The Association Between Autistic Traits and Serum Testosterone, Oxytocin and Androstenedione Levels in Prepubertal Male Drug Naive Children with Attention-Deficit/Hyperactivity Disorder

Abdulbaki Artık (bakiartik@gmail.com)
Usak University
Sadriye Ebru Çengel Kültür
Hacettepe University
Oytun Portakal
Hacettepe University
Arda Yamaç Karaboncuk

Research Article

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Abstract

Children with Attention Deficit Hyperactivity Disorder (ADHD) might have problems similar to autism spectrum disorders and show impairment in social behaviour. Also, there is a relationship between social relationship skills and ToM (Theory of Mind) skills in children with ADHD. Besides, ASD (Autism Spectrum Disorder) is associated with prenatal exposure to high levels of androgens, and oxytocin plays a role in the modulation of emotions, coping with stress, and social behaviour such as ASD. In this study, the relationship between autistic traits and serum oxytocin, testosterone, and androstenedione levels in prepubertal male drug naive children with ADHD has been investigated. Prepubertal children with ADHD have been included in the study. For the children included in the study, intelligence levels were evaluated with WISC-4 (Wechsler Intelligence Scale for Children-fourth edition) and autistic traits were measured with both social responsiveness scale and theory of mind tests. Serum levels of oxytocin, testosterone, and androstenedione were measured with ELISA (The enzyme linked immunosorbent assay). While serum testosterone of patients with lower autistic traits are significantly lower than those with and severe autistic traits, the serum oxytocin levels are significantly higher. Also, patients with severe autistic traits have significantly higher serum androstenedione levels than those with lower autistic traits and autistic traits. It has been suggested that oxytocin, testosterone, and androstenedione might play roles in impaired social functions such as autistic traits, and this might be related to social relationships and theory of mind skills in patients with ADHD.

Keypoints

- Children with Attention Deficit Hyperactivity Disorder (ADHD) might have problems similar to autism spectrum disorders and show impairment in social behaviour.
- Also, there is a relationship between social relationship skills and ToM (Theory of Mind) skills in children with ADHD. Besides, ASD (Autism Spectrum Disorder) is associated with prenatal exposure to high levels of androgens, and oxytocin plays a role in the modulation of emotions, coping with stress, and social behaviour such as ASD.
- It has been suggested that oxytocin, testosterone, and androstenedione might play roles in impaired social functions such as autistic traits, and this might be related to social relationships and theory of mind skills in patients with ADHD.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood and is seen in 3-7% of school-age children [1]. ADHD leads to severe social, academic, and psychological impairments such as inadequate social functionality in all stages of child and adolescent development. Children with ADHD have difficulties in behaving emphatically in social situations, as they find it difficult to put themselves in place with another person. These children also have difficulties in interpreting social clues [2]. Besides, it has been shown that children with ADHD might experience problems similar to autism spectrum disorders (ASD) including communication and social reciprocity problems and repetitive behaviours [3]. In a study related to the issue, it has been found that children with ADHD have higher mean scores on the SRS compared to the control group, and 54.7% of these children have experienced sub-threshold or

clinically significant social problems [4]. In another study, it has been mentioned that ADHD, which is related to front striatal dysfunction, is associated with the poor performance in ToM tests [5].

Autism spectrum disorders are neurodevelopmental disorders which emerge with social and communication deficits, repetitive and limited interests, and behaviours. One of the theories that explains ASD is the “extreme male brain” theory proposed by Simon Baron-Cohen [6]. This theory is based on the observation that ASD is predominantly seen in men and states that ASD is associated with prenatal exposure to high levels of testosterone [7]. There is one study in the literature evaluating the relationship between salivary testosterone levels and autistic traits in healthy controls [8]. The results show that saliva testosterone levels are positively associated with autistic traits in both men and women when the effect of age has been controlled. In addition, oxytocin plays a role in the modulation of emotions, coping with stress, and social behaviour [9]. Therefore, testosterone and oxytocin might be listed as peripheral markers of autistic behaviour. As the increased autistic traits in patients with ADHD have been documented well, it can be supposed that there might be a difference in serum testosterone and oxytocin levels between patients with increased autistic traits or not.

Few studies have investigated the role of oxytocin in ADHD until today. Taurines et al. have compared plasma oxytocin levels in ADHD, ASD, and healthy individuals. They have shown that plasma oxytocin concentrations are significantly lower in ADHD patients than healthy controls and individuals with ASD [10]. The aim of this study is to investigate the relationship between autistic traits and the ToM skills with serum oxytocin, testosterone, and androstenedione levels in prepubertal male patients with ADHD.

2. Methods

2.1. Procedure

The study was conducted between May 2017 and March 2018. Children, who were diagnosed with ADHD according to DSM-5 criteria for the first time in the Department of Child and Adolescent Mental Health and Diseases, Hacettepe University Faculty of Medicine, have been referred as the research team. All the patients with ADHD who are suitable for inclusion criteria were asked to participate in the study. 83 patients between the ages of 72 and 120 months who voluntarily accepted to participate have been included in the study. Detailed information was provided to the patients and their families about the purpose and the method of the study. Written consent was obtained from patients and their families. Psychiatric interviews were conducted with patients who volunteered to participate in the study and who gave consent, and their families to confirm the diagnosis of ADHD and to evaluate concomitant psychiatric diseases. In the psychiatric interview, ADHD diagnosis and accompanying psychiatric disorders have been determined according to the “The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)” diagnostic criteria by applying a semi-structured Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL). Wechsler Intelligence Scale for Children-IV (WISC-IV) has been applied to all participants by the clinical psychologist in order to determine the intelligence score. Also, a Social Responsiveness Scale (SRS) has been given to the parents in order to evaluate the patients' autistic traits. In this study, WISC-IV has been used to determine the intelligence score and SRS has been used to evaluate the patients' autistic traits because it was Turkish normed. Autistic traits evaluated with SRS and ToM tests have been performed by a clinical psychologist. In this study, the theory of mind has been measured by storytelling. Visualization with toys has also been used as the story can be understood easily. In this process, while conveying the story verbally and

playing the toys, the tester asks regular “Reminder questions” to the child at the same time to make sure the story is understood correctly. After making sure that the story is understood correctly, the test question is started. At this stage, to be success in the test, it is expected that the child observes the information that one of the story characters does not have and accordingly predicts the path that the character will follow correctly. After that, a series of questions are asked to confirm that the correct answer of the child is not a coincidence. When the correct answer is given in all stages, the Confirmation Question, Reality Question and Memory Question stages, the test is completed successfully. The patients included in the study are divided into three groups as high autistic traits, autistic traits and no autistic traits according to SRS and ToM- true ToM and false ToM- tests. To evaluate the pubertal stage, Tanner staging has been performed at Child and Adolescent Mental Health Outpatient Clinic and an assessment has been made about adolescence.

Psychoactive drug use, female gender, adolescence, accompanying intellectual disability, specific learning disorder, developmental coordination disorder, behavioural disorder, tic disorder, autistic spectrum disorder, psychotic disorder, bipolar disorder, generalized anxiety disorder, separation anxiety disorder or obsessive-compulsive disorder, metabolic or endocrine disease, history of head trauma or chronic neurological disease have been accepted as exclusion criteria. Exclusion diagnoses have been made with K-SADS-PL and DSM-5 diagnostic criteria.

The research has been approved by Hacettepe University Non-Interventional Clinical Research Ethics Committee with the number GO 17/420 on 04.07.2017. Written consent has been obtained from the participants and their families.

2.2. Materials

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)

Gökler et al. [11] adapted the scale to Turkish in 2004 as “ÇDSG-SY," which was originally developed by Kaufman et al [12] and updated version according to DSM-5 criteria were adapted by Ünal et al. [13] ÇDSG-SY is able to evaluate 20 different psychiatric diagnoses.

Wechsler Intelligence Scale for Children-IV (WISC-IV)

The standardization and norm studies of WISC-IV, the latest version of the Wechsler Intelligence Scales, which was reorganized in the US in 2003 [14] and introduced to use, was conducted in our country between 2007-2011 by the Turkish Psychologists Association [15] Unlike previous scales, WISC-IV has been emphasized under four factors; verbal comprehension, perceptual reasoning, working memory, and processing speed.

Screening and Rating Scale for Behavioural Disorders in Children and Adolescents Based on Turgay-DSM-IV (T-DSM-IV-S)

This scale developed according to DSM-IV criteria consists of a total of 41 items, 9 questioning attention deficit, 6 questioning excessive mobility, 3 questioning impulsivity, 8 questioning oppositional defiant disorder, and 15 questioning behavioural disorder [16].

Social Responsiveness Scale (SRS)

The scale, which was originally developed in 2000 by Constantino as Social Reciprocity Scale, later named as the "SRS-Social Responsiveness Scale." In 2003, Constantino stated that the scale could be used to evaluate the OSB-like symptom cluster [17]. There are 65 items in total, including 6 items on the social use of language, 39 items on observable social behaviours, and 20 items on autistic behaviours. It is accepted that patients who score between 60 and 80 points on the scale show signs of autism and patients who get higher than 80 points show severe autism symptoms.

Theory of Mind Evaluation

Since ToM switched to psychopathology terms through developmental psychology theories, the first tests developed are “false belief" tests to understand the developmental process. It was originally developed by Wimmer and Perner [18].

Tanner Staging

The pubertal stage has been evaluated by using the schematic drawing of secondary sex characteristics associated with 5 Tanner staging of pubertal development [19]. Tanner Staging (Sexual Maturity Rating, SMR), is an objective classification system that is used to document and track the development and sequence of secondary sex characteristics of children during puberty [20].

2.2.3. Hormonal evaluation

Participants were asked to apply to the outpatient unit in a relaxed state, between 08:00 and 10:00, avoiding physical exercise and stress. A 10 ml venous blood sample was taken to measure the serum oxytocin concentration. Blood samples were centrifuged for 15 minutes at 1000 g within 30 minutes for the evaluation of serum oxytocin. Separated serum samples were stored at -80°C until analysis. Serum oxytocin concentrations were measured in the biochemistry laboratory by the ELISA method.

For the measurement of plasma concentrations of testosterone and androstenedione, 10 ml venous blood samples were taken into purple capped tubes with EDTA. Blood samples were centrifuged for 15 minutes at 1000 g within 30 minutes. The separated plasma samples were stored at -80°C until analysis. Plasma testosterone and androstenedione levels were measured in the biochemistry laboratory by Liquid Chromatography-Mass-Mass Spectrometry (LC-MS-MS) method.

2.2.4. Statistical Analysis

The obtained data have been evaluated with “SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL)”. Descriptive statistics are presented as mean ± standard deviation (minimum-maximum), frequency distribution, and percentage. Pearson Chi-Square Test has been used to evaluate categorical variables. The suitability of variables to normal distribution has been evaluated by using visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov Test). Since serum testosterone value is normally distributed, Student's T-Test is used to compare it between false and true groups of ToM; and ANOVA (Analysis of Variance) is used to compare it among autistic traits status groups according to SRS. After ANOVA, if an overall significance is observed, pairwise post-hoc test is performed by using Tamhane’s T2 test. As serum oxytocin and androstenedione measurements are not normally distributed, the Kruskal-Wallis tests are conducted to compare the parameters between the results of ToM and autistic trait according to SRS groups.

The Mann-Whitney U test is performed to test the significance of pairwise differences by using Bonferroni correction to adjust for multiple comparisons. The relationship between the variables has been evaluated with the Spearman Correlation Test. An overall p value of less than 0.05 is considered to show a statistically significant result. However, significant level has been accepted as p<0.017 after Bonferroni correction in binary comparison with Mann-Whitney U test.

3. Results

83 males diagnosed with ADHD in the prepubertal period are categorized and divided into three groups called as inattentive (26 patients, 31.4%), hyperactive (8 patients, 9.6%), and combined (49 patients, 59%). Also, 43 of the patients (51.8%) have oppositional defiant disorder (ODD). Mean age has been 94,8±14.6 months (72-120 months).

While the total mean score of the SRS has been 64.5±21.0 (28-127), the mean score of the "social behaviours" subscale has been 38.4±12.7 (13-79), and the mean score of "social use of language" has been 7.1±2.4 (1-12) and "pathognomonic autistic behaviour's" mean score has been 18.8±7.6 (6-40). "Autistic symptom status" is determined according to the cut-off scores of the SRS. While 44 (53.0%) of the patients have no autistic symptoms, 19 (22.9%) have mild, and 20 (24.1%) have severe autistic symptoms. In the theory of mind, the ToM assessment of 48 (57.8%) of the patients is "true," whereas the remaining 35 (42.2%) are "false". The number and percentage of patients, who have the true ToM test, without autism symptoms [SRS score<60] (n=44 and 100%) are found to be significantly higher than the patients with autistic symptoms [SRS score is 60-80] (n=4 and 21%) and patients with severe autistic symptoms [SRS score> 80] (n=0 and 0%). A statistically significant difference has been found between the autistic symptom levels of the patients evaluated with SRS and ToM (*p<0.001*) (Table 1). Mean score of SRS is significantly higher in the patients with the wrong ToM than the patients with the wrong ToM statistically (Score of SRS 84.4±15.4 (64-127) vs 49.9±9.5 (28-68), p<0.001) (Table 2). In our study, no significant difference has been found between ADHD subtypes and SRS scores (p=0.34) and the theory of mind tests (p=0.56).

The levels of testosterone and androstenedione in blood are significantly higher in the patients with the wrong ToM, while oxytocin levels are significantly lower in the patients with the wrong ToM statistically (Testesterone 5.4±1.4 (2.0-9.3) pg/mL vs 3.0±0.9 (1.4-4.6) pg/mL , p<0.0001; Androstenedione 21.2±6.5 (7.7-32.7) pg/mL vs 15.8±5.3 (7.8-36.8) pg(mL ,p<0.0001; Oxytocin 39.9±4.0 (32.3-47.7) pg/mL vs 51.9±10.1 (35.2-74.2) pg/mL, p<0.001) (Table 2).

The blood levels of testosterone, androstenedione, and oxytocin are found statistically significant among non-autistic, mild and severe groups according to SRS scores (Testesterone 2.8±0.8 (1.4-4.6) vs 5.1±1.2 (3.7-8.8) vs 5.4±1.7 (2.0-9.3) pg/mL , p<0.001; Androstenedione 15.7±5.5 (7.8-36.8) vs 17.0±5.8 (7.7-29.2) vs 24.2±4.9 (13.2-32.7) pg/mL, p<0.001; Oxytocin 51.9±9.7 (35.2-74.2) vs 42.0±9.0 (32.6-72.0) vs 40.4±4.1 (32.3-47.7) pg/mL, p<0.001). In binary comparisons, there have been significant differences in serum testosterone and oxytocin levels that are caused by the patients without autistic traits. Also, there is a significant difference in androstenedione levels that is caused by the patients with severe autistic traits. While the serum testosterone levels of patients with no autistic traits are significantly lower than those with mild and severe autistic traits, the serum oxytocin levels are significantly higher. In addition, patients with severe autistic traits have significantly

higher serum androstenedione levels than those without autistic traits and those with mild autistic traits (Table 3).

A positive correlation has been found between ToM and SRS (r=0.90, p<0.0001). A positive correlation has also been found between androgens (testosterone and androstenedione) and SRS or ToM. There is a negative correlation between oxytocin and ToM or SRS or testosterone. In addition, ToM have a negative correlation with age (r=-0.24, p=0.03) (Table 4).

An increase in levels of testosterone and androstenedione, and a decrease in the level of oxytocin have been determined as independent predictors to develop an autistic trait in ADHD according to SRS [testosterone: p=0.004, OR (95% CI)=21.3 (2.6-174.4); androstenedione: p=0.057, OR (95% CI)=1.2 (0.94-1.4); oxytocin: p=0.009, OR (95% CI)=0.6 (0.4-0.88)] (Table 5).

An increase in levels of testosterone and androstenedione, and a decrease in the level of oxytocin and age have been determined as independent predictors for poor performance of ToM [testosterone: p=0.04, OR (95% CI)=13.1 (2.2-75.5); androstenedione: p=0.09, OR (95% CI)=1.2 (0.9-1.5); oxytocin: p=0.02, OR (95% CI)=0.6 (0.4-0.9); age=0.04 OR (95% CI)=0.9 (0.8-0.9)] (Table 6).

There has been no significant difference in terms of Screening and Rating Scale for Behavioural Disorders in Children and Adolescents Based on Turgay-DSM-IV scores, and WISC-4 total and subscales scores between patients who have the true ToM test or not (Table 7 and 8). There has been no significant difference between groups those divided according to SRS scores (non-autistic, mild and severe groups) in terms of Screening and Rating Scale for Behavioural Disorders in Children and Adolescents Based on Turgay-DSM-IV scores, and WISC-4 total and subscales scores (Table 9 and 10).

4. Discussion

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood and is seen in 3–7% of school-age children [21]. In Turkey, ADHD prevalence is reported as 12.39% [22]. ADHD leads to severe social, academic, and psychological impairments in all stages of child and adolescent development.

Some researchers consider that children with ADHD have inadequate social functionality due to its associated behavioural patterns such as attention deficit, difficulty in family, and lack of social skills [23]. Impaired social functionality is often seen as a rejection by peers and engaging in conflict with other children and adults. Social functionality is a concept based on cognitive and social abilities and affected by individual characteristics and environmental factors [24]. Children with ADHD have difficulties in behaving emphatically in social situations as these children find it difficult to put themselves in place with another person. Moreover, they also have difficulties in interpreting social clues [2]. Besides, it has been shown that children with ADHD might experience problems similar to children with autism spectrum disorders (ASD) while involving in communication and they might have social reciprocity problems and repetitive behaviours [25]. It seems worthwhile to consider the presence of socio-communicative and/or repetitive traits in children with ADHD who do not meet diagnostic criteria for ASD. Some researches report that children with ADHD might display clinically significant symptoms of ASD in three core categories; social interaction, social communication, and repetitive behaviours [26]. Other studies report clinical symptoms only in social interaction [27] or only in repetitive behaviours [28]. In the literature, it has been shown

that children with ADHD are likely to have autistic traits. In a study using the social responsiveness scale (SRS), it has been found that children with ADHD have higher mean scores on the SRS compared to the control group, and 54.7% of these children have experienced sub-threshold or clinically significant social problems [4]. To our knowledge, there is no study in which the social functionality and autistic traits of ADHD patients are evaluated together with both SRS and theory of mind tests. In our study, mean score of the SRS is 64.5 ± 21.0 (28–127). Also, the patients with mild and severe autistic traits have higher scores (70.6 and 93.9) than the patients with non-autistic range (48.6). It can be said that the increase in severity of autistic trait can cause higher score in patients with ADHD.

Social cognition is the ability of the individual to consider about the thoughts, feelings, and behaviours of himself and others [29]. It is known as a basic concept for the theory of mind (ToM). ToM, in other words having a mental theory or metallization capacity, is realizing that people (others) other than himself have a mind different from his own, understanding mental states such as intent, belief, desire, and knowledge of himself or others, and representing them mentally [30]. In terms of psychopathology, the concept of ToM disorders was first used to explain the symptoms in children with ASD [30]. In literature, there have been a limited number of studies in which ADHD patients are evaluated with false belief tests for ToM skills. Disorders of the prefrontal cortex affect the ToM skills; therefore, any functional or structural problem in the nerve pathways of this region can disrupt the ToM skills, which is essential for social functionality [31]. Clinical studies have shown that patients with ADHD might show impairment in social behaviour, although their cognitive abilities are normal [31]. It has been thought that there is a relationship between social relationship skills and ToM skills in children with ADHD. It has been shown that ADHD, which is related to front striatal dysfunction, is associated with the poor performance in ToM tests [5] and deficiencies in emotional facial expression, especially in recognition of anger and sadness [32]. “Executive functions” is a common term for various control processes that is responsible for the coordination, the constitution, the observation and the evaluation of sensory, cognitive and motor systems [33]. The deficiencies in executive functions are especially and strongly related to ADHD [34]. Mary et al. (2016) have clearly pointed out that theory of mind deficits among the children with ADHD are related to ruined executive functions [5]. It has been stated that adults with ADHD show social cognition difficulties and the deficiency in executive functions contribute to the weak theory of mind skills in ADHD [35]. It has been shown that the children with ADHD might have difficulties in social perception due to the deficiencies in working memory and theory of mind [36]. In our study, the ToM assessment of 48 patients (57.8%) is "true," whereas the remaining 35 (42.2%) are "false". Patients with mild and severe autistic traits have higher rate of false results (78.9% and 100%) than the patients with non-autistic range (0%). The increase in severity of autistic trait can cause higher false answer rate in patients with ADHD. However, the patients with non-autistic range have all true answers. We have found higher SRS scores in impaired ToM groups. SRS scores are higher in patients with false ToM skills (84.4) than the patients with trues (49.9). It shows that ToM skills can fail due to autistic traits and its severity in patients with ADHD. Besides, ToM have a strong correlation with SCR in our study ($r = 0.90$, $p < 0.0001$). SRS total score is found to be as a possible risk factor in univariate analysis. The increase in SRS total score has made ToM performance 1.9 times worse. However, age has been 0.9 times effective on ToM poor performances. Thus, the increase in age has a protective effect on ToM performance. Age also has a negative correlation with ToM poor performance. In our study, no significant difference has been found between ADHD subtypes and SRS scores and the theory of mind tests.

Our knowledge of neuro-hormones in relation to ADHD is based on few studies and only a few of them are focused on comorbidity or traits associated to ADHD. To the best of our knowledge, our study is the first investigating the relationship between autistic traits and serum oxytocin, testosterone, and androstenedione levels in prepubertal boys with ADHD. We hypothesized that prepubertal boys with ADHD associating higher autistic traits and false ToM tests would be correlated with low oxytocin, high testosterone, and high androstenedione levels.

In literature, there are several studies showing the relationship between increased androgen levels and autistic traits. Some psycho-endocrinology studies have shown that saliva testosterone level is strongly associated with social cognition [37]. Takagishi et al. have investigated the relationship between salivary testosterone levels and autistic traits in adults. In their study, they have found out a positive correlation between testosterone levels and autistic traits [8]. Compared to the children who are in puberty at the usual time, children with early puberty showed a significant increase in features such as social withdrawal, social problems, problematic behaviours, and language development impairment [38].

Studies investigating the association between testosterone and autistic traits are rooted from extreme male brain theory (EMB). In this theory, Baron-Cohen have proposed two basic cognitive styles, defined as male brain type which defines individuals in whom systemizing is more developed than empathizing and female brain type which defines individuals in whom empathizing is more developed than systemizing, measured by Empathizing Quotient (EQ) and Systemizing Quotient (SQ)[39]. The EMB theory states that ASD is associated with reduced empathy and increased systemizing that is hypothesized to be related to prenatal testosterone exposure [40]. The fact that ASD is approximately four times higher in men suggested that an effect such as prenatal androgen exposure might be significant in this disorder. There is some evidence that testosterone might play a role in the pathophysiology of autism. Females make more eye contact than males, learn to speak and read earlier, and they have a wider vocabulary [41]. In a recent study, it has been suggested that higher levels of autistic traits are associated with less feminine facial structures in females and less masculine structures in males [42]. Moreover, a negative relationship has been shown between prenatal testosterone levels and eye contact and language development [41]. Various diseases associated with high androgen levels, such as polycystic ovarian syndrome, hirsutism, acne, irregular menstrual cycle, and dysmenorrhea are found to be higher in patients with ASD. In clinical studies, androgen levels are examined in patients diagnosed with ASD. For instance, Tordjman et al. [43] showed a significant increase in plasma testosterone levels in one out of every three children diagnosed with ASD compared to healthy children. Similarly, in patients diagnosed with ASD, DHEA, and serum testosterone levels have been shown to increase significantly compared to age and gender-specific reference intervals [44]. Besides that, androstenedione is the precursor of testosterone, hormone-sensitive tissue uptake circulating androstenedione, and converts it to the active androgen metabolites. In another study, serum androstenedione levels have been found significantly higher in patients with ASD compared to healthy individuals [45]. All these studies emphasize the association between prenatal androgen exposure and autistic traits and ASD which are highly comorbid with ADHD. In our study, we have found out that patients with more severe autistic traits according to both SRS scores and ToM test results have higher serum testosterone and androstenedione levels. There is a significant positive correlation between serum testosterone and androstenedione levels and higher autistic traits in ADHD patients. The increase in testosterone and androstenedione levels have made 21.3 and 1.2 times worse for SRS score and 13.1 and 1.2 times worse for ToM performance, respectively. Our study extends the findings of previous research in ASD to autistic trait in ADHD and supports the idea that early foetal

environment might play a role in the development of cognitive phenotype associated with autistic traits coexisting with ADHD. In addition, no evidence has been found to support the idea of brain theory in the light of a large scale randomized controlled studies. Testosterone has any effects on cognitive empathy, and/or that there might be a complex and not linear effect of testosterone [46].

Oxytocin plays a role mainly in the regulation of emotions, coping with stress, and social behaviours [9]. It has been suggested that the dysfunction of social skills in ASD might be associated with dysfunction of the central oxytocin system [9]. Genetic studies have shown the relationship of variants of the oxytocin receptor gene and abnormalities in the oxytocin receptor gene methylation with autistic symptoms in patients with ASD [47]. Studies comparing serum oxytocin levels of patients with ASD and serum oxytocin levels of healthy individuals show inconsistent results. While some studies have shown lower oxytocin levels in patients with ASD compared to healthy individuals [48], others have indicated higher oxytocin levels [49]. In some other studies, no difference is found between oxytocin levels [50]. Various studies have shown that serum oxytocin concentrations have a negative correlation with autism symptoms in children with ASD, and individuals with low oxytocin levels show autism symptoms more frequently [51]. Up to date, few studies have investigated the role of oxytocin in ADHD. Park et al. [52] have associated specific oxytocin receptor polymorphisms with inadequate social cognition in children with ADHD diagnosed based on the DSM-IV criteria. These results are supported by the results of another study which shows that serum oxytocin levels are negatively correlated with aggression and positively correlated with empathy in the ADHD group [53]. In addition to these findings in clinical cases, it has been shown that oxytocin levels in healthy children have a positive correlation with their communication skills [54]. In our study, we have found that serum oxytocin levels are significantly lower in patients with higher autistic traits that are consistent with the results of previous studies. Besides, patients with poor performance of ToM have lower oxytocin level than others. Oxytocin has a negative correlation with testosterone, poor performance of ToM and SRS score. The decrease in oxytocin has a protective effect from poor performance of ToM and higher SRS score. We believe that our finding of negative correlation between oxytocin and autistic traits in ADHD is accurate since we have defined autistic traits by using two different measures (SRS and ToM tests) which are correlated with each other and neuro-hormone levels including oxytocin.

Although there are many other studies about neuroendocrine correlates of autistic traits and ASD, the results are seemed to be contradictory. It is sensible that a number of limitations might have influenced the contradictory results obtained in the previous studies. It is aimed to overcome some of the limitations such as puberty, gender, the presence of comorbid psychiatric disorders and/or mental retardation in our study. Thus, only prepubertal boys are included in our study, considering the hormone changes that might be observed in the adolescence. Since many psychiatric diseases affect hormone levels, patients with additional psychiatric diagnoses other than diagnoses frequently accompanied to ADHD like ODD and CD disorder, and who have a score below 70 in the WISC-4 intelligence test are not included in this study. We are of the opinion that the method of defining autistic traits in our study is a methodological power. Autistic traits have been defined by using SRS, and this definition is also supported by ToM tests. To our knowledge, there is no study in the literature investigating the relationship between ToM skills, autistic characteristics, and serum oxytocin levels in ADHD patients. This study is the first study investigating this relationship.

Considering that the ToM test and SRS applied to the patients in the study might be affected by the level of intelligence, the severity of ADHD symptoms and conduct disorder, this relationship has been controlled

(Tables 7, 8, 9 and 10). It has been shown that such a relationship does not exist. It confirms the results in our study.

There are several limitations in our study. First of all, this study does not include a healthy control group. Secondly, it does not have another clinical condition frequently accompanied by autistic traits. We have not included additional comparison groups such as children with just ASD and another group with both ADHD and ASD. Therefore, further studies are required to understand the specificity of these results for autistic traits. Thirdly, in our study, only boys, and children diagnosed with prepubertal ADHD are included. Therefore, it is not possible to generalize the study results to the whole ADHD diagnosis group. The inclusion of only 6–10 boys in the study is an important limitation. Some studies have found a relationship between poor theory of mind performance and executive dysfunction. This relationship has not been examined in our study. In addition, we have not used an ADHD specific evaluation method during our diagnosis process. Thus, using only K-SADS-PL could be listed as another limitation. Also, there is a methodological limitation about our study such as the probability of measuring social consequences of ADHD rather than autistic traits with SRS. This could interfere with our results. However, we have presented the analysis examining the difference between autistic-non autistic traits group and IQ, ADHD symptom severity in the result section in order to minimalize this limitation.

As a conclusion, it has been suggested that oxytocin, testosterone, and androstenedione might play roles in impaired social functions such as autistic traits, and so they could be related to the social relationships and theory of mind skills in patients with ADHD. Further progress in understanding the neurobiological processes underlying autistic traits can help develop more targeted interventions and also enhance the early detection of children before the phenomenological manifestation of autism-like traits in ADHD.

Declarations

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Author Contribution Statement

Abdulbaki Artık data collection and wrote the main manuscript text

Ebru Çengel Kültür methodology and wrote the main manuscript text

Oytun Portakal wrote the main manuscript text

Arda Yamaç Karaboncuk applied the Wechsler Intelligence Scale for Children-IV (WISC-IV) test

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Tables

Table 1

Comparison of ToM results according to SRS scores

			Autistic Traits according to SRS scores			p
		Unit	Non-Autistic Range	Mild	Severe	
			n (%)	n (%)	n (%)	
Test	ToM	**True**	44 (100)	4 (21.1)	0	**<0.0001**
		False	0	15 (78.9)	20 (100)	

SD: Standard deviation, ToM: Theory of Mind, SRS: Social Responsiveness Scale.

Table 2

Comparasion of Serum hormone levels and score of SRS according to ToM Test Results

		ToM		p*
		True (n=48)	False (n=35)	
	Unit	Mean±SD (Range)	Mean±SD (Range)	
Age	month	97.6±14.7(72-120)	90.5±13.7(76-119)	**0.03**
Score of SRS	point	49.9±9.5(28-68)	84.4±15.4 (64-127)	**<0.0001**
Testosterone	pg/mL	3.0±0.9 (1.4-4.6)	5.4±1.4 (2.0-9.3)	**<0.0001**
Androstenedione	ng/mL	15.8±5.3 (7.8-36.8)	21.2±6.5 (7.7-32.7)	**<0.0001**
Oxytocin	pg/mL	51.9±10.1 (35.2-74.2)	39.9±4.0 (32.3-47.7)	**<0.0001**

SD: Standard deviation, SRS: Social Responsiveness Scale, ToM: Theory of Mind

Table 3

Comparison of serum hormone levels in groups of autistic traits according to SRS scores

			Autistic Traits according to SRS scores			p*	p**
		Unit	**Non-Autistic range**	**Mild**	**Severe**		
			Mean**±SD (min-max)**	Mean**±SD (min-max)**	Mean**±SD (min-max)**		
SRS score		point	48.6±8.6 (28-59)	70.4±3.9 (62-78)	93.9±14.1 (82-127)		**<0.0001**
Hormones	Testosterone	pg/mL	**2.8±0.8 (1.4-4.6)**	**5.1±1.2 (3.7-8.8)**	**5.4±1.7 (2.0-9.3)**		**<0.0001**
			2.8±0.8 (1.4-4.6)	5.1±1.2 (3.7-8.8)		**<0.0001**	
				5.1±1.2 (3.7-8.8)	5.4±1.7 (2.0-9.3)	**0.60**	
			2.8±0.8 (1.4-4.6)		5.4±1.7 (2.0-9.3)	**<0.0001**	
	Androstenedione	ng/mL	**15.7±5.5 (7.8-36.8)**	**17.0±5.8 (7.7-29.2)**	**24.2±4.9 (13.2-32.7)**		**<0.0001**
			15.7±5.5 (7.8-36.8)	17.0±5.8 (7.7-29.2)		**0.40**	
				17.0±5.8 (7.7-29.2)	24.2±4.9 (13.2-32.7)	**<0.0001**	
			15.7±5.5 (7.8-36.8)		24.2±4.9 (13.2-32.7)	**<0.0001**	
	Oxytocin	pg/mL	**51.9±9.7 (35.2-74.2)**	**42.0±9.0 (32.6-72.0)**	**40.4±4.1 (32.3-47.7)**		**<0.0001**
			51.9±9.7 (35.2-74.2)	42.0±9.0 (32.6-72.0)		**<0.0001**	
				42.0±9.0 (32.6-72.0)	40.4±4.1 (32.3-47.7)	**0.76**	
			51.9±9.7 (35.2-74.2)		40.4±4.1 (32.3-47.7)	**<0.0001**	

p**<0.05 is significant, p*<0.017 is significant according to Bonferroni correction, SD: Standard deviation.SRS: Social Responsiveness Scale.

Table 4

Correlation between some parameters.

Parameters	r	p
ToM poor performanceAge	-0.24	0.03
Testestorene-Androstenedione	0.39	<0.0001
Testestorene-Oxytocin	-0.52	<0.0001
Testestorene-ToM poor performance	0.76	<0.0001
Testestorene-SRS	0.73	<0.0001
Androstenedione-ToM poor performance	0.42	<0.0001
Androstenedione-SRS	0.49	<0.0001
ToM poor performance-Oxytocin	-0.65	<0.0001
SRS-Oxytocin	-0.65	<0.0001
ToM poor performance-SRS	0.90	<0.0001

SRS: Social Responsiveness Scale, ToM: Theory of Mind

Tablo 5

Risk factors on developing autisitic trait in ADHD according to SRS

		Univariate analysis			Multivariate analysis		
Parameters	Category	OR	p	CI 95%	OR	p	CI 95%
Testosterone		10.1	<0.0001	3.6-27.2	21.3	0.004	2.6-174.4
Androstenodione		1.2	0.001	1.1-1.3	1.2	0.057	0.94-1.4
Oxytocin		0.7	<0.0001	0.5-0.8	0.6	0.009	0.4-0.88
ToM	False/True	1.1	0.99	0.66-1.8			
Age		0.9	0.05	0.9-1.1			
Subtype of ADHD	Inattentive/hyperactive/combined	1.5	0.08	0.9-2.5			

SRS: Social Responsiveness Scale, ToM: Theory of Mind

Tablo 6

Risk factors on ToM poor performance

		Univariate analysis			Multivariate analysis		
Parameters	**Category**	**OR**	**p**	**CI 95%**	**OR**	**p**	**CI 95%**
Testosterone		9.2	<0.0001	3.4-27.7	13.1	0.04	2.2-75.5
Androstenodione		1.1	<0.0001	1.1-1.2	1.2	0.09	0.9-1.5
Oxytocin		0.7	<0.0001	0.6-0.8	0.6	0.02	0.4-0.9
SRS total score		1.9	0.012	1.2-3.4			
Age		0.9	0.02	0.9-0.99	0.9	0.04	0.8-0.9

SRS: Social Responsiveness Scale, ToM: Theory of Mind

Table 7

The comparison of AtillaTurgay scores according to ToM results.

AT Scores		N	Mean	±SD	T	p
Total (I+II+III)	TOM:TRUE	48	45,29	13,461	-,179	,858
	TOM:FALSE	35	45,83	13,496		
III	TOM: TRUE	48	3,52	2,414	-,527	,599
	TOM: FALSE	35	3,80	2,336		
II	TOM: TRUE	48	10,90	5,635	,189	,850
	TOM: FALSE	35	10,66	5,713		
IA+IB	TOM: TRUE	48	30,60	8,631	-,098	,922
	TOM: FALSE	35	30,80	9,464		
IB	TOM: TRUE	48	14,54	6,301	-,377	,707
	TOM: FALSE	35	15,06	5,950		
IA	TOM: TRUE	48	16,02	4,102	,287	,775
	TOM: FALSE	35	15,74	4,674		

AT: Atilla TURGAY, IA: I. Section A. Inattention item point, IB: I. Section B. Hyperactivity and impulsivity item point, II: II. Section Problem point, III: III. Section problem point

Table 8

The comparison WISC-4 scores according to ToM results

WISC 4 Abilities		n	Mean	±SD	T	p
Verbal comprehension	TOM:TRUE	48	97,33	9,861	,733	,465
	TOM:FALSE	35	95,66	10,841		
Perceptual reasoning	TOM: TRUE	48	93,85	10,468	1,810	,074
	TOM:FALSE	35	89,94	8,578		
Working Memory	TOM: TRUE	48	95,48	11,680	,927	,357
	TOM: FALSE	35	93,20	10,143		
Speed of processing	TOM: TRUE	48	95,27	10,868	,830	,409
	TOM: FALSE	35	93,46	8,197		
Total IQ	TOM: TRUE	48	94,50	8,822	1,421	,159
	TOM: FALSE	35	91,66	9,245		

IQ: intelligence quotient, ToM: theory of mind, WISC-R: Wechsler Intelligence Scale for Children – Revised Form

Table 9

The comparison of Atilla Turgay scores in groups of autistic traits according to SRS scores

AT scores	SRS scores	n	Mean	±SD	F	p*
IA	between 0-60	44	15,84	4,000	,433	,650
	between 60-80	19	15,32	4,498	,433	,650
	over 80	20	16,60	4,957	,433	,650
	Total	83	15,90	4,327		
IB	between 0-60	44	14,07	6,341	1,558	,217
	between 60-80	19	14,16	5,937	1,558	,217
	over 80	20	16,85	5,603	1,558	,217
	Total	83	14,76	6,124		
IA+IB	between 0-60	44	29,95	8,502	1,288	,281
	between 60-80	19	29,47	9,442	1,288	,281
	over 80	20	33,45	9,265	1,288	,281
	Total	83	30,69	8,936		
II	between 0-60	44	10,57	5,504	1,352	,264
	between 60-80	19	9,58	5,650	1,352	,264
	over 80	20	12,45	5,808	1,352	,264
	Total	83	10,80	5,635		
III	between 0-60	44	3,55	2,435	,082	,921
	between 60-80	19	3,68	2,540	,082	,921
	over 80	20	3,80	2,167	,082	,921
	Total	83	3,64	2,371		
Total (I+II+III)	between 0-60	44	44,34	13,141	1,887	,158
	between 60-80	19	43,05	13,302	1,887	,158
	over 80	20	50,45	13,457	1,887	,158
	Total	83	45,52	13,396		

AT: Atilla TURGAY, IA: I. Section A. Inattention item point, IB: I. Section B. Hyperactivity and impulsivity item point, II: II. Section Problem point, III: III. Section problem point, SRS: Social Responsiveness Scale.

Table 10

The comparison of WISC-4 scores in groups of autistic traits according to SRS scores

WISC 4 Abilities	SRS scores	n	Mean	±SD	F	p*
Verbal comprehension	between 0-60	44	97,23	9,932	,170	,844
	between 60-80	19	95,68	12,601	,170	,844
	over 80	20	96,20	8,847	,170	,844
	Total	**83**	**96,63**	**10,255**		
Perceptual reasoning	between 0-60	44	94,20	10,382	1,995	,143
	between 60-80	19	89,63	9,406	1,995	,143
	over 80	20	90,25	8,447	1,995	,143
	Total	**83**	**92,20**	**9,854**		
Working Memory	between 0-60	44	95,91	11,551	1,026	,363
	between 60-80	19	94,32	11,245	1,026	,363
	over 80	20	91,65	9,599	1,026	,363
	Total	**83**	**94,52**	**11,051**		
Speed of processing	between 0-60	44	95,89	11,027	,944	,393
	between 60-80	19	92,63	9,136	,944	,393
	over 80	20	93,25	7,217	,944	,393
	Total	**83**	**94,51**	**9,817**		
Total IQ	between 0-60	44	94,61	8,491	1,434	,244
	between 60-80	19	93,21	10,427	1,434	,244
	over 80	20	90,50	8,697	1,434	,244
	Total	**83**	**93,30**	**9,058**		

IQ: intelligence quotient, SRS: Social Responsiveness Scale, WISC-R: Wechsler Intelligence Scale for Children – Revised Form