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RESEARCH ARTICLE

Apathy in Parkinson disease

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Abstract **Apathy is one of the least investigated symptom of Parkinson disease (PD). In the article there are data of frequency, diagnostic features, pathophysiology and treatment of apathy in PD. The aim of the investigation was to evaluate the frequency of apathy in PD without dementia, evaluate the relationship with other neuropsychiatric and motor disorders, influence on the life quality. 115 patients (age – 63.84±0.6 years, stage – 2.6±0.3) with PD without dementia were included in the investigation. There were used the following scales: scale of evaluation stages of PD by Hoehn-Yahr, UPDRS (part «activity of daily living», «motor functions »); Beck Depression Inventory, Spielberger State Trait Anxiety Inventory, Parkinson Disease Sleep Scale- PDSS, Epworth Sleepiness Scale, Parkinson Fatigue Scale-PFS-16, SCOPA-Cog, Lilli Apathy Rating Scale LARS and Apathy Scale AS.**

Apathy was found in 25% of patients. The frequency and severity of apathy does not depend on stage and duration of PD. It was found positive correlation of apathy and hypokinesia. In different stages of PD there was variability of relationships of apathy with depression, executive functions and sleep disorders. We suppose the heterogeneity of apathy in PD because of the variability of the association with other neuropsychiatric (affective, cognitive, sleep) disorders. It was found the negative influence of apathy on daily activity, emotional and social aspects of life quality.

Keywords Parkinson disease, neuropsychiatric symptoms, apathy, heterogeneity

Introduction

In the last decade there is increasing interest of examining the factors which could worsen the life quality of patients with Parkinson disease (PD). The active attention is focused on the Neuropsychiatric disorders (NPD)–emotional, cognitive, behavioral, fatigue, disorder of sleep and vigilance. The interest to NPD is caused by high frequency of these disorders and negative influence on the life quality as patients, as their relatives (McKinlay et al., 2008; Aarsland et al., 2009; Barone et al., 2009; Nodel and Yahno, 2009; Gallagher et al., 2010; Vosnesenskaya, 2013). Pathophysiology of most NPD in PD is multifactorial, it could be the result of structural or neurochemical disorders. The high frequency of associated neuropsychiatric manifestations of PD is the cause of probable difficulties in diagnostics and evaluation of the phenomenology of some disorders in PD.

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The least examined aspect of NPD in PD is apathy. In clinical context apathy is defined as diminished motivation. It is characterized by deficits in goal-directed behavior and the simultaneous diminution of the cognitive and emotional concomitants of goal-directed behavior (Starkstein et al., 1992; Levy and Dubois, 2006). Apathy may be one of the most common syndrome of cerebro-vascular disorders and neurodegenerative disorders—Alzheimer disease, dementia with Lewy bodies, Fronto-temporal dementia, Progressive Supranuclear Pulsy, Huntington disease and others.

The diagnostic criteria of apathy were suggested by Marine et al. (1991) and modified by Starkstein et al. (2006). In 2009 these criteria were supplemented and validated by the international group of experts on the population of patients with different neuropsychiatric disorders.

In the base of these criteria the diagnosis of apathy is-loss of diminished motivation in comparison to the patients previous level of functioning together with presence of at least one symptom in a least two of the three following domains: loss of, or diminished, goal-directed behavior, goal-directed cognitive activity and emotions. These symptoms should last for a period of at least 4 weeks and present most of

the time; should cause clinically significant impairment in personal, social, occupational, or other important areas of functioning. The symptoms are not exclusively explained to physical disabilities, motor disabilities, diminished level of consciousness or direct physiological effects of a substance (Robert et al., 2009).

In a study, which examined PD alone there was a high comparability (percentage of agreement) between the diagnostic criteria of Robert et al. and the results which were obtained by Lille apathy rating scale (LARS) (Sockeel et al., 2006), and the Neuropsychiatric Inventory (NPI) sub-score (Cummings et al., 1994). The Movement Disorders Society in 2008 undertook a comprehensive critique of apathy scale and recommended to use the apathy scale (AS) developed by S.E. Starkstein (Starkstein et al., 1992), which is an abbreviated version of Marins original Scale (Marin et al., 1991) for assessment the apathy in PD.

The role of basal ganglia dysfunction in pathophysiology of apathy was explained with both sides disorder of nucleus caudatus, pallidum, mediobasal part of thalamus and putamen (Czernecki et al., 2008). The mechanisms underlined apathy in PD mainly been investigated using functional imaging in patients with STN-DBS. Several studies have demonstrated dopaminergic limbic cortex denervation(Thobois et al., 2013), cortex hypometabolism in patients with apathy (Le Jeune et al., 2009). It is suggested, that the motivational components of behavior are regulated by dopaminergic connections between ventral part of brainstem and ventral part of pallidum with mesolimbic and prefrontal mesocortical structures. One of the main structure, which provides functional connectivity of these parts of the brain and modulation of goal-directed behavior is nucleus accumbens (Robbins and Everitt, 1996). The role of the nucleus accumbens and it is connections in pathophysiology of apathy in PD was demonstrated in recent study of Carriere et al., where was used Magnetic Resonance Imaging Shape analysis. Dopa-resistant apathy in patients with PD is associated with atrophy of left nucleus accumbence (Carriere et al., 2014).

The questions of phenomenology of independency the apathy in PD are tightly connected with the evaluation of it is association with depression. From one side, apathy is the syndrome-one of the additional criteria of depression, from the other –is diagnosed in patients with PD without other major signs of depression (the feeling of sadness, anhedonia), is remarkable of emotional inactivity (Levy et al., 1998). The association of apathy with degree of motor and non motor symptoms in PD is not enough investigated. It was shown the association of apathy with depression, cognitive disorders, with more severe stage of PD, with predominantly akinetiko-rigid form of the disease (Reijnders et al., 2009).

The independent risk factor of apathy is the rapid progression of speech and postural disorders (Pedersen et al., 2009). It is actual to specify the prognostic value of diagnosis the apathy in progression of PD. By the data of prospective longitudinal investigation of Dujardin et al. (2009), the presence of apathy worsen the prognosis and is associated with more rapid progression of cognitive impairment, developing dementia and worsen the daily activity. The decreasing of foodstuff motivation in PD could be the cause of excessful loose of the bodyweight (Shore et al., 2011). The results of cross-sectioned investigations of the influence of apathy on life quality are controversial. By the data of many investigations the apathy is one of the major fact of the worsening the life quality in PD (Barone et al., 2009; Benito-León et al., 2012). Other investigations show depression, fatigue, anxiety, sleep disorders as the major symptoms, which worsen life quality in PD (Martinez-Martin et al., 2007; McKinlay et al., 2008).

Treatment of apathy in PD also needs to be investigated. It is important to specify the dynamic of apathy on dopamine-enhancing treatment, possibility to use "symptomatic" drugs. Moderate efficacy of the dopamine agonists, inhibitors of acetylholinesterase in patients with PD and dementia is described (Aarsland et al., 2000; Czernecki et al., 2008; Thobois et al., 2013).

The questions of pathophysiology and phenomenological independence of apathy in PD, the influence on life quality and treatment approaches need to be specified.

The aim of investigation is the analysis of the frequency of apathy in the spectrum of neuropsychiatric disorders in PD, its relationship with motor and other non motor signs of disease, evaluation of the impact of apathy to the worsening of life quality on different stages of PD.

Patients and methods

115 patients with idiopathic PD without dementia were investigated.

Inclusion criteria: diagnosis of PD based on UK Brain Bank criteria (Hughes et al., 1992). Exclusion criteria: suspected dementia; current uncontrolled psychiatric disorder (e.g. substance abuse, major depressive disorder), history of neurologic illness (other than PD). Patients received dopaminergic medications. Informed consent was obtained according to local guidelines. Mean age was 63.84 ± 0.6 years, duration of PD – 6.3 ± 2.1 years. Mean indices of the severity: stage – 2.6 ± 0.3 Hoehn-Yahr scale. For evaluation of motor dysfunction there was used the scale of evaluation stages of PD by Hoehn-Yahr, part «Motor Function» UPDRS (Fahn et al., 1987).

Neuropsyhiatric disorders (NPD) were evaluated by Beck Depression Inventory (21-item questionnaire)(Beck et al., 1996), Spielberger State Trait Anxiety Inventory (Spielberger et al., 1983), Parkinson Disease Sleep Scale (PDSS) (Neugarten et al., 1968), Epworth Sleepiness Scale (Johns, 1991), Parkinson Fatigue Scale (PFS-16) (Brown et al., 2005), Scales for Outcomes of Parkinsons disease-Cognition (SCOPA-Cog) (Marinus et al., 2003). SCOPA-Cog scores

divides into categories: memory (immediate and delayed recall), attention, executive functions, visuo-spatial functions; score range from 0 to 43, higher scores indicate the better state of cognitive function.

The Lilli Apathy Rating Scale (LARS) comprises 33 queries belonging to nine domains: Everyday productivity, Interests, Talking the initiative, Novelty seeking, Motivation-Voluntary actions, Emotional responses, Concern, Social life, Self-awareness factorial sub-scores. The scale's overall score ranges from –36 to + 36. The severity of apathy divides into four categories: – 36 to – 22 for non-apathetic, – 21 to – 17—slightly, – 16 to – 10— moderately, 29 to – 36— severely apathetic subjects(Sockeel et al., 2006).

For evaluation the connection with other symptoms and parameters of life quality were used LARS and Apathy Scale (AS) (Marin et al., 1991). The AS is a 14-item self-reported questionnaire, score range from 0 to 42, higher scores indicate greater apathy. The recommended clinical cutoff score for apathy is 14.

To evaluate the influence of apathy on life quality and daily activity was used Parkinson's Disease Quality of life questionnaire (PDQ-39), part 2 «Activity daily living» UPDRS (Peto et al., 1998). The PDQ-39 comprises 39 queries divides into categories: Mobility; Activities of daily living; Emotional well-being; Stigma; Social support; Cognitions; Communication; Bodily discomfort; score range from 0 to 156; higher scores indicate greater impairment of quality of life. For statistical analysis we used STATISTICA 7.

For evaluation the relationship of the symptoms in PD linear correlation coefficients were calculated, for evaluation groups of tight associated indexes was used the method of hierarchic clustered analysis, which gives the possibility to combine groups by joining to the group more correlated parameters. The measure of closeness was 1-*r*, *r*- correlation between the parameters in all patients. The combination was done by Warda method.

Results

By LARS scale, apathy was found in 29 (25%) patients. The light degree was in 10 (8.7%), moderate— in 14 (12.2%), severe— in 5 (4.3%) of patients. In 23% of patients there was found comorbidity with depression, in 80% patients with apathy and 20% of all groups of the patients.

Significant correlation was not found between the apathy, gender, age, duration of PD, stage (Table1), side of the onset. There was positive correlation between apathy and the age of the beginning of PD ($r = 0.45$, $p < 0.05$); depression ($r = 0.33$, $p < 0.05$), sleep disorders ($r = 0.28$, $p < 0.05$).

There were positive significant correlations between apathy, motor and other neuropsychiatric disorders on different stages of PD with total score of UPDRS «Motor function» ($r = 0.59$, $p < 0.001$) and hypokinetic signs – hypomimia ($r = 0.32$, $p < 0.05$), speech disorders($r = 0.24$, $p < 0.05$), hypokinesia in dynamic probes in hands ($r = 0.297$, $p < 0.05$), body hypokinesia ($r = 0.241$, $p < 0.05$) on 3 stage of PD; depression on 2 stage ($r = 0.59$, $p < 0.001$) 3 ($r = 0.46$, $p < 0.001$) stages of PD, apathy and fatigue ($r = 0.59$, $p < 0.001$), executive function ($r = 0.52$, $p < 0.001$) on 2 stage, sleep disorders (total score PDSS) on 3 stage ($r = 0.58$, $p < 0.001$).

There was significant correlation between total score of apathy with parameters of daily activity, UPDRS (part II «Activity daily living») and life quality PDQ-39 (Table 2).

By cluster analysis we have found that in one group were combined the total score of apathy LARS, AS and age of the beginning of PD, cognitive disorders (SCOPA-Cog total score, SCOPA-Cog-executive function) and sleep disorders (total score PDSS). The second group combined depression, anxiety, fatigue, which were tightly connected with PDQ-39, and subgroup of scores the parts Motor function, Activity Daily Living UPDRS (Fig. 1).

Discussion

In our investigation the frequency of apathy in patients with PD without dementia was 25%.By data of other investigations apathy was in 13% – 60% patients with PD (Bogart, 2011). These differences are probably because of the different methods of evaluation the apathy and heterogeneity of the groups of patients (e.g. different degree of cognitive disorders, PD stages). Our data are similar to the results of Aarsland et al., which were obtained with the use of NPI and recent investigation of the frequency of apathy by different neuropsychiatric diseases of Mulin et al. with the use of new additional criteria. In both investigations the apathy in patients was found in 27% (Aarsland et al., 1999; Mulin et al., 2011).

In our investigation there was shown the positive correlation between apathy and the age of the PD onset. The disorders of emotional part and apathy could be the sign of normal aging, because of socio-environmental and biologic

Table 1 Patients according to the degree of apathy on different stages of PD by LARS scale

	Light degree	Moderate degree	Severe degree	Total
1 stage	2	1	1	4 (13.8%)
2 stage	4	7	2	13 (44.8%)
3 stage	2	4	2	8 (27.6%)
4 stage	1	1	2	4 (13.8%)
Total	9	13	7	29 (100%)

Table 2 The influence of apathy on life quality

	LARS interests	LARS novelty seeking	LARS motivation-voluntary actions	LARS total score	AS total score
PDQ- total score	$r = 0.73$, $0.05 < p < 0.1$ (1 stage)				
PDQ-emotional well-being	$r = 0.76$, $p < 0.05$ (1 stage)				
PDQ- Stigma		$r = 0.89$, $p < 0.05$ (1 stage) $n = 0.69$, $0.05 < p < 0.1$(4 stage)	$r = 0.52$, $p < 0.05$ (2 stage)		
PDQ-cognitions	$r = 0.75$, $0.05 < p < 0.1$ (1 stage)		$r = 0.54$, $p < 0.05$ (2 stage)	$r = 0.52$, $p < 0.05$(2 stage)	
PDQ-social support		$r = 0.63$, $0.05 < p < 0.1$ (4 stage)			
PDQ-body discomfort	$r = 0.71$, $0.05 < p < 0.1$ (1 stage)				
UPDRS Activity of daily living				$r = 0.52$, $p < 0.05$ (3 stage)	$r = 0.52$, $p < 0.05$(2 stage)

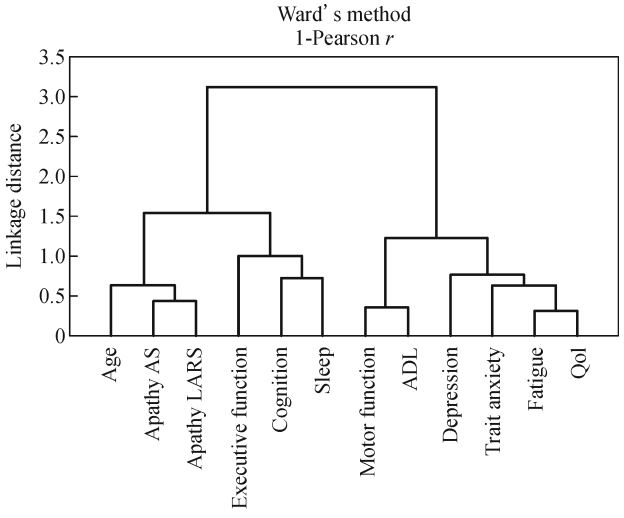

Figure 1 The distance between groups is calculated, and does not have interpretive value. Age – the age of onset PD; Apathy AS – total score AS; Apathy LARS – total LARS score; Executive function – Executive function domain SCOPA- Cog; Cognition – total score SCOPA-Cog ; Sleep – total score PDSS; Motor functions – part 3 UPDRS , ADL – Activity daily living-part 4 UPDRS; Depression–total score BDI ; Trait Anxiety –score STAI; Fatigue – mean score PFS-16; Qol – total score PDQ-39.

factors (Neugarten et al., 1968; Marin, 1990). Discussing the multilayer relationship of apathy with age, it is important to use the description of Singer (1973), where apathy in patients with PD is the example of "premature social ageing" (Singer, 1973). It is found that the frequency of apathy in PD is much higher than in population. In the investigation of Aarsland et al. the frequency of apathy in patients with PD is 27% against 1% in control group(Aarsland et al., 1999). 44% of PD patients were apathic compared with 20% of healthy controls in recent study of Jordan et al. (2013). Apathy in PD is more frequent than in other chronic disorder— osteoarthritis, which is compared with PD by limitation of motor activity. In comparative investigation of Pluck et al. apathy was in 40% – 44% of patients with PD, there was found no apathy in control group with osteoarthritis with the same degree of disability (Pluck and Brown, 2002). So apathy could not be explained only by age factors or psychological reaction on chronic disease, but as structural and neurochemical disorders in PD.

MRI study utilizing voxel-based morphometry to determine the structural correlations of apathy found that higher apathy scores in PD patients correlated with lower gray matter density in various brain regions including bilateral precentral, inferior parietal gyri, inferior frontal gyri, right posterior cingulate gyrus and right precuneus (Reijnders et al., 2010). Study of Carriere et al. demonstrated positive correlations between the severity of apathy and atrophy of the left nucleus accumbence (Carriere et al., 2014).

The data of clinical investigations of correlation apathy and age are contradictive. Aarsland et al.1999 did not find any correlation between apathy with age of PD onset (Aarsland et al., 1999), while in other investigations there was found significant correlation (Kirsch-Darrow et al., 2006; Oguru et al., 2010). Our data confirm the positive influence of age on apathy in PD.

We did not find the statistical difference between the severity of apathy on different stages of PD. It could be explained by the fact of relatively small groups on 1 and 4 stage of (Table 1). But significant differences could not be excluded between the severity of apathy in different stages of PD. The data of the evaluation of apathy are contradictory – there was found the increase of the severity of apathy by the progression of PD (Kirsch-Darrow et al., 2006), and no changes of apathy (Pluck and Brown, 2002).

The study confirmed positive correlation between apathy and hypokinesia, which specified the previous data of the association of apathy with akinetico-rigid form of PD (McKinlay et al., 2008; Reijnders et al., 2010). We suppose

that correlation of apathy and hypokinesia provides the consideration of the same pathophysiological mechanisms of these symptoms. It is important to remember about the heterogeneity of hypokinesia. Narabayashi suggested 3 pathogenetic types of hypokinesia in PD: secondary hypokinesia (caused by rigidity), primary and psychomotor (Narabayashi, 1999). Clinically it is very difficult to divide different types of hypokinesia. The primary hypokinesia is characterized by slowing the speed, decreasing the amplitude of movement. Psychomotor hypokinesia is characterized by insufficiency of activity, initiating of motor programs, which are common with apathy.

According to the modern views, in pathophysiology of hypokinesia is disconnection between basal ganglia and prefrontal cortex. The dysfunction of prefrontal medial and basal parts of the frontal lobes and their connection with basal ganglia could cause behavior disorder in form of the apathy.

The present study confirmed previous research that PD is associated with high comorbidity of depression and apathy. Only in 20% cases there was no association between depression and apathy. This finding is similar with previous data, demonstrating 26%–28% of isolated apathy from depression and dementia (Aarsland et al., 1999; Starkstein et al., 2006; Oguru et al., 2010).

There were significant correlations between apathy and depression on 2 and 3 stages without any correlations on 1 and 4 stages. We suppose that different correlations between apathy and depression on different stages of PD show phenomenological heterogeneity of apathy in PD. Apathy could be a part of depressive symptom, comorbid symptom or could be the independent PD symptom.

The results of cluster analysis which showed that depression and apathy belong to different groups could be the major argument of independency of apathy. The comorbidity of depression and apathy could be described by the common pathophysiological mechanisms-dysfunction of limbic structures (amygdala, nucleus accumbens) and medioorbital prefrontal cortex, which are responsible for the motivational behavior and reward (Robbins and Everitt, 1996; Remy et al., 2005; Leroi et al., 2012).

In the light of actual questions of differential diagnosis of apathy and depression and the fact of the common symptom-anhedonia, really important are the data of the investigation, performed by Jordan et al.(2013) who confirmed that PD is associated with increased apathy and anhedonia. Moreover, apathy in PD is characterized by deficits in anticipatory pleasure and reduced pursuit of desire goals (behavioral drive) rather than consummatory pleasure or reward responsiveness. Previous studies have indentified dissociable neural circuitry in anticipatory (dopaminergic dysfunction in the nucleus accumbens) versus consummatory (prefrontal cortex) anhedonia (Carver and White, 1994; Smith et al., 1996) .

The results of present investigation confirm the significant correlation of apathy with frontal cognitive functions in PD without dementia. In major investigations of apathy in PD was found association of apathy and cognitive disorders (dementia and non demented disorders) (Starkstein et al., 1992; Marinus et al., 2003; Reijnders et al., 2010).

In 1022, Naville described a clinical profile in PD consistent with criteria of bradyphrenia as a lack of initiative, slowness of thinking, deficits in attention and interest (Cummings et al., 1994). In the investigation of Starkstein was found the association of apathy and disorder of executive functions with time related parameters of cognitive activity, that gives possibility to discuss the comorbidity of apathy and bradyphrenia (Starkstein et al., 1992).

The disorder of executive functions are associate with disorder of goal-directed behavior and reduction of self-activity because of disconnections of planning mechanisms and changing activity from one to the other (Tekin and Cummings, 2002; Bonelli and Cummings, 2007). The statistical correlations of apathy with disorder of executive functions make possible to suggest common pathophysiological mechanisms, which could be caused by disorder of functional connections between basal ganglia, lateral and medioorbital prefrontal cortex. The common pathophysiological mechanisms of apathy and executive functions in PD were found by Carriere et al. (2014): the greater atrophy of dorsolateral head of the nucleus caudatus in apathetic patients. The striatal regions are known to be involved in the dorsolateral cognitive circuit (Alexander et al., 1990).

Statistical correlations of apathy with sleep disorders are also important. Besides of the probable negative influence of sleep disorders on emotions and the level of alertness, we could suppose that there are common pathophysiological components of apathy and insomnia. The dysfunction of pedunculopontine nucleuse (PPN) could be one of the mechanisms. In PD there is found the degeneration of PPN and it is disconnection with basal ganglia and other nucleuses of brainstem. PPN plays important role in modulation the REM sleep. One of the variant of parasomnia- behavior disorder in REM sleep (RBD) could be also associated with the dysfunction of PPN. We have already discussed the positive correlation between apathy and RBD (Nodel et al., 2010). According to investigations that RBD could be risk factor of more rapid progression of cognitive disorders (Robert et al., 2009; Postuma et al., 2012), we could suppose that apathy, cognitive and sleep disorders are interrelated (could be parts of common spectrum of NPD).

The variability of associations between apathy, hypokinesia, cognitive and sleep disorders on different stages of PD could be related with heterogeneity and different degree of evidence of these clinical signs. Different functional subsystems of multilevel neural connections between basal ganglia, limbic system and prefrontal cortex could be involved on different stages of PD according to the individual variability of the disease (Tekin and Cummings, 2002). According to the preferable localization of pathologic process Levy and Dubois suggested to differentiate 3 major subtypes of apathy— apathy, connected with disorder of emotional and

affective processes, apathy connected with disorder of cognitive functions and apathy connected with the disorder of self activity (Levy and Dubois, 2006). According to the diffuse and multi-component pathological process in PD we suppose only probable domination of separate pathophysiological subtypes of apathy.

Inspite of the fact, that major factors of worsening the self evaluation of the life quality were depression, fatigue and anxiety, we found significant data of negative influence of apathy on life activity aspects. The values of apathy were significantly connected with data of daily activity (the degree of home activity) of the patients. There was found correlations of apathy with decrease of social contacts, emotional, cognitive evaluations of daily activity. Our data of the influence of apathy on life quality are related to the results of multi central Italian investigation (Barone et al., 2009). The data of observation of 1072 (mean duration PD-5,1 years, stage- 1,5-2,5 by Hoehn-Yahr), showed that apathy is the leading symptom, connected with low self evaluation of life quality.

The data of Spanish investigation of 557 patients with PD (less than 2 years) (Beck et al., 1996), showed that apathy is one of the major factor of low evaluation of life quality in patients on the early stages. So apathy puts major impact in social and home disability.

The treatment of apathy is very actual because of it is negative influence on life quality, which was found in our investigation even in light and moderate degree of the syndrome. But the approaches to the correction of apathy in PD are not yet distinguished. Single data show the moderate efficacy of dopamine agonists by reducing the fluctuations of motor and non motor symptoms in PD (Czernecki et al., 2008; Thobois et al., 2013). The evaluation of the efficacy of dopaminergic treatment in different variants and degree of apathy must be approach of future investigations.

The use of antidepressive therapy with light stimulating mechanism could be probably used in the treatment of apathy especially with its connection with depression. However the study, which investigated the efficacy of atomoxetine, where depression was the primary outcome measure, showed no improvement of apathy scores (Weintraub et al., 2010).

We should differentiate apathy from depression with it is monitoring on therapy because of the possibility of appearing apathy on antidepressants- inhibitors of rebound intake of serotonin(serotonin induced apathy) (Weintraub et al., 2010). In case of isolated apathy the antidepresive therapy is not effective.

The efficacy of rivastigmine- inhibitor of acetylcholinesterase was shown in PD and dementia (Campbell and Duffy,1997; Aarsland et al., 2000).

The non pharmacological methods–psychotherapy, cognitive-behavior treatment could be used in PD besides of pharmaceutical methods. PD patients with apathy would likely benefit from psychotherapeutic treatment that encourages structured, goal-directed plans for pleasurable events and stimulation that provide adaptive hedonistic effects (Jordan et al., 2013). Alternative types of non pharmacological methods as music, aroma, light, activation, multi-sensor therapy are not enough investigated.

Pharmacotherapy and non pharmacological methods should be conducted by active interaction with relatives or medical stuff. The complex of neuro-reabilitation methods must include motor, cognitive and social activation of patients.

Conclusions

The present study confirmed that apathy is the frequent sign of neuropsychiatric disorders in patients with PD without dementia. We suppose the common pathophysiological mechanisms between apathy and hypokinesia. We suggest that apathy in PD is heterogeneous because of the variability of the connections between apathy, depression, executive functions and sleep disorders on different stages of PD. It was shown the negative influence of apathy on daily activity, emotional and cognitive aspects of life quality. The valuable influence of apathy on life quality makes very perspective the future investigations in order to find the possible treatment. The limitations of our investigation are – not very large number of patients with apathy, no data of the dynamic on dopaminergic treatment in patients with PD. Despite limitations, the current results have important implications for conception of pathophysiology of PD, the heterogeneity of apathy on different stages of PD, influence on life quality of patients.

Compliance with ethics guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional-(University committee of ethical standards 15.12.2011 (N11-11) in the field of dissertation “Neuro-psychiatric disorders in Parkinson disease and their influence on the quality of life) and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study. Marina Nodel, Nikolay Yahno, Anastasia Medvedeva and Michail Kulikov declare that they have no conflict of interests.

References

Aarsland D, Larsen J P, Lim N G, Janvin C, Karlsen K, Tandberg E, Cummings J L (1999). Range of neuropsychiatric disturbances in patients with Parkinson’s disease. J Neurol Neurosurg Psychiatry, 67 (4): 492–496

Aarsland D, Mosimann U P, McKeith I G (2000). Role of cholinesterase inhibitors in Parkinsons disease and dementia with Lewy bodies. J

Geriatr Psychiatry, 15(5): 387–392

Alexander G E, Crutcher M D, DeLong M R (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res, 85: 119–146

Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello T P, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio R M, Giglia R M, Iemolo F, Manfredi M, Meco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri F E, Quatrale R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio A R, Stocchi F, Trianni G, Dotto P D, the PRIAMO study group (2009). The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord, 24(11): 1641–1649

Beck A T, Streer R A, Brown K G, (1996). Manual for the Beck Depression Inventory –II. San Antonio, TX: Psychological Corporation

Benito-León J, Cubo E, Coronell C, the ANIMO Study Group (2012). Impact of apathy on health-related quality of life in recently diagnosed Parkinson's disease: the ANIMO study. Mov Disord, 27 (2): 211–218

Bogart K R (2011). Is apathy a valid and meaningful symptom or syndrome in Parkinson's disease? A critical review. Health Psychol, 30(4): 386–400

Bonelli R M, Cummings J L (2007). Frontal-subcortical circuitry and behavior. Dialogues Clin Neurosci, 9(2): 141–151

Aarsland D, Brønnick K, Alves G, Tysnes O B, Pedersen K F, Ehrt U, Larsen J P (2009). The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. J Neurol Neurosurg Psychiatry, 80(8): 928–930

Brown R G, Dittner A, Findley L, Wessely S C (2005). The Parkinson fatigue scale. Parkinsonism Relat Disord, 11(1): 49–55

Campbell J J, Duffy J D (1997). Treatment strategies in amotivated patients. Psychiatr Ann, 27(1): 44–49

Carriere N, Besson P, Dujardin K, Duhamel A, Defebvre L, Delmaire C, Devos D (2014). Apathy in Parkinson's disease is associated with nucleus accumbens atrophy: A magnetic resonance imaging shape analysis. Mov Disord, 14: 1–7

Carver C S, White T L (1994). Behavior inhibition, behavior activation, and affective responses to impending reward and punishment: the BIAS/BAS scales. J Pers Soc Psychol, 67(2): 319–333

Cummings J L, Mega M, Gray K, Rosenberg-Thompson S, Carusi D A, Gornbein J (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology, 44(12): 2308–2314

Chaudhuri K R, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, Pezzela F R, Forbes A, Högl B, Trenkwalder C (2002). The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry, 73(6): 629–635

Czernecki V, Schüpbach M, Yaici S, Lévy R, Bardinet E, Yelnik J, Dubois B, Agid Y (2008). Apathy following subthalamic stimulation in Parkinson disease: a dopamine responsive symptom. Mov Disord, 23(7): 964–969

Dujardin K, Sockeel P, Delliaux M, Destée A, Defebvre L (2009). Apathy may herald cognitive decline and dementia in Parkinson's disease. Mov Disord, 24(16): 2391–2397

Fahn S, Elton R L, the UPDRS Development Committee(1987). Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden C D, Calne D B, Goldstein M, eds. Recent Developments in Parkinson's Disease. Florham Park, NJ: Macmillan, 153–163

Gallagher D A, Lees A J, Schrag A (2010). What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? Mov Disord, 25(15): 2493–2500

Hughes A J, Daniel S E, Kilford L, Lees A J (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry, 55(3): 181–184

Johns M W (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep, 14(6): 540–545

Jordan L L, Zahodne L B, Okun M S, Bowers D (2013). Hedonic and behavioral deficits associated with apathy in Parkinson's disease: potential treatment implications. Mov Disord, 28(9): 1301–1304

Kirsch-Darrow L, Fernandez H H, Marsiske M, Okun M S, Bowers D (2006). Dissociating apathy and depression in Parkinson disease. Neurology, 67(1): 33–38

Le Jeune F, Drapier D, Bourguignon A, Péron J, Mesbah H, Drapier S, Sauleau P, Haegelen C, Travers D, Garin E, Malbert C H, Millet B, Vérin M (2009). Subthalamic nucleus stimulation in Parkinson disease induces apathy: a PET study. Neurology, 73(21): 1746–1751

Leroi I, David R, Robert P H(2012). Apathy in Parkinsons disease. In: Edmeier K P, Obriien J T, Taylor J-P, eds. Psychiatry of in Parkinsons Disease. Adv Biol Psychiatry. Basel, Karger, 27: 27–40

Levy M L, Cummings J L, Fairbanks L A, Masterman D, Miller B L, Craig A H, Paulsen J S, Litvan I (1998). Apathy is not depression. J Neuropsychiatry Clin Neurosci, 10(3): 314–319

Levy R, Dubois B (2006). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex, 16(7): 916–928

Marin R S (1990). Differential diagnosis and classification of apathy. Am J Psychiatry, 147(1): 22–30

Marin R S, Biedrzycki R C, Firinciogullari S (1991). Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res, 38(2): 143–162

Marinus J, Visser M, Verwey N A, Verhey F R J, Middelkoop H A M, Stiggelbout A M, van Hilten J J (2003). Assessment of cognition in Parkinson's disease. Neurology, 61(9): 1222–1228

Martinez-Martin P, Schapira A H V, Stocchi F, Sethi K, Odin P, MacPhee G, Brown R G, Naidu Y, Clayton L, Abe K, Tsuboi Y, MacMahon D, Barone P, Rabey M, Bonuccelli U, Forbes A, Breen K, Tluk S, Olanow C W, Thomas S, Rye D, Hand A, Williams A J, Ondo W, Chaudhuri K R (2007). Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. Mov Disord, 22 (11): 1623–1629

McKinlay A, Grace R C, Dalrymple-Alford J C, Anderson T, Fink J, Roger D (2008). A profile of neuropsychiatric problems and their relationship to quality of life for Parkinsons disease. Park Relat Disord, 14: 37–42

Mulin E, Leone E, Dujardin K, Delliaux M, Leentjens A, Nobili F, Dessi B, Tible O, Agüera-Ortiz L, Osorio R S, Yessavage J, Dachevsky D, Verhey F R J, Cruz Jentoft A J, Blanc O, Llorca P M, Robert P H (2011). Diagnostic criteria for apathy in clinical practice. Int J Geriatr Psychiatry, 26(2): 158–165

Narabayashi H (1999). Akinesia in parkinsonism. In: Joseph A B, Young R R (Eds.). Movement disorders in Neurology and neuropsychiatry.

2nd ed. Oxford: Blackwell Science, 185–188

Neugarten B L, Havighurst R J, Tobin S S(1968). Personality and pattern of aging, in middle age and aging. University of Chicago Press

Nodel M R, Yahno N N (2009). Nevropsichiatricheskie zabolevania pri bolezni Parkinsona. Nevrologia. Psihiatria. Psyhosomatika. (Neuropsychiatric disorders in Parkinson disease. Neurology. Neurology. Neuropsychiatry. Psychosomatic), 2: 3–8

Nodel M R, Rusakova I M, Yakhno N N(2010). Klinicheskaya otsenka narushenii sna i bodrstvovaniya pri bolezni Parkinsona. Nevrologicheskii zhurnal (Clinical evaluation of sleep and alert disorders in PD. Journal of Neurology-Russian), 2: 19–25

Oguru M, Tachibana H, Toda K, Okuda B, Oka N(2010). Apathy and depression in Parkinsons disease. J Geriatric Psych Neurol, 23: 35–41

Pedersen K F, Larsen J P, Alves G, Aarsland D (2009). Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study. Parkinsonism Relat Disord, 15(4): 295–299

Pedersen K F, Alves G, Aarsland D, Larsen J P (2009). Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. J Neurol Neurosurg Psychiatry, 80(11): 1279–1282

Peto V, Jenkinson C, Fitzpatrick R (1998). PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. J Neurol, 245(Suppl 1): S10–S14

Pluck G C, Brown R G (2002). Apathy in Parkinsons disease. British Medical J, 73: 636–642

Postuma R B, Bertrand J A, Montplaisir J, Desjardins C, Vendette M, Rios Romenets S, Panisset M, Gagnon J F (2012). Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. Mov Disord, 27(6): 720–726

Reijnders J S, Ehrt U, Lousberg R, Aarsland D, Leentjens A F G (2009). The association between motor subtypes and psychopathology in Parkinson's disease. Parkinsonism Relat Disord, 15(5): 379–382

Reijnders J S, Scholtissen B, Weber W E, Aalten P, Verhey F R J, Leentjens A F G (2010). Neuroanatomical correlates of apathy in Parkinson's disease: A magnetic resonance imaging study using voxel-based morphometry. Mov Disord, 25(14): 2318–2325

Remy P, Doder M, Lees A, Turjanski N, Brooks D (2005). Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain, 128(Pt 6): 1314–1322

Robbins T W, Everitt B J (1996). Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol, 6(2): 228–236

Robert P, Onyike C U, Leentjens A F G, Dujardin K, Aalten P, Starkstein S, Verhey F R J, Yessavage J, Clement J P, Drapier D, Bayle F, Benoit M, Boyer P, Lorca P M, Thibaut F, Gauthier S, Grossberg G, Vellas B, Byrne J (2009). Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. Eur Psychiatry, 24(2): 98–104

Shore D M, Rafal R, Parkinson J A (2011). Appetitive motivational deficits in individuals with Parkinson's disease. Mov Disord, 26(10): 1887–1892

Singer E (1973). Social costs of Parkinson's disease. J Chronic Dis, 26 (4): 243–254

Smith M C, Smith M K, Ellgring H (1996). Spontaneous and posed facial expression in Parkinson's disease. J Int Neuropsychol Soc, 2 (5): 383–391

Sockeel P, Dujardin K, Devos D, Denève C, Destée A, Defebvre L (2006). The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. J Neurol Neurosurg Psychiatry, 77(5): 579–584

Spielberger C D, Gorsuch R L, Lushene R V (1983). Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press

Starkstein S E, Mayberg H S, Preziosi T J, Andrezejewski P, Leiguarda R, Robinson R G (1992). Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci, 4 (2): 134–139

Starkstein S E, Jorge R, Mizrahi R, Robinson R G (2006). A prospective longitudinal study of apathy in Alzheimer's disease. J Neurol Neurosurg Psychiatry, 77(1): 8–11

Tekin S, Cummings J L (2002). Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J Psychosom Res, 53(2): 647–654

Thobois S, Lhommée E, Klinger H, Ardouin C, Schmitt E, Bichon A, Kistner A, Castrioto A, Xie J, Fraix V, Pelissier P, Chabardes S, Mertens P, Quesada J L, Bosson J L, Pollak P, Broussolle E, Krack P (2013). Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. Brain, 136(Pt 5): 1568–1577

Vendette M, Gagnon J F, Décary A, et al (2007). REM sleep behavior disorder predicts cognitive impairment in without dementia. Neurology, 69(19): 1843–1849

Vosnesenskaya T G (2013). The syndrom of apathy. Journal of Neurology-Russian, 3: 4–10

Weintraub D, Mavandadi S, Mamikonyan E, Siderowf A D, Duda J E, Hurtig H I, Colcher A, Horn S S, Nazem S, Ten Have T R, Stern M B (2010). Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. Neurology, 75(5): 448–455

Wongpakaran N, van Reekum R, Wongpakaran T, Clarke D (2007). Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. Ann Gen Psychiatry, 6 (1): 7