

Features of Neurotrophic Control and Correlation with Eosinophils and CD2- Receptors of Peripheral Blood T-Lymphocytes in Patients with Post-Traumatic Gunshot and Non-Gunshot Injuries of Nerves and Plexuses of Limbs

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ABSTRACT

Introduction: Peripheral nerve injuries are common conditions with a broad spectrum of symptoms depending on the severity and nerves involved. Although a large amount of knowledge about the mechanisms of damage and regeneration has been accumulated, but the number of reliable methods of treatment that ensure full functional recovery is not enough.

Materials and Methods: The study included 93 men aged 21 to 59 years with neuropathies and plexopathies, which were divided into 3 groups. All patients underwent neurological, electroneuromyographic, and ultrasound examination. Immunological research was carried out during 12 to 24 months after the onset of the disease.

Results: In our study, we found a statistically significant correlation between the content of Beta-NGF and the level of peripheral blood eosinophils ($R=0.41$, $p=0.0191$) in patients with post-traumatic gunshot neuropathies and plexopathies. A correlation between the content of Beta-NGF and the CD2+ indicator levels ($R=0.56$, $p=0.00105$) in patients with post-traumatic non-gunshot neuropathies and plexopathies was revealed.

Conclusion: The analysis of the received research data and literature resources demonstrates an important correlation between the neurotrophins and immunological indicators, which opens up further promising opportunities in the development and use of complex pathogenetic therapy of post-traumatic neuropathies and plexopathies in order to improve the restoration of impaired functions and the quality of life of patients.

Keywords

Neurotrophins, Injuries of nerves and plexuses, Immunological indicators, Eosinophils, CD2-receptors.

Introduction

Peripheral nerves and plexuses are particularly vulnerable to injury and are involved in numerous pathologies [1]. Peripheral nerve injuries are common conditions with a broad spectrum of symptoms depending on the severity and nerves involved. Although a large amount of knowledge about the mechanisms of

damage and regeneration has been accumulated, but the number of reliable methods of treatment that ensure full functional recovery is not enough [2]. A key role in the maintenance and functioning of peripheral nerves is played by cells that perform a different function than neurons. Schwann cells cover nerves with a myelin sheath and provide trophic support through the release of important neurotrophins such as nerve growth factor (NGF). Myelin improves conduction velocity by restricting the regions of ionic transfer along the axon to the nodes of Ranvier, resulting in faster propagation of the action potential, called saltatory conduction

[3,4]. Schwann cells play a significant role in promoting axonal regeneration as they are a major source of neurotrophic factors that normally interact with tyrosine kinase receptors to alter the gene expression profile of the neuron to promote regeneration [5,6]. NGF has a low level of expression in healthy nerves, but is activated in Schwann cells under injury. NGF promotes Schwann cell growth and proliferation, also is contained in Schwann cell receptors, which line up the bands of Bungner to provide trophism for the sprouting axon. Many neurotrophic factors have been identified, the functions of which vary from improving cell survival through apoptosis prevention mechanisms to promoting regeneration factors in neurons and Schwann cells [7]. It was found that NGF interacts with a number of other target cells in the nervous system, as well as with extraneuronal targets, such as mast cells, T- and B-lymphocytes, granulocytes, monocytes, keratinocytes, endotheliocytes, and hormone-secreting cells of the reproductive system [8-10]. Immune cells are also required for the beneficial effects produced by NT-3 in neurological injury animal models. NT-3 can enhance the sprouting of corticospinal axons preserved after unilateral corticospinal axotomy in rats, but not in immunosuppressed or athymic rats, indicating the importance of T-cells in neuroplasticity [11,12].

Basophils, eosinophils and mast cells secrete the contents of their granules into the surrounding tissue, thereby realizing chemical protection against the large pathogens. Numerous studies at the molecular, genetic and immunological levels revealed the presence of a large number of morphological and functional systems in eosinophils. The universal influence of eosinophils on normal and pathological processes in the body is associated with the presence on their surface and in the granules of various receptors for biologically active substances, especially H1 and H2, enzymes, aggregated IgE and IgG, the accumulation of which in the granules leads to the release of such various lympho- and chemokines, such as leukotrienes, interleukins, prostaglandins, as well as trace elements and enzymes. Eosinophil formation is probably regulated by T-cells through secretion of hematopoietic growth factors such as granulocyte-macrophage colony-stimulating factor, interleukin-3, and interleukin-5. Granulocyte-macrophage colony-stimulating factor and interleukin-3 increase the production of other myeloid cells, and interleukin-5 stimulates the formation only of eosinophils. Eosinophilic granules contain a core protein and an eosinophilic cationic protein that are toxic to a number of parasites and mammalian cells. Eosinophilic neurotoxin can cause severe damage to the myelin sheath of neurons. Most eosinophilic leukocytes in the human body are localized in mucosa; however, the role of eosinophils in human disease is not fully understood. An important role in increasing the number of eosinophils in tissues, leading to the development of eosinophilic inflammation and necrosis of the covering epithelium of the mucous membrane, is played by the content of such proteins as large basic protein, cationic protein, neurotoxins, and eosinophilic X-protein [13]. Thus, further research of the relationship and influence of the nervous and immune systems on each other will contribute to the deepening of knowledge and the development of drug treatment.

The aim is to study the features of neurotrophic control and its correlation with immunological indicators in patients with post-traumatic gunshot and non-gunshot injuries of the limb's nerves and plexuses.

Materials and Methods

In the Military Medical Clinical Center, Kharkiv, Ukraine from 2015 to 2021, 93 men aged 21 to 59 with neuropathies and plexopathies were examined, who were divided into 3 groups. Group I included 30 patients with compression-ischemic neuropathies and plexopathy, out of which neuropathy - 25, plexopathy - 5. Patients who had manifestations of neuropathic pain syndrome were not included into group I. Group II included 30 patients with post-traumatic non-gunshot neuropathies and plexopathies, out of which neuropathy - 26, plexopathies - 4. In-group II, chronic neuropathic pain syndrome was diagnosed in 5 patients (16.6%). Group III included 33 patients with post-traumatic gunshot neuropathies and plexopathies (22 shrapnel and 11 bullet wounds of the limbs), out of which 27 patients had neuropathy, 6 had plexopathies. In-group III, chronic neuropathic pain syndrome was diagnosed in 28 patients (84.8%).

All patients underwent neurological, electroneuromyographic, and ultrasound examination. Immunological research was carried out during 12 to 24 months after the onset of the disease. Quantitative determination of 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. Quantitative determination of neurotrophin-3 (NT-3) in serum was carried out by enzyme immunoassay using the Ray Bio Human NT-3 ELISA Kit. To evaluate the expression of CD2+, CD3+, CD4+, CD8+ differentiation clusters in T- and B-lymphocyte subpopulations, the immunofluorescence method was used with monoclonal antibodies labeled with FITC dye.

Data processing and analysis were performed using the STATISTICA 6.0 program (StatSoftInc., USA) and SPSS 27.0 (IBM, USA). Quantitative comparisons were carried out by non-parametric methods using the median test, the Mann-Whitney U test. The relationship between indicators was assessed using Spearman's rank correlation (R). Differences at $p < 0.05$ were considered as statistically significant.

Results

A correlation between the content of Beta-NGF and NT-3 ($R=0.53$, $p=0.00234$) in peripheral blood in patients with post-traumatic non-gunshot neuropathies and plexopathies was found (see Figure 1). According to the results of the study, the level of NT-3 in patients of group II directly depends on the level of Beta-NGF in the peripheral blood, i.e. as the level of Beta-NGF in the peripheral blood increases, the level of NT-3 increases too, which indicates the relationship between the neurotrophins Beta-NGF and NT-3 in patients with post-traumatic non-gunshot neuropathies and plexopathies.

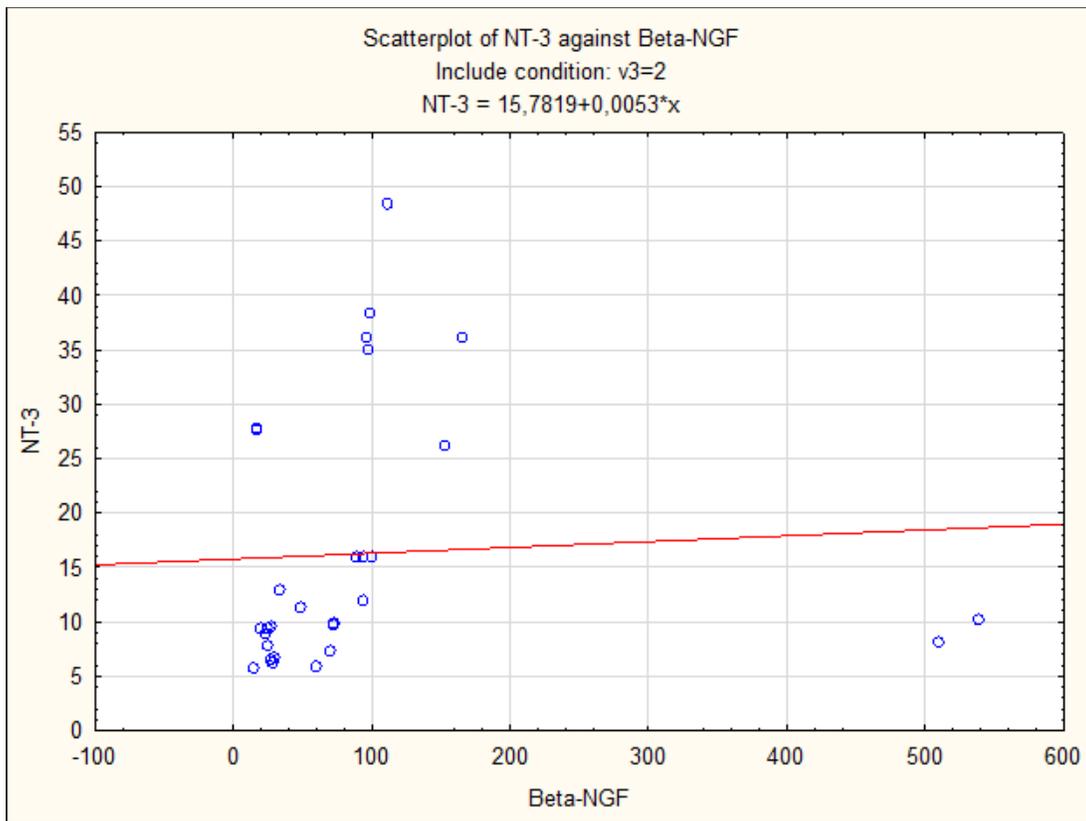


Figure 1: Correlation between nerve growth factor (Beta-NGF) and NT-3 content in peripheral blood patients with post-traumatic non-gunshot neuropathies and plexopathies peripheral blood (pg/ml).

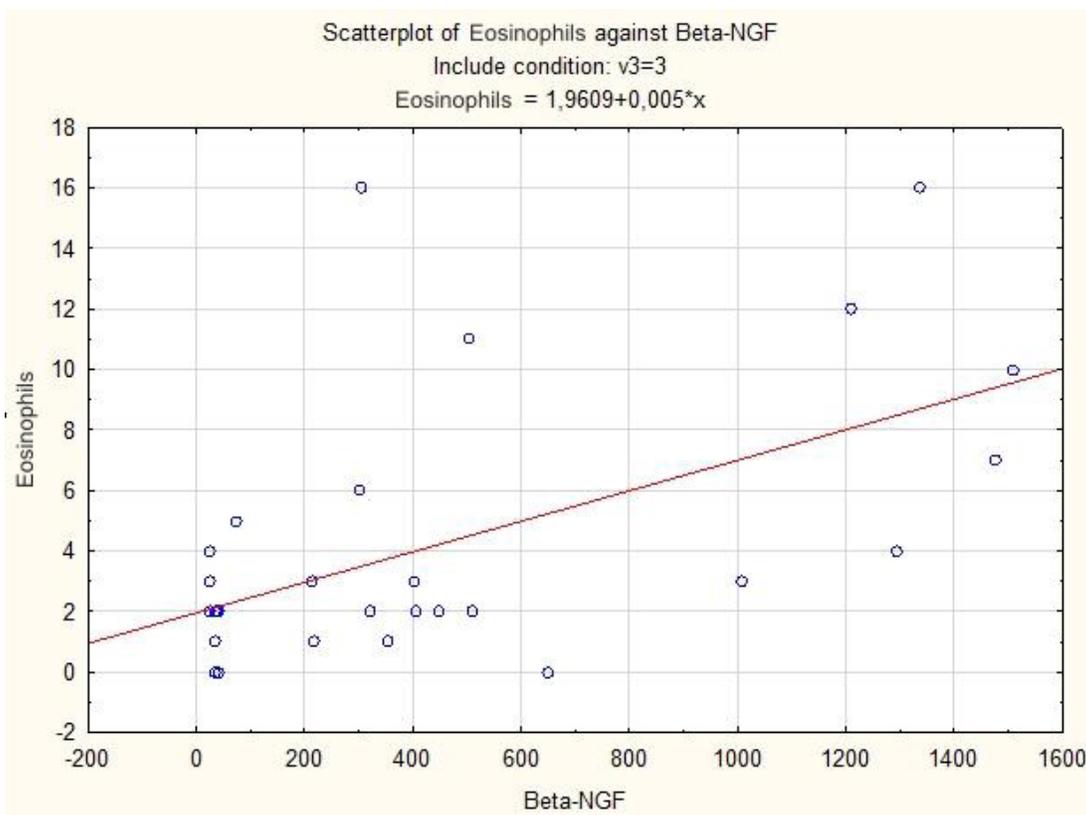
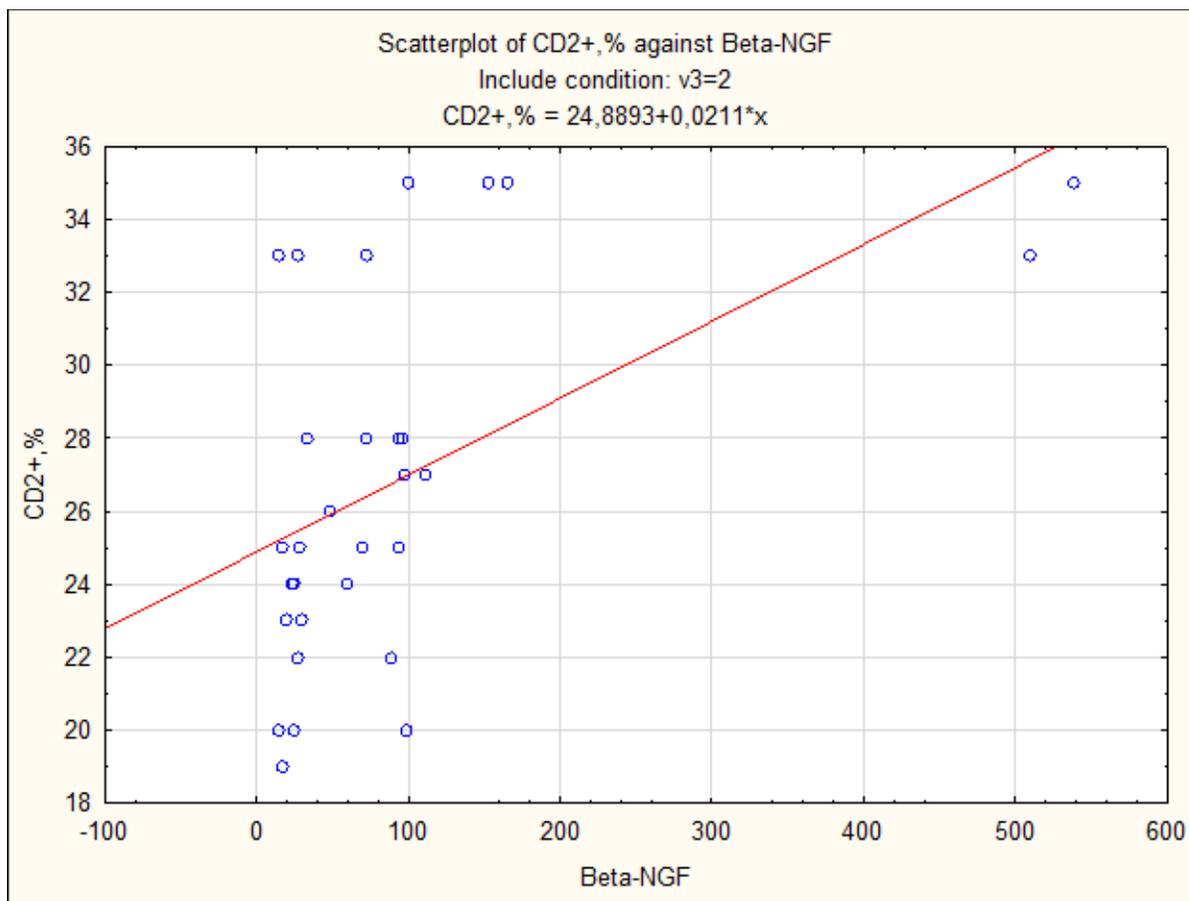


Figure 2: Correlation between Beta-NGF content and the level in peripheral blood eosinophils in patients with post-traumatic gunshot neuropathies and plexopathies (pg/ml).



contacts occurs, which further allows T-lymphocytes to respond to a lower concentration of antigens. This pair of receptors, working in a complex with other adhesion molecules, mediates the successful course of the body's immune response [15]. In our study, we found that in patients with post-traumatic non-gunshot neuropathies and plexopathies, with the increase of peripheral blood Beta-NGF levels, the level of CD2+ increases too, indicating a correlation between Beta-NGF and CD2-markers of T-lymphocytes, which affects the immune response.

Conclusions

A statistically significant correlation between the content of Beta-NGF and peripheral blood eosinophils level ($R=0.41$, $p=0.0191$) was found in patients with post-traumatic gunshot neuropathies and plexopathies. With an increase in Beta-NGF, the level of peripheral blood eosinophils also increases. Thus, the release of NGF from eosinophils is aimed at supporting the survival of neurons, while the concomitant release of other eosinophils' mediators, such as large basic protein, neurotoxin, supports eosinophilic inflammation and contribute to the damage of nerve or plexus the myelin sheath, which is one of the pathophysiological mechanisms of the formation and preservation of chronic neuropathic pain syndrome in patients with post-traumatic gunshot neuropathies and plexopathies after 12 months from an injury with damage to the nerves and plexuses of the limbs.

It was established that in patients with post-traumatic non-gunshot neuropathies and plexopathies with an increase in the level of Beta-NGF in the peripheral blood, the level of CD2+ increases ($R=0.56$, $p=0.00105$), which indicates a relationship between Beta-NGF and CD2 markers T-lymphocytes, thus Beta-NGF induces an immune response to the process of chronic inflammation and damage to peripheral nerves and plexuses of limbs.

The analysis of the received research data and literature resources demonstrates an important correlation between the neurotrophins and immunological indicators, which opens up further promising opportunities in the development and use of complex pathogenetic therapy of post-traumatic neuropathies and plexopathies in order to improve the restoration of impaired functions and the quality of life of patients.

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