate levels of inattention, hyperactivity, and/or impulsivity, with onset before the age of 12 years.[1] ASD and ADHD frequently co-occur, and a substantial body of research has shown that many similarities are present in genetic factors, brain characteristics, and cognitive profiles of these disorders.[2,3]

ASD and ADHD both are more prevalent in males than females. Males are approximately four times more likely than females to receive a diagnosis of ASD[4] and males are more likely than females to receive a diagnosis of ADHD, with ratios varying from 2:1 to 9:1.[5]

Oppositional defiant disorder/ODD and conduct disorder/CD are childhood and adolescent onset disruptive behavior disorders/DBDs, characterized by symptoms including angry/irritable mood, argumentative/defiant behavior and vindictiveness in ODD and violating the basic rights of others or major age-appropriate societal norms or rules, aggression to people or animals, destruction of property, deceitfulness or theft in CD.[1] ODD and CD frequently co-occur with ADHD[6] and similar to that in ASD and ADHD, ODD and CD are also more prevalent in males with ratios found 1.59:1 for ODD[7] and varying between 2.4:1 and 3:1 for CD.[8,9]

Prenatal androgen exposure has been proposed to account for the male predominance in ASD.[10] In accordance with this, elevated prenatal testosterone levels have shown to be associated with autistic traits in children between 18-24 months[11] and 6-10 years;[12] but recent research has reported contradictory findings.[13-16]

To date, more research has been conducted regarding hormone exposures in the prenatal environment for ASD compared to ADHD.[17] However, there are studies showing a link between ADHD or DBDs and lower second and fourth digits (2D:4D) ratio.[18-20] Being lower in males than in females, the 2D:4D ratio is a sexually dimorphic trait;[18-20] and evidence suggests that sex differences in 2D:4D is associated with prenatal testosterone exposure.[18,19] Furthermore, in their recent study utilizing maternal polycystic ovary syndrome (PCOS) as a model for prenatal androgen exposure in the offspring, Kosidou et al.[17] reported an increased risk of ADHD in children of women with PCOS.

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that impairs adrenal synthesis of cortisol. The most common form of CAH is caused by mutations in the CYP21A2 gene encoding 21-hydroxylase, which interferes with cortisol production and increases androgen production beginning prenatally.[21] Classic forms of CAH result in exposure to excess androgen levels in utero; therefore, CAH has been suggested as a model to elucidate the organizational effects of prenatal androgen exposure since

direct manipulation of the prenatal hormones to investigate its effects on human behavior is unethical.[22] Although they are diagnosed and treated early due to genital virilization at birth,[23] studies in females with CAH have shown masculinization in various aspects of behavior such as childhood play preferences, physical aggression, empathy, sexual orientation and gender identity.[22] Conversely, males with CAH generally do not differ from the normal population regarding sex-linked behavior;[22] and the evidence does not support that they are exposed to heightened levels of androgens prenatally.[24,25]

Research on ASD, ADHD and DBD symptomatology in children and adolescents with CAH is sparse and had produced inconsistent findings.[14,26-28] The aim of this cross-sectional study is to investigate the prevalence of ASD, ADHD, and DBD traits in children and adolescents with CAH. We hypothesized that traits of these male-skewed disorders would be increased in girls with CAH compared to unaffected girls and we also hypothesized that boys with or without CAH would not differ either in ASD, ADHD or DBD traits.

METHODS

Participants

This cross-sectional study was conducted in the Pediatric Endocrinology Clinic of the Kanuni Sultan Suleyman Training and Research Hospital in Istanbul, Turkey, between September 2013 and August 2014. The study group (SG) included children and adolescents with CAH aged 6-18 years (27 girls, 60%; 18 boys 40%). The control group (CG) consisted of unaffected siblings of CAH participants (16 girls, 53.33%; 14 boys, 46.67%). Subjects with intellectual disability, hearing or visual impairments, and neurological disease (e.g. epilepsy, cerebral palsy) were excluded from the study. All the eligible patients and their parents accepted participation.

Procedure

Participants were invited to participate in the study during their visit to the endocrinology clinic. The purpose and procedure of the study were explained to them by an attending pediatric endocrinologist. Upon their agreement, parents were asked to complete the questionnaires both for the subjects and their siblings to measure ASD (Social Communication Questionnaire), ADHD and DBD symptoms (Turgay DSM-IV-Based Disruptive Behavior Disorders Checklist).

Materials

Demographic and Clinical Data Form: A self-reported form was used to collect information about the demographic characteristics including age, gender, and education of the participants and age and education of the parents. The clinical data of the subjects with CAH (e.g., medical history, presence of genital surgery) were collected from the medical records.

Social Communication Questionnaire (SCQ): The SCQ is a parent-report questionnaire used to screen ASD symptoms. The SCQ consists of 40-item, of those each assesses the presence or absence of developmentally inappropriate behaviors.[29] It measures three areas of functioning: reciprocal social interaction, language and communication, and repetitive and stereotyped patterns of behavior. SCQ is adapted into Turkish by Avcil et al.[30] and reported as a valid and reliable instrument. The Turkish Version of SCQ was reported to have good internal consistency (α=0.80). In this study, the Cronbach's alpha values for the SCQ Social Relating, Communication, and Range of Interests dimensions were 0.83, 0.78, and 0.77 respectively.

Turgay DSM-IV-Based Child and Adolescent Disruptive Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S): The T-DSM-IV-S is based on the DSM-IV diagnostic criteria and nine items assess inattention (IA), nine items assess hyperactivity (HA), eight items assess oppositional defiant disorder (ODD), and 15 items assess conduct disorder (CD). The T-DSM-IV-S was developed by Turgay[31] and adapted into Turkish by Ercan et al.[32] In this study, the Cronbach's alpha values for T-DSM-IV-S IA, HA, ODD and CD subscales were 0.91, 0.84, 0.90, and 0.75 respectively.

Ethics

The study was approved by the Medical Ethics Committee of the Bakırköy Training and Research Hospital for Psychiatric and Neurological Disorders. Parents of all children had signed informed consent forms prior to participation in the study. In addition, children older than 12 years signed the consent forms themselves.

Analysis

Statistical analyses were done using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were reported as mean±standard deviation. Categorical variables were described using frequency distribution and reported as numbers and percent-

ages. Kolmogorov-Smirnov test was performed to test distribution of the data, and according to the results, an Independent t-test or Mann-Whitney U test used to compare continuous variables between the two groups. The chi-square test was performed for the comparison of categorical variables. A p-value of less than 0.05 (two tailed) considered as statistically significant.

RESULTS

Forty-five children and adolescents (27 girls, 18 boys) aged 6-18 years with CAH were recruited from the Pediatric Endocrinology Clinic of the Kanuni Sultan Suleyman Training and Research Hospital in Istanbul, Turkey. 25 participants with CAH had the salt-losing type of the disease, 15 had simple virilizing type, and 5 had non-classical (late onset) CAH. The control group was consisted of 30 (16 girls, 14 boys) unaffected siblings (aged 6-18 years) of CAH participants. The demographic characteristics of the groups were summarized in Table 1.

Table 1. Demographic characteristics of the groups

	SG (n=45)	CG (n=30)	χ^2/t	p
Age[1]	11.0±3.3	12.0±4.0	-1.18	0.243
Gender (girl/boy)[2]	27/18	16/14	0.33	0.567
Education[1]	5.5±2.9	6.6±3.9	-1.36	0.179

[1]: Independent-t-test; [2]: Chi-square test; SG: Study Group; CG: Control Group

Table 2. Demographic and behavioral characteristics of the girls

	SG (n=27)	CG (n=16)	t/z	p
Age[1]	11.1±3.1	11.4±3.9	-0.303	0.764
Education[1]	5.6±2.9	6.0±3.7	-0.433	0.668
T-DSM-IV-S inattention[2]	4.6±4.8	3.2±5.4	-1.222	0.222
T-DSM-IV-S hyperactivity[2]	3.4±3.7	2.6±3.2	-0.560	0.575
T-DSM-IV-S ODD[2]	3.2±2.8	3.7±4.2	-0.278	0.781
T-DSM-IV-S CD[2]	0.6±0.9	0.8±1.7	-0.128	0.899
SCQ-social relating[1]	11.6±1.9	11.6±1.9	-0.067	0.947
SCQ-communication[1]	7.1±2.0	6.4±2.6	0.984	0.331
SCQ-range of interests[2]	0.5±0.9	0.4±1.2	0.227	0.821
SCQ-total[1]	19.2±3.8	18.5±4.7	0.556	0.581

[1]: Independent-t-test; [2]: Mann-Whitney-U test; SG: Study Group; CG: Control Group; T-DSM-IV-S: Turgay DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale; SCQ: Social Communication Questionnaire ; ODD:oppositional-defiant disorder ; CD:conduct disorder

Table 2 and Table 3 shows demographic and behavioral characteristics of the girls with CAH and their unaffected counterparts and of the boys with CAH and unaffected boys respectively. Between-group comparisons were also shown.

DISCUSSION

This study investigated the prevalence of ASD, ADHD and DBD traits in children and adolescents with CAH. In this study, boys with CAH but not girls showed higher autistic traits than their unaffected counterparts. There are two prior studies in the literature investigating the prevalence of autistic traits in individuals with CAH. Knickmeyer et al.[26] reported increased rates of autistic traits in females with CAH compared to their unaffected female relatives. The study included 60 individuals with CAH (34 females, 26 males) aged 12 to 45 years. In their study, Knickmeyer et al.[26] used a self-report questionnaire, The Autism Spectrum Quotient, that may not have been adequately sensitive for younger participants. In a more recent study, Kung et al.[14] reported no significant difference with respect to

Table 3. Demographic and behavioral characteristics of the boys

	SG (n=18)	CG (n=14)	t/z	p
Age[1]	10.8±3.6	12.6±4.2	-1.300	0.203
Education[1]	5.3±3.0	7.3±4.1	-1.597	0.121
T-DSM-IV-S inattention[2]	4.9±5.1	3.0±2.6	-0.901	0.367
T-DSM-IV-S hyperactivity[2]	6.1±5.5	3.0±2.2	-1.541	0.123
T-DSM-IV-S ODD[2]	5.6±4.9	2.4±3.7	-2.659	**0.008**
T-DSM-IV-S CD[2]	2.2±3.5	0.4±0.6	-1.685	0.092
SCQ-social relating[1]	12.3±1.7	10.6±2.8	2.088	**0.045**
SCQ-communication[1]	7.7±2.0	5.8±2.7	2.298	**0.029**
SCQ-range of interests[2]	0.7±1.3	0.8±1.5	-0.221	0.827
SCQ-total[1]	20.7±3.2	17.2±5.9	2.135	**0.041**

[1]: Independent-t-test; [2]: Mann-Whitney-U test; SG: Study Group; CG: Control Group; T-DSM-IV-S: Turgay DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale; SCQ: Social Communication Questionnaire; ODD:oppositional-defiant disorder ; CD:conduct disorder

autistic traits between children (aged 4-11 years) with and without CAH either in girls or boys although there was a trend for both girls and boys with CAH to have more autistic traits. Kung et al.'s[14] study included 81 children with CAH (43 girls, 38 boys) and 72 unaffected relatives (41 girls, 31 boys). A parent-report questionnaire, the Childhood Autism Spectrum Test (CAST), was employed to assess autistic traits. Although prenatal testosterone is proposed to be associated with increased autistic traits in typically developing children[11,12] recent research in larger groups present contradictory results.[13-16] Our study confirms Kung et al.'s[14] findings suggesting no significant association between prenatal androgen exposure and higher autistic traits in girls with CAH. As stated by Kung et al.[14] methodological differences and older age of the participants in the first study group might have produced different results.

However, in the current study, we found significantly higher rates of autistic traits in boys with CAH. Neither the trend for boys with CAH found in Kung et al.'s[14] study nor our findings are likely to be explained by elevated prenatal androgen levels since there is no evidence that male fetuses with CAH are exposed to heightened levels of androgens.[24,25] As above mentioned, boys with CAH tend to receive a diagnosis later than affected girls. Thus, delayed treatment in boys may cause a longer exposure to excess adrenal androgens postnatally.[23] Early postnatal testosterone levels[33] and serum or saliva androgen levels of older children or adults have been associated with autistic traits or ASD[34-36] although there are two studies with opposite results.[37,38] It is noteworthy that these researches with opposite results are limited to the testosterone surge observed in early postnatal life.[37,38] Therefore, in the current study, not elevated prenatal androgen levels but postnatal androgen excess may be associated with increased autistic traits observed in boys with CAH.

Hormonal abnormalities in CAH also include cortisol and mineralocorticoid deficiency, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and increases in CRH. Oral glucocorticoids used in the treatment of CAH cannot completely mimic the normal circadian rhythm of cortisol.[21] Studies evaluating the diurnal rhythm and responsiveness of cortisol in individuals with ASD has generally found disregularity in the diurnal or circadian rhythm of cortisol and an overall sluggishness of the HPA axis in responding to physiological or physical manipulation.[39] In addition, Baron-Cohen et al.,[13] utilizing the amniotic fluid samples of all males born between 1993 and 1999 in Denmark, reported that not testosterone alone but a generalized latent steroidogenic factor presenting a shared variance of hormones in Δ4 sex steroid pathway (progesterone, 17.-hydroxy-progesterone, androstenedione, and testosterone) and cortisol was associated with higher autistic traits. Taking into account the aforementioned hormonal abnormalities characteristic of classical CAH; dysregulation in HPA axis or impairment in the normal circadian rhythm of cortisol acting together with increased levels of androgens in peripheral blood samples may be responsible for the increased rates of autistic traits found in boys with CAH in the current study.

In this study, we found no significant difference

between either in boys or girls with and without CAH with respect to inattention or hyperactivity symptoms. ODD symptoms were significantly higher in boys with CAH, and there was also a trend for CD symptoms in boys with CAH, although not statistically significant. Prior studies of aggressive behavior and activity level in children with CAH have produced inconsistent results. Although most of these studies conducted in females, findings of studies that included boys are also contradictory.[40] Previously, two studies particularly focused on ADHD and DBD symptomatology in individuals with CAH. In line with our results, Oner et al.[28] found no significant difference in females with CAH versus age and gender-matched Diabetes Mellitus Type 1 (DM1) and healthy controls with respect to HA and CD symptoms although females with CAH had higher aggressiveness scores. Oner et al.'s[28] study did not include male participants. Mueller et al.[27] reported higher rates of ADHD and DBD in boys but not girls with CAH. Our study revealed only a trend for ODD/CD symptoms in boys with CAH. Similar to our findings regarding the increased level of autistic traits in boys with CAH, this trend could unlikely be ascribed to prenatal testosterone exposure. Externalizing behaviors namely ADHD, ODD and CD symptoms have been shown to be related to increased levels of testosterone or adrenal androgens obtained from saliva, hair or peripheric blood samples although there is a great degree of inconsistency across studies.[41-46] Lower basal cortisol levels are suggested as a moderator for the relationship between aggression and higher testosterone levels.[42] Furthermore, there is a growing body of evidence suggesting a link between lower basal cortisol levels or blunted cortisol response to challenging situations/attenuated HPA axis activity and ODD/CD.[47-49] In addition, previous literature suggests that ODD comorbidity may be responsible for the association found between lower cortisol levels and ADHD. It is noteworthy that the same relationship for CD is not as strong as those for ODD.[49] However, higher comorbidity rates including anxiety disorders or different underlying neurobiological mechanisms in CD were proposed to account for the negative results with respect to the link between lower basal cortisol levels and CD.[47-49] Therefore, the increased rates of ODD/CD symptomatology found in the current study might be related to blunted cortisol response/attenuated HPA axis activity, lower plasma cortisol levels or higher plasma testosterone/cortisol ratio.

There are some limitations to the current study that should be considered. One of these limitations is the small sample size. In addition, the current study included only 18 boys with CAH. Therefore, although statistically significant, the results reported in this group are highly imprecise and this imprecision increases the probability of incidental findings. However, it is difficult to reach a large group of participants for the generalization of findings due to the rare occurrence of CAH.[21] Furthermore, our results should be interpreted carefully since we haven't conducted diagnostic interviews. Thereby, the continuity between autistic traits and ODD/CD symptoms and ASD and ODD/CD diagnosis per se remains unclear. Finally, researchers argue that atypical cognitive features in individuals with CAH might be related to disease characteristics rather than prenatal androgen exposure.[10]

Authors' contributions: H.G.: *study concept and design, data collection, statistical analysis, interpretation of data, manuscript writing; C.T.: study concept and design, data collection, statistical analysis, interpretation of data, manuscript writing, study supervision; H.D.: study concept and design, data collection, interpretation of data; Z.Ö.: data collection, interpretation of data, manuscript writing; E.K.: data collection, interpretation of data; H.Ö.: data collection, interpretation of data, manuscript writing; K.M.: study concept and design, manuscript writing*

REFERENCES

1. *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Fifth Ed. Arlington: American Psychiatric Association, 2013.*
2. *Rommelse N, Buitelaar JK, Hartman CA. Structural brain imaging correlates of ASD and ADHD across the lifespan: a hypothesis-generating review on developmental ASD-ADHD subtypes. J Neural Transm 2017; 124 (2):259-271.*
3. *Rosen TE, Mazefsky CA, Vasa RA, Lerner MD. Co-occurring psychiatric conditions in autism spectrum disorder. Int Rev Psychiatry 2018; 30(1):40-61.*
4. *Baron-Cohen S, Lombardo MV, Auyeung B, Ashwin E, Chakrabarti B, Knickmeyer R. Why are autism spectrum conditions more prevalent in males? PLoS Biol 2011; 9(6):e1001081.*

5. *Rucklidge JJ. Gender differences in attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2010; 33(2):357-373.*
6. *Pliszka SR. Patterns of psychiatric comorbidity with attention-deficit/hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 2000; 9(3):525-540.*
7. *Demmer DH, Hooley M, Sheen J, McGillivray JA, Lum JAG. Sex differences in the prevalence of oppositional defiant disorder during middle childhood: a meta-analysis. J Abnorm Child Psychol 2017; 45(2):313-325.*
8. *Erskine HE, Ferrari AJ, Nelson P, Polanczyk G V., Flaxman AD, Vos T, et al. Epidemiological modelling of attention-deficit/ hyperactivity disorder and conduct disorder for the Global Burden of Disease Study 2010. J Child Psychol Psychiatry 2013; 54(12):1263-1274.*
9. *Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011; 21(9):655-679.*
10. *Auyeung B, Lombardo MV, Baron-Cohen S. Prenatal and postnatal hormone effects on the human brain and cognition. Pflügers Arch - Eur J Physiol 2013; 465(5):557-571.*
11. *Auyeung B, Taylor K, Hackett G, Baron-cohen S. Foetal testosterone and autistic traits in 18 to 24-month-old children. Mol Autism 2010; 1(1):11.*
12. *Auyeung B, Baron-Cohen S, Ashwin E, Knickmeyer R, Taylor K, Hackett G. Fetal testosterone and autistic traits. Br J Psychol 2009; 100(Pt1):1-22.*
13. *Baron-Cohen S, Auyeung B, Nørgaard-Pedersen B, Hougaard DM, Abdallah MW, Melgaard L, et al. Elevated fetal steroidogenic activity in autism. Mol Psychiatry 2015; 20(3):369-376.*
14. *Kung KTF, Spencer D, Pasterski V, Neufeld S, Glover V, Connor TGO, et al. No relationship between prenatal androgen exposure and autistic traits: convergent evidence from studies of children with congenital adrenal hyperplasia and of amniotic testosterone concentrations in typically developing children. J Child Psychol Psychiatry 2016; 57(12):1455-1462.*
15. *Park BY, Lee BK, Burstyn I, Tabb LP, Keelan JA, Whitehouse AJO, et al. Umbilical cord blood androgen levels and ASD-related phenotypes at 12 and 36 months in an enriched risk cohort study. Mol Autism 2017; 8(1):3.*
16. *Whitehouse AJO, Mattes E, Maybery MT, Dissanayake C, Sawyer M, Jones RM, et al. Perinatal testosterone exposure and autistic-like traits in the general population: a longitudinal pregnancy-cohort study. J Neurodev Disord 2012; 4(1):25.*
17. *Kosidou K, Dalman C, Widman L, Arver S, Lee BK, Magnusson C, et al. Maternal polycystic ovary syndrome and risk for attention-deficit/hyperactivity disorder in the offspring. Biol Psychiatry 2017; 82(9):651-659.*
18. *De Bruin EI, Verheij F, Wiegman T, Ferdinand RF. Differences in finger length ratio between males with autism, pervasive developmental disorder-not otherwise specified, ADHD, and anxiety disorders. Dev Med Child Neurol 2006; 48(12):962-965.*
19. *Fink B, Manning JT, Williams JHG, Podmore-Nappin C. The 2nd to 4th digit ratio and developmental psychopathology in school-aged children. Pers Individ Dif 2007; 42(2):369-379.*
20. *McFadden D, Westhafer JG, Pasanen EG, Carlson CL, Tucker DM. Physiological evidence of hypermasculinization in boys with the inattentive type of attention-deficit/hyperactivity disorder (ADHD). Clin Neurosci Res 2005; 5(5-6):233-245.*
21. *Engberg H, Butwicka A, Nordenström A, Lindén A, Falhammar H, Lichtenstein P, et al. Congenital adrenal hyperplasia and risk for psychiatric disorders in girls and women born between 1915 and 2010: A total population study. Psychoneuroendocrinology 2015; 60:195-205.*
22. *Hines M. Gender development and the human brain. Annu Rev Neurosci 2011; 34(1):69-88.*
23. *Turcu AF, Auchus RJ. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinol Metab Clin NA 2015; 44(2):275-296.*
24. *Pang S, Levine LS, Cederqvist LL, Fuentes M, Riccardi VM, Holcombe JH, et al. Amniotic fluid concentrations of Δ5 and Δ4 steroids in fetuses with congenital adrenal hyperplasia due to 21 hydroxylase deficiency and in anencephalic fetuses. J Clin Endocrinol Metab 1980; 51(2):223-229.*
25. *Wudy SA, Dörr HG, Solleder C, Djalali M HJ. Profiling steroid hormones in amniotic fluid of midpregnancy by routine stable isotope dilution / gas hydroxylase deficiency. J Clin Endocrinol Metab 1999; 84(8):2724-2728.*
26. *Knickmeyer R, Baron-cohen S, Fane BA, Wheelwright S, Mathews GA, Conway GS, et al. Androgens and autistic traits: A study of individuals with congenital adrenal hyperplasia. Horm Behav 2006; 50(1):148-153.*
27. *Mueller SC, Ng P, Sinaii N, Leschek EW, Green-Golan L, VanRyzin C, et al. Psychiatric characterization of children with genetic causes of hyperandrogenism. Eur J Endocrinol 2010; 163(5):801-810.*
28. *Oner O, Aycan Z, Tiryaki T, Soy D, Cetinkaya E, Kibar E. Variables related to behavioral and emotional problems and gender typed behaviors in female patients with congenital adrenal hyperplasia. J Pediatr Endocrinol Metab 2009; 22(2):143-151.*

29. Rutter M, Bailey A, Lord C, Cianchetti C, Fancello G. SCQ: Social Communication Questionnaire: Manuale, Giunti OS, 2007.

30. Avcil S, Baykara B, Baydur H, Münir KM, Inal Emiroğlu N. The validity and reliability of the social communication questionnaire-Turkish form in autistics aged 4-18 years. Turk Psikiyatr Derg 2015; 26(1):56-64.

31. Turgay A. Disruptive behavior disorders child and adolescent screening and rating scales for children, adolescents, parents and teachers. West Blomfield (Michigan): Integrative Therapy Institute Publication, 1994.

32. Ercan, ES, Amado, S, Somer, O, Cikoglu S. Development of a test battery for attention deficit hyperactivity and disruptive behavior disorders. Turk J Child Adolesc Ment Heal 2001; 8:132-144. (In Turkish)

33. Alexander GM. Postnatal testosterone concentrations and male social development. Front Endocrinol Lausanne 2014; 5:15.

34. Geier DA, Geier MR. A prospective assessment of androgen levels in patients with autistic spectrum disorders: Biochemical underpinnings and suggested therapies. Neuro Endocrinol Lett 2007; 28(5):565-573.

35. Takagishi H, Takahashi T, Yamagishi T, Shinada M, Inukai K, Tanida S, et al. Salivary testosterone levels and autism-spectrum quotient in adults. Neuro Endocrinol Lett 2010; 31(6):837-841.

36. Tordjman S, Ferrari P, Sulmont V, Duyme M, Roubertoux P. Androgenic activity in autism. Am J Psychiatry 1997; 154(11):1626-1627.

37. Auyeung B, Ahluwalia J, Thomson L, Taylor K, Hackett G, O'Donnell KJ, et al. Prenatal versus postnatal sex steroid hormone effects on autistic traits in children at 18 to 24 months of age. Mol Autism 2012; 3(1):17.

38. Kung KTF, Constantinescu M, Browne WV, Noorderhaven RM, Hines M. No relationship between early postnatal testosterone concentrations and autistic traits in 18 to 30-month-old children. Mol Autism 2016; 7(1):15.

39. Taylor JL, Corbett B. A review of rhythm and responsiveness of cortisol in individuals with autism spectrum disorders. Psychoneuroendocrinology 2014; 49:207-228.

40. Pasterski V, Hindmarsh P, Geffner M, Brook C, Brain C, Hines M. Increased aggression and activity level in 3- to 11-year-old girls with congenital adrenal hyperplasia (CAH). Horm Behav 2007; 52(3):368-374.

41. Bakker-Huvenaars MJ, Greven CU, Herpers P, Wiegers E, Jansen A, van der Steen R, et al. Saliva oxytocin, cortisol, and testosterone levels in adolescent boys with autism spectrum disorder, oppositional defiant disorder/conduct disorder and typically developing individuals. Eur Neuropsychopharmacol. 2020; 30:87-101.

42. Grotzinger O, Grotzinger AD, Mann FD, Patterson MW. Hair and salivary testosterone, hair cortisol, and externalizing behaviors in adolescents. Psychol Sci 2018; 29(5):688-689.

43. Loney BR, Butler MA, Lima EN, Counts CA, Eckel LA. The relation between salivary cortisol, callous-unemotional traits, and conduct problems in an adolescent non-referred sample. J Child Psychol Psychiatry 2006; 47(1):30-36.

44. Van Goozen SHM, Van Den Ban E, Matthys W, Cohen-Kettenis PT, Thijssen JHH, Van Engeland H. Increased adrenal androgen functioning in children with oppositional defiant disorder: A comparison with psychiatric and normal controls. J Am Acad Child Adolesc Psychiatry 2000; 39(11):1446-1451.

45. Van Goozen SHM, Matthys W, Cohen-Kettenis PT, Thijssen JHH, Van Engeland H. Adrenal androgens and aggression in conduct disorder prepubertal boys and normal controls. Biol Psychiatry 1998; 43(2):156-158.

46. Wang LJ, Lee SY, Chou MC, Lee MJ, Chou WJ. Dehydroepiandrosterone sulfate, free testosterone, and sex hormone-binding globulin on susceptibility to attention-deficit/hyperactivity disorder. Psychoneuroendocrinology 2019; 103:212-218.

47. Schoorl J, Rijn SV, Wied M, van Goozen S, Swaab H. The role of anxiety in cortisol stress response and cortisol recovery in boys with oppositional defiant disorder/conduct disorder. Psychoneuroendocrinology 2016; 73:217-223.

48. Schoorl J, van Rijn S, de Wied M, van Goozen S, Swaab H. Neurobiological stress responses predict aggression in boys with oppositional defiant disorder/conduct disorder: a 1-year follow-up intervention study. Eur Child Adolesc Psychiatry 2017; 26(7):805-813.

49. Freitag CM, Hanig S, Palmason H, Meyer J, Wust S, Seitz C. Cortisol awakening response in healthy children and children with ADHD: Impact of comorbid disorders and psychosocial risk factors. Psychoneuroendocrinology 2009; 34(7): 1019-1028.