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Highlights

Patients with Wilson's disease (WD) have more frequent and severe insomnia than controls

Insomnia is more severe in WD patients with neurological phenotype than hepatic.

Insomnia in patients with WD has consequences on patient's quality of life

In WD, the severity of insomnia is correlated with the severity of depressive symptoms.

Abstract

Background/ Objectives

Wilson's disease (WD) is a rare genetic disorder that leads to copper overload, mainly in the liver then, in the brain. Patients with WD often complain about sleep disorders. We aimed to explore them.

Patients/Methods

Sleep complaints and disease symptoms were compared in 40 patients with WD (20 patients with hepatic phenotype matched to 20 neurologic one) and 40 age, sex and BMI matched healthy controls.

Results

Patients with WD had more frequently (32.5 vs 10.0%, $p<0.05$) and more severe (10.5±6.0 vs 7.6±4.8, $p<0.01$) insomnia than controls and insomnia was more severe in neurologic than hepatic form of the disease (8.73±5.8 vs 7.6±4.80, $p<0.05$). Insomnia severity was correlated with the severity of depressive symptoms ($r=0.53$, $p<0.001$). Compared to controls, patients reported more difficulties staying asleep and more consequences of insomnia on their quality of life. REM sleep behavior disorder was more frequent in WD (20 vs 0%, $p= 0.005$) than controls. Patients complained more frequently of nycturia (22.8 vs 7.6%, $p=0.003$) than controls. Patients did not differ from controls for sleepiness, restless legs syndrome and obstructive sleep apnea syndrome. Patients did not report cataplexia.

Conclusion

In patients with WD, insomnia and REM sleep behavior disorder are the two main sleep complaints. Insomnia is more frequent in neurologic than hepatic form of the disease. Severity of insomnia is associated with the severity of depressive symptoms.

Introduction

Wilson's disease (WD) is a rare autosomal recessive disorder associated with pathogenic mutations in the copper-transporting gene ATP7B located on chromosome 13.[1,2] The disease is characterized by a copper overload, initially in the liver. The spectrum of the liver disease is wide, from slight variations of liver enzymes to fulminant hepatitis or compensated cirrhosis. In more than a third of patients, the initial hepatic overload becomes multisystemic with brain involvement. Copper deposition in the brain concentrates mainly in the putamen and globus pallidus but also in the brainstem[3,4] with possible lesions of sleep/wake pathways.[5] Main neurologic features are motor symptoms[6] but non motor symptoms are also frequent associating depression, anxiety, psychosis, irritability and apathy, cognitive abnormalities, autonomic disturbances and sleep disorders.[7,8] Patients with WD complain frequently about their sleep but data on the subject are scarce.[9,10] Frequent nocturnal awakening, poor nocturnal sleep quality, delayed morning wake-up and sleepiness with frequent naps during the day have been reported.[11–15] Restless legs syndromes (RLS), REM sleep behavior disorders (RBD), and cataplexia were described. [12,13]

Many mechanisms may explain sleep disorders in WD including lesions of sleep wake pathways, motor, dysautonomic and psychiatric disorders, and treatments.[9,10]

The aim of our study was (1) to measure with validated scales the frequency of sleep disorders in patients with WD compared to healthy controls, and (2) to compare sleep disturbances among patients, depending on the severity of neurologic and hepatic impairments, cognition, depression and treatments.

PATIENTS AND METHODS

Patients

Twenty consecutive patients with neurologic form of WD were matched for age, sex and body mass index (BMI) to 20 patients with hepatic pattern of WD. They were recruited from the Wilson's disease national reference center in Paris (France). The 40 patients with WD (39 ± 11.7 years old, 19 males) were then matched for age, sex and BMI to 40 healthy controls. Controls were community-dwelling adults recruited via the volunteers' database of the Beau Soleil Clinic and the Lariboisière University Hospital. WD diagnosis was established according to international criteria with a Leipzig score ≥4.[16]

The present study was approved by the ethics evaluation committee of Inserm (Institutional Review Board IRB00003888, IORG0003254, FWA00005831 of the French Institute of medical research and Health) and all the participants gave informed consent to the protocol.

Methods

The severity of the disease was measured with 1) a hepatic score calculated from the clinical, biological and ultrasonographic evaluations[17] and 2) a neurological and functional assessment using the Unified Wilson's Disease Rating Scale (UWDRS).[18] The brain MRI score was done in neurological patients to evaluate the copper overload and the dissemination of the lesions.[17] Cognitive performance was explored using Montreal Cognitive Assessment (MoCA) score,[19] depression with Beck Depression Inventory,[20] excessive daytime sleepiness

with the Epworth Sleepiness Score (ESS).[21] Chronic insomnia was diagnosed according to the International Classification of Sleep Disorders (ICSD-3)[22] as (1) difficulty initiating or maintaining sleep, or waking up too early, or non-restorative or poor in quality sleep, (2) despite adequate opportunity and circumstances to sleep, (3) with daytime consequences for at least three months. Insomnia severity was measured with the Insomnia Severity Index.[23] Restless Legs Syndrome (RLS) was diagnosed if the patients fulfilled the international clinical criteria of RLS[24] and the severity of the syndrome was measured using the International RLS Rating Scale (IRLSRS).[25] Symptoms of obstructive sleep apnea syndrome (OSAS) were explored using the Berlin questionnaire[26] and clinical RBD the single-question screen for RBD;[27] symptoms were confirmed by clinical interview.

Statistical analysis

Categorical variables were presented as percentages and quantitative variables as means and standard deviations. Groups were compared using independent-sample t tests, or Mann–Whitney tests, depending on the normality of the distribution for continuous variables. Chi-squared tests or Fisher's exact tests were used for categorical ones. Pearson correlation coefficient was calculated for continuous variables. Significance level was set at $P < 0.05$.

RESULTS

WD Patients compared to controls

Description of our populations, WD characteristics and sleep complaints are presented table 1. Patients had a long disease duration (20.23 years ± 10.76) and were stabilized on a maintenance phase therapy. All patients were treated by chelators or zinc salt (D-Penicillamine 18/40, mean dose 994.1 mg/d; Trientine 2HCL 8/40, mean dose 975.0 mg/d; zinc acetate 12/40, mean dose 158.3 mg/d), except two. One neurological patient had a liver transplant and one hepatic patient was on low copper diet alone.

Patients complained of chronic insomnia much more frequently than controls and the severity of insomnia was higher in patients than controls. Patients with WD reported more frequently than controls difficulties staying asleep and noticeable consequences of their insomnia on their quality of life (figure 1). Patients reported to urinate at night more frequently than controls (22.8 vs 7.6%, p=0.003), and four of them had more than two urinations per night while no control had. Interestingly, 20.0% of the patients reported RBD when none of the controls did. RBD was not more frequent in patients under antidepressants then in patients without antidepressants (25% vs 75%, p= 0.4). RBD had started two years before the diagnosis of WD in one patient and after, (from 10 to 29 years) in the others. Among the eight patients complaining about RBD, episodes were frequent, occurring more than twice a week in six patients, and aggressive with violence in two patients, one having injured his bed partner seriously. WD patients and controls did not report cataplexia.

The number of subjects with moderate or severe depression and the depressive symptoms were higher in patients than controls, even though patients were more frequently under anti-depressants (10.1 vs 1.3%, *p=0.02*).

Complaints about RLS, sleepiness and OSAS did not differ between patients and controls. However, one patient complained about severe sleepiness (ESS>16) and two about severe RLS (IRLSRS>20).

WD treatments and sleep complaints

RLS was reported in 7/40 patients with WD (17.5% of our population) and 18/40 patients were under D-Penicillamine but none of the patients treated with D-Penicillamine had RLS *(p=0.008).* We did not find any other differences on sleep disorders frequency depending on the treatments of WD.

Comparison of the patients with WD depending on the clinical phenotype (hepatic vs neurologic).

Patients with neurologic phenotype were more depressed and were taking many more antidepressants (17.9 vs 2.6%, *P<0.01*) than patients with hepatic form. Insomnia was more severe in patients with the neurologic form of the disease than with the hepatic one. Both groups did not differ statistically for RLS, RBD, sleepiness, nycturia or OSAS complaints.

Correlations between sleep disorders severity and psychopathological and neurological severity of the disease.

Insomnia severity and depressive symptoms correlated for all subjects (r=0.56, *p<0.0001*), for patients with WD alone (r=0.53, *p<0.001*) and for patients with neurologic form of the disease (r=0.52, *p<0.002*). We did not find correlations between the number of micturitions at night, the disease duration and severity (hepatic score, UWDRS and brain MRI score), and insomnia.

Discussion

We explored the prevalence of sleep disorders with validated scales, in the rare population of patients with WD compared to controls. We observed that the frequency and severity of insomnia in WD were increased and that the severity of insomnia was higher in the neurologic than hepatic form of the disease. Moreover, the severity of insomnia was correlated with the severity of depression that was also increased in this population. Finally, the frequency of RBD was higher in WD compared to controls. Our patients did not have RLS, OSAS or sleepiness more frequently than controls. However, some of them had severe symptoms needing exploration and treatment.

In the few studies on sleep in WD,[11–15,28] symptoms of insomnia were also reported. These results were combined in a meta-analysis showing a higher frequency and severity of insomnia in WD compared to controls.[29]Here, we confirm these results in a population of WD patients treated in a long-term basis, but also identify neurologic form of the disease and depression as factors associated with insomnia.

We demonstrated that insomnia is severe in WD with consequences on the quality of life of the patients. Others have suggested that it could also have consequences on recovery after liver transplantation.[31] Even if anti-depressants were frequently prescribed in our population, many patients remained depressed and insomniac. Specific treatments of insomnia such as cognitive behavioral therapy, hypnotics or melatonin should be discussed more frequently in this peculiar population.

The frequency of RBD was increased in our population. Among the patients with RBD, the episodes were disabling because of the high frequency of the episodes, in 75% of the

patients, or because of their violence, in 25% of them. In one patient, RBD had appeared two years before symptoms of WD. The diagnosis of RBD could have allowed an earlier treatment. Moreover, it has been shown that anticopper therapies could treat RBD in patients with WD, reducing the copper overload in the subcoeruleus region responsible for REM sleep atonia. WD could be one of the rare diseases where RBD, sometimes very disabling, could be cured.[32] Symptomatic treatments of RBD such as melatonin or clonazepam can be used.

RLS was not more frequent in WD than in controls. This is in line with the result also obtained in the meta-analysis on sleep in WD.[29] Our patients were recruited consecutively in the WD reference center where they were followed. They were not recruited in a sleep laboratory. This might explain the discrepancy with the results of other studies on the topic.[15] RLS was severe in two patients in our study. They were both efficiently treated with gabapentin (600 mg/day). Because RLS might be directly linked to the neurological lesions of the disease, it might be severe in some patients and thus should be precisely explored and treated. Interestingly, patients under D-Penicillamine did not have RLS in our study. This treatment could have a protective effect on RLS acting on iron metabolism, also disturbed in WD.[30]

Finally, liver transplantation in selected patients with neurologic WD resistant to anticopper therapies might have beneficial effects on motor symptoms, but its potential effects on sleep disorders remain to be explored.[33]

Our study group was limited but WD is a rare disease especially in its neurological form. We have not been able to record sleep in these patients, but larger studies with sleep recordings

are needed to confirm these results, especially concerning OSAS diagnosis, because the screening value of the Berlin questionnaire is controversial.[34]

Conclusion

Insomnia and RBD are frequent and severe in WD. Insomnia severity is associated with depression and neurological pattern of the disease. RBD can precede WD symptoms for a few years. Other sleep disorders are not more frequent than in the general population but can be severe. These sleep disorders have important consequences on patients' quality of life and though should be more systematically explored and treated.

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Table1 Clinical and Sleep characteristics of patients with Wilson's disease compared to controls and depending on their hepatic or neurologic phenotype.

Figure 1 Comparison of Insomnia Severity Index total score and items in patients with Wilson's disease compared to controls. Patients have more insomnia (total score), more difficulties staying asleep and more impaired quality of life than controls.

Table 1 Clinical and Sleep characteristics of patients with Wilson's disease compared to controls and depending on their hepatic or neurologic phenotype.

	Controls	Wilson's Disease			*p*	
		All	Hepatic	Neurologic	Wilson's disease vs controls	Hepatic vs Neurologic Wilson's disease
Clinical characteristics						
Number of subjects	40	40	20	20		
Age (in years)	39.26 ± 12.07	39 ± 11.63	37.60±11.82	40.40 ±11.57	0.90	0.92
Sex *(% male)*	47.5	47.5	55.0	40.0	1	0.34
BMI (kg/m^2)	23.09 ± 3.07	22.87 ±2.68	22.95 ± 2.79	22.79 ± 2.63	0.93	0.94
Disease characteristics						
Disease duration (years)	-	20.23 ± 10.76	19.10 ± 10.94	21.35 ±10.72	-	0.34
Hepatic score	-	1.28 ± 0.96	1.40 ± 0.75	1.15 ± 1.14	-	0.12
Neurologic UWDRS score	-	-	0	9.05 ± 11.10	-	**<0.0001**
Brain MRI score	-	-	-	2.00± 1 .45		
Cognitive and psychopathological evaluation						
MOCA	28.44 ± 1.93	27.95± 5.09	27.63 ± 2.24	28.25± 6.84	**0.04**	0.6
Beck depression inventory (BDI)	6.0 ± 4.37	10.53 ± 6.02	6.55 ± 6.33	13.50 ± 10.52	0.13	**0.03**
Symptoms of depression (BDI >20, in *%)*	0	22.5	5.0	25.0	**<0.005**	0.18
Sleep complaints						
Restless legs syndrome (RLS, %)	10.0	17.5	10.00	25.00	0.31	0.18
RLS severity (IRLSSG/40)	15.25 ± 8.18	18.86 ± 7.47	18.50 ± 0.71	19.00 ± 9.14	0.5	1
Clinical RBD (%)	0	20.5	25.0	15.0	**0.005**	0.42
Epworth sleepiness score (ESS)	8.57 ± 4.08	7.72 ± 4.97	8.10 ± 5.36	7.35 ± 4.65	0.28	0.72
Subjects with sleepiness complaints (ESS>10, in %)	35.0	30.0	35.0	25.0	0.63	0.49
Sleep onset while driving (%)	20.0	17.1	15.8	18.7	0.91	0.82
Insomnia according ICSD-3 criteria (in %)	10.0	32.5	20.0	45.0	**0.02**	0.09
Insomnia severity index (ISI)	7.56 ± 4.80	10.53 ± 6.02	8.73 ± 5.78	12.25 ± 5.89	**0.008**	**0.03**
Subjects moderate or severe insomnia (ISI>14, in %)	7.5	27.5	15.0	40.0	**0.02**	0.08
High likelihood of sleep disordered breathing	7.5	17.5	15.0	20.0	0.17	0.67

UWDRS : unified Wilson's disease rating scale,ICSD-3 : International Classification of Sleep Disorders-3rd edition. IRLSSG : International RLS Rating Scale, RBD : REM sleep behavior disorder; Bold for $p<0.05$