ing to IDF criteria among the indigenous female population was 22.6% (95% CI: 19.5-26.1). With standardization on the age structure of the world's population, the prevalence of MS was 21.2% (95% CI: 17.7-24.7). The most common variant of the clinical manifestations of MS was a combination of abdominal obesity with high blood pressure and dyslipidemia (in 62.7% of cases). A combination of 4 risk factors (abdominal obesity, elevated blood pressure, dyslipidemia, fasting hyperglycemia/diabetes) was detected in 14.8% of cases of MS. Variants with the inclusion of disorders of carbohydrate metabolism in the form of FHG/DM were recorded from the age of 40-49 years. The dynamics of the frequency of metabolic disorders in different age groups suggests that abdominal obesity is the main pathogenetic factor contributing to the development of a chain of metabolic disorders in a given population. The statement of this fact contains the potential for correction by informing the public about the risks, creating conditions for an active lifestyle, improving the eating habits of the population, restricting advertising of unhealthy foods in the media, etc.

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THE HETEROGENEITY OF NON-MOTOR SYMPTOMS IN PATIENTS WITH PARKINSON'S DISEASE IN TOMSK REGION

This study was designed to survey the prevalence and distribution of non-motor symptoms (NMS) in Parkinson's disease (PD) patients in Siberian region, Russia, and to investigate the association between NMS and health-related quality of life.

Materials and methods. Two hundred six PD patients were evaluated using a battery of validated scales recommended by leading PD research Societies (Movement Disorders Society and the European Academy of Neurology). Clinical assessments were conducted using Uniform Parkinson's Disease Rating Scale (UPDRS), Hospital Anxiety and Depression Scale, Beck depression inventory II, Apathy Scale, Montreal Cognitive Assessment (MoCAtest), Epworth Sleepiness Scale, Sleep Assessment Questionnaire, Columbia-Suicide Severity Rating Scale, Parkinson's Disease Questionnaire-39 – PDQ-39. **Results.** Each PD patient had eight different individual NMS on average. The constipation (87%), depression (67%), insomnia (66%), anxiety (52%), apathy (35%), and impulsive behavior disorders (27%) were the most frequent complaints. NMS prevalence in PD patients in Tomsk region was consistent with that in the international study, although the composition proportions were different. There was a significant association of PDQ-39 score with anxiety (r = 0,474, p = 0,000), depression (r = 0,471, p = 0,000), apathy (r = 0,322, p = 0,000), UPDRS III score (r = 0,316, p = 0,000), Hoehn and Yahr stage (r = 0,267, p = 0,000), disease duration (r = 0,220, p = 0,005), and levodopa equivalent dosage (r = 0,213, p = 0,001).

Conclusion. This study confirmed that NMS are common in PD, occurring across all disease stages and have a great impact on quality of life. NMS progression contributes significantly to health-related quality of life decline, and should be well recognized and treated.

Keywords: Parkinson's disease, apathy, anxiety, depression, impulsive behavioral disorders, insomnia, constipation.

Introduction. Parkinson's Disease (PD) is one of the most common neurological disease reaching 1% among population with age more than 60. PD's morbidity is up to 40 cases per 100 000 of population per year. According to the results of different epidemiological researches conducted in the USA and some European countries the prevalence of this neurodegenerative disease ranges in wide limits from 18 to 328 cases per 100 000 of population, but on the average it is about 120 cases per 100 000 of population [9]. In the Russian Federation the prevalence of PD is at worldwide level and according to the epidemiological

researches conducted in different regions it is in the limit from 40 to 140 cases per 100 000 of population. The amount of patients with Parkinson's disease (PwPD) is suggested to increase in 1,5-2 times to 2030 year [4].

Non-motor symptoms of PD are common but might stay unrecognized in clinical practice due to the insufficient targeted detection by physicians and absence of active complaints from patients and their relatives [1]. While dominating in clinical case and being main factors that influence life quality and length of PwPD, such non-motor symptoms like emotional-affective, behavioral and psychotic symptoms accelerate progressing of invalidization and cause patients' accommodation in nursing home [13].

For the first time non-motor symptoms of PD were systematically described in 2006 by K. Ray Chaudhuri and all [9] and nowadays non-motor symptoms are paid great attention [7, 23]. Wide range of non-motor symptoms includes vegetative, neuropsychic, sensor disorders, fatigue, sleep and wakefulness disturbances. Some PD's non-motor symptoms are registered in almost all patients regardless of the age of onset and Hoehn and Yahr stage of disease and become more expressed with the course of the disease [2]. Some of non-motor symptoms (anxiety, fatigue and vegetative disorders) are registered at the early stage of disease before the beginning of treatment [12]; the others according to literature data and own clinical observations precede PD's motor symptoms for a few years (olfactory dysfunction, disturbed eye movement in the sleep phase with fast eye movement – REM sleep phase, constipation, pain and depression) [1]. At late stages of disease non-motor symptoms are observed in almost all patients with motor fluctuations [10]. A lot of researches have established that at the time of PD diagnose verification its prevalence is 21%, but in only 7 years after the disease onset it is 88% [12].

The **aim** of this study is to analyze heterogeneity of non-motor manifestation of PD in Tomsk region.

Materials and methods. This study was performed on the base of Department of Neurology and Neurosurgery, Siberian State Medical University. We examined 206 PwPD, 57 % (118 people) out of them were women. The examination of all patients was held according to our own designed individual registration card including information about social status, history of previous diseases, passport details, neurological status and results of neuropsychological testing with scales and questionnaries. Diagnose of PD was established according to UK Parkinson's Disease Society Brain Bank Diagnostic Criteria. While establishing the diagnosis clinical form, Hoehn and Yahr stage of disease (according to «Modified Hoehn and Yahr Scale», 1967), rate of progression, presence of postural unsteadiness, impaired walking, sidedness with a predominance of motor symptoms in the limbs, severity of different non-motor manifestations (depression, anxiety, apathy, cognitive and vegetative disorders) were considered.

Average age of examined patients was about 65,9±9,8 years (66 (60;74) years), varying from 40 to 85 years. People with secondary professional education (39,3%) and with higher education (46,6%) prevailed.

The study involved patients matching certain criteria: men and women from 50 to 86 years; presence of PD's diagnosis with I-IV stage by Hoehn and Yahr scale; patients who signed and dated voluntary informed agreement for taking part in the research.

Severity of motor manifestations of PD such as resting tremor, hypokinesia, rigidity and postural unsteadiness was determined according to III part of the Unified Parkinson's Disease Rating Scale (UPDRS) [11].

Validated neuropsychological tests provided in the study were focused on detection of such non-motor manifestations of PD as impulsive behavioral disorders, cognitive and emotional-affective disorders, psychotic manifestation and sleep disorders. Impulsive-compulsive disorders were evaluated by questionnaire for Questionnaire for Impulsive-Compulsive Disorders in PD Rating Scale (QUIP-RS). Anxiety-depressive disorders were evaluated according to Hospital Anxiety and Depression Scale (HADS), Beck's Depression Inventory – II (BDI-II), Apathy Scale and Columbia Suicide Severity Rating Scale (C-SSRS). Cognitive status was analyzed according to Montreal Cognitive Assessment (MoCA). Sleep disorders were studied according to Epworth Sleepiness Scale (ESS) and Sleep Attack Questionnaire (SAQ). Quality of life was studied by using specialized self-questionnaire for life quality assessment in PwPD, PDQ-39.

Statistical result processing was performed by using application package SPSS 11.5 for Windows.

Results and discussion. During results analysis it was revealed that among the examined 206 PwPD 27% (56 patients) had subclinical anxiety according to HADS and 25% (51 patients) had clinically manifested anxiety (table 1).

The average was 66 (61; 73) years in the group without anxiety, 64 (60; 74) years in the group with subclinical anxiety and 64 (57; 75) years in the group with clinically manifested anxiety (χ^2=0,162, p=0,922). During intergroup comparison it was revealed that younger patients (aged 50-59 years, 31,4%) prevailed in the group with clinically manifested anxiety as opposed to groups without anxiety and with subclinical anxiety which consisted of more older patients.

Table 1

Characteristics of patients with Parkinson's disease, depending on the presence and severity of anxiety according to the HADS scale

Indicator abs. %	Выраженность тревоги по шкале HADS, баллы		
	Norm 0—7	subclinical 8—10	Clinical ≥11
n=206 100 %	99 48.06	56 27.18	51 24.76

In the result of our research it was revealed that patients with clinically manifested anxiety had the longest duration of PD – about 8 (4; 10) years, patients with subclinical anxiety had the shortest – 4 (3; 9) years and without anxiety – 6 (3; 10) years. The received data correspond to the literary described as "parkinsonian personality" according to which anxiety preceding to first motor manifestations of PD is characteristic. On advanced stages of the disease PwPD with motor fluctuations have anxiety level depending on levodopa action phase. Thus, anxiety symptoms are increased by relative overdose of dopaminergic drugs [11, 16].

Analisys of motor disorders by III part of UPDRS depending on severity of anxiety revealed that patients with anxiety had more expressed motor manifestations of PD: in the group of patients without anxiety, with subclinical expressed and manifested anxiety average mean by UPDRS was 32 (25; 43), 33 (27; 46) и 35 (28; 44) points respectively. This fact can be explained on the one side by progressive

neurodegenerative process, from the other side by not always correct usage of antiparkinsonian drugs treatment in patients with emotional-affective disorders. While analyzing clinical form of PD debut we revealed that anxiety prevailed in patients with acinetic-rigidity form.

Statistically significant positive mean force correlation between anxiety and depression was revealed both by HADS (r=0,446; p<0,0001) and BDI-II (r=0,436; p<0,0001) questionnaires. Statistically significant difference in severity of apathy in patients with clinically manifested anxiety 14 (7; 19), with subclinical anxiety – 12 (7; 15) and without anxiety – 8 (5; 14), p=0,001 (table 2) was also detected. The obtained results indicate that anxiety in PD more often is not a separate neuropsychological disorder but a part of depression structure.

That means PwPD and more expressed anxiety usually have other emotional-affective disorders.

It was revealed that among our 206 researched patients with clinically significant diagnosis of PD there were only 4 patients with identified suicidal intent in history according to Columbia suicide severity rating scale C-SSRS and subsequent interviewed physicians. Herewith no active suicidal attempts were observed in anamnesis of these patients. Our results prove the literary data that "suicidal thoughts are rarity for PwPD" [7].

Analysis of drug-induced dyskinesia prevalence in PwPD with anxiety demonstrated statistically more significant prevalence (39,2%) in comparison with patients without anxiety (17,2%), z=2,77; p=0,006.

Significant influence of anxiety on quality of life in PwPD was revealed. Common health status index by self-questionnaire quality of life PDQ-39 in patients without anxiety was significantly lower in comparison with patients with subclinical and clinically manifested anxiety and means 28 (20; 44), 37 (26; 46) и 48 (39; 57) points, p<0,001 respectively. The more the total overall health status index is, the worse the quality of life of the subject is (table 2).

Among studied PwPD with anxiety there are statistically more occurring impulsive behavior disorders such as gambling (p=0,004), hobbysm (p=0,042) and compulsive obsessive taking of dopaminergic drugs within dofamin dysregulation syndrome (p=0,010) that correlates with literary data according to which anxiety disorders can be manifested both by common anxiety and panic attacks, social phobia and obsessive-compulsive disorders. Although impulsive compulsive disorders are different from obsessive-compulsive, there is phenomenological duplication indicating community of certain neurobiologocal mechanisms. Both disorders have common diagnostic criteria such as "excessive behavior" leading to "significant deterioration" in the main areas of life [13].

Analysis of impulsive behavior disorders rate indicates that it occurs in 27% of cases (in 56 patients) with the majority prevailing in men: gambling was registered in 6,7 %, among women – 2,7 %, p>0,05, hypersexuality – in 6,7 %, among women – 0,0 %, p>0,05, punding – in 20,0 %, among women – 8,1 %, p>0,05, hobbysm – in 20,0 %, among women – 5,4 %, p>0,05, dofamin dysregulation syndrome – in 20,0 %, among women – 13,5 %, p>0,05. Whereas among women such disorders as shopping mania prevailed in women and occurs in 8,1 %; among men such impulsive behavior disorder was not registered in men p>0,05 and compulsive overeating was registered in women – 10,8 % was not registered in men – 0,0 %, p>0,05. It should be noted that there are no statistically significant differences between the groups of both men and women in terms of the prevalence of any behavioral disturbance.

According to literary data prevalence of depression is 3-10% among population [10]. On the early stages of PD depression occurs in 27,6% patients [15], on later stages in 40-50% of patients [5, 8]. The last one is characteristic for all stages of PD. At the same time, it was established that in 30% of cases the diagnosis of depression preceded the first motor symptoms of PD. Emotional affective disorders can manifest themselves in some cases 20 years before the motor manifestation, but on average this period is 3–6 years [10]. According to the results of a study conducted at the Mayo Clinic, the risk of developing PD is 1.9 times higher in patients with depressive disorders, with anxious disorders - 2.2, and with both - 2.4 [9, 12].

Depression can be manifested by dysthymia (the frequency of which is about 13% in PwPD), major (17%) and minor (22%) depressive disorders. About 35% of PwPD have clinically expressed depressive symptoms [12, 16], however, according to various literary, the proportion of patients with severe depression is 3-8%, reaching a psychotic level, and it does not end with suicide attempts. In patients with motor fluctuations, transient depression ("off-period") occurs that is changes in depression and maniacal state, marked against the background of motor fluctuations [15].

One of the main problems that impede the diagnosis of depression in PD is similarity, common features inherent in depressive syndrome and PD: hypomimia, hypophony, decreased psychomotor activity, attention disorders, increased fatigue, decreased appetite, decreased libido and sleep disorder [3, 4, 13].

There is a point of view that depression in PwPD does not depend on the age, duration of PD and severity of disease [10]. However, some researchers claim that the most prevalence of this emotional and affective disorder occurs in patients with the initial stage of PD (first stage by Hoehn and Yahr scale). Such dependence can be explained by the importance of psychological factors in the development of depressive disorders in the early stages of PD associated with the onset of the disease and the establishment of a diagnosis. Then it decreases slightly to stage II (due to the patient's internal adaptation to a chronic

Table 2

Severe apathy and characteristic of quality of life in people with Parkinson's disease, depending on the severity of anxiety, in points; - Me (Q1; Q3)

	Norm n=99	Subclinical anxiety n=56	Clinical anxiety n=51	Kruskal-Wallis Criteria		Mann-Whitney Criteria
	Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)	χ^2	p	
Apathy, points	8 (5;14)	12 (7;15)	14 (7;19)	13.193	0.001*	p_{1-2}=0.093 p_{1-3}=0.002* p_{2-3}=0.170
PDQ-39, points	28 (20;44)	37 (26;46)	48 (39;57)	32.704	<0.001*	p_{1-2}=0.090 p_{1-3}<0.001* p_{2-3}<0.001*

Note. In the Tables 2, 3 * - statistically significant differences at p <0.005. Quantitative attributes are presented in the form of a median and interquartile interval - Me (Q1; Q3).

disease and the start of antiparkinsonian dopaminergic therapy, which has an antidepressant effect [2, 4]. Stages III — IV again are characterized by high prevalence of depression due to a continuously progressive neurodegenerative process. Among patients with stage V of PD the proportion of people with severe depression is reduced. Other researchers think that the frequency of depression is higher at the oneset of PD with akinetic-rigid form, at a younger age, in women, as well as at a faster rate of disease progression and burdened family anamneses of neurodegenerative pathology [9].

Among researched PwPD 10% had severe depression and 27% had depression with middle severity according to Beck's depression inventory scale (BDI-II).

The results of our researches prove that prevalence of depression in PD is more at the initial stage of the disease (up to 54%); it decreases at stage II of the disease to 45% and increases again up to 58% in patients with stages III and IV of PD.

Using a correlation analysis of the obtained data, a middle strength of the positive relationship between depression and poor quality of life was revealed in PwPD (r = 0.471; p<0.001 under the PDQ-39 questionnaire "cognitive functions" (r=0.451; p<0.001) and "emotional well-being"(r=0,450; p<0.001).

A special place in our work was devoted to analysis of motor disorders severity and drug-induced movement disorders in PwPD depending on the severity of emotional-affective disorders. In individuals without depression the lowest frequency of occurrence of drug-induced movement disorders was found (9.0%), while in patients with depression this index reached 31.7% (z=2.39; p=0.019).

Analyzing the frequency of occurrence of motor disorders in PwPD according to III part of the UPDRS scale depending on the severity of depression, it was found that in patients with severe depression they were more pronounced (p=0.007). It can be assumed that this fact is not always explained by the incorrect treatment of antiparkinsonian dopaminergic drugs by patients with emotional-affective disorders. So in patients without depression overall average score for UPDRS was 31 (24; 37), with slight depression - 32 (27; 43), with moderate - 35 (27; 47) and severe - 39 (33; 47), (table 3).

When assessing drowsiness it was found that the average score according to the Epworth sleepness scale (ESS) was statistically significantly higher in the group of patients with depression - (5; 11) points, compared with those without chronically lowered mood - 6 (3; 8), (χ2=8.424; p=0.038).

In recent years a new approach to defining apathy has been taken as a "loss of initiative" [12], that is, a lack of desire for any activity and indifference to what is happening around. Particular attention should be paid to the differential diagnosis of depression and apathy in PD, because they have such common symptoms as hypomimia, fatigue, social isolation, a decrease in pleasure from previously favorite activities and a decrease in interest in them. Often, these two emotional and affective states are combined in PD [16]. However, anxiety and melancholy affects are not characteristic of apathy as an independent syndrome [15].

Apathy is one of the most frequent affective disorders in PD, characterized by a loss of interest in the environment, a decrease in motivation, initiative and emotional dullness [4, 10, 19]. According to some researchers, the apathy rate in PD varies from 7 to 70% [4], while others researches suggest the much lower spread - from 30% to 40% [19]. It can occur both in the structure of depression, and independently of it (approximately in 14% of patients) [4].

According to our research 35% (71 PwPD) had apathy according to Apathy Scale.

It has been established that the onset of apathy is not affected by the age of PwPD and the age of neurodegenerative disease onset. Patients with apathy have a longer duration of the disease (U=3791.5; p=0.020), as a result, a more developed stage of PD according to Hoehn and Yahr scale (III and IV) and accordingly more severe motor disorders (U=3548.5; p=0.003).

In the group of patients with apathy, there are statistically significantly more patients with daytime sleepiness (z=0.93; p=0.352), anxiety (z=2.63; p=0.009), depression (z=2.13; p=0.034) and impulsive behavioral disorders (z=2.70; p=0.008), drug-induced dyskinesias (z=2.77; p=0.006), and cognitive impairment in the field of visual and constructive skills (χ2=3542,000; p=0,002).

Analyzing antiparkinsonian dopaminergic therapy, it was found that patients with apathy had a daily dose of various levodopa preparations in terms of equivalent dose of levodopa, LED (L-Dopa), higher - 300 (156; 375) mg, compared to patients without apathy - 150 (0; 350) mg, p<0.001.

After assessing the quality of life according to the specialized questionnaire for PwPD PDQ-39, it was found that the overall health index in patients without apathy was statistically significantly lower - 33.3 (21.8; 47.4) than in patients with apathy - 43.6 (32.7; 55.8) 43,6 (32,7; 55,8) (χ^2=3346,5; p<0,001).

Sleep disorders have significant impact on the quality of life registered in 66% of cases of PD (136 patients). Comparable results were obtained in a study conducted in Honolulu (The Honolulu-Asia Aging Study, HAAS), the risk of developing PD in patients with excessive daytime sleepiness was significantly higher compared with people not suffering from it (3.3 times). In contrast, the presence of other sleep-related disorders - insomnia, naps, morning shakiness (intoxication), and frequent nighttime awakenings - is not significant when considering the risk of developing PD. It should be noted that sleep disorders in the REM – phase precede the onset of other disease symptoms [9].

Constipation is perhaps the most common symptom in PD, due to the formation of α-synuclein in the dorsal motor nucleus of the vagus nerve (nucleus dorsalis nervi vagi), pre-vertebral ganglia and intestinal submucosal plexuses [6]. It has been

Table 3

Characteristics of the severity of motor disorders in patients with Parkinson's disease (according to the sum of the third part of the UPDRS) depending on the severity of depression, in points - Me (Q1; Q3)

	Norm n=67	Mild depression n=62	Moderate depression n=56	Severe depression n=21	Kruskal-Wallis criterion		Mann-Whitney criterion
	Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)	χ^2	p	
Movement impairments UPDRS	31 (24;37)	32 (27;43)	35 (27;47)	39 (33; 47)	12.0	0.007*	p_{1-2}=0.139 p_{1-3}=0.264 p_{1-4}=0.003* p_{2-3}=0.614 p_{2-4}=0.185 p_{3-4}=0.103

recently established that the pathology of α-synuclein can be detected by biopsy of the colon submucosa in patients with PD [9]. Studies have shown that constipation usually precedes the development of PD for more than 10–18 years [1, 2]. According to the results of our study, it was found that 87% of patients with PD had these gastroenterological disorders (constipation was regarded as reduction of the bowel movements frequency to once or less a week). This is one of problems of current interest for patients with PD and their physicians, as problems with the evacuation function of the intestine lead to a decrease in the bioavailability of dopaminergic antiparkinsonian therapy, and, as a result, to a deterioration in the physical activity of PwPD. In addition, interest to the studying of gastroenterological disorders in PwPD remains on high level due to the fact that constipation, along with depression and olfactory disorders, is the "Non-motor stage" of PD, which already is the beginning of a systemic degenerative process preceding the onset of motor disorders [1, 14]. Thus, according to the history of our patients, gastroenterological symptoms such as constipation, nausea, and flatulence were present 5–12 years before the clinical diagnosis of PD.

Conclusion. Questions about phenomenological independence of non-motor disorders in PwPD, their pathophysiological commonality with the motor manifestations of the disease due to the multifactorial nature of PD and insufficiently developed approaches to therapy are very relevant today. Well-timed and adequate identification of risk factors for the progression of non-motor manifestations of PD will allow correct therapy to be given to patients with high risk of their development. Thus in recent years the understanding of the essence of PD as a pathological, pathophysiological and developing clinical process has significantly changed, covering not only the motor sphere, but also causing a violation of the vegetative regulation, obvious changes in the psychoemotional state of patients and their behavior.

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