Current Neurology and Neuroscience Reports (2019) 19:84
https://doi.org/10.1007/s11910-019-1001-4

SLEEP (M. THORPY AND M. BILLIARD, SECTION EDITORS)

Sleep Disorders in Wilson's Disease

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Abstract

Purpose of Review We aimed to review the sleep disorders described in Wilson's disease (WD), focusing on their mechanisms and treatments.

Recent Findings REM sleep behavior disorder or sleepiness can be warning signs of future WD. These early symptoms may significantly reduce the time to WD diagnosis. Early anti-copper therapies (chelators or zinc salts), reducing copper accumulation in the brain and though saving brain tissue, can allow the complete disappearance of these sleep disorders and of course improve the other symptoms of WD.

Summary Insomnia, restless legs syndrome (RLS), daytime sleepiness, cataplexy, and REM sleep behavior disorder (RBD) are present in WD and should be explored with video polysomnography and multiple sleep latency test. Suggested immobilization test could be useful in the diagnosis of RLS in WD. Motor and non-motor symptoms, dysautonomic dysfunctions, drugs, and lesions of the circuits regulating wake and sleep may be involved in the mechanisms of these sleep abnormalities. Adapted treatments should be proposed.

Keywords Wilson's disease · REM sleep behavior disorder · Sleepiness · Cataplexy · Insomnia · Restless legs syndrome

Introduction

Wilson's disease (WD) is a rare autosomal recessive disorder that leads to a copper overload, mainly in the liver and the brain. More than 600 pathogenic mutations in the copper-transporting gene ATP7B located on chromosome 13 have been described. The defective ATP7B function impairs both (1) copper incorporation in ceruloplasmin with consequently a release of free copper in the bloodstream, and (2) copper release into the bile, resulting in accumulation that leads to hepatocytes death [1, 2•, 3]. The spectrum of the liver disease is wide, from slight variations of liver enzymes to fulminant hepatitis or compensated cirrhosis. The European clinical prevalence of Wilson's disease is estimated to be between 1.2 and 2/100000 but the genetic prevalence is higher at around 1/7000. Incomplete gene penetrance or the presence of modifying genes could explain the difference between calculated genetic prevalence and clinical prevalence [4, 5].

If the copper overload is not controlled by anti-copper therapies, the initial hepatic disease becomes a multisystemic disorder with brain involvement. Copper deposition in the brain leads to specific cellular damage and concentrates mainly in the putamen and globus pallidus and also in the brainstem [6, 7•]. These lesions may be responsible for different motor and non-motor symptoms (NMS) especially sleep disorders if they reach sleep/wake pathways [8].

The two main clinical patterns of the extra-hepatic presentation are psychiatric and neurologic, the two groups sometimes being combined [1]. Those symptoms are present at the diagnosis in 18 to 68% of the patients. They typically begin from 20 to 30 years of age, a decade after the onset of liver disease. Main neurologic features are motor symptoms with dysarthria, dystonia, mixed tremor, chorea, Parkinsonism, and

This article is part of Topical Collection on *Sleep*

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Published online: 13 November 2019

drooling [2•, 3]. NMS can appear before and during ongoing WD process and include anxiety, depression, psychosis, irritability and apathy, cognitive abnormalities, autonomic disturbances, and sleep disorders [9].

Along with the lifetime use of copper-chelating agents or zinc salts, symptomatic treatments of neuropsychiatric symptoms may also be necessary and have consequences on behavior and on sleep regulation. Finally, motor, dysautonomic, psychopathological, or metabolic disorders associated with WD may also have consequences on sleep.

Sleep complaints are classical in WD patients whether they have a liver or extrahepatic phenotype, but data on sleep are scarce. The few studies available reported a frequency of sleep disturbances between 42 [10] and 80% [11••]. Reports on subjective sleep complaints showed frequent nocturnal awakenings [8], poor nocturnal sleep quality [10, 11••, 12, 13••, 14], delayed morning wake-up, and sleepiness with frequent naps during the day [10, 11••]. Agitation during sleep and cataplexy were also reported [11••, 13••]. Only three papers studied sleep recordings in WD patients ($n = 24$ to 36) [11••, 13••, 14••, 15••]. They did not either demonstrate differences between hepatic and neurological forms [10].

The goal of this paper is to make an update of important advances in the understanding of sleep anomalies in Wilson's disease.

Insomnia

Insomnia is defined by the international classification of sleep disorders as a repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate time and opportunity for sleep and results in some form of daytime impairment [16]. Sleep quality is impaired in WD according to all the studies on the topic [10, 11••, 12, 13••]. Poor nocturnal sleep is reported in 27.5% of the patients [11••]. They report increased sleep latency with an increased time falling asleep of 23 ± 21 min compared with 13 ± 14 in the control group ($p < 0.05$), and an increased number of awakenings of 2.0 ± 1.8 per hour compared with 0.9 ± 1.0 in the control group ($p < 0.01$) [10]. Finally, patients reported feeling less rested after sleep than controls [10]. Interestingly, insomnia can precede WD, being the first symptom to occur. Then, insomnia can get worse with the evolution of the disease. After all, insomnia can be associated with WD-specific medication withdrawal [14].

Sleep recordings of patients with WD compared with healthy controls have confirmed the altered sleep quality with reduced total sleep time and sleep efficiency and increased sleep fragmentation [11••, 13••, 14, 15]. Results about sleep latencies and the percentages of the different sleep stages varied among studies. The usual causes of sleep fragmentation on sleep recordings were most of the time not present. Apnea/hypopnea indexes were not different in patients with WD compared with controls (3.4 ± 3.7 vs 3.7 ± 3.6, $p = 0.6$) [17]. Periodic limb movements indexes were not significantly increased either (5.0 ± 9.0 vs 2.8 ± 5.3, $p = 0.4$) [17].

Many factors may trigger insomnia in WD such as pain and motor discomfort, psychiatric disorders, and also treatments and neuronal lesions modifying sleep-wake cycle (Fig. 1). Sleep can be delayed and disrupted in WD because of nocturnal akinesia, rigidity, dystonia, or tremor-inducing pain. Awakenings

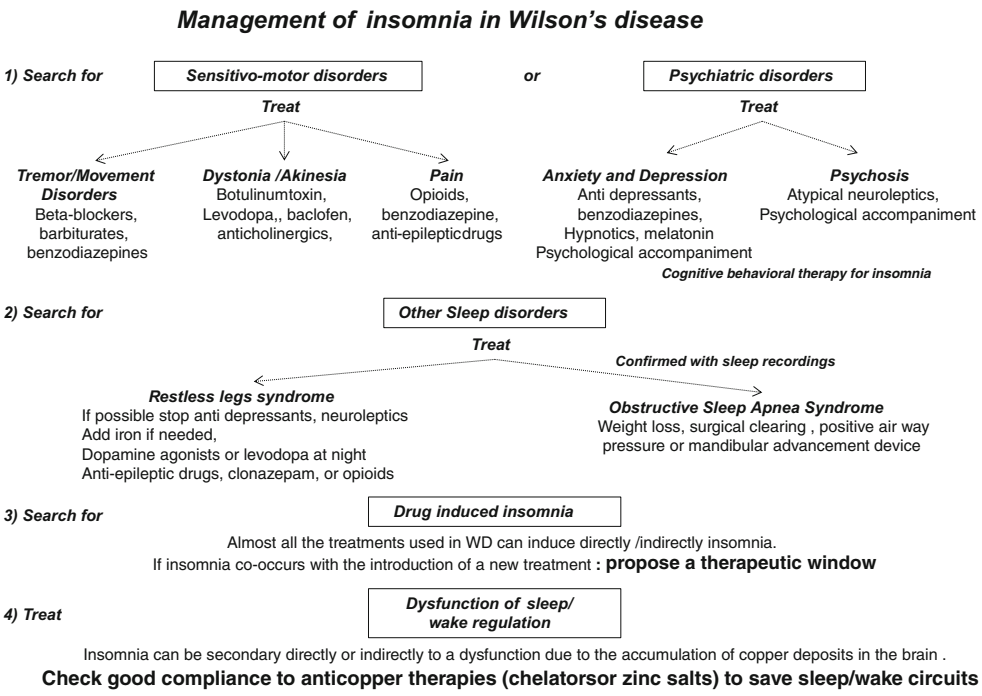

Fig. 1 Management of insomnia in WD

secondary to nocturia are more frequent in patients with WD (1.2 ± 1.1) compared with healthy subjects (0.2 ± 0.5, $p < 0.0001$) [10]. Psychiatric and behavioral disorders may be present in all patients with WD [3] associating anxiety, depression and personality troubles, behavioral disorders, and affective, psychotic, and cognitive abnormalities [3, 18]. Depression and anxiety are frequent comorbidities of insomnia in the general population. Depression is reported in different studies in 20 to 30% of the patients with WD [18, 19] and anxiety in around 10% [3]. Suicide attempts are reported in 4 to 16% of the patients with mood disturbances [20]. Psychiatric disorders may though play a major role in insomnia associated with WD. Finally, patients with WD can be treated with liver transplantation, a treatment which is per se very stressful for the patients. It is indicated in patients with fulminant hepatitis, end-stage liver disease, or even intractable neurological forms [21, 22]. Insomnia is reported in 45 to 77% of the patients after transplantation probably because of increased anxiety and stress, especially concerning allograft function monitoring and immunosuppressive therapy complications [23].

As in many other diseases, in WD, insomnia may be secondary to other sleep disorders such as RLS [13••], periodic limb movements, nightmares [10], and RBD [17]. Many treatments used in WD may contribute to insomnia. Dopaminergic drugs especially may disturb sleep, increasing sleep fragmentation at high doses [24]. De-coppering therapy, trihexyphenidyl, and anti-depressants may modify sleep structure especially REM sleep latency and duration [15].

The neuronal lesions of WD may be involved in insomnia because of their widespread diffusion including most of the sleep/wake regulating pathways [9]. Recent studies in animal models of WD [25–27] have identified in rats a pineal night-specific ATPase (PINA) that is a splice variant of the ATP7B gene and possesses some copper transport activity. The expression of PINA 100-fold higher during the night than during the day suggests an involvement of rhythmic copper metabolism in circadian rhythm and melatonin secretion. This has however never been demonstrated in humans with WD.

Cirrhosis, whatever the cause, might also be implicated in insomnia because it tends to be associated with circadian abnormalities and subsequent inversion of sleep pattern [28].

Sleepiness

The need of daytime napping is increased in WD with 70% of the patients reporting naps compared with 24% in the control group ($p < 0.001$) [11••]. One-fourth of the patients complained about sleepiness during the day when it was only reported in 9% of the controls ($p < 0.05$) [9]. It is surprising that only one-fourth of the patients complained about sleepiness during the day when 70% of them needed a nap. Probably their nap, resting them reduced their sleepiness between naps. However, the need to nap is usually considered as a component of sleepiness by definition.

Results on sleepiness measures on the Epworth Sleepiness Scale (ESS) [29] varied among studies. In one study, almost one-third of the patients reported being sleepy [11••]. This sleepiness was more severe in patients than in healthy controls (8 ± 5 [5–11] vs 6 ± 3 [4–9], $p < 0.05$) [11••]). Interestingly, ESS scores tended to be higher in patients with neurological compared with hepatic forms of the disease (9 ± 5 vs 7 ± 3) [11••]. This sleepiness was higher in patients with sleep complaints compared with those who did not have nighttime sleep problems (9 ± 5 vs 5 ± 3, $p < 0.05$) [11••]. These results on ESS were not confirmed in another study where they did not observe any difference comparing patients and healthy controls [12].

Only one study [11••] explored sleepiness with objective measures using the Multiple Sleep latency test (MSLT) in 28 patients with WD and sleep complaints [30]. Mean sleep latency was abnormal (< 8 min) confirming sleepiness in 14% and in the borderline range for sleepiness (> 8 min and < 10 min) in 11% of the patients. Most of them had a neurological form of the disease. No patient had the sleep onset REM periods characteristics of narcolepsy. This objective measure of sleepiness was not correlated with reduced total sleep time, and the sleep fragmentation caused by periodic limb movements and apnea/hypopnea [11••].

Many factors may be involved in the sleepiness observed in WD. First, it can be secondary to insomnia whatever its cause, through disturbed nocturnal sleep and compensating sleep rebound during the day. Second, the treatments used to improve WD can have sedative effects. Finally, the metabolic disorders and the lesions of the sleep/wake pathways may induce sleepiness. In a questionnaire-based study, [12] individuals with longer duration of the disease and on decoppering treatment complained less of sleepiness than the others, suggesting that the reduction of copper deposits in the brain may have improved the dysfunctions in the sleep/wake regulation. Such a hypothesis was also suggested by a case report [31] of a 21-year-old male patient with excessive daytime sleepiness and increased total sleep time as the first symptoms of WD. He had no cataplexy, sleep paralysis, or hallucinations. His sleep complaints were confirmed by a 24-h sleep recording with an increased total sleep time of 16 h. He also had many sleep onset REM periods and an increase REM sleep percentage on the 24-h recording as it is seen in narcolepsy. Anyway, all these abnormalities had disappeared after 14 months of D-penicillamine treatment suggesting a reversible sleep regulation dysfunction under chelators treatments. However, in some other cases, the sleep wake pathways may be destroyed by the deposits and the sleep dysfunctions may be final. This was the case in a less fortunate 26-year-old woman [32] with a hepatic form of WD diagnosed 9 years before. She reported excessive daytime sleepiness despite sleeping 7–8 h/night, which manifested in falling asleep at work, usually leading to a refreshing 3- to 5-min nap. The nighttime sleep recording did not detect any significant abnormality but the MSLT

confirmed a severe objective sleepiness with a mean sleep latency of 2.2 min. She had no sleep onset REM periods thus excluding secondary narcolepsy. She was diagnosed with secondary hypersomnia. Unfortunately, the treatment of WD with chelating agents did not improve her sleepiness suggesting the destruction of some sleep/wake pathways.

Restless Legs Syndrome

Restless legs syndrome (RLS) is defined by an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. It begins or worsens during periods of rest or inactivity such as lying or sitting, and in the evening or at night. It is partially or totally relieved by movement such as walking or stretching. It must not be the primary symptoms of another medical or behavioral condition [33].

RLS frequency is not higher in patients with WD (15/55 patients) than in controls (10/55, $p = 0.4$) in the first study questioning the patients on this phenomenon [11••]. This result is confirmed in a more recent study [13••], using the international criteria for the diagnosis [17] with only 13 patients on 42 fulfilling the criteria. The severity of the disease was moderate with a mean score on the International RLS Rating Scale [34] of 16.6 ± 7.9 (0–27).

Frequent movement disorders in WD such as tremor, chorea, akathisia, painful legs, and moving toes may mimic RLS. Sensory dysfunctions are usually absent in WD [35, 36], but the discomfort secondary to the movement disorders may induce a misleading sensation difficult to differentiate from RLS [13••].

The diagnosis of RLS in WD is challenging even using the validated criteria. The Suggested Immobilization Test (SIT) is a tool developed to diagnose primary RLS assessing both subjective leg discomfort and objective leg movements during a 1-h period of immobility prior to bedtime. When comparing patients with primary RLS and controls, SIT has high specificity and sensitivity for diagnosing RLS. It has been also validated in patients in PD where the confounding factors are mostly the same as in WD [37]. It could be a very interesting tool to diagnose RLS in WD.

Periodic limb movements (PLM) are stereotypic, repetitive, non-epileptiform movements of the legs, usually consisting of dorsiflexion of the ankle. They are usually reported by the co-sleeper and confirmed on the sleep recordings. They often increase sleep fragmentation. They are usually associated with RLS. No clinical complain of PLM in WD was reported to our knowledge.

In the main study focusing on RLS in WD [13••], RLS had appeared many years after WD onset and patients with RLS were older and had suffered longer from WD than patients without RLS. The main characteristics usually associated with primary RLS such as feminine predominance, positive family history, iron deficiency, and kidney abnormalities or polyneuropathy were not observed suggesting that RLS might be caused by WD.

In RLS, iron metabolism [38], central opiate system, and dopaminergic transmission are dysfunctional. Brain imaging and postmortem studies in RLS have shown an increase in presynaptic dopaminergic activity [39, 40] However, neither dopaminergic neuronal loss nor reduction of dopamine content in post mortem brains have ever been observed [41]. In WD, on the contrary, dopaminergic neuronal loss at presynaptic and postsynaptic levels has been described [42].

Another mechanism that could explain RLS in WD is the copper accumulation described in medial thalamic nuclei and thalamocortical circuit because these structures are dysfunctional in RLS according to PET and functional MRI studies.

Finally, WD is characterized by an iron accumulation in the brain secondary to the ferroxidase activity of ceruloplasmin, catalyzing Fe2+ to Fe3+ incorporating iron into ferritin. This pathological overload of iron has been described in the putamen, caudate, and pontine tegmentum of neuropsychiatric patients with WD [43] but has never been studied in patients with WD and RLS.

On the other hand, an iatrogenic mechanism of RLS in WD can also be discussed [44]. The treatments with anti-depressants, whatever their type, have been associated with RLS. This mechanism should always be discussed in the treatment. Finally, dopaminergic treatments sometimes used in WD patients could, in some cases, trigger RLS through an augmentation syndrome, a sensitization of the dopaminergic receptors increasing RLS.

Cataplexy

Cataplexy is characterized by sudden and bilateral loss of muscle tone provoked by strong emotions. These triggering emotions are usually positive (laughter, pride…). The duration of cataplexy is usually short, lasting few seconds [16]. Cataplexy is pathognomonic for narcolepsy. Cataplexy was reported in WD more frequently than in controls (24.1% vs 3.6, $p = 0.005$) [11••]. It is however surprising that so many controls had also reported cataplexy in this study. No details were given on the association between cataplexy and the other symptoms of narcolepsy (sleepiness, hallucinations, sleep paralysis, or RBD) in these patients.

REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is a parasomnia characterized by abnormal motor behaviors occurring during REM sleep because of the loss of the physiological atonia normally present during this sleep stage. Able to move, patients make the gesture that they are dreaming of. They laugh, talk, shout, fight, kick, cycle, exercise their job… [43]. RBD may be associated with injuries of the patient or the co-sleeper

because of the violence often associated with the dream contents or the gestures [44].

RBD was reported in half of the patients with WD whatever the neurological or hepatic form of the disease [11••, 14]. As in other conditions associated with RBD, patients with RBD had more symptoms when they had more vivid dream content. Some treatments of WD could influence RBD with patients under D-penicillamine having more symptoms of RBD than those treated with zinc salts [11••]. RBD had started before any other symptom of WD in three patients out of five. As in other pathologies associated with RBD, in WD, violent behaviors and injuries were reported although patients had no aggressiveness during the day. Most of the patients had psychiatric history with bipolar, ongoing depression, anxiety, and depressive disorder or psychotic disorder in the past. Patients with WD and RBD had more sleepiness, less sleep quality, more psychiatric symptoms and tended to have a younger onset of the disease than patients with WD without RBD [17].

Looking for RBD, one study with sleep recordings found increased muscle tone in several patients during 10 to 15% of their REM sleep time, but none of them reached the commonly accepted threshold for the diagnosis of RBD [11••]. Another study on the topic identified 12.2% (5/41) of the patients fulfilling both clinical and polysomnographical criteria for RBD [14]. Nine patients did not have a clear history of dream enactment but had increased tone during REM sleep suggesting that RBD might have been underestimated. REM sleep without atonia was increased in patients with WD compared with controls (17.7 ± 13.5 vs 8.7 ± 4.0, $p < 0.001$) and in patients with WD with RBD compared with patients without RBD (41.4 ± 19.5 vs 13.7 ± 6.5, $p = 0.001$) [17].

The lesions or dysfunctions in the descending pathways responsible for muscle atonia during REM usually cause RBD. The fearful and violent dreams enacted during RBD would result from the disconnection between the midbrain and the limbic system. Mesencephalic tegmental/tectal sonographic hyperechogenicities have been described in all (4/4) patients with RBD and WD and ponto-mesencephalic tegmental MRI hyperintensities half (2/4) of them in the only study focusing on the subject [14]. It suggests that the mechanisms of RBD in WD are similar to those described in other diseases.

In WD, sleep abnormalities whatever their type may be secondary to the copper deposits in the brain leading to the destruction (usually irreversible) or the dysfunction (reversible) of the sleep/wake circuits. The two specific treatments of WD, the chelators or the zinc salts, may allow in the majority of cases a complete resolution of the sleep/wake disorders by removing the copper from brain tissues. The treatment of WD is though the first line treatment of all the sleep disorders associated with WD. It will be prescribed anyway the patient having or not sleep disorders. The appearance of sleep disorders under anti-copper treatment may reflect looseness in the compliance that should be corrected. A side effect of these treatments should also be discussed. Then, the treatment of the symptoms of WD that can impact on sleep quality should be proposed. Finally, the symptomatic treatments of the sleep disorders are indicated.

Insomnia

Insomnia can be improved by reducing nocturnal discomfort using specific treatments against motor symptoms and pain [45] (Fig. 1). Botulinum toxin can be used to relieve pain in dystonia. Levodopa, baclofen, and anticholinergics can reduce rigidity and movement disorders [45]. Beta-blockers/propranolol, barbiturates/primidone, and benzodiazepines/clonazepam can improve tremor. Finally, treatments such as anticholinergics (trihexyphenidyl), baclofen, benzodiazepines (clonazepam), and anti-epileptic drugs (oxcarbamazepine...) may also reduce pain.

When insomnia is associated with psychological or psychiatric disorders (Fig. 1), a psychological accompaniment including cognitive behavioral therapy for insomnia (CBT-I) should be proposed. CBT-I is based on a structured program allowing the patient to identify and replace thoughts and behaviors that cause or worsen insomnia with habits that promote sound sleep. Antidepressants, clonazepam, hypnotics (Z-drugs), or melatonin may also be needed. In one patient, WD started with insomnia. This sleep disorder was associated with mania, increased energy, and delusions of thought control. Then psychotic symptoms became predominant. Primary treatment of WD and psychotropic medication improved insomnia [46].

Sleep disorders disrupting or delaying sleep must be researched by questioning the patients and recording sleep if necessary (Fig. 1). Obstructive sleep apnea syndrome may be treated as it is usually done, proposing surgical clearing if there is an identified and reachable obstacle, weight loss if body mass index is increased, positive air way pressure, or mandibular advancement device otherwise.

If an iatrogenic mechanism of insomnia is suspected because of the co-occurrence of the insomnia and the introduction of a new treatment, then this treatment should be stopped if possible, to see if insomnia is reversible. We recently observed this phenomenon in a 17-year-old patient with a neurological form of WD associating Parkinsonism, dysarthria, and writing difficulties. Liver explorations detected cirrhosis. Insomnia appeared a few days after the introduction of D-penicillamine, a first-line chelator and fully resolved after switching to another copper chelator, the trientine, suggesting the iatrogenic origin of insomnia in this case.

Sleepiness

If patients complain about impaired night time sleep, a video-polysomnography can identify sleep disruptors such as apnea or PLM that should be treated (as described before for sleep apnea and further for PLM). If insomnia is not liked to other sleep

disorders, then sedative drugs at night should paradoxically be proposed to treat indirectly this somnolence. Patients should be informed of the risk of increased somnolence in the morning, at least in the beginning of the treatment, and should avoid driving.

On the other hand, WD patients may be sleepy during the day because of the sedative effects of their symptomatic treatments. These treatments are most of the time opiates, benzodiazepines, anti-depressants, anti-epileptic drugs, or dopaminergic drugs. A reduction or the interruption of these sedative treatments should be proposed to improve sleepiness. However, this reduction is not always possible when these drugs are requested.

When sleepiness is severe, scheduled naps during the day may be useful and stopping the driving is necessary. If sleepiness has been objectively measured on MSLT, psycho stimulants such as modafinil, pitolisant, or methylphenidate may be used even if they have never been validated to date in WD.

Restless Legs Syndrome

RLS in WD should be treated in the same way as in primary RLS. First, if ferritinemia is lower than 75 ng/ml, an iron supplementation should be tested. Second, all treatments known to be associated with RLS should be reduced or excluded if possible, especially anti-depressants, anticholinergics, neuroleptics, and antihistaminic agents. Finally, dopamine agonists, calcium channel alpha-2-delta ligands, clonazepam, or opioids can be used to treat the symptoms in the evening. Sometimes, promoting the intake of dopamine agonists and levodopa in the evening might be enough to reduce the symptoms. Augmentation syndrome has never been reported in RLS in WD to our knowledge.

If PLM induce sleep fragmentation and disturbed sleep, they should be treated with the same treatment as for RLS.

REM Sleep Behavior Disorder

In WD, RBD could be reversible because of the improvement of the brain dysfunctions with anti-copper therapies (chelators or zinc salts) that could restore REM sleep atonia circuits. In one patient, treated with trientine, RBD symptoms have progressively vanished as the pontine and mesencephalic tegmental lesions on RMI almost completely disappeared too. Brain saving with early treatment in WD may allow a complete disappearance of the lesions inducing RBD.

If RBD persists, is frequent, or is violently impacting the patient's or the co-sleeper's quality of life, it should receive a specific treatment. First, it consists in the reduction or the interruption, if possible, of all the treatments that can trigger RBD especially anti-depressants. Then, the patients should be informed of the possible violence of this phenomenon and advised to secure the environment of their bed: to keep away the contending objects, to avoid bedside lamps, and sometimes to put the mattress on the floor in order not to fall out of bed. At last, clonazepam (0.5–2 mg) or melatonin (3 to 12 mg) at night [47] can be prescribed.

WD represents an interesting model of reversibility of different kind of sleep disorders (insomnia, sleepiness and RBD). This condition is usually rare: most of the sleep disorders associated with neurological diseases are final because of the irreversible neuro-degeneration. This should motivate further studies to explore these sleep disorders, their mechanisms, and their reversibility with early anti-copper treatments. For example, cataplexies were described in some patients but there was no information about the other symptoms of narcolepsy and about the results of the MSLT of these patients (Sleep onset REM periods, short sleep latency…). The diagnosis of narcolepsy in WD should be first confirmed. Then, hypocretin levels have never been measured in these patients. It would be interesting to explore this neuropeptide, fallen in narcolepsy-type 1 [48]. Would it be decreased? And, would this decrease be reversible with anti-copper therapies? Many questions remain on this domain. Functional imagery would also be critical to understand the reversibility of these sleep disorders and their transitory impaired pathways.

Sleep disorders in WD are probably underestimated and neglected although they might have important consequences on the quality of life of the patients. Insomnia, sleepiness, RLS, and RBD should be looked after, explored with video-polysomnography at the slightest symptoms, and of course treated. Sleep recordings should be repeated in time because of the variability of the sleep disorders according to the evolutions of the disease. Anti-copper therapies (chelators or zinc salts) used as early as possible may allow a complete disappearance of the sleep disorders.

Compliance with Ethical Standards

Conflict of Interest Valérie Cochen De Cock, France Woimant, and Aurélia Poujois each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent All the studies have already been published and follow ethical standards.

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