Original article

Sleep Disorders in Cervical Dystonia, Parkinson's Disease and Depression – What is the Difference?

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Abstract

Introduction: Sleep disorders are among the most common non-motor symptoms in patients with cervical dystonia (CD), Parkinson's disease (PD), and depression. The study aimed to assess the prevalence and characteristics of sleep disorders in patients with cervical dystonia compared to healthy controls, patients with Parkinson's disease, and patients with depression.

Methods: In this cross-sectional study, we evaluated 122 patients (30 control patients, 30 with cervical dystonia, 32 with Parkinson's disease, and 30 with depression). Demographic data were collected. All of them, except for the depression group, were tested for depression and anxiety using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). Sleep disorders were evaluated using the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS). Statistical significance was defined at α =0.05.

Results: Patients with cervical dystonia differed from the healthy control group in terms of PSQI score and some subscales. The depression group differed in most PSQI subscales when compared to the patients with Parkinson's disease and cervical dystonia, while the latter two groups of patients differed only in the duration subscale. Patients with Parkinson's disease differed from other groups of patients only in one subscale - daytime sleepiness.

Conclusion: Cervical dystonia patients suffer from more sleep disturbances when compared to healthy controls. There are differences in the frequency and extent of sleep disturbances with less pronounced symptoms in patients with cervical dystonia and Parkinson's disease, while patients with depression present the most pronounced symptoms. Symptoms of depression and anxiety correlate with sleep disturbances in patients with Parkinson's disease and cervical dystonia. Patients with cervical dystonia do not experience daytime sleepiness problems.

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Introduction

Circadian rhythm can be defined as changes in biological and behavioural conditions between the states of high and low activity during 24 hours. It is regulated by two paired nuclei located in the hypothalamus, called the suprachiasmatic nucleus (SCN). The process starts with retinal light stimulation that generates a signal through the retinohypothalamic tract to the SCN, which then generates a signal that stimulates the pineal gland. The process of stimulation involves a multi-synaptic link through the superior cervical ganglion, which releases noradrenaline during the night, inducing the activity of the serotonin-N-acetyltransferase (SNAT) enzyme via cyclic adenosine monophosphate (cAMP). This stimulates the pineal gland to produce the hormone melatonin during the night and release it into the circulation to facilitate sleep [1]. The neurotransmitters that are important in the process of wakefulness are serotonin, noradrenaline, and acetylcholine, and they are released by the neurons located in the ventrolateral preoptic nucleus [2]. Introduction to the rapid-eye-movement (REM) phase of sleep is characterized by a decrease in monoaminergic (serotonin, norepinephrine, and dopamine) tone with a parallel increase in cholinergic tone [3]. In non-REM sleep, glutamate signalling is important during thalamocortical slow oscillations [4]. The secretion of the hormone cortisol is decreased during normal deep sleep and hypercortisolaemia can induce insomnia [5]. Sleep disorders could be classified into several types: delayed sleep phase syndrome (DSPS), advanced sleep phase syndrome (ASPS), irregular sleep-wake pattern, and non-24-hour sleep-wake syndrome in blind and sighted persons. Delayed sleep phase syndrome is a sleep disorder where the patient has problems falling asleep and waking up at conventional times, and the assumption is that the pathophysiological basis lies in delayed endogenous melatonin secretion [6]. Advanced sleep phase syndrome is characterized by persistent early evening sleep onset and early morning awakening with no sleep-maintenance problems. It is an age-related problem, the pathophysiology of which is as a consequence of diminution in the output of the circadian pacemaker [7]. The syndrome of an irregular sleep-wake pattern is characterized by temporally disorganized and variable episodes of sleeping and waking behaviour.

Focal dystonia is characterized by sustained or intermittent muscle contraction causing abnormal, often repetitive movement, posture, or both. Cervical dystonia (CD) is a focal dystonia type where neck muscles are involved [8]. The aetiology of CD is still unknown. Recent articles suggest miscommunication between the basal ganglia and cerebellar loops [9]. In CD, besides typical motor symptoms, patients also experience non-motor symptoms, such as depression, anxiety, cognitive decline, pain, and sleep disorders [10,11]. The aetiology of sleep disorders in this patient group remains unresolved. There is no evidence that it is related to motor symptoms or that the relief from botulinum toxin treatment used for motor symptoms does not improve sleep disorders [12]. Video-polysomnographic recordings in CD patients showed that the activity over cervical muscles disappeared during all sleep stages and thus could not influence sleep impairment [13]. One of the theories is that sleep disturbance is related to the dysfunction of some brain regions, such as the basal ganglia, with dopaminergic system disturbance. Another theory is that it is related to depression [14].

Parkinson's disease (PD) is a neurodegenerative disorder with alpha-synuclein inclusions as the main hallmark of disease pathology. During the disease course, α-synuclein pathology spreads from the brain stem to higher cortical regions, with consequential neuron degeneration. As a result of degeneration, there is a loss of many neurotransmitters in the brain, such as dopamine, serotonin, noradrenaline, and acetylcholine. This causes many motor and non-motor symptoms, including sleep disorders, among many other non-motor symptoms described [15]. Multiple factors could influence sleep disturbances, such as age-related

changes in sleep, nocturnal motor symptoms (rigidity, resting tremor, akinesia, tardive dyskinesia, and the 'wearing-off' phenomenon), non-motor symptoms (pain, hallucination, and psychosis), nocturia, and medication. Besides that, as part of PD pathology, there are changes in the neurotransmitter systems (dopamine, norepinephrine, serotonin, and acetylcholine) responsible for regulating sleep structure and the sleep/wake cycle [16].

Major depressive episodes are characterized by a period of depressed mood or anhedonia lasting for 2 or more weeks, with at least three additional signs, i.e. weight change or change in appetite, psychomotor agitation or retardation, feeling of worthlessness or guilt, diminished ability to concentrate, suicidal ideations or attempts, and insomnia or hypersomnia. Changes in neurotransmitter levels, such as a decrease of serotonin, norepinephrine and dopamine, and hypercortisolaemia are possible aetiologic factors of depression. Sleep disturbance is one of the most consistent symptoms. It can precede the symptoms of depression or persist after the disease remission and it is not related to depression itself. There are several theories on the aetiology of sleep disturbance in depression. One of them refers to monoaminergic level disruption, another one to glutamate level decrease, and one to hypercortisolaemia. However, none of them includes a clear conclusion regarding its aetiology [4].

The aim of the study was to assess the prevalence and characteristics of sleep disorders in patients with cervical dystonia, compared to healthy controls, patients with Parkinson's disease, and patients with depression.

Subjects and Methods

In this cross-sectional study, we analysed 122 subjects, 30 of whom were healthy controls, 30 CD patients, 32 PD patients, and 30 were subjects diagnosed with depression. The study was conducted at the Department of Neurology and Department of Psychiatry, University Hospital Centre Osijek, from February to May 2017. All the participants signed a written informed consent. The study protocol was reviewed and approved by the University Hospital Centre Osijek Ethics Board and it was in accordance with the Declaration of Helsinki. CD patients were recruited from the botulinum toxin clinic and tested during their regular follow-up examinations (without relation to their botulinum injections schedule). The control group included sex- and age-matched healthy relatives and friends of CD patients. PD patients were recruited from the movement disorders clinic. PD diagnosis was made according to the UK PD Society Brain Bank (UKPDSBB) diagnostic criteria and both early and advanced PD patients were analysed [17]. Depressed patients were recruited from the psychiatric ward where they were hospitalized due to depression problems. Control, PD, and CD groups were tested for symptoms of depression and anxiety by using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). Severity of depression and anxiety were not evaluated in depressed patients. All patients were tested for sleep disturbances using the Pittsburgh Sleep Quality Index (PSQI) for night-time disturbances and Epworth Sleepiness Scale (ESS) for daytime sleepiness problems. The PSQI has been designed to assess sleep quality and disturbances over a 1-month time interval. It is a self-rated questionnaire that can be filled in 10-15 minutes. There are 19 individual questions divided into 7 subscales assessing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of all 7 subscales provides the global PSQI score ranging from 0 to 21, where lower scores denote better sleep quality [18]. The ESS is a simple self-administered questionnaire designed to measure daytime sleepiness. It consists of 8 questions about how likely would it be for the subject to doze off in 8 different situations (sitting and reading; watching TV; sitting, inactive, in a public place; as a passenger in a car for an hour without a break; lying down to rest in the afternoon; sitting and talking to someone; sitting quietly after lunch without alcohol; and, in a car, while stopped for

a few minutes in the traffic). After scoring every situation on a scale from 0 (would never doze off) to 3 (high chance to doze off), the total sum is calculated. The maximum score is 24. The score is higher in patients having more problems with daytime sleepiness [19]. A demographic questionnaire was designed for the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Study was approved in 2016 by local Ethical Committee of Medical school in University of J. J. Strossmayer in Osijek. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Categorical data were expressed as absolute frequencies and percentages, while the differences between the groups were tested by Fisher's exact test. Numerical data were expressed as median and interquartile ranges or as mean and standard deviations, depending on whether the data indicated normal distribution, which was tested by the Kolmogorov-Smirnov test. Correlation between variables that did not indicate normal distribution was tested with Spearman's rank correlation coefficient. Differences between the groups in which the data did not indicate normal distribution were tested by the Kruskal-Wallis test. Statistical significance was defined as α=0.05. Post hoc analysis of differences between the two groups was done with the Mann-Whitney U test and, after the Bonferroni correction, statistical significance was defined as P<0.016. Statistical analysis was conducted by using STATISTICA 13 (StatSoft Inc., Tulsa, Oklahoma, USA).

Results

There were differences among the patient groups in terms of age (PD patients were older than subjects from other groups), while the study groups were quite homogeneous in terms of sex (Table 1). There was no difference in disease duration among the three groups of subjects (Table 2).

Table 1 Demographic data regarding sex and age

	CONTROL	PARKINSON'S DISEASE	FOCAL DYSTONIA	DEPRESSION	*P*
	N/%	N/%	N/%	N/%	
SEX					
• male	10 (33.3)	20 (62.5)	10 (33.3)	11 (36.7)	
• female	20 (66.7)	10 (37.5)	20 (66.7)	19 (63.3)	0.052*
AGE					
• 20-30	1 (3.3)	0 (0)	1 (3.3)	0 (0)	
• 31-40	2 (6.7)	0 (0)	2 (6.7)	3 (10.0)	
• 41-50	3 (10.0)	3 (9.4)	3 (10.0)	4 (13.3)	
• 51-60	10 (33.3)	3 (9.4)	10 (33.3)	16 (53.3)	
• 61-70	8 (26.7)	18 (56.3)	8 (26.7)	4 (13.3)	
• 71-80	6 (20.0)	8 (25.0)	6 (20.0)	3 (10.0)	**0.004***

*Fisher's Exact Test

Table 2 Differences in disease duration, symptoms of depression and anxiety between groups

	CONTROL	PARKINSON'S DISEASE	FOCAL DYSTONIA	DEPRESSION	
	median (IQR) mean	median (IQR) mean	median (IQR) mean	median (IQR) mean	P
DISEASE DURATION	-	5.00 (2.00-9.75) 6.31	7.00 (2.25-12.25) 7.20	7.00 (2.75-15) 9.42	0.315†
BDI	1.00 (1.00-1.25) 1.37	2.00 (1.00-3.00) 2.19	1.50 (1.00-2.25) 1.83	-	**0.020†**
BAI	1.00 (1.00-1.00) 1.13	1.00 (1.00-2.00) 1.56	1.00 (1.00-2.00) 1.37	-	**0.021†**

BDI – Beck Depression Inventory; BAI – Beck Anxiety Inventory; †Kruskal-Wallis test

Post hoc analysis performed between groups by applying the Mann-Whitney U test indicated to the following significant differences: BDI between control and PD group (P < 0.008); BAI between control and PD group (P < 0.006).

There were significant differences in BDI and BAI scores between control, PD, and CD groups (BDI p<0.020 and BAI p<0.021). The post hoc analysis conducted between the groups by using the Mann-Whitney U test and the Bonferroni correction indicated a significant difference in BDI and BAI only between the PD and the control group (Table 2). A positive correlation between the BDI and PSQI scores in both patient groups (CD group rs 0.409, p<0.025; PD group rs 0.668, p<0.001) was found, but not between BDI and ESS (CD group rs 0.191, p<0.312; PD group rs 0.093, p<0.612). When correlating BAI and PSQI, positive correlations both for PD and CD groups (PD group rs 0.604, p<0.001; CD group rs 0.370, p<0.044) was found, whereas for BAI and ESS a positive correlation only for the CD group was found (CD group rs 0.393, p<0.032; PD group rs 0.271, p<0.133). The frequency of severity in the PSQI scale, ESS, and PSQI subjective score are shown in Table 3.

Table 3 Frequency of severity of sleep disorders and subjective assessment between groups

	CONTROL	PARKINSON'S DISEASE	FOCAL DYSTONIA	DEPRESSION	
	N/%	N/%	N/%	N/%	***P***
ESS					
• lower normal DS	17 (56.7)	11 (34.4)	19 (63.3)	14 (46.7)	
• higher normal DS	9 (30.0)	9 (28.1)	6 (20.0)	10 (33.3)	
• mild excessive DS	2 (6.7)	2 (6.3)	3 (10.0)	1 (3.3)	
• moderate excessive DS	2 (6.7)	8 (25.0)	1 (3.3)	1 (3.3)	
• severe excessive DS	0 (0)	2 (6.3)	1 (3.3)	4 (13.3)	**0.035***
PSQI					
• normal	23 (76.7)	7 (21.9)	10 (33.3)	0 (0)	
• poor sleep quality	7 (23.3)	25 (78.1)	20 (66.7)	30 (100)	**0.001***
PSQI SUBJECTIVE					
• very good	14 (46.7)	9 (28.1)	8 (26.7)	3 (10.0)	
• fairly good	11 (36.7)	8 (25.0)	12 (40.0)	10 (33.3)	
• fairly bad	3 (10.0)	11 (34.4)	7 (23.3)	11 (36.7)	
• very bad	2 (6.7)	4 (12.5)	3 (10.0)	6 (20.0)	**0.004***

DS – daytime sleepiness; ESS – Epworth Sleepiness Scale; PSQI – Pittsburgh Sleep Quality Index; * Fisher's Exact Test

Post hoc analysis showed the following differences between the groups: control and CD (PSQI score P < 0.001); PD and CD (ESS score P < 0.017); PD and depression (PSQI score P < 0.007); CD and depression (PSQI score P < 0.001; subjective PSQI P < 0.042)

We found significant differences among the groups for both scales and subjective PSQI scores. Post hoc analysis showed differences between the two groups (Table 3). Table 4 shows PSQI subscale scores, while Figure 1 shows global PSQI scores for the groups.

Table 4 Differences in PSQI subscale scores between healthy control, Parkinson disease (PD), focal dystonia (FD) and depression groups

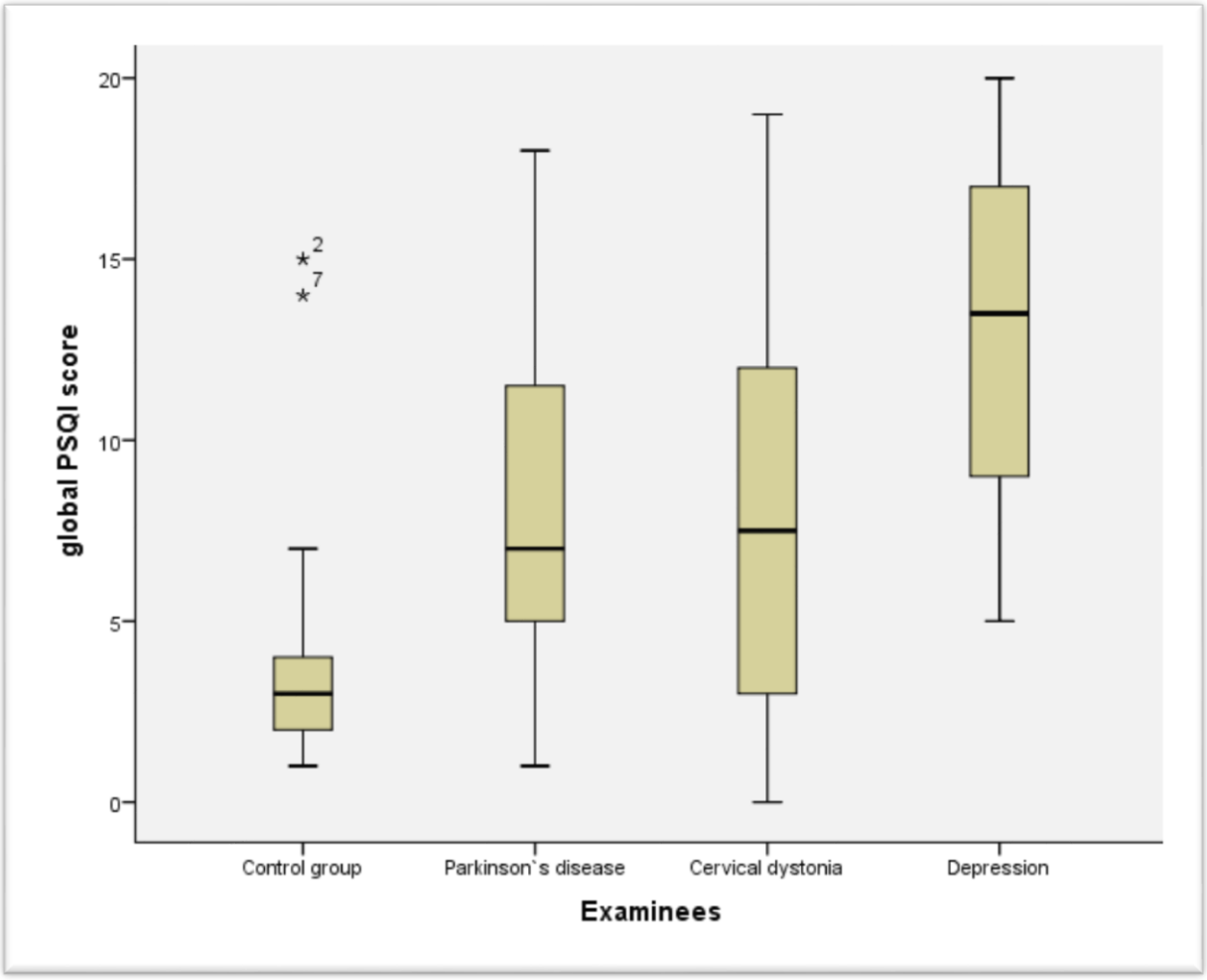
	CONTROL median (IQR)	PARKINSON'S DISEASE median (IQR)	FOCAL DYSTONIA median (IQR)	DEPRESSION median (IQR)	P
Latency	0.00 (0.00-0.00)	1.00 (0.00-1.00)	1.00 (0.00-1.25)	2.00 (1.00-3.00)	**0.001†**
Effectiveness	0.00 (0.00-0.25)	1.00 (0.00-2.75)	0.00 (0.00-2.00)	2.00 (0.00-3.00)	**0.001†**
Duration	1.00 (0.00-2.00)	1.50 (0.00-2.00)	0.00 (0.00-0.00)	2.00 (0.00-3.00)	**0.001†**
Disturbances	0.00 (0.00-1.25)	0.00 (0.00-1.75)	2.00 (0.00-3.00)	2.00 (2.00-3.00)	**0.001†**
Awakening	1.00 (0.00-2.00)	3.00 (1.00-3.00)	2.50 (1.00-3.00)	3.00 (2.00-3.00)	**0.001†**
Toilet	1.00 (0.00-2.00)	3.00 (1.25-3.00)	2.00 (0.00-3.00)	3.00 (1.00-3.00)	**0.001†**
Breathing	0.00 (0.00-0.00)	0.00 (0.00-1.00)	0.00 (0.00-0.25)	0.00 (0.00-3.00)	**0.043†**
Snoring	0.00 (0.00-1.00)	2.00 (0.00-3.00)	0.00 (0.00-3.00)	3.00 (0.00-3.00)	**0.001†**
Cold	0.00 (0.00-0.00)	0.00 (0.00-1.75)	0.00 (0.00-0.00)	0.00 (0.00-3.00)	**0.029†**
Hot	0.00 (0.00-0.00)	0.00 (0.00-1.75)	0.00 (0.00-2.25)	2.00 (0.00-3.00)	0.079†
Nightmares	0.00 (0.00-0.00)	1.00 (0.00-2.00)	0.00 (0.00-1.25)	2.00 (0.00-3.00)	**0.001†**
Pain	0.00 (0.00-0.00)	2.00 (0.00-3.00)	2.00 (0.00-3.00)	1.00 (0.00-3.00)	**0.001†**
Other	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	3.00 (0.00-3.00)	**0.001†**
Hypnotics usage	0.00 (0.00-0.00)	0.00 (0.00-2.00)	0.00 (0.00-2.25)	3.00 (3.00-3.00)	**0.001†**
Dysfunctionality	0.00 (0.00-0.00)	0.00 (0.00-1.75)	0.00 (0.00-1.00)	2.00 (0.00-2.00)	**0.001†**
Vigilance	0.00 (0.00-0.00)	0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.00 (0.00-1.25)	**0.009†**
Enthusiasm	0.00 (0.00-0.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	3.00 (0.00-3.00)	**0.001†**

PSQI – Pittsburgh Sleep Quality Index; †Kruskal-Wallis test

Post hoc analysis of differences between two groups carried out by applying the Mann-Whitney U test yielded significant differences for this subscale, and they are as follows: control and CD (P<0.001); PD and depression (P<0.001); CD and depression (P<0.001); duration score between control and CD (P<0.001); PD and CD (P<0.001); CD and depression (P<0.001); disturbance score between PD and depression (P<0.001); snoring score between CD and depression (P<0.009); nightmare score between control and CD (P<0.004); CD and depression (P<0.003); pain score between control and CD (P<0.001); other score between PD and depression (P<0.001); CD and depression (P<0.001); hypnotics usage score between PD and depression (P<0.001); CD and depression (P<0.001); dysfunctionality score PD and depression (P<0.006); CD and depression (P<0.001); enthusiasm score between PD and depression (P<0.001); CD and depression (P<0.001).

The median score did not differ between some groups, but the interquartile range indicated to differences among them. Significant differences among the groups in terms of global scores were observed (Figure 1), but also with regard to many subscales. Post hoc analysis, following the application of the Bonferroni correction, showed differences between the two groups (Table 4).

Figure 1 Global PSQI score between groups



PSQI – Pittsburgh Sleep Quality Index.

Post hoc analysis consisting of the Mann-Whitney U test, caried out after Bonferroni correction in order to determine differences between two groups: PSQI score between control and CD groups (P < 0.004); PD and depression groups (P < 0.001); and CD and depression groups (P < 0.001).

Table 5 shows results pertaining to ESS subscale scores, while Figure 2 shows total ESS scores for all the groups. There were no significant differences in total ESS scores between the CD and control group, or between patient groups (after Bonferroni correction) (Figure 2). Only the subscale "sitting in a public place" presented lower results in the PD group when compared to CD and depression groups (Table 5).

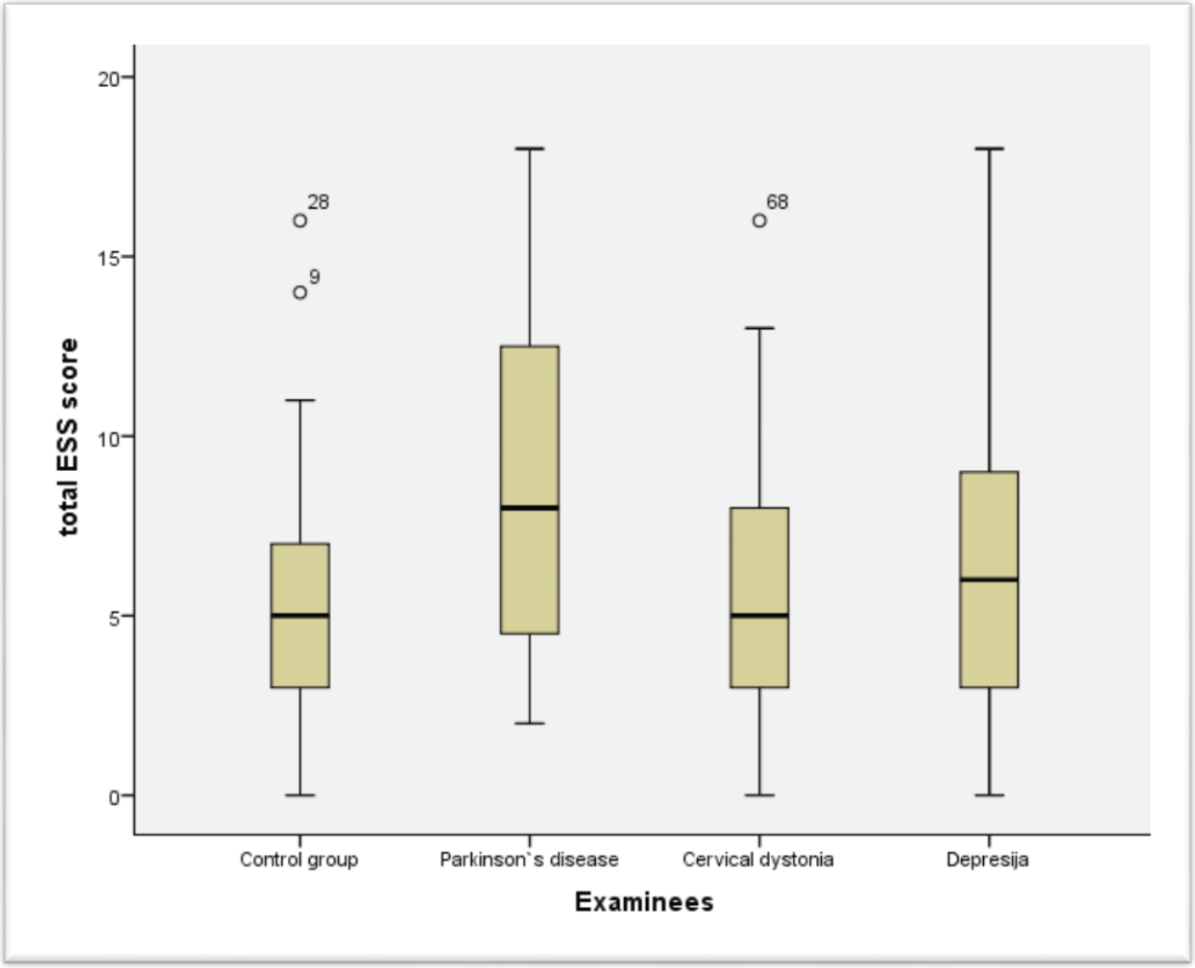
Table 5 Differences in ESS subscale scores in between healthy control, Parkinson disease, focal dystonia, and depression groups.

	CONTROL	PARKINSON'S DISEASE	FOCAL DYSTONIA	DEPRESSION	
	median (IQR)	median (IQR)	median (IQR)	median (IQR)	***P***
Watching TV	1.50 (1.00-2.00)	1.50 (1.00-2.00)	1.00 (0.00-2.00)	1.00 (0.00-2.25)	0.208†
Sitting, inactive, in a public place	0.00 (0.00-1.00)	1.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.25)	0.147†
Passenger in a car	0.00 (0.00-1.00)	0.00 (0.00-2.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.458†
Lying down to rest in the afternoon	2.00 (1.00-3.00)	2.00 (1.00-3.00)	2.00 (1.00-2.00)	2.00 (0.75-2.25)	0.402†
Sitting and talking	0.00 (0.00-0.00)	0.00 (0.00-1.00)	0.00 (0.00-0.25)	0.00 (0.00-1.00)	0.129†
Sitting after lunch	0.00 (0.00-1.00)	1.00 (0.00-3.00)	0.00 (0.00-1.00)	1.00 (0.00-2.00)	**0.011†**
Sitting in a public place	0.00 (0.00-0.00)	0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	**0.005†**
In a car, while stopped for a few minutes	0.00 (0.00-1.00)	1.00 (0.00-2.00)	1.00 (0.00-1.00)	0.00 (0.00-2.00)	0.390†

ESS – Epworth Sleepiness Scale; †Kruskal-Wallis test

Post hoc analysis of differences between two groups carried out by applying the Mann-Whitney U test, which after applying the Bonferroni correction (P<0.016) yielded significant differences for this subscale, and they are as follows: sitting after the lunch for PD and CD (P < 0.042); sitting in public for PD and CD (P < 0.013); PD and depression (P < 0.005).

Figure 2 Total ESS scores between groups



ESS – Epworth Sleepiness Scale.

Post hoc analysis consisting of the Mann-Whitney U test that was performed to determine the differences between two patient groups showed the following differences: ESS score for PD and CD groups ($P < 0.031$).

Discussion

Patients with CD were analysed for sleep disturbance relative to the control group, and all three patient groups were analysed for sleep disturbances relative to each other. When compared to the control group, CD patients displayed more frequent sleep problems that included higher PSQI scores. However, there was no difference with regard to daytime sleepiness problems. They have reported longer latency to fall asleep, lower duration of sleep during the night, more frequent nightmares, and more pain that disturbed their night-time sleep. Avanzino et al. reported impairment in sleep duration, latency, and efficiency of sleep in patients with blepharospasm, but not in the CD patient group. Likewise, Antelmi et al. also found decreased sleep efficiency and increased sleep latency in video-polysomnographic recordings of CD patients [13,20]. Impairment in sleep latency has its pathophysiological basis in delayed endogenous melatonin secretion, probably due to lower noradrenaline and serotonin levels that are an important part of this process [1].

Although all three patient groups suffered from sleep disturbances, we still found differences among them. Sleep of PD patients during the night is of shorter duration when compared to the CD group. PD group was older than the CD group, so this difference could be related to age,

i.e. it could be a consequence of age-related diminution in the output of the circadian pacemaker [7]. The depression group differed from the CD group in terms of PSQI scores and most subscales. They reported prolonged latency, shorter duration of sleep, and worse quality of sleep resulting from snoring and nightmares. They also use hypnotics more often and are more likely to suffer from dysfunctionality and loss of enthusiasm during the day arising from their sleep problems. The depression group reported more of such similar problems when compared to the PD group (latency, duration of sleep, disturbances, and other problems and disturbances). They also used hypnotics more often and reported dysfunctionality and loss of enthusiasm during the day arising from their sleep problems. So, of the three patient groups, sleep problems were most pronounced in the depression group, followed by PD, and finally the CD group. Smit et al. published a paper about altered presynaptic serotonin transporter (SERT) binding in CD patients. They found that sleep disturbances were strongly linked to SERT binding in the raphe nuclei in CD patients [21]. Depression and anxiety in CD patients are related to serotonergic system impairment. Patients with CD accompanied by depression and anxiety present lower SERT (serotonin transport) binding in the midbrain/diencephalon [22]. We found that both anxiety and depression symptoms correlate with sleep disturbances in the CD group. This indicates that neurotransmitter impairment leading to depression and anxiety could be the aetiological factor of sleep disturbances in the CD group.

All three patient groups had problems with waking up and there was no significant difference among them. Dopamine-containing neurons are involved in the regulation of the waking process [23]. There is evidence that the dopaminergic system is disturbed in CD patients with depression. Zoons et al. found alterations of striatal DAT (dopaminergic transport) and D2/3 receptor binding in CD patients with depression [24]. In addition to dopamine, noradrenaline and acetylcholine are also important in the waking process. Noradrenaline levels are high during the waking state and low during sleep [25]. Noradrenergic and cholinergic cells in the pons increase firing to activate the waking pattern [26,27]. There is a case report about pathologic findings from an autopsy of a patient with primary segmental dystonia (Meige syndrome). The authors found moderate-to-severe neuronal loss in several brainstem nuclei, including the substantia nigra pars compacta, locus coeruleus, raphe nuclei, and pedunculopontine nucleus [28]. Another paper with histopathologic findings in CD patients did not report a neuronal loss in the pedunculopontine region, but described a pedunculopontine nucleus choline acetyltransferase deficiency with a functional cholinergic deficit [29]. This could explain the lower noradrenaline and acetylcholine levels in CD patients, which are an important part of the wake-sleep cycle.

There was no difference in ESS scores between the CD and control group, but the PD group reported lower ESS scores more frequently when compared to the CD patient group. In terms of subscales, and after the Bonferroni correction, a significant difference was found only with regard to the risk of falling asleep while sitting in public, where PD patients reported higher chances of falling asleep when compared to the CD and depression group. Although excessive daytime sleepiness has not been indicated in CD patients [10,20,30], Trotti et al. reported opposite results for their CD patients when compared to the control group. They explained that this could be attributed to the use of anticholinergics that can affect sleepiness during the day in a certain percentile of patients [14,32]. There is no evidence that impairment of sleep quality has an impact on daytime sleepiness [19,32].

Conclusion

Sleep disturbances are frequent non-motor symptoms in CD, PD, and depression patients. According to our data, all three groups of patients had sleep disorders, but they differed in the frequency and extent of those disorders, with less pronounced symptoms found in CD

and PD patients. Symptoms of depression and anxiety correlate with sleep disturbances in PD and CD patient groups. CD patients do not experience daytime sleepiness problems. The aetiology of sleep disturbances in CD patients is probably related to monoamine neurotransmitter system impairments similar to those of PD patients, but to a lesser extent than in patients with depression.

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References

1. Zisapel N Circadian rhythm sleep disorders pathophysiology and potential approaches to management. CNS Drugs 2001; 15(4):311-28.

2. Gallopin TFP, Eggermann E, Caull B, Luppi PH, Rossier J, Audinat E, Mühlethaler M, Serafin M. Identification of sleep promoting neurons in vitro. Nature 2000; 404:992-5.

3. Pace-Schott EF, Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. Nat Rev Neurosci 2002; 3(8):591-605.

4. Murphy MJ, Peterson MJ. Sleep disturbances in depression. Sleep Med Clin 2015; 10(1):17-23.

5. Hinkelmann K, Moritz S, Botzenhardt J, Muhtz C, Wiedemann K, Kellner M, Otteet C. Changes in cortisol secretion during antidepressive treatment and cognitive improvement in patients with major depression: a longitudinal study. Psychoneuroendocrinology 2012; 37(5):685-92.

6. Oren DA, Turner EH, Wehr TA. Abnormal circadian rhythms of plasma melatonin and body temperature in the delayed sleep phase syndrome. J Neurol Neurosurg Psychiatry 1995; 58(3):379.

7. Czeisler CA, Dumont M, Duffy JF, Steinberg JD, Richardson GS, Brown EN, Sánchez R, Ríos CD, Ronda JM. Association of sleep-wake habits in older people with changes in output of circadian pacemaker. Lancet 2013; 340(8825):933-6.

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8. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VSC, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Telleret JK. Phenomenology and classification of dystonia: a consensus update. Mov Disord 1992; 28(7):863-73.

9. Filip P, Gallea C, Lehéricy S, Bertasi E, Popa T , Mareček R, Lungu OV, Kašpárek T, Vaníček J, Bareš M. Disruption in cerebellar and basal ganglia networks during a visuospatial task in cervical dystonia. Mov Disord 2017; 32(5):757-68.

10. Yang J, Shao N, Song W, Wei Q, Ou R, Wu Y, Shang H-F. Nonmotor symptoms in primary adult-onset cervical dystonia and blepharospasm. Brain Behav 2016; 7(2):e00592.

11. Eichenseer SR, Stebbins GT, Comella CT. Beyond a motor disorder: a prospective evaluation of sleep quality in cervical dystonia. Parkinsonism Relat Disord 2014; 20(4):405-8.

12. Charles PD, Manack AA, Davis T, Bradley K, Schwartz M, Brin MF, Patel AT. Neck pain and cervical dystonia: treatment outcomes from CD PROBE (Cervical Dystonia Patient Registry for Observation of On a botulinum toxin A Efficacy). Pain Pract. 2016; 16(8): 1073–1082. doi: 10.1111/papr.12408.

13. Antelmi E, Ferri R, Provini F, Scaglione CML, Mignani F, Rundo F, Vandi S, Fabbri M, Pizza F, Plazzi G, Martinelli P, Liguori R. Modulation of the muscle activity during sleep in cervical dystonia. Sleep. 2017; 40(7). /doi: 10.1093/sleep/zsx088.

14. Hertenstein E, Tang NK, Bernstein CJ, Nissen C, Underwood MR, Sandhu HK. Sleep in

patients with primary dystonia: a systematic review on the state of research and perspectives. Sleep Med Rev 2016; 26:95-107.

15. Jankovic J, Tolosa E (2007) Parkinson's Disease and Movement Disorders, fifth edn. Lippincott Williams¸Wilkins, Philadelphia.

16. Suzuki K, Miyamoto M, Miyamoto T, Hirata K. Parkinson's disease and sleep/wake disturbances. Curr Neurol Neurosci Rep 2015; 15(3):8.

17. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992; 55:181-4.

18. Buysse DJ, 3rd Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989; 28(2):193-213.

19. Johns WM. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991; 14(6):540-5.

20. Avanzino L, Martino D, Marchese R, Aniello MS, Minafra B, Superbo M, Defazio G. Abbruzzese G. Quality of sleep in primary focal dystonia: a case-control study. Eur J Neurol 2010; 17(4):576-81.

21. Smit M, Vállez García D, de Jong BM, Zoons E, Booij J, Dierckx RA, Willemsen AT, de Vries EF, Bartels AJ, Tijssen AM. Relationships between serotonin transporter binding in the raphe nuclei, basal ganglia, and hippocampus with clinical symptoms in cervical dystonia: A [11C] DASB Positron Emission Tomography Study. Front Neurol 2018; 28(9):88.

22. Zoons E, Booij J, Speelman JD, Dreissen YEM, Smit M, Tijssen MAJ. Lower serotonin transporter binding in patients with cervical dystonia is associated with psychiatric symptoms. EJNMMI Res 2017; 7(1):87.

23. Monti JM, Monti D. The involvement of dopamine in the modulation of sleep and waking. Sleep Med Rev 2007; 11(2):113-33.

24. Zoons E, Tijssen MAJ, Dreissen YEM, Speelman JD, Smit M, Booij J. The relationship between the dopaminergic system and depressive symptoms in cervical dystonia. Eur J Nucl Med Mol Imaging 2017; 44(8):1375-82.

25. Takahashi K, Kayama Y, Lin JS, Sakai K. Locus coeruleus neuronal activity during the sleep-waking cycle in mice. Neuroscience 2010; 169:1115-26.

26. Eschenko O, Magri C, Panzeri S, Sara SJ. Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. Cereb Cortex 2012; 22:426-35.

27. Boucetta S, Cisse Y, Mainville L, Morales M, Jones BE. Discharge profiles across the sleep-waking cycle of identified cholinergic, GABAergic, and glutamatergic neurons in the pontomesencephalic tegmentum of the rat. J Neurosci 2014; 34:4708-27.

28. Zweig RM, Hedreen JC, Jankel WR, Casanova MF, Whitehouse PJ, Price DL. Pathology in brainstem regions of individuals with primary dystonia. Neurology 1988; 38(5):702-6.

29. Mente K, Edwards NA, Urbano D, Ray-Chaudhury A, Iacono D, Di Lorenzo Alho AT, Lopes Alho EJ, Amaro E Jr., Horovitz SG, Hallett M. Pedunculopontine nucleus cholinergic deficiency in cervical dystonia. Mov Disord 2018; 33(5):827-34.

30. Paus S, Gross J, Moll-Müller M, Hentschel F, Spottke A, Wabbels B, Klockgether T, Abeleet M. Impaired sleep quality and restless legs syndrome in idiopathic focal dystonia: a controlled study. J Neurol 2011; 258(10):1835-40.

31. Yang J, Shao N, Song W, Wei Q, Ou R, Wu Y, Shang H-F. Nonmotor symptoms in primary adult-onset cervical dystonia and blepharospasm. Brain Behav 2016; 7(2):e00592.

Trotti LM, Esper CD, Feustel PJ, Bliwise DL, Factor SA. Excessive daytime sleepiness in cervical dystonia. Parkinsonism Relat Disord 2009; 15(10):784-6.

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