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APATHY AS THE NON-MOTOR SYMPTOM OF PARKINSON DISEASE AND HUNTINGTON DISEASE

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Apathy is one of the most frequent, disabling and difficult to treat non-motor symptoms manifesting in many neurodegenerative diseases, particularly in Parkinson disease and Huntington disease. Aim is to evaluate and compare the clinical profile of apathy in patients with Parkinson disease (PD) and Huntington disease (HD).

Materials and methods. The individual registration card was filled in for each patient containing demographic data, clinical features of the disease, the results of validated scales and questionnaires evaluating motor activity (The Movement Disorder Society-Unified Parkinson's Disease Rating Scale – MDS-UPDRS, the Unified Huntington's Disease Rating Scale – UHDRS), cognitive functions (MoCA-test), anxiety-depressive symptoms (hospital scale for evaluating anxiety and depression, Beck's depression scale-II), apathy (apathy rating scale). Patients with dementia or severe depression were excluded from the study.

Results. The study included 265 patients: 250 with PD and 15 with HD. Apathy was diagnosed in 57.8% of cases in patients with neurodegenerative diseases (139 out of 250 patients with PD and 9 out of 15 patients with HD). In both groups of patients apathy was associated with the severity of motor manifestations. Patients with PD showed a positive correlation of apathy with more severe depression ($r=0.488$; $p<0.0001$), anxiety ($r=0.300$; $p<0.0001$) and drowsiness ($r=0.254$; $p<0.0001$); a negative correlation with a short duration of the disease ($r=-0.160$; $p=0.021$), a lower dose of dopaminergic drugs, LEDD ($r=-0.203$; $p=0.03$). In patients with HD, apathy was associated with disease duration (8 (4; 11) years in patients without apathy and 5 (3;9) years in patients with apathy, $U=3791.5$; $p=0.020$) and cognitive impairment (26 (19;37) points, without apathy – 18 (12;26), $U=3548.5$; $p=0.003$).

Conclusions. Similar frequency of apathy was found in patients with PD and HD, but with different clinical correlations due to the involvement of different brain regions in the pathological process, which requires further research to develop targeted therapy.

Keywords: apathy, Huntington disease, Parkinson disease, cognitive disorders, depression, psychopathological symptoms, non-motor symptoms.

Introduction. Apathy is considered as a disorder of the emotional-volitional sphere, characterized by a lack of emotional manifestations, lethargy, indifference to oneself and relatives, to what is happening around, lack of desires, life motives and inactivity. 3 main components are distinguished in apathy: emotional-affective, cognitive and auto-activity deficit: the first is the apathy associated with impaired emotional-affective processes; the second is the apathy associated with the violation of cognitive processes; and the third is the apathy associated with the disorder of self-activity process [1].

Each component of apathy is caused by different neuronal connections affecting the basal ganglia, thalamus, and cortical connections. According to research data, the apathy prevalence in cortex and subcortical nuclei lesions ranges from 40 to 60% [4, 7, 12, 14]. Such high rates of apathy in brain diseases are the result of quite frequent involvement of frontal-subcortical neuronal connections between the prefrontal cortex and basal ganglia in the neurodegenerative process, affecting the anterior cingulate gyrus, ventral striatum, pallidum and thalamus [1, 19].

Both PD and HD are motor neurodegenerative disorders caused mainly by lesions of the basal ganglia and manifesting by motor and various non-motor symptoms, including cognitive, behavioral, and emotional-affective manifestations, with apathy among them [19, 20]. In PD, apathy is a frequent neuropsychiatric disorder with prevalence varying from 7 to 70%, and, according to a number of studies, it might even precede motor symptoms with a frequency reaching 36% of cases [7, 8]. The prevalence of apathy usually decreases after the starting of dopaminergic replacement therapy, but it increases again up to 40% in patients without severe cognitive impairment and up to 60% in patients with dementia after 5-10 years of the disease [8]. Apathy in PD is associated with the male sex, old age, the presence of depression and severe motor disorders, deterioration of executive function, and an increased risk of dementia [8, 22].

The prevalence of apathy in HD, according to various literature data, also varies widely: from 11 to 76% [9, 10, 15-17, 21]. One point of view is that apathy is mildly present in almost all patients with HD during the course of the disease, and that its prevalence increases due to the progression of the disease. As a result of the "TRACK-HD" study (UK, 2012-2014), establishing sensitive and reliable biomarkers in identified carriers of the HD gene and in patients with HD at early clinical stages, it was proved that a significant increase in apathy can be detected among patients with HD at the preclinical stage. Apathy in this case was the most reliable psychotic non-motor symptom, which is important for predicting functional disorders at the early stages of HD [9, 16, 18]. According to these studies, apathy in HD was more common in older male patients with a lower overall functional ability score, a higher score of motor function evaluation on the Unified Huntington's Disease Rating Scale – UHDRS, more psychotropic drugs usage, depression, and cognitive impairment.

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Despite the fact that both PD and HD characterized by severe motor disorders, often manifest by apathy, its profile and correlations with other symptoms differ significantly. The purpose of this study was to evaluate and identify the role of apathy in the clinical picture of PD and HD.

The **aim** of our study was to evaluate non-motor symptoms in patients with PD and HD, on the basis of the apathy presence and its severity.

Materials and methods. The advantage of this work is that a quite large category of patients with neurodegenerative diseases was examined using the same, validated, recommended by the world's leading neurological organizations – «The International Parkinson and Movement Disorder Society (MDS)» and «European Academy of Neurology (EAN)» clinical scales for apathy, cognitive dysfunction and depressive symptoms assessing.

The plan and performing of the study are fully complying with the principles of Good Clinical Practice (GCP) and the Helsinki Declaration (including amendments). The research protocol was approved by the ethics Committee of the Siberian State Medical University (registration number 7813 of may 27, 2019).

265 patients with neurodegenerative disorders were studied: 15 with HD and 250 with PD at different disease stages on base of the department of neurology and neurosurgery Siberian State Medical University, Tomsk, Russian (head of department, professor, MD V.M. Alifirova).

Inclusion criteria: verified diagnosis of idiopathic PD according to the diagnostic Criteria of the United Kingdom Parkinson's Disease Society Brain Bank [13], verified diagnosis of HD with a positive genetic test (the number of trinucleotide CAG repeats in one of the alleles of the HTT gene≥36) and characteristic clinical manifestations in the form of motor symptoms, with UHDRS motor assessment.

Exclusion criteria: the presence of severe depression and dementia, according to the diagnostic criteria of ICD-10; patients with PD who had deep brain stimulation surgery.

The individual registration card was filled in each patient of the study, containing information about demographic data (age, gender, education level), medical history (duration, stage of symptoms development, used drug therapy, the dose of dopaminergic drugs for patients with PD translated into the equivalent daily dose of levodopa (levodopa equivalent daily dose-LEDD) and for both groups, the analysis of symptomatic therapy); for patients with HD - the number of CAG repeats.

Evaluation of motor disorders in patients with HD was performed using the Unified rating scale for HD manifestations evaluation, the part "motor assessment" (UHDRS-Motor), in patients with PD – using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale – MDS-UPDRS, part III (MDS-UPDRS-III). The analysis of motor and psychoemotional disorders in patients with PD was carried out in the on-phase. Depressive symptoms were studied using the Beck-II depression scale. Cognitive impairment was recorded using the Montreal cognitive assessment scale (MoCA test).

There is an extensive list of psychometric scales published to assess apathy, but for the purposes of this study, we focused on those that could be used in both patients with HD and PD [3]. Apathy was evaluated using the Apathy Scale, which is a self-questionnaire consisting of 14 statements distributed on a 4-point Likert scale (1-not at all, 2-slightly, 3-partially, and 4-to a large extent) and being a modified, abbreviated version of the Marin (Apathy Evaluation Scale - AES) [11]. Answers to questions should contain information about the previous four weeks. The questionnaire has items reflecting various symptoms, according to which you can track their dynamics. Energy, sleep, fatigue, appetite, psychomotor disorders, speed and clarity of thinking, memory, ability to concentrate, the presence of plans and goals for the future, loss of interest and initiative are the main factors for determining the presence and severity of apathy. The main advantages of the scale are the following: ease of use, well-defined score values for apathy screening, high specificity and sensitivity to changes (on the background of treatment). The disadvantages are that this self-questionnaire is not acceptable for patients with moderate to severe dementia.

Statistic results processing was performed using the pack of application programs SPSS 11. 5 for Windows. The critical significance level in our study was 0.05. The description of qualitative features is carried out by specifying absolute and relative (%) frequency of occurrence (Pearson's criterion $\chi 2$ with Yates correction and Fisher's exact criterion). Quantitative characteristics were checked for compliance with the normal distribution law using the Shapiro-Wilk test. The description of quantitative characteristics is presented as the average value and standard deviation M; □. Description of quantitative features whose distribution does not correspond to the normal law – in the form of the median and the interquartile range Me (Q1;Q3). We used for comparison of quantitative data criteria Mann–Whitney and Kruskal-Wallace. The relationship between quantitative and ordinal features was evaluated using correlation analysis.

Results. In our sample patients with PD were of average age of 67.2±7.8 years, 130 (52%) were men and 120 (48%) were women, the average duration of education was 9.2±6.3 years, and the average duration of the disease was 7.4±5.1 years. All PwPD received specific antiparkinsonian therapy, 110 (44%) patients were treated with antidepressants, and 2 (0.8%) received neuroleptics.

For patients with HD, the average age was 51.3±7.8 years; there were 6 men and 9 women, the average level of education was 7.2±4.9 years, the average duration of the disease was 7.1±4.2 years, 9 patients received neuroleptic treatment and 10 received antidepressants (4 patients were treated with the combination of these drugs). According to the obtained data, patients with HD were significantly younger than those with PD ($p<0.001$).

The analysis of the examined groups revealed that patients with PD had a higher average level of education ($p=0.032$), patients with HD – received neuroleptic treatment more often ($p<0.001$). In our sample, the average duration of the disease in patients with PD and HD was equivalent, with no significant differences ($p>0.05$).

High incidence of apathy in patients with various neurodegenerative diseases was found in this study, manifested both by hypokinetic-hypertensive syndrome in PD and hyperkinetic-hypotonic syndrome in HD: 55.6% (n = 139/250) and 60.0% (n = 9/15), respectively, at $p>0.05$. Cognitive disorders were observed in all patients with diagnosed apathy in HD (n=9), while in patients with PD – in 44.6% (n=62) of cases, $p<0.001$. In turn, patients with PD and apathy were more likely to have depressive symptoms – in 93.5% (n=130) of individuals, compared with patients with HD – in 55.5% (n=5), with $p<0.001$. This data is consistent with the results of international studies [7-10, 15-17]. However, there is a wide variability of the apathy frequency in both diseases in the literature, which is due to various factors, such as the location of the patients' sample (e.g. patients from special clinics for movement disorders in comparison with individuals from the

general population), the inclusion of patients with severe depression and / or dementia, the severity of the disease, different methodological approaches (e.g., assessment of the patient or his relatives) and usage of various diagnostic tools for apathy assessment.

The clinical profile of the studied neurodegenerative disorders is represented by various motor symptoms (in PD – bradykinesia, tremor, hypokinesia and postural instability, in HD – chorea in the form of abnormal short and irregular uncontrolled movements) and non-motor (cognitive, emotional-affective, mental and behavioral) symptoms. Although both diseases are mainly associated with lesions affecting the basal ganglia, the neurodegenerative process in PD and HD develops in different ways. So, the PD manifestation is observed at 70-80% loss of the substantia nigra pars compacta, first in its ventral and then in the dorsal parts, which subsequently leads to a loss of the striatum dopamine content. In HD, the neurodegenerative process is initiated by the loss of striatum neurons [2, 5]. However, despite all these differences, both diseases seem to have an equally high apathy inclination but with features in its profile.

Patients with PD and apathy studied by the MDS-UPDRS-III scale showed a significantly higher level of motor disorders – 38 (30;48), while without apathy – 29 (23;38), (U=3658.5; p=0.003), a shorter duration of the disease – 6 (4;10) compared with 9 (5;12) points - without emotional-affective disorder, (U=3793.5; p=0.020), a lower dose of LEDD – 150 (0;350) and 300 (156;375), (u=3321.5; p<0.0001) and had pronounced depressive symptoms according to BDI-II – 20 (16;27) compared to PD – without apathy – 15 (11;20), (U=2781.5; p<0.0001).

According to the results of our study, patients with PD and apathy have more severe motor disorders (according to MDS-UPDRS-III), a shorter duration of the disease, and more pronounced symptoms of depression. On this basis it can be assumed that the short duration of clinically expressed neurodegenerative disease and the presence of pronounced motor symptoms might be the apathy predictors in PD.

An interesting result is that the majority of apathy patients with PD and apathy patients with HD had combined depression and / or cognitive disorders, and only 5.6% of those with PD (n = 14) and 1 patient with HD (6.7%) had isolated apathy. According to previous studies, apathy is a hypodofaminergic symptom in PD, with the severity decreasing when taking dopaminergic drugs [5]. In our sample, patients with PD and apathy have a lower total daily dose of levodopa, compared to patients with PD without apathy (p = 0.05). Despite the fact that there were no statistically significant differences in dopaminergic drugs dose taken in the group of patients with PD and apathy and without it, there was a trend in which patients who did not suffer from apathy received drugs of dopamine receptor agonists more often.

Moreover, it was found that patients with PD and apathy are significantly more likely to take antidepressants than patients without apathy; however, this can be explained by the fact that apathy is combined with depression in most cases, and patients receive depression pathogenetic treatment that does not affect the severity of such an emotional-affective disorder as apathy.

The connection between apathy and cognitive impairment is contradictory and widely discussed [4, 8, 20]. As a result of neuropsychological testing, it was found that the cognitive profile of patients with apathy in the studied neurodegenerative diseases differs: in patients with HD attention, working memory (p <0.001) and speech (p = 0.007) domains are significantly reduced according to the MoCA test compared to patients with PD.

In HD apathy was also significantly associated with the duration of the disease and the presence of cognitive impairments. Thus, in patients without apathy the duration of the disease was 5 (3;9) years, with apathy – 8 (4;11) years, U =3791.5; p=0.020.

During the study it was found that all patients with HD had cognitive disorder (n = 15). However, patients with clinically expressed apathy had the worst result of cognitive tests of 16 (10;24) points, without apathy – 20 (12;29) points, U =3548.5; p=0.003. Our data partially confirm the results received earlier indicating that apathy in HD might be a predictor of cognitive impairment up to dementia [3]. We did not find a predominance of patients taking neuroleptics in the group of patients with apathy. However, this might be connected to the fact that neuroleptics are used at the advanced stage of HD.

As the result of the study it was found that patients with PD have two peaks of apathy in the course of the disease: in the early, before-treatment stages by Hoehn and Yahr (as a rule, they are first-time applying patients of the 1st and 2nd stages by Hoehn and Yahr), when the specific antiparkinsonian therapy, supporting optimal or close to the physiological level of dopamine, has not been prescribed and the second peak is on extensive stages of PD (4th and stage 5th stages) when extensive neurodegenerative process can't be compensated by the drugs and is accompanied by a number of non-motor symptoms. In addition, the association of apathy with hospitalization of the patient was found due to the development of an akinetic crisis, regardless of the PD stage. This might be connected to the constant use of a low dose of dopaminergic drugs, which increases the likelihood of apathy and other associated emotional and affective disorders that contribute to the violation of compliance in this category of patients.

Despite the fact that there are two different disorders of the basal ganglia in the studied diseases, the greater severity of motor symptoms seems to lead to a higher predisposition of apathy in both HD and PD.

Conclusion. As a result of the study, it can be noted that apathy is a frequent and important non-motor manifestation of PD and HD. In the studied neurodegenerative diseases with lesions of the basal ganglia, various neuronal pathways going from the prefrontal cortex to the basal ganglia suffer [2, 6]. Thus, in PD apathy is mostly associated with the emotional component, while in HD it is associated with cognitive areas, that might determine the need for different therapeutic approaches.

According to our data, apathy as a non-motor symptom of the two neurodegenerative pathologies studied in this research, has a similar prevalence, but the clinical profile is different. Apathy in PD is primarily associated with emotional and affective disorders ("emotional apathy"), while in HD it is associated with cognitive functions ("cognitive apathy").

In clinical practice, these results lead us to consider apathy as an independent nosological unit, caused by dysfunction, on the one hand, of different, but at the same time interconnected neuronal projections, which might differ depending on the nosology and even within the same pathology, depending on the stage of the disease. Our study confirms the fact that apathy has a multifactorial nature and depending on the type of neurodegenerative disease might have different points of pharmacotherapy application.

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