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# Evaluation of oxytocin and serotonin levels in autism spectrum disorder

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## Abstract

### Objective

Autism spectrum disorder (ASD) is a complex neurological and developmental disorder that affects how a person acts and interacts, communicates with others, and learns. Endocrine and neuropeptide factors are some among the list of possible etiologic or predisposing contenders. Abnormalities in the brain serotonin system are reported in ASD, including evidence of altered serotonin synthesis and receptor binding, as well as dystrophic serotonergic axons. Blood oxytocin levels are also a focus of ASD research. This work aimed to assess oxytocin and serotonin levels as biomarkers in individuals with ASD.

### Participants and methods

Serotonin and oxytocin levels, as biochemical parameters related to neurochemistry, were determined in the sera of 40 autistic patients (29 males and 11 females). They were categorized as mild to moderate and severe as indicated by their Childhood Autism Rating Scale and as low average intelligence, slow learner, and mentally retarded according to their intelligence quotients. The parameters were then compared with that of 40 age-matched and sex-matched control samples (30 males and 10 females).

### Results

Our patients showed a highly significant increase in serotonin levels and a highly significant decrease in oxytocin levels as compared to controls. Diagnostic validity test was carried out for both serotonin and oxytocin and showed excellent results. A correlation done between serotonin and oxytocin levels among the patient group showed significant negative correlation.

### Conclusion

Our results significantly reinforce the reliability of increased serotonin blood levels and decreased oxytocin levels as biomarkers in ASD, providing possible indications potentially useful for their inclusion in multimarker diagnostic panels for clinical use. Identifying relationships between identified ASD biomarkers may be a useful approach to connect the different findings of multiple systems in this heterogeneous disorder and to find the causes of ASD and to identify potential interventions.

**Keywords:** Autism spectrum disorder, oxytocin, serotonin

## INTRODUCTION

Autism spectrum disorder (ASD) is a complex developmental disability that typically appears during the first 3 years of life. Children with ASD typically show disabilities in social interaction skills, verbal and nonverbal communication, as well as repetitive and stereotypic behaviors [1]. It is possible that ASD has a multifactorial cause along with more than one predisposing and perpetuating factor, all of which culminate in the expression of this disorder. Endocrine and neuropeptide

factors are some among the list of possible etiologic or predisposing contenders [2].

Examining biomarkers may give us ways to identify individuals who demonstrate specific developmental

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trajectories and etiological factors related to ASD [3]. Biomarkers could potentially be used to parse the heterogeneity of ASD, which may ultimately lead to individualized interventions [4].

Serotonin is a neurotransmitter found throughout the brain and body. It has long been of interest in the study of ASD. Repeated findings of increased serotonin levels in approximately one-third of children with ASD has led some to believe that dysfunctional serotonin signaling may be a causal mechanism for the disorder [5]. Abnormalities in the brain serotonin system are reported in ASD, including evidence of altered serotonin synthesis and receptor binding, as well as dystrophic serotonergic axons [6].

In contrast, oxytocin is a neuropeptide (i.e. it has nine amino acids). Oxytocin is synthesized in magnocellular neurons in the paraventricular nucleus and the supraoptic nucleus of the hypothalamus. It is released into the bloodstream by way of axon terminals in the posterior pituitary. Oxytocin is released both peripherally, where it is involved in milk let down and the facilitation of uterine contractions, and centrally, where it acts as a neuromodulator [7].

Blood oxytocin levels are also a focus of ASD research. Children with ASD have lower average levels of blood oxytocin in comparison to typically developing children matched for age. In contrast, a study of adults with ASD suggests that oxytocin levels are higher at baseline in adults [8].

The serotonin and oxytocin systems interact in the brain, both during development and in adulthood. The serotonin system regulates oxytocin release in human adults, as evidenced by the increased oxytocin levels after treatment with 3,4-methylenedioxymethamphetamine (popularly known as 'Ecstasy'), a drug that causes the release of serotonin [9].

This work aimed to assess oxytocin and serotonin levels as biomarkers in individuals with ASD.

## PARTICIPANTS AND METHODS

### Participants

The study was carried out on 80 individuals classified into two groups:

- (1) Group 1: patient group consisted of 40 ASD patients selected from Phoniatics Unit of Hearing and Speech Institute attending for language therapy. They comprised 29 male and 11 female participants, of average age of 2–7 years ( $4.04 \pm 1.53$  years).
- (2) Group 2: control group consisted of 40 healthy children (30 males and 10 females), of average age of 2–7 years ( $4.58 \pm 1.25$  years).

All participants were subjected to complete physical, audiological, and phoniatic examination after taking verbal consent from their parents. They were also screened to have

no psychiatric medications and no medication use during the time that the neurochemistry assays were conducted.

The patients met the diagnostic criteria of ASD according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. Both patient and control groups were subjected to Childhood Autism Rating Scale (CARS) [10] as a diagnostic tool to exclude the controls and to evaluate children who were suspected of having ASD. Cognitive abilities and social competence were measured in both groups by intelligence quotient test (IQ test) according to Stanford–Binet Intelligence Scale, 4<sup>th</sup> ed. (S-B IV) classification [11] and Vineland Social Maturity Scale [12].

Routine laboratory investigations (complete blood picture, fasting blood sugar and liver and kidney function tests) were carried out to exclude other abnormalities. Both serotonin and oxytocin concentrations were assessed in sera of both groups by enzyme-linked immunosorbent assay method.

### Sampling

Parents were instructed to abstain their children from serotonin rich food (e.g. avocados, bananas, coffee, plums, pineapple, tomatoes, and walnuts) before blood sampling.

A volume of 7 ml of venous blood from all patients and controls was aseptically collected after fasting for 6–8 h using vacutainer system (BD vacutainer system; Belliver Industrial Estate, Plymouth, UK), 5 ml of which was collected in the vacutainer tube with gel. The sera were separated for the routine biochemical analysis, and the remaining sera were collected individually and stored at  $-20^{\circ}\text{C}$  as two aliquots for each sample until assay of serotonin and oxytocin. A volume of 2 ml of blood was collected on EDTA tube for complete blood picture.

### Statistical analysis

Data analysis was performed using SPSS of the International Business Machines Corporation, version 22 (2013; IBM Corp., Armonk, New York, USA). Data were expressed as mean  $\pm$  SD for quantitative parametric measures in addition to both number and percentage for categorized data. Comparison between two independent mean groups for parametric data was performed using Student's *t*-test. Pearson's correlation test was carried out to study the relationship between every two variables among each group for parametric data. The probability of error, *P* value was considered as follows. *P* value of greater than 0.05 is nonsignificant, *P* value of less than 0.05 is significant, and *P* value of less than 0.01 is highly significant. Diagnostic validity test including sensitivity, specificity, positive predictive value, negative predictive value, and efficacy was carried out.

## RESULTS

Autistic patients (29 males and 11 females) were categorized as mild to moderate (90%) and severe (10%) according to their CARS, and according to their IQs as low average intelligence (17.5%), slow learner (32.5%), and mentally retarded (50%) (Figs 1 and 2).

A comparative analysis of mean ± SD of each IQ test, CARS test, and serotonin and oxytocin levels in patients compared to that of controls was performed using Student's *t*-test. The CARS scores and the serotonin levels showed a highly significant increase in patients group as compared to that of controls ( $P < 0.01$ ). On the other hand, the IQ scores and the oxytocin levels were highly significantly lower in patients group as compared to that of controls ( $P < 0.01$ ) (Tables 1 and 2).

Another comparative analysis of mean ± SD of each IQ test, CARS test, serotonin and oxytocin levels in male participants compared to that of female participants among the control group (Table 3) and the patient group (Table 4) was performed. No significant differences were found among both the control group and the patient group, between male and female participants as regards IQ, CARS, serotonin, and oxytocin.

Correlation studies were carried out between the IQ scores and the other parameters in the patient's group using Pearson's correlation test (Table 5). No significant correlation was noticed between the IQ scores of the patients and each of the CARS scores ( $r = 0.067$  and  $P = 0.682$ ), the serotonin levels ( $r = 0.001$  and  $P = 0.996$ ), and oxytocin levels ( $r = -0.139$  and  $P = 0.394$ ).

**Table 1: Statistical comparison of mean values of clinical parameters among control and patient groups**

Parameters	Control group (n=40) (mean±SD)	Patients group (n=40) (mean±SD)	P	Significance
IQ test score	98.1±9	68.48±8.56	0.0027	HS
CARS test score	16.58±1.47	33.1±3	0.0082	HS

CARS, Childhood Autism Rating Scale; HS, highly significant; IQ, intelligence quotient.

**Table 2: Statistical comparison of mean values of laboratory parameters among control and patient groups**

Parameters	Control group (n=40) (mean±SD)	Patients group (n=40) (mean±SD)	P	Significance
Serotonin (ng/ml)	145.25±7.92	327.45±9.02	0.0044	HS
Oxytocin (pg/ml)	32.03±6.82	19.6±1.39	0.0073	HS

HS, highly significant.

**Table 3: Statistical comparison of mean values of the parameters between male and female participants among the control group**

Parameters	Males (n=30) (mean±SD)	Females (n=10) (mean±SD)	P	Significance
IQ test score	96.333±7.84	103.4±10.56	0.075	NS
CARS test score	16.733±1.50	16.1±1.28	0.214	NS
Serotonin (ng/ml)	146.933±7.96	140.2±5.41	0.06	NS
Oxytocin (pg/ml)	32.433±7.11	30.8±5.99	0.486	NS

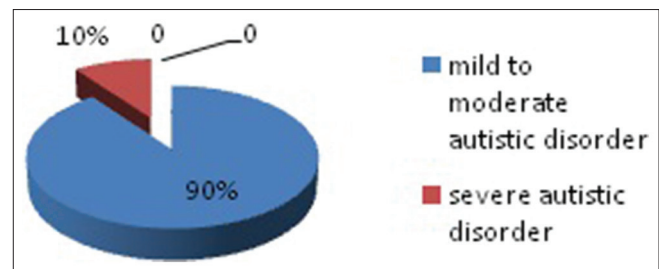
CARS, Childhood Autism Rating Scale; IQ, intelligence quotient.

Table 6 shows the correlation between CARS scores and both serotonin levels ( $r = 0.056$  and  $P = 0.734$ ) and oxytocin levels ( $r = 0.074$  and  $P = 0.649$ ) in the patient group. There was no significant correlation between CARS scores and both serotonin and oxytocin levels.

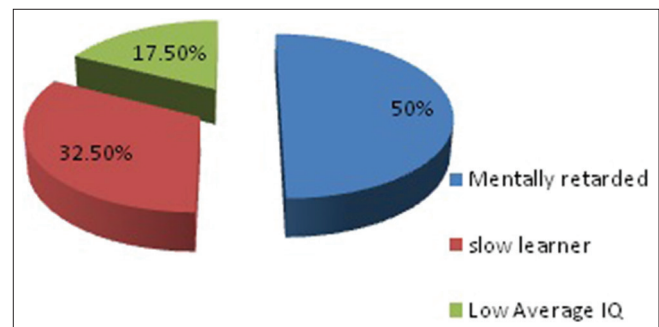
Another correlation study was carried out between serotonin and oxytocin levels which showed significant negative correlation ( $r = -0.372$  and  $P = 0.018$ ) in the patient's group (Table 7).

**Correlation studies**

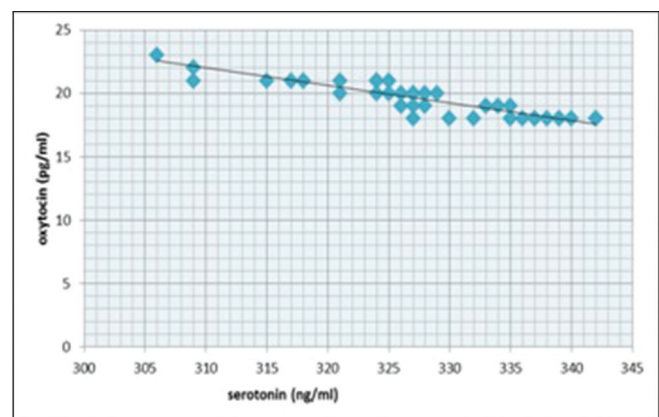
A significant negative correlation ( $r = -0.372$  and  $P = 0.018$ ) was noted between serotonin and oxytocin levels in the patient's group (Fig. 3).



**Figure 1:** Distribution of autistic group into mild to moderate autistic disorder and severe autistic disorder.



**Figure 2:** Distribution of intelligence quotient range among the patient group.



**Figure 3:** Correlation between serotonin and oxytocin levels among patients group.

Finally, diagnostic validity test was carried out for both serotonin and oxytocin which showed excellent results (Table 8).

## DISCUSSION

In our study, no significant correlation was noticed between the IQ scores of the patients and each the CARS scores, the serotonin levels, and the oxytocin levels. This is an expected result as there is a discrepancy between the adaptive skills in the children with ASD and their IQ scores. So, the adaptive

**Table 4: Statistical comparison of mean values of the parameters between male and female participants among the patient group**

Parameters	Males (n=29) (mean±SD)	Females (n=11) (mean±SD)	P	Significance
IQ test score	67.69±8.79	70.545±7.91	0.335	NS
CARS test score	33.155±2.94	32.955±3.29	0.862	NS
Serotonin (ng/ml)	326.345±7.68	330.364±11.8	0.738	NS
Oxytocin (pg/ml)	19.552±1.37	19.727±1.48	0.313	NS

CARS, Childhood Autism Rating Scale; IQ, intelligence quotient.

**Table 5: Correlation between intelligence quotient and Childhood Autism Rating Scale, serotonin, and oxytocin among patients group**

	r	P	Significance
CARS score	0.067	0.682	NS
Serotonin (ng/ml)	0.001	0.996	NS
Oxytocin (pg/ml)	-0.139	0.394	NS

CARS, Childhood Autism Rating Scale.

**Table 6: Correlation between Childhood Autism Rating Scale and both serotonin and oxytocin among patients group**

	r	P	Significance
Serotonin (ng/ml)	0.056	0.734	NS
Oxytocin (pg/ml)	0.074	0.649	NS

**Table 7: Statistical comparison of mean values of laboratory parameters among control and patient groups**

Parameters	Control group (n=40) (mean±SD)	Patients Group (n=40) (mean±SD)	P	Significance
Serotonin (ng/ml)	145.25±7.92	327.45±9.02	0.0044	HS
Oxytocin (pg/ml)	32.03±6.82	19.6±1.39	0.0073	HS

HS, highly significant.

**Table 8: Diagnostic validity of both serotonin and oxytocin**

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Efficiency (%)
Serotonin	100	100	100	100	100
Oxytocin	100	100	100	100	100

outcome could be impaired even for those children with average intelligence (Charman *et al.*, 2011). [29] Correlations between IQ and serotonin or oxytocin have not been done in previous studies.

There was no significant correlation between CARS scores and serotonin levels in our ASD patients. Similarly, Alabdali *et al.* [20] reported that there was a lack of biochemical correlation between serotonin levels in autistic children and severity of autism (by CARS).

In the present study, no significant correlation between CARS scores and oxytocin levels was found. This result is in discrepancy with Jacobson *et al.* (2014) [30] who found a positive correlation between oxytocin levels and Autism Diagnostic Observation Schedule scores.

The serotonin levels of our patients showed a highly significant increase as compared to controls. This suggestion is supported by many previous studies such as Schain and colleagues [13–19]. However, there is a discrepancy between our results and the results of Alabdali *et al.* [20] who found that platelet-free plasma serotonin levels were significantly lower in patients with autism as compared to that of controls. The previous lower level was explained on the basis that serotonin was measured in platelet-free plasma that could have lower levels of serotonin as a result of (a) increased serotonin production and ultrafiltration of serotonin from platelets, or (b) increased expression of the transporter on the platelet surface or both.

The sensitivity for serotonin in the present study was 100% at cut-off greater than 166 to less than 306. This is in discrepancy with the sensitivity which was recorded by Kuperman *et al.* [21] at 25%, Schain and Freedman [13] at 35%, and Anderson *et al.* [22] at 41%. The discrepancy in sensitivity may be due to the different measurement protocols, technologies, and biomaterials that have been used through the years. Despite some limitations mainly due to small study sample sizes, our results significantly reinforce the reliability of increased serotonin blood levels as a biomarker in ASD.

As regards the oxytocin levels in our patients, they were highly significantly lower as compared to that of controls. This result is by Modahl *et al.* [23], Hammock *et al.* [4], Alabdali *et al.* (2014), and Ruggeri *et al.* [24]. In contrast, Jansen *et al.* [8] in a study of adults with ASD suggests that oxytocin levels are higher at baseline in adults. This contradiction can be explained by the differences in the age group. However, Taurines *et al.* [25] and Parker *et al.* [26] in their studies reported that there was no significant difference in oxytocin levels of

ASD patients in comparison with healthy controls. Differences in oxytocin levels in these studies may be related to:

- (1) Developmental differences [as the study of Tourines *et al.* (2014b) [31] was on adolescents and young adults].
- (2) Diagnostic tool differences.
- (3) Differences in the severity of autism as there was correlation reported between oxytocin levels and severity of autism [27].

The studies suggested that there might be dysfunction in oxytocin processing associated with ASD and that there might be developmental changes associated with the oxytocin system over the lifespan of individuals with ASD. Further longitudinal studies or more extensive studies of broader age range are necessary to confirm this finding along with control for intellectual development across age groups.

Another correlation study carried out between serotonin and oxytocin levels of patients group showed significant negative correlation. The negative correlation between oxytocin and serotonin levels in the patients' data can be interpreted in some ways, as this relationship could be mediated at multiple levels. Peripheral serotonin is unlikely to affect central oxytocin release because it does not cross the blood–brain barrier, but it could affect the peripheral metabolism of oxytocin.

Similarly, Hammock *et al.* [4] recorded a negative correlation between oxytocin and serotonin levels in autistic patients and explained their findings that peripheral oxytocin could affect gastrointestinal synthesis of serotonin, platelet serotonin uptake or serotonergic release from platelets. However, this correlation was limited to children with ASD in both studies, so it is not possible to know whether the relationship between oxytocin and serotonin is specific to ASD or is true regardless of diagnosis. Future research should examine whether this relationship is specific to children with ASD or extends into the general population.

However, Martin *et al.* [28], have previously reported that early exposure to a nonselective serotonin receptor agonist in rats and voles results in fewer oxytocin cells in the paraventricular nucleus of the hypothalamus, less affiliative behavior, and less social interaction. Conversely, the serotonin system regulates oxytocin release in human adults, as evidenced by the increased oxytocin levels after treatment with 3,4-methylenedioxymethamphetamine (popularly known as 'Ecstasy'), a drug that causes the release of serotonin [9]. The previous findings suggest that the relationship between these two systems in the periphery may differ according to age, thus highlighting the importance of patient age in the identification of biomarker interrelationships and subsequent reproducibility.

## CONCLUSION

Our results significantly reinforce the reliability of increased serotonin blood levels and decreased oxytocin levels as biomarkers in ASD, providing possible indications potentially useful for their inclusion in multimarker diagnostic panels

for clinical use. Identifying relationships between identified ASD biomarkers may be a useful approach to connect the otherwise disparate findings that span multiple systems in this heterogeneous disorder.

Further longitudinal studies are needed with:

- (1) Larger sample size.
- (2) Broader age range.
- (3) Different diagnostic tools.
- (4) Correlation studies on control group as well as on patient group.

## Conflicts of interest

None declared.

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