Fatigue in patients with chronic inflammatory demyelinating polyneuropathy

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is a peripheral neuropathy, predominantly motor neuropathy, with a progressive or relapse-remitting course. Fatigue is a condition characterized by a physical or mental feeling of lack of energy or lack of motivation for action, which is often present in patients with CIDP.

Objective: *to assess the severity of asthenia in CIDP patients.*

Patients and methods. *Examinations were made in 34 inpatients treated for documented CIDP that met the international European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria. A study group included patients with CIDP, whereas a comparison group consisted of volunteers without psychiatric illness, who were compensated for somatic diseases.*

Results and discussion. *In the patients with CIDP, the level of fatigue was found to be much higher than normal. Approximately half of the CIDP patients had obvious asthenia. However, the level of fatigue did not correlate with the severity of the course of CIDP.*

Conclusion. *The findings suggest that fatigue is important in patients with CIDP that should be taken into account in the treatment of these patients.*

Keywords: *chronic inflammatory demyelinating polyneuropathy; fatigue; electroneuromyography; neuropathy; peripheral nervous system.*

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is a clinically heterogenous immune-mediated disease of the peripheral nervous system with progressive or relapse-remitting course, muscle weakness, sensory disturbances and areflexia developing in 2 or more months [1, 2].

Worldwide prevalence of CIDP is estimated as 2.81/100,000 with annual prevalence of 0.33/100,000 according to meta-analysis by M. C. Broers et al [3].

In Russia, the prevalence of CIDP estimated as 1-3/100,000 [4]. It can occur at any age with a tendency to develop among the elderly; average age of CIDP onset is 47.6 years [5]. In childhood CIDP occurs less frequently – 0.48/100,000 [5].

Fatigue is a condition with pathological exhaustion after adequate physical activity, lack of energy in solving problem requiring concentration, or a generalized decrease in the ability to act [6]. CIDP patients often note that fatigue is one of the major symptoms, which affects their quality of life [7].

The aim of the study was to assess severity of fatigue in CIDP patients.

Patients and methods. 39 inpatients treated in the 3rd neurological department of City Hospital №2 and 2nd neurological department of the clinic of Research Institute of Neurology of I.P. Pavlov First Saint-Petersburg State Medical University were examined in the period of 2017–2020.

CIDP diagnosis was made according to the international criteria of European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) including clinical presentation and electrophysiological data [8]. Exclusion criteria: mismatch with the EFNS/PNS criteria, decompensated somatic pathology in inpatients.

Of 39 examined patients, 34 had typical CIDP, 2 – multifocal acquired demyelinating sensory and motor polyneuropathy (MADSAM), 1 – sensory, 1 – motor, and 1 – distal acquired demyelinating symmetric polyneuropathy (DADS). Due to a small number of patients with atypical CIDP, the study was performed only in patients with typical CIDP.

Of 34 patients, 18 were male and 16 – female. Age groups at the time of the disease onset were the following: 8 patients of young age (22–42 years, median age – 34.63±1.48 years), 19 patients of middle age (45–59 years, median age – 52.56±0.63 years), 7 patients of older age (60–82 years, median age – 70.43±3.59 years). The comparison group included 15 patients without psychiatric pathology, compensated for somatic pathology (8 males and 7 females, median age – 54.40±4.26 years). There were no differences in sex and age between the groups.

Neurological examination included neurological deficit assessment by Neuropathy Impairment Scale (NIS) and Medical

Research Council scale (MRC). Fatigue was assessed by Fatigue Severity Scale (FSS).

NIS is used for neurological deficit assessment in different polyneuropathies and evaluates muscle strength, sensory function, and reflexes. 26 muscle groups are assessed on both sides: 25% decrease in strength – 1 point, 50% – 2 points, 75% – 3 points, action against gravity – 3.25 points, action without opposition to gravity – 3.5 points, separate muscle contractions – 3.75 points, paralysis – 4 points. Tendon reflexes are assessed as follows: normal – 0 points, decreased – 1 point, absent – 2 points. Tactile, pain, vibration and muscle-joint senses are measured in the index and hallux and assessed similarly: normal – 0 points, decreased – 1 point, absent – 2 points [9].

MRC scale is related to muscle strength measurement in limbs. Actions which are assessed include: shoulder abduction, elbow flexion, hand extension, hip flexion, knee extension, foot dorsiflexion on both sides. Every action is assessed as: full strength – 5 points, decreased strength, but with resistance – 4 points, no resistance, but action can be made against gravity – 3 points, no action against gravity – 2 points, separate muscle contractions – 1 point, paralysis – 4 points [10, 11].

FSS is a 9-item questionnaire measuring fatigue severity and its influence on job and activities of daily living. Answers can range from 1 (absolutely disagree) to 7 (absolutely agree) points with minimum score – 9, and maximum – 63 points. Higher scores mean higher levels of fatigue [12]. This questionnaire is used in many studies and was also validated for Russian population [13].

Database was formed in Microsoft Excel 2007. Statistical data were processed using SPSS Statistics version 22. Normal distribution was tested by Kolmogorov–Smirnov criterion. Assessment of quantitative parameters with normal distribution was made using Student's criterion, without normal distribution – using Mann–Whitney's U-criterion. Statistical analysis was performed at the significance level of 5%.

Results. Level of fatigue in patients with CIDP was estimated as 4.68±0.24 points. Severe level of fatigue (FSS>5) was found in 18 patients (53%).

Fatigue was statistically significantly more severe in females (5.23±0.32 points) in comparison with males (4.19±0.39 points; $p<0.05$; Fig. 1).

The level of fatigue in patients with CIDP was also statistically significantly higher (4.68+0.24 points), than in the comparison group (3.53±0.34; $p<0.05$; Fig. 2).

Correlations between the level of fatigue and disease severity were not found ($p>0.05$). Age had no influence on the fatigue severity either ($p>0.05$; Table).

Discussion. Fatigue is a condition characterized by physical or mental sense of lack of energy or motivation to act [7]. Fatigue can also be described as a disturbance of initiation or support of voluntary activity [14]. Voluntary activity depends on nerve impulse transmission in sensory and motor fibers in the central (CNS) and peripheral nervous system. Sensory signals from muscles, skin and sensory organs pass information to the CNS. After information processing, the motor cortex activates motor nuclei of the brainstem and anterior horns of the spinal cord. Then, signals from the anterior horns are transferred by peripheral nerves to neuromuscular junctions, where the act of motion is performed. Disturbance in any element of these sequence leads to changes in the level of force [14].

Fatigue can be central and peripheral. Peripheral fatigue is inability to support the necessary force of muscle contraction as a result of disturbance of the muscle itself, neuromuscular junction or nerve [12, 14, 15]. Central fatigue develops when the CNS lacks the ability to activate muscles necessary to perform an action. Muscles receive a suboptimal signal form the CNS and cannot perform appropriate contraction due to inability to use all available motor units – it is known as central activation failure (CAF) [15, 16].

Both central and peripheral fatigue occurs in inflammatory demyelinating polyneuropathies. Damage of motor nerves restricts signal flow from the CNS to muscles. Segmental demyelination of myelinated fibers type A slows down the flow of impulses into the CNS while conduction in nonmyelinated fibers type C remains intact. This sensory imbalance decreases the threshold of muscle force perception and painful sensations associated with

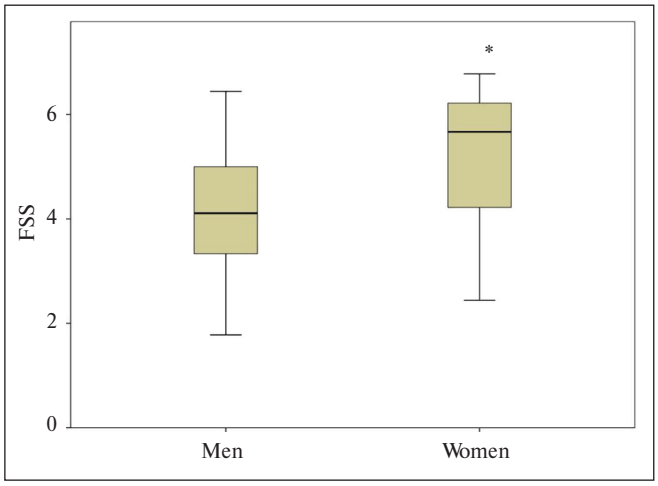

Fig. 1. *Differences in the level of fatigue in patients of a different gender. This graph shows that the level of fatigue is substantially higher in women than in men ($p<0.05$)*

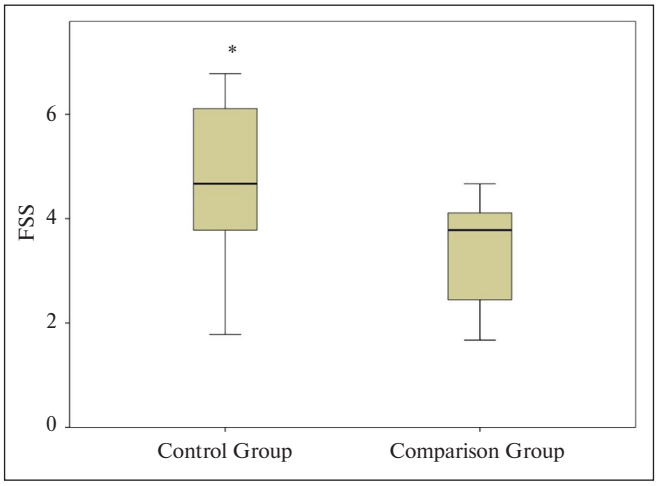

Fig. 2. *Differences in the level of fatigue in the patients of the study and control groups. The graph shows that the level of fatigue is substantially higher in patients with CIDP than in those of the comparison group ($p<0.05$)*

muscle activity are registered earlier than normal [14]. Fatigue can also develop due to a decrease in the amount of motor fibers in peripheral nerves, which leads to a rapid increase in CAF [17].

Fatigue can be the main symptom of autoimmune polyneuropathies as it was demonstrated by S. Boukhris et al [18] in a case series. One possible explanation could be that demyelinating lesions are scattered and mild, so that the lesion load in one individual nerve could not be sufficient to induce major changes in the conduction velocity. Myelin damage can also appear in those segments of nerves that are less accessible to routine nerve conduction studies [18]. In majority of patients the first line therapy of CIDP was effective in decreasing the level of fatigue.

Among patients with CIDP fatigue is present in most cases, but severe fatigue is observed in 38–74% of patients. Some patients refer to fatigue as their main symptom [12]. According to the data of M. E. Westblad et al [19], in 53% of patients the level of fatigue was higher than 4 points, in 38% – higher than 5 points. K. L. Gable et al showed that the level of fatigue is higher in patients with a relapse of CIDP than in remission. This result can be explained by less nerve damage at the remission stage.

I. S. Merkies et al [12, 21] showed that fatigue level was higher in 113 patients with acute and chronic inflammatory demyelinated polyneuropathy and polyneuropathy associated with monoclonal gammapathy of undetermined significance (MGUS) than in the control group. There were 22 patients with CIDP in this study. Severe fatigue (FSS>5) was noted in 80% of patients. There was no association between fatigue severity and sensory, motor deficit and disease duration. Severe fatigue was present in 81–86% of patients with full muscle strength without sensory disturbances, and fatigue level was approximately the same in outpatients and wheelchair-bound patients. However, the authors showed that fatigue negatively affects the quality of life of these patients.

The level of fatigue is higher in females than in males. Probably, it can be related to sex hormones levels, especially in the lutein phase, when the levels of estradiol and progesterone are elevated [22].

A study by A. Lawley et al [7] showed that fatigue level reversely correlated with the level of muscle force, sensory disturbances and the quality of life. These findings can be explained by fatigue pathogenesis – damage to myelinated fibers with intact unmyelinated fibers, though in our study we did not obtain such data. It may be related to different degrees of damage to myelinated fibers and rate of remyelination in different patients.

Correlations between the level of fatigue, the severity of neurological deficits, and the age of patients

Measure	NIS	MRC	Age
Correlation coefficient	0.240	-0.205	0.029
Level of significance, p	0.146	0.212	0.861

Note: No statistically significant correlations were found (p>0.05).

The role of physical exercises was assessed in patients with CIDP. In a study by M. P. Garssen et al [23], patients with AIDP and CIDP did physical exercises on the bicycle ergometer 3 times a week for 12 weeks. Physical training helped to decrease levels of fatigue, depression, anxiety and increase muscle strength. But the number of patients was small, and the authors underscored a huge role of clear instructions how to do exercises and the importance of moral support. L. K. Markvardsen et al [24] reported the absence of changes in the fatigue levels after 12 weeks of regular aerobic exercises despite an increase in muscle strength.

K. L. Gable et al [20] gave recommendations for prophylaxis and correction of fatigue in patients with CIDP: minimization of sedative drugs intake, adequate aerobic physical activity, increase in sleep quality with cognitive behavioral therapy and morning phototherapy, correction of depression.

The number of patients with severe fatigue (53%) and the absence of correlation with severity of neurological deficit in this study are comparable with the data obtained by I. S. Merkies et al (80%) and M. E. Westblad et al (53%). The absence of correlation between the level of neurological deficit and fatigue complicates making prognosis of fatigue development in CIDP, but it is more likely to develop in women than in men. The FSS scores reflect the influence of fatigue on the quality of life and should be taken into account. The obtained data suggest that fatigue is one of the major syndromes in CIDP, and it should be taken into account during primary medical examination.

Conclusion. In spite of its seeming insignificance in comparison with motor and sensory deficits, fatigue is one of the major symptoms in approximately 50% of CIDP patients. This study included 34 patients with typical CIDP, and this number of patients was greater by one third than in the previous studies. The results show that fatigue is present in 50% or more patients with CIDP, and half of them have severe fatigue. In spite of similarity of these data to the results of previous studies, further studies with a greater number of patients are needed to investigate characteristics of fatigue in CIDP in order to predict its development and choose appropriate methods of treatment.

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Conflict of Interest Statement

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