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ORIGINAL ARTICLE

Sleep disturbances in newly diagnosed treatment-naïve patients with Wilson's disease

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Abstract

Introduction Most neurodegenerative and chronic liver disorders are associated with sleep disturbances (SD). SD may be expected to occur in patients with Wilson's disease (WD), an inherited disorder of copper metabolism that mostly affects the liver and brain; however, there is a lack of observations, particularly in treatment-naïve WD patients.

Methods We evaluated SD in 19 newly diagnosed treatment-naïve WD patients. All patients completed the Beck Depression Inventory (BDI), the Athens Insomnia Scale (AIS) and the Epworth Sleepiness Scale (ESS), and underwent nightlong video polysomnography (vPSG). Results of vPSG in WD patients were compared with results from 19 sex- and age-matched healthy controls.

Results Depressive symptoms were not reported by patients on routine examination although three patients were diagnosed with mild depression. No patients reported SD during routine examination; three patients had insomnia according to the AIS and all patients scored 0 on the ESS. Despite the lack of reporting of SD by patients, significant differences were observed between WD patients and controls following vPSG analysis: WD patients had shorter mean total sleeping time (366.2 vs. 451.7 min), a lower percentage of rapid-eye movement (15.4 vs. 20.6%), longer sleep latency (36.7 vs. 10.4 min) and lower sleep efficiency (76.2 vs. 93.8%) (all $P \leq 0.01$). SD tended to be worse in patients with neurological WD compared with hepatic WD.

Conclusions As SD may precede depression and severely affect quality of life, our findings suggest that patients with WD should be screened for SD with suitable methods.

Keywords Copper · Sleep disorders · Depression, polysomnography

Introduction

Wilson's disease (WD) is an inborn disorder of copper metabolism with pathological copper accumulation and subsequent clinical symptoms in various organs, but particularly in the liver and brain [1–4]. The disease is caused by mutations in the copper transporting ATPase, ATP7B, which is responsible for copper excretion by hepatocytes [1–4].

The onset of symptoms usually occurs between the age of 5 and 35 years, most frequently with hepatic presentation (50−60% cases) ranging from clinically asymptomatic elevations in liver enzymes, through to hepatosplenomegaly, fatty liver disease, acute hepatitis, compensated or decompensated liver cirrhosis (up to 50% of patients) and in rare cases, to acute liver failure [1–5]. Occurring later than hepatic manifestations, neurological symptoms are observed in up to 40% of patients and mainly include movement disorders, such as dystonia, tremor, bradykinesia, chorea associated with dysphagia, dysarthria, drooling, gait and posture disturbances [4, 6]. Rarer neurological WD symptoms include epilepsy, neuropathy, olfactory disturbances and restless leg syndrome [4, 6]. Also common in patients with WD are psychiatric symptoms, which may be the first manifestation and lead to diagnosis in almost 25% of patients [7]. Psychiatric symptoms of varying severity may occur in around 70% [8] to 100% [9] of patients with WD and include subclinical cognitive deficits (diagnosed in psychological tests only), behavioral and mood disorders, mainly depression and less

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often, severe symptoms, such as psychosis or schizophrenia-like episodes [7]. Importantly, WD is potentially treatable if the treatment is started early and patients adhere to treatment recommendations [8–13], as also reported by recent observations related to the neuropsychiatric manifestations of WD during the COVID-19 pandemic [14].

Currently, sleep disturbances (SD) are suggested clinical symptoms of WD that may precede depression, as well as exacerbate psychiatric conditions including mood and anxiety disorders [15, 16]. Since WD is a primary liver disease as well as a neurodegenerative disorder, SD may be expected to occur at a similar frequency in WD as seen in chronic liver diseases and neurodegenerative disorders (e.g. Parkinson's disease, multiple system atrophy, Lewy body disease) [17–19]. However, limited data are available and most previous studies included treated patients with longstanding WD, most commonly of the neurological form, and with additional psychiatric manifestations [20–24]. Only four studies and one case report used video-polysomnography (vPSG) to evaluate SD in WD [22–26]. Some of these studies report an incidence of SD in WD of between 42 and 80% [23–26]; however, not all papers confirm such high incidence [25].

The pattern of sleep changes across the human lifespan. In healthy adults total sleep time is seven to eight hours. Light sleep (stage 1 N) accounts for about five% of total sleep time, stage 2 N between 45 and 55%. Slow wave sleep (deep sleep, stage 3) states between 15 and 25% and REM sleep 20–25%. Time of sleep latency should be less than 30 min., wake time after sleep onset less than 5%. Sleep efficiency should be more than 90%. A good quality of sleep depends primarily on the right amount of slow wave sleep and REM sleep, the possible shortest sleep latency and short wake after sleep onset. Consequently, sleep efficiency should be above 90 percent [27].

Given the importance of early detection of SD, which may precede other more severe psychiatric symptoms like depression [7], we used clinical scales and vPSG as an objective method to analyze SD in newly diagnosed, treatment-naïve WD patients.

Methods

Participants

This was a prospective study of consecutive, adult treatment-naïve patients with newly diagnosed WD seen at the Second Department of Neurology, Institute of Psychiatry and Neurology in Warsaw, Poland, between March 2015 and July 2018. The protocol was approved by the local ethics committee. Key eligibility criteria were a confirmed diagnosis of WD (Leipzig score of 4 points or more) [28], signed informed consent and the ability to participate in vPSG.

Assessments

WD patients were classified according to the predominant clinical symptoms (neurological or hepatic form) and according to the presence or absence of clinical symptoms (symptomatic or presymptomatic) as described previously [29]. All patients were evaluated by a trained neurologist using the Unified Wilson Disease Rating Scale (UWDRS) part I (consciousness), part II (activities of daily living) and part III (neurological deficits) [29].

All WD patients were examined by a psychiatrist, who is also a sleep specialist (WJ), and evaluation was performed according to the following scales: Beck Depression Inventory (BDI) [30], Epworth Sleepiness Scale (ESS) [31] and Athens Insomnia Scale (AIS) [32]. Diagnosis of insomnia was stated by experienced psychiatrist based on criteria proposed by American Academy from Sleep Medicine [33] and depression by American Psychiatric Association [34].

All WD patients underwent a routine electroencephalogram (EEG). Standardized vPSG was performed between 20:00 and 06:00 using a Grass Comet USA system with 200 Hz sampling. The vPSG consisted of six EEG leads, two electrooculography channels, chin and anterior tibialis muscles electromyographic channels, sensors necessary to assess breathing and saturation, electrocardiological sensors and body position sensors.

Video polysomnograms from age- and gender-matched healthy controls were obtained from our database, excluding any individuals with somatic or mental disorders and those taking chronic medications. Polysomnographic records were coded according to the American Academy from Sleep Medicine [27].

All WD patients had brain magnetic resonance imaging which is a part of routine diagnostic tests in our center. Typical abnormalities in brain MRI were defined as: symmetric hyperintense or mixed-intensity changes in T2-weighted images located in the caudate nuclei, putamen, thalami, midbrain, cerebellum, and pons; increased T1-weighted signal in MRI in the globus pallidus, substantia nigra and red nucleus; diffuse brain atrophy in the subcortical region and upper brainstem. Brain MRI was performed in all patients using the Philips Achieva 1.5T system (Philips Healthcare, Eindhoven, Netherlands).

Statistical analysis

Calculations were carried out using Statistica v.10 (Stat Soft Inc. 2011, Tulsa, OK, USA). Data are presented as number with percentage or mean with standard deviation (SD) or range. Comparisons of vPSG parameters between

WD patients and healthy controls or between neurological and hepatic subgroups with WD were performed using the two-tailed Fisher's exact test or the Mann–Whitney U test, as appropriate. $P < 0.05$ was considered statistically significant.

Results

Nineteen consecutive patients hospitalized due to newly diagnosed WD were recruited to the study. Demographic and clinical characteristics of analyzed WD patients are presented in Table 1. The mean age at recruitment/diagnosis was 28.4 years, with a mean latency period of 3.2 years between symptom onset and WD diagnosis. Nine patients had the hepatic form of the disease, while eight had the neurological form and two had no symptoms. Six WD patients had cirrhosis confirmed by liver biopsy and hepatologist consultation. Abnormal findings in brain MRI were present in our studied group in globus pallidus (8 patients, 42.1%), putamen (8 patients, 42.1%), caudate nuclei (5 patients, 26%), thalamus (6 patients, 31.6%), mesencephalon (10 patients, 52.6%), pons (9 patients, 47.4%), cerebellum (3 patients, 15.8%) and brain atrophy (4 patients, 21%). None of the WD patients had consciousness disturbances (UWDRS part I) as clinical symptoms of hepatic encephalopathy. In addition, there were no typical EEG abnormalities initiative of hepatic encephalopathy, with EEG results in the normal range in all included patients.

Table 1 Demographic and clinical characteristics of the analyzed patients

	Value
Total number of patients	**19**
Gender, male, *n* (%)	14 (73)
Age at study recruitment, mean ± SD (years)[a]	28.4 ± 8.6
Age at WD symptoms onset, mean ± SD (years)	25.2 ± 9.5
Disease latency, mean ± SD (years)[b]	3.2 ± 5.1
Clinical form of WD, *n* (%)	
Hepatic form	9 (47.3)
Neurological form	8 (42.1)
Presymptomatic form	2 (10.5)
Severity of neurological manifestations using UWDRS, mean [range] (points)	
UWDRS part I	0
UWDRS part II	1.5 [0−13]
UWDRS part III	7.8 [0−29]

[a]Equal to the age of diagnosis

[b]The time between first symptoms onset and disease diagnosis

SD standard deviation, *UWDRS* Unified Wilson's Disease Rating Scale, *WD* Wilson's disease

None of the patients complained of sleep problems or depressed mood in their medical history or routine examination. Mean BDI score was 5.9 points (0 points, $n = 2$; 1 point, $n = 1$; 2 points, $n = 2$; 4 points, $n = 4$; 5 points, $n = 1$; 6 points, $n = 2$; 7 points, $n = 2$; 10 points, $n = 2$; 15 points, $n = 1$; 17 points, $n = 1$; 19 points, $n = 1$). According to the standard diagnostic criteria validated in the Polish population [29], 16 (86%) patients had no depression, while 3 (14%) had mild depression (defined as > 10 points). Using the AIS scale, only 3 patients subjectively showed an insomnia-type disorder (2 points, $n = 2$; 3 points, $n = 1$), while ESS was 0 in all WD patients.

Comparing the results of vPSG in patients with WD and 19 matched healthy controls, all parameters of sleep were significantly affected in WD patients, except for stage 3 non-REM (NREM) sleep ($P = 0.08$) (Table 2). Total sleeping time was considerably shorter in WD patients compared with controls (366.2 vs 451.7 min, respectively; $P < 0.01$). Furthermore, the proportion of REM was 15.4% in WD patients and 20.6% in the control group ($P = 0.01$). We also observed differences in sleep latency, with a mean of 36.7 min in the WD group compared with 10.4 min in healthy controls ($P = 0.01$). Moreover, sleep efficiency was significantly lower in WD patients compared with the control group (76.2 vs. 93.8%, respectively; $P = 0.01$).

In a sub-analysis of vPSG comparing the neurological and hepatic form of WD, we found only one statistically significant difference, REM latency, which was twice as short

Table 2 Comparison of sleep parameters in groups of patients with Wilson's disease and healthy volunteers

	Wilson's disease $n = 19$	Healthy control $n = 19$	*P* value
Age, years	28.4 ± 8.6	29.1 ± 8.7	NS
Gender, male, *n*	14	14	NS
TIB, min	485 ± 7.9	478 ± 1.3	< 0.01
TST, min	366.2 ± 68.1	451.7 ± 16.2	< 0.01
N1, %	11.8 ± 6.7	5.2 ± 4.8	0.01
N2, %	31.4 ± 11.3	53.5 ± 5.7	< 0.01
N3, %	15.8 ± 5.4	19.4 ± 5.2	NS
REM, %	15.4 ± 6.1	20.6 ± 4.1	0.01
WASO, min	103.8 ± 64.2	4.3 ± 4.3	0.01
SL, min	36.7 ± 27.6	10.4 ± 3.1	0.01
RL, min	127 ± 91	106 ± 47	0.01
SE, %	76.2 ± 14.0	93.8 ± 4	0.01

Data are presented as mean ± standard deviation; $P < 0.05$ was considered statistically significant

N1 Stage 1 NREM sleep, *N2* Stage 2 NREM sleep, *N3* Stage 3 NREM sleep, *NREM* non-rapid eye movement sleep, *NS* not significant, *REM* rapid-eye movement sleep, *RL* REM latency, *SE* sleep efficiency, *SL* sleep latency, *TIB* time in bed, *TST* total sleeping time, *WASO* wake after sleep onset

Table 3 Comparison of sleep parameters in groups of patients according to the form of Wilson's disease

	Neurologic form $n=9$	Hepatic form $n=8$	P value
Age, years	27.7 ± 10.1	31.9 ± 8.0	NS
TIB, min	486 ± 5.1	487 ± 9.9	NS
TST, min	344.5 ± 77.1	383.4 ± 62.9	NS
N1, %	11.4 ± 4.6	13.3 ± 6.2	NS
N2, %	25.7 ± 9.1	35.4 ± 11.9	NS
N3, %	16.5 ± 6.3	16.3 ± 5.4	NS
REM, %	17.6 ± 7.9	13.6 ± 3.4	NS
WASO, min	126.5 ± 78.8	80.2 ± 41.7	NS
SL, min	32.7 ± 19.7	40.6 ± 38.4	NS
RL, min	80.3 ± 73.2	160.6 ± 77.6	0.04
SE, %	71.0 ± 16.7	78.6 ± 12.1	NS

Data are presented as mean ± standard deviation; $P<0.05$ was considered statistically significant

N1 Stage 1 NREM sleep, *N2* Stage 2 NREM sleep, *N3* Stage 3 NREM sleep, *NREM* non-rapid eye movement sleep, *NS* not significant, *REM* rapid-eye movement sleep, *RL* REM latency, *SE* sleep efficiency, *SL* sleep latency, *TI* time in bed, *TST* total sleeping time, *WASO* wake after sleep onset

in neurological patients when compared with patients having the hepatic form (80.3 vs 160.6 min; $P=0.04$) (Table 3). Additionally, there was numerically less NREM sleep stage 2 in patients with neurological form when compared with hepatic presentation (25.7 vs. 35.4%; $P=0.09$).

Among patients with neurological WD, two men had sleep pattern parameters that were similar to patients with narcolepsy. One 49-year old man had a REM sleep latency of 4 min, REM sleep percentage of 18.7%, wakefulness of 26.7% and sleep efficiency of 73.3%. Showing slightly different vPSG data, a 22 year old man had a REM sleep latency of 15.5 min, REM sleep percentage of 38.4%, wakefulness of 13.1% and sleep efficiency of 86.9%. However, it should be stressed that both patients did not report clinical symptoms of narcolepsy. They were also not confirmed by examining physician—sleep specialist.

Discussion

Our study is the first to show that, based on clinical scales and vPSG in newly diagnosed drug-naïve WD patients, SD may occur at early stages of the disease.

Theoretically, the high incidence of SD in WD patients could be explained by pathological copper accumulation in sleep pathways in the brain, especially in the brainstem, with affected monoaminergic neurons (so-called rapid eye movement [REM]-off neurons) and impaired γ-amino butyric acid-mediated neurotransmission [22–25]. Further, abnormal metabolism of neurotransmitters, especially dopamine deficiency, with increased noradrenaline levels have been detected in WD patients, which may explain restless leg syndrome or other SD [20–25]. This has been recently hypothesized in other SD arising from the brainstem dysfunction that REM-sleep behavior disorder (RBD) precede the onset of future extrapyramidal syndromes in Parkinson's disease and other neurodegenerative disorders [35, 36]. In our studied group also 9 patients (47.4%) had typical for WD lesions in pons confirmed in brain MRI. Our previous study revealed also abnormalities in blink reflex in newly diagnosed and treated patients which also supports possible pathological influence of copper deposits in the circuit linking the basal ganglia and brainstem [37]. Another potential mechanism for SD in WD, so far only observed in a rat WD model, relates to pineal night-specific ATPase (PINA), a variant of the *ATP7B* gene with copper transporter activity, which is involved in rhythmic copper metabolism, circadian rhythm, melatonin secretion and sleep regulation [20]. Additionally, liver cirrhosis due to WD may be another factor associated with circadian abnormalities and inversion of sleep pattern. Hepatic encephalopathy leads to increased levels of ammonia, a neurotoxin that affects levels of various neurotransmitters [20] as well as metabolism of melatonin (impaired hepatic metabolism of melatonin) [21].

The majority of included to our study WD patients showed features of insomnia, of considerable intensity in some cases, with adverse effects on sleep latency and sleep efficiency. However, most patients presented with mixed patterns of SD. Patients did not report SD during routine examination, which may suggest that they were not considered severe or that patients have adapted to them.

Our findings of significant SD in newly diagnosed drug-naïve WD patients are consistent with previous observations in older patients with long-standing WD on long-term pharmacotherapy [23–26]. Sleep parameters were disturbed similarly in drug-naïve and pretreated patients, without apparent worsening over time, which may suggest that de-coppering treatment not only suppresses the development of neurological symptoms, but also maintains or improves the quality of sleep in these patients. Some authors have suggested that de-coppering therapy may itself modify sleep patterns, mostly affecting REM sleep latency and duration [24]; however, the lack of de-coppering treatment ruled out such an effect on vPSG in our study.

In the current study, vPSG data were not consistent with data obtained from the medical history or inventory scales (AIS and ESS). Although a previous study has suggested the usefulness of Pittsburg Sleep Quality Index (PSQI) and ESS [24], our results did not confirm this, which may indicate that the questionnaires are not adequate in WD and may not accurately evaluate sleep disorders in patients with the disease. The discrepancy could be partly

explained by behavioral abnormalities in WD patients, resulting from frontal lobes deficits [7, 38], which was also observed when analyzing quality of life questionnaires as patients reported better quality of life than healthy volunteers (data not shown). Portala and colleagues [39], who assessed many clinical parameters, including quality of sleep and mood, found that WD patients reported better self-esteem than suggested by objective assessment. This supports the thesis that vPSG and not clinical tests should be a gold standard of SD diagnostic test for WD patients.

A previous study by Nevsimalova et al. [23] compared the sleep-pattern parameters of WD patients with hepatic ($n = 22$) and neurological ($n = 28$) forms. The authors found that patients with the neurological form showed a mild tendency towards more frequent awakenings, with a lower sleep efficiency and towards more light sleep (NREM 1). In our cohort, patients with neurological symptoms also had unfavorable sleep parameters compared with the hepatic form; however, most differences were not statistically significant.

In our study, two WD patients had sleep pattern similar to narcolepsy, although neither reported these symptoms during their routine examination. During their stay in the clinic, none of them showed clinical symptoms of narcolepsy. Moreover, in the medical examination, both of them denied the presence the clinical symptoms which are typical spectrum of narcolepsy symptoms. Nevismalova et al. [23] suggested that around 70% of WD patients felt the need for daytime napping compared with 24% in the control group. Additionally, in one case report, excessive sleepiness was reported in a patient who was diagnosed with WD in Hungary [40]. The fact that patients did not report symptoms of narcolepsy may result from their lack of criticism, which is part of the spectrum of symptoms of this disease [39].

Thus, it appears from our results, and those of other studies, that SD are frequent but underdiagnosed in WD patients. SD may anticipate more severe psychiatric disorders, like depression [17], affecting quality of life, compliance with WD treatment and often leading to anti-psychotic treatment introduction, which may result in severe drug-related neurological deterioration in WD [41, 42]. In our cohort, depression of medium severity was diagnosed in three out of 19 patients. In the literature, between 20 and 60% of WD patients develop depression over the course of the disease, with a high rate of suicide attempts, ranging between 4 and 16% [7]. Hence, we postulate that SD should be more frequently evaluated in WD as early diagnosis may help to avoid further serious psychiatric and neurological complications. Based on the limitations of AIS or ESS in WD, a new SD scale could be developed specifically for WD patients. Suspected patients with SD should also be further screened for depression.

Limitations of the study

The main limitation of our study was the relatively small number of participants. However, WD is a rare disease and even in clinical multicenter trials, the number of patients with newly diagnosed WD recruited within a few years is low and comparable to ours [41]. Furthermore, we did not analyze serum ammonia levels which may be increased in patients with liver cirrhosis (especially with hepatic encephalopathy); however, none of our patients presented with clinical symptoms of hepatic encephalopathy (UWDRS part I) or with any typical EEG abnormalities. We also did not perform plasma assessment of melatonin or catecholamines (dopamine, noradrenaline, etc.) and their products of degradation to analyze neurotransmitter disruption as a potential mechanism for SD in WD patients. Moreover patients from control group did not have brain imaging studies to exclude any potential subclinical/preclinical lesions. Additionally we did not correlate abnormal brain MRI findings with SD because of the small study group and the fact that brain MRI was performed in accordance with protocol evaluating structures and typical changes for WD and not for SD.

Conclusions

Patients with WD often suffer from SD even if they are not aware of it. Our results encourage further studies that should focus on larger cohorts of drug-naive WD patients with additional detailed psychiatric examination and follow-up to explore the impact of SD as well as its recovery/persistence over the course of anti-copper treatment.

Authors' contributions All authors helped to perform the research and contributed to the manuscript writing. WJ performed vPSG and psychiatric examination.

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