

THE CORRECTION OF NON-MOTOR SYMPTOMS IN DIFFERENT FORMS OF PARKINSON'S DISEASE BY OPTIMIZATION THERAPY WITH LEVODOPA

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Non-motor symptoms in Parkinson's disease (PD) are usually more complicated and difficult to manage than typical PD motor symptoms. However, they are usually overlooked and not properly treated. Physicians should be aware of the need to evaluate the neuropsychiatric, cognitive, autonomic, and sleep complications of PD. Early recognition of non-motor symptoms is essential, as effective treatment can reduce morbidity and improve the quality of life of PD patients. The aim of the study was to evaluate the impact of optimization levodopa therapy in patients with PD and motor fluctuations on severity of non-motor symptoms. The results of the examination of 80 patients with various forms of Parkinson's disease who were examined and treated at the Center for patients with CP and other neurodegenerative diseases of the Department of Neurological Diseases of Poltava State Medical University are presented. Patients were examined according to the UPDRS scale, the severity of non-motor symptoms was assessed according to the Non-motor symptoms scale (NMSS). We have found that optimization of the treatment by changing the regimen of the levodopa may significantly improve motor function. The improvement of motor function by usage of extended-release levodopa is associated with decreasing motor fluctuations severity.

It has been established that the use of long-acting levodopa-containing drugs has a positive effect in the treatment of non-motor symptoms. Dominant reliable changes are more typical for patients with a akinetic-rigid form of the disease.

Key words: non-motor symptoms, correction therapy, Parkinson's disease.

Connection of the publication with the planned scientific research.

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Introduction.

The phenomenology of Parkinson's disease includes a triad of core motor signs, such as bradykinesia, muscle rigidity, and tremor, and a wide range of non-motor syndromes that result from neurodegenerative changes in the human brain. These manifestations are used by doctors to determine the clinical form and treatment strategy of patients. Recently, a classification that divides patients with PD into 3 forms is becoming widely used: tremor-dominant, akinetic-rigid, and mixed (akinetic-rigid-tremor). These forms differ not only in the predominance of certain motor symptoms, but also in the frequency and severity of non-motor signs, which is due to differences in localization and degree of damage to the nervous system [1].

At the current stage, Parkinson's disease (PD) is considered not as an isolated lesion of the dopaminergic system, but as a multisystemic neurodegenerative disease with the involvement of various mediator systems, which causes a wide range of motor, neuropsychological and autonomic disorders. Non-motor symptoms of PD include autonomic, sensory, psychiatric, metabolic disorders and sleep and circadian rhythm disorders. These manifestations develop in the structure of the clinical picture of the disease and depend on the type of therapy chosen. However, they can be a separate disease that exacerbates or mimics the symptoms of PD and requires separate treatment [2]. Thus, recently, the most discussed disturbances of smell, sleep and mental health in PD, as they can occur in the early stages of the disease and determine

its course, as well as intensify the manifestations of other non-motor symptoms on the part of various body systems. In particular, mood disorders can affect the state of the cardiovascular and gastrointestinal systems [3-5]. Among the non-motor symptoms of mental disorders in PD, there are emotional-volitional disorders, affective disorders, and cognitive decline, which may be associated with neurotransmitter imbalance [6-8].

Despite the wide spectrum of non-motor symptoms in PD, as in other neurological diseases, the attention of scientists is mainly directed to disturbances in the motor sphere [9, 10]. Thus, the latest studies are mainly aimed at optimizing the treatment of movement disorders in PD, although there are claims that it is non-motor symptoms that significantly worsen the quality of life of patients [11]. By the way, motor fluctuations are often accompanied by non-motor phenomena associated with fluctuations in the severity of mental, sensory, vegetative symptoms (non-motor fluctuations), which increases the maladaptive effect. In the «on» period, a hypomanic state, euphoria, obsessive states, impulsivity can be observed, and in the «off» period – dysphoria, anxiety, palpitations, shortness of breath, imperative urges to urinate, pain syndromes [12].

However, the influence of various therapeutic approaches to the treatment of motor complications of PD on the severity of non-motor symptoms has not been thoroughly studied.

The aim of the study.

To evaluate the impact of optimization levodopa therapy in patients with PD and motor fluctuations on severity of non-motor symptoms.

Object and research methods.

We have examined 80 patients with different forms of PD from the Centre for patients with PD and other neurodegenerative diseases of the department of Neurological disorders of Poltava State Medical University. Patients, depending on the prevalence of symptoms and

Table 1 – Sociodemographic characteristics of patients with different forms of Parkinson’s disease, abs. (%)

Feature	Group		p-value	
	Group 1 (n=40)	Group 2 (n=40)		
Age, years (M±m)	62,57±1,48	61,12±1,35	0,497	
Sex, abs. (%)	Male	25 (51,0%)	28 (48,3%)	0,898
	Female	24 (49,0%)	30 (51,7%)	
Disease duration, years (M±m)	7,61±0,75	7,93±0,68	0,754	
Disease onset localization, abs. (%)	left hand	24 (49,0%)	21 (36,2%)	0,566
	right hand	20 (40,8%)	31 (53,4%)	
	left leg	3 (6,1%)	3 (5,2%)	
	right leg	2 (4,1%)	3 (5,2%)	

results of electroneuromyographic examination, were divided into following groups:

Group 1 – 40 patients with akinetic-rigid form (AR);

Group 2 – 40 patients with a mixed akinetic-rigid-tremor (ART) form.

All patients included in the study were treated with levodopa drugs. Depending on levodopa therapy, patients of both groups were divided into subgroups.

Patients of the both groups are divided into following subgroups:

a subgroup – patients received therapy with short-acting levodopa drugs 4 times a day.

B subgroup – patients received combined short-acting levodopa 3 times per day with extended-acting levodopa before sleep.

All studied patients gave informed consent to participate in the study. The research protocol was approved by the Bioethics Committee of Poltava State Medical University.

Inclusion criteria were clinically verified PD according to MDS guideline (2015), treatment with levodopa more than 3 years.

Exclusion criteria: secondary parkinsonism, atypical parkinsonism, Hoehn and Yahr stage more than 4, more than 90 years old.

Clinical assessments were performed after the 3 months of the regimen changing of the treatment by levodopa. We collected date about patients’ age, sex, duration of the disease and localisation of disease onset. We also examined the severity of PD by the UPDRS scale. Intensity and level of non-motor symptoms were assessed by Non-motor symptoms scale (NMSS). It consists of 30 questions relating to the patient’s condition during the last month and combined into 9 domains: cardiovascular and falling, sleep/fatigue, mood/cognition, perception/hallucinations, attention/memory, gastrointestinal tract, urination, sexual function and others. The answer to each question includes a frequency

Table 2 – Dynamic of the clinical severity of different forms of Parkinson’s disease depending on the regimen of the treatment by levodopa, M±m

Feature	Group			
	Group 1 (n=40)		Group 2 (n=40)	
	1a (n=20)	1b (n=20)	2a (n=20)	2b (n=20)
UPDRS I	2,8±1,3	1,7±0,5	2,9±0,8	1,9±0,7
UPDRS II	12,9±6,5	11,4±4,8	13,2±11,2	10,1±3,4
UPDRS III	33,7±11,4	28,4±10,6*	28,4±12,4*	24,1±9,8**/^
UPDRS IV	3,2±1,3	2,0±1,6	2,8±0,8	2,1±0,9

Notes: * – p₁<0.05 compared to the 1a group; ** - p₂ compared to the 2a groups, ^ – p₃<0.05 compared to the 1b group.

that is rated as 1 – rarely (<1 time/week), 2 – sometimes (1 time/week), 3 – often (several times/week), 4 – very often (daily or constantly), and the severity expressed as 0 – absence, 1 – easy, 2 – moderate, 3 – severe. To calculate the score in each domain, their products are summed. The total score consists of the sum of all domains and varies from 0 to 360, where the higher value corresponds to the more pronounced non-separate characters [13].

Statistical processing of the obtained results was carried out using the EZR Statistics 1.34 (Jichi University, Japan) and IBM SPSS Statistics v.26.0 (IBM inc., USA) programs. The normality of the distribution of quantitative data was determined by the Shapiro-Wilk test. The results of the study were analyzed using descriptive statistics methods with determination of mean values (M) and standard error (m) for quantitative variables and relative (%) and absolute (abs.) values for qualitative variables. The t-test for independent or dependent groups was used for statistical processing of quantitative results in two groups. Statistical analysis of qualitative indicators of frequency between two groups was performed using the Pearson’s Chi-square test with Yates’ correction. A p-value of 0.05 was considered critical.

Research results and their discussion.

Sociodemographic characteristics of the studied population are demonstrated in **table 1**.

We have demonstrated no statistically significant differences between group by age, sex, duration of the disease and localisation of disease onset. It noticed that compared groups were clinically relevant.

The impact of optimization therapy in comparison with standard treatment by levodopa on motor functions and severity of clinical condition is shown in **table 2**.

Patients in group 2a had lower scores by UPDRS III compared to group 1a (p₁=0.009), but did not differ from group 1b. At the same time group 2b had a lower score vs. Group 1b (p₃=0.034). It is demonstrated that modified therapy is associated with better motor function, but motor subtype impact on this, namely AR form have more severe motor dysfunction [14].

It was shown that in patients with both forms of PD modified therapy significantly improved UPDRS-III (p₁=0.007 and p₂=0.014). We have found that optimization of the treatment by changing the regimen of the levodopa may significantly improve motor function. The absence of significant differences by other UPDRS subscore can be explained by fragmentation of the questions related to non-motor symptoms between different domains. The improvement of motor function by usage of extended-release levodopa is associated with decreasing motor fluctuations severity [15].

Effects of the modified therapy with levodopa on the both forms of PD are presented in **table 3**.

It was established that the use of the prolonged form of levodopa during evening administration is accompanied by a significant decrease in severity on the scales «cardiovascular and falling» (p=0.005), «attention/memory» (p=0.027), «gastrointestinal tract» (p=0.008) and by the total NMSS score (p=0.002) in group 1b compare to the group 1a and by the «gastrointestinal tract»

scales ($p=0.034$) and by the total NMSS score ($p=0.017$) in group 2b compare to the group 2a. At the same time, no statistically significant differences were found in the severity of non-motor symptoms in patients with various forms of Parkinson's disease during the administration of standardized short-acting levodopa therapy, besides higher scores by the "mood disorders" ($p<0.001$) and total score of NMSS ($p=0.003$) in group 2a compare to the group 1a. Patients in group 2b had more severe disturbances with "attention/memory" ($p=0.018$) and total score of NMSS ($p=0.009$) than in group 1b.

The detected changes in non-motor symptoms may be associated with a decrease in the severity of motor fluctuations, which affects the psycho-emotional state of the patient [16]. At the same time, the improvement of the somatic condition may be caused by maintaining a constant concentration of levodopa in the patient's blood and thus determine the constancy of its effect [17].

Conclusions.

We have found that treatment of patients with various forms of PD with levodopa drug is associated with a wide range of non-motor symptoms, which are more pronounced in the AR form of PD. Addition of

Table 3 – Dynamic of the severity of non-motor symptoms in different forms of Parkinson's disease depending on the regimen of the treatment by levodopa, M±m

Domain of the NMSS	Group			
	Group 1 (n=40)		Group 2 (n=40)	
	1a (n=20)	1b (n=20)	2a (n=20)	2b (n=20)
Cardiovascular and falling	2,27±0,39	1.84±0.28*	2,10±0,33	2.08±0.31
Sleep/fatigue	5,94±0,51	6.11±0.49	6,19±0,43	5.96±0.54
Mood/cognition	10,35±0,99	10.23±0.84	5,93±0,72*	6.17±0.95
Perception/hallucination	1,00±0,13	1.03±0.22	1,17±0,12	1.13±0.16
Attention/memory	5,49±0,49	3.26±0.58*	5,78±0,62	5.69±0.78^^
Gastrointestinal tract	4,98±0,30	2.96±0.44*	4,54±0,33	2.71±0.38^
Urination	5,37±0,44	5.26±0.51	5,95±0,45	5.73±0.53
Sexual function	4,39±0,36	4.29±0.39	4,28±0,35	4.35±0.33
Others	9,21±0,74	8.93±0.81	8,76±0,63	9.13±0.69
Total score of the NMSS	40,98±0,51	35.63±0.87*	33,39±1,29*	29.23±0.94^/^^

Notes: * – $p_1<0.05$ compared to the 1a group; ^ – $p_3<0.05$ compared to the 2a group, ^^ – $p_4<0.05$ compared to the 1b group

the retard forms of levodopa may improve severity of motor fluctuations and decrease intensity of non-motor symptoms, especially in patients with AR form.

Perspectives for further research.

Further studies should investigate the impact of different regimens of levodopa influencing mostly motor symptoms in patients with Parkinson's disease on the severity of non-motor symptoms and discover personalized approaches for the improvement treatment strategy.

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КОРЕКЦІЯ НЕМОТОРНИХ СИМПТОМІВ ПРИ РІЗНИХ ФОРМАХ ХВОРОБИ ПАРКІНСОНА ШЛЯХОМ ОПТИМІЗАЦІЙНОЇ ТЕРАПІЇ ЛЕВОДОПОЮ**Таряник К. А.**

Резюме. Хвороба Паркінсона характеризується дофамінергічним дегенеративним процесом, що вражає нейрони чорної субстанції. Захворювання в основному розглядається як руховий розлад, але пацієнти страждають не лише від моторних симптомів, а й від немоторних симптомів, які також є поширеними та можуть значно впливати на якість життя пацієнтів. Ці ускладнення включають когнітивні, психіатричні, вегетативні розлади, розлади сну та сенсорні розлади. Немоторні симптоми можуть з'явитися ще до появи перших моторних симптомів, але вони більш неприємні на пізніших стадіях ХП, коли можуть стати серйозними проблемами для пацієнтів і часто становлять виклик для лікуючих лікарів.

Метою нашого дослідження було оцінити вплив оптимізації терапії леводопою у пацієнтів із ХП та руховими флуктуаціями на вираженість немоторних симптомів.

Було обстежено 80 хворих на різні форми ХП із Центру хворих на ХП та інші нейродегенеративні захворювання кафедри неврологічних захворювань Полтавського державного медичного університету. Пацієнти, залежно від поширеності симптомів та результатів електронейроміографічного дослідження, були розподілені на групи. Клінічні оцінки проводили через 3 місяці після зміни режиму лікування леводопою. Збирали дані про вік, стать пацієнтів, тривалість захворювання та локалізацію дебюту захворювання, досліджували тяжкість хвороби за шкалою UPDRS, інтенсивність та рівень немоторних симптомів – за шкалою немоторних симптомів (NMSS).

Було встановлено, що оптимізація лікування шляхом зміни режиму прийому леводопи може значно покращити рухову функцію. Відсутність суттєвих відмінностей за іншими субіндексами UPDRS можна було пояснити фрагментацією питань, пов'язаних з немоторними симптомами, між різними доменами. Поліпшення рухової функції при застосуванні леводопи пролонгованої дії було пов'язане зі зменшенням вираженості моторних флуктуацій.

Встановлено, що застосування пролонгованої форми леводопи під час вечірнього прийому супроводжується достовірним зниженням вираженості за шкалами «серцево-судинні та падіння», «увага/пам'ять», «шлунково-кишковий тракт» та за сумарним балом NMSS у групі пацієнтів із акінетико-ригідною формою захворювання.

Таким чином, нами встановлено, що лікування пацієнтів із різними формами ХП препаратом леводопи асоціюється з широким спектром немоторних симптомів, які більш виражені при акінетико-ригідній формі ХП. Додавання ретардних форм леводопи може покращити вираженість моторних флуктуацій і зменшити інтенсивність немоторних симптомів, особливо у пацієнтів з акінетикозригідною формою захворювання.

Ключові слова: немоторні симптоми, корекція лікування, хвороба Паркінсона.

THE CORRECTION OF NON-MOTOR SYMPTOMS IN DIFFERENT FORMS OF PARKINSON'S DISEASE BY OPTIMIZATION THERAPY WITH LEVODOPA**Tariyanik K. A.**

Abstract. Parkinson's disease is characterized by a dopaminergic degenerative process affecting the neurons of the substantia nigra. The disease is mainly seen as a movement disorder, but patients suffer not only from motor symptoms, but also from non-motor symptoms, which are also common and can significantly affect patients' quality of life. These complications include cognitive, psychiatric, autonomic, sleep and sensory disturbances. Non-motor symptoms may appear even before the first motor symptoms appear, but they are more troublesome in the later stages of CP, when they can become serious problems for patients and often pose a challenge for treating physicians.

The aim of our study was to evaluate the effect of optimization of levodopa therapy in patients with CP and motor fluctuations on the severity of non-motor symptoms.

80 patients with various forms of CP from the Center for Patients with CP and other neurodegenerative diseases of the Department of Neurological Diseases of Poltava State Medical University were examined. Patients were divided into groups depending on the prevalence of symptoms and the results of the electromyographic examination. Clinical evaluations were performed 3 months after changing the levodopa treatment regimen. We collected data on the age, gender of patients, duration of the disease and localization of the onset of the disease, studied the severity of the disease according to the UPDRS scale, the intensity and level of non-motor symptoms – according to the non-motor symptom scale (NMSS).

It has been established that optimizing treatment by changing the regimen of levodopa can significantly improve motor function. The lack of significant differences on the other UPDRS sub-indices could be explained by the fragmentation of questions related to non-motor symptoms between different domains. Improvement of motor function with the use of long-acting levodopa was associated with a decrease in the severity of motor fluctuations.

It was established that the use of the prolonged form of levodopa during evening administration is accompanied by a significant decrease in severity on the scales «cardiovascular and falls», «attention/memory», «gastrointestinal tract» and the total NMSS score in the group of patients with akinetic rigid form of the disease.

Thus, we found that levodopa treatment of patients with various forms of CP is associated with a wide range of non-motor symptoms, which are more pronounced in the akinetic-rigid form of CP. The addition of retarded forms of levodopa can improve the severity of motor fluctuations and reduce the intensity of non-motor symptoms, especially in patients with an akinetic-rigid form of the disease.

Key words: non-motor symptoms, correction of treatment, Parkinson's disease.

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