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Sleep Disorders in Patients with Dementia in Parkinson's Disease

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Dementia and psychotic diseases represent a common complication of Parkinson's disease (PD), occurring in 40–70% of cases. These complications are commonly accompanied by sleep disorders, which constitute non-motor manifestations of PD. The aims of the present work were to assess the relationship between the severity of daytime drowsiness and REM sleep behavior disorder on the one hand and the severity of cognitive deficits and hallucinations on the other; to compare methods for assessing sleep impairments in Parkinson's disease using questionnaires and polysomnograms; and to evaluate the effects of treatment with galantamine in sleep disorders. A number of scales (MMSE, FAB, ESS, PDSS), as well as polysomnographic investigations, were used to assess sleep and cognitive functions in 26 patients with PD with dementia before and after treatment with galantamine. The results revealed a significant negative correlation between the severity of sleep disorders (increased daytime drowsiness and REM sleep behavior disorder) with hallucinations and cognitive deficits. Treatment with galantamine produced significant improvements in the quality of nocturnal sleep (restoration of its structure, decreased fragmentation), with reductions in the severity of REM sleep behavior disorder and decreases in daytime drowsiness, along with reductions in cognitive deficits and hallucinations.

Keywords: Parkinson's disease, dementia, sleep disorders, cognitive deficits, hallucinations, galantamine.

Classical signs of Parkinson's disease (PD) include motor impairments such as hypokinesia, rigidity, tremor, and postural abnormalities. However, recent years have seen increasing recognition that the clinical picture of PD is not restricted to motor disorders. Successes in the symptomatic treatment of Parkinson's disease, with increases in the longevity of patients with this disease, have made it clear to physicians that as PD progresses, the so-called non-motor symptoms become ever more apparent. These include cognitive impairments, sleep disorders, mental disorders (hallucinations, depression), fatigue, and many others.

Dementia is seen in 40–70% of PD patients. Damage to dopaminergic neurons in the medial part of the substantia nigra and dopaminergic neurons in the ventral tegmental area, which form the mesocortical pathway, is significant in the formation of dementia, as are damage to noradrenergic neurons in the locus ceruleus and the progressive death of cholinergic neurons in the basal nucleus of Meynert and the cerebral cortex. The pathogenesis of the death of cholinergic and other neuron populations involves excitotoxic mechanisms associated with chronic tonic stimulation of NMDA glutamate receptors and the subsequent development of secondary hypofunction of the glutamatergic neurotransmitter system. Thus, the interaction of the glutamatergic and cholinergic systems is of particular interest for investigators [2].

Sleep disorders are seen in 80–90% of PD patients. These affect the whole of the sleep–waking cycle [18] and can consist of sleep fragmentation, increased daytime drowsiness, and REM sleep behavior disorder. Insomnia is present in 60–98% of patients with PD [14] and consists of structural sleep impairments and fragmentation (frequent

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waking). Sleep fragmentation in PD is more frequent than other disorders and is directly dependent on the Hoehn and Yahr stage of the disease [34]. The causes of secondary insomnia may include nocturnal rigidity, tremor, dyskinesia, and restless legs syndrome. These cases require correction of dopaminergic treatment. Hypersomnia consists of increased daytime drowsiness, which occurs in 15–50% of PD patients [21]. Some patients develop attacks of suddenly falling asleep, as seen in narcolepsy (rapid falling asleep during the day, with onset of REM sleep) [10]. There are some data indicating a relationship between daytime drowsiness and the severity of cognitive deficits and hallucinations in PD [15, 51].

The pathogenesis of increased daytime drowsiness in PD remains incompletely understood. The question of impairments to the cyclicity of acetylcholine levels has been addressed as one possible mechanism of the development of this disorder. Several groups of neurons, located in the brainstem, are involved in maintaining the cyclicity of sleep and waking. During waking, the aminergic (noradrenaline and serotonin) system is dominant, though the histaminergic and cholinergic systems are also in the active state. Brain acetylcholine levels undergo circadian oscillations. Maximal concentrations occur during arousal and waking, decreasing significantly during slow-wave sleep. Animals experiments have demonstrated that the peak of acetylcholine release from the primary somatosensory cortical fields correlates with the maximal level of behavioral activity [16]. Experiments on cats have also demonstrated that acetylcholine production in the cortex and hippocampus increases during waking and REM sleep as compared with slow-wave sleep. It can be suggested that patients with PD complicated by daytime drowsiness have decreases in acetylcholine concentrations.

Among all the types of sleep disorders in PD, there is particular interest in impairments associated with the REM phase, particularly parasomnia, which was first described in cats [31]. Later, in 1986, Schenck et al. [37] described this syndrome in humans.

The neuropharmacology of sleep disorders in the REM phase have mainly been studied in animal experiments. Summarizing the experimental results, Boeve et al. [12] suggested that there are two groups of neurons responsible for controlling the REM phase in humans: those generating this phase (REM-on) and those blocking it (REM-off). REM-on neurons include cells in the cholinergic pedunculopontine and laterodorsal nuclei of the tegmentum, where decreases in activity can lead to impairments to the generation of the REM phase. This suggestion is supported by the studies of Albin et al. [5], in which the use of positron emission tomography (PET) demonstrated decreases in activity in the pedunculopontine nuclei in patients with behavioral disorder during this phase.

These sleep disorders were for a long time diagnosed only on the basis of clinical signs, though in 2005 the American Academy of Sleep Medicine recommended the use of polysomnographic investigations for their detection. The diagnostic criteria for this disorder in terms of the International Classification of Sleep Disorders (ICSD-2) [6] are: 1) the presence of a REM phase without atonia, defined as prolonged or periodic increases in tone on EMG recordings from the chin, or increases in phasic muscle activity on EMG recordings from the legs; 2) the presence of at least one of the following signs: a) history of behavior leading to or capable of leading to trauma during sleep; b) impairments to the REM phase identified by polysomnography; 3) the absence of epileptiform activity on the EEG; 4) these impairments cannot be due to neurological or somatic diseases, mental disorders, or use of medications.

Impairments to sleep in the REM phase occur more frequently in men aged 50–65 years and are apparent as vocalization, cries, and swearing during sleep; motor activity varies from single thrusts to complex movements; dream content often consists of pursuit or attacks by animals or humans, inducing the corresponding behavior on the part of the patient [17]. These impairments have a tendency to appear in the later part of the sleep period.

Sleep disorders in the REM phase are divided on the basis of their origin into idiopathic and secondary, though it is not entirely clear whether the idiopathic form of behavioral impairment exists or whether it is a cryptogenic variant of this pathology. Thus, autopsies of patients with the presumptive idiopathic form of behavioral impairment in this phase revealed Lewy bodies [5, 46]. Additional evidence against the idiopathic form of this impairment is provided by the fact that 38–65% of subjects with suspected REM sleep behavior disorder develop synucleinopathy 10–29 years after manifestation. This is most commonly associated with PD, Lewy body dementia, and multisystems atrophy [22, 35, 40, 42]. These impairments may also be associated with the use of various substances or with their withdrawal. Studies have been reported presenting data on the development of this syndrome in patients taking various antidepressants (paroxetine, fluoxetine, imipramine, venlafaxine, mirtazapine) [33, 34, 39, 44].

There are as yet no clear recommendations for the treatment of sleep impairments in PD [9]. A multitude of agents with different mechanisms of action have been proposed to combat daytime drowsiness. Given that these sleep disorders can be encountered simultaneously in a single patient, there is a need to prescribe an agent with complex actions against this pathology. Positive results have been obtained [1, 25, 48] in the treatment of daytime drowsiness in patients with PD using the selective noradrenaline reuptake inhibitor atomoxetine. This agent has also been found to be effective in correcting cognitive impairments in this group of patients. There are no data on the effects of atomoxetine on REM sleep behavior disorder.

Clonazepam has been proposed for the treatment of sleep disorders and the behavioral disorders described

above. However, it should be used with caution in patients with dementia [41], gait abnormalities [33], and obstructive sleep apnea syndrome (OSA) [43]. Increases in daytime drowsiness have also been seen during clonazepam treatment [49]. Selection of the clonazepam dose must be gradual and careful. Treatment with clonazepam has been found to be effective in patients with synucleinopathy [20, 33, 44]. The mechanism of action of clonazepam in behavioral impairments is unknown. Clonazepam has no effect on the pathogenesis of REM sleep behavior disorder [27], as it acts selectively on physical motor activity regulated by the brainstem, without affecting the serotoninergic or acetylcholinergic mechanisms of development of atonia [24, 38]. The clinical effect of clonazepam can be summarized in terms of the order of decreasing influences on the symptoms of behavioral impairments: sudden movements, loud vocalizations → complex non-energetic movements → simple limb or body movements → increased EMG activity during the REM phase.

Melatonin has also been used to treat these impairments; this clearly differs from clonazepam in producing fewer side effects. Studies reporting successful treatment of sleep disorders in patients with synucleinopathy [11, 23], memory impairments [7, 8, 23], and OSA [7, 8] have appeared. Dose-dependent side effects include headache, morning drowsiness, and hallucinations [11]. Polysomnography on the background of melatonin treatment showed reductions in the number of REM periods without atonia [23, 45], in contrast to clonazepam [24].

Data on impairments to the functions of the dopaminergic nigrostriatal system in patients with the idiopathic form identified using PET scans [5] and spectroscopy [17] led to attempts to treat this pathology with dopamine D_2–D_3 receptor agonists. The actions of dopaminergic substances on sleep structure are dose-dependent (increases in the durations of the slow-wave and REM phases of sleep and, consequently, the development of drowsiness during treatment with low doses; reductions in sleep duration using high doses) [4, 13]. Use of dopamine receptor D_2–D_3 agonists can disturb the sleep–waking cycle, leading to the development of insomnia and more intense sleep fragmentation. There is a multitude of contradictory reports on the effects of pramipexole on sleep disorders in PD. Results from Russian studies [3, 4] noted significant improvements in sleep quality on the background of pramipexole treatment assessed by self-assessment by PD patients (decreases in the frequency of disorders of falling asleep, reductions in the numbers of nocturnal wakings). Patients noted moderate drowsiness.

Particular attention has recently been paid to a group of acetylcholinesterase inhibitors (iAChE) in the treatment of sleep disorders in PD patients. We have already noted the involvement of acetylcholine in regulating sleep. The use of iAChE is justified in hypersomnia, as they normalize the sleep–waking cycle. In fact, there is a report [32] indicating positive effects with iAChE in terms of reductions in the severity of narcolepsy. Data showing decreases in daytime drowsiness during treatment with the iAChE donepezil have been reported [32]. The fact that sleep disorders in the REM phase occur in conditions of damage to the regulatory cholinergic system is well established [36]. There are many reports demonstrating the efficacy of iAChE in such cases – in Lewy body dementia [19, 26, 29] and Alzheimer's disease [19, 26, 30]. Treatment of sleep disorders in PD with iAChE is preferred because of positive results obtained using galantamine in PD patients complicated by hypersomnia and dementia [2].

The aims of the present work were to assess the relationship between the severity of sleep disorders and cognitive impairments and hallucinations in PD, to identify the diagnostic potential of scales and questionnaires, and to perform polysomnographic studies with assessment of the potential for the treatment of REM sleep behavior disorder and increased daytime drowsiness in PD patients using galantamine.

Materials and Methods

Studies were performed at the Nervous Diseases Department and Clinic, St. Petersburg Military Medical Academy and at the A. M. Nikiforov All-Russia Center for Emergency and Radiation Medicine.

The study involved 26 patients (11 women and 15 men) with PD complicated by dementia, aged 66.6 ± 7.8 years, with durations of illness of 5.1 ± 1.2 years.

Inclusion criteria were: diagnosis of PD corresponding to the British Brain Bank; stage III disease on the Hoehn and Yahr scale; presence of dementia in accordance with ICD-10 criteria developing two years after the onset of PD; subjective complaints of sleep disorder; ability of patient to perform neuropsychological tests; access to a person able to provide continuous care for the patient. Exclusion criteria were the presence of significant cardiovascular diseases (alterations to cardiac rhythm), bronchial obstructive diseases, signs of liver and kidney pathology; use of cholinolytics, cholinesterase inhibitors, or nootropics; history of acute impairment to cerebral circulation in the six months prior to the study; presence of marked depression (>18 points on the Hamilton scale), delirium, and neuroimaging signs of focal vascular brain lesions in strategically important areas (thalamus, hippocampus, bilateral lacunae in the globus pallidus) and other organic brain lesions.

All patients were investigated using the following scales: the mini mental state examination (MMSE), the frontal assessment battery (FAB), the Parkinson's Disease Sleep Scale (PDSS), and the Epworth Sleepiness Scale (ESS).

A total of 17 patients also underwent complex polysomnographic investigations (PSI) with assessment of sleep efficiency (TST/TIB × 100%), where TIB is the time in bed and TST is the total sleep time, and the latency of onset of sleep (LS); in addition, the REM phase of sleep was investigated for behavioral impairments.

TABLE 1. Changes in the Severity of Cognitive Impairments, Sleep Disorders, and Hallucinations during Treatment with Galantamine ($M \pm SD$)

Parameter	Before treatment	End of 12 weeks of treatment
MMSE, points	24.0±3.2	26.1±4.7**
FAB, points	11.1±4.4	14.4±3.5**
ESS, points	9.5±4.9	2.4±2.0*
PDSS, total points	76.4±18.5	99.8±13.4**
7-point PDSS, points	6.5±2.9	8.8±1.3**
15-point PDSS, points	4.5±3.3	8.7±1.2
TST/TIB, %	57.3±12.3	83.0±11.4**
LS, min	9.7±5.1	19±1.4

Note. Significant differences compared with baseline: *$p < 0.001$; **$p < 0.005$.

In patients in whom sleep disorders were detected, ongoing treatment (Levodopa at a mean daily dose of 520.5 ± 250.5 mg) was supplemented with galantamine (Reminyl, Janssen Cilag) as 8-mg capsules in the morning for the first four weeks, followed by 16-mg capsules in the morning for four weeks, and then capsules of 24 mg in the morning to 12 weeks. In two patients, doses were not increased to 24 mg because of the development of side effects. At 12 weeks of galantamine treatment, patients were re-tested using the scales. Patients undergoing PSI before treatment underwent repeat PSI.

Results were processed statistically using a personal computer running Statistica for Windows 8.0. Significant differences between groups on repeat assessment of patients during the study and on comparison with baseline levels were identified by analysis of variance for repeat measures using nonparametric tests (Spearman's test, the Wilcoxon ranked test for paired comparisons (W)).

Results and Discussion

Increased daytime drowsiness was detected in 22 patients (84.5%). Mean measures were: ESS = 9.5 ± 4.9 points and 15-point PDSS = 4.5 ± 3.3 points. Measures of cognitive impairments were as follows: MMSE = 24.0 ± 3.2 points and FAB = 11.1 ± 4.4 points. These patients presented complaints of hallucinations (7-point PDSS = 6.5 ± 2.9 points). There were significant negative correlations between ESS and FAB ($r = –0.44$, $p < 0.05$) and between ESS and the 7-point PDSS ($r = –0.56$, $p < 0.05$). Assessment of daytime drowsiness using scales corresponded to assessments of the time of onset of sleep obtained on PSI: the latency of going to sleep averaged 9.7 ± 5.1 min, with rapid entry in sleep phase 2. A significant negative correlational relationship was identified between the ESS and the latency of going to sleep ($r = –0.62$; $p < 0.05$). Nocturnal sleep quality was reduced in all patients: the total points score on the PDSS was 76.4 ± 18.5. In 16 of the 17 patients (93%) who underwent PSI investigation of REM phases, impairments to sleep structure wee seen, with fragmentation, decreases in sleep quality apparent as increases in the duration of waking during sleeping time, and, thus, decreased sleep effectiveness: the TST/TIB ratio averaged 57.3 ± 12.3%, which corresponded to the results obtained on the PDSS. Sleep impairments in the REM phase were identified in 12 patients (80%). The severity of cognitive impairments in this group was significantly greater: MMSE = 22.3 ± 4.3 points and FAB = 6.2 ± 3.1 points ($p < 0.05$).

At 12 weeks of galantamine treatment, repeat investigations showed significant reductions in the severity of daytime drowsiness (improvement on the ESS, $p = 0.0006$), decreased sleep fragmentation, improved sleep quality (improvement on PDSS, $p = 0.0007$) and improved sleep effectiveness in terms of TST/TIB ($p = 0.0007$). No behavioral impairments during the REM phase were seen during treatment. There was also a decrease in the severity of hallucinations in terms of the 7-point PDSS ($p = 0.001$) and cognitive impairments on the MMSE ($p = 0.001$) and FAB ($p = 0.001$) (see Table 1).

Sleep disorders during the REM phase could be combined with cognitive impairments or could precede their development. Vendette et al. [47] published results in which of 34 patients with PD without dementia (mean disease duration 5 years), PSI confirmed behavioral impairments during the REM phase in 18, with significant reductions in verbal memory and visuospatial and executive functions as compared with 16 patients without these impairments. Marion et al. [28] reported a study of 65 patients with PD complicated and not complicated by dementia and found that 77% of patients with dementia had sleep impairments during the REM phase, while behavioral impairments were present in only 27% of patients without dementia. In addition, dementia developed in patients with sleep disorders during the REM phase at earlier ages than in those without these disorders.

The severity of sleep disorders was found to correlate with the severity of cognitive impairments and the presence of hallucinations. This observation can be explained by the common pathogenesis of these abnormalities, with involvement of the cholinergic system of the brain: sleep disorders appear at the second pathomorphological stage, where abnormalities in the acetylcholinergic pedunculopontine nuclei can arise. These non-motor manifestations may be

precursors of the onset of the third pathogenetic stage, which is marked by motor disorders. Cognitive impairments develop at subsequent stages. This supports the predictive value of non-motor manifestations and the need for their early diagnosis.

Measures of sleep disturbance assessed on the PDSS and ESS were consistent with PSI data, which reflects the high sensitivity of these scales in the diagnosis of sleep disorders in PD. These scales should be used in the routine investigation of PD patients because of the high predictive value of sleep disorders for the development of cognitive impairments and hallucinations.

During treatment with galantamine, there were significant reductions in the severity of daytime drowsiness and REM sleep behavior disorder, decreases in sleep fragmentation, and improvements in sleep quality. The need for using iAChE in sleep disorders in the REM phase in patients with PD is also linked with the high predictive value of these disorders for the subsequent development of dementia.

At the late stages of PD, one of the factors decreasing quality of life but inherent to the treatment of these patients is the frequent taking of large quantities of medications. Prescription of galantamine produces simultaneous reductions in a number of problems: is promotes correction of cognitive impairments and sleep disorders and decreases the severity of hallucinations, in some cases completely eliminating them.

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