Relationship between Impulsivity and Serum Oxytocin in Male Children and Adolescents with Attention-Deficit and Hyperactivity Disorder: A Preliminary Study

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ABSTRACT

Introduction: Here we aimed to determine the relationship between oxytocin levels and impulsivity, which is an important aspect at Attention Deficit Hyperactivity Disorder (ADHD) clinics.

Methods: The study population comprised 40 ADHD patients diagnosed based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version, without other psychiatric disorders and chronic diseases aged between 8 and 15 years. The control group comprised 40 healthy, age-matched, male children and adolescents who voluntarily participated in the study. Patients and controls filled the Barratt impulsivity scale-11 (BIS-11). Ten cubic centimeters of blood was collected at 8 am for determining serum oxytocin levels. ELISA kits were used to measure serum oxytocin

levels in a biochemistry laboratory. The obtained data were evaluated using appropriate statistical methods.

Results: In this study, compared with the control group, the impulsivity scores were significantly higher and serum oxytocin levels were lower in the ADHD group (52.5 ± 18.1 and 37.62 ± 9.0 , respectively, $p < 0.001$). Serum oxytocin levels showed a negative correlation with impulsivity and attention subscale scores of BIS-11 in the ADHD group.

Conclusion: ADHD and impulsivity, which comprise an aspect of ADHD, may be associated with oxytocin. Serum oxytocin levels may contribute to inattention subtypes of impulsivity observed in ADHD.

Keywords: ADHD, impulsivity, oxytocin

INTRODUCTION

By definition, impulsivity can be described as “to act without forethought or move on without forethought as a result of instantaneous action.” By psychiatric definition, impulsivity is the action that is prematurely expressed and risky, resulting in undesirable consequences and inappropriate situations. Impulsivity not only reflects anger or aggressiveness but also decreased tolerance to inhibition and inability to plan (1,2).

Impulsivity is a major aspect of many neurological and psychiatric disorders. Psychiatric disorders accompanied by impulsivity include antisocial and borderline personality disorders, schizophrenia, bipolar disorder, attention-deficit hyperactivity disorder (ADHD), eating disorders, and substance abuse. However, it is considered to be a diagnostic criterion in pathological gambling, intermittent explosive disorder, pyromania, kleptomania, and trichotillomania (3,4).

Attention Deficit Hyperactivity Disorder is a disorder characterized by deficiency in social skills and difficulty in maintaining peer relations owing to impulsive symptoms such as frequent switches in interactive conversations, failure to listen to others, frequent interruption when another person is speaking, to beginning a conversation at an inappropriate time, and mistreatment (5). In ADHD, increased impulsive behaviors, particularly observed during puberty, lead to behavioral problems experienced with parents and siblings, academic failure and classroom behavior problems, and failure in maintaining relations with family, teachers, and peers (6). Social exclusion can be observed owing to increased behavioral problems, noisome behaviors, and impulsivity. Additional problems can occur secondary to familial, academic, and social disruptions that appear during late childhood and puberty (7).

Although the relationship between impulsivity and oxytocin, which play an important role in maternal attachment to children besides their roles in breastfeeding and delivery, has not been directly studied to date, it has been assessed in various psychiatric disorders wherein impulsivity forms an important aspect at clinical presentation (8). An association between the severity of positive symptoms and elevated serum oxytocin levels was shown in patients with schizophrenia (9). Serum oxytocin levels were found to have been elevated in manic episodes of BAD when compared to the levels in healthy controls, emphasizing that the elevation could be associated with increased dopamine levels during manic episodes and responsible for impulsive behaviors such as hypersexuality and aggressiveness observed in clinical settings (10). In addition, it was reported that plasma oxytocin levels were low in female patients diagnosed with borderline personality disorders, suggesting that decreased oxytocin levels were a result of childhood trauma and attachment as well as derangements in serotonin and dopamine levels and could be associated with declined social cognition and impaired award system (11). However, it was also shown that in addition to psy-

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chiatric disorders such as BAD and schizophrenia, there was a relationship between elevated peripheral oxytocin levels, antipsychotics, and mood stabilizers used in the treatment of impulsivity (4,12). A limited number of studies have investigated the relationship between ADHD and oxytocin. Park et al. (13) linked specific oxytocin receptor polymorphism to low social cognition in children with ADHD. In another study on ADHD, plasma oxytocin levels were found to be lower in boys with ADHD compared with those in healthy controls, emphasizing that the decreased levels could result from difficulties in emotion regulation and recognition of emotion observed in ADHD (14).

To the best of our knowledge, there is no study on the relationship between impulsivity and oxytocin in ADHD. Although oxytocin levels were investigated in psychopathologies related to impulsivity, the relationship between impulsivity and oxytocin has not been evaluated in these studies. Given the fact that a relationship is reported between oxytocin levels and dopamine in oxytocin studies and that oxytocin levels are linked to impulsive behaviors such as hypersexuality and aggressiveness as well as award systems known to be disrupted in borderline personality disorder and ADHD (11,15), this study was aimed to assess whether there is a difference in serum oxytocin levels between ADHD patients and healthy controls and to identify the relationship between oxytocin levels and impulsivity, which is an important aspect at ADHD clinics.

METHODS

Participants

The study included male patients aged 8–15 years who consecutively presented at the outpatient clinic and were diagnosed to have ADHD according to the DSM-IV TR criteria between 2012 and 2013 but did not receive any therapy. The reason for choosing males as the study group is the fact that ADHD is 9 times more prevalent among boys in clinical practice (5), ADHD symptoms become apparent in this age group, and patients with ADHD visit clinics at this age (16). In addition, this allowed the elimination of sex-related variation in oxytocin and the effects of estrogen on oxytocin (17).

The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) and Wechsler Intelligence Scale for Children-Revised (WISC-R) tests were applied to all participants. Patients with mental retardation (MR; IQ<85), autistic spectrum disorders (ASD), psychiatric comorbidities, including specific learning difficulties, and known neurological and metabolic disorders and those receiving hormone therapy were excluded. Patients with abnormal thyroid function tests, as measured based on the blood samples obtained, were excluded because thyroid hormones influence oxytocin levels (18).

Overall, 40 boys and male adolescents were included in the study. In addition, 40 age-matched volunteers (boys and male adolescents) (with parental consent) aged 8–15 years who were assessed based on K-SADS-PL and WISC-R and had no MR, psychiatric, chronic disorder, or abnormal thyroid function test were employed as the control group.

Method

The parents were asked to complete sociodemographic data sheets and the Turgay DSM-IV-based Child and Adolescent Behavior Disorders Screening and Rating scale. BIS-II was applied to the study and control groups.

In all subjects and controls, 10 cc of blood was drawn at 8 am after overnight fasting for measurement of serum TSH, fT3, fT4, and oxytocin levels. For oxytocin measurement, an aliquot of blood was transferred to vacuum

tubes and centrifuged at 1000 g for 15 minutes within 30 minutes. Serum samples were stored at –80°C until assays. Serum oxytocin levels were measured using the CUSABIO Human Oxytocin ELISA kit (assay range: 24–400 µIU/mL; sensitivity <14 µIU/mL). Optic density measurements obtained were transformed to serum concentrations using the formula produced from linear regression analysis.

The study was supported by Erciyes University Board on Scientific Research Projects. The study was approved by the Erciyes University Ethics Committee (06.11.2012; #2012-673). Detailed information was provided to all subjects and controls regarding objectives and the study protocol. All parents gave written informed consent while children gave verbal consent.

Materials

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version: This scale was developed by Kaufman et al. (19) after publication of DSM-IV in 1994. Turkish validation and reliability studies were performed by Gökler et al. (20) in 2004. K-SADS-PL allows screening of more than 20 different psychiatric disorders.

Wechsler Intelligence Scale for Children-Revised (WISC-R):

This was developed to assess the mental capacity of children aged 6–16 years with adequate levels of speaking and language skills by Wechsler, which was then revised as WISC-R. Its standardization study for Turkish children was performed and the WISC-R scale was adapted to Turkish culture by Savaşır and Şahin (21).

Turgay DSM-IV-based Child and Adolescent Behavior Disorders Screening and Rating scale:

This scale was developed by Atila Turgay based on DSM-IV diagnostic criteria. The scale is used to screen and assess behavioral disorders, including ADHD, oppositional defiant disorder, and general behavioral disorders (5). The scale comprises 41 questions, including 9 for attention-deficit, 9 for hyperactivity, 8 for oppositional-defiant, and 15 for general behavioral disorders. Each question is rated as follows: none, some, more, and most (5).

Barrat Impulsiveness Scale-II (BIS-II):

This is a self-rated scale used to assess impulsivity (22). It comprises 30 items. Three second-order factors are obtained by factor analysis: attentional, motor, and non-planning impulsiveness. The level of impulsiveness increases as BIS-II scores increase. The Turkish reliability and validity study was performed on college students by Güleç et al. (22). It has already been used in some studies on adolescents (23,24).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics; Armonk, NY, USA) version 21.0 and SigmaStat 3.5 statistics software. Summary statistics were expressed as count (n), percent (%), mean, and standard deviation. The Shapiro–Wilk test was used to assess normality of data. The Mann–Whitney U and Kruskal–Wallis tests were used to compare groups. The chi-square exact test was used to compare categorical variables. Spearman's correlation analysis was used to assess association between numerical variables. P<0.05 was considered statistically significant.

RESULTS

This study included 40 boys and male adolescents who were diagnosed with ADHD for the first time and did not receive treatment. The control group comprised 40 age-matched boys and adolescents who had no psychiatric, neurological, and metabolic disorders.

Table 1. The comparison of demographic data between the ADHD and control groups

		ADHD group n=40		Control group n=40		Comparison
		Number	%	Number	%	
Education (year)	4 years	25	62.5	22	55	$\chi^2=19.56$ df=6 p=0.404
	8 years	15	37.5	18	45	
	Total	40	100	40	100	
History of drug and alcohol use during pregnancy		3	7.5	0	0	$\chi^2=3.117$ df=1 p=0.77
Time of birth	<38 weeks	1	2.5	4	10	$\chi^2=1.920$ df=1 p=0.166
	>38 weeks	39	97.5	36	90	
Difficult birth story		13	3.5*	2	5	$\chi^2=9.928$ df=1 p=0.002

Chi-square test; *significantly higher than controls. ADHD: attention-deficit hyperactivity disorder

Table 2. ADHD and control group impulsivity scores and oxytocin levels

	ADHD	Controls	Comparison
BIS-I I total scores	68.92±5.65*	46.28±3.13	Z=-7.746 p<0.001
Attentional	19.34±3.39*	12.64±2.18	Z=-7.689 p<0.001
Motor	20.50±2.80*	15.43±4.32	Z=-7.592 p<0.001
Non-planning	28.45±3.65*	17.24±3.60	Z=-7.763 p<0.001
Atila Turgay impulsivity scores	5.63±1.56*	1.33±1.02	Z=-7.594 p<0.001
Serum oxytocin levels (μIU/mL)	37.62±9*	52.5±18.1	Z=-4.384 p<0.001

Mann-Whitney U test and Kruskal-Wallis analysis; *significantly higher than controls. ADHD: attention-deficit hyperactivity disorder

The history of difficult delivery was significantly higher, but there were no significant differences in drug-substance use during pregnancy and incidence of preterm delivery between groups (Table 1).

When subtypes were assessed in children with ADHD, it was seen that the most common subtype was the combined type (40%) followed by inattentive (32.5%) and hyperactive-impulsive types (27.5%).

Compared with the control group, the total and subscale scores of BIS-I I were found to be significantly higher in the ADHD group (Table 2). When serum oxytocin levels were compared, it was seen that serum oxytocin levels were significantly lower in the ADHD group than those in the control group (Table 2).

When the relationship between serum oxytocin levels and total BIS-I I scores in the ADHD and control groups were assessed, negative correlations were detected between serum oxytocin levels and total BIS-I I scores in both groups (Table 3). When the relationship between subscale scores and serum oxytocin levels were assessed, negative correlations were detected between attention subscale scores and serum oxytocin levels (Table 3).

DISCUSSION

Dopamine (DA) is the primary neurotransmitter linked to ADHD (25). DA, implied in the ADHD etiology, is a physiologically important neurotransmitter in attention, dependency, award seeking behaviors, and hormonal regulation (25,26). It is accepted that alterations in DA levels result from gene variations related to DA transporters and DA receptors (25,27). In recent years, there has been evidence suggesting that hypothalamic oxytocin producing cells are regulated by dopamine receptors and that dopamine secretion increases oxytocin levels in animal studies (28,29). Oxytocin-rich hypothalamic nuclei are innervated by dopamine fibrils and regulated by DA via D2-like dopaminergic receptors (30,31). However, it was reported that plasma oxytocin level is an important determinant of oxytocin concentrations in the cerebrospinal fluid (CSF) of children and that there is a positive correlation between plasma and CSF oxytocin levels (32). Despite this fact, a limited number of studies have evaluated the association between ADHD and oxytocin. In these studies, specific oxytocin receptor polymorphisms were linked to low social cognition in ADHD (13), and plasma oxytocin levels were found to be lower in boys with ADHD when compared with those in healthy controls in a study on autism (14). However, there has been no study comparing serum oxytocin levels with healthy controls and assessing its association with impulsivity in the literature. In our study, serum oxytocin levels were found to be significantly lower in the ADHD group when compared with those in the control group.

Impulsivity is one of the core symptoms of various psychiatric disorders that manifests with inattention, impatience, novelty seeking, risk taking, sensation and pleasure seeking, underestimating probability of harm, and extraversion (33). It is reported that impulsivity is an absolute criterion for the diagnosis of manic episodes in BAD, but other symptoms may be variable (34). In patients with schizophrenia, impulsivity causes difficulties in the treatment and social domain in those with higher symptom severity (35). It is shown that dysfunctions observed at the orbital frontal cortex plays a role in the etiology of impulsivity in ADHD (36). In children with ADHD, impulsive behaviors, such as difficulty in waiting for his/her turn, failure in delaying desires, restlessness, and interrupting speech begin before 7 years of age. This causes problems in academic and social domains (27). In addition, it is known that children with ADHD tend to over-interpret, misinterpret, and express aggressive outbursts (37). As anticipated in our study, the total and subscale scores of BIS-I I were found to be higher in ADHD group when compared to the controls. In the literature, BIS-I I scores were reported to be higher in a study that investigated impulsivity in ADHD (38).

Table 3. Impulsivity and oxytocin level correlations of ADHD and control groups

		Serum oxytocin levels (µIU/mL) of ADHD	Serum oxytocin levels (µIU/mL) of controls
BIS-II			
Total Scores	r	0.732**	0.585**
	p	<0.001	0.002
Attentional	r	-0.391*	-0.114
	p	0.013	0.482
Motor	r	-0.275	-0.210
	p	0.085	0.179
Non-planning	r	-0.285	-0.295
	p	0.075	0.085
Atila Turgay Impulsivity scores	r	-0.322*	-0.384*
	p	0.043	0.014
Spearman correlation analysis; *0.05 level significant correlation, **0.01 level significant correlation. ADHD: attention-deficit hyperactivity disorder			

In our study, negative correlations were detected between serum oxytocin levels and total BIS-II scores in both groups. When the scores of BIS-II subscales were assessed, it was found that there was a negative correlation between the scores of the attention subscale and serum oxytocin levels. Serotonin, DA, noradrenalin, glutamate, and GABA are the main neurotransmitters implied in the etiology of impulsivity (26,33). In ADHD, disruption occurs in the mesolimbic pathway, including the nucleus accumbens and frontoventral striatal reward circuits, which in turn, cause insufficient signal production in case of delayed reward, resulting in symptoms of impulsivity (15). It is proposed that low peripheral oxytocin levels could be associated with disruption in the reward system in women with borderline personality disorder (11). It is reported that oxytocin-rich hypothalamic nuclei are innervated by DA fibrils and regulated by DA (30,31). It is known that antipsychotic and stimulants affecting DA levels through various ways are also used in the treatment of impulsivity in addition to disorders accompanied by impulsivity and that each agent acts on impulsivity via several different mechanisms (4,12,39). Given this data, a negative correlation was detected between oxytocin levels and impulsivity scores in ADHD despite exclusion of comorbidities that suggest the impulsivity observed in ADHD is related to oxytocin. Although neurotransmitters such as serotonin, DA, noradrenalin, glutamate, and GABA have been implied in the etiology of impulsivity (26,33), it can be suggested that oxytocin also plays role in the etiology. Moreover, this may be interpreted as variations in the genes related to DA receptors. DA receptor derangements and impaired DA levels involved in ADHD etiology impair oxytocin levels in children with ADHD, which in turn, contribute to the inattention subtype of impulsivity, an important aspect at ADHD clinics. However, it is apparent that there is a need for further investigations including clinical, molecular, and genetic studies that would support this hypothesis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University School of Medicine.

Informed Consent: Written informed consent was obtained from patients and the parents of the patients who participated in this study.

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