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, yıktıcı davranış bozuklukları belirtileri

ÖZ

Amaç: Yapılan araştırmalar sonucunda, prenatal androjen maruziyetinin otizm spektrum bozukluğu (OSB), dikkat eksikliği hiperaktivite bozukluğu (DEHB), yıktıcı davranış bozuklukları/YDB (karşı olma karşı gelme bozukluğu/KOKG ve davranış bozukluğu/DB) ve bunların subklinik belirtilerinin gelişmesinde rolü olduğu düşünülmektedir. Bu
Prenatal androgens and autistic, attention deficit hyperactivity disorder, and disruptive...
direct manipulation of the prenatal hormones to investigate its effects on human behavior is unethical.  

Although they are diagnosed and treated early due to genital virilization at birth, 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. Conversely, males with CAH generally do not differ from the normal population regarding sex-linked behavior and the evidence does not support that they are exposed to heightened levels of androgens prenatally.

Research on ASD, ADHD and DBD symptomatology in children and adolescents with CAH is sparse and has produced inconsistent findings. 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. 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. 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 and adapted into Turkish by Ercan et al. 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

<table>
<thead>
<tr>
<th></th>
<th>SG (n=45)</th>
<th>CG (n=30)</th>
<th>χ²/t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age¹</td>
<td>11.0±3.3</td>
<td>12.0±4.0</td>
<td>-1.18</td>
<td>0.243</td>
</tr>
<tr>
<td>Gender (girl/boy)²</td>
<td>27/18</td>
<td>16/14</td>
<td>0.33</td>
<td>0.567</td>
</tr>
<tr>
<td>Education¹</td>
<td>5.5±2.9</td>
<td>6.6±3.9</td>
<td>-1.36</td>
<td>0.179</td>
</tr>
</tbody>
</table>

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

Table 2. Demographic and behavioral characteristics of the girls

<table>
<thead>
<tr>
<th></th>
<th>SG (n=27)</th>
<th>CG (n=16)</th>
<th>t/z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age¹</td>
<td>11.1±3.1</td>
<td>11.4±3.9</td>
<td>-0.303</td>
<td>0.764</td>
</tr>
<tr>
<td>Education¹</td>
<td>5.6±2.9</td>
<td>6.0±3.7</td>
<td>-0.433</td>
<td>0.668</td>
</tr>
<tr>
<td>T-DSM-IV-S inattention²</td>
<td>4.6±4.8</td>
<td>3.2±5.4</td>
<td>-1.222</td>
<td>0.222</td>
</tr>
<tr>
<td>T-DSM-IV-S hyperactivity²</td>
<td>3.4±3.7</td>
<td>2.6±3.2</td>
<td>-0.560</td>
<td>0.575</td>
</tr>
<tr>
<td>T-DSM-IV-S ODD²</td>
<td>3.2±2.8</td>
<td>3.7±4.2</td>
<td>-0.278</td>
<td>0.781</td>
</tr>
<tr>
<td>T-DSM-IV-S CD²</td>
<td>0.6±0.9</td>
<td>0.8±1.7</td>
<td>-0.128</td>
<td>0.899</td>
</tr>
<tr>
<td>SCQ-social relating¹</td>
<td>11.6±1.9</td>
<td>11.6±1.9</td>
<td>-0.067</td>
<td>0.947</td>
</tr>
<tr>
<td>SCQ-communication¹</td>
<td>7.1±2.0</td>
<td>6.4±2.6</td>
<td>0.984</td>
<td>0.331</td>
</tr>
<tr>
<td>SCQ-range of interests²</td>
<td>0.5±0.9</td>
<td>0.4±1.2</td>
<td>0.227</td>
<td>0.821</td>
</tr>
<tr>
<td>SCQ-total²</td>
<td>19.2±3.8</td>
<td>18.5±4.7</td>
<td>0.556</td>
<td>0.581</td>
</tr>
</tbody>
</table>

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
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\textsuperscript{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\textsuperscript{11,12} recent research in larger groups present contradictory results.\textsuperscript{13-16} Our study confirms Kung et al.’s\textsuperscript{14} findings suggesting no significant association between prenatal androgen exposure and higher autistic traits in girls with CAH. As stated by Kung et al.’s\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{23} Early postnatal testosterone levels\textsuperscript{32} and serum or saliva androgen levels of older children or adults have been associated with autistic traits or ASD\textsuperscript{34-36} although there are two studies with opposite results.\textsuperscript{37,38} It is noteworthy that these researches with opposite results are limited to the testosterone surge observed in early postnatal life.\textsuperscript{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.\textsuperscript{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.\textsuperscript{39} In addition, Baron-Cohen et al.,\textsuperscript{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

Table 3. Demographic and behavioral characteristics of the boys

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

\textsuperscript{1} Independent-t-test; \textsuperscript{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
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.'s28 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 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 persists 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.O.: data collection, interpretation of data, manuscript writing; E.K.: data collection, interpretation of data; H.O.: data collection, interpretation of data, manuscript writing; K.M.: study concept and design, manuscript writing

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