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Oxytocin levels and sex differences in autism spectrum disorder with severe intellectual disabilities

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ABSTRACT

There were few reports of oxytocin (OXT) concentrations of autism spectrum disorder (ASD) patients with severe intellectual disabilities. We measured serum OXT concentrations in 79 hospitalized patients with severe intellectual disabilities (16–60 years old, 50 males and 29 females, 54 ASD patients) and investigated the associations between serum OXT concentration, symptom scores, sex differences, and autism spectrum disorder. There were no significant effects of diagnosis, severity of intellectual disabilities, and total score of the Japanese version of the Aberrant Behavior Checklist (ABC-J), the Childhood Autism Rating Scale-Tokyo Version (CARS-TV), and the Japanese version of the Repetitive Behavior Scale-Revised (RBS-R). However, there were sex differences in the correlations between OXT concentrations and subscale scores in the ASD group. The male ASD group ($n = 39$) showed negative correlations between RBS-R Self-injurious and Sameness subscale scores and serum OXT concentrations. In the female ASD group ($n = 15$), CARS-TV Nonverbal communication subscale scores and RBS-R Compulsive subscale scores were seen to positively correlate with serum OXT concentrations. These findings suggest that OXT functions differ in males and females with severe intellectual disabilities and that OXT partly affects autism and related to some of the repetitive behaviors and nonverbal communication, in ASD patients with severe intellectual disabilities.

1. Introduction

Autism spectrum disorder (ASD) is an early onset neurodevelopmental disorder with complex etiology and is generally not diagnosed before a median age of 53 months in the United States (Centers for Disease Control and Prevention, 2014; Christensen et al., 2016). ASD is characterized by severe disruptions in language and reciprocal social interactions, and restricted repetitive behaviors and interests.

There are sex differences in ASD clinical symptoms. For example, Circumscribed interests (CI) in females with ASD, eye tracking may align more closely with interests reported in typical females development than those typically reported for ASD males (Harrop et al., 2018). Also Camouflaging effect makes it difficult to diagnose and Screen female with ASD (Ratto et al., 2018). However, in the direct

assessment sample using the Social Communication Questionnaire (SCQ), girls with ASD showed greater impairment in social communication/interaction than boys with ASD (Evans et al., 2018). Another study with a large European ASD sample adds to the studies on sex and age variations of ASD symptomatology. In one study utilizing ADI-R, early childhood restricted and repetitive behaviors were lower in females than males, alongside comparable levels of social interaction and communication difficulties in females and males (Tillmann et al., 2018). ASD girls are also noted to have greater risk for developing anxiety, depression, suicidal ideation, and for psychiatric hospitalization. ASD boys appear to be at greater risk for co-occurring ADHD, OCD and tics (Rynkiewicz et al., 2018).

Oxytocin is a peptide hormone demonstrated to be important in the formation of pair bonds and social behaviors in animal studies, as well

Abbreviations: ASD, autism spectrum disorder; OXT, oxytocin; DIQ, deviation intelligence quotient; DQ, developmental quotient

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as being integral in parturition, milk let-down, and maternal behaviors. Recognition of OXT as an important regulator of human social behaviors, has increased in recent times. OXT may be a common factor important in multiple psychiatric disorders such as ASD, schizophrenia, mood and anxiety disorders (Cochran et al., 2013).

Intranasal OXT has been shown to be useful in accelerating and augmenting contractions during child birth (MacVicar, 1973). However, research in past decades has revealed many other potential uses for intranasal OXT. Many studies have investigated the effects of intranasal OXT on social interaction in ASD patients (Anagnostou et al., 2012; Kosaka et al., 2016; Watanabe et al., 2015; Yatawara et al., 2015). Some studies have evaluated the effects of OXT on restricted and repetitive behaviors. In a study concerning 15 subjects with ASD comprised of mainly adolescents and adult men, a statistically significant reduction in repetitive behaviors was reported after an OXT infusion in comparison with placebo infusion over 240 min (Hollander et al., 2003). Anagnostou et al. (2012) found only a trend toward reduction in repetitive behaviors, such as stereotypy and self-injury, following intranasal OXT in 19 adults with ASD. Hoffmann et al. (2015) conducted a meta-analysis of 16 studies. In this study OXT reduced symptoms of depression, anxiety, autism/repetitive behaviors, psychotic symptoms, and general psychopathology, and the overall placebo-controlled effect size was moderately strong.

Previous studies involving OXT and ASD, have reported that autistic children had significantly lower plasma OXT levels. Modahl et al. (1998) and Alabdali (2014), while other studies have reported conflicting findings. For instance, ASD diagnosis was shown not to have a significant effect on plasma OXT levels in a study conducted in a population of child and adolescent ASD patients (Miller et al., 2013), and another study showed increased basal plasma OXT levels in ASD adults (Jansen et al., 2006). The differing reports on OXT levels may be due to developmental differences caused by the differing age groups, or differences in intellectual development. It can be inferred from these previous studies that a dysfunction in OXT processing associated with ASD may exist, and there also may be OXT system associated developmental changes occurring throughout the lifespan of an individual with ASD (Cochran et al., 2013). In addition to these studies, a study conducted as a follow-up indicated a defect in peptide processing of OXT (Green et al., 2001), by showing decreased plasma OXT to be associated with increased peptide inactive forms of OXT derived from the same prohormone.

From the results of the preceding studies above, it is unclear the relation between OXT concentration and ASD symptoms.

Munesue et al. (2016) conducted a randomized pilot study of intranasal OXT for male subjects with ASD and comorbid intellectual disabilities. Though there were no differences in CARS or other standard scales were found between the OXT and placebo groups, significantly more frequent social interactions were observed in play sessions and daily life in the OXT arm of the crossover trial. In addition to these significant correlations between the plasma OXT concentration and baseline scores on the ABC were also seen.

Miller et al. (2013) reported sex differences and associations between OXT and symptoms in children and adolescents with ASD. There were significant sex effects (girls showed higher concentrations of OXT than boys) but no significant effects of diagnosis. In a report by Kosaka et al. (2016), OXT dosage and genetic background of the OXT receptor are suggested to be associated with the efficacy of long-term OXT administration in young men with high functioning ASD. Kosaka et al. (2016) suggest the need for further studies to examine the associations between OXT gene polymorphisms, sex, and OXT efficacy.

Although patients with ASD often show intellectual disabilities, there have been only few reports on peripheral OXT concentrations of hospitalized patients with ASD complicated with severe intellectual disabilities (Martin et al., 1998; Munesue et al., 2016). In the present study, we measured peripheral OXT concentrations of hospitalized patients with ASD complicated with severe intellectual disabilities and

investigated the relationship between OXT concentrations, neuropsychiatric parameters, and sex differences in these patients.

2. Methods

2.1. Subjects

Eligible participants were hospitalized patients of a special ward for severe intellectual disabilities at Hizen Psychiatric Center. Of the 84 patients who underwent analysis of OXT concentration in blood serum, data for 79 participants (aged 16–60 years) were analyzed (participants whose OXT concentration was greater than three standard deviations above the mean were excluded from the analysis). Participants had been diagnosed with intellectual disabilities and 54 participants were also diagnosed with ASD using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) (American Psychiatric Association, 2000), and 36 participants were also diagnosed with epilepsy. All diagnoses were confirmed using the Childhood Autism Rating Scale-Tokyo Version (CARS-TV) (Kurita et al., 1989) by the first author (who is a child psychiatrist).

This study was approved by the institutional review board of the Hizen Psychiatric Center and Saga University, Japan, and was conducted according to the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labor and Welfare. Owing to their severe intellectual disabilities, participants could not give their informed consent, so consent was obtained from their adult guardians.

2.2. Tests administered to all subjects

Intellectual and developmental levels were assessed using the Tanaka–Binet Intelligence Scale V (fifth edition) (Tanaka Institute for Education, 2005) and the Enjoji Scale of Infant Analytical Development (Enjoji, 2009). The Tanaka–Binet Intelligence Scale was published in Japan in 1947. This scale is suitable for individuals between 2 years and above, including adulthood. The Tanaka–Binet Intelligence Scale V was published in 2005, a revised version of the scale capable of assessing development under 1 year of age, as well as being able to measure IQ for adults. Deviation intelligence quotient (DIQ) evaluation criteria, rather than conventional IQ measures, are calculated for subjects over 14 years of age (Tanaka Institute for Education, 2005).

The Enjoji Scale of Infant Analytical Development appeared in 1958. This scale is suitable for individuals from birth to 4 years and 7 months. Assessments are drawn from observations and from interviews with caregivers with respect to six areas of functioning: locomotive movements, hand movements, basic habits, interpersonal relationships, speech, natural language understanding, which are used to calculate the developmental quotient (DQ). Participants who could not be assessed with the Tanaka–Binet Intelligence Scale V were assessed using the Enjoji Scale of Infant Analytical Development (Enjoji, 2009).

Challenging behaviors were evaluated using the Japanese version of the ABC (ABC-J: Aberrant Behavior Checklist-community Japanese version) (Ono, 1996).

2.3. Assessment of autistic symptoms

The ASD group were assessed using the CARS-TV (Kurita et al., 1989) and the Japanese version of the Repetitive Behavior Scale-Revised (RBS-R). The RBS-R was published in 2000 and was a revision of Bodfish's original RBS (Bodfish et al., 1999, 2000). Items from the Autism Diagnostic Interview-Revised (Lord et al., 1994) that referred to limited, repetitive behavioral patterns were taken in to account and were added to the RBS-R. The Japanese version of the RBS-R was reported 2012, and the reliability and validity when performed by specialists/professionals was noted in this study (Inada et al., 2015).

2.4. OXT peptide assay

We obtained a blood sample from each subject at approximately the same time of the day (13:00–14:00) over 2 week period. Blood OXT concentration fluctuates depending on physical contact and is reported to show no differences between morning and afternoon levels. Therefore, we the sampling time to be 1 h after the midday meal, time before occupational therapy and play therapy begins. Blood samples to test serum OXT concentration (4 ml) were similarly centrifuged at $2600 \times g$ for 15 min. Serum samples were stored in a freezer at -80° until shipment, on dry ice, to the Saga University Faculty of Medicine for analysis. Assays were performed using an enzyme immunoassay kit (extraction-free kit for human serum, by Peninsula Laboratories International, Inc. San Carlos, USA) as previously reported (Imamura et al., 2017). The inter-assay coefficient of variation was 9.77% and the intra-assay coefficient of variation was 12.98%.

2.5. Data analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS Statistics 23, by IBM Japan, Tokyo). Between-group differences in average values were tested using *t*-tests and two-factor analysis of variance. Regression analysis was used to calculate Pearson product-moment correlation coefficients for variable correlations. The significance level was set at 0.05, and Bonferroni corrections were employed for multiple comparisons.

3. Results

3.1. Clinical variables and OXT concentration

Table 1 shows average serum OXT concentrations for each group of participants. DQ/DIQ were not correlated with serum OXT concentrations ($r = -0.202, p = 0.075$). There were no significant correlations between, respectively, serum OXT concentrations and age ($r = -0.123, p = 0.281$), or body weight ($r = -0.039, p = 0.734$), body mass index ($r = -0.077, p = 0.503$). The characteristic relationship between serum OXT concentrations and menstruation in female subjects were not found.

3.2. Sex differences and clinical diagnosis

There were no gender differences including both ASD and non ASD groups in the mean serum OXT concentrations (Fig. 1). No significant differences in mean serum OXT concentrations were found between the ASD group ($n = 54$) and non-ASD group ($n = 25$) or between the epilepsy group ($n = 36$) and the non-epilepsy group ($n = 43$) (Fig. 2). The two-factor analysis of variance showed no interaction between

diagnosis and sex (ASD and sex for serum concentration $F(1,75) = 0.264, p = 0.609$; epilepsy and sex for serum concentration $F(1,75) = 0.559, p = 0.457$).

3.3. OXT concentration and total score of behavior symptom measures

There was no correlation between serum OXT concentrations and ABC-J total and subscale scores ($n = 79$). This result was similar for the male group ($n = 50$) and the female group ($n = 29$). ABC-J total scores and ABC-J Irritability subscale scores were correlated. This result was similar for the male group ($n = 50$) and the female group ($n = 29$). (Table 2).

3.4. OXT concentration and subscale scores of behavior and autism symptom measures

Table 3 shows means and standard deviations of scale and subscale scores for male and female participants with ASD. There was no statistical difference between each of the scores of male and female participants with ASD by *t*-test.

CARS-TV total scores and RBS-R total scores were not correlated with serum OXT concentrations for the ASD group (males and females combined, $n = 54$). CARS-TV total scores, RBS-R total scores, ABC-J total scores, and ABC-J Irritability subscale scores were positively and significantly correlated, as were CARS total scores and RBS-R total scores (Table 2).

For the total ASD group ($n = 54$, males $n = 39$ and females $n = 15$), CARS-TV scores and RBS-R total scores showed no correlation with serum OXT concentrations (Table 2). However, regression analysis showed the following significant correlations between serum OXT concentrations and some of the subscale scores.

In the total ASD group ($n = 54$), there was correlation between CARS-TV Nonverbal communication subscale scores and serum OXT concentrations ($r = 0.319, p = 0.019$) and there was a negative correlation between RBS-R Self-injurious behavior subscale scores and serum OXT concentration ($r = -0.294, p = 0.031$). All results were found to be significant when regression analysis with serum OXT concentration as a independent variable was performed on subscale scores in which correlations were found using Pearson's correlation coefficient (Table 4).

3.5. Sex differences in OXT concentration and subscale scores of behavior and autism symptom measures

For the male ASD group ($n = 39$), there were negative correlations between, respectively, RBS-R Self-injurious behavior and Sameness subscale scores and serum OXT concentration ($r = -0.376, p = 0.018$; $r = -0.323, p = 0.045$). One significant result was obtained regression

Table 1
Sample clinical variables.

	All($n = 79$) (male50/female29)	ASD($n = 54$) (male39/female15)	Non-ASD($n = 25$) (male11/female14)
Age (years)	39.53 \pm 11.65(16–60)	36.69 \pm 11.70(17–60)	45.68 \pm 8.97(16–56)
Weight (kg)	51.43 \pm 9.77(31–78)	53.70 \pm 9.82(33–78)	46.54 \pm 7.82(31–64)
DQ or DIQ	13.20 \pm 8.48 (3–42)	14.35 \pm 8.07 (3–37)	10.72 \pm 8.98 (3–42)
Profound	$n = 64$	$n = 43$	$n = 21$
Severe	$n = 11$	$n = 8$	$n = 3$
Moderate	$n = 4$	$n = 3$	$n = 1$
ABC-J total score	56.73 \pm 30.96(5–117)	61.09 \pm 31.29(5–117)	47.32 \pm 28.60(13–109)
CARS-TV total score	—	46.32 \pm 5.44(31.5–53.5)	—
RBS-R total score	—	30.09 \pm 16.7(5–89)	—
Serum OXT	0.072 ng/ml \pm 0.081(0.003–0.416)	0.078 ng/ml \pm 0.091(0.003–0.416)	0.061 ng/ml \pm 0.051(0.003–0.162)

Reported values are means \pm S.D. (standard deviation),ranges.

Abbreviations: ASD, Autism Spectrum Disorder; DIQ, Deviation intelligence quotient (by the revised Tanaka–Binet Intelligence Scale V); ABC-J, Aberrant Behavior Checklist-community Japanese version; CARS-TV, Childhood Autism Rating Scale-Tokyo Version; RBS-R, The Japanese version of the Repetitive Behavior Scale-Revised.

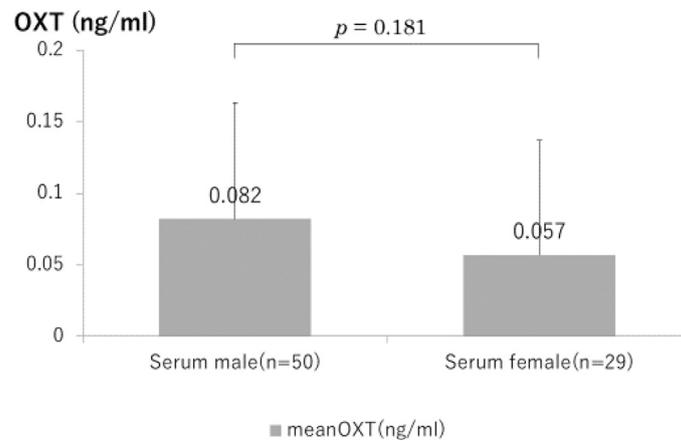


Fig. 1. Serum oxytocin (OXT) by gender. Mean serum OXT concentration was not different by gender. Abbreviations: OXT, oxytocin. .

on independent variables for each subscale scores by Pearson's correlation coefficient correlation was found, serum OXT concentration (Table 4).

For the female ASD group (n = 15), there were positive correlations between CARS-TV Nonverbal communication subscale scores and serum OXT concentration (r = 0.605, p = 0.017), and between RBS-R Compulsive subscale scores and serum OXT concentration (r = 0.527, p = 0.044). A significant result was obtained when regression analysis was performed on subscale scores shown to correlate using Pearson's coefficient correlation, with the serum OXT concentration as an independent variable. (Table 4).

When examining the difference between the correlation coefficients of male and female, significant differences were found in the RBS-R Compulsive subscale scores (z = -2.530, p = 0.005), RBS-R Ritualistic subscale scores (z = -1.937, p = 0.026).

4. Discussion

4.1. OXT concentration and intellectual disabilities

In one study examining the association between intellectual disabilities and OXT concentration, Martin et al. (1998) reported high OXT concentrations in cerebrospinal fluid patients with Prader-Willi syndrome with intellectual disabilities compared with a normal control group. However, these authors suggest that their findings reflect

obsessive–compulsive symptoms rather than intellectual disabilities. In the present study, all 79 participants (who were hospitalized patient) were judged to have severe or profound intellectual disabilities based on DIQ or DQ results as well as various functional levels. We suppose that we could not find any correlation between serum OXT concentrations and DIQ or DQ scores due to the lack of variation in the intellectual ability of the participants in the first place. In addition, serum OXT concentrations showed no correlation with the degree of challenging behaviors (ABC-J total and subscale scores). Our results differ from those reported by Munesue et al. (2016) in a study of adult males with ASD and severe/profound intellectual disabilities. Munesue et al. (2016) found significant correlations between plasma OXT concentration and ABC Irritability subscale baseline scores. This difference may be related not only to degree of intellectual disability and OXT concentration, but also to age, sex, and other factors, as described below.

4.2. OXT concentration and autistic symptoms, repetitive behaviors

We found that the total ASD group (n = 54) showed negative correlations between RBS-R (it is one of the evaluation scale of repetitive behavior) Self-injurious behavior subscale scores and serum OXT concentration. Males with ASD (n = 39) showed negative correlations between RBS-R Self-injurious behavior and Sameness subscale scores and serum OXT concentration, whereas females with ASD (n = 15) showed

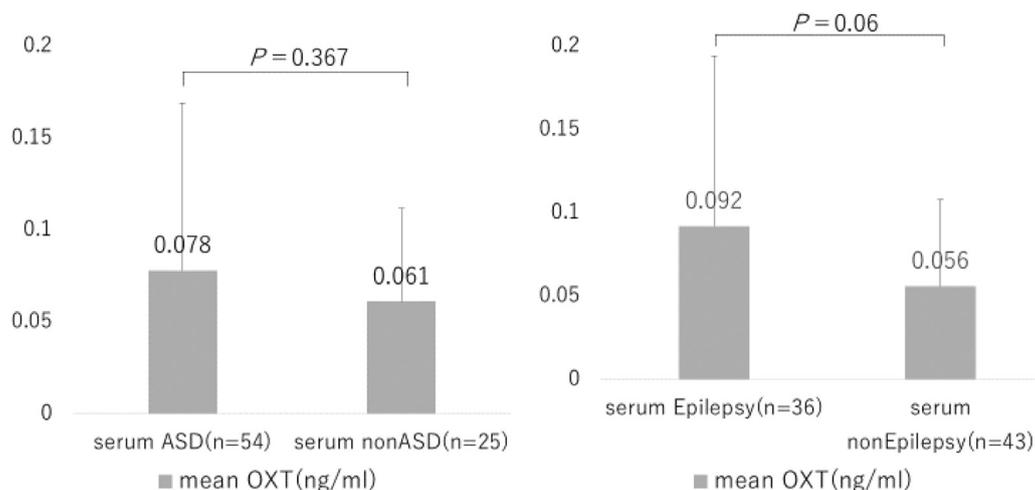


Fig. 2. Serum oxytocin (OXT) by diagnosis. No significant differences in mean serum OXT concentrations were found between the ASD group (n = 54) and non-ASD group (n = 25) or between the epilepsy group (n = 36) and the non-epilepsy group (n = 43). Abbreviations: ASD, Autism Spectrum Disorder.

Table 2
Pearson's correlations between variables.

All participants (n = 79)	Serum OXT	ABC-J total score	ABC-J Irritability
Serum OXT	-	-0.081	-0.087
ABC-J total score	-	-	0.832***
ABC-J Irritability	-	-	-

ASD (n = 54)	Serum OXT	ABC-J total score	ABC-J Irritability	CARS-TV total score	RBS-R total score
Serum OXT	-	-0.206	-0.211	0.037	-0.105
ABC-J total score	-	-	0.853***	0.592***	0.259
ABC-J Irritability	-	-	-	0.416*	0.364
CARS-TV total score	-	-	-	-	0.482**
RBS-R total score	-	-	-	-	-

There was no correlation between serum OXT concentrations and ABC-J total and subscale scores (n = 79). ABC-J total scores and ABC-J Irritability subscale scores were correlated. CARS-TV total scores and RBS-R total scores were not correlated with serum OXT concentrations for the ASD group (n = 54). CARS-TV total score was positively correlated with each score of ABC-J total and ABC-J Irritability subscale. RBS-R total score was positively correlated with CARS total score. There were no associations of CARS-TV total score with ABC-J total score and irritability subscale. For the ASD group, CARS-TV score and RBS-R total score showed no correlation with serum OXT concentration. Bonferroni corrections were employed for multiple comparisons.

Abbreviations: ASD, Autism Spectrum Disorder; ABC-J, Aberrant Behavior Checklist-community Japanese version; CARS-TV, Childhood Autism Rating Scale-Tokyo Version; RBS-R, The Japanese version of the Repetitive Behavior Scale-Revised.

* p < 0.05.

** p < 0.01.

*** p < 0.001.

Table 3
Means and standard deviations for ASD total and subscale scores, and Statistical difference between two groups.

	ASD males (n = 39)	ASD females (n = 15)
Age (years)	35.64 ± 11.35 (18–55)	39.4 ± 12.54 (17–60)
Weight (kg)	53.67 ± 9.92 (37.1–78)	53.77 ± 9.90 (33.4–73.0)
DQ or DIQ	13.28 ± 7.09 (3–37)	17.13 ± 9.92 (5–35)
Serum OXT	0.082 ng/ml ± 0.086 (0.010–0.349)	0.068 ng/ml ± 0.107 (0.003–0.416)
ABC-J total score	63.69 ± 30.15 (20–117)	54.33 ± 34.22 (5–104)
Irritability	16.72 ± 11.48 (0–40)	14.93 ± 11.44 (0–36)
Lethargy	18.74 ± 10.34 (2–39)	16.27 ± 11.90 (0–35)
Stereotypic behavior	7.95 ± 4.95 (0–19)	5.53 ± 6.27 (0–21)
Hyperactivity	16.85 ± 9.18 (1–41)	11.93 ± 8.10 (1–24)
Inappropriate speech	3.44 ± 3.95 (0–12)	5.67 ± 7.21 (0–28)
CARS-TV total score	46.54 ± 5.35 (35–53.5)	45.77 ± 5.81 (31.5–53)
RBS-R total score	29.95 ± 16.42 (6–89)	30.47 ± 18.01 (5–56)
Stereotyped	7.77 ± 5.02 (0–18)	5.93 ± 4.73 (0–15)
Self-injurious	4.00 ± 3.54 (0–14)	4.67 ± 5.41 (0–21)
Compulsive	4.00 ± 4.33 (0–20)	3.27 ± 3.79 (0–12)
Ritualistic	4.44 ± 4.44 (0–15)	5.67 ± 5.64 (0–18)
Sameness	7.59 ± 6.05 (0–21)	9.33 ± 7.53 (0–24)
Restricted interests	2.15 ± 2.27 (0–8)	1.60 ± 2.23 (0–6)

Reported values are means ± S.D.(standard deviation),ranges.

Abbreviations: ASD, Autism Spectrum Disorder; DIQ, Deviation intelligence quotient (by the revised Tanaka–Binet Intelligence Scale V); ABC-J, Aberrant Behavior Checklist-community Japanese version; CARS-TV, Childhood Autism Rating Scale-Tokyo Version; RBS-R, The Japanese version of the Repetitive Behavior Scale-Revised.

correlations between RBS-R Compulsive subscale scores and serum OXT concentration.

Early intervention research identified repetitive behavior mostly in males. Hollander et al. (2003) used a crossover design study of 15 patients (only one of who was female) and reported that OXT infusion reduced repetitive behaviors (need to know, repeating, ordering, need to ask, self-injury, and touching). Repetitive behavior in adult ASD may be related to abnormalities in the OXT system and may be partially ameliorated by synthetic OXT. In a randomized controlled study of 19 patients (3 of who were female), Anagnostou et al. (2012) reported a trend-level difference in RBS-R lower-order behaviors (Stereotyped and

Self-injurious) after 6 weeks of intranasal OXT treatment. They suggest that RBS-R lower-order behaviors are mainly pleasure-seeking behaviors and respond differently to OXT compared with RBS-R higher-order behaviors (Compulsive, Ritualistic, Sameness, Restricted interests). This may be of particular interest given the paucity of available interventions for lower-order repetitive behaviors. Though there is a difference between serum and plasma, findings from this study on repetitive behavior and OXT in females with ASD also were similar to those from an observational study by Miller et al. (2013). Trend-level positive correlations were found between plasma OXT concentration and RBS-R Ritualistic, Sameness, and Restricted interests subscale scores (RBS-R higher-order domains). Miller's results suggest that there are distinct and sexually dimorphic mechanisms of action for OXT that underlie repetitive behaviors. Some findings indicate that in ASD patients restricted, repetitive, and stereotyped patterns of behavior are associated with sex differences in young children and adults (Kim and Lord, 2010; Mandy et al., 2012). In similar repetitive or obsessive-compulsive behaviors, excessive OXT or an increase in OXT sensitivity is associated with OCD patients, as opposed to ASD patients, where a lack of OXT is associated with such behaviors. (Bartz and Hollander, 2008). Our results only partially support the prevailing interpretation of the OXT and RBS-R association. Also it is reported that there is less age-related improvement in repetitive behaviors of autistic children compared with improvements in social skills and communication (Fecteau et al., 2003).

4.3. OXT concentration and autistic symptoms, self-injurious behavior

We found that the total ASD group (n = 54) showed negative correlations between RBS-R Self-injurious behavior subscale scores and serum OXT concentration. Males with ASD (n = 39) showed negative correlation between RBS-R Self-injurious behavior and serum OXT concentration.

When severely self-injurious Repetitive behaviors exist, patients may require individual treatment in a closed environment. If serious physical complications (such as blindness) are also present, long-term confinement may be necessary because individuals with such problems may also experience difficulties in social conformity and may be at risk of injury. Synthetic OXT administration may ameliorate such symptoms and improve quality of life. This can help individuals to eventually be discharged and to make decisions about where they wish to live. It may also help prevent physical complications caused by challenging

Table 4
Regression analysis results: Beta coefficients.

	ASD total (n = 54) Serum OXT	ASD male (n = 39) Serum OXT	ASD female (n = 15) Serum OXT
ABC-J total score	−0.206	−0.247	−0.164
Irritability	−0.211	−0.245	−0.159
Lethargy	−0.177	−0.230	−0.104
Stereotypic behavior	−0.149	−0.056	−0.358
Hyperactivity	−0.049	−0.116	0.045
Inappropriate speech	−0.179	−0.235	−0.095
CARS total score	0.037	0.007	0.083
Relating to people	0.109	0.088	0.141
Imitation	0.085	0.031	0.175
Emotional response	0.158	0.186	0.144
Body use	0.054	0.125	−0.099
Object use	−0.017	−0.005	−0.088
Adaptation to change	−0.121	−0.179	−0.037
Visual response	−0.028	−0.093	0.13
Listening response	−0.186	−0.057	−0.386
Taste, smell, and touch response and use	0.034	0.014	0.055
Fear or nervousness	0.063	0.116	−0.067
Verbal communication	−0.023	−0.041	0.003
Nonverbal communication	0.319 (R ² = 0.101)	0.213	0.605 (R ² = 0.366)
Activity level	0.085	0.057	0.146
Level and consistency of intellectual functioning	−0.109	−0.245	0.109
General impressions	−0.080	−0.226	0.09
RBS-R total score	−0.105	−0.277	0.239
Stereotyped	0.144	0.156	0.087
Self-injurious	−0.294 (R ² = 0.086)	−0.376 (R ² = 0.142)	−0.17
Compulsive	−0.023	−0.252	0.527 (R ² = 0.277)
Ritualistic	−0.028	−0.249	0.373
Sameness	−0.222	−0.323 (R ² = 0.104)	−0.027
Restricted interests	0.180	0.065	0.415

In the total ASD group (n = 54), there was correlation between CARS-TV Nonverbal communication subscale scores and serum OXT concentrations and there was a negative correlation between RBS-R Self-injurious behavior subscale scores and serum OXT concentration. For the male ASD group (n = 39), there were negative correlations between, respectively, RBS-R Self-injurious behavior and Sameness subscale scores and serum OXT concentration. For the female ASD group (n = 15), there were correlations between CARS-TV Nonverbal communication subscale scores and serum OXT concentration, and between RBS-R Compulsive subscale scores and serum OXT concentration.

Abbreviations: ASD, Autism Spectrum Disorder; DIQ, Deviation intelligence quotient (by the revised Tanaka–Binet Intelligence Scale V); ABC-J, Aberrant Behavior Checklist-community Japanese version; CARS-TV, Childhood Autism Rating Scale-Tokyo Version; RBS-R, The Japanese version of the Repetitive Behavior Scale-Revised.

* Statistically significant at $p < 0.05$.

behaviors. Future intervention research should take into account sex and age and perform detailed assessments of repetitive behavior in ASD patients with severe intellectual disabilities.

4.4. OXT concentration and autism symptom, communication

Similar to Modahl et al. (1998), we found that CARS-TV Nonverbal communication subscale scores and serum OXT concentrations were positively correlated in the total ASD group and female ASD group. Modahl et al. (1998) found that in normal children, higher OXT concentration was associated with greater interaction skills and daily living skills, independent of age. For the autistic group as a whole and for the “aloof” subgroup, higher OXT concentration was correlated with deficits in these areas (Modahl et al., 1998). However, Modahl et al. (1998) findings were based on evaluation of male patients, and therefore the results cannot automatically be inferred to fit the results of this study which consisted of female ASD patients as well.

4.5. OXT concentration and sex differences

The sex differences we found in the association between subscale scores and serum OXT concentration, and the differences between our findings and those of Miller et al. (2013), could be explained by sex differences in the mechanism of the pituitary posterior lobe hormones. Miller et al. (2013) findings on high-functioning ASD children and adolescents showed females to have higher OXT concentrations. In another study, it was reported that there were sex differences in the

neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction (Rilling et al., 2014). However, the male–female ratio in nine previous randomized controlled trials was 216 males vs. 23 females; therefore, there is a lack of female data in this area (Anagnostou et al., 2012; Andari et al., 2010; Dadds et al., 2014; Guastella et al., 2015; Hollander et al., 2003; Kosaka et al., 2016; Munosue et al., 2016; Watanabe et al., 2015; Yatawara et al., 2015). In assessing OXT concentrations and the difference in effectiveness of intranasal OXT between individuals, we need to carefully take into account the factors such as Intellectual ability, social development, age and especially sex.

Compared with previous studies, we had a large sample of participants with severe intellectual disabilities (n = 79). These included 29 female subjects and 54 individuals with ASD. We conducted detailed analyses of the association between serum OXT concentration and levels of intellectual disabilities, autistic traits, and challenging behaviors (particularly repetitive behaviors). We found no significant effects of OXT on sex, diagnosis, severity of intellectual disabilities, and challenging behaviors. A recent meta-analysis on OXT and psychiatric disorders has also revealed no difference between healthy comparisons and patients diagnosed as ASD, BD, or Psychosis. Rutigliano et al. (2016). However there were sex differences in the correlations between subscale scores and serum OXT concentration in the ASD group in this study. The findings suggest that OXT functions differ in males and females and that OXT partly affects autism and OXT is correlated with some of the repetitive behaviors and nonverbal communication, in patients with severe intellectual disabilities.

4.6. OXT administration to patients with severe intellectual disabilities and challenging behavior

Often individuals with severe intellectual disabilities require special treatment, particularly if they also have ASD or other challenging behaviors. Common interventions are behavioral therapy, the TEACCH® autism program, and pharmacotherapy. Antipsychotic and mood stabilizing drugs are often used, but their effect can vary greatly and physical side effects are a concern. Therefore, new pharmacotherapy with fewer side effects are needed. Interventions using synthetic OXT administration for challenging behavior in ASD need to be validated and their effects and side effects (including possible sex differences) assessed. Munesue et al. (2016) reported a pilot study of intranasal OXT for male subjects with ASD and comorbid intellectual disabilities including severe levels. In that report, except for seizures experienced by one participant, other serious adverse events did not occur. Yamasue et al. (2018) suggests oxytocin as a possible way to treat ASD repetitive behaviors in the large-scale trial only for adult men without intellectual disabilities.

4.7. Limitations

The present study had several potential limitations. First, OXT concentration was measured using an extraction-free kit (Suena et al., 2016; McCullough et al., 2013; Szeto et al., 2011). Measurements of oxytocin made on unextracted samples could result in the tagging and detection of other molecules in addition to oxytocin leading to an overestimation of oxytocin levels. We understand that a method utilizing extraction procedure would be the best way to measure oxytocin concentration levels. However, we decided to use a measurement method without extraction as utilizing methods with extraction would be too complicated and expensive in a clinical setting. Second, we did not diagnose ASD according to the Autism Diagnostic Observation Schedule Second Edition (ADOS-2) or the Autism Diagnostic Interview-Revised (ADI-R), because their intellectual disabilities were too severe, and additionally, recollection of old parental memories were difficult. The third is the problem with the sample population. This study used a sample of hospitalized patient from a special ward for severe intellectual disabilities, but there was no normal control group. As another point, including 15 ASD female is a valuable point in comparison with other previous studies, male and female ASD groups differed on age and DIQ (DQ). Also, of the 79 patients, 36 had epilepsy. Future research on this topic needs to consider the influence of antiepileptic drug medication (Clynen et al., 2014).

5. Conclusions

Compared with previous studies, we had a relatively large sample of participants with severe intellectual disabilities ($n = 79$). These included female subjects and 54 individuals with ASD. We conducted detailed analyses of the association between OXT concentration and levels of intellectual disabilities, autistic traits, and challenging behaviors (particularly repetitive behaviors). We found no significant effects of diagnosis, severity of intellectual disabilities, and challenging behaviors. However, there were sex differences in the correlations between subscale scores and OXT concentration in the ASD group. The findings suggest that OXT functions differ in males and females and that OXT partly affects autism and OXT is correlated with some of the repetitive behaviors and nonverbal communication, in patients with severe intellectual disabilities.

Conflict of interest

The authors have no conflicts of interest.

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Supplementary materials

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