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【 ORIGINAL ARTICLE 】

The Relationship between the Serum Oxytocin Levels, Disease Activity, the ADLs and the QOL in Patients with Rheumatoid Arthritis

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Abstract:

Objective To investigate the factors associated with depression, including the serum oxytocin (OXT) levels, disease activity, activities of daily living (ADLs) and quality of life (QOL), and their effects on rheumatoid arthritis (RA).

Methods This study included 42-RA-patients. We measured the following variables before and after 6 months of treatment with biological disease-modifying antirheumatic drugs (bDMARDs): the baseline characteristics (including age, sex, disease duration, smoking, and body mass index), the doses of prednisolone and methotrexate, the serum level of matrix metalloprotease-3, the erythrocyte sedimentation rate and the C-reactive protein 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), the ADLs were assessed using the Health Assessment Questionnaire disability index and the QOL was assessed using the Short Form (SF)-36. The serum OXT levels were determined using an enzyme-linked immunosorbent assay.

Results The HAM-D score was significantly correlated with the SDAI, and the mental component summary score of the SF-36. However, the serum OXT levels were not correlated with the HAM-D score. The serum OXT levels before and after bDMARDs treatment did not differ to a statistically significant extent, regardless of the presence of depression. Although the differences in the serum levels of OXT were observed prior to the initiation of treatment, there was no gender difference after treatment.

Conclusion Although RA complicated by depression may be related to the following high disease activity, a poor QOL and poor ADLs, the serum OXT levels were not directly correlated.

Key words: rheumatoid arthritis, serum oxytocin level, depression

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Introduction

Rheumatoid arthritis (RA) patients suffer from various complications. Depression, which accounts for approximately 15% of all complications, is the most common complication of RA (1). The odds ratio for depression in RA patients was 1.42 (95% confidence interval (CI): 1.3, 1.5; relative to healthy individuals) (2). The treatment of RA with biological disease-modifying antirheumatic drugs (bDMARDs) is known to be highly effective in reducing the disease activity as well as the severity of depression that occurs in association with RA (3).

The oxytocin (OXT) level-also referred to as the "happy hormone"-is reported to be decreased in various psychiatric diseases such as depression (4, 5), bipolar disorder (6), schizophrenia (7, 8), autism (9), eating disorders (10), developmental disorders (11) and social anxiety disorder (12). In some diseases, the OXT levels are reported to be increased or decreased, with no consistent pattern across studies. With regard to autoimmune disease, depression, anxiety and hypochondriasis have been reported in patients with Sjögren's

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syndrome (13) and depression has been reported in patients with fibromyalgia (14). However, there has been no previous reports on the relationship between depression and the serum OXT levels in RA patients.

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

Materials and Methods

Participants

The study used a cross-sectional design. The study period was from October 1, 2005, to June 30, 2016. This multicenter study involved the Division of Rheumatology, Department of Medicine, Showa University Hospital; Showa University Koto-Toyosu Hospital; and Showa University Northern Yokohama Hospital. A total of 391 RA patients who were included in the registry (All RA patients at Showa University; ASHURA Registry) and who were reported to have undergone bDMARDs treatment at Showa University Hospital, participated in the present study. The criteria for the classification of RA complied with the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria (15). The variables were measured before the initiation of bDMARD treatment and after 6 months of treatment with bDMARDs. The variables that were investigated included the patient background, age, sex, body mass index (BMI), smoking history, history of bDMARD treatment, disease duration, dose of prednisolone, dose of methotrexate (MTX), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level and serum matrix metalloprotease-3 (MMP-3) level. The disease activity of RA was evaluated using the Simplified Disease Activity Index (SDAI) (16), depression was evaluated using the Hamilton Depression Rating Scale (HAM-D) (17), the activities of daily living (ADLs) were assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI) (18), and the quality of life (QOL) was assessed using the Short Form-36 (SF-36) (19, 20). The SF-36 results were analyzed according to three summary scores: the physical component summary (PCS), the mental component summary (MCS) and the role/social component summary (RCS). The HAM-D assessment was conducted under the guidance of SK. Patients were classified into two groups (depression vs. no depression), with depression defined as a HAM-D score of ≥8.

The exclusion criteria were as follows: antidepressant use, pregnancy, lactation and comorbidities aside from depression affecting the serum OXT level (bipolar disorder, schizophrenia, autism, eating disorders, developmental disorders and social anxiety disorder). There were no restrictions on the use of other antirheumatic drugs or nonsteroidal anti-inflammatory drugs. There were no limits on age or disease duration. Patients who requested that the examination be stopped and patients who were judged by a doctor to be inappropriate for the study were excluded.

The measurement of serum OXT

The serum samples obtained at the baseline assessment were stored at normal temperature for 30 minutes, centrifuged at 1,500×*g* for 10 minutes and then stored at -80℃ until the analysis. The serum OXT levels were measured using an enzyme-linked immunosorbent assay (ELISA) (Catalog No. ADI-900-153A; ENZO Life Sciences, Farmingdale, USA). Blood samples were collected in the morning because the serum OXT levels exhibit 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 minutes at 4℃, after which the supernatant was collected. A C18 Sep-Pak column (200 mg; Bachem, San Carlos, USA) was equilibrated with 1 mL of acetonitrile and then 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; 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. Next, the solvent was evaporated at 4℃ using a vacuum centrifugal concentrator and was stored at -20℃ until analysis.

Statistical analyses

We analyzed (1) the differences in background characteristics due to the presence or absence of depression (2), the correlation coefficients between HAM-D and the other factors (3), the correlation coefficients between the serum OXT levels and other factors, and (4) the serum OXT levels before and after bDMARD treatment. The following statistical analyses were performed: a Mann-Whitney U test, chi-squared test, Pearson's moment correlation coefficient and a repeated-measure analysis of variance (ANOVA). The JMP Pro 13.0 software program (SAS Institute, Cary, USA) was used to perform all of the statistical analyses. 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 391 patients in the ASHURA Registry considered for the study, 349 patients were excluded due to primary failure, secondary failure, complications, lack of data, lack of serum samples, transfer, withdrawal from the study, or other circumstances.

At the baseline, 42 patients were included; 12 were complicated by depression and 30 were not complicated by depression. The median SDAI among patients with depression was 24 (interquartile range, 20-31), and differed significantly from that in patients without depression (p=0.035).

Table 1. Summary of Demographics and Baseline Characteristics of 42 RA Patients.

		with depression	without depression	p
n		12	30	
Age (years)		62 (50-72)	51 (40-63)	0.079*
Sex (female: male)		10:2	23:7	0.491**
Body mass index		21 (20-23)	21 (20-23)	0.606*
Smoking history (yes : no)		6:6	22:8	0.277**
bDMARD-naïve or switch		7:5	23:7	0.938**
Disease duration (years)		8.5 (3.5-24.3)	2 (0.90-6.3)	0.210*
Prednisolone dosage (mg/d)		1 (0-5)	0 (0-5)	0.581*
MTX dosage (mg/w)		9 (5.5-10)	9 (6.5-11.5)	0.541*
ESR (mm/H)		30 (11-54)	17 (8-43)	0.411*
CRP (mg/dL)		1.3 (0.31-3.7)	0.56 (0.2-1.5)	0.427*
Serum MMP-3 level (ng/mL)		151 (84-378)	114 (65-191)	0.316*
Serum OXT level (pg/mL)		76 (59-81)	74 (58-93)	0.796*
SDAI		24 (20-31)	20 (13-27)	0.035*
TJC		6 (4.75-12.75)	4 (3-6.75)	0.079*
SJC		2 (2-4)	3 (2-4)	0.362*
PtGA (VAS, mm)		64 (58.75-73.5)	54.5 (24.25-69.5)	0.094*
PGA (VAS, mm)		71 (41.25-76)	38 (22.5-74.25)	0.315*
HAQ-DI		0.8125 (0.125-1.625)	0.375 (0-0.75)	0.055*
HAM-D		10 (9-12.25)	3 (1-5)	0.000*
SF-36	PCS	31 (22-36) n=11	34 (23-42) n=29	0.671*
	MCS	48 (36-52) n=11	53 (48-55) n=29	0.101*
	RCS	37 (34-46) n=11	57 (35-62) n=29	0.214*

median (interquartile range). bDMARDs: biological disease-modifying antirheumatic drugs, MTX: methotrexate, ESR: erythrocyte sedimentation rate, MMP-3: matrix metalloproteinase-3, OXT: oxytocin, SDAI: simplified disease activity index, TJC: tender joint count, SJC: swollen joint count, PtGA: patient's global assessment, PGA: physician's global assessment, 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, *analysis using a Mann-Whitney U test, **analysis using a chi-squared test for independence

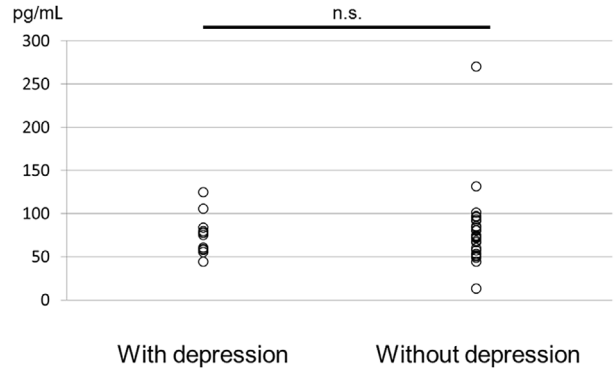

Figure. The serum OXT levels before bDMARD treatment.

However, the serum OXT levels and the other parameters of the two groups did not differ to a statistically significant extent (Table 1, Figure).

The SDAI (r=0.422, p=0.008) and the MCS score (r=-0.555, p=0.000) on the SF-36 were significantly correlated with the HAM-D score. The tender joint count (TJC) (r=0.390, p=0.014), the patient's global assessment (PtGA) (r=0.380, p=0.017), the physician's global assessment (PGA) (r=0.391, p=0.014), and the HAQ-DI (r=0.347, p=0.031) were weakly correlated with the HAM-D score. However, the serum OXT levels were not significantly correlated with the HAM-D score (r=0.083, p=0.617) and no other factors were significantly correlated with the serum OXT levels (Table 2).

The serum OXT levels before and after bDMARD treatment, did not differ to a statistically significant extent, regardless of the presence of depression. Thus, no treatments were observed to improve the serum OXT levels (Table 3, 4). Although differences in the serum levels of OXT prior to the initiation of treatment were observed between men [median, 65 (25-75% quartile, 53-70)] and women [83 (60-94); p=0.045], there was no gender difference in OXT levels after treatment (data not shown). No gender difference was observed in the serum OXT levels of patients with or without depression.

Discussion

In this report, we first measured the serum OXT levels in RA patients. Although disease activity, the MCS in SF-36, TJC, PtGA, PGA and HAQ-DI were found to be correlated with depression in RA, the serum OXT levels were not.

Table 2. Correlation Coefficient between Serum OXT Levels, HAM-D Score and Other Factors.

		OXT		HAM-D	
		r	p	r	p
Age (years)		-0.026	0.874	0.253	0.121
Sex (female)		0.206	0.208	-0.021	0.898
Body mass index		0.046	0.782	-0.090	0.586
Smoking history (yes)		0.143	0.385	-0.248	0.129
bDMARD-naïve		-0.091	0.821	0.027	0.872
Disease duration (years)		-0.055	0.741	0.153	0.353
Prednisolone dosage (mg/d)		0.029	0.860	0.286	0.077
MTX dosage (mg/w)		0.255	0.117	0.113	0.492
ESR (mm/H)		-0.254	0.119	0.109	0.509
CRP (mg/dL)		-0.235	0.151	0.171	0.299
Serum MMP-3 level (ng/mL)		-0.099	0.549	0.159	0.334
Serum OXT level		Ref		0.083	0.617
SDAI		-0.055	0.741	0.422	0.008
TJC		0.037	0.823	0.390	0.014
SJC		-0.252	0.122	-0.093	0.575
PtGA (VAS, mm)		0.197	0.228	0.380	0.017
PGA (VAS, mm)		0.013	0.937	0.391	0.014
HAQ-DI		0.101	0.540	0.347	0.031
HAM-D		0.083	0.617	Ref	
SF-36	PCS	-0.099	0.551	-0.165	0.316
	MCS	-0.261	0.109	-0.555	0.000
	RCS	0.015	0.926	-0.165	0.315

Analyses by Pearson's moment correlation coefficient. MTX: methotrexate, ESR: erythrocyte sedimentation rate, MMP-3: matrix metalloproteinase-3, OXT: oxytocin, SDAI: simplified disease activity index, TJC: tender joint count, SJC: swollen joint count, PtGA: patient's global assessment, PGA: physician's global assessment, 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

Table 3. Serum OXT Levels and HAM-D Score before and after bDMARD Treatment.

	OXT		HAM-D	
	Before	After 6 months	Before	After 6 months
With depression	76 (59-81)	68 (56-74)	10 (9-12.25)	2 (2-7.5)
Without depression	74 (58-93)	77 (66-88)	3 (1-5)	1 (0-2)

Median (interquartile range). OXT: oxytocin, HAM-D: Hamilton Depression Rating Scale, bDMARD: biological disease-modifying antirheumatic drug

Table 4. Serum OXT Levels before and after bDMARDs Treatment.

	f value	p value	f value (0.95)
Interaction	0.102	0.752	4.085
Interindividual variation	0.659	0.422	4.085
Individual variation	0.729	0.398	4.085

Analysis by repeated measure ANOVA. OXT: oxytocin, bDMARD: biological disease-modifying antirheumatic drug, ANOVA: analysis of variance

The level of OXT, also known as the "happy hormone", is reported to be decreased in various psychiatric diseases, including depression (4, 5). It has been reported that the intranasal administration of OXT improves refractory major depression (22). The methods of assessing the serum OXT level included an ELISA and a radioimmunoassay (RIA). In recent years, most reports evaluated the serum OXT levels via an ELISA using a kit from ENZO; thus, an ELISA was used in the present study.

In previous reports, the serum OXT levels in women with post-traumatic stress disorder (PTSD) associated with a traffic accident, PTSD associated with other events, and women with schizopherenia were reported to be 69.5±32.7 pg/mL (23), 101.59±55.89 pg/mL (24), and 100±35 pg/mL (25), respectively. Attention deficit hyperactivity disorder (ADHD) (26, 27) and autism spectrum disorder (ASD) (28, 29) in children as well as treatment-resistant depression in adolescents (30) are reported to be associated with OXT levels. Depression was only reported to be associated with OXT levels based on the RIA method (5, 31, 32).

Table 5. Serum Oxytocin Levels across Clinical Conditions.

Reference	Disease	Age	Sex	Serum OXT Level	Unit	Method
21	PTSD	44.9 ± 15.6	female	69.5 ±32.7	pg/mL	ELISA
		34.8 ± 14.4	male	65.5 ± 23.3	pg/mL	ELISA
24	PTSD	no data	male	101.6 ± 55.9	pg/mL	ELISA
25	Schizophrenia	44.7 ± 2.4	both	100 ± 35	pg/mL	ELISA
26	ADHD	6-15	both	60.7 ± 37.1	pg/mL	ELISA
27	ADHD	7-18	both	37.62 ± 9	μIU/mL	ELISA
28	ASD	2-9	both	124.1 ± 90.6	pg/mL	ELISA
29	ASD	21.8 ± 2.0	both	21.8 ± 2.0	pg/mL	ELISA
30	TRDIA	14.40 ± 1.71	both	394.3 ± 371.23	pg/mL	ELISA
	non-TRDIA	12.89 ± 1.99	both	94.34 ± 31.24	pg/mL	ELISA
5	Depression	42.5 ± 12.8	female	8.98 ± 7.28	ng/mL	RIA
			male	5.70 ± 4.54	ng/mL	RIA
31	Depression	40.6 ± 14.7	both	1.2 ± 0.2	ng/mL	RIA
32	Depression	19-59	both	3.67 ± 1.34	ng/mL	RIA
14	Fibromyalgia	27-61	both	15 ± 5	pmol/L	RIA
33	Healthy elderly	65-	male	50 ± 38	pg/mL	EIA
			female	140 ± 133	pg/mL	EIA

Mean ± standard deviation values or range are used. OXT: Oxytocin, PTSD: post traumatic stress disorder, ADHD: attention deficit hyperactivity disorder, TRDIA: treatment resistant depression in adolescents, ASD: autism spectrum disorder, ELISA: enzyme-linked immunosorbent assay, RIA: radioimmunoassay, EIA: enzyme immunoassay

The serum OXT levels show no fixed value and vary with disease, age, and gender. Fibromyalgia is the only connective tissue disease for which the OXT levels have been reported (14); the OXT levels have not been previously reported in patients with RA. In a study of healthy subjects, the OXT levels were in elderly women and men were 140± 133 pg/mL and 50±38 pg/mL, respectively (33) (Table 5). Although the serum OXT levels in RA patients were lower than those of healthy elderly subjects, the difference was small, even in comparison to other psychiatric diseases.

In this study, we hypothesized that after treatment with bDMARDs, the RA disease activity would decrease, the depression status would improve, and that the serum OXT levels would increase. Previous reports have suggested that OXT has an anti-inflammatory function (34). However, the results showed that there was no difference in the serum OXT levels before and after bDMARDs treatment.

There are several possible reasons for our unexpected results. First, it is possible that no significant difference was detected due to the low number of cases of RA with depression. The bDMARDs that were used to treat RA might have affected the OXT levels. The anti-inflammatory effect of oxytocin may not be involved in RA. The old age of the patients in comparison to other diseases for which reports are available makes comparisons difficult. Although a slight gender difference was observed in OXT levels before the start of bDMARD treatment, there was no gender difference after treatment. The serum OXT levels were higher in men with RA than in healthy elderly men but they were lower in women. It is important to note that there is no defined normal OXT level; it is therefore difficult to judge whether the levels in this patient population were high or low. The serum OXT level also varies according to disease, age, and sex; thus, it is necessary to study the serum OXT levels in a disease other than those that have been previously reported and to consider a large number of cases.

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

Conclusion

RA complicated with depression may be related to high disease activity, a poor QOL and poor ADLs. However, the serum OXT levels may not be directly related to RA complicated with depression.

Author's disclosure of potential Conflicts of Interest (COI).
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