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CLINICAL AND NEUROLOGICAL MANIFESTATIONS OF PAIN SYNDROME OF PARKINSON'S DISEASE

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Annatation
A chronic progressive brain disease characterized by degeneration of dopaminergic neurons of the substantia nigra is Parkinson's disease. In addition to classical motor disorders, Parkinson's disease is characterized by a wide range of non-motor (non-motor) manifestations, which include vegetative, sensory, mental, affective disorders, sleep and wakefulness disorders. The most common non-motor symptoms of the disease, such as pain syndromes, cause severe discomfort and a significant decrease in the quality of life of patients, but they are poorly understood, although they are an important symptom of Parkinson's disease.

Keywords: Parkinsonism, clinical and neurological changes, pain, types, diagnostics.

Аннотация
Хроническое прогрессирующее заболевание головного мозга, которое характеризуется дегенерацией дофаминергических нейронов черной субстанции является болезнь Паркинсона. Помимо классических двигательных нарушений, для болезни Паркинсона характерен широкий спектр недвигательных (немоторных) проявлений, к которым относятся вегетативные, сенсорные, психические, аффективные расстройства, нарушения сна и бодрствования. Наиболее частые немоторные симптомы заболевания такие как болевые синдромы вызывают выраженный дискомфорт и значительное

снижение качества жизни пациентов, но при этом плохо изучены, хотя являются важным симптомом болезни Паркинсона.

Ключевые слова: Паркинсонизм, клинико-неврологические изменеия, боль, виды, диагностика.

Introduction

Cerebrovascular diseases account for 1 to 15% of parkinsonism cases, "... 200 out of every 100,000 people worldwide suffer from this disease ..." (14). According to the International Parkinson's Foundation and the Working Group (MDS Task Force), by 2020 the number of cases of Parkinson's disease worldwide will exceed 10 million, and the incidence of this disease in people of working age will increase in the near future - 5% of patients. up to 40 years and 10% up to 50 years.

In addition to classical motor disorders, such as hypokinesia, rigidity, rest tremor and postural instability, Parkinson's disease is characterized by a wide range of non-motor (non-motor) manifestations, which include vegetative, sensory, mental, affective disorders, sleep and wakefulness disorders [5,7]. Non-motor symptoms of the disease are a consequence of the involvement of other structures of the central and peripheral nervous system in the degenerative process [3]. Pain syndromes cause severe discomfort and a significant decrease in the quality of life of patients, but they are poorly understood, although they are an important symptom of Parkinson's disease. According to various authors, the frequency of chronic pain syndromes lasting more than three months in patients with Parkinson's disease ranges from 40 to 70% [6].

Pain is very frequent, poorly recognized and poorly understood in MS Parkinsonism, which significantly reduces the quality of life of patients [3, 6]. A survey evaluating the most "problematic" symptoms of the disease showed high pain rates at all stages of the disease [6]. Nevertheless, pain is very often not recognized even by the most experienced specialists and remains unexplained in approximately 40% of patients [3]. The prevalence of various types of pain experienced by patients with parkinsonism, according to various data, is approximately 80% [6].

The Purpose of the Work

Thus, the purpose of this study was to study the state of clinical and neurological features of pain syndrome in patients with Parkinsonism.

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Materials and Methods of Research

The study was conducted on the basis of the 1st clinic of the SamMI Department of Nervous Diseases, in the period from 2017 to 2021. 107 patients with Parkinson's disease (PARKINSONISM) were examined (74 men and 33 women) and 29 people made up the control group. The average age of patients was 56.5±8.9 years (minimum 45 years, maximum 75 years), the duration of the disease ranged from 1.2 years to 15 years (average 6.2±3.6 years). The group of examined patients complaining of various manifestations of pain syndrome in Parkinsonism consisted of 107 patients, 74 of them men and 33 women. The average age is 56.5±8.9 years. The clinical examination in the main group of patients present at the time of the initial treatment included the study of the types of pain syndrome, anamnesis, neurological symptoms, and the form of the disease.

Examination of all patients was carried out by a clinical and anatomical method, women were necessarily examined by a therapist, an oculist, and hardware research methods were also used.

The clinical-analytical method was based on a respectable analysis, anamnestic data, objective and clinical-laboratory data.

The criterion for selecting patients was the absence of dementia according to the ICD-10 criteria. Physiological research methods included the study of somatic status (studies of hemodynamic and respiratory parameters), neurological status. Clinical research methods: magnetic resonance tomography (MRT)and CT of the brain, neuromyography, ECG, ultrasound of the abdominal cavity and pelvis. From laboratory research methods, a general blood test, a biochemical blood test (homocysteine, cyanocobalamin) and a general urine test were studied.

The assessment of emotional status was carried out based on the results of the examination of patients using: Hamilton Scale for assessing depression, hospital scale of anxiety and depression.

Neuropsychological testing included the use of questionnaires and scales: Hamilton Depression Assessment Scale (HDRS) is a clinical manual developed in 1960 by M. Hamilton (for quantifying the condition of patients before, during and after treatment). The Hamilton Depression Assessment Scale (HDRS) consisting of 21 points is filled in during a clinical interview (taking approximately 20-25 minutes). The total score is determined by the first 17 points (9 of which are evaluated by scores from 0 to 4, and 8 - from 0 to 2). The total score of the first 17 points:0-7 - norm 8-13 - mild depressive disorder 14-18 - moderate depressive disorder 19-22 - severe depressive disorder more than 23 - extremely severe depressive disorder.

To evaluate the different manifestations of pain used visual analogue scale (VAS) (Visual Analogue Scale— VAS) (E. C. Huskisson, 1976) to assess the severity of pain questionnaire pain Mak-Gill (The McGill Pain Questionnaire) (by Melzack R., 1975) - for touch-discriminative and affective-motivational components of pain, UPDRS (Unified Parkinson's Disease Rating Scale - unified rating scale for Parkinson's disease),

the questionnaire DN4 pain (Bouhassiraa D., Attala N. et al., 2005) for the diagnosis of neuropathic pain. From laboratory studies in the preparations of the main and control groups, the level of homocysteine (Hc) was determined by high-performance liquid chromatography (HPLC analysis). Cyanocobalamin (vitamin B12) was determined by enzyme immunoassay (ELISA). The limits of the reference limits of the norm for biochemical parameters of blood plasma were:1) for the level of homocysteine up to 12.0 mmol / l; 2) for the level of vitamin B12 - 180-900 pg /ml.

Statistical processing of the obtained data was carried out using the computer program "Excel 7.0". To determine the reliability of the differences between the mean values, the Student's t – test was used. The differences between the groups were considered statistically significant at $p < 0.05$.

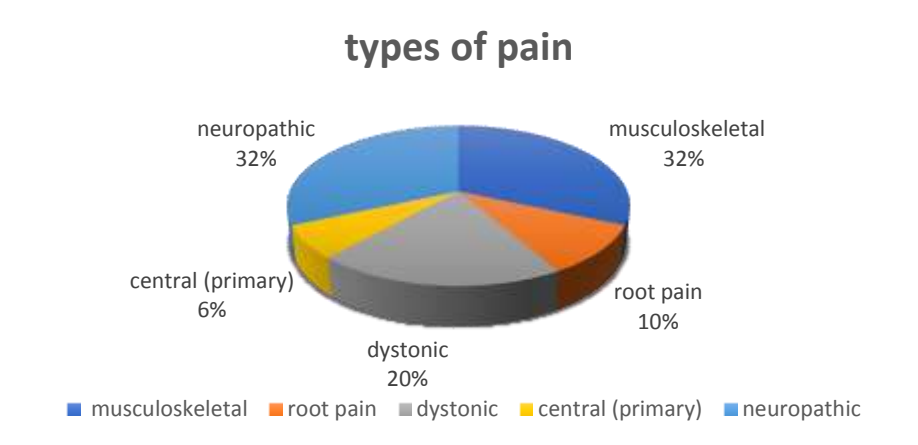
Results and Discussion

The study included 136 patients (78 men and 58 women), the average age of patients was 56.5±8.9 years (minimum 45 years, maximum 75 years), the duration of the disease ranged from 1.2 years to 15 years (average 6.2±3.6 years), the age of onset of symptoms was 56.0±4.6 years. In 58 (51.8%) patients, the pain syndrome was detected or was more intense on the side of more pronounced motor manifestations (hypokinesia and rigidity). In 16 (14.3%) patients, the pain syndrome was detected on the opposite side in relation to the side of the onset of parkinsonism symptoms. In a quarter of 27 patients (24.1%), pain syndrome was registered from two sides.

Pain syndrome was more often localized in the proximal parts of the upper extremities in 46 (41.1%) patients than in the distal parts in 17 (15.2%) patients, in contrast to the symptoms of Parkinsonism, which in Parkinsonism initially involve the distal parts of the upper extremities to a greater extent. On the upper extremities, pain syndrome was more often localized in the shoulder area in 39 (34.8%) patients, less often in the hand in 17 (15.2%) patients. Pain in the lumbar region was noted by 34 (30.4%) patients. Hip pain was detected in 28 (25%) patients, in the lower leg - in 22 (19.6%) patients, foot - in 16 (14.3%) patients. Multiple localization of pain syndrome was registered in 33 (29.5%) patients. The severity of the pain syndrome varied during the day. According to the analysis of diaries, pain syndrome occurred more often in

patients in the morning and afternoon hours of 47 (42%) patients, less often in the morning and evening hours of 37 (33%) patients. Pain, mainly in the evening and at night, bothered 28 patients (25%).In the study of pain syndromes in patients with PARKINSONISM, the study was carried out in combination with other symptoms, such as bradykinesia, rigidity, tremor, dystonia. In the study of pain syndromes in patients with Parkinsonism, five different types of pain were described (Fig. No. 1.).

Figure N. 1. Types of pain syndrome in the examined patients



The results of the assessment of the severity of the pain syndrome using the visual analog scale (VAS) (Appendix 8) ranged from 2 to 10 points and averaged 7.0 ± 1.8 points. The maximum discomfort was accompanied by muscle spasms and dystonia. When assessing the sensory-discriminative and affective-motivational components of pain using The McGill Pain Questionnaire (Appendix 9), the total average score was 24.4±22.5. As a result of the diagnosis of neuropathic pain or the presence of its neuropathic component, including an assessment of both subjective complaints and objective neurological symptoms when using the DN4 questionnaire, the total average score was 5.0±2.6.

The largest number of patients - 43 (38%) - complained about the manifestation of pain symptoms as a result of pathology of the musculoskeletal system. Muscle spasms and stiffness of the paravertebral and calf muscles (10 patients), as well as osteoarthritis of large joints (12 patients), such as shoulder, hip and knee, and degenerative-dystrophic changes of the spine (16 patients) were the cause of this type of pain. The musculoskeletal type of pain not associated with rigidity in Parkinsonism was characterized by the detection of local muscle soreness during examination, limited mobility in the affected areas. There was also a connection between pain and rigidity and bradykinesia. Pain, spasms and arthralgias in patients with Parkinsonism were associated with a lack of active movements in the affected limbs and joints, impaired posture, difficult movements in the limbs and violations of the kinetic

"melody" of movement. Musculoskeletal pain increased during periods of increased symptoms of the disease. Radicular pain occurred in 9 (8%) patients. Pain manifestations and unpleasant sensations were localized in the area of innervation of the roots L4 and L5 of the lumbar spine.

Pain associated with dystonia (dystonic) was diagnosed in 15 (14%) patients. Pain in dystonia was determined by visible twisting, spasmodic contractions, forced position of a limb or part of the body. Basically, these were short-term spasms, lasting up to several minutes.

Central (primary) neuropathic pain occurred in 6 (5%) patients and was a direct consequence of the disease itself, and not the result of dystonia, musculoskeletal and other disorders. The manifestations of this type of pain were unexplained piercing, burning, burning sensations involving the face, head and body. Another manifestation of pain syndrome was pain with a burning sensation, tingling, "crawling goosebumps", prevailing in the distal extremities. This type of pain was characterized as pain in polyneuropathy (neuropathic pain) and occurred in 39 (35%) patients.

The severity of the pain syndrome according to VAS ranged from 1.7 to 8.3 points and averaged 5.5 ± 1.6 points (tab. № 1

Table № 1. Localization of pain syndrome in the examined patients

Localization of pain syndrome	Number of patients with (N=64) %
Axial departments	
Head	5 (4,5%)
Neck area	9 (8%)
Chest	6 (5,4%)
Belly	3 (2,7%)
Lumbar region	34 (30,4%)
Upper limbs	
Shoulder	39 (34,8%)
Brush	17 (15,2%)
Lower extremities	
Hip	28 (25%)
Shin	22 (19,6%)
Foot	16 (14,3%)
Multiple localization of pain syndrome	33 (29,5%)

Note: * - data reliability between the groups (P<0.05)

Patients with pain had higher score on the UPDRS part III, mainly due to hypokinesia and postural instability, which patients without pain, it was not identified differences between the two groups in the severity of tremor and rigidity (p<0.05).

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A correlation was detected between the intensity of pain measured at YOURS, as well as the severity of hypokinesis (R=0.5, p<0.01). There was a significant correlation between the assessment of pain syndrome according to VAS (R=0.32, p<0.001). The severity of pain was assessed by VAS. On average, back pain was assessed by patients by 7.1±0.6 points, headache - by 5.3±1.1 points, widespread musculoskeletal pain - by 6.9±0.7 points. The overall pain intensity was 6.5±0.4 points. At the same time, in patients with stage 1 of the disease, the severity of BS was estimated at 5.1 ± 0.6 points, from the 2nd - 6.8 + 0.8 points, from the 3rd - 7.5 + 0.3 points.

In the study of the type of pain in patients with neuropathic character of algic disorder was detected in 18 (16%) patients, nociceptive – in 66 (59%), mixed – in 28 (25%). Thus, the vast majority of patients suffered from nociceptive BS. The chronic nature of the algic disorder was detected in 25 (22.3%) people. At the same time , the increase in the number of cases of chronic pain with an increase in the duration of the disease was natural .

The intensity of pain measured at YOURS, correlated with the estimate in part III and UPDRS (11=0,43, p<0.01), and the evaluation of hypokinesia (11=0,5, p<0.01). In patients with the threshold of pain sensitivity, assessed by press algometry, was significantly lower compared to those in the control group (p<0.05).

Chronic pain syndrome persisting for more than three months was detected in 58 (51.7%) of 107 patients, 31 men and 27 women. Pain syndrome lasting more than 1 year was detected in 69 (61.6%) of 107 patients. A persistent variant of chronic pain syndrome was noted in 74 (66.1%) patients, 38 (33.9%) patients suffered from recurrent pain syndrome with remissions for no more than 3 months.

Of 107 patients with chronic pain syndrome, 41 (36.6%) had it almost simultaneously with the appearance of motor disorders or shortly before them, 71 (63.4%) developed later, as the disease progressed further. During the year UNACLA disease pain syndrome, occurred in 52 patients (46,4%), after hody more than 60 patients (53.6 per cent).

Above we can assume that the temporal relation of pain syndrome with disease, its main motor and no motor manifestations, changes of pain threshold, a positive reaction to anti-Parkinsonian therapy suggest that most patients with chronic pain syndrome is pathogenetically associated with the disease.

In connection with the above, we can distinguish four main signs that allow us to establish a connection between pain syndrome and :

1) the development of pain simultaneously with the onset of the disease and / or against the background of an increase in symptoms of parkinsonism; 2) the correspondence of the localization (congruence) of pain to the distribution of the main

motor manifestations (predominance on the side of more pronounced symptoms of parkinsonism);
3) reduction of pain when prescribing or correcting antiparkinsonian therapy or their connection with motor fluctuations, phases of action of levodopa drugs or dyskinesia;
4) the absence of other reasons that can explain the pain syndrome.
If the pain associated with parkinsonism is possible in the case of a clear positive reaction to antiparkinsonian therapy, including in connection with fluctuations in the effect of PPP (in the presence of the 3rd criterion) or in the presence of the 1st, 2nd or 4th criteria. Based on these criteria, pain syndrome can be consistently associated with 33.9% of patients.
Drawing a conclusion, we can say that the allocation of certain types of pain in parkinsonism is conditional due to the frequent presence of combined or transitional forms with different ratios of certain components. Moreover, they can serve as guidelines structuring a single spectrum of pain syndromes detected in patients with this pathology.
The emotional-affective sphere in the majority of the examined patients with the initial stages of the disease (44 patients out of 107, 39.3%) revealed depressive symptoms of varying severity, represented by increased guilt, helplessness, irritability, decreased ability to enjoy, as well as suicidal thoughts without suicidal intentions (the latter-in 5% of cases with identified depressive symptoms). If symptoms such as insomnia, general weakness or fatigue were also observed in non-depressive patients at the initial stage of the disease, then complaints of hopelessness, dissatisfaction with life, lack of cheerfulness and sadness already indicated the formation of depression in the structure of the disease.
The assessment of depressive symptoms on the Beck scale (Table 6) varied from 4 to 34 points, the average score was 27.0±8.5 points. As can be seen in Figure 1, mild depression was detected in 50 patients with initial stages (44.6% of the total number of subjects), moderate in 28 (25%), and severe in 5 (4.5%) patients.
In 29 (25.9%), the score on the Beck scale was no more than 10 points (which corresponds to the absence of depression). The assessment of depressive symptoms on the Hamilton scale in the examined group of patients ranged from 6 to 16 points (on average 11.1 ± 4.6 points). The distribution of patients with initial stages by severity of depression on this scale was similar to the Beck scale.
In the study, the relationship between the development of depression on and the female sex was noted: in female patients, the indicators of the Beck depression scale were 29±3.2 points, in men - 22± 4.6 points (the difference obtained is statistically significant, (p0,05)).

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The level of homocysteine in the studied samples was 17.5±5.1 mmol/l in the 1st group of patients and 14.2±3.9 mmol/l in the 2nd group of examined patients, respectively, which significantly differed (p<0.001). It should be noted that the cyanocobalamin (vitamin B12) levels in the 1st group of patients were lower than in the other group of examined patients and amounted to 296.0±63.8 pg/ml, but that was within the reference values of the norm. There were no significant changes with the 2nd group (p>0.05).

Table №. 3 Biochemical parameters of the examined groups of patients

As a result, we detected an increase in homocysteine with a normal vitamin B12

Indicator	Group 1 (patients with , with pain syndrome), (n=64)	Group 2 (patients with , without pain syndrome), (n=43)
Duration of dopaminergic therapy, years	6,1±3,6	4,2±2,0*
Homocysteine level, mmol/l (norm up to 12)	17,5±5,1	14,2±3,9**
Vitamin B12 level, pg/ml (norm 180-900)	296,0±63,8	346,0±119,0

content, which indicates the formation of secondary mitochondrial dysfunction in individuals of this group, despite the satisfactory level of this source of coenzyme. As a result of levodopa demethylation, adenosyl cobalamin deficiency occurs in the mitochondria, resulting in methylmalonic acidemia, and with a lack of methyl cobalamin in the cytoplasm, hyperhomocysteinemia also develops.

The lack of folic acid in the mitochondria, in turn, can lead to disruption of the functioning of the glycine - decarboxylase complex. Systemic mitochondrial disorders depend on the activity of methyl malonyl Co-mutase, its coenzyme adenosyl cobalamin, and factors of its transfer to mitochondria. As a result of the study, a positive relationship was revealed between the severity of motor fluctuations and the severity of pain on the VAS scale (g=0.4; p<0.05), but there was no connection between the presence of motor fluctuations and the severity of polyneuropathy. In group 2, 4 patients were diagnosed with mild polyneuropathy, which was asymptomatic, and patients did not complain about various manifestations of pain syndrome.

The results of our study showed that out of 136 patients with (78 men and 58 women), 64 (57%) patients complained of various manifestations of pain syndrome. Among these people with motor complications, this percentage was significantly higher (in 92 out of 107 or 82%). Pain syndromes accompanied motor disorders at different stages and were ahead of their appearance in 67 (60%) patients. The pain prevented the correct diagnosis in 17 patients. At the same time, it was pain that could cause an

erroneous diagnosis of Parkinsonism syndrome itself, especially at the initial stage, and turn into a serious problem at the advanced stages of the disease. It was a pain associated with rigidity and hypokinesia in the muscles of the shoulder girdle and upper extremities, which in the onset of the disease could lead to an incorrect diagnosis of shoulder periarthritis or osteochondrosis of the cervical spine. Basically, the pain was localized on the side of the maximum severity of motor symptoms.

Also in our study, we determined the level of homocysteine in blood plasma, as this is of increased interest due to the available data on their direct neurotoxic effects. When examining patients with, an increase in homocysteine levels was detected in 84% of all patients suffering from this disease with signs of polyneuropathy. The mean values of homocysteinemia in patients of groups 1 and 2 who received L-dopa therapy significantly differed ($p<0.001$). At the same time, a relationship was revealed between the dose of drugs containing levodopa and an increase in the level of homocysteine in blood plasma. An association was found between the duration of treatment with levodopa drugs and an increased level of homocysteine in blood plasma. It is noteworthy that in patients with more than 10 years of illness, hyperhomocysteinemia occurred in 100% of the subjects. Multivariate regression analysis showed a strong positive correlation between the duration of the disease, the duration of taking L-dopa drugs and elevated homocysteine levels. Therefore, the daily dose of drugs containing levodopa is the main risk factor for an increase in homocysteine in blood plasma, and as a consequence, the development of polyneuropathy in. Statistical analysis using the Toronto Clinical Neuropathy Assessment Scale revealed a strong positive correlation between the severity of neuropathy and the daily dose of levodopa, especially with duodenal administration of levodopa. The severity of neuropathy also correlates positively with the concentration of homocysteine. These data once again confirm the results of our work. Of course, the problem of the presence of polyneuropathy in patients suffering from, and which undoubtedly aggravate the overall clinical picture, has not been completely solved and needs further study. However, already today, it is obvious that studies of pain syndromes and polyneuropathy in the structure of this disease require close attention from practitioners. This, in turn, will expand the understanding of the pathogenesis of the disease and its clinical manifestations, which in the future will help to avoid erroneous diagnosis of the Parkinsonism syndrome itself and will provide recommendations for optimizing the treatment process.

Conclusions

Thus, the study demonstrated a high prevalence of various pain syndromes in patients suffering from Parkinsonism. As a result of the study of pain syndromes in patients with Parkinson's disease, five different types of pain were described: musculoskeletal - 23 (33%); radicular - 6 (9%); pain associated with dystonia (dystonic) - 12 (19%); central (primary) neuropathic pain - 4 (6%); pain with polyneuropathy (neuropathic) -19 (30%) patients. The nature of pain formation in Parkinson's disease can have both central and peripheral mechanisms. Axon- and myelopathy revealed during neurophysiological examination are an additional cause of pain syndrome and a manifestation of the disease. At the same time, the revealed significant changes during neuro orthopedic examination in them emphasize the role of violations of the biomechanics of the motor act and require a comprehensive approach to pain therapy in this category of patients.

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