Specific Aspects of Neurophysiological and Neuroimaging Study of Multiple Sclerosis Patients with Spasticity

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***Abstract**. The objective of the study was to assess the functional state of muscle fibers in spasticity and prognostic value of the number and localization of MRI lesions for its development in MS patients. Material and methods. We studied findings of electroneuromyography in 51 multiple sclerosis patients with spasticity. The study was performed using non-invasive stimulation technique with a Nihon Kohden device. Results. In patients with MS with minimal clinical signs of spasticity, a significant decrease in the amplitude of the M-response was revealed when examining both the upper and lower extremities. Indicators of late electrophysiological phenomena (F-wave) changed only in the lower limbs, where the level of spasticity was higher. We identified threshold levels of M-amplitude to assess the risk of developing a high spasticity score of >12. The number of T2 and T1 lesions, as well as their localization in the spinal cord, have prognostic value for early development of spasticity. Conclusion. The results of the study revealed the main electrophysiological indicators of early manifestations of spasticity in MS patients and prognostic value of the number and localization of MRI lesions.*

Keywords: spasticity, multiple sclerosis, M-amplitude, electrophysiologic phenomena, lesions.

Introduction. Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that most often affects active people aged 20-30 years and leads to disability [11, 16]. Spasticity is a typical symptom of multiple sclerosis (MS). According to a survey conducted by the North American Research Consortium on MS (NARCOMS, 2001), spasticity occurs in 60-85% of MS patients [12, 13]. Increased muscle tone leads to limited participation in public life, primarily due to limited motor functions. These factors lead to decreased independence, impair quality of life and may affect the role that a person plays in the family [5]. Spasticity affects the functions of the nervous system, which is reflected in the scale of functional systems (FS) and the level of disability on the extended scale of disability assessment (EDSS) [1, 6].

However, thorough examination of muscle tone and the degree of spasticity is not required during a routine examination by a neurologist, although the diagnosis of these disorders in the early stages of the disease can lead to timely treatment and improvement of quality of life.

Objective assessment of severity of spasticity is important. In addition to clinical examination, spasticity can be assessed on the basis of clinical scales, biomechanical and electrophysiological methods [3, 8]. Currently, the Modified Ashworth Scale is most commonly used to assess the severity of spasticity due to its ease of use and extensive assessment of the patient's muscle condition. This scale is time-tested and is widely used to assess the condition of a patient with spasticity and the effectiveness of treatment [3, 6, 7, 8, 9, 10, 16].

Electrophysiological examination (electroneuromyography) allows a detailed study of the functional state of muscle fibers and is an objective method of studying spasticity [2, 14].

Although MS is a disease of the central nervous system and it is believed that electrodiagnostic tests of the peripheral nervous system should not be abnormal, studies suggest that peripheral nerves may also be affected by MS [4]. The studies evaluated the late electrophysiological phenomena: the H-reflex, since an increase in the excitability of α-motor neurons is an important mechanism of spasticity [9, 15]. An analysis of more than 185 sources showed that the following methods are most often used to assess spasticity: H-reflex, T-reflex and extended reflex. Moreover, the correlation with other biomechanical or clinical indicator for assessing spasticity was moderate or weak [15]. Studies of the characteristics of the F-wave indicate early changes in the average amplitude of the F-wave (decrease) even before the development of spasticity [4]. The importance of early electrophysiological phenomena (amplitude and latency of the M-response) in the diagnosis of spasticity has NOT been receiving enough attention.

To understand the pathophysiological mechanisms of spasticity in MS, it is important to consider the level of damage with the formation of sclerotic plaques. The prognostic value of the number and location of lesions (in the brain and spinal cord) for the period of development of spasticity has not been covered in the available literature.

Objective: To assess the functional state of muscle fibers in spasticity and prognostic value of the number and localization of MRI lesions for its development in MS patients.

Materials and methods: We examined 51 patients with signs of spasticity who were being treated at the Kyiv City Center for Multiple Sclerosis. The age of the patients ranged from 24 to 71 years, the mean age was 43.8±1.6. The patients were 26 women and 25 men. There were 15 patients with secondary-progressive course, 5 patients with primary-progressive course and 31 patients with recurrent-remitting course of the disease. The duration of the disease ranged from 1 to 33 years, on average 13,22±0,84.

The Modified Ashwort Scale was used to quantify the severity of changes in muscle tone. Tone was measured in extensor and flexor muscle groups, and scores ranged from 0 to 3 (maximum Ashworth score is 4, but no such patients were studied). The total spasticity score was calculated by adding the Ashworth scale of spasticity in 4 lower limb muscle groups (thigh, knee flexors, knee extensors, feet) and 2 upper limb muscle groups (shoulder and forearm flexors and extensors).

Electroneuromyography was performed using non-invasive stimulation technique with a Nihon Kohden device in the following areas:

- Motor fibers of n. medianus, n. tibialis
- Sensory fibers of m. medianus

- F-wave of n. medianus, n. tibialis
- H-reflex

We evaluated the following findings:

- When examining motor and sensory fibers of n.medianus and n. tibialis: M-Response Amplitude, Latency, Interval, Velocity.
- When examining the F-wave of n.medianus, n. tibialis: M-Latency, M-Amplitude, F-Frequency, Average F-Latency, Average F-Amplitude.
- When examining the H-Reflex: M-Latency, Maximum M, Maximum H, M/H Ratio, H-Latency.

Statistical processing of the data was performed using the methods of descriptive statistics: the mean value and standard error of the mean value (M±m), median and interquartile range Me (Q1-Q3) were calculated.

Significance assessment was performed according to the Mann-Whitney U test for 2 groups of observations and using the Kraskel-Wallis test for 3 groups of patients.

Results and discussion:

By duration of the disease, patients were distributed as follows: from 1 to 9 years — 18 patients, from 10 to 20 years — 24 patients, from 21 to 33 years — 9 patients (Table 1).

The level of spasticity in patients on the Ashworth scale ranged from 0.4 to 3 points. The average score of spasticity was 1.68±0.06. The total score of spasticity in patients ranged from 4 to 24 points. Depending on the total score of spasticity, patients were divided into two groups with a total score of 4–12 points and 13–24 points. Patients were also divided into 3 groups depending on the level of spasticity. The first group consisted of 18 patients with a mild level of spasticity (0.4–1 point), the second of 24 patients with a medium level of spasticity (1.5–2 points), and the third group of 9 patients with severe level of spasticity (2.1–3 points).

Table 1. Distribution of patients by level of disability on the EDSS scale, type of course, duration of disease and level of spasticity

EDSS, points N	Number of patients (N)								
	Course of the disease			Duration of the disease			Spasticity, points		
	SPMS	RRMS	PPMS	1-9	10-20	21-33	0.4-1	1.5-2	2.1-3
1.5-3.5 10 (20%)	0	9 (18%)	1 (2%)	8 (16%)	2 (3%)	0	7 (14%)	3 (6%)	0
4.0-5.0 27	5 (10%)	20 (40%)	2 (4%)	5 (10%)	14 (28%)	8 (16%)	9 (18%)	12 (24%)	6 (12%)
5.5-7.0 14	10 (20%)	2 (4%)	2 (4%)	5 (10%)	8 (16%)	1 (2%)	2 (4%)	9 (18%)	3 (6%)

Patients were divided into groups according to the level of spasticity on the Ashworth scale. Although the vast majority of patients did not have upper extremity spasticity (only 8 patients [16%] had upper extremity spasticity), an electromyographic examination of the upper extremity was performed in all patients to assess the functional status of the muscle fibers. Patients with spasticity of the upper extremities (n=8) had from 0 to 1+ points on the Ashworth scale (mean score 0.86±0.12). The functional state (M-response) of the muscles of the upper limb (motor fibers of n. medianus) in patients with MS was assessed depending on the presence or absence of spasticity. No significant differences were found. There was a tendency of increased M-latency with stimulation of the hand (4.86±0.41 ms) and elbow (11.03±0.37 ms) in patients with spasticity, the amplitude of the M-response was lower in patients with spasticity in all points of stimulation: wrist (10.38±1.12 mV), elbow (11.03±0.37 mV), armpits (12.01±0.53 mV).

The functional state (M-response) of the muscles of the upper extremity (motor fibers n. Medianus) in patients with MS was also assessed depending on the total score of spasticity (the first group — 4–12 points, the second group — 13–24 points) (table 2). Recording of muscle M-response is the most common electrophysiological study of motor fibers. M-response is the total potential of muscle fibers that is registered from the muscle when the innervating nerve is stimulated by a single stimulus. The decrease in the amplitude of the M-response when stimulating the distal point occurs when axons are affected, during muscular processes (both primary and secondary). There was a significant difference between the findings in these groups. At stimulation of the elbow area (11.60±0.25 ms; $p<0.01$) and armpit (12.99±0.25 ms; $p <0.05$) in patients with a higher total score of spasticity there is an increase in M-latency, the amplitude of the M-response was lower in patients with a higher total score of spasticity at all points of stimulation: wrist (9.85±0.58 mV; $p<0.03$), elbow (4.27±0.42 mV); $p<0.01$), and armpits (6.05±0.78 mV; $p<0.01$). It should be noted that a decrease in the amplitude of the M-response in patients with spasticity means a decrease in the number of muscle fibers involved in the generation of the M-response due to impaired conduction along the axons. A decrease in the amplitude of the M-response was registered in the absence of clinical manifestations of spasticity in the upper extremities and in the presence of spasticity in the lower extremities. Therefore, a decrease in the amplitude of the M-response is an early indicator of spasticity. Latency is a time delay from the moment of stimulation to the occurrence of the M-response when the nerve is stimulated at the distal point. As we know, the increase in latency is characteristic of demyelinating nerve damage.

Table 2. Assessment of the functional state (M-response) of the upper limb muscles (motor fibers of n. medianus) in patients with MS depending on the total spasticity score

Indicator	Total score	Stimulation point		
		Wrist	Elbow	Armpit
M-Latency, ms	4-12	4.73±0.34	10,34±0,36	11,52±0,34
	13-24	4,77±0.26	11,60±0,25	12,99±0,55
	p	>0,05	0,01	0,004
M-Amplitude, mV	4-12	11,19±0,57	6,43±0,64	12,89±3,49
	13-24	9,85±0,58	4,27±0,42	6,05±0,78
	p	0,03	0,01	0,01
Interval, ms	4-12	4,98±0,32	5,71±0,21	6,73±3,85
	13-24	5,14±0,24	6,53±0,16	1,45±0,17
	p	>0,05	0,04	>0,05
Velocity, m/s	4-12	-	53,43±2,83	177,43±23,09
	13-24	-	46,01±1,08	158,57±30,31
	p	-	0,05	>0,05

p – confidence estimation based on the Mann-Whitney test

We identified threshold levels of M-amplitude to assess the risk of developing a high spasticity score of >12 (Fig.1).

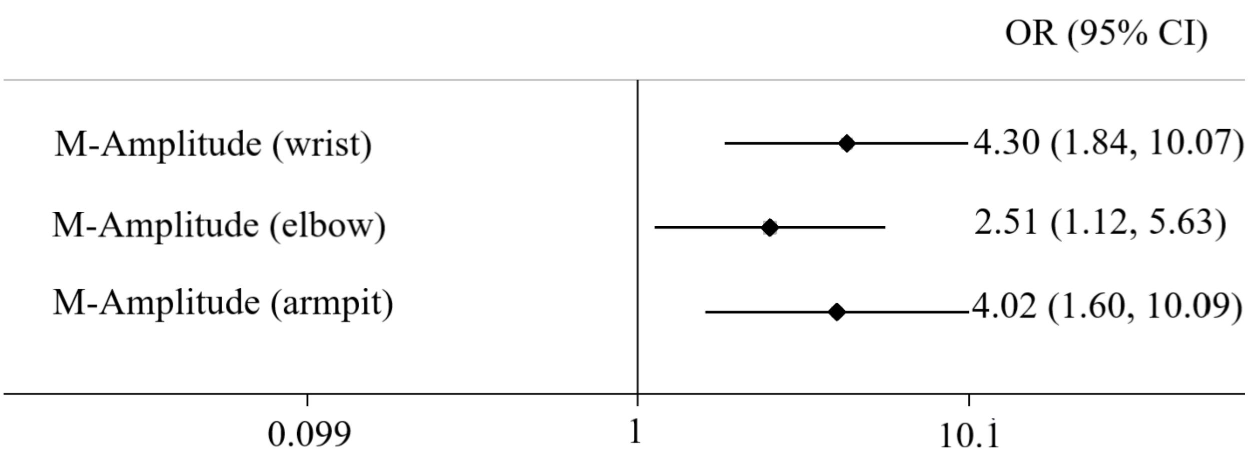

Fig. 1 Prognostic assessment of the risk of severe spasticity (> 12 points) with a decrease in M-amplitude below the threshold level

Decreased level of M-amplitude on the wrist less than 9.85 mV increased the risk of developing high spasticity > 12 points (OR (95% CI) = 4.30 (1.84-10.07)), (p = 0.001). Decreased level of M-amplitude in the armpits to less than 6.05 mV also significantly increased the chances of developing spasticity > 12 points (OR (95% CI) = 4.02 (1.60-10.09)), (p = 0.001).

We also evaluated late electrophysiological phenomena: F-wave and H-reflex depending on the presence and absence of spasticity (Table 3).

According to current data, F-wave is motor response of the muscle, which occurs periodically during supramaximal stimulation, and in its physiological essence is a muscular response to reverse discharge, which occurs as a result of antidromic excitation of the motoneuron. Thus, the parameters of the F-wave characterize the changes in the functional state of the spinal cord motoneurons depending on the degree of spinal and supraspinal exposure.

We identified significant changes in F-wave latency during stimulation of the n.medianus (table 3).

Table 3. Assessment of the functional state (F-wave) of the muscles of the upper extremity n. medianus in MS patients depending on the presence of spasticity in the upper extremity

Indicator	Presence (+) or absence (-) of spasticity	F-wave of n. medianus	p
Latency, ms	+	2.17±0.72	0.01
	-	4.60±0.30	
Amplitude, mV	+	7.58±1.74	>0.05
	-	8.17±0.62	
F-frequency, Hz	+	61.11±4.84	>0.05
	-	49.00±3.37	
Average F-latency, ms	+	62.48±31.51	0.04
	-	29.77±0.59	
Average F-amplitude, mV	+	632.78±98.67	>0.05
	-	567.79±71.10	

p – confidence estimation based on the Mann-Whitney test

F-wave latency in n. medianus decreased in patients with clinical signs of spasticity of the upper extremities to 2.17±0.72 ms (p=0.01). While the average F-latency increased in patients with spasticity to 62.48±31.51 ms (p=0.04). No significant changes in F-amplitude were identified.

The M-response of the muscles of the lower extremity (motor fibers of n. tibialis) was evaluated in patients with MS depending on the total score of spasticity, as well as in groups with different mean levels of spasticity.

Table 4. Assessment of the functional state of the muscles (M-response) of the lower extremity (motor fibers of n. tibialis) in MS patients depending on the total score of spasticity

Indicator	Stimulation point	Total spasticity score		
		4-12	13-24	p
M-Latency, ms	Ankle	7.29±0.27	7.24±0.33	>0.05
	Knee	16.75±0.47	17.21±0.63	>0.05
M-Amplitude, mV	Ankle	13.73±1.21	8.68±1.06	0.003
	Knee	25.21±14.49	3.17±0.80	0.03
Interval	Ankle	7.29±0.26	7.56±0.28	>0.05
	Knee	11.44±1.34	10.08±0.41	>0.05
Velocity, m/s	Ankle	-	-	>0.05
	Knee	50.49±2.60	46.30±3.36	0.05

p – confidence estimation based on the Mann-Whitney test

There was a significant decrease in the amplitude of M-response at the point of stimulation of the ankle in a group of patients with a higher total spasticity score from 13.73±1.21 mV (4–12 points) to 8.68±1.06 (13–24 points) (p=0.003) and knees from 25.21±14.49 (4–12 points) to 3.17±0.80 (13–24 points) (p=0.03). Differences in latency were statistically insignificant (Table 4). Therefore, the M-amplitude is the most sensitive indicator of subclinical manifestations of spasticity.

At the same time, when studying the latency of motor fibers of n. tibialis in three groups of patients with different average levels of spasticity we found a significant difference between this indicator in groups of patients and its reduction at the ankle point from 7.78±0.34 to 6.95±0.47 (p=0.018), which is not typical for demyelinating lesions of nerve fibers (table 5).

Table 5. Assessment of the functional state (M-response) of the muscles of the lower extremity (motor fibers of n. tibialis) in patients with MS depending on the level of spasticity.

Indicator	Stimulation point	Spasticity level			p
		0,4-1	1,5-2	2,1-3	
Latency, ms	Ankle	7.78±0.34	7.05±0.32	6.95±0.47	0.018
	Knee	17.74±0.64	16.10±.55	17.69±0.44	>0.05
Amplitude, mV	Ankle	15.12±1.67	10.13±1.11	5.90±1.20	0.01
	Knee	20.64±16.30	16.11±12.70	4.63±1.31	>0.05
Interval	Ankle	7.81±0.34	7.21±0.29	7.30±0.39	>0.05
	Knee	11.58±1.51	10.48±1.19	10.44±0.57	>0.05
Velocity, m/s	Ankle	-	-	-	>0.05
	Knee	48.26±3.92	50.25±2.89	44.36±2.17	>0.05

p – confidence estimation based on the Kruskal-Wallis test

With increasing spasticity, the amplitude of the M-response decreased in proportion to the amount of spasticity from 15.12 ± 1.67 (group 0.4 -1 points) to 5.90 ± 1.20 (group 2.1 - 3 points) (p = 0, 01). Therefore, in patients with severe spasticity, the amplitude of the M-response is the lowest.

When assessing the late electrophysiological phenomenon (F-wave) during stimulation of the muscles of the lower extremity (n. tibialis), we found that the average F-latency significantly increased (p=0.007) with increasing levels of spasticity in patients (Table 6). Thus, in the group of patients with the lowest level of spasticity (0.4–1 points) the average F-latency was 52.93±1.15 ms, and in the group with the highest level of spasticity (2.3–3 points) — 58.48±0.91 ms. F, the average amplitude depending on the level of spasticity, respectively, decreased from 621.27±118.62 mV to 476.12±119.67 mV (p=0.008).

Table 6. Assessment of the functional state of the muscles of the lower extremity (F-wave of n. tibialis) in patients with MS depending on the level of spasticity.

Indicator	Spasticity level			p
	0,4–1	1,5–2	2,1–3	
M-Latency, ms	4.4±0.52	5.19±0.36	6.18±0.83	>0.05
M-Amplitude, mV	3.92±0.81	6.78±1.09	8.56±0.95	0.008
F-Frequency, Hz	78.85±4.72	65.53±4.80	74.62±8.82	>0.05
Average F-Latency, ms	52.93±1.15	53.38±1.14	58.48±0.91	0.007
Average F-Amplitude, mV	621.27±118.62	487.97±79.44	476.12±119.67	< 0.05

p – confidence estimation based on the Kruskal-Wallis test

The prognostic value of neuroimaging study for the development of spasticity in patients with MS was assessed using the Kaplan-Mayer method and Fisher's test.

We evaluated the prognostic value of the number of T2- and T1- lesions, as well as their localization for the period of spasticity (Fig. 2).

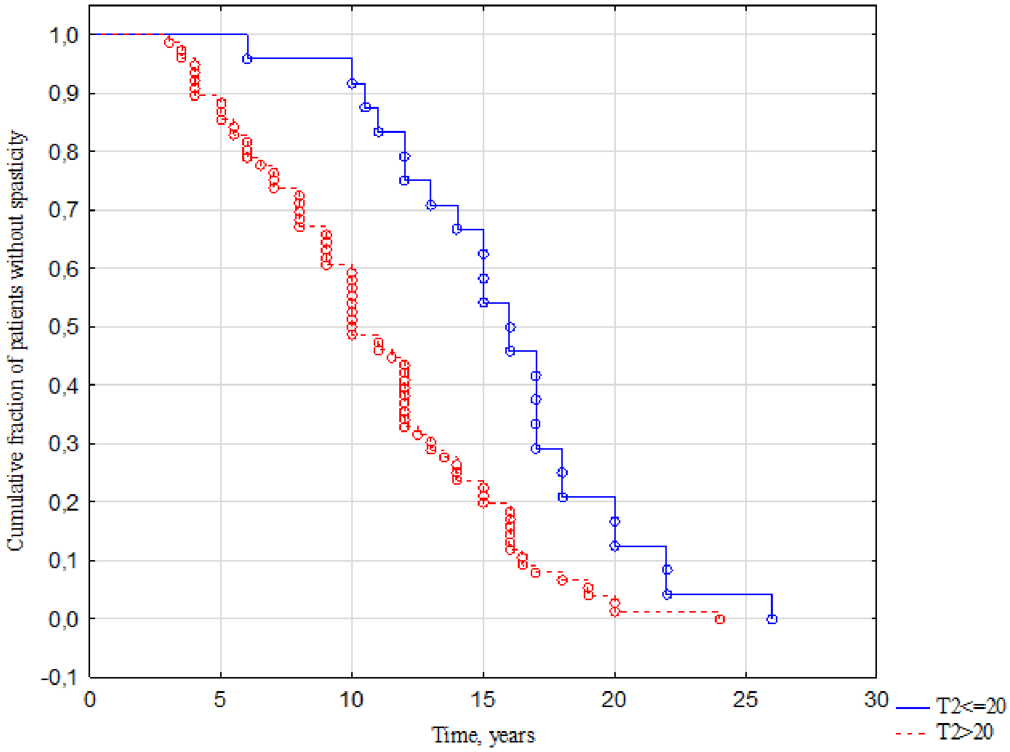

Fig. 2. Cumulative frequency of development of spasticity in MS patients depending on the number of T2 lesions

40% of patients are likely to develop spasticity if they have > 20 T2 spasticity lesions after 10 years from the onset of the disease, and after 15 years if they have ≤ 20 T2 lesions (Fig. 2). The difference between these indicators was statistically significant ($F=2.22$, $p=0.00013$).

Additionally, the early development of spasticity is associated with the development of neurodegenerative processes, which is reflected in the number of T1 lesions (Fig. 3). Earlier development of spasticity is likely in patients with > 5 T1 lesions ($F=1.93$, $p=0.00054$).

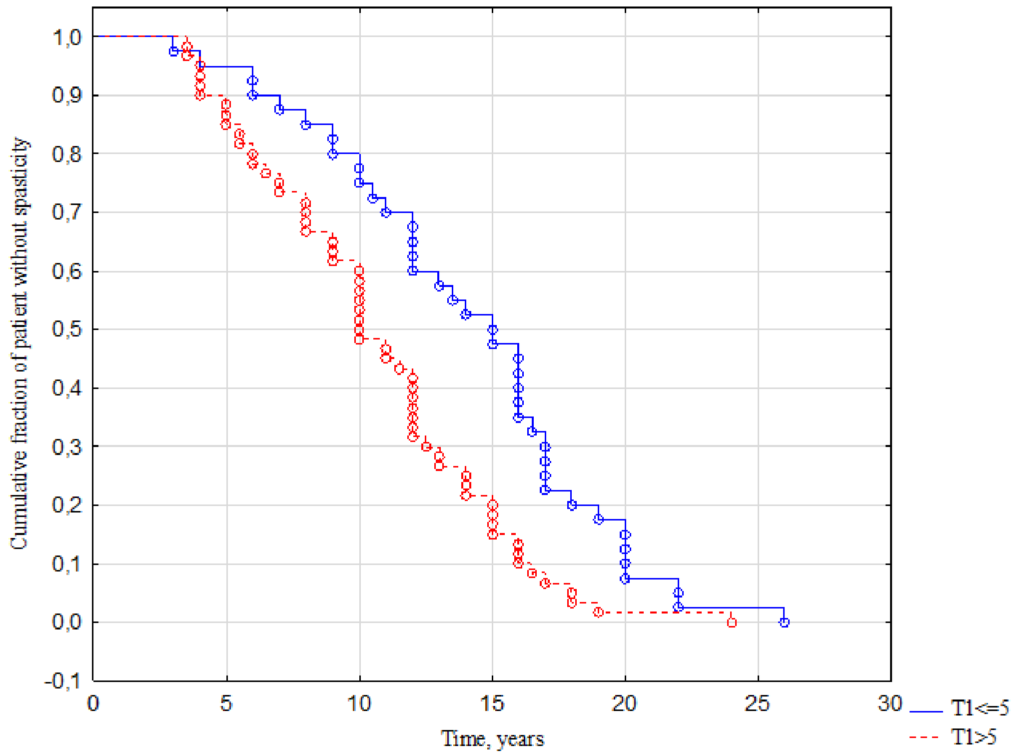

Fig. 3. Cumulative frequency of development of spasticity in MS patients depending on the number of T1 lesions

We assessed the influence of localization of lesions on the development of spasticity. Localization of lesions in the subcortical, juxtacortical, periventricular area did not have a significant effect on the emergence of spasticity. And the localization of lesions in the spinal cord significantly influenced the earlier development of spasticity (F=1,67, p=0,0054) (Fig.4).

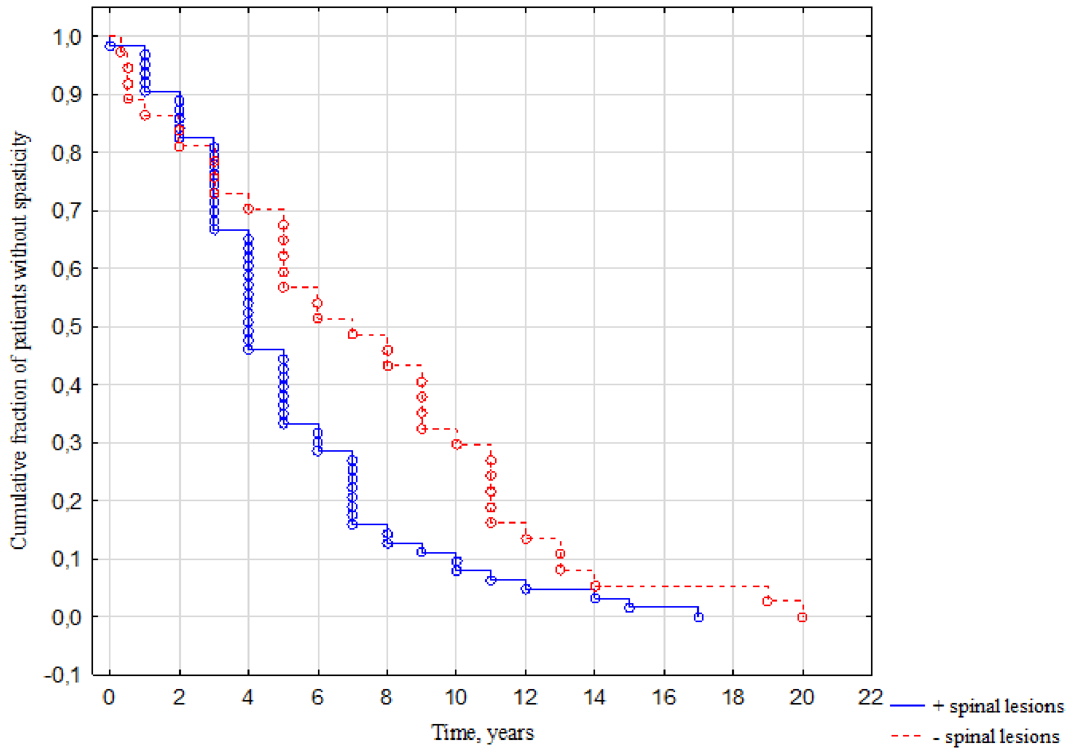

Fig. 4. Cumulative frequency of development of spasticity in MS patients depending on the presence of lesions in the spinal cord

To sum up the results of our study, we note once again that multiple sclerosis patients with different levels of spasticity showed a significant decrease in the amplitude of the M-response in the study of both upper and lower extremities, which means a decrease in the number of muscle fibers involved in M-responses due to violation of the conduction of the axons. This is the most sensitive indicator of early manifestations of spasticity. While indicators of late electrophysiological phenomena (F-wave), especially average F-amplitude, vary in patients with spasticity only on the lower extremities.

Summary. As a result of the clinical and electrophysiological study of patients with MS, one of the urgent problems of neurology, determination of indicators of early signs of spasticity, which is one of the main disabling factors in patients with MS, was further developed. It is also important to consider the prognostic value of the location and number of lesions when examining patients. The obtained results are of practical importance, due to the fact that early diagnosis of spasticity in MS allows a decision to be made on the timely appointment of symptomatic therapy and delay the development of disability.

Based on the results of the study, the following conclusions were made:

1. The results of electroneuromyographic examination showed that the main electrophysiological indicator of early manifestations of muscle spasticity of the upper and lower extremities in patients with multiple sclerosis is a decrease in the amplitude of the M-response.

2. Late electrophysiological phenomenon — average F-amplitude decreases with increase of spasticity increases in the lower extremities in multiple sclerosis patients experiencing different levels of spasticity.
3. The number of T2 and T1 lesions, as well as localization in the spine affect the earlier development of spasticity in multiple sclerosis patients.

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