Neurological Sciences (2023) 44:209–214
https://doi.org/10.1007/s10072-022-06401-4

ORIGINAL ARTICLE

Sleep disorders in Wilson's disease: a questionnaire study

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Received: 11 May 2022 / Accepted: 9 September 2022 / Published online: 15 September 2022

Abstract

Objective To examine the clinical characteristics and influencing factors related to sleep disorders in patients with Wilson's disease (WD), and investigate its potential mechanisms.

Methods A total of 150 patients with WD (76 hepatic, 42 neurological, 32 asymptomatic form) and 150 age- and sex-matched control subjects were investigated using 3 standardized sleep questionnaires. Differences among 3 subtypes were discussed.

Results The mean Parkinson's disease sleep scale (PDSS) score of WD was lower than the controls ($Z = -4.426$, $P = 0.000$), and their mean Epworth Sleepiness Scale (ESS) score as well as Pittsburgh sleep quality index (PSQI) score of WD was higher than that of the controls ($t = 2.005$, $P = 0.048$; $t = 3.342$, $P = 0.001$). The incidence of excessive daytime sleepiness (EDS) in WD group were significantly higher than the controls ($X^2 = 6.064$, $P = 0.014$). Further analysis showed that total PDSS score of neurologic presentation group was lower than others ($X^2 = 6.131$, $P = 0.047$), while the ESS score was higher ($F = 3.817$, $P = 0.029$). UWDRS showed a negative correlation with PDSS ($r = -0.440$, $P = 0.022$) and has a higher negative correlation with PDSS in neurologic presentation group ($r = -0.732$, $P = 0.000$).

Conclusions Patients with WD often suffer from sleep disturbances, mainly characterized by difficulty falling asleep, difficulty staying asleep, nocturnal motor symptoms (numbness, cramps, tremor), and daytime dozing. And the incidence of EDS is significantly higher than that of the controls. Sleep quality is worse in patients with WD of neurologic presentation than the other two groups. Furthermore, the worse of the symptoms, patients with WD suffer more serious of the sleep disorders especially in neurologic presentation group.

Keywords Wilson's disease · Questionnaire study · Sleep disorders · Sleepiness · Sleep quality

Introduction

Besides motor symptoms, movement disorders such as Parkinson's disease and Huntington's disease also have non-motor symptoms, which more seriously affect the quality of life, especially sleep disorders as a result of sleep cycle fragmentation [1–3]. Wilson's disease (WD) is an autosomal recessive inherited disorder which caused by a deficiency of a copper-transporting P-type ATPase, a condition encoded by mutation of the ATP7B gene. And then positive copper balance results in tissue copper accumulation and damage of the liver, brain, cornea, and so on [4–7]. Research showed that WD is associated with the dopamine deficit [8], and it has been proved that dopamine has a regulatory effect on the sleep–wake cycle [9]. It is not surprising that WD patients have a sleep disorder; however, only sporadic data exist in the relevant articles. Therefore, 150 patients with WD were selected from the Shanghai Jiao Tong University School of Medicine from 2015 to 2020 to conduct a questionnaire. It was used to verify the incidence and clinical characteristics of sleep disorders in WD.

Subjects and methods

Study subject

A total of 150 patients with WD in hospital were selected from the Shanghai Jiao Tong University School of Medicine

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from 2015 to 2020. All subjects were in accordance with the diagnostic criteria for Wilson's disease of European Association for the Study of the Liver (EASL) [10]. There were 99 males and 51 females, at the age of 18 to 50 years (mean 27.96 ± 7.95 years), and course of disease was 2 months to 18 years (mean 8.88 ± 6.67 years). Furthermore, patients were divided into three groups (hepatic presentation group, neurologic presentation group, and asymptomatic presentation group) according to phenotypic classification [11]. There were 46 males and 30 females, at the age of 20 to 43 years (mean 26.67 ± 7.87 years), and course of disease was 1 to 18 years (mean 9.04 ± 8.04 years) in the neurologic presentation group. There were 25 males and 17 females, at the age of 18 to 50 years (mean 27.38 ± 7.74 years), and course of disease was 2 months to 15 years (mean 7.40 ± 5.82 years) in the hepatic presentation group. There were 20 males and 12 females, at the age of 20 to 40 years (mean 27.60 ± 8.62 years), and course of disease was 1 to 13 years (mean 7.08 ± 6.56 years) in the asymptomatic presentation group. An additional 150 healthy persons were considered as the control group, including 100 males and 50 females aged 18 to 50 years (mean 61.10 ± 5.12 years). No significant difference in sex composition ratio ($X^2 = 0.015$, $P = 0.903$) and age ($t = 0.593$, $P = 0.555$) was detectable among WD and control groups with comparability. And there was no significant difference in sex composition ratio ($X^2 = 0.069$, $P = 0.966$), age ($F = 0.772$, $P = 0.468$), and course of disease ($F = 0.378$, $P = 0.688$) among three subgroups with WD.

Methods

All subjects completed Unified Wilson's disease rating scale (UWDRS), Parkinson's disease sleep scale (PDSS), the Epworth Sleeping Scale (ESS), and Pittsburgh sleep quality index (PSQI) after dinner in a quiet environment by the same neurologist clinician.

(1) Unified Wilson's disease rating scale (UWDRS) [12] was used to assess the whole spectrum of clinical symptoms in WD; the higher the score, the more serious.
(2) Parkinson's disease sleep scale (PDSS) [13] includes 15 commonly symptoms associated with sleep disturbance, like overall quality of night's sleep, sleep onset and maintenance insomnia, nocturnal restlessness, nocturnal psychosis, nocturia, nocturnal motor symptoms, sleep refreshment, and daytime dozing. The maximum cumulative score for the PDSS is 150 (patient is free of all symptoms).
(3) The Epworth Sleeping Scale (ESS) [14] was utilized to determine daytime sleepiness and excessive daytime sleepiness. The global score ranges from 0 to 24, scores higher than 6 suggesting a diagnosis of daytime sleepiness and scores higher than 10 suggesting a diagnosis of excessive daytime sleepiness (EDS) [15].
(4) Pittsburgh sleep quality index (PSQI) [16] is a questionnaire that assesses sleep quality and disturbances. The maximum cumulative score is 21, which is higher than or equal to 8 suggesting a poor sleep quality.

Statistical analysis

Date was analyzed with SPSS 19.0 software. Measurement data were expressed as mean ± SD, and enumeration data were expressed as ratio (%). A value of $\alpha = 0.05$ was considered statistically significant difference.

Results

Sleep characteristics of WD group and the control group

The mean PDSS score of WD group was significantly lower than the control group ($Z = -4.426$, $P = 0.000$). And the scores of subtests such as overall quality of sleep ($Z = -2.364$, $P = 0.018$), difficulty falling asleep ($Z = -2.497$, $P = 0.013$), difficulty staying asleep ($Z = -1.993$, $P = 0.046$), numbness or tingling with awakening at night ($Z = -2.099$, $P = 0.036$), painful muscle cramps at night ($Z = -1.986$, $P = 0.047$), tremor on waking ($Z = -2.946$, $P = 0.003$), and unexpectedly fallen asleep during the day ($Z = -2.762$, $P = 0.006$) were significantly decreased in WD group compared with the control group (Table 1). The ESS and PSQI scores were significantly higher in WD group than that in the control group ($t = 2.005$, $P = 0.048$; $t = 3.342$, $P = 0.001$; Table 1). On the basis of PSQI, scores higher than or equal to 8 suggest poor sleep quality, as described in Fig. 1A; the incidence of a poor sleep quality was significantly higher in WD group (24%) than that in the control group (8%). ESS scores of 48 patients in WD group (32%) were higher than 6, while there is 18 people (12%) in the control group (Fig. 1B). ESS scores of 19 patients in WD group (12.7%) were higher than 10 diagnosed with EDS, while there is only 7 people (4.7%) in the control group. The incidence of EDS was significantly increased in WD group ($X^2 = 6.064$, $P = 0.014$; Fig. 1C).

Sleep disorders in subtype of WD group

As displayed in Fig. 2C, there was no significant difference in PSQI among the neurologic presentation group (5.52 ± 2.61), hepatic presentation group (5.31 ± 1.89), and asymptomatic presentation group (5.20 ± 2.04) ($F = 0.081$, $P = 0.922$). Analysis of variance results demonstrated

Table 1 Comparison of sleep disorders in WD group and the control group

Item	WD group ($n=150$)	Control group ($n=150$)	Z or t values	P values
PDSS1	7.69 ± 2.18	8.86 ± 1.12	− 2.364	0.018
PDSS2	7.71 ± 2.92	9.19 ± 1.09	− 2.497	0.013
PDSS3	8.38 ± 1.82	9.26 ± 0.77	− 1.993	0.046
PDSS4	9.00 ± 2.01	9.36 ± 0.88	− 0.402	0.688
PDSS5	9.24 ± 1.46	9.50 ± 1.09	− 1.090	0.276
PDSS6	8.86 ± 1.82	9.12 ± 1.31	− 0.034	0.973
PDSS7	9.69 ± 0.68	9.88 ± 0.99	− 1.523	0.128
PDSS8	8.00 ± 2.53	9.00 ± 1.17	− 1.182	0.237
PDSS9	9.79 ± 1.09	10.00 ± 0.00	− 1.753	0.080
PDSS10	9.19 ± 1.84	9.88 ± 0.40	− 2.099	0.036
PDSS11	9.48 ± 1.23	9.93 ± 0.26	− 1.968	0.047
PDSS12	9.62 ± 0.96	9.88 ± 0.33	− 0.802	0.423
PDSS13	9.43 ± 1.17	9.98 ± 0.15	− 2.946	0.003
PDSS14	6.98 ± 3.00	8.21 ± 1.80	− 1.758	0.079
PDSS15	7.45 ± 2.71	8.93 ± 1.44	− 2.762	0.006
PDSS	130.50 ± 13.12	141.00 ± 5.88	− 4.426	0.000
ESS	5.38 ± 3.00	4.21 ± 2.29	2.005	0.048
PSQI	5.26 ± 2.52	3.57 ± 2.10	3.342	0.001

PDSS1 overall quality of sleep, *PDSS2* difficulty falling asleep, *PDSS3* difficulty staying asleep, *PDSS4* restlessness of legs or arms at night or in the evening, *PDSS5* fidgety in bed, *PDSS6* distressing dreams at night, *PDSS7* distressing hallucination at night, *PDSS8* nycturia, *PDSS9* incontinence because of "off" symptoms at night, *PDSS10* numbness or tingling with awakening at night, *PDSS11* painful muscle cramps at night, *PDSS12* early morning wake-up with painful posturing, *PDSS13* tremor on waking, *PDSS14* tiredness and sleepiness after waking up in the morning, *PDSS15* unexpectedly fallen asleep during the day

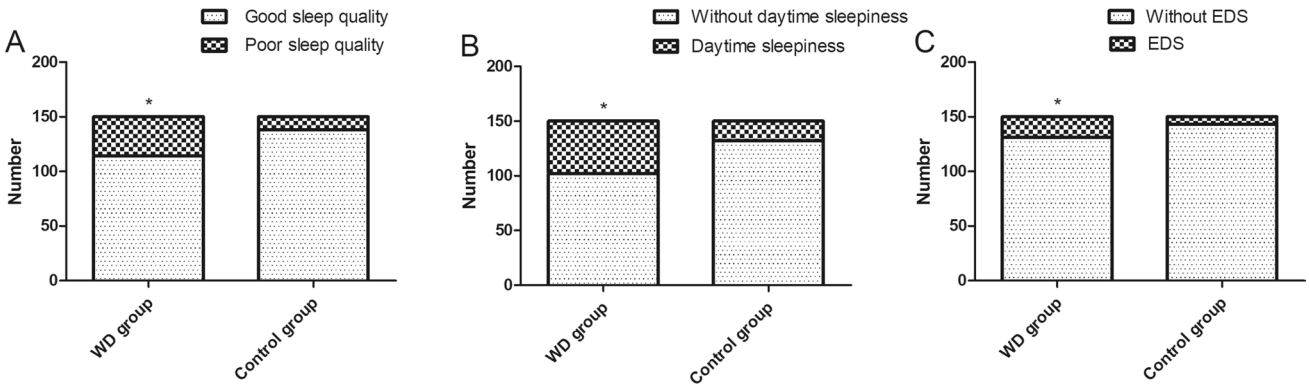

Fig. 1 Comparison of the incidence of sleep disorders in each group. Note: $^*P<0.05$, vs. control group

significant differences in ESS score among the neurologic presentation group (6.22 ± 3.03), hepatic presentation group (4.15 ± 2.58), and asymptomatic presentation group (3.90 ± 2.28) ($F=3.817$, $P=0.029$). Furthermore, Student–Newman–Keuls pairwise comparison test results showed that ESS score was significantly higher in the neurologic presentation group than in the hepatic presentation and asymptomatic presentation groups ($P=0.033$, $P=0.029$). And no significant difference was determined between the hepatic presentation and asymptomatic presentation groups (Fig. 2B). As displayed in Fig. 2A, the global scores of PDSS were 127.53 ± 15.39, 136.46 ± 6.59, and 138.50 ± 8.06 in the neurologic presentation, hepatic presentation, and asymptomatic presentation groups, respectively. There was significant difference among the three groups ($X^2=6.131$, $P=0.047$). The global scores of PDSS were significantly lower in the neurologic presentation group compared with the hepatic presentation and asymptomatic presentation groups ($P=0.049$, $P=0.014$). To clarify the clinical characteristics of sleep disorders in the neurologic presentation, hepatic presentation, and asymptomatic presentation groups, analysis of variance results showed that the scores of three

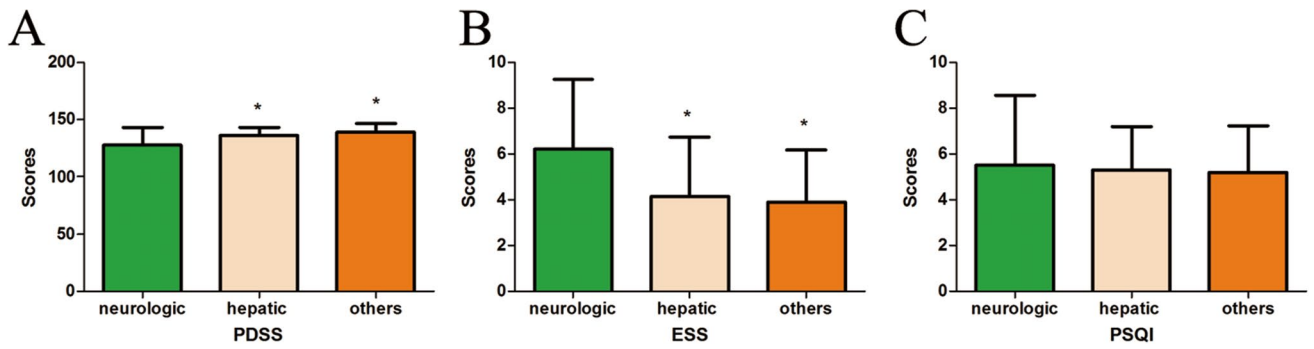

Fig. 2 Comparison of the score of PDSS, ESS, and PSQI in each group. Note: $^*P < 0.05$, vs. the neurologic presentation group

subtests such as PDSS2, PDSS13, and PDSS15 were significantly lower in the neurologic presentation group compared with the hepatic presentation and asymptomatic presentation groups ($X^2 = 8.757$, $P = 0.013$; $X^2 = 7.667$, $P = 0.022$; $X^2 = 6.107$, $P = 0.047$). So, it is worse for the neurologic patients in difficulty falling asleep, tremor on waking, and daytime sleepiness (Table 2).

Correlation and regression analysis

Spearman's correlation showed that UWDRS has a positive correlation with PSQI ($r = 0.404$, $P = 0.037$), and a negative correlation with PDSS ($r = -0.440$, $P = 0.022$). We did not find a significant correlation among the mean ESS, sex, age, and UWDRS of WD patients (Table 3). As displayed in Table 4, a more in-depth Spearman's correlation analysis in subtype of WD group shows that UWDRS has a higher negative correlation with PDSS in the neurologic presentation group ($r = -0.732$, $P = 0.000$). Furthermore, in the neurologic presentation group, we tried to analyze PDSS and UWDRS with linear regression analysis, but the data are not statistically significant (Fig. 3). Besides, we did not find a significant correlation in the hepatic presentation and asymptomatic presentation groups.

Table 2 Comparison of PDSS score in each sub-group. Note: $^*P < 0.05$, vs. the neurologic presentation group

Item	WD group ($n = 150$)	Control group ($n = 150$)	Z or t values	P values
PDSS1	7.69 ± 2.18	8.86 ± 1.12	− 2.364	0.018
PDSS2	7.71 ± 2.92	9.19 ± 1.09	− 2.497	0.013
PDSS3	8.38 ± 1.82	9.26 ± 0.77	− 1.993	0.046
PDSS4	9.00 ± 2.01	9.36 ± 0.88	− 0.402	0.688
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PDSS6	8.86 ± 1.82	9.12 ± 1.31	− 0.034	0.973
PDSS7	9.69 ± 0.68	9.88 ± 0.99	− 1.523	0.128
PDSS8	8.00 ± 2.53	9.00 ± 1.17	− 1.182	0.237
PDSS9	9.79 ± 1.09	10.00 ± 0.00	− 1.753	0.080
PDSS10	9.19 ± 1.84	9.88 ± 0.40	− 2.099	0.036
PDSS11	9.48 ± 1.23	9.93 ± 0.26	− 1.968	0.047
PDSS12	9.62 ± 0.96	9.88 ± 0.33	− 0.802	0.423
PDSS13	9.43 ± 1.17	9.98 ± 0.15	− 2.946	0.003
PDSS14	6.98 ± 3.00	8.21 ± 1.80	− 1.758	0.079
PDSS15	7.45 ± 2.71	8.93 ± 1.44	− 2.762	0.006
PDSS	130.50 ± 13.12	141.00 ± 5.88	− 4.426	0.000
ESS	5.38 ± 3.00	4.21 ± 2.29	2.005	0.048
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PDSS1 overall quality of sleep, *PDSS2* difficulty falling asleep, *PDSS3* difficulty staying asleep, *PDSS4* restlessness of legs or arms at night or in the evening, *PDSS5* fidgety in bed, *PDSS6* distressing dreams at night, *PDSS7* distressing hallucination at night, *PDSS8* nycturia, *PDSS9* incontinence because of "off" symptoms at night, *PDSS10* numbness or tingling with awakening at night, *PDSS11* painful muscle cramps at night, *PDSS12* early morning wake-up with painful posturing, *PDSS13* tremor on waking, *PDSS14* tiredness and sleepiness after waking up in the morning, *PDSS15* unexpectedly fallen asleep during the day

Table 3 Relationship between the score of PDSS, PSQI, ESS, and baseline condition—Spearman rank order correlation

	PDSS		PSQI		ESS	
	r	*P*	*r*	*P*	*r*	*P*
Sex	−0.024	0.904	0.069	0.732	−0.209	0.294
Age	0.160	0.426	−0.068	0.737	−0.137	0.494
Course of disease	0.216	0.280	0.008	0.967	−0.293	0.138
UWDRS	−0.440	0.022	0.404	0.037	−0.351	0.073

Table 4 Relationship between the score of PDSS, PSQI, ESS, and baseline condition in Neurologic presentation group—Spearman rank order correlation

	PDSS		PSQI		ESS	
	r	*P*	*r*	*P*	*r*	*P*
Sex	−0.024	0.904	0.069	0.732	−0.209	0.294
Age	0.160	0.426	−0.068	0.737	−0.137	0.494
Course of disease	0.216	0.280	0.008	0.967	−0.293	0.138
UWDRS	−0.440	0.022	0.404	0.037	−0.351	0.073

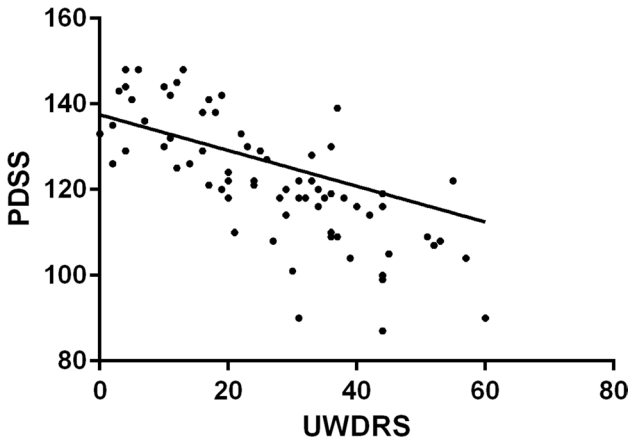

Fig. 3 Relationship between PDSS and UWDRS in the neurologic presentation group

Discussion

The present study revealed that patients with WD often suffer from sleep disturbances, mainly characterized by difficulty falling asleep, difficulty staying asleep, nocturnal motor symptoms, and daytime dozing, which is positive correlation to the severity of the disease. Nevsimalova et al. [17] assessed sleep disorders with other measures and got the same conclusions. Excessive daytime sleepiness or hypersomnolence is defined as the urge to sleep in a situation when a person is normally expected to be awake and alert [15]. And we found that the incidence of EDS is significantly increased, which reaches 12.7%. In addition, we found that UWDRS showed a negative correlation with PDSS ($r = -0.440$), and UWDRS has a higher negative correlation with PDSS in the neurologic presentation group ($r = -0.732$), which suggested the worse of the symptoms, the more serious of the sleep disorders. Currently, its internal mechanism may include damage of rapid eye movements (REM) cell and imbalance of neurotransmitter. The distribution of neuronal damage by copper deposition could be responsible for the disorders of REM-on cells (acetylcholinergic neurons) and REM-off cells (noradrenergic neurons) in brainstem. Because of the disorders of REM sleep, WD patients suffer from excessive daytime sleepiness [18, 19]. An abnormal metabolism of neurotransmitters, probably due to an increase in the activity of copper containing enzymes like dopamine β-hydroxylase with increased noradrenaline and loss of dopamine, has been reported [17, 18]. Dopamine is involved in the regulation of circadian rhythms, by dopaminergic D(2) receptors [20, 21]. Lima et al. [22] reported that blockage of dopaminergic D(2) receptors produces decrease of REM.

Moreover, we found that sleep quality was worse in patients with WD of neurologic presentation than that of hepatic presentation and others mainly cause difficulty falling asleep, tremor on waking, and daytime sleepiness. It is associated with excessive copper deposition in the brain. The distribution of neuronal damage in the brains of patients with WD is widespread, especially neurologic presentation, and includes structural abnormalities in corpus striatum and a certain degree of brain atrophy [23, 24]. High risk of tremor for the patients of neurologic presentation may be associated with the damage of striatum. Neuroimaging findings in WD suggest that copper deposition could cause a loss of a dopamine transporter and loss of D2 receptors in striatum [25, 26], which may be the mechanisms related to sleep disorder.

We are still facing the inevitable bias caused by the small-sample size and loss of objective auxiliary inspection data.

Our study provides references for following multicenter clinical research. Further in-depth study needs longitudinal follow-up with a larger sample and other factors that affect sleep.

Declarations

Ethical approval and Informed consent All include patients gave their oral and written informed consent. The study was approved by the Ethics Committee of the Jiangsu Taizhou People's Hospital.

Conflict of interest The authors declare no competing interests.

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