EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2018.17021

Original Article

Is the serum oxytocin level altered by treatment in rheumatoid arthritis patients complicated with depression?

Yusuke Miwa[1], Hidekazu Furuya[1], Ryo Yanai[1], Tsuyoshi Kasama[1], Kenji Sanada[2]

Abstract

Objective: The objective of this study was to investigate the factors associated with depression, including serum oxytocin (OXT) levels, disease activity, activities of daily living (ADL), and quality of life (QOL), and their effects on rheumatoid arthritis (RA).

Methods: This study included 42 RA patients who received treatment with a biological agent. We measured the following variables before and after 6 months of treatment: baseline characteristics, including age, sex, disease duration, smoking, and body mass index (BMI); prednisolone and methotrexate dose; serum level of matrix metalloproteinase-3 (MMP-3); erythrocyte sedimentation rate (ESR); and C-reactive protein (CRP) level. The disease activity of RA was assessed using the Simplified Disease Activity Index (SDAI); depression was assessed using the Hamilton Depression Rating Scale (HAM-D); ADL was assessed using the Health Assessment Questionnaire; and QOL was assessed using the Short Form (SF)-36. Serum OXT levels were determined using enzyme-linked immunosorbent assay.

Results: The HAM-D score significantly correlated with the SDAI, and the mental component summary (MCS) score of SF-36. However, the serum OXT levels did not correlate with the HAM-D score. Regression analysis using the HAM-D score as the objective variable identified female sex, smoking, BMI, and all the three component scores of SF-36, but not serum OXT levels, as significant factors. Comparisons between before and after treatment showed that the HAM-D score improved from 5 to 1.5; however, the serum OXT levels did not change.

Conclusion: The variables of female sex, smoking, BMI, and QOL correlated with depression complicated with RA. However, serum OXT levels did not correlate directly.

Keywords: Rheumatoid arthritis, serum oxytocin level, depression

ORCID ID of the corresponding author:
Y.M. 0000-0001-5956-7974.

Cite this article as: Miwa Y, Furuya H, Yanai R, Kasama T, Sanada K. Is the serum oxytocin level altered by treatment in rheumatoid arthritis patients complicated with depression? Eur J Rheumatol 2018; 5: 22-6.

[1] Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan
[2] Department of Psychiatry, Showa University School of Medicine, Tokyo, Japan

Address for Correspondence:
Yusuke Miwa, Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

E-mail: y.miwa@mbf.ocn.ne.jp

Submitted: 22 January 2017
Accepted: 12 July 2017
Available Online Date: 22 January 2018

Introduction

In rheumatoid arthritis (RA) patients, there are various complications. Depression is the most common complication of RA, constituting approximately 15% of all complications (1). The odds ratio of depression in RA patients is 1.42 (95% confidence interval [CI]: 1.3, 1.5) relative to healthy people (2). Biological agents for the treatment of RA are known to be highly effective in reducing the disease activity as well as the severity of depression as a complication of RA (3).

The level of oxytocin (OXT), also referred to as a happy hormone, is reported to be reduced in various psychiatric diseases, such as depression, bipolar disorder, schizophrenia, autism, eating disorder, developmental disorder, and social anxiety disorder (4-12). There are also reports that the level of OXT is elevated by antidepressant treatment or electroconvulsive therapy (5). In autoimmune diseases, there are reports of a mood disorder in patients with Sjogren's syndrome and fibromyalgia (13, 14). However, there is no report of the relationship between depression and serum OXT levels in RA patients.

Therefore, our aim was to investigate the relationship between serum OXT levels and depression and disease activity in RA.

Methods

Participants

The study used a cross-sectional design. The research period was from January 1, 2013, to June 30, 2016. The single-center study was conducted in the Division of Rheumatology, Department of Medicine,

Showa University Hospital. A total of 131 RA patients included in the registry (all RA patients at Showa University; ASHURA Registry) using biological agents at Showa University Hospital participated in this study. The criteria of RA classification complied with the 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria (15). Variables were measured before the start of treatment and after 6 months of treatment with the biological agent. The studied variables included patient background, age, sex, disease duration, smoking history, history of use of the biological agent, body mass index (BMI), dosage of prednisolone, dosage of methotrexate (MTX), serum matrix metalloprotease-3 (MMP-3) level, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. The disease activity of RA was evaluated using the Simplified Disease Activity Index (SDAI); depressive status was evaluated using the Hamilton Depression Rating Scale (HAM-D); activities of daily living (ADL) were assessed using the Health Assessment Questionnaire (HAQ); and quality of life (QOL) was assessed using Short Form-36 (SF-36) (16-20). SF-36 was analyzed by dividing it into three summary scores: the physical component summary (PCS), the mental component summary (MCS), and the role/social component summary (RCS). The assessment using the HAM-D was conducted under the guidance of SK.

Table 1. Background summary of demographics and baseline characteristics of 42 RA patients

Age (years)		56 (42-67) n=42
Sex (female:male)		33:9
BMI		21 (20-23) n=42
Smoking history (yes: no)		14:28
Biologic-naive or switch		30:12
Disease duration (years)		3.5 (1.0-11.8) n=42
Prednisolone dosage(mg/d)		0 (0-5) n=42
MTX dosage (mg/w)		9 (6-10) n=42
ESR (mm/H)		20 (8-45) n=42
CRP (mg/dL)		0.56 (0.24-2.2) n=42
Serum MMP-3 level (ng/mL)		122 (73-290) n=42
Serum OXT level (pg/mL)		75 (58-90) n=42
SDAI		21 (14-29) n=42
TJC		4.5 (3-7) n=42
SJC		3 (2-4) n=42
PtGA (VAS, mm)		60 (40-73) n=42
PGA (VAS, mm)		55 (24-76) n=42
HAQ-DI		0.44 (0-0.88) n=42
HAM-D		5 (2.3-8) n=42
SF-36	PCS	33.5 (22.4-40.9) n=40
	MCS	51.6 (46.3-54.6) n=40
	RCS	50.2 (33.9-60.4) n=40

RA: rheumatoid arthritis; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MMP-3: matrix metalloprotease-3; MTX: methotrexate; OXY: oxytocin; SDAI: simplified disease activity index; TJC: tender joint count; SJC: swollen joint count; PtGA: patient's global assessment; PGA: physician's global assessment; VAS: visual analog scale; HAQ-DI: Health Assessment Questionnaire Disability Index; HAM-D: Hamilton Depression Rating Scale; SF-36: Short Form-36; PCS: physical component summary; MCS: mental component summary; RCS: role/social component summary

Exclusion criteria included patients using antidepressants, pregnant women, lactating patients, and patients complicated with diseases apart from depression affecting serum OXT levels (bipolar disorder, schizophrenia, autism, eating disorders, developmental disorder, and social anxiety disorder). There were no restrictions on the use of other anti-rheumatic drugs or nonsteroidal anti-inflammatory drugs. There were no limits on age or disease duration. Patients who requested to stop the examination and patients judged as inappropriate for the study by the doctors were excluded.

Serum OXT measurements

The serum obtained at the baseline assessment was stored at normal temperature for 30 min, centrifuged at 1,500 rpm for 10 min, and then stored at -80°C until analysis. Serum OXT levels were measured using enzyme-linked immunosorbent assay (ELISA) (Catalog No. ADI-900-153A; ENZO Life Sciences, Farmingdale, NY, USA). Blood samples were collected in the morning because serum OXT levels show a diurnal variation. The solid-phase extraction of the serum samples was performed to eliminate the effects of potentially interacting molecules, as described previously (21). Briefly, an equal volume (125 µL) of 0.1% trifluoracetic acid in water (TFA-H_2O) was added to the serum sample (125 µL) and centrifuged at 17,000 g for 15 min at 4°C and the supernatant was collected. A C18 Sep-Pak column (200 mg; Bachem, San Carlos, CA, USA) was equilibrated with 1 mL of acetonitrile, and subsequently equilibrated 4 times with 3 mL of 0.1% TFA-H_2O. The supernatant was applied to the C18 Sep-Pak column and washed 4 times with 3 mL of 0.1% TFA-H_2O, and the flow-through fraction was discarded. The sample was eluted slowly by applying a 3-mL solution of 60% acetonitrile and 40% 0.1% TFA-H_2O, followed by collection in a plastic tube. Thereafter, the solvent was evaporated using a vacuum centrifugal concentrator at 4°C and stored at -20°C until analysis.

Table 2. Correlation coefficient between HAM-D and other factors

	r
SDAI	0.412
SF-36 (MCS)	-0.555
TJC	0.391
PtGA	0.380
PGA	0.391
HAQ-DI	0.347
Serum OXT level	0.083

TJC: tender joint count; PtGA: patient's global assessment; PGA: physician's global assessment; HAQ-DI: Health Assessment Questionnaire Disability Index; OXT: oxytocin; SDAI: simplified disease activity index; HAM-D: Hamilton Depression Rating Scale; SF-36: Short Form-36; MCS: mental component summary

Statistical analysis

Analysis methods were as follows: (1) correlation between HAM-D and each parameter, (2) multiple regression analysis with HAM-D as the objective variable, and (3) comparison between before and after treatment with a biological agent. All of the statistical analyses were performed using univariate and multivariate analyses in the JMP12.2 software program (SAS Institute Inc., Cary, NC, USA). We obtained written informed consent from all of the patients who enrolled in the study. The study received approval from the Bio-Ethics Committee of the Department of Medicine, Showa University School of Medicine (No. 1950).

Results

Of the 131 patients considered for the study, 42 were excluded because of primary failure, secondary failure, complications, lack of data, lack of serum samples, transfer, withdrawal from the study, and other circumstances.

Patient background data were as follows: the median patient age was 56 years (interquartile range [IQR], 42-67 years); the female:male ratio was 33:9; the SDAI was 21 (IQR, 14-29), reflecting a group of patients with moderate disease activity. The serum OXT level was 75 pg/mL (IQR, 58-90 pg/mL), and the depressed status on the HAM-D was 5 (IQR, 2.3-8; Table 1).

The SDAI (r=0.412) and MCS score (r=-0.555) on the SF-36 had a significant correlation with the HAM-D score. The tender joint count (TJC; r=0.391), patient's global assessment (PtGA; r=0.380), physician's global assessment (PGA; r=0.391), and HAQ score (r=0.347) had a weak correlation with the HAM-D score. However, the

serum OXT levels were not significantly correlated with the HAM-D score (r=0.083; Table 2).

In the multiple regression analysis with HAM-D as the objective variable, sex (p=0.042, 95% CI: 0.12, 6.07); BMI (p=0.049, 95% CI: -0.77, -0.05); smoking status (p=0.025, 95% CI: -0.54, -0.01); and the PCS (p=0.002, 95% CI: -0.31, -0.08); MCS (p=0.000, 95% CI: -0.66, -0.35); and RCS (p=0.004, 95% CI: -0.14, -0.03) components of SF-36, but not serum OXT levels (p=0.073, 95% CI: -0.05, 0.00) were identified as significant factors (Table 3).

The comparison between before and after treatment with a biological agent showed improvement in the HAM-D score from 5 (2.25-8) before treatment to 1.5 (0.75-2.25) after treatment (p=0.000). However, the serum OXT levels were unchanged from 75 (IQR, 58-90) pg/mL before treatment to 75 (IQR, 63-86) pg/mL after treatment (p=0.326). Thus, no treatment-induced improvement in serum OXT levels was observed (Table 4).

Table 3. Regression models for various factors of RA

Dependent Variable	HAM-D	R^2=0.6206	F=8.7659	p=0.0000	
Explanatory variable	Unbalanced recurrence coefficient	Standard unbalanced recurrence coefficient	95% CI	p	VIF
sex	3.0973	0.2773	0.12, 6.07	0.042	1.7053
BMI	-0.4132	-0.2664	-0.77, -0.05	0.049	1.2849
smoking	-2.7071	-0.2879	-0.54, -0.01	0.025	1.9794
PCS	-0.1905	-0.5919	-0.31, -0.08	0.002	3.0722
MCS	-0.5015	-1.0040	-0.66, -0.35	0.000	2.3278
RCS	-0.0882	-0.3500	-0.14, -0.03	0.004	1.2709
Serum OXT level	-0.0251	-0.2112	-0.05, 0.00	0.073	1.2903

Multiple regression analysis was used

BMI: body mass index; PCS: physical component summary score; MCS: mental component summary Score; RCS: role/social component summary score; OXT: oxytocin; VIF: variance inflation factor; RA: rheumatoid arthritis; CI: confidence interval; HAM-D: Hamilton Depression Rating Scale

Table 4. HAM-D and serum OXT levels before and after treatment

	Before	After 6 months	p
HAM-D	5 (2.25-8)	1.5 (0.75-2.25)	0.000
Serum OXT level	75 (58-90)	75 (63-86)	0.326

Analysis using Wilcoxon Signed-rank test median (interquartile range)

HAM-D: Hamilton Depression Rating Scale; OXT: oxytocin

Discussion

Although the factors of depression, sex, BMI, smoking status, and QOL were correlated with RA in the study cohort, serum OXT levels were not correlated with RA in this study. The level of OXT, also known as a happy hormone, is reported to be reduced in various psychiatric diseases such as depression (4, 5). There are reports that intranasal administration of OXT improves refractory major depression (22).

Several studies in recent years have evaluated OXT levels using ELISA from the ENZO kit. Hence, we used ELISA and radioimmunoassay (RIA) for the assessment of serum OXT levels were. In previous reports, serum OXT levels were reported to be 69.5±32.7 pg/mL in women with post-traumatic stress disorder (PTSD) associated with a traffic accident, 101.59±55.89 pg/mL in those with PTSD associated with other events, and 100±35 pg/mL in those with schizophrenia (23-25). In children, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are reported to be associated with OXT levels (26-29). Depression was reported to be associated with OXT levels only based on the RIA method (5, 30, 31). Of all the collagen diseases, fibromyalgia is the only disease for which

Table 5. Clinical feature of serum OXT levels

Author	Year	Disease	Age	Sex	Serum OXT level	Unit	Method	Reference
Nishi D	2014	PTSD	44.9±15.6	Female	69.5±32.7	pg/mL	ELISA	23
			34.8±14.4	Male	65.5±23.3	pg/mL	ELISA	
Cao C	2014	PTSD	no data	Male	101.6±55.9	pg/mL	ELISA	24
Goldman	2008	Schizophrenia	44.7±2.4	Both	100±35	pg/mL	ELISA	25
Sasaki T	2015	ADHD	6-15	Both	60.7±37.1	pg/mL	ELISA	26
Demirci E	2016	ADHD	7-18	Both	37.62±9	μIU/mL	ELISA	27
Husarova VM	2016	ASD	2-9	Both	124.1±90.6	pg/mL	ELISA	28
Jansen	2006	ASD	21.8±2.0	Both	21.8±2.0	pg/mL	ELISA	29
Ozsoy S	2009	Depression	42.5±12.8	Female	8.98±7.28	ng/mL	RIA	5
				Male	5.70±4.54	ng/mL	RIA	
Parker KJ	2010	Depression	40.6±14.7	Both	1.2±0.2	ng/mL	RIA	30
Scantamburlo G	2007	Depression	19-59	Both	3.67±1.34	ng/mL	RIA	31
Anderberg UM	2000	Fibromyalgia	27-61	Both	15±5	pmol/L	RIA	14
Kunitake Y	2016	Healthy elderly	65-	Male	50±38	pg/mL	EIA	32

Mean±standard deviation values or range is used

OXT: oxytocin; PTSD: Post-traumatic stress disorder; ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; ELISA: enzyme-linked immunosorbent assay; RIA: immunoassay; EIA: enzyme immunoassay

the OXT levels have been 14, and OXT levels have not been reported in patients with RA. In healthy subjects, OXT levels were 140±133 pg/mL for elderly women and 50±38 pg/mL for elderly men (32) (Table 5).

In this study, we speculated that the disease activity of RA would be decreased, the depression status would be improved, and the serum OXT levels would be increased following treatment with the biological agent. However, the results showed no difference in serum OXT levels between before and after treatment. There are several reasons that may account for this finding. The HAM-D score before the start of treatment was not high and was not stratified by the presence or absence of a depressive state. The serum OXT levels in RA patients before treatment were not low compared to those with other diseases or healthy individuals. The normal range of serum OXT levels in RA patients is unknown and did not correlate with depression that is a complication of RA. Moreover, drugs used to treat RA may affect OXT levels.

Our study had 4 limitations. First, the number of valid analysis cases was low (42 cases); thus, the small sample size may have contributed to a lack of statistical significance of the results. Second, we did not perform a radiographic evaluation of the joints, although we are aware that a radiographic evaluation is expected to influence depression. Third, no socioeconomic factors were included in our analysis. Fourth, the history of major depression was not examined.

Rheumatoid arthritis complicated with depression may be related to the following variables: female sex, a history of smoking, low BMI, and poor QOL. However, serum OXT levels may not be directly related to RA complicated with depression.

Ethics Committee Approval: The study received approval from the Bio-Ethics Committee of the Department of Medicine, Showa University School of Medicine (No. 1950).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.M., H.F., R.Y., T.K., K.S.; Design - Y.M., H.F., R.Y., T.K., K.S.; Analysis and/or Interpretation - Y.M., K.S.; Execution of Data - H.F., R.Y., T.K.; Writing Manuscript - Y.M., H.F., R.Y., T.K., K.S.; Critical Review - Y.M., H.F., R.Y., T.K., K.S.

Acknowledgements: We would like to thank all members of the Showa University Rheumatoid Arthritis Group (ASHURA groups).

Conflict of Interest: Yusuke Miwa received research grants from Astellas Pharma Inc., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., and Chugai Pharmaceutical Co., Ltd. Tsuyoshi Kasama received research grants from Mitsubishi Tanabe Pharma Corporation and AbbVie CK. The other authors declare that they have no potential conflicts of interest to disclose.

Financial Disclosure: This work was supported by JSPS KAKENHI Grant.

References

1. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis 2014; 73: 62-8. [CrossRef]
2. Margaretten ME, Katz P, Schmajuk G, Yelin E. Missed opportunities for depression screening in patients with arthritis in the United States. J Gen Intern Med 2013; 28: 1637-42. [CrossRef]
3. Miwa Y, Isojima S, Saito M, Ikari Y, Kobuna M, Hayashi T, et al. Comparative Study of Infliximab Therapy and Methotrexate Monotherapy to Improve the Clinical Effect in Rheumatoid Arthritis Patients. Intern Med 2016; 55: 2581-5. [CrossRef]
4. Cochran DM, Fallon D, Hill M, Frazier JA. The role of oxytocin in psychiatric disorders: a review of biological and therapeutic research findings. Harv Rev Psychiatry 2013; 21: 219-47. [CrossRef]
5. Ozsoy S, Esel E, Kula M. Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment. Psychiatry Res 2009; 169: 249-52. [CrossRef]
6. Rotzinger S, Lovejoy DA, Tan LA. Behavioral effects of neuropeptides in rodent models of depression and anxiety. Peptides 2010; 31: 736-56. [CrossRef]
7. Strauss GP, Keller WR, Koenig JI, Gold JM, Frost KH, Buchanan RW. Plasma oxytocin levels predict social cue recognition in individuals with schizophrenia. Schizophr Res 2015; 162: 47-51. [CrossRef]
8. Shin NY, Park HY, Jung WH, Park JW, Yun JY, Jan JH, et al. Effects of Oxytocin on Neural Response to Facial Expressions in Patients with Schizophrenia. Neuropsychopharmacology 2015; 40: 1919-27. [CrossRef]
9. Abdulamir HA, Abdul-Rasheed OF, Abdulghani EA. Low oxytocin and melatonin levels and their possible role in the diagnosis and prognosis in Iraqi autistic children. Saudi Med J 2016; 37: 29-36. [CrossRef]
10. Lawson EA, Holsen LM, Santin M, DeSanti R, Meenaghan E, Eddy KT. Postprandial oxytocin secretion is associated with severity of anxiety and depressive symptoms in anorexia nervosa. J Clin Psychiatry 2013; 74: e451-7. [CrossRef]
11. Xu XJ, Zhang HF, Shou XJ, Li J, Jing WL, Zhou Y, et al. Prenatal hyperandrogenic environment induced autistic-like behavior in rat offspring. Physiol Behav 2015; 138: 13-20. [CrossRef]
12. Hoge EA, Pollack MH, Kaufman RE, Zak PJ, Simon NM. Oxytocin levels in social anxiety disorder. CNS Neurosci Ther 2008; 14: 165-70. [CrossRef]
13. Karaiskos D, Mavragani CP, Sinno MH, Dechelotte P, Zintzaras E, Skopouli FN, et al. Psychopathological and personality features in primary Sjogren's syndrome-associations with autoantibodies to neuropeptides. Rheumatology (Oxford) 2010; 49: 1762-9. [CrossRef]
14. Anderberg UM, Uvnas-Moberg K. Plasma oxytocin levels in female fibromyalgia syndrome patients. Z Rheumatol 2000; 59: 373-9. [CrossRef]
15. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Binham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010; 69: 1580-8. [CrossRef]
16. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum 2005; 52: 2625-36. [CrossRef]
17. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23: 56-62. [CrossRef]
18. Ziebland S, Fitzpatrick R, Jenkinson C, Mowat A, Mowat A. Comparison of two approaches to measuring change in health status in rheumatoid arthritis: the Health Assessment Questionnaire (HAQ) and modified HAQ. Ann Rheum Dis 1992; 51: 1202-5. [CrossRef]
19. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. J Clin Epidemiol 1998; 51: 1037-44. [CrossRef]
20. Fukuhara S, Ware JE, Jr., Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. J CLin Epidemiol 1998; 51: 1045-53. [CrossRef]
21. Nishi D, Hashimoto K, Noguchi H, Matsuoka Y. Serum neuropeptide Y in accident survivors with depression or posttraumatic stress disorder. Neurosci Res 2014; 83: 8-12. [CrossRef]
22. Scantamburlo G, Hansenne M, Geenen V, Legros JJ, Ansseau M. Additional intranasal oxytocin to escitalopram improves depressive symptoms in resistant depression: an open trial. Eur Psychiatry 2015; 30: 65-8. [CrossRef]
23. Nishi D, Hashimoto K, Noguchi H, Kim Y, Matsuoka Y. Serum oxytocin, posttraumatic coping and C-reactive protein in motor vehicle accident survivors by gender. Neuropsychobiology 2015; 71: 196-201. [CrossRef]
24. Cao C, Wang L, Wang R, Qing Y, Zhang J. Oxytocin is associated with PTSD's anxious arousal symptoms in Chinese male earthquake survivors. Eur J Pssychotraumatol 2014; 5: 26530. [CrossRef]
25. Goldman M, Marlow-O'Connor M, Torres I, Carter CS. Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits. Schizophr Res 2008; 98: 247-55. [CrossRef]
26. Sasaki T, Hashimoto K, Oda Y, et al. Decreased levels of serum oxytocin in pediatric patients with Attention Deficit/Hyperactivity Disorder. Psychiatry Res 2015; 228: 746-51. [CrossRef]

27. Demirci E, Ozmen S, Kilic E, Oztop DB. The relationship between aggression, empathy skills and serum oxytocin levels in male children and adolescents with attention deficit and hyperactivity disorder. Behav Pharmacol 2016; 27: 681-8. [CrossRef]
28. Husarova VM, Lakatosova S, Pivovarciova A, Babinska K, Bakos J, Durdiakova J, et al. Plasma Oxytocin in Children with Autism and Its Correlations with Behavioral Parameters in Children and Parents. Psychiatry Investig 2016; 13: 174-83. [CrossRef]
29. Jansen LM, Gispen-de Wied CC, Wiegant VM, Westenberg HG, Lahuis BE, van Engeland H. Autonomic and neuroendocrine responses to a psychosocial stressor in adults with autistic spectrum disorder. J Autism Dev Disord 2006; 36: 891-9. [CrossRef]
30. Parker KJ, Kenna HA, Zeitzer JM, Keller J, Blasey CM, Amico JA, et al. Preliminary evidence that plasma oxytocin levels are elevated in major depression. Psychiatry Res 2010; 178: 359-62. [CrossRef]
31. Scantamburlo G, Hansenne M, Fuchs S, Pitchot W, Marechal P, Pegueux C, et al. Plasma oxytocin levels and anxiety in patients with major depression. Psychoneuroendocrinology 2007; 32: 407-10. [CrossRef]