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PREDICTORS OF TREATMENT RESISTANCE IN ANKYLOSING SPONDYLITIS

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The study aimed to determine the predictors of treatment resistance in patients with ankylosing spondylitis with a neuropathic component of pain syndrome. We examined 142 patients who were diagnosed with ankylosing spondylitis according to the modified New York criteria. Among the examined patients, 113 (79.6 %) were men, and 29 (20.4 %) were women; the average age was 42±8.8 years, and the duration of the disease was 6.8±3.5 years. The control group consisted of 25 practically healthy individuals (19 men and 6 women) of the same age. It was found that in patients with ankylosing spondylitis with the presence of a neuropathic component of pain syndrome, the level of glial neurotrophic factor (GDNF) was significantly ($p<0.05$) lower not only compared to the control group: 2,644±1,166 pg/ml vs. 4,959±2,070 pg/ml, but also compared to patients without neuropathic pain: 4.344±2.936 pg/ml ($p<0.05$). To determine the predictors of resistance to treatment of ankylosing spondylitis, we followed the results of 12 – week treatment of 43 patients who were divided into two groups depending on the content of glial neurotrophic factor (up to 3.0 pg/ml, 21 patients) and with normal GDNF levels (over 3.0 pg/ml, 22 patients) before treatment. The proportion of ASAS20 responders among patients with normal GDNF levels was three times higher than among patients with reduced GDNF levels: 45.5 % vs. 14.3 %, $p<0.05$. Thus, reduced plasma GDNF levels are associated with a more severe course of the disease, higher activity of the pathological process, poorer functional capacity, quality of life, the state of the affective sphere of patients, and a poorer response to treatment, which allows us to consider reduced levels of glial neurotrophic factor as a predictor of resistance to therapy.

Key words: ankylosing spondylitis, neuropathic pain, glial neurotrophic factor, predictors of resistance.

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ПРЕДИКТОРИ РЕЗИСТЕНТНОСТІ ДО ЛІКУВАННЯ ПРИ АНКІЛОЗИВНОМУ СПОНДИЛІТІ

Метою дослідження було визначити предиктори резистентності до лікування у хворих на анкилозивний спондиліт з нейропатичним компонентом больового синдрому. Обстежено 142 пацієнти, яким був встановлений діагноз анкілозивного спондиліту згідно з модифікованими Нью-Йоркськими критеріями. Серед обстежених 113 осіб (79,6 %) склали чоловіки, 29 осіб (20,4 %) – жінки; середній вік – 42±8,8 років, тривалість захворювання: 6,8±3,5 років. Контрольну групу склали 25 практично здорових осіб (19 чоловіків і 6 жінок) відповідного віку. Встановлено, що у пацієнтів з анкілозивним спондилітом з наявністю нейропатичного компоненту больового синдрому рівень гліального нейротрофічного фактору (GDNF) був достовірно ($p<0,05$) нижче не тільки порівняно з контролем: 2,644±1,166 пг/мл проти 4,959±2,070 пг/мл, а ї порівняно з хворими без нейропатичного болю: 4,344±2,936 пг/мл ($p<0,05$). Для визначення предикторів резистентності до лікування анкілозивного спондиліту нами були простежені результати 12-тижневого лікування 43 пацієнтів, які були розподілені на дві групи в залежності від вмісту гліального нейротрофічного фактору (до 3,0 пг/мл, 21 особа) і з нормальним рівнем GDNF (понад 3,0 пг/мл, 22 особи) до початку лікування. Встановлено, що питома вага респондерів ASAS20 серед пацієнтів з нормальним рівнем GDNF виявилася втричі вищою, ніж серед пацієнтів зі зниженим рівнем GDNF: 45,5 % проти 14,3 %, $p<0,05$. Отже, знижений вміст GDNF у плазмі крові асоційований з більш важким перебігом захворювання, вищою активністю патологічного процесу, гіршою функціональною здатністю, якістю життя, станом афективної сфери пацієнтів та гіршою відповіддю на лікування, що дозволяє вважати знижений рівень гліального нейротрофічного фактору предиктором резистентності до терапії.

Ключові слова: анкілозивний спондиліт, нейропатичний біль, гліальний нейротрофічний фактор, предиктори резистентності.

The study is a fragment of the research work "Genetic and environmental factors in the onset and progression of major rheumatological diseases" (state registration No. 0115U001282), and "Markers of disease severity and predictors of treatment resistance in major rheumatic diseases" (state registration No. 0121U100280).

The diagnosis and treatment of ankylosing spondylitis (AS) remains a challenging problem in modern rheumatology for both clinical and medical and social reasons [4, 5, 7, 9]. AS mostly affects men of young working age (15–40 years), the disease is characterized by a steadily progressive course with rapid disability, deterioration in quality of life (QOL), and shortened life expectancy [5].

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease of connective tissue with predominant involvement of sacroiliac joints and spine, formation of syndesmophytes and ankyloses, combined with enteritis, uveitis, and internal organ damage [2, 15]. The clinical phenomenology of AS is characterized by significant individual variability; the leading clinical symptom of AS is chronic pain with persistence due not only to an inflammatory reaction but also to the presence of a neuropathic component [6, 12]. Modern studies have shown a significant prevalence of the neuropathic component of pain syndrome in patients with connective tissue diseases; in particular, it is detected in 34.9 % of men and

50.0 % of women with AS [5]. At the same time, the features of the neuropathic component of pain in AS remain insufficiently studied, and the available scientific data are incomplete. Insufficient study of the etiopathogenetic mechanisms of AS, including genetic, immunological, neurobiological, biochemical, and other factors, which determine the current unsatisfactory level of AS treatment, so any studies aimed at improving the understanding of the patterns of development of the ankylosing process are important and can help in finding effective means of treatment and prevention of AS [14].

Glial-Derived Neurotrophic Factor (GDNF) is an important factor regulating neuropathic pain. It plays an important role in the complex of reactions accompanying the development of neuropathic pain through the normalization of cellular changes resulting from neuronal damage associated with allodynia and changes in cytokine expression locally in the area of injury and by glia remotely in the spinal cord [3]. Like members of the neurotrophin family, GDNF is structurally related to cysteine knot proteins responsible for the development and maintenance of various sets of sensory and sympathetic neurons; in addition, GDNF is also responsible for the development and survival of enteric neurons and, unlike neurotrophins, has effects outside the nervous system. GDNF has been shown to have an analgesic effect on neuropathic pain by restoring the subcellular distribution of K+ channel domains, but the detailed mechanisms of its action are still unknown. The pathogenetic aspects of GDNF in AS remain unclear, which makes it important to conduct research in this area and has important theoretical and practical implications.

Despite the algorithms for the treatment of AS prescribed in current guidelines, the problem of sufficient control of the pain syndrome remains unresolved. According to current research, first- and second-line therapy, despite significant reductions in pain severity, does not provide adequate analgesia in about 20 %, and another 30-40 % would like a greater pain reduction. That is why identifying additional predictors of resistance to AS treatment is an urgent task in modern medicine.

The purpose of the study was to determine the predictors of treatment resistance in patients with ankylosing spondylitis with a neuropathic component of pain.

Materials and methods. The study was conducted based on the Municipal Non-Profit Enterprise "Vinnytsia Regional Clinical Hospital named after M.I. Pirogov of Vinnytsia Regional Council" in the period from 2019 to 2023. The study was conducted in compliance with the main provisions of GCP (2018), the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the Declaration of Helsinki of the World Medical Association for the Ethical Principles of Scientific Medical Research Involving Human Subjects (1964–2000), and the order of the Ministry of Health of Ukraine No. 28 of December 2018.) and the Order of the Ministry of Health of Ukraine No. 281 of 01.11.2000. The study protocols were approved by the Bioethics Committee of Vinnytsia M.I. Pirogov Memorial National Medical University (protocol No. 7 of October 1, 2020, and No. 6 of October 12, 2023).

At the first stage, 142 patients aged 18 to 65 years who were diagnosed with AS according to the modified New York criteria, who provided informed consent to participate in the study, and were able to adequately communicate and understand the content of the questionnaires during the study were selected to participate in the study. Among the subjects, 113 people (79.6 %) were men, 29 people (20.4 %) were women; the average age of the participants was 42±8.8 years, the duration of the underlying disease ranged from 1 to 15 years, and averaged 6.8±3.5 years. The control group consisted of 25 practically healthy individuals (19 men and 6 women) of the same age.

As a result of the examination, all 142 patients were divided into two groups: the first group, consisting of 94 patients, included patients with AS with no signs of neuropathic pain (NP); the second group, consisting of 48 patients, included patients with AS with signs of NP. The assignment of a patient to one group or another was based on the results of the examination using the Leeds Neuropathic Pain Scale (LANSS) [8] and the Diagnostic Neuropathic Pain Questionnaire (DN4).

The clinical examination of patients included the following components: a clinical conversation structured as a semi-structured clinical interview, during which complaints were identified and detailed, anamnestic data were collected, and a physical examination was performed according to a standardized scheme. The data obtained during the clinical examination were verified by comparing them with the medical records.

Anthropometric parameters (body weight and height) were determined according to a standard method.

To determine the neuropathic component of pain (NCP), the Leeds Neuropathic Pain Scale (LANSS), the Diagnostic Neuropathic Pain Questionnaire (DN4), and the Standardized Evaluation of Pain (StEP) questionnaire were used, the validation and transcultural adaptation of the StEP questionnaire was carried out by us.

The BASFI (Bath AS Functional Index) and BASMI (Bath Ankylosing Spondylitis Metrology Index) indices were used to assess functional impairment in AS.

Disease activity was assessed using the BASDAI (Bath AS Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score) indices.

The general state of health and function of patients with AS was assessed by the HAQ index (Health Assessment Questionnaire).

The Ukrainian-language adapted version of the ASAS HI/EF (ASAS Health Index and 195 Environmental Factors) questionnaire and the BAS–G (the Bath Ankylosing Spondylitis Patient Global Score) index with patient self-assessment of symptoms for 1 week (BAS–G 7 days), for the last six months (BAS–G 6 months) and the average (BAS–G Score) were used to assess the health status of the examined patients.

The content of glial neurotrophic factor in blood plasma was determined by enzyme-linked immunosorbent assay (ELISA) using the Human GDNF (Glial Cell Line Derived Neurotrophic Factor) ELISA Kit (Elabscience, USA, Lot CV09HB482125) according to the manufacturer's instructions. The studies were performed in the clinical diagnostic laboratory of the Municipal Non-Profit Enterprise "Vinnytsia Regional Clinical Hospital named after M.I. Pirogov of Vinnytsia Regional Council". The total number of patients in whom GDNF was measured was 90 (65 patients – 50 men and 15 women, and 25 healthy patients – 19 men and 6 women).

Laboratory tests included: a complete blood count with ESR determination; determination of C-reactive protein; total protein, creatinine, urea, ALT, AST, glucose level.

The complex of psycho-diagnostic and psychometric methods included the following techniques: The Zung Self-Rating Depression Scale, the Spilberger Scale for Assessment of Personal and Reactive Anxiety, the MMSE (Mini–Mental State Examination) questionnaire was used to identify and assess cognitive impairment.

The ASQoL (Ankylosing Spondylitis Quality of Life Questionnaire) and the Mezzich et al. methodology for assessing the quality of life and social functioning of patients in the adaptation of N.O. Maruta were used.

Statistical and mathematical processing of the study results. The study data were analyzed using modern methods of statistical and mathematical analysis. The analysis of differences in quantitative traits between groups with normal distribution and distribution close to normal was carried out using Student's t test. For intergroup analysis of differences in quantitative traits with a different from normal distribution, nonparametric statistics methods were used: the Mann-Whitney test for independent variables and the Wilcoxon test and the sign criteria statistics for dependent variables. The nature of the distribution was assessed using the Shapiro-Wilk test. The intergroup analysis of differences in categorized features was performed using Fisher's exact test. The analysis of correlations was carried out using Spearman's rank correlation method. The study data were processed on a personal computer using the licensed Microsoft Excel office suite and the Statistica (StatSoft Inc., USA) and SPSS22 (©SPSS Inc.) application packages.

Results of the study and their discussion. The analysis of the results showed that high and very high disease activity prevailed in patients with AS. The average value of the ASDAS index was within 3.8±0.8 points, and BASDAI – 5.5±1.2 points.

The majority of the examined patients had radiological stage III (52.1 %), twice as many had stage IV (28.2 %), three times as many had stage II (16.9 %), and the least number had stage I (2.8 %). The structure of radiological stages in patients with and without NP did not differ significantly: 194 patients with NP had slightly more patients with stage I (4.2 % vs. 2.1 %, $p>0.05$), stage II (20.8 % vs. 14.9 %, $p>0.05$) and stage IV (29.2 % vs. 27.7 %, $p>0.05$), and patients without NP had stage III (55.3 % vs. 45.8 %, $p>0.05$).

HLA B27 – positive were 71.8 % of patients, and among patients with NP there were insignificantly more of them: 75.0 % vs. 70.2 % ($p>0.05$).

Severe functional impairment (BASFI ≥ 192.4 points) was observed in 79.6 % of patients, and the spinal range of motion according to BASMI was 5.2±2.3 points. According to the ASQoL, the mean QOL score in patients with AS was 8.3±4.4 points.

We have analyzed for the first time the peculiarities of GDNF content in patients with AS with NP. The general trend inherent in patients with AS was a reduced level of GDNF compared with healthy subjects: 3.508±2.388 pg/ml versus 4.959±2.070 pg/ml, respectively ($p<0.05$) [1]. At the same time, the GDNF level in healthy subjects was significantly higher both when compared with patients with NP (2.644±1.166 pg/ml, $p<0.01$) and when compared with patients without NP (4.344±2.936 pg/ml, $p<0.05$). In patients with AS with NP, GDNF levels in blood plasma were significantly ($p<0.05$) lower than in patients with AS without NP, indicating an important role of GDNF in the pathogenetic mechanisms of NP in AS. It was found that the level of GDNF in the blood plasma of patients with AS significantly directly correlates with body weight ($r_S=0.389$, $p<0.01$) and body mass index ($r_S=0.328$, $p<0.01$), and inversely correlates with the severity of NP according to LANNS ($r_S=0.253$, $p<0.05$) and DN4 ($r_S=(-0.308)$, $p<0.05$), with BAS-G 6-month health status ($r_S=(-0.269)$, $p<0.05$) and BAS-G average ($r_S=(-0.265)$, $p<0.05$), as well as with depression severity ($r_S=(-0.293)$, $p<0.05$) [1].

Given the important role of GDNF in the pathogenetic mechanisms of AS, we also studied the possibility of using plasma GDNF levels as a predictor of resistance to AS therapy. For this purpose, we followed the clinical results of 12-week treatment of 43 patients with AS. Among these patients, two groups were identified: with a pretreatment plasma GDNF level of up to 3.0 pg/mL (group with a reduced GDNF level, numbering 21 patients), and with a pretreatment plasma GDNF level of more than 3.0 pg/mL (group with a normal GDNF level, numbering 22 patients). Comparison of indicators of pathological process activity, functional capacity of patients, health status, quality of life and mental state was performed in each of these groups before and after treatment, the result was presented as a percentage of decrease or increase in the indicator on the appropriate scale before and after treatment (Table 1).

Table 1

Dynamics of indicators of pathological process activity, functional capacity of patients, health status, neuropathic pain, quality of life and mental state (change in the mean value after treatment in % to the value of the corresponding indicator before treatment)

Indicator	Dynamics of the indicator in the course of treatment, % (M ± C)		P
	With a reduced level of GDNF (<3.0 pg/ml). N=21	With normal GDNF level (>3.0 pg/ml). N=22	
Indicators of neuropathic pain severity			
LANNS score	1.6±3.7	25.0±31.0	0.042
Index by DN4	1.5±4.9	28.8±36.0	0.010
Indicator for StEP	17.7±37.6	3.6±16.9	0.138
Indicators of pathological process activity			
BASDAI score	20.1±6.2	25.9±11.9	0.094
ASDAS-ESR score	12.5±4.1	13.5±6.8	0.836
Indicators of patients' functional capacity			
BASMI score	13.3±23.7	24.5±25.1	0.049
Indicator for BASFI	21.0±5.7	23.9±8.2	0.243
Health indicators			
ASAS HI score	20.5±16.3	22.1±12.6	0.276
ASAS EF score	26.4±34.2	32.7±30.7	0.253
BAS-G score for 7 days	23.3±11.5	27.0±13.6	0.207
HAQ score	4.8±21.8	14.2±31.3	0.206
Indicators of quality of life			
ASQoL score	14.7±9.0	25.0±14.6	0.015
Indicator of quality of life	4.0±7.8	8.6±9.4	0.065
Indicators of mental state			
Indicator of depression	14.7±18.7	31.1±28.9	0.055
Indicator of reactive anxiety	5.5±7.0	20.8±20.6	0.01

The study of the dynamics of indicators during treatment in patients with different levels of GDNF revealed certain differences, in particular, the severity of NP showed a significant improvement in patients with normal GDNF levels: LANNS score – 25.0±31.0 % vs. 1.6±3.7 % ($p<0.05$), DN4 score – 28.8±36.0 % vs. 1.5±4.9 % ($p<0.01$). Significantly better dynamics in patients with normal GDNF levels was found in terms of functional capacity of patients according to BASMI: 24.5±25.1 % vs. 13.3±23.7 % ($p<0.05$), quality of life according to ASQoL: 25.0±14.6 % vs. 14.7±9.0 % ($p<0.05$) and reactive anxiety: 20.8±20.6 % vs. 5.5±7.0 % ($p<0.05$). Somewhat better (although not statistically significant) dynamics was also found in terms of pathological process activity, health status, general quality of life and depression. Thus, neuropathic pain severity scores showed a significant improvement in patients with normal GDNF levels, while in patients with reduced GDNF levels, the dynamics was insignificant.

The results of the analysis of the distribution of the number of responders and non-responders according to the ASAS20 criteria in the groups with normal and reduced GDNF levels revealed patterns that confirm the possibility of using GDNF levels as a predictor of treatment resistance. Thus, the proportion of ASAS20 responders among patients with normal GDNF levels was three times higher than among patients with reduced GDNF levels: 45.5 % vs. 14.3 % ($p<0.05$). The proportion of ASAS40 respondents among patients with normal GDNF levels was also higher than among patients with reduced GDNF levels, although these differences were not statistically significant: 13.6 % vs. 4.8 % ($p>0.05$).

The analysis of serum GDNF levels in relation to clinical outcomes showed that lower GDNF levels were associated with worse clinical outcomes: the mean GDNF level in ASAS20 non – responders was 2.915±1.466 pg/ml, which was 1.5 times lower than in ASAS20 responders, where the quantitative value was 4.395±2.298 pg/ml ($p<0.01$). The mean level of GDNF in ASAS40 non – responders was 3.228±1.758 pg/mL, which is less than in ASAS40 responders, where the value was 4.672±2.610 pg/mL ($p>0.05$).

We have proposed a mathematical model that describes the probability of achieving clinical efficacy according to the ASAS 20 criterion depending on GDNF levels. The model was based on a binary

response model (logit regression) with nonlinear estimation. The main characteristics of the model are shown in Table 2.

Table 2

Main characteristics of the ASAS 20 logit response model depending on GDNF levels and NSCLC severity

Indicator	B0	GDNF	Chi-square	p
Score	-2.18475	0.4885	5.8831	0.01529
Odds ratio (one)	0.11251	1.6299		
Odds ratio (range)		132.0750		

The chi-square of this model is quite high, and the p – value is small, which indicates that this model is sufficiently adequate.

The model allows us to establish that there is a significant relationship between the clinical outcome of treatment and GDNF levels. This relationship can be approximated by the following logit regression equation:

ASAS20 = GDNF ((-2.18475)+0.4885 GDNF) / (1 + GDNF ((-2.18475)+0.4885))

The model shows that a higher level of GDNF increases the predicted values of clinical effectiveness of treatment according to ASAS 20; accordingly, the higher the level of GDNF, the greater the likelihood of achieving a clinical outcome of therapy. This allows us to consider a reduced level of GDNF as a predictor of resistance to therapy.

The results obtained in the course of the study indicate a complex relationship between GDNF levels and NP. On the one hand, statistically significant correlations were found between anthropometric parameters, the severity of the NP, the health status of patients with AS and the affective sphere, and the level of GDNF, and on the other hand, the quantitative values of the correlation coefficients are generally low. Obviously, the pathogenetic role of GDNF in pain is complex, however, the data obtained allow us to conclude that the neuropathic component of pain syndrome is associated with a decrease in GDNF levels [1]. In our opinion, the association of reduced GDNF levels with poorer health status and greater severity of depressive manifestations may be mainly mediated by persistent neuropathic pain syndrome, as we found worse indicators of inflammatory process activity, functional capacity of patients, health status, quality of life and affective sphere in patients with AS and NP [1]. Low plasma levels of GDNF are associated not only with NP, but also with higher disease activity, poorer functional capacity, poorer general health, lower quality of life, and worse affective state. The data obtained in our study on the association of reduced GDNF levels with greater severity of pain is consistent with the data of other authors who have established the effectiveness of GDNF in reducing the intensity of pain, which, in turn, confirm the data of fundamental studies on the ability of GDNF to reduce discharge activity in sensory neurons and prevent and reverse sensory abnormalities through the regulation of nociceptors, as well as to promote the regeneration of damaged neurons [10, 11].

Some differences in inflammatory process activity in patients with normal GDNF levels, in our opinion, have a multifactorial genesis and require further in-depth studies. The involvement of GDNF in inflammatory processes remains unexplored, although recent studies indicate that GDNF may play an important role in pathogenesis. In our opinion, the effects of improving patients' functional capacity and health status at higher levels of GDNF are natural, as they are based on a positive impact on the restoration of normal neural network activity, which is consistent with other studies [13]. Similarly, the positive correlations of GDNF with patients' quality of life appear to be mainly due to a decrease in pain severity and better functional capacity in patients with higher levels of GDNF, which is consistent with other authors who have found improved functioning under the influence of GDNF [2]. The effect of GDNF on the mental sphere, in addition to the indirect effect by reducing the severity of pain, may also be related to the dopaminergic effects of GDNF: for example, some studies have shown that GDNF increases dopamine metabolism and improves brain biodistribution, which has a positive effect on mental functioning. Experimental studies have shown that GDNF is necessary for the normal implementation of behavioral patterns and provides resistance to stress while maintaining basic behavioral responses, emotional status, and mnemonic and cognitive abilities [2, 8, 10]. This also helps to explain the improved cognitive functioning in patients with normal GDNF levels found in our study. It should be noted that, regardless of the neurobiological mechanisms of improved mental functioning, the actual role of GDNF in the normalization of the mental sphere in patients with NP can be considered confirmed, which opens up new opportunities for the comprehensive treatment of diseases with a neuropathic pain component.

Our data on the lower efficacy of therapy in patients with reduced levels of GDNF are generally consistent with the data of current studies, which have demonstrated that higher levels of GDNF are associated with less severity of pain, better functional capacity of patients, quality of life and mental functioning [2; 10; 13]. At the same time, there are currently no studies investigating the association of GDNF with AS treatment outcomes, so our data are important both to supplement the existing scientific information on the therapeutic role of GDNF and to the prospects of using GDNF levels as a predictor of therapeutic resistance.

Thus, the data obtained in our study strongly suggest that reduced plasma GDNF levels are associated with worse clinical outcomes in terms of pathological process activity, functional capacity of patients, health status, quality of life, and affective state, as well as a significantly worse response to treatment. This allows us to consider the reduced level of GDNF as a predictor of resistance to therapy.

During the preparation of this manuscript, several limitations were identified, including a relatively small sample size, incomplete follow-up data, and limited access to certain laboratory and instrumental investigations.

Conclusion

It has been confirmed that AS is accompanied by pronounced changes in the psychoemotional sphere of patients, which are an integral part of the complex clinical picture of the disease.

Higher levels of GDNF increase the predicted values of clinical efficacy of treatment according to ASAS 20; accordingly, the higher the level of GDNF, the greater the likelihood of achieving a clinical outcome of therapy.

Normal levels of GDNF can be considered as a predictor of greater sensitivity to treatment and expectation of better therapeutic outcomes.

Reduced plasma GDNF levels are associated with worse clinical outcomes in terms of disease activity, patient functional capacity (BASMI), health status (ASAS EF, BAS-G 7 days, HAQ), quality of life, and psychoemotional status (depression and reactive anxiety). Therefore, reduced levels of GDNF can be considered as a factor in the worse clinical, functional and psychological state of patients during treatment, which will require more complex and prolonged therapy, which allows us to consider reduced GDNF levels as a predictor of resistance to therapy.

A promising direction for further research is to study the features of the dynamics of GDNF production, taking into account biological, individual-typological, circadian factors, concomitant pathology and other factors, as well as to study the dynamics of GDNF during treatment. Further research in this area will improve the stratification of patients with ankylosing spondylitis, increase the effectiveness of diagnosis and treatment, which will affect the quality of life of patients and improve the prognosis of the disease.

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