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Anxiety-Depressive Disorders and Neurotrophic Control in Post-Traumatic Gunshot Neuropathies and Plexopathies Accompanied by Chronic Neuropathic Pain Syndrome

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Abstract: *Introduction:* Injuries of peripheral nerves and plexuses usually cause serious impairment of the function of the affected limb. Peripheral nerve injuries not only affect the physical capabilities of the injured person due to the loss of motor or sensory function, but also have a significant impact on psychosocial aspects of life. *Materials and Methods:* The study included 93 men aged 21 to 59 years with neuropathies and plexopathies of traumatic and non-traumatic origin, which were divided into 3 groups. Neurological, electroneuromyographic, and ultrasound examinations were performed on the patients. The visual analog scale (VAS), the questionnaire DN4 (Douleur Neuropathique 4 Questions), and the questionnaire Pain Detect were used to determine the pain syndrome. The Hospital Anxiety and Depression Scale (HADS), the Center for Epidemiologic Studies Depression (CES-D) Scale, Spielberger State-Trait Anxiety Inventory (STAI) was used to assess and identify psycho-emotional disorders. Immunological examination was performed from 12 to 24 months from the onset of the disease. *Results:* The content of nerve growth factor (Beta-NGF) in patients of the III group at a statistically significant level depends on the presence of anxiety and depressive disorders in patients (Mann–Whitney U test, p=0.0231). Thus, in patients with post-traumatic gunshot neuropathies and plexopathies in the presence of an anxiety and depressive disorder, the level of Beta-NGF is 404.9 [352.1; 1007] pg/ml, which is significantly higher than in patients without an anxiety and depressive disorder 58.3 [26; 322, 1] pg/ml. A correlation between the content of Beta-NGF and the visual analog scale (VAS) (R=0.88, p=0.00001) was revealed in patients with post-traumatic gunshot neuropathies and plexopathies accompanied by chronic neuropathic pain syndrome. *Conclusion:* According to the obtained research data, signs of a subclinical and clinically expressed anxiety and depression can negatively affect the severity of the pain syndrome and its subjective assessment by the patient, thus reducing the effectiveness of drug correction of chronic neuropathic pain. It was found that in patients with post-traumatic gunshot neuropathies and plexopathies in the presence of an anxiety and depressive disorder, the level of Beta-NGF is significantly higher (p=0.0231) than in patients without an anxiety and depressive disorder, which indicates the initiation of the homeostatic function of Beta-NGF in order to compensate for the existing pathophysiological changes.

Keywords: Post-Traumatic Neuropathies and Plexopathies, Chronic Neuropathic Pain Syndrome, Anxiety, Depression, Lymphocytotoxicity, Nerve Growth Factor

1. Introduction

Injuries of peripheral nerves and plexuses usually cause serious impairment of the function of the affected limb. The frequency of neuropathic pain is very high and can reach 95% of cases [1]. Pain after a nerve injury can prevent recovery and return to normal life [2]. Peripheral nerve injuries not only affect the physical capabilities of the injured person due to the loss of motor or sensory function, but also have a significant

impact on psychosocial aspects of life [3].

The number of traumatic injuries to the nerves of the limbs is increasing annually, which is associated with ongoing military conflicts, terrorist acts, industrial injuries and extreme sports. Neuropathic pain is characterized by sensory as well as affective disorders, which may indicate that pain and mood disorders share common pathogenetic mechanisms. According to the obtained biological and neuroimaging data, it was found that common areas of the brain are involved in the regulation of painful and emotional experiences [4]. Chronic pain with a neuropathic component has been shown to be associated with poorer quality of life, reduced work capacity and greater psychological distress than chronic pain without a neuropathic component [5]. Neuropathic pain is characterized by sensory symptoms such as increased or loss of somatosensory function, burning and evoked pain, and abnormal temporal summation [6]. Models of nerve damage have shown that sensory disturbances occur due to interactions between neurons, immune and immune-like glial cells, as well as other immune cell-derived inflammatory mediators, in this sense neuropathic pain is a neuroimmune disorder [7]. Supraspinal neuroinflammation plays a potential role in the development of affective disorders in patients with neuropathic pain. In a number of studies, it was found that sick behavior, cognitive impairment, depression and other neuropsychiatric disorders have immune mechanisms associated with pro-inflammatory cytokines and chemokines [8]. It has been assumed that changes in neurotrophins are the basis of the violation of neuroplasticity, which may be associated with the development and course of depression. According to this data, antidepressant therapy can have a positive effect by strengthening trophic signaling on synaptic and neuronal plasticity [9]. Chronic neuropathic pain syndrome has a negative effect on the patient's emotional state - the mood decreases, irritability and unmotivated anxiety appear. Against the background of such changes, depressive disorders often arise.

Further study of the pathogenetic mechanisms of the formation of chronic neuropathic pain syndrome and the identification of the relationship with affective disorders, timely detection and correction of anxiety and depressive disorders, can contribute to the acceleration of the rehabilitation process of this category of patients.

The aim is to study the role of anxiety and depressive disorders and their relationship with nerve growth factor in patients with post-traumatic gunshot neuropathies and plexopathies accompanied by chronic neuropathic pain syndrome.

2. Materials and Methods

2.1. Study Design

This was a prospective, observational study of patients hospitalized due to neuropathies and plexopathies in Military Medical Clinical Center, Kharkiv, Ukraine from 2015 to 2021. The study included 93 men aged 21 to 59 with neuropathies and plexopathies of traumatic and non-traumatic genesis, who were divided into 3 groups. The I group included 30 patients with compression-ischemic neuropathies and plexopathies, of which 25 had neuropathy, 5 had plexopathy. The II group included 30 patients with post-traumatic non-gunshot neuropathies and plexopathies, as a result of bone fractures of the lower and upper limbs, joint dislocations, soft tissue injuries, injuries inflicted by a knife, glass, of which neuropathy - 26, plexopathies - 4. Group III included 33 patients with post-traumatic gunshot neuropathy and plexopathy (22 shrapnel and 11 bullet wounds of the extremities), of which neuropathy - 27, plexopathy - 6.

All patients were invited to participate, and signed the informed consent. The study was conducted according to the guidelines of Helsinki, and approved by the Academic Board of Kharkiv Medical Academy of Postgraduate Education (protocol# 9 and date of approval 13 November 2019) as part of a larger study.

2.2. Exclusion Criteria

Patients were excluded from the study if they were diagnosed with chronic viral and bacterial infections, central nervous system diseases, autoimmune, oncological and hematological disorders. Patients with compression-ischemic neuropathies and plexopathies were evaluated on scales and questionnaires to detect chronic neuropathic pain. If patients in group I with compression-ischemic neuropathies and plexopathies were diagnosed with chronic neuropathic pain, they were excluded from the study.

2.3. Methods

Neurological, electroneuromyographic, and ultrasound examinations were performed on the patients. The visual analog scale (VAS) was used to assess the severity of pain. To assess neuropathic pain, we used the DN4 questionnaire, which is convenient for a screening study. It was created as a tool for the diagnosis and differential diagnosis of neuropathic pain [10]. The Pain Detect questionnaire was used to identify spontaneous and induced symptoms, the nature of the course (constant, paroxysmal) of neuropathic pain. The questionnaire most fully reflects all possible parameters of pain and allows you to visually monitor the picture of the pain syndrome in dynamics. Its sensitivity is 83% [11]. The Hospital Anxiety and Depression Scale (HADS) was used to assess and detect psycho-emotional disorders. The HADS scale reflects the psychogenic component of the pain syndrome, the degree of symptoms of anxiety and depression present in patients, and allows them to be detected both at the clinical and subclinical levels [12]. The Center for Epidemiologic Studies Depression (CES-D) scale was used to detect depression. The scale includes 20 items, each of which determines the subjective frequency of depressive symptoms and is ranked from 0 (the symptom occurs very rarely or never at all) to 3 (the symptom is present all the time) [13]. The definition of anxiety was carried out according to the Spielberger State-

Trait Anxiety Inventory (STAI), the scale allows differentiating anxiety as a personal property and as a state [14]. Immunological research was carried out from 12 to 24 months after the onset of the disease. Determination of the content of membranotropic cytotoxic factors was carried out using the Terasaki test. The level of membranotropic cytotoxic factors was judged by the percentage of living and damaged cells [15]. Quantitative determination of the beta subunit of human nerve growth factor (Beta-NGF) in serum was carried out by enzyme immunoassay using the Ray Bio Human Beta-NGF ELISA Kit.

2.4. Data Analysis

Data processing and analysis were performed using the STATISTICA 10 (StatSoftInc., USA) and SPSS 27 (IBM, USA). Quantitative comparisons were carried out by non-parametric methods using the median test, Mann–Whitney U test. Quantitative variables are presented as mean with standard deviation (M ± SD) in case of normal distribution and median with 25% - 75% interquartile range (Me [LQ;UQ]) for variables with non-normal distribution, where Me is the median, LQ is the lower quartile, UQ is the upper quartile. Qualitative variables - in the form of numerical values with a percentage of the total number. The relationship between indicators was assessed using Spearman's rank correlation (R). Differences at $p<0.05$ were considered statistically significant.

3. Results

In patients of the I group with compression-ischemic neuropathies and plexopathies anxiety was diagnosed in 7 (23.3%), and depression in 6 (20%) cases. In patients of the II group with post-traumatic non-gunshot neuropathies and plexopathies, anxiety was detected in 9 (30%) patients, depression in 8 (26.7%) cases. In the II group, chronic neuropathic pain syndrome was detected in 5 patients (16.6%). Among patients of the III group with post-traumatic gunshot neuropathies and plexopathies, anxiety was detected in 11 (33.3%) patients, depression in 11 (33.3%) patients. In group III, chronic neuropathic pain syndrome was diagnosed in 28 patients (84.8%).

Pursuant to the CES-D scale, in group I, depressive disorders were detected in 6 (20%) patients, most of whom had mild depression 4 (13.3%); patients with moderate 1 (3.3%) and severe 1 (3.3%) depression were found much less often. In accordance with the HADS, anxiety was detected in 23.3% of patients and depression in 20% of cases: subclinically expressed anxiety and depression were observed in 3 (10%) and 4 (13.3%) patients, respectively, clinically expressed anxiety and depression in 4 (13.3%) and 2 (6.7%) patients.

In the II group, pursuant to the CES-D scale, depressive disorders were detected in 8 (26.6%) patients, 6 (20%) of whom had mild depression; patients with moderate 1 (3.3%) and severe depression met much less frequently 1 (3.3%). In accordance with the HADS, anxiety was detected in 9 (30%) and depression in 8 (26.6%) cases: subclinical anxiety and depression were observed in 3 (10%) and 3 (10%) patients, respectively, clinically expressed anxiety and depression in 6 (20%) and 5 (16.6%) patients.

According to the CES-D scale in group III, depressive disorders were detected in 11 (33.3%) patients, of whom 6 (18.1%) had mild depression, 4 (12.1%) had moderate depression and 1 (3.1%) had severe depression. In compliance with the hospital anxiety and depression scale (HADS), anxiety was found in 33.3% of patients and depression in 33.3% of cases: subclinical anxiety and depression were observed in 5 (15.1%) and 5 (15.1%) patients, clinically expressed anxiety and depression in 6 (18.2%) and 6 (18.2%) patients, respectively. Anxiety disorders were also diagnosed using the Spielberger State-Trait Anxiety Inventory. Low state anxiety was detected in group I in 3 (10%), in group II in 3 (10%), in group III in 4 (12.1%) patients. Moderate state anxiety was detected in group I in 4 (13.3%), in group II in 6 (20%), and in group III in 7 (21.2%) patients. Low trait anxiety was found in 3 (10%) of the I group, 4 (13.3%) of the II group, 6 (18.2%) of the III group. Moderate trait anxiety was found in 4 (13.3%) of the I group, 5 (16.7%) of the II group, 5 (15.2%) of the III group of patients.

Most patients complained of physical weakness, increased fatigue, low mood, anxiety, irritability. During the conversation with the patients, a decrease in mood, depression, a tendency to increase fears regarding the future of life and the prognosis of their disease were noted, during a detailed survey, complaints of sleep disturbances and appetite were revealed. A targeted survey of patients with chronic neuropathic pain syndrome revealed such symptoms as increased fatigue, anxiety, and irritability. Most of such patients presented only complaints related to the disease of the peripheral nervous system: chronic pain, paresthesias, limitation of movements in the limb due to pain (difficulties in sensory evaluation and clear description of pain were often observed), increased fatigue, weakness. The analysis of the results of testing as per psychometric scales revealed that patients often experience feelings of guilt, difficulty in making decisions, and a vision of the future being hopeless due to disability.

According to the research results, we found that the level of Beta-NGF (see Figure 1) in patients of the III group with post-traumatic gunshot neuropathies and plexopathies at a statistically significant level depends on the presence of an anxiety disorder in patients (Mann–Whitney U test, $p=0.0231$). Thus, in patients with post-traumatic gunshot neuropathies and plexopathies in the presence of an anxiety disorder, the level of Beta-NGF is 404.9 [352.1; 1007] pg/ml, which is significantly higher than in patients without an anxiety disorder 58.3 [26; 322.1] pg/ml.

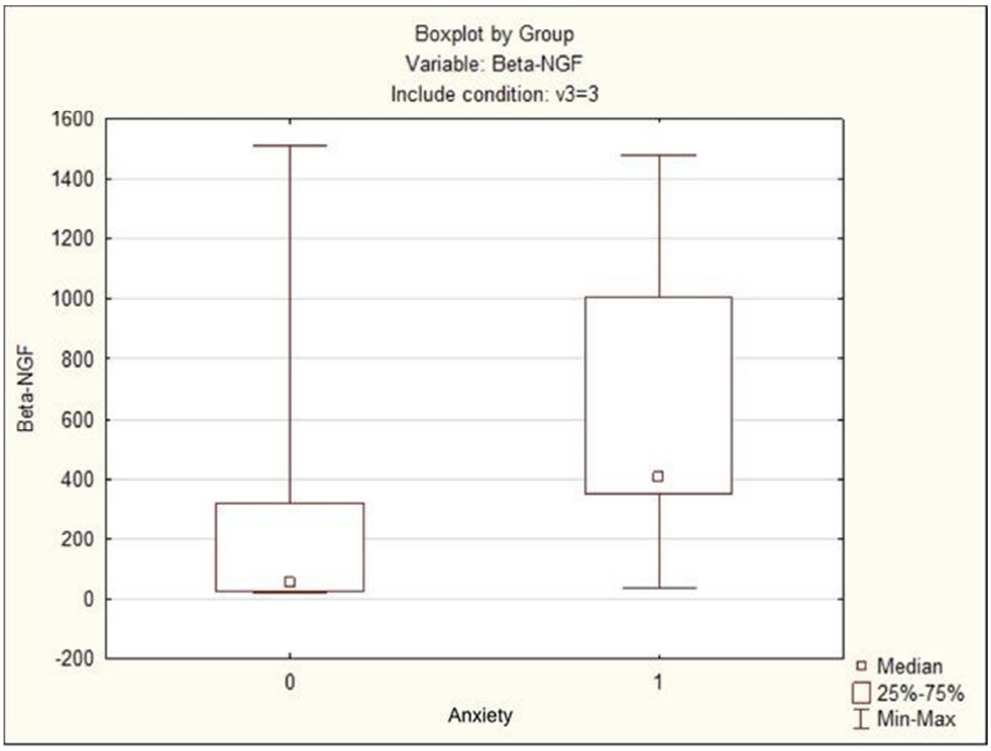

Figure 1. *Quantitative content of nerve growth factor (Beta-NGF) in patients with post-traumatic gunshot neuropathies and plexopathies in the presence/absence of anxiety (pg/ml).*

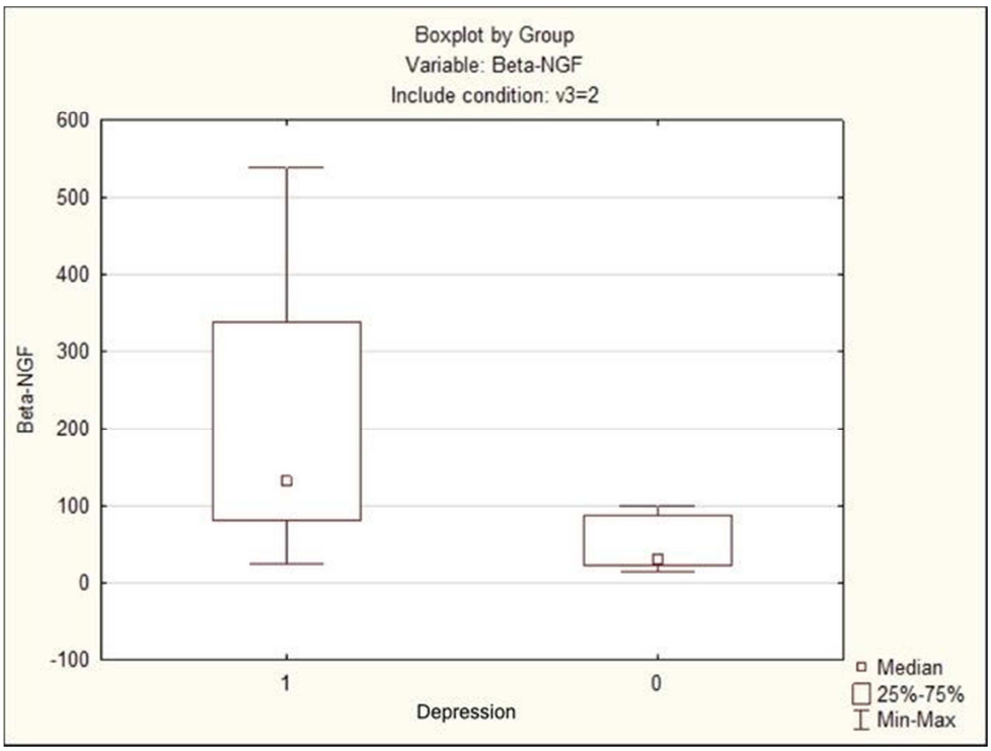

Figure 2. *Quantitative content of nerve growth factor (Beta-NGF) in patients with post-traumatic non-gunshot neuropathies and plexopathies in the presence/absence of depression (pg/ml).*

It was also found that the level of Beta-NGF (see Figure 2) in patients of the II group with post-traumatic non-gunshot neuropathies and plexopathies at a statistically significant level depends on the presence of depression in patients (Mann–Whitney U test, p=0.0056). Thus, in patients with post-traumatic neuropathies and plexopathies in the presence of a depressive disorder, the level of Beta-NGF is 132.4 [81.1; 337.9] pg/ml, which is significantly higher than in patients without a depressive disorder 31.1 [22.8; 88] pg/ml.

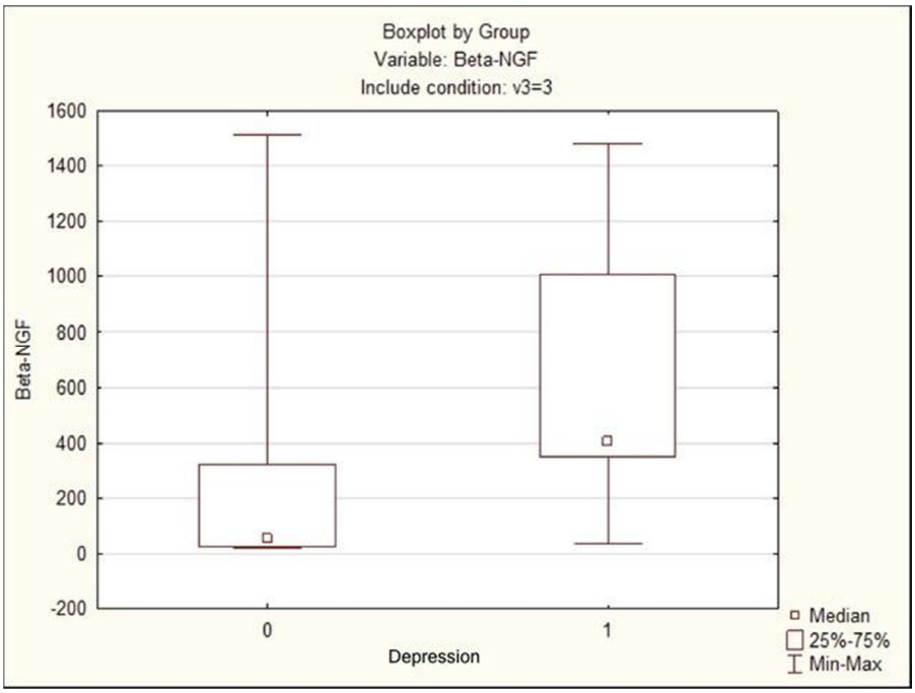

Figure 3. *Quantitative content of nerve growth factor (Beta-NGF) in patients with post-traumatic gunshot neuropathies in the presence/absence of depression (pg/ml).*

Conforming to the obtained research data, the level of Beta-NGF (see Figure 3) in patients of the III group with post-traumatic gunshot neuropathies and plexopathies at a statistically significant level depends on the presence of depressive disorder in patients (Mann–Whitney U test, p=0.0231). Thus, in patients with post-traumatic gunshot neuropathies and plexopathies in the presence of a depressive disorder, the level of Beta-NGF is 404.9 [352.1; 1007] pg/ml, which is significantly higher than in patients without a depressive disorder 58.3 [26; 322.1] pg/ml.

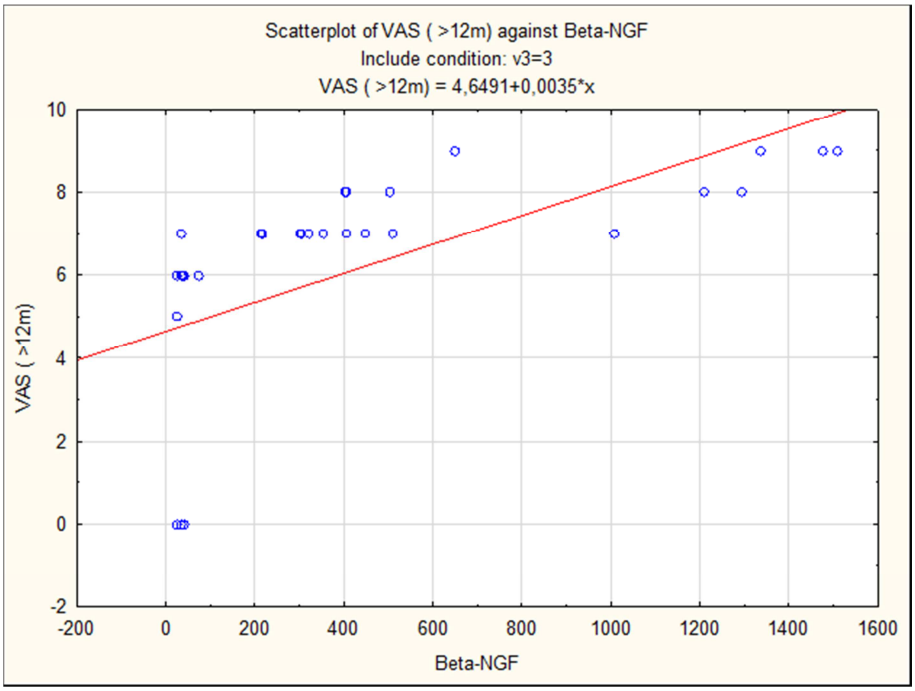

Figure 4. *Correlation content of nerve growth factor (Beta-NGF) with the visual analog scale (VAS) (pg/ml).*

A correlation was found between the content of Beta-NGF (see Figure 4) and the visual analog scale (VAS) (R=0.88, p=0.00001) in patients with post-traumatic gunshot neuropathies and plexopathies accompanied by chronic neuropathic pain syndrome. According to the research results, the visual analog scale (VAS) score directly depends

on the level of Beta-NGF in the peripheral blood.

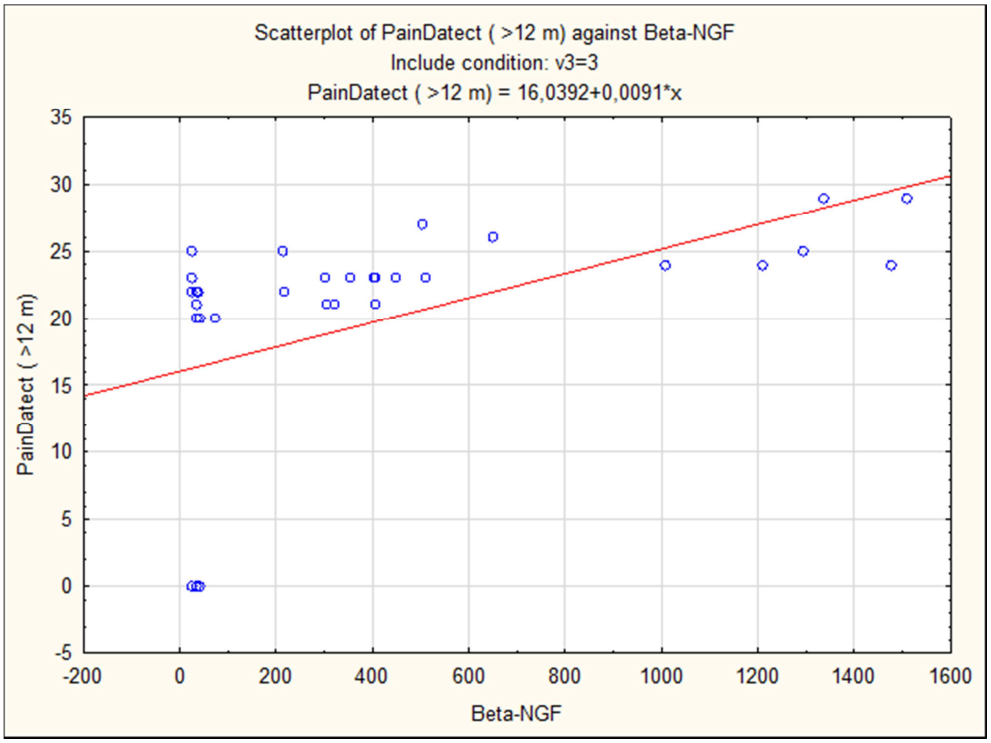

Figure 5. *Correlation content of nerve growth factor (Beta-NGF) with the questionnaire PainDetect (pg/ml).*

A correlation was found between the content of Beta-NGF (see Figure 5) and the PainDetect questionnaire score (R=0.67, p=0.000017) in patients with post-traumatic gunshot neuropathies and plexopathies accompanied by chronic neuropathic pain syndrome. The obtained research results show that the PainDetect questionnaire score directly depends on the level of Beta-NGF in the peripheral blood. Patients rate their pain as more pronounced with a high content of nerve growth factor.

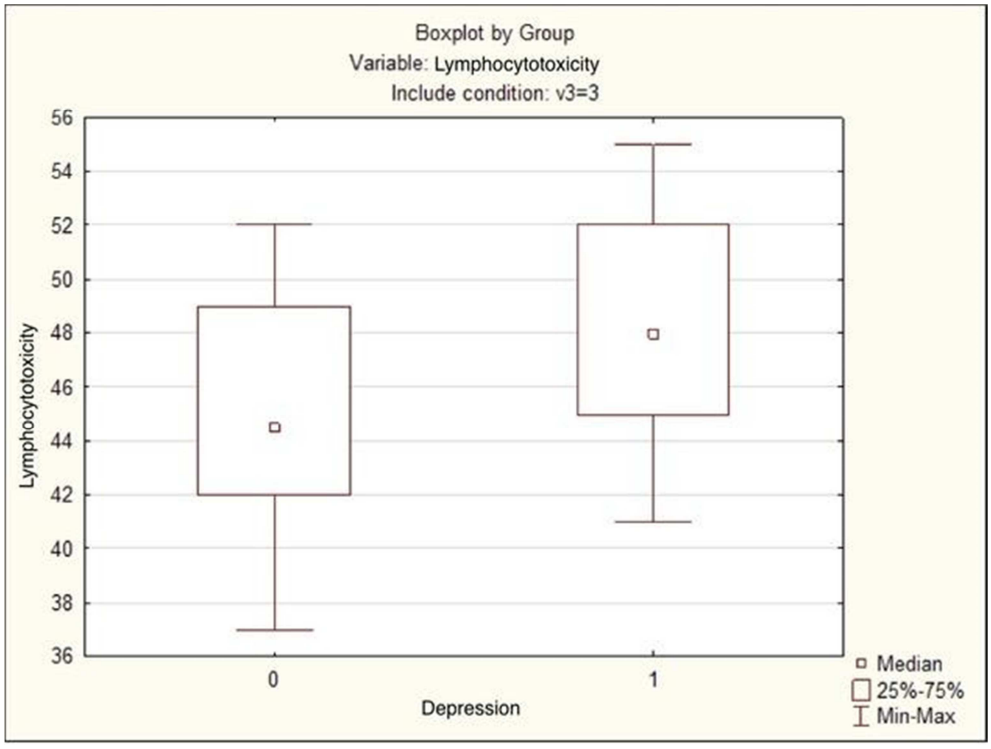

Figure 6. *Indicators of lymphocytotoxicity in patients with post-traumatic gunshot neuropathies and plexopathies in the presence/absence of depression.*

It was also found that, at a statistically significant level, lymphocytotoxicity (see Figure 6) depends on the presence of a concomitant depressive disorder (Mann–Whitney U test, p=0.0419). Thus, in patients of III group in the presence of depression, an increase in lymphocytotoxicity is noted, compared to patients without a depressive disorder, which demonstrates neuroimmune regulation and its influence on the course of post-traumatic gunshot neuropathies and plexopathies accompanied by chronic neuropathic pain syndrome.

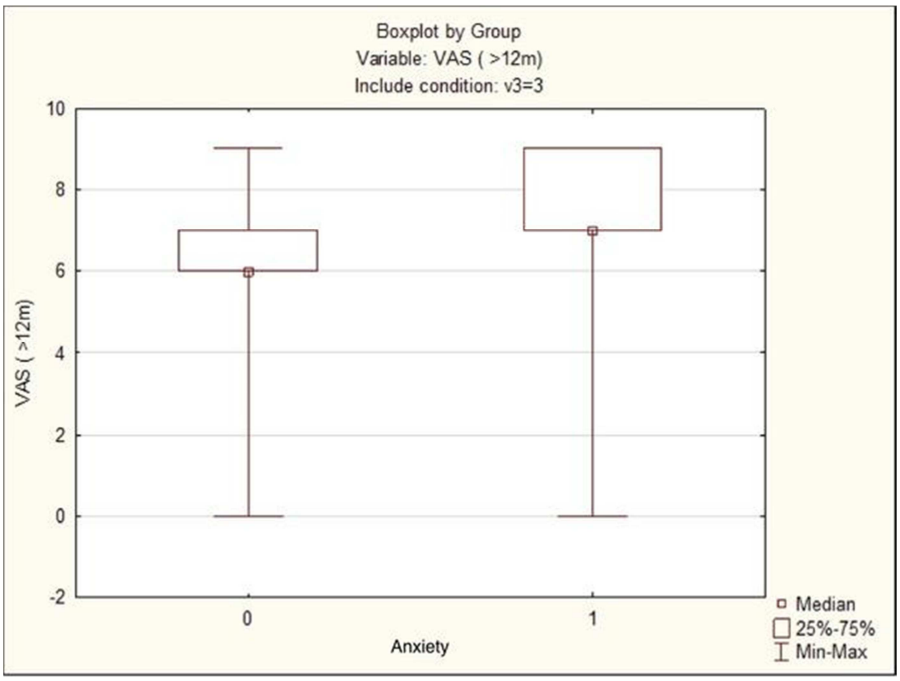

Figure 7. *Visual analogue scale (VAS) scores in patients with post-traumatic gunshot neuropathies and plexopathies in the presence/absence of anxiety.*

The visual analog scale (VAS) indicators, and thus the subjective assessment of the severity of the pain syndrome (see Figure 7), in patients with post-traumatic gunshot neuropathies and plexopathies accompanied by chronic neuropathic pain syndrome at a statistically significant level depends on the presence of anxiety in the patient (Mann–Whitney U test, p=0.0242). In the presence of anxiety, the pain on the visual analog scale (VAS) is assessed as more pronounced.

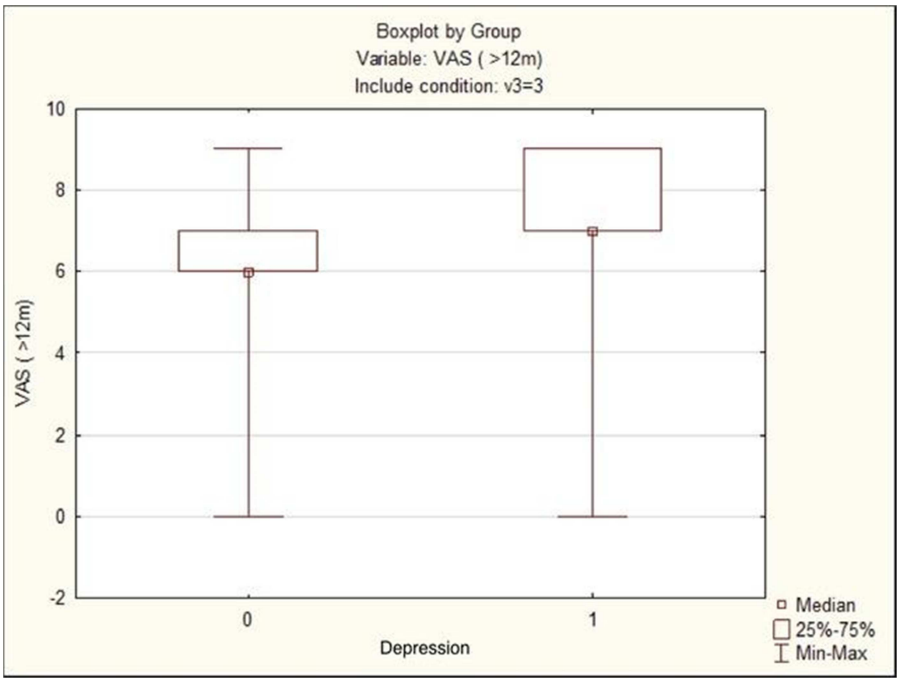

Figure 8. *Visual analogue scale (VAS) scores in patients with post-traumatic gunshot neuropathies and plexopathies in the presence/absence of depression.*

Scores of the visual analog scale (VAS), namely the subjective assessment of the severity of the pain syndrome (see Figure 8), in patients with post-traumatic gunshot neuropathies and plexopathies accompanied by chronic neuropathic pain syndrome at a statistically significant level also depend on the presence of depression (Mann–Whitney U test, $p=0.0242$). In the presence of depression, pain on the visual analog scale (VAS) is assessed as more pronounced. It should be noted that as the duration of the chronic pain syndrome increases, the severity of disorders of the affective sphere (of an anxious and depressive nature) increases, but the indicators of each of these disorders were different depending on the duration of the disease. A significant relationship ($p<0.05$) was found between the duration of the pain syndrome and the severity of anxiety and depressive disorders, namely, the manifestations of anxiety disorders decreased with the increase in the duration of the neuropathic pain and depressive disorders increased.

4. Discussion

According to a study by Pittenger and Duman, among many candidates, neurotrophic growth factors and related signaling pathways are major players in neuroplasticity, and the obtained data indicate that impaired nerve growth factor signaling is associated with depressive mood [16]. As a result of our study, we found that in patients with post-traumatic gunshot neuropathies and plexopathies in the presence of depression, the level of Beta-NGF in the peripheral blood is significantly higher than in patients without a depressive disorder.

In a study by Overstreet D. H., Fredericks K., Knapp D., Breese G., McMichael J. described that 14-day subcutaneous administration of NGF to rats of the Flinders Sensitive line (a genetic model of depression in animals) contributes to a decrease in immobility time in the forced swim test, indicating a reduction in depressive disorders on the background of NGF administration [17]. Thus, according to the obtained results of the study, we associate that a statistically significant increase in the level of Beta-NGF in patients with post-traumatic gunshot neuropathies and plexopathies accompanied by chronic neuropathic pain syndrome and depressive disorders compared to patients without depressive disorders indicates the initiation of the homeostatic function of Beta-NGF in order to compensate for the existing pathophysiological changes.

5. Conclusions

Chronic neuropathic pain increases depression and anxiety, worsens physical and mental functioning of patients. Thus, the severity of anxiety and depressive states depends, first of all, on the severity of the neuropathic pain syndrome. Therefore, according to the obtained research data, signs of subclinical and clinically expressed anxiety and depression can negatively affect the severity of the pain syndrome and its subjective assessment by the patient, thus reducing the effectiveness of medication correction of chronic neuropathic pain syndrome. In young people who do not have concomitant pathology and define the pain syndrome as moderate, post-traumatic neuropathies and plexopathies can have a course without affective disorders. The development of affective disorders is influenced by many factors, among which the characteristics of the pain syndrome itself (duration, frequency of occurrence, intensity), presence and compensation of concomitant pathology can be distinguished. As a result of the study, it was found that in patients with post-traumatic gunshot neuropathies and plexopathies in the presence of anxiety and depressive disorders, the level of Beta-NGF is significantly higher ($p=0.0231$) than in patients without anxiety and depressive disorders, which indicates the initiation of the homeostatic function of Beta-NGF in order to compensate for existing pathophysiological changes. The approach to the treatment of patients with chronic neuropathic pain syndrome should be carried out comprehensively, combining treatment of the main disease, therapy and achieving compensation of accompanying disorders, correction of affective manifestations.

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