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THE DYNAMICS OF MOTOR SYMPTOMS IN PARKINSON'S DISEASE UNDER THE INFLUENCE OF TRANSCRANIAL MAGNETIC STIMULATION

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ABSTRACT

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized clinically by a combination of hypokinesia, muscle rigidity, and resting tremors. In other cases, it presents with progressively worsening postural instability, and a variety of non-motor symptoms, such as autonomic dysfunction, affective and cognitive symptoms, and sleep disturbances [4].

Globally, the prevalence of PD (age-dependent) is approximately 1%. The disease typically occurs between the ages of 60 and 65, but in 15% of cases, it can occur before the age of 40. There are also gender differences: men are 1.5 times more likely to develop the disease compared to women [4]. The risk of developing the disease increases with age; thus, after the age of 65, the incidence rate is about 1%.

Key words: Parkinson's disease, hypokinesia, tremor, serotonin, motor symptoms, rTMS, Levodopa.

INTRODUCTION

PD has a significant medical and social impact due to high rates of disability, making it crucial to preserve the work capacity of each patient. PD can affect 120-180 per 100,000 people, with an annual incidence rate of 5 to 25 cases per 100,000 people. As noted earlier, the incidence rate increases with age. Factors contributing to the increase in PD cases include a decline in physical activity, mental stress, coexisting conditions, and inadequate preventive measures.

Despite successful studies on the molecular and genetic aspects of the disease, its etiology remains unknown. PD typically occurs sporadically, with genetic factors accounting for approximately 10% of cases [1]. It is important to note that

not only genetic predisposition but also environmental factors and age-related changes in the nervous system may contribute to the onset of the disease. The pathogenesis of PD involves the degeneration of dopaminergic neurons in the substantia nigra, followed by the accumulation of alpha-synuclein and the formation of intraneuronal Lewy bodies. This explains neurotransmitter disturbances due to neuronal loss, such as dopamine deficiency and the accumulation of excess glutamate and acetylcholine. Additionally, there is a deficiency of norepinephrine and serotonin due to insufficient synthesis [2, 3].

Motor symptoms play a leading role in the clinical manifestation of PD, including hypokinesia, muscle rigidity, and resting tremors. Hypokinesia is manifested by a slowing of movements and a reduction in their amplitude. The frequency and variability of motor movements also decrease. Postural instability is considered the fourth cardinal symptom of PD, but it is observed in the later stages of the disease and is not as important as the above-mentioned symptoms for early diagnosis. However, gait and balance disturbances significantly impact the patient's level of disability.

Postural instability is characterized by increasing difficulty in maintaining balance while changing body positions or walking ("propulsive gait") [4, 6].

Currently, the primary drugs used to treat PD are dopamine receptor agonists and monoamine oxidase-B inhibitors. For patients over 70, levodopa preparations are primarily prescribed due to the higher risk of side effects from agonists. The goal of the aforementioned therapy is to maintain the patient's activity for as long as possible and to preserve their quality of life, although some complications cannot be completely eliminated.

Additionally, various groups of drugs are used to correct other manifestations of the disease. When motor symptoms are accompanied by affective and psychotic disorders, antidepressants and antipsychotic agents are prescribed [7].

Physiotherapy, including reflexology, balneotherapy, and electrical stimulation, is used as adjunctive treatment for PD [9].

The use of therapeutic physical exercises is a necessary element in treating diseases at any stage [1].

In recent times, the frequency of using neurostimulation in the treatment of Parkinson's disease (PD) has increased. There are several types of neurostimulation. In the early stages of the disease, if there are no significant side effects or contraindications to the treatment, the use of invasive methods should be considered. Neurosurgical treatment of PD involves deep brain stimulation (DBS) [7, 8, 9, 10].

The stimulation of electrodes placed in different parts of the brain changes the rhythm of impulses, which significantly reduces the severity of motor impairments [5]. Additionally, destructive surgical procedures are rarely used. Non-invasive methods of stimulating brain neurons include transcranial magnetic stimulation (TMS) and electrical stimulation.

There are two types: early and late. Early mediators lead to changes in synaptic transmission after redistribution and ion activity, which lasts approximately 30-60 minutes. The late (long-term) potentiation is associated with changes in gene expression and protein synthesis and can last for several hours, days, or even weeks [11]. The activation of NMDA receptors also participates in long-term potentiation but in a slightly different way. A rapid increase in the level of postsynaptic calcium enhances this phenomenon, while their slow currents lead to long-term depression [10].

The potential neuroprotective effect of rTMS has also been confirmed by several scientific studies. Mai and other researchers performed low-frequency stimulation of the left superior temporal gyrus of the brain for 5 days at an amplitude of 110%, resulting in an increase in the volume of gray matter, confirmed by morphometric measurements.

There is convincing evidence of the long-term effects of rTMS, which offers the possibility of its clinical application in a wide range of neurological and psychiatric diseases. Although the mechanisms of delayed effects are not fully understood, they are recognized as related to changes in synaptic plasticity. The response to rTMS can be highly variable. This variability limits the assessment of the effectiveness of this method to some extent. One potential solution to this problem is to identify specific predictors that allow optimizing stimulation parameters for each patient. Thus, the variability of response during rTMS appears not as a weakness of rTMS but as an opportunity to study individual differences in the brain [6].

From the perspective of potential side effects related to PD, some deterioration in motor changes was detected during rTMS [4]. For example, Boylan and others reported poorer performance in the spiral drawing test in 5 out of 16 patients when stimulating the supplementary motor area (SMA) at a frequency of 10 Hz [6]. In another study conducted by Ghabra and others, muscle movement was identified at 80% amplitude of the motor threshold. Such changes may result from a decrease in the motor threshold in patients during motor cortex activation while performing a task. When the rTMS amplitude was reduced to 70%, all patients performed the tasks without difficulty. Thus, risk reduction and

increased effectiveness of stimulating the SMA area can be achieved by reducing the intensity of the procedure.

Research objective: to evaluate the dynamics of major motor disorders in Parkinson's disease under the influence of rhythmic transcranial magnetic stimulation.

Materials and Methods:

The diagnosis of Parkinson's disease in patients (diagnosed according to the International Society for Parkinson’s Disease and Movement Disorders clinical diagnostic criteria for Parkinson’s disease) was made.

Inclusion criteria for patients: patients with Parkinson’s disease in the third and fourth stages of the disease on the Hen-Yahr scale were included in the study. The age of patients ranged from 46 to 82 years.

Exclusion criteria for patients:

• Patients with metal implants in the body, excluding prosthetics of the hip and knee joints;

• History of epileptic seizures and episodes of unexplained loss of consciousness;;

• Oncological and severe somatic diseases associated with severe heart or respiratory failure affecting movement;

• Clinically significant depression (11 points on the Hospital Anxiety and Depression Scale) or psychotic symptoms and dementia.

The study involved 80 patients with Parkinson's disease in the third and fourth stages on the Hen-Yahr scale. The average age was 63.5 ± 5.8 years. Patients were randomly divided into 2 groups: the main group consisted of 40 patients, and the comparison group also included 40 patients. The main group consisted of 34 men (85%) and 6 women (15%), while the comparison group included 28 men (70%) and 12 women (30%). The groups were compared based on age, disease stage, duration, and symptom severity. The main characteristics of the groups are presented in Table 1.

Table 1.

Main Characteristics of the Examined Groups

	Main group	**Control group**
Patients, n	40	40
Age Indicator	62,16±7,4	68±4,9
Duration of Disease	3,5±2,2	7,5±2,6
Levodopa Dose Equivalence	685,6±142,5	674,8±132,2

To comprehensively evaluate motor symptoms of PD and cover all aspects, three scales were used: MDS-UPDRS-III, GABS, and FOG.

Methodology of Conducting Rhythmic Transcranial Magnetic Stimulation:

Each patient in the main group received a therapeutic rTMS course consisting of 10 sessions at the "Neurology and Psychiatry" medical clinic. Inhibitory stimulation was performed at the primary motor area (M1) bilaterally and at Cz points with a frequency of 1.5 Hz and an amplitude of 70-80% of the motor threshold. The Neuro-MS/D transcranial magnetic stimulator device was used for stimulation. The control group did not receive rTMS. Due to the necessity of maintaining head immobility for 30 minutes, the procedure was performed in a seated or lying position.

Study Results:

The dynamics of motor manifestations of Parkinson's disease under the influence of rhythmic transcranial magnetic stimulation were studied using MDS-UPDRS-III, GABS, and FOG scales before and after treatment. The results of assessing the therapeutic effect of rTMS on motor symptoms of Parkinson's disease are presented in Table 2.

Table 2.

Comparative Dynamics of Motor Symptoms Under the Influence of rTMS in the Main and Comparative Groups During the Study

Scales and Questionnaires		**Main group**	**Control group**
MDS-UPDRS	Before R TMS	49,5 [40,5; 58,5]	50,5 [44,5; 60,5]
	After R TMS	45,5 [38,5; 52,5]	
	After 6 months	42,5 [36,5; 48,5]	48 [42,5; 58,5]
GABS	Before R TMS	46 [32; 62]	44 [40; 48]
	After R TMS	44 [30; 58]	
	After 6 months	40 [32; 46]	42[40; 47]
FOG	Before R TMS	12 [11; 16]	12 [10; 16]
	After R TMS	11 [10; 12]	
	After 6 months	12 [11; 14,5]	12 [10; 16]

The analysis of the obtained data showed a statistically significant improvement. After 10 sessions of 1.5 Hz stimulation of M1 and Cz points according to the MDS-UPDRS-III scale, motor functions in patients in the main group and the average score on the GABS scale decreased. The total reduction was on average 8.0±2.9 points (16.13%) according to the MDS-UPDRS-III scale ($p<0.05$), mainly associated with a decrease in resting tremor and hypokinesia, as

well as a decrease in the total score. According to the GABS scale, the average decrease was 5.5±4.9 points (12.12%) ($p<0.05$), due to an increase in walking speed and a decrease in postural instability. Six months after the rTMS course, the severity of the symptoms returned to the initial level.

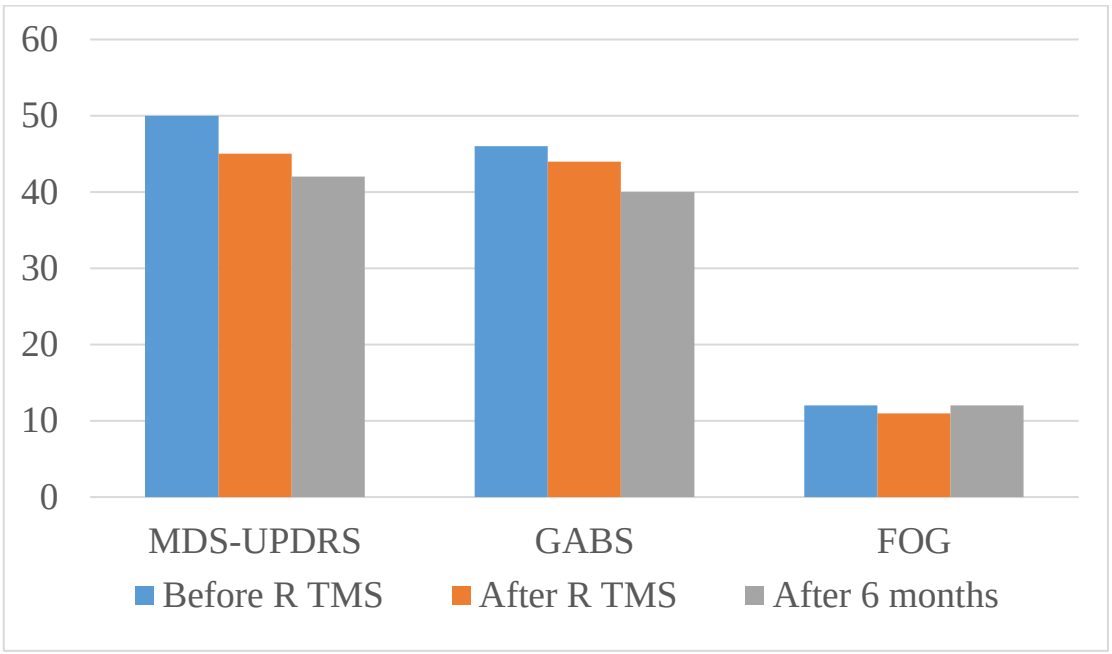

Figure 1. Dynamics of Motor Symptoms Over 6 Months in the Main Group

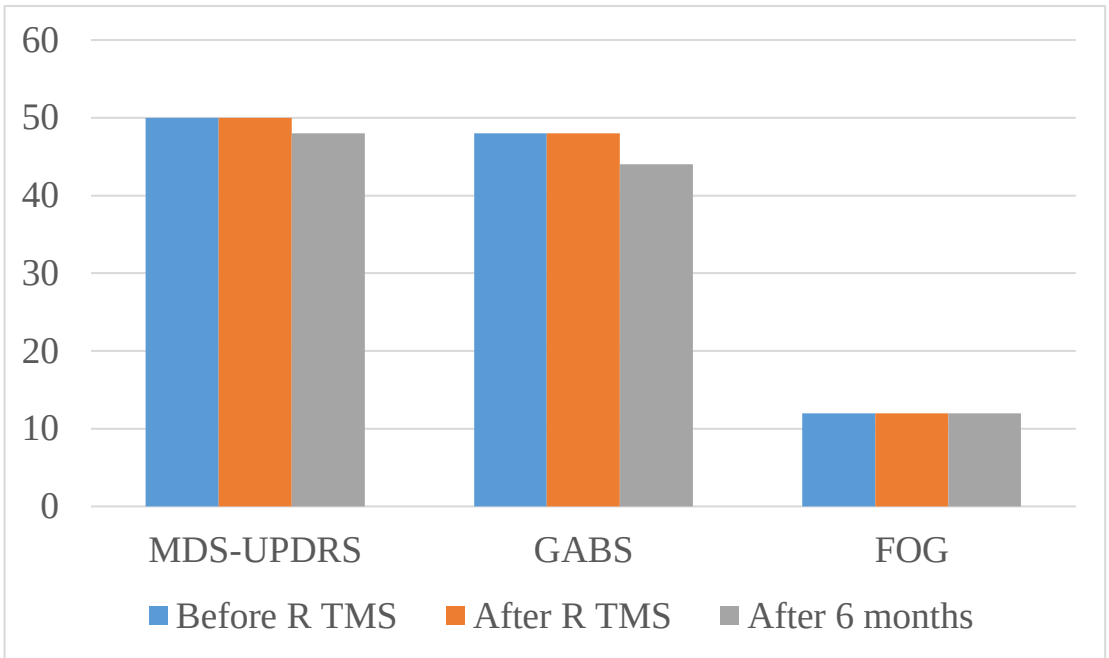

Figure 2. Dynamics of Motor Symptoms Over 6 Months in the Comparative Group

When assessing the effect of rTMS on intermediate symptoms, changes in scores according to the individual segments of the MDS-UPDRS-III scale

associated with tremor, rigidity, bradykinesia, and axial symptoms (as they are very specific for the diagnosis of PD) were also analyzed. The results of assessing the therapeutic effect of rTMS on PD motor symptoms are presented in Table 3.

Table 3.

Dynamics of Motor Symptoms According to the MDS-UPDRS-III Scale.

MDS-UPDRS-III шкаласи		Main group	Control group
Tremor	Before R TMS	10 [4; 15]	12 [7; 16]
	After R TMS	8 [3; 13]	
	After 6 months	8 [3; 12]	12 [8; 16]
Rigidity, points	Before R TMS	8 [6; 12]	9 [8; 11]
	After R TMS	6 [5; 10]	
	After 6 months	8 [6; 11]	9 [9; 10]
Hypokinesia, points	Before R TMS	16 [14; 21]	17 [13; 22]
	After R TMS	12 [10; 18]	
	After 6 months	14 [12; 20]	16 [12; 20]
Axial Symptoms	Before R TMS	13 [10; 18]	14 [12; 20]
	After R TMS	10 [8; 15]	
	After 6 months	12 [9; 16]	13 [12; 18]

The analysis of the obtained data identified a statistically significant improvement in motor symptoms in patients in the main group after 10 sessions of stimulation of M1 and Cz at a frequency of 1.5 Hz, associated with individual segments of the MDS-UPDRS-III scale. The most noticeable decrease was in the total score for tremor (average 1.55 ± 0.29 points (15.65%) ($p < 0.05$) (Figure 5)) and hypokinesia (average 3.32 ± 2.97 points (17.99%)). The decrease in the total score for rigidity (average 0.4 ± 0.95 points (4.65%) ($p < 0.05$)) and axial symptoms (average 0.85 ± 1.07 points (7.72%)) ($p < 0.05$) was also statistically significant. However, six months after the rTMS course, the intermediate symptom indicator returned to the initial level. In the comparison group, no significant changes were observed in these indicators. This can be seen in Figure 3.

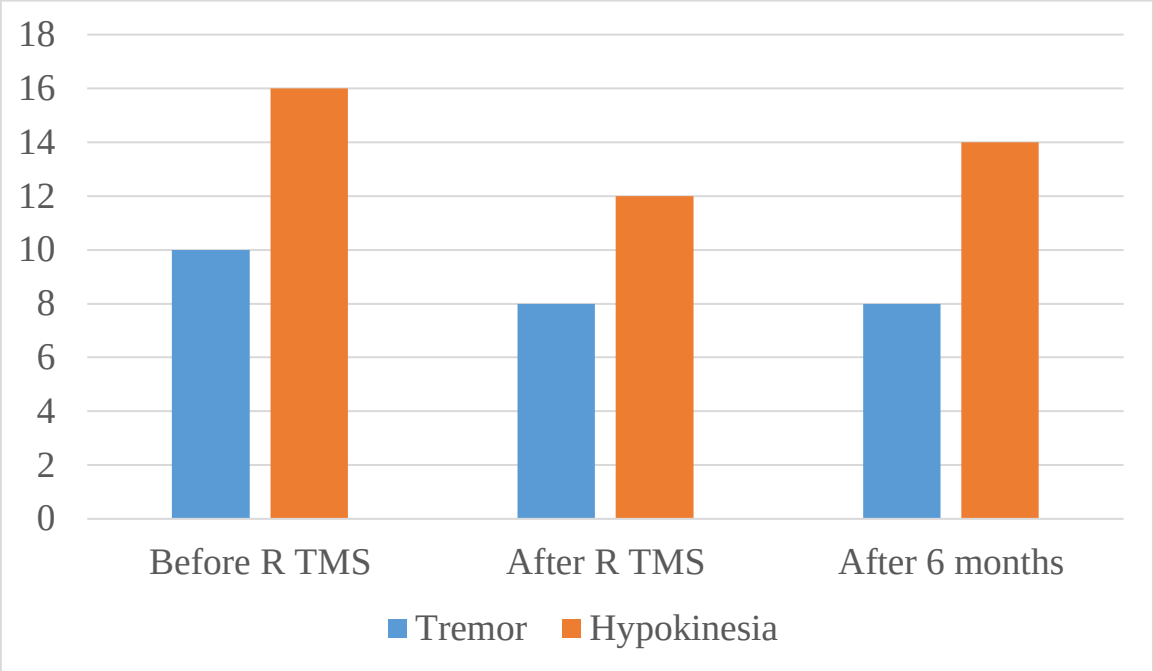

Figure 3. Dynamics of Tremor and Hypokinesia in the Main Group.

Conclusions:

High-frequency rhythmic transcranial magnetic stimulation has been found effective in improving motor symptoms according to the MDS-UPDRS-III scale, with an improvement of 8.0 ± 2.9 points (16.1%) ($p < 0.05$), mainly evident in patients with Parkinson's disease suffering from tremor and hypokinesia.

High-frequency rhythmic transcranial magnetic stimulation improves walking performance in patients with Parkinson's disease, mainly increasing speed and reducing postural instability complaints on the GABS scale by 5.5 ± 4.9 points (12.1%) ($p < 0.05$), but this indicator does not affect the tremor frequency.

As discussed earlier, the frequency of PD motor symptoms increases depending on the stages of the disease, and over time, the effectiveness of treatment decreases, the severity of symptoms increases, and patients lose the ability to take care of themselves. Each patient not only loses their working capacity but also increases the potential level of disability, leading to additional financial expenses.

To conclude, in the future, it is necessary to properly plan preventive and rehabilitation measures, along with treating patients with PD who already have motor symptoms, to prevent progression to more severe forms of the disease. The TMS therapy used in this study can be included in the above treatment methods because, with this treatment method, the earlier the disease is treated, the sooner and longer-lasting the results will be.

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