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Level of glial cell derived neurotrophic factor in the blood plasma of rheumatoid arthritis patients and its relationship with alexithymia

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Abstract

Introduction: Glial cell derived neurotrophic factor (GDNF) has an important role in the pathogenetic mechanisms and clinical manifestations of rheumatoid arthritis (RA). Alexithymia is associated with a severe clinical course and worse prognosis, while the relationship between alexithymia and GDNF in RA patients has not been investigated before. The aims of the study were to investigate the GDNF level in blood plasma in RA patients depending on the presence of alexithymia and to evaluate the relationship of GDNF level with clinical manifestation and quality of life.

Material and methods: Fifteen men and 73 women with RA were examined using the Disease Activity Score with 28-joint count (DAS28) with erythrocyte sedimentation rate (ESR) index, the Simple Disease Activity Index (SDAI), the Rheumatoid Arthritis Clinical Disease Activity Index (CDAI), the Visual Analogue Scale (according to the assessment of the patient – VAS-P and the assessment of the doctor – VAS-D), the Health Assessment Questionnaire (HAQ), the Toronto Alexithymia Scale (TAS-20), the Disability Rating Index (DRI) and SF-36 indexes. Glial cell derived neurotrophic factor level in the blood plasma was determined by enzyme-linked immunosorbent assay (ELISA).

Results: Forty percent of RA patients had alexithymia. Glial cell derived neurotrophic factor level in the examined patients was 3.73 ±2.59 pg/ml, in patients with alexithymia 4.08 ±2.87 pg/ml, without alexithymia 3.48 ±2.37 pg/ml (p = 0.295). Patients with alexithymia had a higher erythrocyte sedimentation rate (ESR) and index scores than patients without alexithymia – ESR: 34.29 ±14.22 vs. 22.73 ±12.03 mm/h (p = 0.017), DAS28: 6.53 ±0.66 vs. 6.09 ±0.55 (p = 0.017), VAS-D: 7.19 ±0.81 vs. 6.53 ±0.83 (p = 0.020), HAQ: 1.78 ±0.58 vs. 1.51 ±0.54 (p = 0.040). Also they had worse SF-36 indicators – physical functioning: 39.52 ±13.78 vs. 51.00 ±14.90 (p = 0.019), role functioning due to physical condition: 30.95 ±20.77 vs. 46.67 ±24.76 (p = 0.041), physical component of health: 31.47 ±11.44 vs. 41.61 ±15.88 (p = 0.028). In patients with alexithymia, a correlation was found between the GDNF level and severity of pain according to VAS-P: r_S = 0.338, p = 0.044, and VAS-D: r_S = 0.446, p = 0.006.

Conclusions: Alexithymia was found in 40% of RA patients. Rheumatoid arthritis patients with alexithymia had a nonsignificantly higher GDNF level compared to patients without alexithymia. In RA patients with alexithymia, an association of GDNF level in the blood plasma with RA activity, loss of functional capacity and reduced quality of life was established. Alexithymia in RA patients is an important factor in the clinical manifestation of RA and modification of the pathophysiological role of GDNF.

Key words: rheumatoid arthritis, glial cell derived neurotrophic factor, alexithymia.

Introduction

Glial cell derived neurotrophic factor (GDNF) has an important role in the regulation of neuroinflammatory processes and pain syndrome of many diseases. Neuroinflammation causes GDNF expression in activated astrocytes and microglia, infiltrating macrophages, nestin-positive reactive astrocytes and neuroglial cells. Disease-related overexpression of GDNF can be compensatory and have a tissue-protective effect, as well as being harmful with negative consequences, depending on the location in the brain and the level and duration

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of glial cell activation [1]. Studies of GDNF have demonstrated its neuroprotective properties [2] and its ability to regulate dopamine metabolism and improve brain biodistribution [3]. The available data indicate an important role of GDNF in the regulation of the psycho-emotional sphere; the disturbance of the psycho-emotional sphere is quite often associated with chronic pain syndrome [4].

Alexithymia – difficulties with describing and verbalizing one's own emotions and sensations – belongs to disorders of the psycho-emotional sphere. Modern studies have shown the association of alexithymia with chronic pain [5], systemic autoimmune diseases [6] and pathological conditions with somatic symptoms of uncertain origin [7]. Rheumatoid arthritis (RA) patients are characterized by significantly higher scores of alexithymic scales [6]; alexithymia in these patients is closely related to the deterioration of the psycho-emotional state and the severity of chronic pain [8].

The relationship between alexithymia and GDNF level in the blood plasma of RA patients needs more detailed research. The results of the study may provide valuable information regarding the biological role of GDNF in RA and the details of the relationship between alexithymia and GDNF in the pathogenetic mechanisms of RA.

The aim of the study was to determine the level of GDNF in the blood plasma of RA patients according to the presence of alexithymia and evaluate the relationship of GDNF level with clinical manifestations and quality of life.

Material and methods

We examined 88 patients (15 men and 73 women) who were hospitalized at the Center of Rheumatology, Osteoporosis and Biological Therapy of the communal non-profit enterprise Vinnytsya Regional Clinical Hospital named after M.I. Pirogov. Diagnosis of RA was established according to the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria. For the measurement of plasma GDNF level, a total of 10 ml of blood was drawn from each participant. All blood samples were centrifuged and stored at –70°C immediately after collection. The GDNF in the blood plasma was determined by the ELISA method using the Human GDNF (Glial Cell Line Derived Neurotrophic Factor) ELISA Kit (Elabscience, USA, Lot CV09HB482125) according to the manufacturer's instructions. Rheumatoid arthritis activity was assessed by the DAS28 (ESR) index [9], the Simple Disease Activity Index (SDAI) [10] and the Rheumatoid Arthritis Clinical Disease Activity Index (CDAI) [11]. Pain intensity was assessed by the Visual Analogue Scale (according to the assessment of the patient – VAS-P and the assessment of the doctor – VAS-D) [12]. General state of health and functions was assessed according to the Health Assessment Questionnaire (HAQ) [13]. Alexithymia was revealed by the Ukrainian version of the Toronto Alexithymia Scale (TAS-20) [14]; if the value of the TAS-20 was above 60 points, alexithymia was established in patients. The disability was determined by the validated and cross-cultural adapted Ukrainian version of the Disability Rating Index (DRI) questionnaire [15]. Quality of life was assessed by the SF-36 Health Survey [16].

Statistical analysis

The differences were statistically evaluated using Fisher's and the Mann-Whitney non-parametric tests. Correlational analysis was performed by the Spearman rank order correlations method.

Bioethical standards

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Bioethics Committee of National Pirogov Memorial Medical University, Vinnytsya (protocol No. 9 from 25 Oct 2021).

Results

Clinical characteristics of rheumatoid arthritis patients

According to the results from Table I we can conclude that the group of patients consisted of middle-aged people with a duration of disease more than 8 years. Approximately one third (34.1%) of patients were seropositive. Among the examined patients the second radiological stage prevailed (40.9%); the percentage of patients with the first and third stages was approximately equal (28.5% and 26.1%, respectively); and the smallest group comprised patients with the fourth stage (4.5%). The examined patients were characterized by high disease activity, low indicators of health status and functioning and low quality of life.

Characteristics of rheumatoid arthritis patients with different levels of glial cell derived neurotrophic factor in blood plasma

The average GDNF level in the examined patients was 3.73 ±2.59 pg/ml (95% confidence interval [95% CI]: 3.18–4.28 pg/ml, median: 2.96 pg/ml, interquartile range [IQR]: 1.93–4.74 pg/ml).

Based on the results of measuring the level of GDNF in blood plasma, we distinguished two groups of the examined patients. The median value of the GDNF level was 2.96 pg/ml, and it was determined as the borderline level. Accordingly, patients with the GDNF level up to and including 2.96 pg/ml (GDNF level below the median) were assigned to the first group, and patients with GDNF

Table I. Clinical characteristics of RA patients

Indicator	Value [*n* (%) or M ±SD]
Age [years]	50.8 ±10.9
Sex	
Male	15 (17.0)
Female	73 (83.0)
Duration of the disease [years]	8.2 ±4.5
Seropositivity	30 (34.1)
X-ray stage I	25 (28.5)
X-ray stage II	36 (40.9)
X-ray stage III	23 (26.1)
X-ray stage IV	4 (4.5)
ESR [mm/h]	23.36 ±14.47
DAS28 (ESR) [points]	5.66 ±1.15
SDAI [points]	33.98 ±11.80
CDAI [points]	32.93 ±11.80
VAS-P [points]	6.52 ±1.51
VAS-D [points]	5.94 ±1.33
HAQ [points]	1.24 ±0.69
DRI [points]	34.14 ±18.43
TAS-20 [points]	49.31 ±14.72
Alexithymia	36 (40.9)
GDNF level in blood plasma [pg/ml]	3.73 ±2.59
Quality of life according to the SF-36 Health Survey [points]	
Physical functioning	54.77 ±19.03
Physical role functioning	50.85 ±27.97
Bodily pain	48.38 ±22.98
General health perceptions	44.66 ±20.44
Physical component of health	49.68 ±20.58
Mental health	55.57 ±19.66
Emotional role functioning	52.65 ±24.12
Social role functioning	54.69 ±26.21
Vitality	53.47 ±18.06
Mental component of health	54.00 ±19.40

CDAI – Clinical Disease Activity Index, DAS28 (ESR) – Disease Activity Score with 28-joint count with erythrocyte sedimentation rate, DRI – Disability Rating Index, ESR – erythrocyte sedimentation rate, GDNF – glial cell derived neurotrophic factor, HAQ – Health Assessment Questionnaire, SDAI – Simple Disease Activity Index, VAS-P – Visual Analogue Scale Patient, VAS-D – Visual Analogue Scale Patient Doctor, TAS-20 – Toronto Alexithymia Scale.

above 2.96 pg/ml were assigned to the second group (GDNF level above the median). The number of patients in each group was 44.

According to the results from Table II, patients with the GDNF level in blood plasma above the median had higher indicators of the TAS-20; at the same time, differences were found for the general indicator of alexithymia ($p < 0.1$).

Patients with GDNF level above the median had higher RA activity rates, pain intensity, and worse functional activity and health status, although differences between groups were not statistically significant ($p > 0.05$). The most significant were the differences in RA activity according to the DAS28 ($p < 0.1$).

Characteristics of rheumatoid arthritis patients with and without alexithymia and different levels of glial cell derived neurotrophic factor in blood plasma

To evaluate the features of the relationship between GDNF and alexithymia, patients were divided into two groups based on the results of the TAS-20. The first group included 52 patients without alexithymia (values of the TAS-20 up to and including 60 points). The second group included 36 patients with alexithymia (TAS-20 score – 61 points and above) and each of these groups was divided according the GDNF level. The average age of patients without alexithymia was 49.1 ±11.7 years, of patients with alexithymia 53.4 ±9.2 years, duration of RA was 7.0 ±3.9 years and 9.9 ±4.8 years, respectively.

Glial cell derived neurotrophic factor level in RA patients with alexithymia was higher than in patients without alexithymia: 4.08 ±2.87 pg/ml (95% CI: 3.11–5.06 pg/ml, median 3.11 pg/ml, IQR: 2.40–4.74 pg/ml) vs. 3.48 ±2.37 pg/ml (95% CI: 2.82–4.14 pg/ml, median 2.71 pg/ml, IQR: 1.87–4.66 pg/ml). The differences between groups with and without alexithymia were not statistically significant ($p = 0.295$).

According to the results in Table III, alexithymia has a significant effect on the differences in the indicators of patients with different levels of GDNF.

Slightly higher disease activity, pain intensity and worse functional activity were found in patients without alexithymia with the GDNF level below the median. The differences between the groups with the GDNF level below and above the median were not statistically significant.

Significantly higher ESR ($p < 0.05$), RA activity index according to the DAS28 ($p < 0.05$), pain intensity according to the VAS-P ($p < 0.1$) and VAS-D ($p < 0.05$), and worse general state of health and functions according to the HAQ index ($p < 0.05$) were found in the group of patients with alexithymia and with the GDNF level above the median.

Patients with alexithymia and the GDNF level above the median had worse quality of life detected by the SF-36 questionnaire: physical functioning ($p < 0.05$),

Table II. Characteristics of RA patients with different levels of GDNF in blood plasma (M ±SD)

Indicator	Patients with GDNF level below the median (n = 44)	Patients with GDNF level above the median (n = 44)	p-value
Results of assessment of alexithymia according to the TAS-20 [points]			
Difficulty identifying feelings	14.98 ±5.83	17.09 ±6.12	0.121
Difficulty describing feelings	11.34 ±3.81	12.43 ±3.64	0.142
Externally oriented thinking	20.57 ±5.86	22.20 ±6.20	0.224
Indicator according to TAS-20	46.89 ±14.41	51.73 ±14.79	0.068
Clinical indicators			
ESR [mm/h]	21.11 ±13.71	25.61 ±15.02	0.134
DAS28 (ESR) [points]	5.56 ±0.94	5.76 ±1.33	0.096
SDAI [points]	33.11 ±10.10	34.85 ±13.34	0.502
CDAI – Clinical Disease Activity Index [points]	31.93 ±9.78	33.93 ±13.57	0.433
VAS-P [points]	6.34 ±1.33	6.70 ±1.66	0.205
VAS-D [points]	5.80 ±1.17	6.09 ±1.48	0.207
HAQ [points]	1.15 ±0.64	1.32 ±0.73	0.170
DRI [points]	32.70 ±17.47	35.59 ±19.43	0.545
Quality of life according to the SF-36 Health Survey [points]			
Physical functioning	58.75 ±17.39	50.80 ±19.94	0.076
Physical role functioning	55.68 ±26.34	46.02 ±29.01	0.087
Bodily pain	50.61 ±21.72	46.14 ±24.22	0.354
General health perceptions	48.64 ±20.72	40.68 ±19.58	0.062
Physical component of health	53.43 ±19.45	45.93 ±21.22	0.063
Mental health	58.05 ±19.84	53.09 ±19.39	0.212
Emotional role functioning	56.82 ±25.52	48.48 ±22.13	0.080
Social role functioning	58.24 ±24.40	51.14 ±27.73	0.194
Vitality	56.82 ±17.49	50.11 ±18.19	0.081
Mental component of health	57.50 ±18.75	50.51 ±19.62	0.076

CDAI – Clinical Disease Activity Index, DAS28 (ESR) – Disease Activity Score with 28-joint count with erythrocyte sedimentation rate, DRI – Disability Rating Index, ESR – erythrocyte sedimentation rate, GDNF – glial cell derived neurotrophic factor, HAQ – Health Assessment Questionnaire, SDAI – Simple Disease Activity Index, VAS-P – Visual Analogue Scale Patient, VAS-D – Visual Analogue Scale Patient Doctor, TAS-20 – Toronto Alexithymia Scale.

physical role functioning ($p < 0.05$), physical component of health ($p < 0.05$), social role functioning ($p < 0.1$), vitality ($p < 0.1$) and mental component of health ($p < 0.1$).

Comparison of patients with the same GDNF level depending on the presence of alexithymia revealed even more significant differences which proved the significant influence of alexithymia on the clinical characteristics of patients and the relationship with GDNF. Patients with alexithymia had significantly worse results for all evaluated clinical indicators and indicators of quality of life. In patients with the GDNF level below the median, significant differences were found between patients with and without alexithymia according to the DAS28 ($p < 0.01$), SDAI ($p < 0.05$), VAS-P ($p < 0.001$) and VAS-D ($p < 0.01$), HAQ ($p < 0.01$), DRI ($p < 0.05$), scales of physical functioning ($p < 0.05$), bodily pain ($p < 0.01$), general health perceptions ($p < 0.001$), physical component of health ($p < 0.01$), mental health ($p < 0.001$), emotional role functioning ($p < 0.001$), social role functioning ($p < 0.001$), vitality ($p < 0.001$) and mental component of health ($p < 0.001$). In the group of patients with the GDNF level above the median, the differences were even more significant: statistically significant differences were found for all indicators, and the level of statistical significance of the differences was very high ($p < 0.001$).

The assessment of correlations between alexithymia and GDNF level proved their complex nature. Analyzing correlations in all patients (without differentiation into

Table III. Characteristic of RA patients with and without alexithymia and different level of GDNF in blood plasma (M ±SD)

Indicator	Patients without alexithymia			Patients with alexithymia			*p***	*p****
	Patients with GDNF level below the median (*n* = 29)	Patients with GDNF level above the median (*n* = 23)	*p**	Patients with GDNF level below the median, (*n* = 15)	Patients with GDNF level above the median, (*n* = 21)	*p**		
Clinical indicators								
ESR [mm/h]	20.28 ±14.63	17.70 ±10.93	0.747	22.73 ±12.03	34.29 ±14.22	0.017	0.321	0.000
DAS28 (ESR) [points]	5.29 ±0.99	5.06 ±1.40	0.672	6.09 ±0.55	6.53 ±0.66	0.017	0.004	0.000
SDAI [points]	30.59 ±9.51	30.17 ±15.69	0.489	37.98 ±9.68	39.98 ±7.70	0.386	0.044	0.000
CDAI [points]	29.81 ±8.93	29.67 ±16.40	0.423	36.04 ±10.35	38.60 ±7.50	0.268	0.092	0.000
VAS-P [points]	5.86 ±1.36	5.61 ±1.37	0.734	7.27 ±0.59	7.90 ±0.98	0.051	0.000	0.000
VAS-D [points]	5.41 ±1.15	5.09 ±1.20	0.372	6.53 ±0.83	7.19 ±0.81	0.020	0.002	0.000
HAQ [points]	0.97 ±0.62	0.90 ±0.60	0.746	1.51 ±0.54	1.78 ±0.58	0.040	0.006	0.000
DRI [points]	28.76 ±16.98	24.73 ±14.78	0.444	40.31 ±16.34	47.49 ±16.95	0.275	0.021	0.000
Quality of life according to the SF-36 Health Survey [points]								
Physical functioning	62.76 ±17.45	61.09 ±19.30	0.940	51.00 ±14.90	39.52 ±13.78	0.019	0.019	0.000
Physical role functioning	60.34 ±26.32	59.78 ±28.94	0.985	46.67 ±24.76	30.95 ±20.77	0.041	0.115	0.001
Bodily pain	58.28 ±19.29	62.50 ±18.86	0.378	35.80 ±18.65	28.21 ±14.98	0.160	0.001	0.000
General health perceptions	56.72 ±17.44	53.04 ±17.43	0.385	33.00 ±17.71	27.14 ±11.02	0.286	0.000	0.000
Physical component of health	59.54 ±18.47	59.13 ±19.47	0.993	41.61 ±15.88	31.47 ±11.44	0.028	0.002	0.000
Mental health	68.76 ±11.76	67.83 ±12.79	0.766	37.33 ±15.32	36.95 ±10.27	0.672	0.000	0.000
Emotional role functioning	66.68 ±19.93	62.33 ±18.29	0.430	37.75 ±24.79	33.30 ±14.91	0.620	0.000	0.000
Social role functioning	70.26 ±19.02	73.37 ±16.98	0.705	35.00 ±15.09	26.79 ±12.05	0.090	0.000	0.000
Vitality	64.66 ±14.01	64.13 ±12.22	0.852	41.67 ±13.18	34.76 ±8.58	0.081	0.000	0.000
Mental component of health	67.61 ±12.79	66.93 ±11.59	0.775	37.95 ±11.50	32.52 ±5.46	0.052	0.000	0.000

** Statistical significance of differences between groups of patients with GDNF level below the median and above the median.*

*** Statistical significance of differences between groups of patients with and without alexithymia with GDNF level below the median.*

**** Statistical significance of differences between groups of patients with and without alexithymia with GDNF level above the median.*

CDAI – Clinical Disease Activity Index, DAS28 (ESR) – Disease Activity Score with 28-joint count with erythrocyte sedimentation rate, DRI – Disability Rating Index, ESR – erythrocyte sedimentation rate, GDNF – glial cell derived neurotrophic factor, HAQ – Health Assessment Questionnaire, SDAI – Simple Disease Activity Index, VAS-P – Visual Analogue Scale Patient, VAS-D – Visual Analogue Scale Patient Doctor, TAS-20 – Toronto Alexithymia Scale.

groups with and without alexithymia) and in patients without alexithymia significant relationships were not found. Patients with alexithymia had significant correlations of moderate strength between the level of GDNF and pain severity: VAS-P – r_S = 0.338, p = 0.044; VAS-D – r_S = 0.446, p = 0.006.

Discussion

Comparing the results of our study with previous studies, which found in patients with RA an increase in the level of brain-derived neurotrophic factor (BDNF) and a decrease in the level of GDNF compared to the control group [17], there can be noted some consistency of the data we obtained with the results of previous studies. Experimental models of GDNF influence proved the dependence of GDNF effects on the duration of its action: in an acute process GDNF showed neuroregenerative properties [18–20], while long-term expression and high concentration of GDNF caused a negative effect on the homeostasis of neurotransmitters [21–24]. The patients in our study represented persons with a chronic disease (average duration more than 8 years); the association of GDNF level with disease activity and worse quality of life could be due to this factor. Interpreting the data of our study, one should take into account the report of Lundborg et al. that the level of GDNF in chronic pain increased intrathecally but decreased in blood plasma [25], as well as the data of Hulander et al., indicating that a reduced serum level of GDNF may lead

to reduced activation of inflammatory pathways and that GDNF expression is significantly modulated by external influences [26].

Higher levels of RA activity, pain intensity and worse functional capacity and health status of patients were associated with a higher level of GDNF – generally in line with data from research by Elfving et al.; the authors found that the level of GDNF in the plasma of RA patients was higher than in the control group and correlated with the severity of the pain syndrome [27]. At the same time the available studies testify to the complex and ambiguous nature of the physiological function of GDNF [28], and in evaluating the regularities, one should take into account as many relevant factors as possible that can influence the effects of GDNF.

In our opinion, alexithymia can be one of these factors. The data of our study proved that the RA patients had a higher level of alexithymia. This data are consistent with the results of Vadacca et al. [6] and Chimenti et al. [29]; they found a significant prevalence of alexithymia in RA patients, as well as the relationship of alexithymia in RA with the psychoemotional state of patients [8] and pain perception [30].

As the relationship between alexithymia and the level of GDNF in RA patients has not been studied yet, based on the data of our study we can assume that the presence of alexithymia not only modifies the clinical manifestation of RA, but also significantly changes the physiological effect of GDNF.

In the group of patients with alexithymia the level of GDNF was directly correlated with disease activity and pain intensity, while in the group of patients without alexithymia, significant correlations were not found. At the same time, in the group of patients with alexithymia, significant differences in disease activity, severity of pain, functional activity and health status of patients were found between patients with different levels of GDNF, while in the group of patients without alexithymia, such differences were not found.

In our opinion the features of the quality of life are a natural reflection of the trends revealed regarding disease activity, pain intensity, functional activity, general state of health and the state of the psycho-emotional sphere. As patients with a higher level of GDNF were characterized by a worse state of these functions, it seems logical that the quality of life in the related areas would decrease.

Conclusions

Alexithymia was found in 40% of RA patients.

Rheumatoid arthritis patients with alexithymia had a nonsignificantly higher GDNF level compared to patients without alexithymia.

In RA patients with alexithymia, an association of GDNF level with rheumatoid arthritis activity, loss of functional capacity and reduced quality of life was established.

Alexithymia in RA patients is an important factor in the clinical manifestation of RA and modification of the pathophysiological role of GDNF.

Disclosures

Conflict of interest: *The authors declare no conflict of interest.*
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Data availability: *The data that support the findings of this study are available on request from the corresponding author (Y.S.).*

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