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ABSTRACT

Viktoria Vasylets
http://orcid.org/0009-0003-1172-3060
Department of Internal Medicine No. 1, National Pirogov Memorial Medical University, Vinnytsia, Ukraine

Mykola Stanislavchuk
http://orcid.org/0000- 0001-8505-5999
Department of Internal Medicine No. 1, National Pirogov Memorial Medical University, Vinnytsia, Ukraine

BDNF LEVEL IN THE BLOOD OF PATIENTS WITH ANKYLOSING SPONDYLITIS COMORBID WITH ALEXITHYMIA, ITS CORRELATION WITH CLINICAL COURSE AND TREATMENT EFFICACY

Introduction. The treatment of ankylosing spondylitis is a complex and still unresolved problem due to the complexity and polymorphism of pathogenetic mechanisms and the variability of the clinical course. One of the important factors modifying the clinical course and resistance to treatment is alexithymia. A promising way to develop new approaches to the treatment of ankylosing spondylitis is to study the role of BDNF in pathogenesis, clinical manifestations, and resistance to therapy. The objective of this study was to examine BDNF levels in the blood of patients with ankylosing spondylitis comorbid with alexithymia, as well as its correlation with the clinical course and treatment efficacy.

Materials and Methods. 127 patients with ankylosing spondylitis were examined using the BASDAI, ASDAS, BASFI, BASMI, HAQ, ASAS HI/EF, BAS-G, ASQoL, MAF, PSQI, HAM-D, and MMSE scales; alexithymia was determined using the Ukrainian TAS-20 adapted version. The level of BDNF in blood plasma was determined by enzyme-linked immunosorbent assay.

Results. Patients with AS have been found to have higher levels of BDNF compared to healthy individuals: 273.13±69.58 pg/ml versus 160.40±61.08 pg/ml ($p<0.001$). Patients with elevated BDNF levels in the blood (above the median) had significantly higher disease activity indicators: ESR – 37.03±22.19 mm/h vs. 22.13±14.29 mm/h ($p<0.01$); BASDAI – 6.97±1.73 points vs. 5.42±2.00 points ($p<0.01$); ASDAS-ESR – 4.04±0.83 points vs. 3.31±0.75 points ($p<0.001$); functional capacity of patients by BASMI – 5.19±2.13 points vs. 3.84±1.83 points ($p<0.05$); BAS-G – 7.44±1.78 points vs. 5.88±2.01 points ($p<0.01$). In these patients, the ASAS HI index was 10.53±3.13 points versus 8.84±3.56 points ($p<0.05$); ASAS EF – 4.22±1.50 points versus

3.22±1.34 points (p<0.05); there were also higher TAS-20 indicators: 61.22±8.06 points versus 56.19±9.01 points (p<0.05). In patients with no alexithymia, BDNF levels were lower compared to patients with possible alexithymia: 222.50±60.10 pg/ml versus 275.93±21.10 pg/ml; while in patients with alexithymia, BDNF levels were higher than in patients of these groups: 286.08±82.75 pg/ml. ASAS-20 responders had lower BDNF levels compared to non-responders: 236.43±59.01 pg/ml versus 285.37±69.04 pg/ml (p<0.05).

Conclusions. In patients with ankylosing spondylitis, there is an increase in blood BDNF levels. Alexithymic traits are associated with higher levels of BDNF in the blood, which indicates the possible involvement of BDNF in the pathogenetic mechanisms of alexithymia formation. Elevated BDNF levels are associated with a worse clinical course of ankylosing spondylitis and are a predictor of treatment resistance.

Keywords: ankylosing spondylitis, brain-derived neurotrophic factor, alexithymia, treatment.

Corresponding author: *Viktoria Vasylets, National Pirogov Memorial Medical University, Vinnytsia, Ukraine*
e-mail: vasilets2005@yahoo.com

РЕЗЮМЕ

Вікторія Василець
http://orcid.org/0009-0003-1172-3060
Кафедра внутрішньої медицини № 1 Вінницького національного медичного університету імені М.І. Пирогова, м. Вінниця, Україна

Микола Станіславчук
http://orcid.org/0000- 0001-8505-5999
Кафедра внутрішньої медицини № 1 Вінницького національного медичного університету імені М.І. Пирогова, м. Вінниця, Україна

РІВЕНЬ BDNF В КРОВІ ХВОРИХ НА АНКІЛОЗИВНИЙ СПОНДИЛІТ, КОМОРБІДНИЙ З АЛЕКСИТИМІЄЮ, ТА ЙОГО ЗВ'ЯЗОК З КЛІНІЧНИМ ПЕРЕБІГОМ ТА ЕФЕКТИВНІСТЮ ЛІКУВАННЯ

Вступ. Лікування анкілозивного спондиліту є складною і досі не вирішеною проблемою внаслідок складності та поліморфності патогенетичних механізмів і варіабельності клінічного перебігу. Одним з важливих чинників модифікації клінічного перебігу та резистентності до лікування є алекситимія. Перспективним шляхом для розробки нових підходів до лікування анкілозивного спондиліту є вивчення ролі BDNF у патогенезі, клінічних проявах та резистентності до терапії. Мета роботи – вивчити рівні BDNF в крові хворих на анкілозивний спондиліт, коморбідний з алекситимією, його зв'язок з клінічним перебігом та ефективністю лікування.

Матеріали і методи дослідження. Обстежено 127 хворих на анкілозивний спондиліт з використанням індексів BASDAI, ASDAS, BASFI, BASMI, HAQ, ASAS HI/EF, BAS-G, ASQoL, MAF, PSQI, HAM-D та MMSE, з визначенням алекситимії за допомогою адаптованої нами україномовної версії TAS-20. Вміст BDNF в плазмі крові визначали імуноферментним методом.

Результати дослідження. У хворих на АС виявлено вищі рівні BDNF у порівнянні зі здоровими особами: 273,13±69,58 пг/мл проти 160,40±61,08 пг/мл (p<0,001). У хворих з підвищеним вмістом BDNF у крові (вище медіани) виявлені значуще вищі показники активності захворювання: ШОЕ – 37,03±22,19 мм/год проти 22,13±14,29 мм/год (p<0,01); BASDAI – 6,97±1,73 балів проти 5,42±2,00 балів (p<0,01); ASDAS-ESR – 4,04±0,83 балів проти 3,31±0,75 балів (p<0,001); функціональної здатності хворих: BASMI – 5,19±2,13 балів проти 3,84±1,83 балів (p<0,05); BAS-G: 7,44±1,78 балів проти 5,88±2,01 балів (p<0,01). У цих хворих індекс ASAS HI становив 10,53±3,13 балів проти 8,84±3,56 балів (p<0,05); ASAS EF

– 4,22±1,50 балів проти 3,22±1,34 балів (p<0,05), а також були вищі показники за TAS-20: 61,22±8,06 балів проти 56,19±9,01 балів (p<0,05). У хворих без алекситимії рівень BDNF був нижчим у порівнянні з хворими з можливою алекситимією: 222,50±60,10 пг/мл проти 275,93±21,10 пг/мл, а у хворих з алекситимією – більшим, ніж у хворих цих груп: 286,08±82,75 пг/мл. Респондери за критеріями ASAS-20 мали нижчий рівень BDNF порівняно з не респондерами: 236,43±59,01 пг/мл проти 285,37±69,04 пг/мл (p<0,05).

Висновки. У хворих на анкілозивний спондиліт має місце підвищення рівня BDNF у крові. Наявність алекситимічних рис асоціюється з вищими рівнями BDNF в крові, що свідчить про можливу причетність BDNF до патогенетичних механізмів формування алекситимії. Підвищені рівні BDNF асоціюються з гіршим клінічним перебігом анкілозивного спондиліту і виступають предиктором резистентності до лікування.

Ключові слова: анкілозивний спондиліт, мозковий нейротрофічний фактор, алекситимія, лікування.

Автор, відповідальний за листування: *Вікторія Василець, кафедра внутрішньої медицини № 1 Вінницького національного медичного університету імені М.І. Пирогова, м. Вінниця, Україна*
e-mail: vasilets2005@yahoo.com

ABBREVIATIONS

ASAS HI/EF – ASAS Health Index and Environmental Factors
ASDAS – Ankylosing Spondylitis Disease Activity Score
ASQoL – Ankylosing Spondylitis Quality of Life Questionnaire
BASDAI – Bath AS Disease Activity Index
BAS-G – Bath Ankylosing Spondylitis Patient Global Score
BASFI – Bath AS Functional Index
BASMI – Bath Ankylosing Spondylitis Metrology Index
BDNF – Brain Derived Neurotrophic Factor
HAM-D – Hamilton Depression Rating Scale
HAQ – Health Assessment Questionnaire
MAF – Multidimensional Assessment of Fatigue Scale
PSQI – Pittsburgh Sleep Quality Index
MMSE – Mini-Mental State Examination
TAS-20 – Toronto Alexithymia Scale
AL – alexithymia
AS – ankylosing spondylitis
CNS – central nervous system
ESR – erythrocyte sedimentation rate
QoL – quality of life

INTRODUCTION / ВСТУП

One of the most common types of spondyloarthropathies is ankylosing spondylitis (AS), a chronic autoimmune inflammatory disease characterized by predominant involvement of the spine and peripheral joints, arthritis, enthesitis, dactylitis, and uveitis [1]. AS is accompanied by severe pain, significant functional limitations, decreased quality of life (QoL), and deterioration of the psychosocial functioning of patients. The etiology of AS remains unknown, and the pathogenetic mechanisms are extremely complex and include genetically determined predisposition, immune response, microbiological and endocrine factors [2–4].

The uncertainty of the etiopathogenetic mechanisms of AS necessitates the study of various factors that influence the onset and progression of the disease. Among such factors, an important place belongs to neurotrophins, in particular, brain-derived neurotrophic factor (BDNF), which regulates synaptic plasticity, neuronal activity, and nociception [5]. Today, BDNF is considered one of the key links in the pathogenesis of central nervous system (CNS) disorders in autoimmune diseases. It affects neuronal survival, modulates pain severity, and regulates signaling pathways involving various neurotransmitters [6]. BDNF plays an important role in the regulation of circadian rhythms, which directly affects sleep quality [7], influences the ratio of different sleep phases [8], and responses to sleep deprivation [9]. BDNF is an important element of nociception in various injuries, including diseases with chronic pain syndrome, due to its involvement in central hypersensitivity and transmission of nociceptive signals

in the spinal and supraspinal pathways [6, 10]. Treatment of autoimmune diseases is accompanied by changes in blood levels of BDNF; however, the peculiarities of the correlation between BDNF and treatment efficacy, as well as the possibility of using BDNF as a predictor of treatment efficacy, require detailed study [11, 12].

Studies of BDNF in spondyloarthritis are currently limited; however, the available data suggest that BDNF plays an important role in the pathogenesis of this disease. Increased BDNF levels have been associated with greater joint inflammation [13], central sensitization, and disease activity in AS [14]. At the same time, data on the specific correlation between BDNF and clinical indicators and treatment efficacy in autoimmune diseases, and, in particular, in AS, are incomplete and contradictory [6, 15, 16].

In addition to genetic, immunobiological, and environmental factors, the characteristics of patients' psychoemotional responses play an important role in the pathogenesis and clinical manifestations of AS. One of the important individual psychological characteristics that can significantly affect the course of the disease is alexithymia (AL) – an impaired ability to identify and describe one's feelings, emotions, and somatic sensations [17]. The impaired ability to identify and verbalize somatic symptoms resulting from AL-associated cognitive dysfunction significantly complicates the diagnosis and differentiation of somatic diseases and affects treatment efficacy, including for autoimmune diseases [18, 19].

All this necessitates the study of BDNF blood levels in AS, taking into account clinical characteristics, functional activity parameters, health status, quality of life, and psychoemotional status of patients, as well as the AL factor. Another important task is to assess the efficacy of treatment in patients with different levels of BDNF. The results of such studies can be the basis for developing ways to improve treatment measures in AS.

The objective of this study was to examine BDNF levels in the blood of patients with ankylosing spondylitis comorbid with alexithymia, as well as its correlation with the clinical course and treatment efficacy.

MATERIALS AND METHODS

In compliance with the principles of biomedical ethics and having obtained informed consent, during 2021–2024, we examined 127 patients who were diagnosed with AS based on the modified New York criteria. These patients were undergoing treatment at the Municipal Non-Profit Enterprise "Vinnytsia Regional Clinical Hospital named after M.I. Pyrogov" and in the Rheumatology Department of the Multidisciplinary Medical Center of Odesa National Medical University. AS was assessed using the Bath AS Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS), the severity of functional impairment was assessed using the Bath AS Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI), the general health status of patients was assessed using the Health Assessment Questionnaire (HAQ), ASAS Health Index and Environmental Factors (ASAS HI/EF) and the Bath Ankylosing Spondylitis Patient Global Score (BAS-G), QoL was assessed using the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL), fatigue severity was assessed using the Multidimensional Assessment Of Fatigue Scale (MAF), the quality of sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI), the severity of depression was assessed using the Hamilton Depression Rating Scale (HAM-D), and the level of cognitive functioning was assessed using the Mini-Mental State Examination (MMSE). AL was detected using the Ukrainian version of the Toronto Alexithymia Scale (TAS-20) after we adapted and validated it.

The subjects were divided into three groups according to the results of the TAS-20 assessment: the first group (62 subjects) consisted of patients with TAS-20 score up to 52 points (“No AL” group), the second group (29 subjects) consisted of patients with TAS-20 score 52 to 60 points (“Possible AL” group); the third group (36 subjects) consisted of patients with TAS-20 score over 60 points (“AL Present” group). The average age of patients in “No AL” group was 40.2±10.6 years, in “Possible AL” group – 43.3±10.5 years, in “AL present” group – 45.8±9.9 years; the average duration of the disease after diagnosis – 5.5±3.7 years, 7.6±6.9 years, and 7.3±4.9 years, respectively.

These subjects were examined twice: at the beginning of standard therapy prescribed according to current clinical protocols and guidelines, which included NSAIDs at a stable dose (started at least 2 weeks before study enrollment and throughout the entire observation period of 12 weeks) and background therapy with methotrexate or sulfasalazine at a stable dose (started at least 4 weeks before study enrollment) and 12 weeks after the start of treatment. The efficacy of treatment was assessed using the above indicators, as well as the ASAS20 and ASAS40 criteria.

The BDNF concentration in blood plasma was determined during the initial examination of patients by ELISA enzyme-linked immunosorbent assay using the “Human BDNF (Brain Derived Neurotophic Factor) ELISA Kit” (Elabscience, USA, Lot GY10V08R8086 96T) according to the manufacturer's instructions. Detection was performed on a STAT-FAX 303+ analyzer (USA) at a wavelength of 450 nm (differential filter – 630 nm). The control group consisted of 23 apparently healthy individuals who did not differ

significantly from the patients in terms of age and gender characteristics.

This study was conducted in accordance with the provisions of GCP (2018), the Council of Europe Convention on Human Rights and Biomedicine (dated 04.04.1997), the Declaration of Helsinki of the World Medical Association on the Ethical Principles for Medical Research Involving Human Participants (1964–2000), and the Order of the Ministry of Health of Ukraine No. 281 dated 01.11.2000. The study protocols were approved by the Bioethics Committee of Vinnytsia National Medical University named after M.I. Pyrogov.

Statistical analysis included descriptive statistics, analysis of variance using the non-parametric Mann–Whitney test and Fisher's exact test, and analysis of correlations using the Spearman rank correlation method. Statistical significance of differences and correlations above 95.0% ($p<0.05$) was considered acceptable.

RESULTS

A study of BDNF concentration in the blood plasma revealed significantly higher BDNF levels in AS patients vs. healthy controls: 273.13±69.58 pg/ml versus 160.40±61.08 pg/ml ($p<0.001$) (Table 1).

Table 1 – **BDNF concentration in AS patients with different AL variants and in healthy individuals**

Indicator	Value, M±SD (-95%CI – +95%CI) / Me [Q_{25}–Q_{75}]				
	Healthy individuals, n=23	All patients, n=64	No AL, n=10	Possible AL, n=19	AL present, n=35
BDNF concentration, pg/ml	160.40±61.08 (133.99–186.81) / 155.50 [122.20–214.40]	273.13±69.58 (255.75–290.51 / 268.30 [232.85–316.00]	222.50±60.10 (179.51–265.49 / 232.65 [176.80–275.30]	275.93±21.10 (265.76–286.10) / 274.20 [257.30–282.80]	286.08±82.75 (257.65–314.51) / 264.50 [221.90–333.70]

Statistical significance of differences (p) when comparing groups

Healthy vs. all patients	Healthy vs. no AL	Healthy vs. possible AL	Healthy vs. AL present	No AL vs. possible AL	No AL vs. AL present	Possible AL vs. AL present
<0.001	0.014	<0.001	<0.001	0.023	0.042	0.921

Note: M = mean value, SD = standard deviation, CI = confidence interval, Me = median value, Q_{25}–Q_{75} = interquartile range

Analysis of the characteristics of blood plasma BDNF concentration in patients with AS revealed significant differences depending on the severity of alexithymic traits (Table 1).

As can be seen from Table 1, there is a trend towards higher BDNF levels in patients with greater alexithymic traits. Thus, the lowest BDNF level was found in patients with no AL (although in this group the BDNF level was still significantly higher vs. healthy individuals): 222.50±60.10 pg/ml ($p<0.05$). In patients with possible AL, BDNF levels were significantly higher vs. patients with no AL: 275.93±21.10 pg/ml ($p<0.05$), while in patients with AL, the levels were the highest among all groups: 286.08±82.75 pg/ml. At the same time, the difference in BDNF levels between the "Possible AL" group and "AL Present" group was not statistically significant ($p>0.05$).

We analyzed the correlation between blood BDNF concentrations and clinical and laboratory indicators of patients with AS at the time of study enrollment. For this purpose, the patients were divided into 2 groups, with 32 patients in each. The first group included patients with plasma BDNF concentration of up to 268.30 pg/ml (below the median), the second group included patients with plasma BDNF concentration of over 268.30 pg/ml (above the median) (Table 2).

It was found that patients with BDNF concentrations above the median had higher indicators of AS activity: ESR – 37.03±22.19 mm/h vs. 22.13±14.29 mm/h ($p<0.01$); BASDAI – 6.97±1.73 points vs. 5.42±2.00 points ($p<0.01$); ASDAS-ESR – 4.04±0.83 points vs. 3.31±0.75 points ($p<0.001$); functional capacity of patients by BASMI – 5.19±2.13 points vs. 3.84±1.83 points ($p<0.05$); health status by BAS-G (6 months) – 7.44±1.78 points vs. 5.88±2.01 points ($p<0.01$); ASAS HI – 10.53±3.13 points vs. 8.84±3.56 points ($p<0.05$); and ASAS EF – 4.22±1.50 points versus 3.22±1.34 points ($p<0.05$). Patients with plasma BDNF concentrations above the median also had significantly higher ($p<0.05$) TAS-20 scores (including difficulty describing feelings).

Table 2 – **Indicators in patients with BDNF concentrations below the median and above the median (268.30 pg/ml)**

Indicator	Value, M±SD		p
	BDNF concentration below the median, n=32	BDNF concentration above the median, n=32	
BEFORE TREATMENT			
ESR, mm/h	22.13±14.29	37.03±22.19	0.001
BASDAI, points	5.42±2.00	6.97±1.73	0.003
ASDAS-ESR, points	3.31±0.75	4.04±0.83	<0.001
BASMI, points	3.84±1.83	5.19±2.13	0.012
BASFI, points	5.37±2.40	6.22±1.88	0.179
BAS-G (7 days), points	6.41±2.00	7.19±1.71	0.134
BAS-G (6 months), points	5.88±2.01	7.44±1.78	0.004
ASAS HI, points	8.84±3.56	10.53±3.13	0.050
ASAS EF, points	3.22±1.34	4.22±1.50	0.013
HAQ, points	1.29±0.71	1.49±0.55	0.199
Visual Analog Pain Scale, points	6.97±1.51	7.66±1.21	0.064
ASQoL, points	10.94±4.02	12.63±2.64	0.139
MAF, points	33.81±11.71	33.13±7.39	0.368
PSQI, points	9.81±4.19	11.53±4.66	0.210
HAM-D, points	15.47±9.68	16.53±9.54	0.501
MMSE, points	28.09±1.51	27.56±1.37	0.136
Difficulty identifying feelings, points	20.56±4.63	22.34±3.53	0.248
Difficulty describing feelings, points	12.97±2.81	15.22±3.35	0.015
Externally oriented thinking, points	22.66±5.93	23.66±3.82	0.526
TAS-20, points	56.19±9.01	61.22±8.06	0.028
AFTER TREATMENT			
ESR, mm/h	16.91±10.82	23.56±12.06	0.011
BASDAI, points	4.55±1.64	6.07±1.80	0.001
ASDAS-ESR, points	2.91±0.71	3.49±0.85	0.001
BASMI, points	3.47±1.80	4.41±2.06	0.049
BASFI, points	4.57±2.14	5.27±2.21	0.105
BAS-G (7 days), points	5.09±1.92	6.25±1.93	0.035
BAS-G (6 months), points	5.25±1.95	6.69±1.99	0.003
ASAS HI, points	7.28±3.38	8.53±3.41	0.137
ASAS EF, points	2.66±1.43	3.38±1.24	0.021
HAQ, points	0.82±0.53	1.02±0.50	0.134
Visual Analog Pain Scale, points	5.56±1.72	6.16±1.53	0.164
ASQoL, points	8.66±3.61	9.84±3.84	0.252
MAF, points	26.69±9.90	28.25±8.04	0.706
PSQI, points	7.78±3.89	9.19±4.92	0.315
HAM-D, points	11.56±7.30	12.50±7.92	0.633
MMSE, points	28.16±1.48	27.66±1.26	0.131
Difficulty identifying feelings, points	18.22±4.80	19.03±3.83	0.762
Difficulty describing feelings, points	12.47±2.57	13.84±3.14	0.112
Externally-oriented thinking, points	19.69±4.99	21.31±3.86	0.200
TAS-20, points	50.38±8.67	54.19±7.63	0.063

Note: M = mean value, SD = standard deviation, CI = confidence interval, Me = median value, Q_{25}–Q_{75} = interquartile range

The significant correlation between BDNF and indicators of clinical activity, functional impairment, and health status in patients with AS was confirmed by correlation analysis (Table 3).

As can be seen from the Table, moderate direct correlations were found for pre-treatment indicators: ESR (r_S=0.432, p<0.001), BASDAI (r_S=0.332, p<0.01), BASMI (r_S=0.337, p<0.01), BASFI (r_S=0.414, p<0.01), BAS-G (7 days) (r_S=0.354, p<0.01), HAQ (r_S=0.289, p<0.05); and post-treatment indicators: ESR (r_S=0.411, p<0.01), BASDAI (r_S=0.409, p<0.01), ASDAS-ESR (r_S=0.340, p<0.01), BASMI (r_S=0.457, p<0.001), BASFI (r_S=0.438, p<0.001), BAS-G (7 days) (r_S=0.295, p<0.001) p<0.05), HAQ (r_S=0.268, p<0.05).

Table 3 – **Results of univariate nonparametric correlation test of the relationship between BDNF concentrations in blood plasma and indicators of AS activity, functional capacity, health status, and quality of life**

Indicator	Before treatment		After treatment	
	r_S	p	r_S	p
ESR, mm/h	0.432	<0.001	0.411	0.001
BASDAI, points	0.332	0.007	0.409	0.001
ASDAS-ESR, points	0.138	0.275	0.340	0.006
BASMI, points	0.337	0.006	0.457	<0.001
BASFI, points	0.414	0.001	0.438	<0.001
BAS-G (7 days), points	0.354	0.004	0.295	0.018
BAS-G (6 months), points	0.198	0.117	0.222	0.078
ASAS HI, points	0.224	0.076	0.255	0.042
ASAS EF, points	0.236	0.060	0.209	0.097
HAQ, points	0.289	0.020	0.268	0.032
Visual Analog Pain Scale, points	0.178	0.159	0.232	0.066
ASQoL, points	-0.060	0.640	0.083	0.512
MAF, points	0.150	0.238	0.238	0.058
PSQI, points	0.048	0.709	0.049	0.700
HAM-D, points	-0.180	0.154	-0.196	0.120
MMSE, points	0.099	0.438	0.149	0.239
Difficulty identifying feelings, points	0.277	0.027	0.079	0.536
Difficulty describing feelings, points	0.478	<0.001	0.248	0.048
Externally-oriented thinking, points	0.180	0.155	0.223	0.077
TAS-20, points	0.463	<0.001	0.316	0.011

Moderate direct correlations were found for the TAS-20 score before treatment (r_S=0.463, p<0.001) and after treatment (r_S=0.316, p<0.05), as well as for the difficulty identifying feelings before treatment (r_S=0.277, p<0.05) and difficulty describing feelings before treatment (r_S=0.478, p<0.001) and after treatment (r_S=0.248, p<0.05).

It was important to assess the significance of BDNF for standard therapy effectiveness in patients with AS. After 12 weeks of standard therapy, patients with BDNF concentrations above the median were found to have much worse indicators of AS activity, functional impairment, and health status (Table 2).

Thus, these patients had higher ESR – 23.56±12.06 points versus 16.91±10.82 points (p<0.05); BASDAI score – 6.07±1.80 points versus 4.55±1.64 points (p<0.01); ASDAS-ESR score – 3.49±0.85 points versus 2.91±0.71 points (p<0.01); BASMI score – 4.41±2.06 points versus 3.47±1.80 points (p<0.05); BAS-G score (7 days) – 6.25±1.93 points versus 5.09±1.92 points (p<0.05); BAS-G score (6 months) – 6.69±1.99 points versus 5.25±1.95 points (p<0.01); and ASAS EF score – 3.38±1.24 points versus 2.66±1.43 points (p<0.05). Patients with post-treatment BDNF concentrations above the median also had higher TAS-20 scores compared to patients with BDNF concentrations below the median: 54.19±7.63 points versus 50.38±8.67 points; however, the statistical significance level of the differences did not reach 95% (p=0.063).

The above patterns were confirmed by the comprehensive indicator of treatment efficacy in patients with AS (ASAS-20). BDNF concentrations in patients who were responders and non-responders according to ASAS-20 criteria differed significantly (Table 4).

Table 4 – **BDNF concentration in non-responders and responders according to ASAS-20**

Indicator	Value, M±SD (-95%CI – +95%CI) / Me [Q_{25}–Q_{75}]		p
	ASAS-20 non-responders, n=48	ASAS-20 responders, n=16	
BDNF concentration, pg/ml	285.37±69.04 (265.32–305.41) / 275.95 [241.45–323.20]	236.43±59.01 (204.98–267.87) / 256.60 [190.40–275.40]	0.024 Note: M = mean value, SD = standard deviation, CI = confidence interval, Me = median value, Q_{25}–Q_{75} = interquartile range

In patients who responded to standard therapy (responders), the plasma BDNF concentrations were significantly lower compared to non-responders: 236.43±59.01 pg/ml versus 285.37±69.04 pg/ml ($p<0.05$). This suggested that the elevated BDNF concentrations could be a predictor of treatment resistance in AS.

DISCUSSION

Literature data on BDNF concentrations in patients with rheumatic diseases are characterized by extreme variability. Bathina S., Das U. N. reported that BDNF levels in the serum of healthy individuals were from 8.0 to 927.0 pg/ml [20]. In our study, BDNF levels ranged from 13.82 pg/ml to 576.30 pg/ml. Our data are consistent with the results of other studies, in particular, by Barbosa A.G. et al., who reported a blood plasma BDNF level in healthy individuals of about 250 pg/ml. At the same time, Shapoval I. et al. observed significant circadian variability of BDNF levels [14], which should also be taken into account when interpreting the study results.

Our data confirmed the association of AS with higher BDNF levels: in AS patients, BDNF levels were 1.7 times higher compared to healthy subjects. This is consistent with the data of other studies which found increased BDNF levels in rheumatic diseases (Sochal M. et al. [6], Wang N., Tian B. [16]), in particular, in AS (Shapoval I. et al.) [14].

Our study was the first to establish the peculiarities of the relationship between AL and BDNF concentrations in patients with AS. Patients with elevated BDNF concentrations had significantly higher TAS-20 scores, which suggested an association between AL and higher BDNF concentrations. The mechanisms of this association are not yet understood; however, this relationship is also confirmed by significant differences in BDNF concentrations in AS patients with different degrees of alexithymic traits. The BDNF concentration increases in parallel with the increase in the severity of alexithymic traits; it is minimal in patients with no AL and maximal in patients with AL. It is worth noting that the differences in BDNF levels in the “Possible AL” group and “AL Present” group were not statistically significant, although they were higher in the “AL Present” group. This allows considering the presence of alexithymic traits and increased BDNF concentrations as interrelated phenomena. However, the pathogenetic and pathopsychological relationships between AL and BDNF concentrations may be more complex.

Overall, current research data, including our study, confirm that increased BDNF concentrations are associated with greater clinical activity of autoimmune diseases, and BDNF is an important link in neuroimmune processes. Our study also found significantly higher indicators of AS activity in patients with increased BDNF concentrations, as evidenced by higher ESR, BASDAI, and ASDAS-ESR scores. We also confirmed the association of increased BDNF concentrations with greater severity of functional impairment, as confirmed by higher BASMI scores, and with worse health status, as confirmed by higher BAS-G, ASAS HI, and ASAS EF scores. The presence of direct correlations between BDNF concentrations and ESR and BASDAI, BASMI, BASFI, BAS-G, and HAQ scores confirms these patterns and indicates the important role of BDNF in the pathogenesis of somatic disorders in AS. At the same time, moderate and weak correlations were found, which is consistent with modern ideas about the complex nature of the relationships between clinical features of AS and BDNF.

It should be noted that although our study did not reveal significant differences and correlations between elevated BDNF concentrations and indicators of the psychoemotional state and patients`quality of life, however, indicators of depression and sleep quality in patients with elevated BDNF concentrations were worse compared to the group with BDNF concentrations below the median. This is consistent with recent studies that have found an association between higher BDNF concentrations and depressive symptoms (Cheon Y.H. et al. [15]) and sleep disorders (Muheim C.M. et al. [8], Rahmani M et al. [9], Garner J.M. et al. [10]). However, it should be mentioned that there is a direct relationship between AS severity, primarily pain severity, and depression and sleep disorders; therefore, the association of higher BDNF concentrations with greater severity of depressive and insomnia symptoms may be

mediated by greater severity of the disease, in particular, by a more pronounced pain syndrome.

Regarding the better treatment efficacy in patients with lower BDNF concentrations found in our study, these data are fully consistent with the general pattern of association between elevated BDNF concentrations and more severe AS and worse functional impairment. Significantly higher BDNF concentrations in patients who failed to meet ASAS-20 criteria after treatment suggest that the elevated BDNF concentrations can be a predictor of treatment resistance in AS. Patients with higher BDNF concentrations also demonstrated significantly worse AS course, functional impairment, and health status after treatment compared to patients with low BDNF concentrations.

CONCLUSIONS

1. Patients with AS have higher concentrations of BDNF in blood plasma compared to healthy individuals: 273.13±69.58 pg/ml versus 160.40±61.08 pg/ml ($p<0.001$). Alexithymic traits in patients with AS are associated with a significant increase in blood BDNF concentrations, which indicates a possible pathogenetic role of BDNF in the formation of the phenomenon of alexithymia.

2. Higher BDNF concentrations are associated with greater AS activity, greater severity of functional impairment, and worse health status of patients, which gives reason to consider elevated BDNF concentrations as a predictor of a worse clinical course of AS.

3. Higher plasma BDNF concentrations are associated with poorer response to AS treatment, as evidenced by significantly higher BDNF concentrations in ASAS-20 non-responders compared to responders: 285.37±69.04 pg/ml versus 236.43±59.01 pg/ml. This suggests that elevated BDNF concentrations can be a predictor of treatment resistance in AS.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Prospects for further research are related to the study of the changes in BDNF concentrations in AS in long-term treatment, as well as the study of BDNF concentrations in various AS treatment regimens.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

Viktoriya Vasylets: conceptualization, methodology, data collection, statistical processing and data analysis, manuscript writing (original draft).

Mykola Stanislavchuk: conceptualization, methodology, writing (review and editing).

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CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

ARTIFICIAL INTELLIGENCE DISCLOSURE / ВИКОРИСТАННЯ ШТУЧНОГО ІНТЕЛЕКТУ

The authors declare that artificial intelligence technologies were not used during the study and in the writing and editing of this article.

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INFORMATION ABOUT THE AUTHORS / ВІДОМОСТІ ПРО АВТОРІВ

Василець Вікторія Вікторівна, аспірант, Вінницький національний медичний університет ім. М.І. Пирогова, кафедра внутрішньої медицини № 1. 21018, м. Вінниця, вул. Пирогова, 56.

E-mail: vasilets2005@yahoo.com

ORCID: http://orcid.org/0009-0003-1172-3060

Станіславчук Микола Адамович, доктор медичних наук, професор, завідувач кафедри, Вінницький національний медичний університет ім. М.І. Пирогова, кафедра внутрішньої медицини № 1. 21018, м. Вінниця, вул. Пирогова, 56.

21018, м. Вінниця, вул. Пирогова, 56.

E-mail: mstanislav53@yahoo.com

ORCID: http://orcid.org/0000- 0001-8505-5999