INTRODUCTION. Sleep and circadian rhythm disturbances can occur at any stage of Parkinson disease (PD) and significantly affect quality of life. Chronotypes of patients with PD are associated with different phenotypes, in particular with the motor subtype. Thus, we hypothesized that patients with different motor subtypes of PD may have differences in the distribution of chronotypes and patterns of daily activity.

METHODS AND MATERIALS. We conducted clinical research on the basis of the Centre for Parkinson Disease and Neurodegenerative Diseases of the Department of Neurological Diseases of Poltava State Medical University. PD was verified according to the recommendations of the International Movement Disorders and Parkinson’s Disease Society. The motor subtype of PD was determined by the Stebbin method, which is based on the calculation of the Stebbins coefficient by the sum of the Unified PD Rating Scale scores. The examined patients were divided into three groups according to the motor subtype of PD: group 1 (n = 38) - patients with PD subtype with the predominance of postural instability and gait disorders (PIGD); group 2 (n = 26) - patients with PD subtype with the predominance of tremor and mixed subtype; control group (n = 30) - conditionally healthy individuals without CNS lesions. Circadian patterns were analyzed using the Munich Chronotype Questionnaire (MCTQ).

RESULTS. It was found that in PD patients sleep onset and time of getting out of bed was later (p<0.001 and p=0.042, respectively), sleep latency was longer (p<0.001), sleep duration was shorter (p=0.001), the mid-sleep corresponded to a later time (p<0.001). Patients with the PIGD subtype had a later time of getting out of bed (p=0.038), longer sleep inertia (p<0.001), shorter sleep duration (p<0.001), and later mid-sleep time (p=0.028). We have shown the tendency of patients with PD, mostly in the PIGD subtype, to later chronotypes (p<0.001). Light exposure indirectly moderately correlated with mid-sleep in all study groups. It was found that both the motor subtype (p<0.001) and the level of light exposure during the day (p<0.001) statistically significantly affect the mid-sleep.

CONCLUSION. Thus, we have found that patients with PD differ from age-matched controls without neurodegenerative diseases by chronotype and circadian pattern of functioning. The motor subtype of the disease is associated with circadian differences, namely, the PIGD subtype is associated with shorter sleep duration, a predisposition to a later chronotype, and longer sleep inertia.

KEY WORDS: circadian rhythm, sleep disorders, Parkinson disease, chronotype, light exposure, daily activity
Introduction

Neurodegenerative diseases are closely related to circadian rhythm disorders. It is assumed that there is a bidirectional relationship between them. Circadian disorders and sleep disorders exacerbate neurodegeneration, and neurodegenerative diseases, in turn, can disrupt circadian rhythms and sleep [6].

The most prevalent neurodegenerative disease is Parkinson’s disease (PD), characterized by impaired α-synuclein secretion and dopamine release, leading to mitochondrial dysfunction and energy metabolism disorders. The pathogenesis of PD is complex, but recent studies have indicated a crucial role of circadian dysfunction in this disease’s development and clinical features [1].

Almost all non-motor symptoms of PD are associated with circadian rhythm disorders. Circadian rhythm disorders are directly related to mental health, in particular anxiety and depression [3]. Recently, there has been increasing evidence that circadian rhythm disturbances are the main culprit for the onset of non-motor symptoms of PD. Sleep and circadian rhythm disturbances can occur at any stage of the disease and significantly affect the quality of life [5].

The circadian system, which contains a network of molecular clocks in the brain and peripheral organs, regulates the sleep-wake cycle in humans. The central pacemaker of the circadian system is the suprachiasmatic nucleus of the hypothalamus, receiving light stimuli through the retina, which is the strongest external time cue regulating the circadian rhythm. The interaction of the internal molecular clock with external time cues, such as light exposure, diet, physical activity, and genetic, metabolic, and behavioral factors, determines a human’s chronotype, defined as the pattern of activity throughout the day [12].

Chronotype can change over the course of a lifetime due to many factors, including age and environment. A decrease in circadian rhythm amplitude with age has been reported, which is associated with the development of neurodegenerative diseases. Individuals with PD have changes in the level of daily rest-activity rhythm, characterized by a decrease in daytime activity and nighttime rest due to a decrease in circadian rhythm amplitude [4].

Chronotypes of patients with PD are associated with different phenotypes of the disease, in particular with the motor subtype. It has been demonstrated that extreme chronotypes show significant differences in the prevalence of postural instability and gait disturbances [8]. Thus, we hypothesized that patients with different motor subtypes of PD may have differences in the distribution of chronotypes and daily activity patterns.

Materials and methods

We conducted clinical research based on the Centre for Parkinson’s Disease and Neurodegenerative Diseases of the Department of Neurological Diseases of Poltava State Medical University. All stages of the study were conducted with the participation of 64 patients with PD and 30 control subjects.

The study was approved by the Bioethics Committee of Poltava State Medical University and was conducted according to the principles of Good Clinical Practice (ICH E2(R6) GCP), the Ethical Code of Scientists of Ukraine, the Ethical Code of Physicians of Ukraine, and the Declaration of Helsinki of the World Health Organization. All patients provided informed voluntary consent to participate in the study.

The inclusion criteria for the study were clinically confirmed PD with Hoehn and Yahr stage <4, disease duration of more than 1 year, age from 45 to 89 years, and treatment with levodopa therapy. Exclusion criteria: probable PD, Hoehn and Yahr PD stage greater than 3, concomitant severe cerebrovascular, inflammatory or mental diseases, age 90 years and older, neurodegenerative lesions of the central nervous system, secondary parkinsonism.

PD was verified according to the recommendations of the International Movement Disorders and Parkinson’s Disease Society. The motor subtype of PD was determined by the Stebbins method, based on calculating the Stebbins coefficient by the sum of the Unified PD Rating Scale scores [13]. The examined patients were divided into 3 groups according to the motor subtype of PD:

Group 1 (n = 38) - patients with PD subtype with a predominance of postural instability and gait disorders (PIGD);

Group 2 (n = 26) - patients with PD subtype with a predominance of tremor and mixed subtype (non-PIGD);

Control group (n = 30) - conditionally healthy individuals without CNS lesions.

The patients belonging to Groups 1 and 2 were administered with levodopa/carbidopa 250/25 mg. This medication was administered in the form of half a tablet, four times a day. The administration period lasted throughout the day, and the medication was distributed at regular intervals.
Circadian patterns were analyzed using the Munich Chronotype Questionnaire (MCTQ) by calculating the following indicators: sleep onset, wake-up time, sleep duration, mid-sleep, average weekly sleep duration, chronotype, weekly sleep deficit (for workers), relative jet lag (for workers), and average weekly light exposure. All these parameters were measured in hours and minutes and converted to fractions of one for statistical processing. The chronotype before 1:00 corresponded to the early type, from 1:01 to 2:00 to the intermediate type, and from 2:01 to the late type [11].

Statistical analysis was performed using IBM SPSS Statistics 23.0. The normality of the distribution was assessed by the Shapiro-Wilk test. Quantitative indicators are presented as medians with an interquartile range (25-75%) (Me (Q1; Q3)), and categorical indicators as absolute and relative values. The Kruskal-Wallis test with pairwise comparison by Dunn's test and Pearson's Chi-square with Bonferroni correction were used to compare the three groups. Correlation analysis was performed by using Spearman's rank test. To analyze the relationship between the two variables, considering the covariates, we performed an Analysis of Covariance (ANCOVA) with a preliminary analysis of Levene's test and White's criterion.

**Results**

Patients in the groups were matched by age, sex and disease severity (Table 1).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Groups</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (M±SD)</td>
<td>Group 1 (n=38)</td>
<td>0.167</td>
</tr>
<tr>
<td></td>
<td>Group 2 (n=26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 3 (n=30)</td>
<td></td>
</tr>
<tr>
<td>Sex, abs. (%)</td>
<td>M</td>
<td>0.719</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>UPDRS score (Me (Q1; Q3))</td>
<td>47.5 (32.5; 64.5)</td>
<td>0.640</td>
</tr>
<tr>
<td></td>
<td>38.0 (31.8; 60.3)</td>
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The studied groups showed no significant differences in terms of age, sex, and disease severity.

According to the results obtained, patients with PD went to bed at 20:46 (20:25; 21:22), and in group 3 at 20:56 (20:13; 21:06). At the same time, patients in group 1 reported going to bed at 20:46 (20:23; 21:22) on average, and in group 2 at 20:46 (20:25; 21:40). Along with this, patients with PD noted that they were getting ready for sleep at 22:05 (21:30; 22:29), in particular in group 1 at 22:16 (21:37; 22:31) and in group 2 at 22:00 (21:25; 22:20), and in group 3 at 21:21 (21:05; 22:17). The time of the onset of sleep in people with PD was 22:20 (22:16; 23:24), namely in group 1 at 23:00 (22:30; 23:30) and in group 2 at 22:30 (22:08; 22:52), while in group 3 it was at 21:29 (21:08; 22:20).

We did not find statistically significant differences between the groups in terms of the time at which patients go to bed (p=0.654) or are about to start sleeping (p=0.053). Patients with PD were found to have a later sleep onset time compared to group 3 (p=0.001) both in group 1 (p=0.001) and group 2 (p=0.006). However, there were no differences between different motor subtypes (p=0.162).

Patients with PD woke up on average at 5:50 (5:33; 6:28), in particular in group 1 at 5:55 (5:44; 6:46) and in group 2 at 5:50 (5:23; 6:07), and in group 3 at 5:44 (5:10; 6:11). In addition, the time at which patients get out of bed in patients with PD was 6:07 (5:49; 6:34), namely in group 1 at 6:10 (6:00; 7:02) and in group 2 at 6:00 (5:30; 6:19), and in group 3 at 5:55 (5:14; 6:21).

It was found that the time of waking up did not differ between the study groups (p=0.055). However, getting out of bed in patients with PD was later (p=0.042). Patients in group 1 demonstrated a later time of getting out of bed compared to group 2 (p=0.038) and group 3 (p=0.011), while there were no statistically significant differences between groups 2 and 3 (p=0.981).

The sleep latency in patients with PD was 42.5 (30.0-85.0) minutes (47.5 (33.8-90.0) minutes in group 1 and 40.0 (10.0; 52.5) minutes in group 2, and in group 3 was 5.0 (2.0-10.0) minutes. The period for patients to get out of bed after waking up, known as sleep inertia, was 15.0 (10.0; 20.0) min, in particular in group 1 was 15 (10.0; 20.0) min and in group 2 was 10 (4.5; 15.0) min, and in group 3 was 10 (5.0; 10.0) min.

We found a longer sleep latency period in patients with PD (p<0.001) compared with group 3. At the same time, patients with both motor subtypes demonstrated a longer sleep latency (p<0.001 in both group 1 and group 2), but no significant differences were found between them (p=0.066). The sleep inertia was statistically different between the groups (p=0.001). In group 1, it was longer compared to groups 2 (p<0.001) and 3 (p<0.001), while the data...
of patients in groups 2 and 3 did not differ statistically (p=0.987).

Among the study subjects, 14 people (36.8%) in group 1, 12 people (46.2%) in group 2, and 8 people (26.7%) in group 3 use an alarm clock. There were no statistically significant differences in the frequency of alarm clock use in the study groups ($\chi^2=2.30$, df=2, p=0.316).

The duration of sleep in patients with PD was 7:15 (6:25; 7:48), in particular in group 1 - 6:53 (6:22; 7:52) and in group 2 - 7:20 (6:37; 7:53) and group 3 - 7:53 (7:14; 9:12). While the total time spent in bed in PD was 9:16 (8:43; 9:49), namely 9:35 (8:52; 10:04) for group 1 and 9:00 (8:23; 9:40) for group 2, and in group 3 - 9:06 (8:22; 9:49).

A shorter sleep duration was found in PD (p=0.001). Patients in group 1 were characterized by a shorter sleep duration compared to group 3 (p=0.003). However, there were no statistically significant differences between groups 1 and 2 (p=0.878) or between groups 2 and 3 (p=0.093). The total time spent in bed did not differ between the study groups (p=0.092).

The mid-sleep time was 2:24 (2:00; 2:49) for patients with PD (2:39 (2:11; 3:07) for group 1 and 2:08 (1:49; 2:37) for group 2) and 1:36 (1:16; 2:05) for group 3. It was found that in PD, the mid-sleep occurs later compared to group 2 (p=0.028) and group 3 (p=0.001), and in group 2, later than in group 3 (p=0.029).

According to the mid-sleep, we determined the patients' chronotypes. In group 1, we identified 6 patients (15.8%) with a moderately early chronotype, 22 patients (57.9%) with a slightly early chronotype, 9 patients (23.7%) with an intermediate chronotype, and 1 patient (2.6%) with a slightly late chronotype. In group 2, 1 person (3.8%) was identified with an extremely early chronotype, 10 people (38.5%) with a moderately early chronotype, and 15 people (57.7%) with a slightly early chronotype. Among patients in group 3, 1 person (3.3%) was identified with an extremely early chronotype, 20 people (66.7%) with a moderately early chronotype, and 9 (30.0%) with a slightly early chronotype (Fig. 1).

Statistically significant differences in the distribution of chronotypes between the study groups were found ($\chi^2=30.67$, df=8, p<0.001), namely, the tendency of patients in group 1 to later types.

In total, 54 patients (84.4%) with morning types, 9 patients (14.1%) with intermediate types, and 1 patient (1.5%) with evening types were identified among patients with PD, which significantly differed from group 3, in which all 30 patients (100.0%) had morning chronotypes ($\chi^2=16.49$, df=4, p=0.002).

The average duration of light exposure was 2:15 (1:42; 5:00) for people with PD (4:00 (3:00; 6:00) for group 1 and 4:00 (2:48; 6:00) for group 2), and 5:00 (3:00; 5:00) for group 3. A shorter duration of light exposure was found in patients with PD (p<0.001), namely in group 1 compared to group 2 (p=0.047) and group 3 (p=0.044). At the same time, no differences were found between groups 2 and 3 (p=0.643).

We conducted a correlation analysis between the mid-sleep and the duration of light exposure. In group 1, a moderate indirect correlation was found (r=-0.576, p=0.001) (Fig. 2).
In patients of group 2, an indirect moderate correlation was also determined ($r=-0.573$, $p=0.002$) (Fig. 3).

An indirect moderate correlation between these parameters was also found in group 3 ($r=-0.510$, $p=0.001$) (Fig. 4).
We performed the covariance analysis to evaluate the relationship between mid-sleep and motor subtype, considering light exposure. The Levene's test confirmed the equality of variance (p=0.365). The absence of heteroscedasticity was confirmed by White's criterion (p=0.117). It was found that both the motor subtypes statistically significantly affect the time of mid-sleep (p<0.001) and the level of light exposure during the day (p<0.001). At the same time, light exposure accounts for 29.7% of the variance, and the motor subtype for 28.3%. Considering both factors, the combined model describes 50.4% of the variance of patients' mid-sleep. Adjusted for the mean light exposure value, the patients' mean sleep time in group 1 was 2:32±0:05, in group 2 - 2:14±0:06, and in group 3 - 1:47±0:06.

Statistically significant differences were found in the adjusted mid-sleep time between the groups, namely, in group 1, this time was later compared to group 2 (p=0.030) and group 3 (p=0.001), and in group 2 later than in group 3 (p=0.001).

**Discussion**

Approximately 90% of patients with PD suffer from sleep and circadian rhythm disorders. Circadian dysregulation has been reported to contribute to poor sleep and concentration. Moreover, most of the motor and non-motor symptoms of PD show diurnal fluctuations, emphasizing the important role of circadian rhythms in the pathogenesis of PD [9].

We have found that patients with PD have a later sleep onset than people of the same age without PD due to increased sleep latency. At the same time, patients with the PIGD subtype of PD have a longer sleep latency than those with the non-PIGD subtype. In addition, patients with the PIGD subtype have a shorter sleep duration, get out of bed later, and have a longer period of getting up, which may be due to morning akinesia. We have found that the frequency of alarm clock use in PD does not differ from individuals of the corresponding age and does not affect the period of getting up.

A previous meta-analysis found a significant reduction in total sleep duration, sleep efficiency, and increased rapid eye movements phase (REM) sleep latency in patients with PD compared to controls [16].

In our study, we determined that patients with PD have a later mid-sleep time, with a later mid-sleep in patients with the PIGD subtype than in patients with the non-PIGD subtype of PD. This is indicated by the distribution of chronotypes between the groups and demonstrates the tendency of the PIGD subtype group to later chronotypes, which may be due to a later sleep onset time due to an increase in its latency period.

Previous studies have also found that most patients with PD belong to the morning chronotype, while patients with the evening chronotype have a longer sleep latency. During the life cycle, the chronotype can change under the influence of age and social changes, and, in particular, aging and PD can cause not only a change in the chronotype but also a dysregulation of circadian rhythms due to reduced melatonin rhythms amplitude and sleep fragmentation [9]. At the same time, studies of the circadian profile and phenotypes of PD revealed a higher prevalence of PIGD among patients with an evening chronotype, which is consistent with the results of our study [8].
We analyzed the mid-sleep in the groups considering the duration of light exposure. The adjusted values confirm the tendency of individuals with the PIGD subtype of PD to have a later mid-sleep compared to the non-PIGD subtype and the control group and also indicate a later mid-sleep onset time in the non-PIGD subtype group compared to individuals of the same age without PD.

Solar light remains one of the main zeitgebers for the human circadian system, despite the growing detachment of society from the natural light-dark cycle. The chronotype is known to be affected by the time of light exposure: morning light advances the circadian rhythm, while evening light delays it. However, recent research suggests that the entrainment phase also depends on the nature of the light. For example, increased exposure to natural light accelerates the entrainment phase in all people [14]. Increasing the time spent outdoors leads to an increase in the photic strength of the Zeitgeber and correlates with the chronotype: the more time spent outdoors, the earlier the chronotype [10].

Despite the novels of our study, it has some limitations. Firstly, patients in the group were not matched by the lifestyle factors that may influenced circadian measurements. Secondly, we did not use objective methods for the assessment of circadian rhythms such as melatonin or cortisol rhythms, actigraphy, or polysomnography. That is why we also could not exclude sleep apnea, restless leg syndrome, or REM behavior disorder, which may impact subjective assessments of sleep.

Therefore, we found that patients with PD not only differ from controls of the same age without neurodegeneration but also there are differences in circadian regulation between phenotypes of the disease. The association of the PIGD subtype with later mid-sleep may be one of the factors contributing to the higher severity of non-motor symptoms in these patients. We also found an increased sleep latency, which may occur against the background of the decreased amplitude of melatonin rhythm or clock gene expression changes [2]. This explains exogenous melatonin’s efficacy in improving sleep quality in PD patients, which was shown in a meta-analysis [7,15]. Reducing the level of light exposure affects the middle of sleep, which is confirmed by our and other studies. Thus, behavioral interventions and daytime activity regimens may be potentially useful for PD patients.

Conclusions

Patients with PD differ from age-matched controls without neurodegenerative diseases by chronotype and circadian pattern of functioning. They have a later sleep onset and time to get out of bed, longer sleep latency, shorter sleep duration, and a later mid-sleep. The predominance of later chronotypes in PD was found against the background of the general dominance of the morning chronotype in all groups. The motor subtype of the disease is associated with circadian differences; namely, the PIGD subtype is associated with shorter sleep duration, a predisposition to a later chronotype, and longer sleep inertia.

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Conflict of interest:
The authors declare no conflict of interest

Ethical statement:
This research was approved by the Commission on Biomedical Ethics of Poltava State Medical University (minutes No.219 as of 29 September 2023).

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ХРОНТИП ТА ДЕННЕ ФУНКЦІОНАВАННЯ ПАЦІЄНТІВ З РІЗНИМИ МОТОРНИМИ ПІДТИПАМИ ХВОРОБИ ПАРКІНСОНА

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Вступ. Порушення сну та циркадних ритмів можуть виникати на будь-якій стадії хвороби Паркінсона (ХП) і суттєво впливати на якість життя. Хронотипи пацієнтів з ХП асоціюються з різними фенотипами, зокрема з моторним підтипом (p<0,001), так і рівень освітленості в добу (p<0,001) статистично значуще важливіше для більш пізніх хронотипів у пацієнтів з ХП, переважно з підтипом PIGD (p<0,001), коротшу тривалість сну (p=0,028). Виявлена тенденція до більш пізніх хронотипів у пацієнтів з ХП, переважно з підтипом PIGD (p<0,001), на фоні переваги ранкового хронотипу в усіх групах.

Методи та матеріали. Клінічне дослідження проведено на базі Центру хвороби Паркінсона та нейродегенеративних захворювань кафедри нервових хвороб Полтавського державного медичного університету. Діагноз ХП визначали за методом Стеббіна, який ґрунтується на розрахунку коефіцієнта Стеббіна за сумою акселерометричних показників.

Результати. Установлено, що у пацієнтів з ХП пізійний початок сну та час підйому з ліжка (p<0,001), коротша тривалість сну (p<0,001), середня сну припадає на пізніший час (p<0,001). Пацієнти з підтипом PIGD мали пізніший час підйому з ліжка (p=0,038), діагноз ХП визначали за методом Стеббіна, який ґрунтується на розрахунку коефіцієнта Стеббіна за сумою акселерометричних показників.

Висновок. Таким чином, пацієнти з ХП відрізняються від осіб відповідного віку без нейродегенеративних захворювань хронотипом та циркадним патерном функціонування. Моторний підтип хвороби пов’язаний з циркадними особливостями, а саме PIGD підтип пов’язаний з коротшою тривалістю сну, сильнішого впливу на час настання середньої сну.

Ключові слова: циркадний ритм, розлади сну, хвороба Паркінсона, хронотип, освітлення, добова активність.