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Review Article

LOW SERUM OXYTOCIN LEVELS IN PROBANDS WITH AUTISM AND THEIR FIRST DEGREE RELATIVE-A PRELIMINARY CASE FOR OXYTOCIN AS AN ENDOPHENOTYPE

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ABSTRACT

Oxytocin (OT) is a peptide hormone that has been reported to be associated with attachment, social memory, emotional cognition, and social interaction. Metabolic abnormalities of OT have exhibited a significant association with impairment in social interaction and communication in Autism Spectrum Disorders (ASD) individuals. Several exogenous OT treatments have managed to normalize impaired social functioning among individuals with ASD. The serum Oxytocin levels in patients with autism, their age, and sex-matched healthy control groups and First-Degree Relatives (FDRs) of patients with autism, and the association between Oxytocin levels and socialization have not been studied.

Aims: This study aimed to assess and compare the serum OT levels in patients with autism, their FDRs, and age-sex-matched healthy controls, and examine the relationship between OT levels & socialization.

Settings and design: Cross-sectional hospital-based study on 20 patients diagnosed with autism according to ICD-10 DCR, 20 their FDRs and 20 age-sex matched healthy controlstion.

Materials and methods: A total of 60, 20 patients were diagnosed with autism according to ICD-10 DCR (n=20), 20 their FDRs (siblings) (n=20) and 20 age-sex matched healthy controls (n=20). Serum oxytocin level was measured using an Enzyme-Linked Immunosorbent Assay (ELISA). Assessments included the INCLEN Diagnostic Tool for Autism Spectrum Disorder (INDT-ASD) and the Indian Scale for Assessment of Autism (ISAA).

Results: A total of 20 autism patients, 20 of their FDRs, and 20 age and sex-matched healthy controls completed the study. The study showed a significant difference in Serum Oxytocin levels among the autism patient group, their first-degree relative, and the healthy control group ($p<0.001$). Post-hoc analysis has revealed that there is a significantly high level of Serum Oxytocin levels in controls compared to the patient group and FDRs. However, there is no significant difference in Serum Oxytocin levels between the patient group and FDRs. The assessment showed significant differences among the patient group and FDRs in ISAA domains of Social relationship and reciprocity, Emotional responsiveness, Speech-language and communication, behavior patterns, sensory aspects, cognitive component & total score ($p<0.001$). There was no significant correlation between Serum Oxytocin levels with age and ISAA domains of Social relationship and reciprocity, Emotional responsiveness, Speech language and communication, behavior patterns, sensory aspects, or cognitive component in the study group.

Conclusion: The study found significantly lower values of OT in patients and FDRs when compared to controls, suggesting a possible role of Oxytocin as a trait marker in autism. Also found that lower levels of Oxytocin in FDRs have no relation with socialization in FDRs as ISAA scores were significantly higher in FDRs compared to patients. Keywords: social interaction and communication deficits, Oxytocin, Autism spectrum disorders, a tool for Social relationship and reciprocity, Emotional responsiveness, Speech language, and communication.

Keywords: Social interaction and communication deficits; Oxytocin; Autism spectrum disorders; Emotional responsiveness; Speech language; Communication

INTRODUCTION

Autism Spectrum Disorders (ASD) are a set of complex neurodevelopmental disorders characterized by a deficit in social interaction and communication as well as restricted, repetitive behaviors [1]. The etiology of ASD likely includes both genetic heritability and environmental risk factors and twin studies have demonstrated an estimated heritability of 70%–90% [2-5]. In children with autism, deficits in social interaction and communication are often observable very early in childhood. These infants may engage less in social behaviors, including responding to their name being called or looking and smiling at other individuals and initiating or sustaining less eye contact than their typically developing peers [6,7]. Later in development, preschoolers with autism may exhibit difficulties with turn-taking and socially approaching others and have a poorer understanding of social norms and others' emotions [8]. Many of these individuals find it difficult to make and maintain friends, and social development deficits represent a strong negative impact on their lives [9]. Some individuals have severe behavioral deficits and remain completely nonverbal throughout their lifespan, while others have milder impairments in speech patterns, eye gaze, and stereotyped behaviors [10]. These large variations in symptoms have significant predictive and diagnostic relevance but have thus far remained unresolved.As a result, many children are not correctly diagnosed with autism until 2 years to 3 years after symptoms appear. Oxytocin (OT) is a nine-amino acid peptide that is synthesized in the magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus and is released through the posterior pituitary into the peripheral circulation. Recent studies have demonstrated an increasing role of oxytocin in modulating social cognition abilities. OT can enhance the processing of positive socio-emotional cues facilitating interpersonal trust and prosocial interactions in humans. Studies on patient groups have demonstrated an association of low OT levels with impaired performance on social cognition tasks in autism. Several components of the OT system such as the genes for OT itself, for its receptor, and for the cluster of differentiation 38 (a transmembrane protein that regulates OT release) have been associated with ASD. Some studies have also suggested a potential association between a primary dysfunction

of the central OT system and core symptoms of social deficits in ASD. Metabolic abnormalities of OT have exhibited a significant association with impairment in social interaction and communication in ASD individuals. Several exogenous OT treatments have managed to normalize impaired social functioning among individuals with ASD. These findings provide evidence that OT may have the potential to improve human social cognition and behavior and to partially restore the damaged social cognitive neurological functions. The above studies support the role of oxytocin in mediating social impairment in ASD. Because behavioral and genetic heterogeneity are hallmark autism features, and because definitive behavioral diagnoses cannot be made in infancy, biomarkers of the disorder are highly desirable. Despite the pressing need, there are few, if any, well-established biomarkers in autism at any level of analysis. Biomarkers could potentially help assist in diagnosis or even prediction of eventual diagnosis in those at increased risk for the disorder. Perhaps the most replicated of the blood-based biomarkers is elevated platelet serotonin, reductions in mean plasma oxytocin levels are particularly prominent in a subgroup of autistic children. Modahl et al. (1998) was the first study to find lower OT plasma levels in autistic boys. The same researchers also found differences in the actual OT peptide forms, suggesting broader differences in OT metabolism. Several studies measured changes in OT levels in the context of behavioral experiments. Feldman et al. (2014) showed that the lower baseline OT levels of autistic children normalized during parent-child interaction, that is, reached the same levels as those of neurotypical children, before returning to relatively lower baseline levels. On this background, the present study was conducted with the following aims:

- To assess and compare the serum OT levels in patients with autism, their FDRs, and age-sex matched healthy controls.
- To assess and compare socialization in autism patients and their FDRs and their relationship with serum OT levels.

LITERATURE REVIEW

Study subjects: The sample size consisted of a total of 60, out of which 20 Children and adolescents were diagnosed with autism (ICD 10 DCR) who were between the ages of 2 years-18 years of either sex and had a sibling of age +5/-5 years to them. Patients' guardians giving written informed consent to participate in the study were recruited from out-patient and in-patient services of the Department of Psychiatry, Tertiary psychiatric institute in eastern India. Diagnosis of Autism was made based on the ICD 10 DCR criteria and confirmed independently by a qualified psychiatrist based on clinical interview and by administering INCLEN Diagnostic Tool for Autism Spectrum Disorder (INDT-ASD). Any other psychiatric illness (schizophrenia, attentiondeficit/hyperactivity disorder, depressive disorder, and bipolar disorder) and severe intellectual disability, significant medical or neurological illness (endocrinopathies) were excluded from the study. 20 healthy siblings of either sex, age +5/-5 years to the age of patients were chosen for the group of FDRs. 20 healthy children and adolescents between 2 years-18 years of age, match with patients for age & sex were included as controls. Written informed consent was taken from guardians before data collection. The study was approved by the institutional ethics committee.

Procedure: The sample was taken from the Out-Patient and In-Patient Department of Tertiary psychiatric institute in eastern India, diagnosed as having autism according to the Diagnostic Criteria for Research (DCR) of the International Classification of Diseases-tenth edition then Patients were assessed on INCLEN to confirm the diagnosis. Written informed consent from the guardians was taken after explaining the objectives and procedure of the study in detail. A detailed physical examination was done to rule out any major medical or neurological illness. Relevant socio-demographic and clinical data were collected from all the participants on the socio-demographic and clinical data sheet. FDRs (siblings) of each of the subjects in the Autism patient group were also recruited in the FDR group. ISAA was applied to compare the impairments in social, communication, and behavior patterns of children with autism and FDRs.

Serum oxytocin assessment: Participants were previously informed to fast in the morning before sampling to avoid the influence of food and/or drink. Five milliliters of venous blood was collected from each participant's antecubital region by trained and qualified nurses between 8:00 a.m and 9:30 a.m. in pro-coagulation tubes. Blood samples were allowed to clot for 10-20 minutes at room temperature. Samples were centrifuged at 3000 RPM for 20 minutes. The serum was separated from the samples and stored in the refrigerator at -80°C. Serum oxytocin levels were measured by using the enzyme Linked Immunosorbent Assay (ELISA), and analyzed by the Optical Density (OD value).

Analysis: Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 25.0. Group differences for sample characteristics were examined with ANOVA and chi-square test wherever applicable. Continuous variable (age) was compared using one way ANOVA, whereas rest of the variables which were discrete were compared using Pearson chi-square test and wherever the cell count was less than 5, Fischer exact test was applied.

Comparison of serum oxytocin levels among three groups. Correlation between Serum Oxytocin levels with age and ISAA domains There was no significant correlation between Serum OT levels with age and ISAA domains of Social relationship and reciprocity, Emotional responsiveness, Speech language and communication, behavior patterns, and cognitive component in study group.

DISCUSSION

The present study was conducted on the total sample size of 60 including 20 each for children and adolescents diagnosed with autism, their first degree relatives and healthy controls. The sample size taken was modest. The previous studies conducted comparing OT levels in children with Autism and healthy control took 19 Autism patients. No study as per our knowledge, has assessed OT levels in FDRs of autism patients. Moreoverthe FDRs accompanying the selected patients were evaluated and were selected on a well-defined set of criteria. Those who were not having any medical or psychiatric co morbidity were selected for the study. The age group selected for FDRs was +5/-5 age of patient's age as usually siblings have age gap of 2 years-3 years and many a times diagnosis of autism is late and by then parents decide to have 2nd child. Great care was also taken to select healthy controls for the current study. They were matched for age and sex of the Autism patient group. Those not having any medical or psychiatric illness were selected for the study. At the end of the study the results revealed that the healthy subjects were comparable or most of the points with the patient group. In the present study, the mean levels of the OT in patient group are 78.74 pg/mL ±45.735 pg/mL while in FDRs and controls, it is 108.47 pg/mL ± 46.669 pg/mL and 149.07 pg/Ml ± 46.709 pg/mL respectively. The levels in the control group were significantly higher than both cases and FDR (p=0.000). Our finding of lower OT levels in autistic children points to an involvement of the OT system in the development or manifestation of ASD. A study compared plasma OT levels in 29 children with Autism with 29 age and sex-matched control groups revealing that the autism group had significantly lower plasma OT levels than the normal controls. OT levels increased with age in normally growing children but not in children with autism, some of them had belowdetectable levels. A similar study compared OT and Vasopressin levels in 77 Autism

patients and matched healthy controls and found significantly lower plasma levels of OT in children with autism as compared to controls. But there was no significant correlation between the degree of autism or the age of the affected child and plasma levels of OT. A meta-analysis conducted by John S et al (2021) showed strong evidence of lower OT levels in autistic children, however, OT levels in autistic adults were virtually indistinguishable from those of neurotypical adults suggesting OT levels in autistic people might normalize as they grow older. We could not find, to the best of our knowledge, studies comparing plasma OT levels in patients with autism and their first-degree relatives. In present study, we found Serum OT levels in FDRs is mean= 108.47±46.669 pg/mL. The levels of the FDR was not significantly higher than the cases (p=0.142). Even though FDRs did not have autism or any psychiatric illness we found Serum OT levels slightly higher to that of patient group but significantly lower than the controls. So that to study socialization and communication aspect of FDR to compare it with patients, we applied Indian Scale for Assessment of Autism (ISAA) on both patient group and FDRs and we found there is significant difference in all the domains of ISAA Social relationship and reciprocity, Emotional responsiveness, Speech language and communication, Behaviour patterns, Sensory aspects and Cognitive component (p= <0.001). Serum OT levels in FDRs were similar to that of patients suggesting a possible role as a trait marker in patients of Autism. However, it would be difficult to come to a definite conclusion considering no existing studies on endophenotypes in Autism and replication is warranted with larger sample size. However it indicates that dysfunction in OT system is related particularly to social impairments in ASD. Furthermore, the negative relationship between plasma OT levels and social skills could reflect more extensive abnormalities at various levels in OT endocrine system as OT gene or the OT receptor (OXTR) abnormalities. There was no significant correlation between serum OT levels with age and ISAA domains of social relationship and reciprocity, emotional responsiveness, speech-language and communication, and behavior patterns cognitive component. A study on Plasma OT in Children with Autism and its correlations with behavioral parameters using Autism Diagnostic Interview (ADI) found a significant positive correlation between plasma OT levels and ADI in reciprocal interaction and communication subscales scores indicating that autism symptoms are not negatively associated with OT levels, they found the opposite pattern that is higher OT levels were connected with more severe autism symptoms. Another study had a contrary finding in which OT levels were negatively associated with socialization items of The Vineland Adaptive Behavior Scales with the strongest correlation with items related to imitation, while in the group of normal controls higher OT levels corresponded with greater interaction skills and daily living skills. A study on the association of social cognitive impairment and various biomarkers including OT in ASD found that there were remarkably impaired plasma levels associated with the severity of social cognitive impairment tested on the Childhood Autism Rating Scale (CARS). Thus it seems that OT levels are associated with particular ASDsymptoms connected with social abilities including reciprocal interaction, imitation, and skills toexpress needs, however, the relationship between these abilities and OT is opposite to that in people without autism spectrum disorder. A study done by Hoge E et al (2008) showed higher circulating OT levels were associated with greater social dissatisfaction and increased severity among individuals with social anxiety disorder. This provides preliminary support for a link between social anxiety and plasma OT level and their findings were consistent with the finding of increased OT in the ASD group of individuals with social deficits. Our study suffered a few limitations, the sample size was modest and the majority of the subjects in the study were males which makes it difficult to generalize the result. Treatment was not controlled, including varying choices and dosages of medications used. The effect of drugs on the biomarkers could be varied and hence could confound the results. Also, peripheral levels of OT may not reflect the central release and the gender difference could also affect OT levels.

CONCLUSION

This study found significantly lower values of OT in cases and FDRs when compared to controls, suggesting a possible role of OT as a trait marker in autism. Also found that lower levels of OT in FDRs have no relation with socialization in FDRs as ISAA scores were significantly higher in FDRs compared to patients. Existing literature suggests very little is known about thepathophysiology of ASD and the various factors that could affect its physiology, course, and outcome. The current study aimed to assess the role of OT as trait markers in autism, and thereby possibly shed some light on the possible contributions of various factors and biomarkers in the pathophysiology of autism spectrum disorders. The current study also focused only on the child and adolescent population. Further research should target the adult population which could yield different results. Moreover, further studies are needed to factor in the heterogenicity of psychotropic drugs used as they can induce changes in the biochemical markers being assessed.

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