

УДК 616.858-036.22-077

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IN PARKINSON DISEASE**

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Parkinson Disease is a progressive neurodegenerative disease that has motor symptoms such as bradykinesia, tremor, muscle rigidity and postural instability. The non-motor symptoms include depression, anxiety, cognitive status changes and dementia at the very advanced stages. There is very little research on PD in Kazakhstan, therefore, this study aimed to assess some of non-motor symptoms in PD patients in Almaty. The assessment of the FAB, MMSE and Clock-drawing scale showed that there was a significant impairment in the cognitive status of the PD patients compared to the control age-matched subjects (n control=39, n PD=39; Anova, p=0,001). The Schwab-England scale for the assessment of activity of the daily living, Spielberg Trait Anxiety Test and Visual Analogue Scale EuroQoL-5D showed that there higher frequency of highly stressed and disabled people in the PD group compared to the age-matched control group.

Key words: Parkinson Disease, neuropsychiatric clinical scales, cognition, anxiety, pain.

The last century has seen a significant rise in life expectancy at birth among developed countries as people, on average, are living longer compared to prior generations [6]. Longer life has also led to corresponding increases in chronic, neurological impairments such as Parkinson disease. Parkinson Disease (PD) in particular, has been identified as the second most prevalent age-related neurodegenerative disease in the world [1]. There are over 5 million people estimated to have the PD world-wide, constituting 1% of the world's population of those 60 and older [69]. Global prevalence of PD is 60-187 cases for 100,000 [1]. The majority of people develop the clinical symptoms of PD over 60 years of age, with those over 80 accounting for 95% of all cases [69]. With an expected increase of 2,1 billion people over the age of 60 world-wide by 2050 [1], will come a corresponding increase of people with PD and an ever-growing challenge to more effectively diagnosis, treat and manage symptoms while maintaining an optimal quality of life of those affected. PD was thought to be exclusively a motor disorder, but later research revealed that there are also non-motor symptoms [5]. Approximately 25% of cognitively intact patients with Parkinson's disease meet the neuropsychological test criteria for MCI and most of them develop dementia as the disease progresses [32]. Clinical studies show that dementia eventually develops in up to 80-85% of people with PD [1, 28].

Huge amount of health related quality of life studies (HRQL) studies show that chronic disorders significantly worsen the quality of life of the patients. PD is a chronic neurodegenerative disease that has motor complications as well as decline of the executive functioning, cognitive functioning, mood changes,

apathy and depression [2, 61, 68]. Many studies show that physical disability severely affects the quality of life, so, Lerois and colleagues assessed the patients' disability through UPDRS and the Schwab England Activities of Daily living tools in 99 PD patients; it was shown that the quality of life was significantly lower due to motor impairment, apathy, anxiety and depression [30, 31, 33]. Moreover, many studies showed that the PD patients suffer from executive function decline in daily life [24, 25, 53]. Plenty of studies demonstrated that PD patients suffer from chronic pain [57, 38, 65]. Skoger and colleagues assessed the pain intensity in PD patients, and it was shown that the median score of the EQ-5D VAS during the 5 days for all patients was 5,0±2 in comparison with 3,3±0,2 for the reference group, suggesting that PD patients experienced more intensive pain. The origin of pain was different, for instance, majority of (71%) indicated the musculoskeletal system, and 28% indicated the nervous system. Moreover, some indicated the kidneys and skin as the origin. Regarding the pain duration, 36% indicated pain all their waking hours whereas only 16% indicated less than 1 hour of pain a day [60]. A proper understanding of PD-related pain and its impact on everyday life is crucial not only for the clinicians but also for all caregivers caring for the patients. Parkinson's disease is an age-associated progressive neurodegenerative disorder characterized by degeneration of dopaminergic neurons in the brain. There is little knowledge on the exact etiology of PD with 90-95% of cases are sporadic [64]. PD was thought to be exclusively a motor disorder, but later research shows that there are also non-motor symptoms. The biochemical or anatomical mechanisms that underlie the cognitive changes in people with neurodegenerative diseases

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is not fully understood. Recent research shows that metabolic deficits as well as diffused toxic Lewy body deposition can lead to brain atrophy resulting in pathological changes in the neural circuits between basal ganglia and different cortical regions such as prefrontal cortex, which in turn leads to cognitive and executive decline in the people effected [14, 19, 45, 61]. However, very little is known about clinically-reliable bio-markers for preclinical cognitive changes for PD-associated MCI or dementia. Some studies showed that olfactory dysfunction may be one of early signs of cortical hypo metabolism, so PD patients with severe hyposmia experienced pronounced cognitive decline compared to those PD patients without severe hyposmia [42]. Pecci and colleagues assessed the quality of life of 630 patients with PD and chronic pain patients through Medical Outcome Study Short Form (MOS-SF36) and STAI questionnaires, it was found that PD patients suffered more from pain, depression, declined physical function and emotional role [46]. Another HQRL study using MOS-SF36 as one of assessing instrument showed that PD group had significantly lower scores in almost all sections compared with mean levels in a reference population, matched for age and sex (P -value, 0.001) for all items except Emotional Role (P -value = 0.021) [58]. PD is a chronic disorder that had not only motor but non-motor symptoms. There is an important association between the functional and cognitive declines that cumulatively influence on the quality of life of the patients. Many studies show that PD patients have MCI and PD dementia (PDD) [12, 47]. There is no golden standard instrument but several tests, such as MMSE and FAB, are used in the clinical practice. The efficiency of these tests is still under arguing some studies showed neither MMSE nor FAB do not reflect cognitive changes to specific to PD, they are rather applied to broad range of neurodegenerative diseases [50]. Furthermore, MMSE not always reflect cognitive changes, so for instance, it was shown that patients with PD MCI showed normal MMSE scores [41]. On the other hand, a cross-sectional and multicenter study showed that MMSE a practical and efficient screening tool for PD-D (Ohta et al., 2014). Nevertheless, frontal lobe-associated cognitive deficits are also common clinical symptoms in patients with PD [46]. In the study by Cohen it was shown that PD patients showed significant dysfunctioning in attention, executive functioning and memory changes and the FAB results significantly correlated with MMSE results [12]. In addition, Marconi and colleagues assessed non-motor signs in 926 PD disease patients, there were also a prominent decline in cognitive aspects such as memory, attention and executive functioning; moreover, FAB results significantly correlated with MMSE results suggesting severe cognitive impairment in PD patients [42]. Heterogeneity in the results might be explained by different level of neurodegeneration in different patients. Therefore, in our study, we applied several instruments that could give an integrative picture on the changes in quality of life of the patients. There are only few studies our country; therefore, the main aim of this study was to evaluate the quality of life of PD patients by assessing the cognitive and quality of life outcomes.

Material and Methods

The ICD-10 criteria, WHO 1992 United Kingdom Brain Bank criteria for the disorder (Gibb, Lees, 1988) were taken

as a clinical standardized guidance, so 78 patients in total were assessed. Features of parkinsonism (e.g. tremor, rigidity, bradykinesia, postural instability, shuffling gait, mask-like facies) were noted when present, and Parkinson's disease was diagnosed if the patient fulfilled We defined cases with PD patients with any diagnosis of PD in the Almaty outpatient hospitals considering both primary and secondary diagnoses and by random sampling we chose 39 patients and 39 age-matched control group. The exclusion criteria for the PD and age-matched control group were the absence the stroke followed by neurological deficits, patients with vascular or drug-induced parkinsonism, patients with severe cognitive changes, patients with brain tumors, patients with severe heart, liver or kidney diseases. In order to assess the severity of PD we used Unified Parkinson's Disease Rating Scale – UPDRS (Unified Parkinson's Disease Rating Scale – UPDRS); for naive patients the UPDRS is composed of a total of 44 sections where each section is given the numerical range 0–4 (0 for healthy and 4 denotes severe symptoms). In final score for UPDRS is the summation of all sections (numerical range 0–176, with 0 representing perfectly healthy individual and 176 total disability). The UPDRS consists of three components: (i) Mentation, behavior and mood (four sections); (ii) Activities of daily living (13 sections) that assess whether the patient is able to complete daily tasks unassisted and (iii) Motor (27 sections) that address muscular control. The third component commonly referred to as motor UPDRS, includes the sections 18–44 and ranges from 0 to 108, with 0 indicating no motor symptoms (such as tremor, rigidity, posture, stability and bradykinesia. 108 denotes total lack of motor control. Speech appears explicitly in two sections: once in section 5 (understandable speech—part of the second UPDRS component) and once in section 18 (expressive speech is a part of the third UPDRS component) that ranges between 0 and 8 with 8 being unintelligible. Hoehn-Yahr scaling, the scaling that assesses the PD progression stage with 1 for unilateral hand shaking and 5 for the almost complete disablement [29].

1 Cognitive status was assessed using the MMSE (Mini Mental State Examination), 6 task based questionnaire that examines functions including registration, attention and calculation, recall, language, ability to follow simple commands and orientation. MMSE helps to differentiate organic from functional psychiatric patients. All sections are given from 0 to 5, 0 stands for complete inability, 5 for good performance, giving altogether 30 scores, with 28–30 denoting no cognitive decline, 27–24 for pre-dementia cognitive decline, 20–23 scores denoting for MCI, 19–11 scores for moderate CI, 10–0 severe dementia [22].

2 Clock-drawing test (CDT) for visual-spacious disturbances is a brief cognitive task that are administered to assess executive functions of the patient. The patient is asked to draw a clock given a specific time (generally 11:10). After the task is complete, the test administrator draws a clock with the hands set at the same specific time. Then the patient is asked to copy the image. Errors in clock drawing are classified according to the following categories: omissions, perseverations, rotations, misplacements, distortions, substitutions and additions. The scores for the drawing are from 10 for the perfect drawing and

thus no cognitive impairment, 9 – slightly notable mistakes in arrow drawing, 8 – notable mistakes, 7 scores for the complete wrong arrows location, 6 scores for when the patient put the circles instead of arrows, 5 scores for wrong number order on the watch, 4 scores for numbers missing on the watch in the picture, 3 scores for numbers and the watch being drawn separately, 2 – for the patients whose trials fall completely, 1 for no reasonable presentation of the clock suggesting severe cognitive deficits [35].

3 For the quality of life assessment we applied Visual Analogue Scale EuroQoL-5D-3L that consists of 2 pages – the EQ-5D descriptive system (page 2) and the EQ visual analogue scale (EQ VAS) (page 3). The EQ-5D-3L descriptive system denotes the patient's mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each section has 3 possible answers: no problems, some problems, extreme problems. The patients indicates his/her health state by placing a cross) in the box against the most reflecting statement. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score. The visual analogue scale is a 20 cm vertical, visual analogue scale with endpoints labeled as 'the best health you can imagine' and 'the worst health you can imagine', this helps to obtain a quantitative measure of health by every patient individually. 0 stands for no pain, 1-3 mild pain, 4-6 moderate pain, 7-10 severe pains imaginable [51].

4 FAB (Frontal Assessment Battery) comprises 6 simple neurophysiological task tests of sequencing, behavioral inhibition, planning and frontal release signs, can be used as a screening test to elicit typical neurological and cognitive features. FAB consists of the following six tasks: (1) Similarities (conceptualization), Lexical verbal fluency (mental flexibility), Motor series (programming), Conflicting instructions (sensitivity to interference), Go – Nogo (inhibitory control) and Prehension behavior (environmental autonomy). The final FAB score was computed by summing up the six individual FAB task scores. 16-18 scores suggest normal frontal functioning, 12-15 scores suggest moderate frontal lobe dysfunctioning, <11 suggests frontal lobe dementia [18].

5 The Schwab–England scale rates ADL (activity of daily living) ability on a scale of 0–100% with 100% being completely independent and with no disability. This scale is a useful global measure of independence and performance on ADLs and has been used to compare the degree of disability in PD compared with non-PD samples such as osteoarthritis. The questionnaire represents a rating scale assigned either by a rate of the patient. 100% denoting complete independence. Ability to do all chores w/o slowness, difficulty, or impairment. 90% denoting complete independence. Ability to do all chores with some slowness, difficulty, or impairment. May take twice as long time. 80% denoting independence in most chores but taking twice as long. Conscious of difficulty and slowing. 70% denoting not complete independence. More difficulty with chores. 3 to 4X along on chores for some. May take large part of day for chores. 60% denoting some dependency. Ability to do most chores, but very slowly and with much effort. Errors, some impossible. 50% denoting more dependence. Help with 1/2 of chores. Difficulty with everything. 40% denoting significant dependence. Ability to

assist with all chores but few alone. 30% denoting requiring a great effort, now and then does a few chores alone of begins alone. Much help needed. 20% denoting that the patient is not able to do anything alone. Can do some slight help with some chores. Severe invalid. 10% denoting total dependence and helpless state. 0% denoting that vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden [58].

6 The State-Trait Anxiety Instrument (STAI) is a commonly used assessment used in mental health for measuring both state and trait anxiety. Concurrent validity of the STAI has been demonstrated through positive correlation scores with The Anxiety Scale Questionnaire (.73) and the Manifest Anxiety Scale (.85). Strong test-retest reliability has also been reported with scores ranging from .65 to .75 over a two month interval [62]. Similar mean scores between the short and full version were reported showing strong concurrent validity (Tilton, 2008). The short form version of the STAI consists of six items and has a reliability coefficient of .95 showing strong correlation to scores of the 20 item full form [62].

The normality of the observations was verified by the Kolmogorov – Smirnov, Shapiro-Wilk test. Statistics was calculated Mann –Whitney U-test, Anova. The threshold for statistical significance was $p < 0.05$; ANOVA $p = 0.001$.

All procedures were approved by the local ethical committees following the procedures at Kazakh National Medical University named after S.D. Asfendiyarov. All patients agreed and signed the written consent.

Results

Cognitive status of the patients. As can be seen from the table 1, the control group had an average of 10 scores on the clock-drawing test with a mean score of 9.44 ± 0.82 ; whereas the patients with Parkinson Disease had an average mean of 7.72 ± 1.57 . An ANOVAs revealed a significant difference between the groups ($p = 0.001$). As can be seen from the Table 1, the PD results of the clock-drawing test found a wide variation of scores ranging from 4 up to 10, with an average of 7.72 suggesting that the majority of the PD patients made significant mistakes while drawing the clock. In contrast, the control group scores varied from 8 to 10 with a mean of 9.44 indicating that the control group demonstrated better visuospatial abilities compared to the PD group. The results of the FAB test, which detects frontal lobe dysfunction, revealed a mean score for the control group of 15.77 ± 1.530 , compared to the PD group of 13.85 ± 2.289 . An ANOVA found significant difference between the groups ($p = 0.001$) on the FAB test. Moreover, we used the MMSE to detect any differences in cognitive status of the patients. According to our results, 51.3% of the control group patients were cognitively intact in contrast to 23.1% in the PD group. Furthermore, there was a higher percentage of patients with mild cognitive impairment among the PD group compared to the control group, (23.1% and 7.7% respectively). Notably, 5.1% had moderate cognitive impairment and 2.6% had severe dementia among this same group.

The values are expressed as mean \pm SD and percentage of subjects (%). PD stands for Parkinson's disease; Control Group represents the age-matched group; UPDRS stands for Unified Parkinson's disease rating scale; LED stands for levodopa equivalent dose.

Table 1 – Demographic and clinical characteristics of PD patients and the age-matched and control group

	PD patients (n=39)	Control Group (n=39)
Age (years)	67,23±11,78	64,03±12,19
Education (years)	8,71±6,60	10,61±3,01
Sex	17 male/22 female (43,6% male/ 56,4% female)	14 male/27 female (35,9% male/ 64,1% female)
PD duration	8,56±5,27	-
HoehnYahr stage		
1	3%	-
1,5	13%	-
2	13%	-
2,5	23%	-
3	30%	-
3,5	5%	-
4	8%	-
5	8%	-
UPDRS-III	25,7±13	-
Levodopa (mg/day)	609,7±6,41	-
MMSE	23,44±3,11	27,18±2,45
FAB	13,85±2,29	15,77±1,53
Clock-drawing test	7,72±1,57	9,44±,82

Anxiety and pain intensity assessments

Next, we assessed the anxiety level among the groups. As noted in the Table 2, there were 25,6% and 23,1% of the patients in the PD group who indicated that they were able to maintain independence in their ADLs but had to dedicate more time (48,7%) on their daily activities than before. In contrast, of the control group 38,5% indicated that they did not have any problems in daily life compared to 5,1% of the PD group. The Spielberg Daily Stress Activity results demonstrated similar findings of low anxiety levels for both groups (20,55 for the PD group and 25,6 for the control group. A slightly higher percentage of the control group indicated medium levels of stress than the PD group (69,2% and 64,1% respectively). However, the PD group had almost a 3-fold increase of those who indicated experiencing a high level of stress, compared to the control group 15,4% and 5,1% respectively. The Visual Analogue Scale EuroQoL-5D scale assessment showed that the majority of the PD group (51,3%) indicated experiencing moderate pain, whereas 13,2% indicated mild pain levels. Furthermore, 10,3% of the PD group indicated experiencing unbearable pain compared to 7,7% in the control group. In contrast, the majority of the patients in the control group indicated mild pain levels (53,8%). No patients within the PD group indicated they were in the mildest or no-pain category compared to 10,3% for the control group (Table 2).

Discussion

The cognitive status of the PD patients. Patients with

Parkinson's disease experience not only motor but also non-motor symptoms such as cognitive impairment, behavioral changes, autonomic and somatosensory disturbances [72]. MRI investigation showed that mild cognitive impairment can be linked with faster rate of grey matter thinning in cortical regions as well as diminishment of limbic subcortical structure in PD patients which in turn could serve as marker for further dementia development [27]. Immunohistological studies showed that patients with PD dementia were differentiated by a significant reduction in hippocampal cholinergic activity suggesting hippocampal dysfunction in patients [26, 52]. Moreover, accumulating data shows that insular plays an important role in the appearance of non-motor symptoms [14, 48]. The frontal lobe contains most of the dopamine-sensitive neurons in the cerebral cortex. The dopamine system is associated with reward, attention, short-term memory tasks, planning, and motivation. Dopamine tends to limit and select sensory information arriving from the thalamus to the forebrain. In human-beings the frontal lobe reaches full maturity around the late 20s, and there is gradual age-associated volumetric decline associated with atrophy. Several studies showed that this process happens not only in the healthy ageing but it is rather accelerated in patients with neurodegenerative diseases [2, 31, 72]. It is believed that the main function of the frontal lobe is to make people able to project future consequences resulting from present actions, to make choice between different actions so that either favor or suppress socially unacceptable responses as well as to discriminate similarities and differences between various things. As can be seen from our results, the PD patients showed significantly lower emotional level and social functioning, declined vitality level and mental health. This partially could be explained by the neurodegenerative processes as well as the psychological state of the patients diagnosed with untreatable disabling condition. Some patients indicated that other people try to escape the patients and the patients felt happy when they come to the doctor as they were deprived of the communication. Moreover, the frontal lobe also participates in recalling of the not-task-related longer term or emotional memories. MMSE results showed that were more obvious cognitive deficits in the PD group compared to the control age-matched people. FAB is a simple test that is sensitive to the frontal lobe dysfunctioning, although it is not specific to PD, there were significant differences amongst the groups in FAB results suggesting that PD patients have more prominent frontal lobe dysfunctions. Parkinson Disease has been though as exclusively motor disorder; however, as the research shows there are also non-motor symptoms at later stages. Unfortunately, one of the findings from our study was that the average delay between the onset of symptoms and an established diagnosis is 2-2,5 years thereby the problems of early stage diagnosis that can help to delay clinical symptoms is still one of the most challenging questions in the clinics. According to the Braak

Table 2 – The anxiety level assessment between the control and PD groups

Schwab-England scale for the assessment of activity of the daily living				
Percentage of physical ability of the patient	Frequency in the PD group	Percentage in the PD group	Frequency in the control group	Percentage in the control group
10%	1	2,6%	0	0%
20%	1	2,6%	0	0%
30%	1	2,6%	0	0%
40%	2	5,1%	0	0%
50%	5	12,8%	0	0%
60%	4	10,3%	1	2,6%
70%	9	23,1%	1	2,6%
80%	10	25,6%	3	7,7%
90%	4	10,3%	19	48,7%
100%	2	5,1%	15	38,5%
Spielberg Trait Anxiety Test				
<30 scores	8	20,5%	10	25,6%
31-45 scores	25	64,1%	27	69,2%
>46	6	15,4%	2	5,1%
Visual Analogue Scale EuroQoL-5D				
Pain intensity scale				
1	0	0%	4	10,3%
2	5	12,8%	3	7,7%
3	5	12,8%	10	25,6%
4	5	12,8%	8	20,5%
5	16	41,0%	5	12,8%
6	4	10,3%	6	15,4%
7	1	2,6%	2	5,1%
8	2	5,1%	1	2,6%
9	1	2,6%	,0	,0%
Total	39	100%	39	100%

staging, the PD starts a first by accumulating Lewy bodies in the olfactory bulb, medulla oblongata and pontinetegmentum; at this stage the patients are asymptomatic. However, when the neurodegeneration evolves, Lewy bodies accumulate in the substantianigra, midbrain and basal forebrain, finally reaching the neocortex [8]; only at this stages the clinical debut of the disease takes place. In this survey the majority of the patients assessed were of 2,5-3 Hoehn-Yahr stage, which might explain why the cognitive status of the PD group was lower compared to the control group. However, it should also be noted that the control group results showed tendency to develop pre-dementia and MCI, which might be explained by natural brain ageing as well as highly stressed daily life. In addition, almost half of our patients come to the doctor a year or later which might explain why our PD patients had significant cognitive impairment compared to the healthy age-matched control [5]. Nonetheless, the results above suggest that there are cognitive changes in both groups; however, in PD patients they are more prominent and accelerated. In this survey we

also assessed the quality of life of the patients, based on our results it might be concluded that the quality of life of the PD group was significantly lower compared to the control group and it was also found that these patients required more time on self-service and daily living performance. To conclude, the PD patients had lower quality of life and higher stress and pain levels compared to the age-matched control group.

Future prospective

The golden standard for PD therapy is dopamine replacement strategy and recently emerging neurosurgery method such as deep brain stimulation; however, neither of the methods prevents further progressive degeneration of dopaminergic neurons in the substantianigra leading to severe motor dysfunction and further disease progression. Currently, cell replacement therapy such as transplantation of human foetal ventral mesencephalic stem cells into caudate or putamen is emerging as a potential cure [15, 32, 36, 44] however there are some serious disadvantages such as graft induced dyskinesias [21, 67] as well as poor grafts survival, immune

response and the possibility of tumor formation require further research before using them in the real life on the daily basis [10, 40]. There are an overwhelming data showing that physical exercises are associated with neuroprotective effects in the nigrostriatal dopaminergic system in animals [4, 59, 68, 69], there were also epidemiological studies with conflicting results [11, 34, 56]. Several prospective studies investigated different levels from moderate to vigorous physical activity on the risk of Parkinson's disease development [53, 64, 70, 71] on addition, recent prospective study of 43 368 people for 12,6 years showed that a medium level of daily total physical activity lowers Parkinson's disease risk [71].

Limitations

Firstly, some research shows that dopamine replacement therapy such as L-DOPA treatment can influence on the cognition of the patients [16,17]. Secondly, this research is one of the very first ones in Kazakhstan, therefore, we had a limitation such as small sizing of the groups. Therefore, future studies should be of bigger sizes, probably have longer follow-up periods and apply more specific neuropsychological tests to distinguish clinical features of PD with MCI, PD with dementia and cognitively intact patients, for instance, MoCa-test as well as applying altered perfusion using fluorodeoxyglucose-PET to detect neuronal dysfunction. Moreover, our study should include biomarkers for comparison or combination e.g. both molecular and structural imaging (Fan et al., 2008), alternatively, corticometry (cortical thickness) versus traditional voxel-based morphometry analyses [27].

REFERENCE

- 1 Aarsland D., Andersen K., Larsen J.P. et al. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study // *Arch Neurol.* – 2003. – Vol. 60. – P. 387–92
- 2 Aarsland D., Bronnick K., Williams-Gray C.H. et al. Mild cognitive impairment in Parkinson's disease: A multicentre pooled analysis // *Neurology.* – 2010. – Vol. 75. – P. 1062–1969
- 3 Achey, M.. Virtual house calls for Parkinson's disease (Connect.Parkinson): study protocol for a randomized, controlled trial // *Trials.* – 2014. – Vol. 15. – P. 465
- 4 Ahlskog J.E. Does vigorous exercise have a neuroprotective effect in Parkinson disease? // *Neurology.* – 2011. – Vol. 77. – P. 288–294
- 5 Akanova A.A., Yeshmanova A.K., Kamenova S.U., Thomas D., Beltenova A.G. The current issues of Parkinson Disease in Kazakhstan: Survey Results // *J. Medicine (Almaty).* – 2015. – No 7 (157). – P. 29-39
- 6 Аканова А.А. Паркинсон ауруының аумақ аралық қорытындысының эпидемиологиялық зерттеуі // *J. Medicine (Almaty).* – 2015. – No 5 (155). – P. 37-41
- 7 Archibald N.K., Hutton S.B., Clarke M.P., et al. Visual exploration in Parkinson's disease and Parkinson's disease dementia // *Brain.* – 2013. – Vol. 136. – P. 739–750
- 8 Braak H., Del Tredici K. et al. Staging of brain pathology related to sporadic Parkinson's disease // *Neurobiol Aging.* – 2003. – Vol. 24, N 2. – P. 197–211
- 9 Beyer M.K., Janvin C.C., Larsen J.P. et al. A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry // *J NeurolNeurosurg Psychiatry.* – 2007. – Vol. 78. – P. 254–259
- 10 Brederlau A., Correia A.S., Anisimov S.V. et al. Transplantation of human embryonic stem cell-derived cells to a rat model of Parkinson's disease: effect of in vitro differentiation on graft survival and teratoma formation // *Stem Cells.* – 2006. – Vol. 24. – P. 1433–1440
- 11 Chen H., Zhang S.M., Schwarzschild M.A. et al. Physical activity and the risk of Parkinson disease // *Neurology.* – 2005. – Vol. 64. – P. 664–669
- 12 Cohen OS, Vakil E, Tanne D et al. The frontal assessment battery as a tool for evaluation of frontal lobe dysfunction in patients with Parkinson disease // *J Geriatr Psychiatry Neurol.* – 2012. – Vol. 25, N2. – P. 71-77
- 13 Costa J., Lunet N., Santos C. et al. Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies // *J Alzheimers Dis.* – 2010. – Vol. 20 (Suppl 1). – P. 221–238
- 14 Christopher L., Koshimori Y., Lang A. et al. Uncovering the role of the insula in non-motor symptoms of Parkinson's disease // *Brain.* – 2014. – Vol. 137. – P. 2143–2154
- 15 Cui Yi-F., Hargus G., Xu J.C. et al. Embryonic stem cell-derived L1 overexpressing neural aggregates enhance recovery in Parkinsonian mice // *Brain.* – 2010. – Vol. 133 – P. 189–204
- 16 Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease // *Neurosci Biobehav Rev.* – 2006. –Vol. 30. – P. 1–23
- 17 Cools R., Barker R.A., Sahakian B.J. et al. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease // *Neuropsychology.* – 2003. – Vol. 41. – P. 1431–1441
- 18 Dubois B., Slachevsky A., Litvan I. et al. The FAB: a Frontal Assessment Battery at bedside // *Neurology.* – 2000. – Vol. 55, N 11. – P. 1621-1626
- 19 Duda J.E., Lee V.M.-Y. and Trojanowski J.Q. Neuropathology of Synuclein Aggregates: New Insights Into Mechanisms of Neurodegenerative Diseases // *J Neurosci Res.* – 2000. – Vol. 61 – N 2. – P. 121-127
- 20 Francardo V., Bez F., Wieloch T. et al. Pharmacological stimulation of sigma-1 receptors has neurorestorative effects in experimental Parkinsonism // *Brain.* – 2014. – Vol. 137. – P. 1998–2014
- 21 Freed C.R., Greene P.E., Breeze R.E. et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease // *N Engl J Med.* – 2001. – Vol. 344. – P. 710–719
- 22 Folstein M.F., Folstein S.E., McHugh P.R. Mini Mental State" A practical method for grading the cognitive state of patients for the clinician // *Journal of Psychiatric Research.* – Vol. 12, N 3. – P. 189-198
- 23 Gibb W.R., Lee A.J., The relevance of Lewy Body to the aetiology of idiopathic Parkinson's Disease // *J NeurolNeurosurgery Psychiatry.* – 1988. – Vol. 51. – P. 745-752
- 24 Giovannetti T., Britnell P., Brennan L. // *Everyday Action Impairment in Parkinson's Disease Dementia // J IntNeuropsychol Soc.* – 2012. – Vol. 18, N 5. – P. 787–798
- 25 Gomperts S.N., Rentz D.M., Moran E. et al. Imaging amyloid deposition in Lewy body diseases // *Neurology.* – 2008. – Vol. 71. – P. 903–910
- 26 Hall H., Reyes S., Landeck, N. et al. Hippocampal Lewy

- pathology and cholinergic dysfunction are associated with dementia in Parkinson's disease // *Brain*. – 2014. – Vol. 137. – P. 2493–2508
- 27 Hanganu A., Bedetti C., Degroot, C. B-M. et al. Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally // *Brain*. – 2014. – Vol. 137. – P. 1120–1129
- 28 Hely M.A., Reid W.G.J., Adena M.A. et al. The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years // *MovDisord*. – 2008. – Vol. 23. – P. 837–844
- 29 Hoehn M.M., Yahr M.D. Parkinsonism: onset, progression and mortality // *Neurology*. – 1967. – Vol. 17. – P. 427–442
- 30 Ibarretxe-Bilbao N., Ramirez-Ruiz B., Tolosa E. et al. Hippocampal head atrophy predominance in Parkinson's disease with hallucinations and with dementia // *J Neurol*. – 2008. – Vol. 255. – P. 1324–31
- 31 Kehagia A.A., Barker R.A., Robbins T.W. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in Parkinson's disease // *Lancet Neurol*. – 2010. – Vol. 9. – P. 1200–1213
- 32 Kordower J.H., Chu Y., Hauser R.A. et al. Lewybodylike pathology in long-term embryonic nigral transplants in Parkinson's disease // *Nat Med*. – 2008. – Vol. 14. – P. 504–506
- 33 Leroi I., Ahearn D.J., Andrews M. et al. Behavioral disorders, disability and quality of life in Parkinson's Disease // *Age and Ageing*. – 2011. – Vol. 40. – P. 614–621
- 34 Logroscino G., Sesso H.D., Paffenbarger R.S. Jr et al. Physical activity and risk of Parkinson's disease: a prospective cohort study // *J Neurol Neurosurg Psychiatry*. – 2006. – Vol. 77. – P. 1318–1322
- 35 Lovestone S., Gauthier S. Management of dementia-London // *Martin Dunitz Ltd*. – 2000. – P. 145
- 36 Li J.Y., Englund E., Holton J.L. et al. Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation // *Nat Med*. – 2008. – Vol. 14. – P. 501–503
- 37 Lilienfeld, D. & Perl D. Projected neurodegenerative disease mortality in the United States, 1990-2040 // *Neuroepidemiology*. – 1993. – Vol. 12 – P. 219-228
- 38 Luo N., Low S., Ngoh Lau P. et al. Is EQ-5D a Valid Quality of Life Instrument in Patients With Parkinson's Disease? A study in Singapore // *Ann Acad Med Singapore*. – 2009. – Vol. 38. – P. 521-528
- 39 Lyoo C.H., Ryu Y.H., Lee M.S. Topographical distribution of cerebral cortical thinning in patients with mild Parkinson's disease without dementia // *MovDisord*. – 2010. – Vol. 15, N 24. – P. 496-499
- 40 Nishimura F., Yoshikawa M., Kanda S. et al. Potential use of embryonic stem cells for the treatment of mouse parkinsonian models: improved behavior by transplantation of in vitro differentiated dopaminergic neurons from embryonic stem cells // *Stem Cells*. – 2003. – Vol. 21. – P. 171–180
- 41 Mamikonyan E., Moberg P.J., Siderowf A. et al., Mild cognitive impairment is common in Parkinson's disease patients with normal Mini-Mental State Examination (MMSE) scores // *Parkinsonism RelatDisord*. – 2009. – Vol. 15, N 3. – P. 226–231
- 42 Marconi R., Antonini A., Barone P. et al. Frontal assessment battery scores and non-motor symptoms in parkinsonian disorders // *Neurol Sci*. – 2012. – Vol. 33, N 3. – P. 585-593
- 43 Maetzler W., Liepelt I., Reimold M. et al. Cortical PIB binding in Lewy body disease is associated with Alzheimer-like characteristics // *Neurobiol Dis*. – 2009. – Vol. 34. – P. 107–112
- 44 Mendez I., Vinuela A., Astradsson A. et al. Dopamine neurons implanted into people with Parkinson's disease survive without pathology for 14 years // *Nat Med*. – 2008. – Vol. 14. – P. 507–509
- 45 Moore D.J, West A.B. and T. M. Dawson. Molecular Pathophysiology of Parkinson's Disease // *Journal of Neuroscience Research*. – 2000. – Vol. 61. – P. 121–127
- 46 Pecci C. Chronic disease and quality of life // *Vertex*. – 2007. – Vol. 18, N 72. – P.111-119
- 47 Pistacchi M., Gioulis M., Contin F. et al. Cognitive profiles in Mild Cognitive Impairment (MCI) patients associated with Parkinson's disease and cognitive disorders // *Ann Indian Acad Neurol*. – 2015. – Vol.18, N 2. – P. 200-205
- 48 Pluck G., Brown, R. Apathy in Parkinson's disease // *Journal of Neurosurgery Psychology*. – 2002. – Vol. 73. – P. 636-642
- 49 Petzinger G.M., Walsh J.P., Akopian G. et al. Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury // *J Neurosci*. – 2007. – Vol. 27. – P. 5291–5300
- 50 Prieto G., Delgado A.R., Perea M.V., et al. Differential functioning of mini-mental test items according to Disease // *Neurologia*. – 2011. – Vol. 26, N 8. – P. 474-480
- 51 Rabin R., de Charro F., EQ-5D: a measure of health status from the EuroQolGroip // *Ann Med*. – 2001. – Vol. 33, N 5. – P. 337-343
- 52 Rochester L., Yarnall A., Baker M.R. et al. Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease // *Brain*. – 2012. – Vol. 135. – P. 2779–2788
- 53 Saaksjarvi K., Knekt P., Mannisto S. et al. Reduced risk of Parkinson's disease associated with lower body mass index and heavy leisure-time physical activity // *Eur J Epidemiol*. – 2014. – Vol. 29. – P. 285–292
- 54 Sabbagh M., Adler C.H., Lahti T.J. et al. Parkinson's disease with dementia: comparing patients with and without Alzheimer pathology // *Alzheimer Dis AssocDisord*. – 2009. – Vol. 23. – P. 295–297
- 55 Sammer G., Reuter, I., Hullmann, K. et al. Training of executive functions in Parkinson's disease // *Journal of Neurological Sciences*. – 2006. – Vol. 248. – P. 115-119
- 56 Sasco A.J., Paffenbarger R.S. Jr, Gendre I. et al. The role of physical exercise in the occurrence of Parkinson's disease // *Arch Neurol*. – 1992. – Vol. 49. – P. 360–365
- 57 Schrag A., Selai C., Jahanshahi M. et al., The EQ-5D—a generic quality of life measure—is a useful instrument to measure quality of life in patients with Parkinson's disease // *J Neurol Neurosurg Psychiatry*. – 2000. – Vol. 69. – P. 67–73
- 58 Schwab R.S., England AC. Projection technique for evaluating surgery in Parkinson's Disease // *Third Symposium on Parkinson Disease*. Edinburgh: Churchill Livingstone. – 1969. – P. 152–157

59 Sinforiana E., Banchieri L., Zucchella C. et al. Cognitive rehabilitation in Parkinson's disease // Archives of Gerontology (Geriatric Supplement). – 2004. – Vol. 9. – P. 387-391

60 Skogar O¹, Fall PA, Hallgren G., et al. Parkinson's disease patients' subjective descriptions of characteristics of chronic pain, sleeping patterns and health-related quality of life // Neuropsychiatr Dis Treat. – 2012. – Vol. 8. – P. 435-442

61 Song S.K., Lee J.E., Park H-J. et al. The pattern of cortical atrophy in patients with Parkinson's disease according to cognitive status // MovDisord. – 2011. – Vol. 26. – P. 289–296

62 Spielberger C.D., Gorsuch R.L., Lushene R. et al. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA // Consulting Psychologists Press, 1983

63 Thacker E.L., Ascherio A. Familial aggregation of Parkinson's disease: a meta-analysis // MovDisord. – 2008. – Vol. 23. – P. 1174–1183

64 Thacker E.L., Chen H., Patel A.V. et al. Recreational physical activity and risk of Parkinson's disease // MovDisord. – 2008. – Vol. 23. – P. 69–74

65 Tinazzi M., Del Vesco C., Fincati E., et al. Pain and motor complications in Parkinson's disease // J NeurolNeurosurg Psychiatry. – 2006. – Vol. 77. – P. 822–825

66 Ohta K., Takahashi K., Gotoh J. Screening for Impaired Cognitive Domains in a Large Parkinson's Disease Population and Its Application to the Diagnostic Procedure for Parkinson's Disease Dementia // Dement Geriatr CognDisord Extra. – 2014. – Vol. 4. – P.147–159

67 Olanow C.W., Goetz C.G., Kordower J.H. et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease // Ann Neurol. – 2003. – Vol. 54. – P. 403–414

68 Williams-Gray C.H., Evans J.R., Goris A. et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort // Brain. – 2009. – Vol. 132. – P. 2958–2969

69 Wirdefeldt K., Gatz M., Pawitan Y. et al. Risk and protective factors for Parkinson's disease: a study in Swedish twins // Ann Neurol. – 2005. – Vol. 57. – P. 27–33

70 Xu Q., Park Y., Huang X. et al. Physical activities and future risk of Parkinson disease // Neurology. – 2010. – Vol. 75. – P. 341–348

71 Yang F., Lagerros Y.L., Bellocco R. et al. Physical activity and risk of Parkinson's disease in the Swedish National March Cohort // Brain. – 2015. – Vol. 138. – P. 269–275

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ПАРКИНСОН АУРУЫМЕН ЗАРДАП ШЕГЕТІН ПАЦИЕНТТЕРДІҢ МОТОРЛЫ-ЕМЕС СИМПТОМДАРЫ МЕН КОГНИТИВТІ СТАТУСЫНЫҢ ӨЗГЕРІСТЕРІН БАҒАЛАУ

Паркинсон ауруы моторлы және моторлы-емес симптомдармен байқалатын нейродегенеративті созылмалы ауру. Негізгі моторлы симптомдарға тремор, постуральды төзімсіздік, гипокинез және бұлшықеттің ригидтілік белгілері жатады. Моторлы-емес симптомдарға аурудың дамуына қарай когнитивті статустың төмендеуі, оның ішінде еске сақтаудың төмендеуі, жағдайды рационалды бағалаудың төмендеуі, депрессия, мазасыздық, эмоционалды деңгейдің төмендеуі мен ангедония. Паркинсон ауруымен зардап шегетін пациенттердің өмір сүру сапасы төмендейді, бұған себеп табиғи және нейродегенеративті процесстер. Жұмыстың мақсаты MMSE клиникалық шкалаларды және сағат салу тестісін, маңдайлық тестілер батареясын, Спиллибергер–Ханинестін, күнделікті белсенділікті бағалау шкаласын және Боли EuroQoL-5D Визуалды Аналогты Шкаласын қолдана отырып нейропсихикалық тестілеудің нәтижелерін сараптау арқасында Паркинсон ауруымен зардап шегетін пациенттердің өмір сүру сапасын анықтау.

Нәтижесінде зерттеуге қатысқан бақылау тобымен салыстырғанда Паркинсон ауруымен зардап шегетін пациенттерде когнитивті статустың төмендеуі, мазасыздық пен ауырсынуудың деңгейі жоғары болғаны анықталды.

Негізгі сөздер: Паркинсон ауруы, нейропсихикалық тесттер, көңіл бөлу, мазасыздық, ауырсыну.

РЕЗЮМЕ

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ОЦЕНКА НЕ-МОТОРНЫХ СИМПТОМОВ И ИЗМЕНЕНИЙ КОГНИТИВНОГО СТАТУСА У ПАЦИЕНТОВ С БОЛЕЗНЬЮ ПАРКИНСОНА

Болезнь Паркинсона – это хроническое нейродегенеративное заболевание, характеризующееся как моторными, так и не-моторными заболеваниями. Основные моторные симптомы включают в себя тремор, постуральную неустойчивость, гипокинез и мышечную ригидность. Не-двигательные нарушения включают снижение когнитивного статуса по мере развития заболевания, в частности, снижение памяти и внимания, способности рационально оценивать ситуацию. На данный момент в РК по теме оценки изменения когнитивного статуса у пациентов с болезнью Паркинсона проведено крайне мало работы, таким образом, целью данной работы было проведение нейропсихического тестирования пациентов с использованием клинических шкал MMSE, теста Рисования Часов, Батарей, Лобных Тестов госпитальной тревожности Спиллибергера-Ханина, шкалу оценки ежедневной активности, а также ВАШ EuroQoL-5D. Таким образом, было выявлено, что пациенты с БП имеют значительное снижение когнитивного статуса, а также высокий уровень тревожности и интенсивности боли (n=39 для пациентов с БП, n=39 для идентичной по возрасту контрольной группы, Anova P<0,01).

Ключевые слова: болезнь Паркинсона, нейропсихические тесты, внимание, тревожность, боль.

Для ссылки: Akanova A.A., Yeshmanova A.K., Akanova K.K., Kamenova S.U., Beltenova A.G., Raimkulova K.B. Evaluation of non-motor symptoms and cognitive changes in Parkinson disease // J. Medicine (Almaty). – 2015. – No 12 (162). – P. 36-43

Статья поступила в редакцию 10.11.2015 г.

Статья принята в печать 14.12.2015 г.