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EVALUATION OF HUMAN IMMUNOGLOBULIN EFFECTIVENESS IN PATIENTS WITH SENSORY-MOTOR POLYNEUROPATHY ASSOCIATED WITH MONOCLONAL GAMMAPATHY OF UNDETERMINED SIGNIFICANCE

Abstract

Introduction. A number of paraproteinemic polyneuropathy is directly linked to the monoclonal gammopathy of undetermined significance (MGUS). One of the first manifestations of MGUS in addition to the secretion of monoclonal immunoglobulin, and long before the manifestation of malignancy is polyneuropathy. **The objective of the study**: To evaluate the efficacy of human immunoglobulin therapy in order to correct signs of peripheral neuropathy associated with MGUS. **Materials and Methods**. 16 patients with MGUS-associated polyneuropathy aged 53–78 were examined. Patients underwent a course of infusion therapy with human immunoglobulin in the dose of 0.4 g/kg for 5 days. **Results.** A decrease in symptoms of sensory component of neuropathy, neuropathic pain and sensitive ataxia was observed, which was confirmed by electroneuromyography and posturography data, a Lovett scale grade, Neuropathy Disability Score, and the Pain detect questionnaire data. The motor component of polyneuropathy had more persistent symptoms. **Conclusion.** Treatment with human immunoglobulin is effective in reduction of neuropathic pain and sensory ataxia and in increase of superficial and deep sensation, while the motor component of polyneuropathy had more persistent symptoms.

Key words: *human immunoglobulin, paraproteinemic polyneuropathy, monoclonal gammopathy of undetermined significance*

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MGUS — monoclonal gammopathy of undetermined significance, BF — biofeedback, VS — vibratory sensation, RR — Romberg ratio, MAG — myelin-associated glycoprotein, WM — Waldenstrom macroglobulinemia, MM — multiple myeloma, PP — paraproteinemic polyneuropathy, SP — solitary plasmacytoma, CIDP — chronic inflammatory demyelinating polyneuropathy, ENMG — electroneuromyography.

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Introduction

Paraproteinemic polyneuropathies (PP) comprise 30% of cases of various chronic inflammatory demyelinating polyneuropathies and 5% of all known polyneuropathies [1, 2]. Peripheral neuropathies induced by paraproteinemia usually develop secondary to paraproteinemia that include such diseases as multiple myeloma (MM), solitary plasmacytoma (SP), Waldenstrom macroglobulinemia (WM), etc. The pathogenic mechanism of paraproteinemia is based on the secretion of monoclonal immunoglobulins (paraproteins). The source of tumor growth in paraproteinemia is a B lymphocyte. It has been confirmed that neoplastic transformation takes place at the level of B cell precursors (they retain the ability to differentiate into immunoglobulin-producing cells: lymphocytes or plasma cells). A clone of neoplastic B cells produces immunoglobulins that are homogeneous in their immunochemical properties (paraproteins). Peripheral nerve damage that manifests itself as sensory, sensory-motor, or motor signs of polyneuropathy is the most common paraneoplastic disorder of the nerve system in paraproteinemias. Paraprotein is a monoclonal serum protein (M-protein) that is produced by a proliferating clone of plasma cells. Clonal proliferation can be neoplastic or non-neoplastic in nature. M-protein is usually an immunoglobulin (IgM, IgG, IgA, or IgD) [2, 3]. Monoclonal Ig can act as an antibody against myelin or axolemma components. Some PPs are directly related to monoclonal gammopathy of undetermined significance (MGUS), which often precedes the development of cancer. Landgren O., Kyle R. A. et al. in their retrospective study of 213 patients with IgM-MGUS noticed a high risk of MGUS progression to MM (68%), WM (11%), or lymphoma (8%) [4, 5]. One of the first symptoms of MGUS, apart from the production of a monoclonal immunoglobulin long before any signs of malignancy, is PP, whose clinical signs often precede the main oncological disease by 3–5 years [6, 7]. The mechanism leading to nerve tissue damage in MGUS is mediated by the production of myelin-associated glycoprotein (MAG). Development of anti-MAG antibodies results in nerve damage and predominantly demyelinating neuropathy [8]. The basis of pathogenic damage to peripheral nerves in PP is the toxic effect of a monoclonal paraprotein. Currently, PP treatment, especially in the case of MGUS, is based on symptoms. At the advanced stages of malignant processes with paraproteinemia, chemotherapy is usually used. However, it is limited due to its neurotoxicity. There are some data on the efficacy of human immunoglobulins and rituximab in PP associated with MGUS [9, 10]. The lack of clear criteria for the diagnosis of PP associated with MGUS and the absence of routine and standardized diagnostic and therapeutic approaches for this polyneuropathy imposes significant difficulties in real practice.

Study Objective

To evaluate the efficacy of human immunoglobulin in order to correct signs of peripheral neuropathy associated with MGUS.

Materials and Methods

A total of 16 patients with paraproteinemia and clinical signs of paraproteinemic peripheral neuropathy were examined. The patients were aged 53 to 78 years, where 5 of them were women (31.25%) and 11 were men (68.75%). The median age was 64 years. The median period between the diagnosis and the patient enrollment to the observation was 11 months (1 to 48 months). All included patients had clinical signs of peripheral neuropathy, which were confirmed by neurological examination and electroneuromyography (ENMG). The paraproteinemic nature of peripheral neuropathy was confirmed by the presence of paraproteins (M-gradient) in patients' blood (the mean concentration was 6.8 g/L), elevated kappa- or lambda-chain levels in serum and urine, albuminocytologic dissociation in the cerebrospinal fluid, and exclusion of other causes of polyneuropathy.

PP associated with MGUS was diagnosed based on the common MGUS diagnostics criteria (proposed by the experts from Anderson Cancer Center in the USA) [11]: M-component: IgG of less than 30 g/L, IgA of 10 g/L, light chains in the urine of less than 1 g/L, plasma cells in the bone marrow biopsy sample of less than 10%,

proliferative index of plasma cells of less than 1%, no destruction lesions or bone tissue damage on X-rays and MRIs, and no kidney failure, hypercalcemia, anemia, bone pain, or extramedullary lesions.

Comprehensive evaluation of neurologic and functional deficiency in PP patients included the following: muscle strength, superficial (pain, temperature) and deep sensitivity (vibration, position sense), assessment of subjective signs of polyneuropathy (complaints of numbness, burning sensation, paresthesias, and other symptoms). A six-grade Lovett scale was used to assess muscle strength [12]. Vibratory sensation (VS) was assessed using a graded tuning fork (C128 Hz) in accordance to Rydel-Seiffer, from 0 to 8 units. The tuning fork was placed on standard points of prominences of the radial bone as well as on the dorsum of the great toe, ankle, and shin. VS was measured three times at each point, and the mean value was then calculated based on these measurements. The obtained parameter was expressed in the graded tuning fork units. ENMG was performed using Viking IV and Viking Select devices, in supine position, both before the initiation of treatment and one month afterwards. To measure the conduction velocity in motor and sensory fibers of peripheral nerves, we stimulated the median, radial, ulnar, tibial, peroneal, and sural nerves. The indicators specified in the *Laboratory Reference for Clinical Neurophysiology* (Jay A. Livenson, Dong M. Ma, 1992) were used as the normal values of ENMG [13]. Patients with PP were tested using the Neuropathy Disability Score (NDS) in order to produce a comprehensive assessment of neurological deficiency [14]. The severity of PP was assessed by testing the threshold of four sensitivity types (touch, pain, temperature, and VS) and studying reflexes (patellar and Achilles reflexes) using internationally-accepted standardized tests for peripheral sensory motor neuropathy. To assess the thresholds quantitatively, each sensitivity type (touch, pain, temperature, VS) was assigned points (0 to 5) depending on the severity of damage. An algorithm was developed to convert VS damage from relative units to points. Reflex damage was also expressed as numerical score in terms of points (0 to 2). The sum of mean values for each sensitivity type on two limbs and the sum of values for each 4 reflexes provided an insight to the presence or absence of peripheral neuropathy. A total score of 1 to 4 points indicated mild peripheral neuropathy. A score of 5 to 13 points indicated moderate neuropathy, and one of 14 to 28 points indicated severe neuropathy.

The Pain Detect questionnaire was used to evaluate neuropathic pain [15, 16]. The Pain Detect questionnaire is completed by a physician and combines a picture with a visual analogue scale for pain distribution and a questionnaire aimed at detecting spontaneous and stimulated symptoms of neuropathic pain. The Pain Detect questionnaire also makes it possible to assess the character of pain: continuous, paroxysmal pain, or both, etc. A Pain Detect score of 0 to 12 points indicates low probability of neuropathic pain (less than 15% probability), one of 13 to 18 points indicates an undetermined result with possible neuropathic component, and one of 19 to 38 points indicates a high probability of neuropathic pain (more than 90% probability).

Peripheral neuropathy was determined based on diagnostic and polyneuropathy criteria identified by Dyck P. J., 1998. These diagnostic criteria included the following: 1. Impulse conduction in motor and sensor nerve fibers; 2. Findings of neurologic examination; 3. Quantitative tests of motor, sensor and autonomic functions; 4. Presence of symptoms (subjective signs) of polyneuropathy. If the patient met less than two of these criteria, this indicated the absence of polyneuropathy [11].

Before and after a course of treatment, each patient underwent a stabilometric test on a ST-150 platform with biofeedback (BF). ST-150 stabilometric testing (Figure 1) was performed on days 1 and 14 of observation. After a preliminary test of balance on a stabilometric platform using a classic variant of the Romberg Test, according to both open-eyed and close-eyed procedures and with plotting of statokinesiograms, the data were processed in Stabip software, including the calculation of the Romberg ratio (RR), which is a parameter that characterizes the relationship between the visual and proprioceptive systems. RR is defined as the percentage (%) ratio of the area of a statokinesiogram obtained with open eyes to that obtained with closed eyes [17]. The mean normal values of RR lie between 150% and 300%.

Figure 1. *Force plate ST-150*

All patients received daily intravenous infusions of 0.4 g/kg of human immunoglobulin with premedication consisting of intramuscular injection of Analgin 50% — 2.0 ml and diphenylhydramine 1% — 1.0 ml.

Standard statistical methods were applied. Statistical analysis included calculation of mean values, standard errors (error of mean), analysis of variance (standard deviation), and parametric t-test, which is a confidence parametric coefficient; p is value (for 95% confidence interval it is equal to: 1 – 0.95 = 0.05) [18], $p < 0.05$ was considered significant. To evaluate the efficacy of the developed diagnostic and therapeutic combinations, we used the following parameters: method sensitivity, specificity and accuracy (diagnostic accuracy, diagnostic efficiency).

Results and Discussion

Before treatment with human immunoglobulin, the mean NDS score in the study group was 16, indicating severe neuropathy. According to a comprehensive assessment of neurologic status, 43.6% of patients experienced a 25% drop in the muscle strength of their lower limbs, 24.07% of patients experienced no decrease in muscle strength, 16.6% of patients experienced a 50% decrease, 11.1% of patients experienced a 75% decrease, and 4.6% of patients experienced a decrease of more than 75%. 62.5% of patients showed decreased Achilles and patellar reflexes, and 37.5% of patients experienced complete loss of deep reflexes in the lower limbs. According to a neurologic status assessment that was performed before treatment, the VS in medial shin was 3.85 ± 0.34 ($p < 0.001$) in this group. The Pain Detect questionnaire showed a mean score of 26, which corresponds to a high probability of the neuropathic pain component (> 90%).

The most common complaints among patients with PP were loss of sensation and prickling in feet which coincided with the findings of the neurologic examination, including a decrease and/or loss of deep reflexes and stocking and glove pattern. It also confirms the findings of ENMG.

The ENMG before the initiation of treatment showed signs of diffuse damage to peripheral nerves (sensory motor polyneuropathy) predominantly in the lower limbs, with decreased amplitude of M-response from the sural nerve down to 3.36 ± 0.35 ($p < 0.05$) in all patients. Therefore, paraprotein-associated polyneuropathy in our patients was predominantly distal, sensory motor (with some predominance of sensory component) and axonal-demyelinating in nature.

According to preliminary testing on a ST-150 platform, the mean RR was 670% ($p < 0.05$) (Table 1). The analysis in Stabip software included statokinesiograms plotted based on Romberg test performed using a stabilometric platform with open and closed eyes.

Statokinesiograms before neurorehabilitation showed significant impairment of balance with closed eyes (Figure 2), which indicated severe signs of sensory ataxia.

Therefore, symptoms of PP associated with MGUS are quite diverse and often have clinical similarities with chronic inflammatory demyelinating polyneuropathy (CIDP) [19, 20]. Axonal damage of peripheral nerves, thin non-myelinated fibers, and multiple asymmetric mononeuropathy syndrome are less common. One of the typical clinical signs of PP associated with MGUS is the presence of severe impairment of superficial and deep sensitivity manifesting as numbness and paresthesia of the limbs, loss of balance

and stability when walking, which are sometimes accompanied by pronounced neuropathic pain syndrome [15, 19, 21].

After the treatment, the parameters were as follows: NDS score was 14, VS from the medial shin was 4.45 ± 0.20 Rydel-Seiffer units (p < 0.001), RR was 560% (p < 0.05) (Figure 3), mean amplitude of M response from the sural nerve was 3.46 ± 0.43 (p < 0.05) (Table 1). The mean Pain Detect score after treatment was 22, indicating a decrease in neuropathic pain.

According to data from the literature, treatment of PP with MGUS uses standard procedures adopted for CIDP [21, 22, 23] despite the presence of paraproteinemia. However, corticosteroids were found to be effective in only 30% of cases of PP with MGUS. Oral or intravenous chemotherapeutic alkylating agents proved themselves to be effective in every second case, but their use is limited due to severe adverse effects, including neurotoxicity. According to the conducted studies, intravenous immunoglobulins are effective in every fifth patient with PP associated with MGUS, and plasmapheresis are effective in every third one [21, 24]. In our case, the preferred treatment option was intravenous administration of

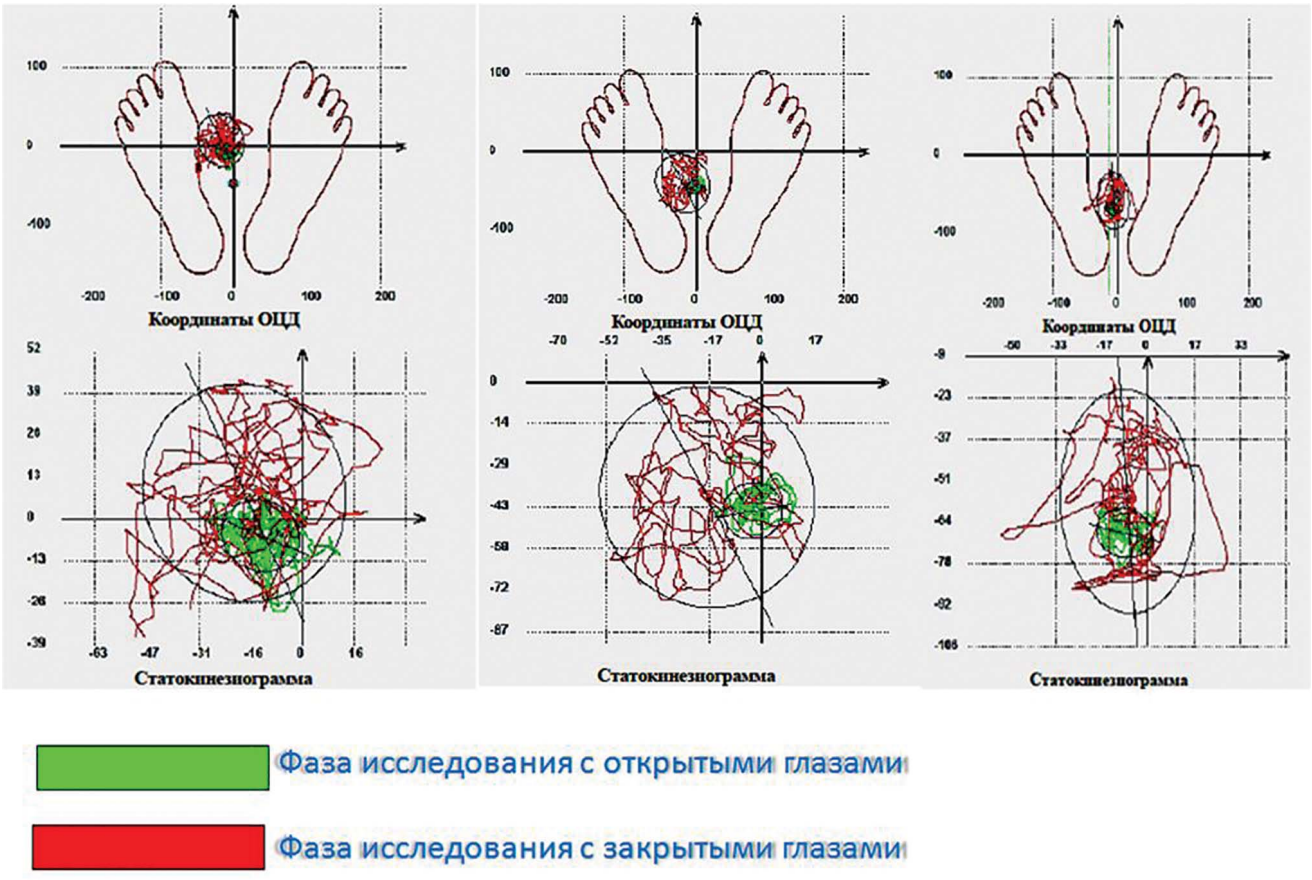

Figure 2. *Examples of statokinesiograms in opened- eyes and closed-eyes phases*

Table 1. *Clinical and laboratory parameters changing in patients on therapy*

	Mean score before therapy	Mean score after therapy	Level of significance
Pallesthesia, UM	3,85±0,34	4,45±0,20	p<0,001
Mean amplitude of M-response from the sural nerve, mV	3,36±0,35	3,46±0,43	p<0,05
Romberg ratio, %	670	560	p<0,05

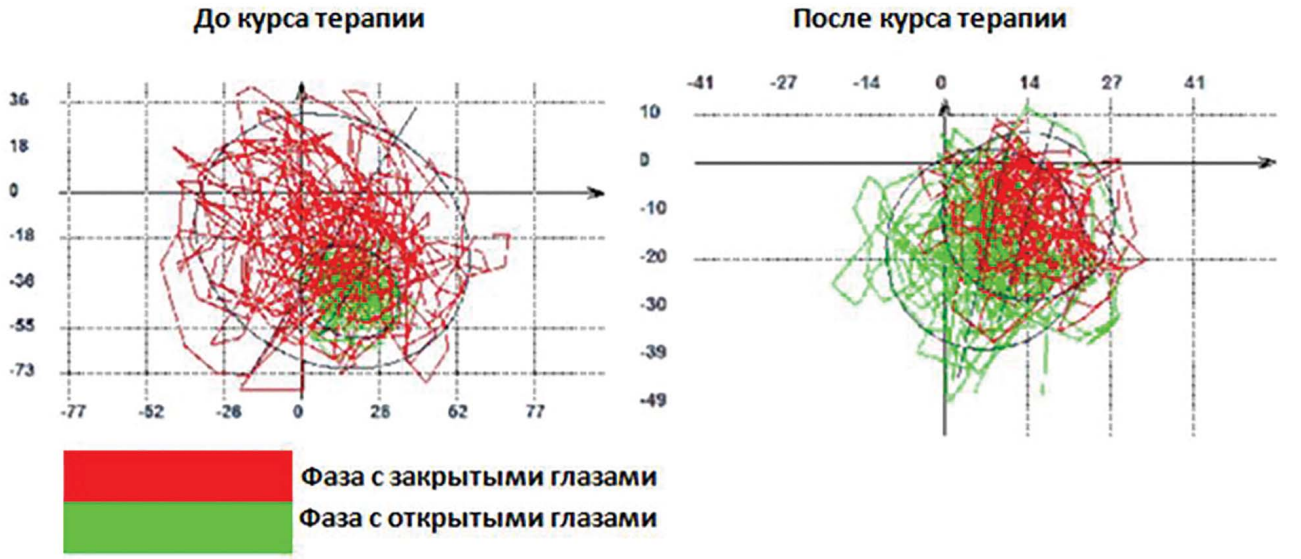

Figure 3. *Example of statokinesiograms before and after therapy*

human immunoglobulins. The choice of human immunoglobulin as the main method of pharmaceutical therapy was based on the relative non-malignancy of MGUS, low concentration of paraprotein (less than 30 g/L), and relatively pronounced damage to peripheral nerves with motor and sensory components where neurotoxic medications (such as cytostatic agents) would impose a risk of the development of toxic (post-cytostatic) polyneuropathy component. The main positive effect after treatment in our case was a decrease in the sensory component of polyneuropathy and reduced neuropathic pain as well as decreased sensory ataxia. The motor component of polyneuropathy was characterized by more persistent signs. No adverse reactions to human immunoglobulin were recorded in our study.

Conclusion

Treatment of peripheral neuropathy associated with MGUS with human immunoglobulin (0.4 g/kg for 5 days) was effective in relation to decreased neuropathic pain and signs of sensory ataxia as well as improved superficial and deep sensitivity (as confirmed by ENMG data). The motor component of polyneuropathy associated with MGUS was more resistant to human immunoglobulin. According to several international studies [21, 24] and our study, therapy based on human immunoglobulin has proven itself to be safe for patients with PP that is associated with MGUS, and these patients have shown that they can tolerate the procedure. The treatment can be recommended as one of the preferred methods to correct for clinical signs of peripheral neuropathy in patients with paraproteinemia and who have a paraprotein level that does not exceed 30 g/L.

Conflict of interests

The authors declare no conflict of interests.

References:

1. Ginzberg M.A., Varlamova E.Y., Ryshko V.V. et al. Clinical and neurophychological assessment of chronic demyelinating polyneuropathy associated with monoclonal secretion. Medical Council. 2015; 10: 93-96 [In Russian].
2. Levin O.S. Polyneuropathies: clinical guidelines. 2nd edition. Moscow; 2006; 486 p. [In Russian].
3. Schmidt E.B., Moller-Petersen J. Monoclonal Gammopathy in General Practice Diagnostic Value of Typing and Quantitation of Immunoglobulins. Scandinavian Journal of Primary Health Care. 1985; 3(2): 91-94. https://doi.org/10.3109/02813438509013923.
4. Kyle R.A. Monoclonal gammopathy of undetermined significance: natural history in 241 cases. Am. J. Med. 1978; 64: 814–26. https://doi.org/10.1016/0002-9343(78)90563-6.

5. Landgren O., Kyle R.A., Pfeiffer R.M. et al. Monoclonal gammopathy of undeterminedsignificance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood 2009; 113(22): 5412–5. https://doi.org/10.1182/blood-2008-12-194241.
6. Belyakov K.M., Gustov A.V. Paraneoplastic polyneuropathies. Nizhnii Novgorod: NizhGMA press; 2007; 96 p. [In Russian].
7. Dyck P.J. Detection, characterization, and staging of polyneuropathy: assessed in diabetics. Muscle Nerve 1988; (11): 21–32. https://doi.org/10.1002/mus.880110106.
8. Larue S., Bombelli F., Viala K. et al. Non-anti-MAG DADS neuropathy as a variant of CIDP: clinical, electrophysiological, laboratory features and response to treatment in 10 cases. Eur. J. Neurol. 2011; 18: 899–905. https://doi.org/10.1111/j.1468-1331.2010.03312.x.
9. Mata S., Borsini W., Ambrosini S. et al. IgM monoclonal gammopathy-associated neuropathies with different IgM specificity. Eur. J. Neurol. 2011; 18: 167–173. https://doi.org/10.1111/j.1468-1331.2010.03345.x.
10. Pestronk A., Florence J., Miller T. et al. Treatment of IgM antibody associated polyneuropathies using rituximab. J. Neurol. Neurosurg. Psychiatry. 2003; 74: 485–489. https://doi.org/10.1136/jnnp.74.4.485.
11. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br. J. Haematol. 2003; 121(5): 749-757. https://doi.org/10.1046/j.1365-2141.2003.04355.x.
12. Petrov K.B., Ivanchin D.M. Medical Gymnastics at Paralyses of the Foot. LFK i massash. Sportivnaya medicina. 2008; 1(49): 37-43 [In Russian].
13. Livenson Jay A., Dong M. Ma. Laboratory reference for clinical neurophysiology (1992). Pain. 2005; 313-314.
14. Young M.J., Boulton A.J.M., Macleod A.F. et al. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993; 36: 150–154. https://doi.org/10.1007/bf00400697.
15. Backonja M-M., Krause S.J. Neuropathic Pain Questionnaire-Short Form. Clin. J. Pain. 2003; 19: 315-316. https://doi.org/10.1097/00002508-200309000-00005.
16. Freynhagen R., Baron R., Gockel U., Tolle T. Pain detect: a new screening questionnaire to detect neropathic components in patients with back pain. Curr. Med. Res. Opin. 2006; 22: 1911-20.
17. Skvortsov D.V. Stabilometric testing. Short guidance. Moscow: Mera-TSP. 2010; 174 p. [In Russian].
18. Banergi A. Medical Statistics Made Clear. Translated from english by Leonov V.P. Moscow: Practical Medicine. 2007; 287 p. [In Russian].
19. Suponeva N.A., Pavlov E.V. Diagnostics and basic treatment of chronic polyneuropathies. Doctor. 2009; 4: 43–44 [In Russian].
20. Rosenberg N., Portegies P., de Visser M. et al. Diagnostic investigation of patients with chronic polyneuropathy: evaluation of a clinical guideline. J. Neurol. Neurosur. Psychiat. 2001; 71: 205–209. https://doi.org/10.1136/jnnp.71.2.205.
21. Suponeva N.A., Nikitin S. Chronic polyneuropathies assotiated with monoclonal gammapathiesю Doctor. Moscow: Publ. house «Russian doctor». 2010; 9: 51-54 [In Russian].
22. Gorson K.C., Allam G., Ropper A.H. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. Neurology. 1997; 48(2): 321-328. https://doi.org/10.1212/wnl.48.2.321.
23. Poncelet A. An algorithm for the evaluation of peripheral neuropathy. Am. Fam. Physician. 1998; 57(4): 755–764.
24. Radl J., Valentijn R.M., Haaijman J.J., Paul L.C. Monoclonal gammapathies in patients undergoing immunosuppressive treatment after renal transplantation. Clin. Immunol. Immunopathol.1985; 37(1): 98-102, https://doi.org/10.1016/0090-1229(85)90140-0.

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