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SCIENTIFIC INVESTIGATIONS

# Sleep Pathology in Creutzfeldt-Jakob Disease

Peter Kang, MD[1,*]; Gabriela S. de Bruin, MD[1,*]; Leo H. Wang, MD, PhD[2]; Beth A. Ward, MD[3]; Beau M. Ances, MD, PhD[1]; Miranda M. Lim, MD, PhD[4]; Robert C. Bucelli, MD, PhD[1]

*[1]Department of Neurology, Washington University School of Medicine, Saint Louis, MO; [2]Department of Neurology, University of Washington School of Medicine, Seattle, WA; [3]St. Luke's Hospital Sleep Medicine and Research Center, Saint Louis, MO; [4]Sleep Disorders Clinic, VA Portland Health Care System; Departments of Medicine, Neurology, and Behavioral Neuroscience, and the Oregon Institute of Occupational Health Sciences, Oregon Health & Science University, Portland, OR; *contributed equally to the manuscript*

**Study Objectives:** Associations between sleep and neurodegenerative diseases have become increasingly evident. This study aims to characterize the prevalence and type of sleep pathology in Creutzfeldt-Jakob disease (CJD), a rapidly progressive, fatal neurodegenerative disease.

**Methods:** In this observational cross-sectional cohort study, we performed a retrospective analysis of sleep signs and symptoms in a consecutive group of patients with definite CJD at a tertiary care medical center (n = 28). Polysomnography was performed in 14 patients.

**Results:** Although only 5 of 28 patients carried a premorbid sleep diagnosis, signs/symptoms of sleep pathology were present in 25 patients. Eleven reported hypersomnia whereas 13 reported insomnia. Seven had restless legs symptoms and/or periodic limb movements of sleep, and nine reported parasomnias. Of the 14 patients who underwent polysomnography, 1 did not show sleep, 9 (69%) had poorly formed or absent sleep spindles and/or K-complexes, and 10 (77%) had sleep-disordered breathing. Of the 8 patients who experienced rapid eye movement (REM) sleep during the polysomnography, 3 (38%) showed REM sleep without atonia, and 2 patients met criteria for REM sleep behavior disorder. Median total sleep time was 226 (interquartile range [IQR] = 195–282) min. Median sleep efficiency was 58.5% (IQR = 41–65.5 %). Median REM time was 0.35% (IQR = 0–7.125%). Five patients (38%) demonstrated periodic limb movements during polysomnography. One case is presented.

**Conclusions:** Sleep pathology is common in CJD, and screening for sleep pathology is indicated in the evaluation of patients with rapidly progressive dementias. Early identification and treatment of sleep pathology may provide an intervenable target for CJD.

**Keywords:** Creutzfeldt-Jakob disease, dementia, neurodegeneration, prion diseases, sleep disorders

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## INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a fatal, neurodegenerative, rapidly progressive dementia (RPD) caused by the accumulation of misfolded prion protein, $PrP^{Sc}$.[1,2] Neuronal cell death in CJD occurs at an accelerated rate compared to other neurodegenerative conditions (e.g., Alzheimer disease [AD] or Parkinson disease [PD]). It has become increasingly evident that sleep dysfunction commonly accompanies chronic neurodegenerative conditions and may predate the onset of cardinal symptoms of these disorders by several years.[3–6] For example, rapid eye movement (REM) sleep behavior disorder (RBD) may precede the development of a synucleinopathy by decades,[7–10] and reduced sleep efficiency is seen in patients with preclinical AD.[11] Furthermore, increasing evidence shows that sleep disruption can accelerate neurodegenerative processes including toxic protein aggregation in preclinical models, and increases the risk of developing symptomatic AD.[4,11–13] Therefore, understanding the relationship between sleep pathology and CJD may enhance our understanding of the bidirectional relationship between sleep and other common neurodegenerative processes. Although sleep symptoms have not been traditionally viewed as a cardinal symptom of CJD, sleep-wake disturbances are a significant source of morbidity and adversely affect quality of life in these patients. Sleep disturbances are also a major cause of caregiver burnout and nursing home placement in individuals with dementia.[14]

Much of our understanding of sleep aberrancies in prionopathies comes from studies of fatal familial insomnia (FFI). The thalamic neurodegeneration in FFI leads to early progressive loss of sleep, oneiric stupor, and autonomic and motor hyperactivity.[15,16] Polysomnography (PSG) is an important diagnostic tool in FFI, demonstrating early and progressive reduction of total sleep time (TST), loss of sleep spindles and K-complexes, disruption of normal sleep structure, sleep fragmentation, and periods of subwakefulness interrupted by brief episodes of REM sleep with or without atonia, often associated with dream enactment behavior.[15]

**BRIEF SUMMARY**

**Current Knowledge/Study Rationale:** Associations between sleep and neurodegenerative diseases have become increasingly evident. Our study aims to characterize the prevalence and type of sleep pathology in Creutzfeldt-Jakob disease (CJD), a rapidly progressive, fatal neurodegenerative disease.

**Study Impact:** Sleep pathology is common in CJD, and screening for sleep pathology is indicated in the evaluation of patients with rapidly progressive dementias. Early identification and treatment of sleep pathology may provide an intervenable target for CJD.

In the most recent classification schema, sleep disturbances have not been included as a principal symptom of CJD.[2] The literature on sleep symptoms in CJD consists primarily of case reports and series. In one large case series of psychiatric manifestations in 126 patients with probable or definite CJD, analyses were limited to self-reported rates of insomnia and hypersomnia, and did not assess for other common sleep disorders.[17] Objective studies including PSG data in patients with CJD have been even more limited, with the largest series to date consisting of only six participants.[18] Our study aims to fill this gap by characterizing the full spectrum of sleep abnormalities in a consecutive group of patients with autopsy-proven CJD at a single institution using reports from both patients and caregivers, as well as PSG data. We also present a case vignette highlighting the importance of identifying sleep pathology in patients with RPD.

## METHODS

### Participants

Clinical history and diagnostic data (cerebrospinal fluid [CSF], electroencephalography [EEG], magnetic resonance imaging [MRI], laboratory values, and PSG from a subset) were retrospectively obtained from 28 consecutive subjects with definite CJD evaluated at our institution between the years of 2005–2014. All participants had a detailed neurologic examination and met the following inclusion criteria: (1) RPD; (2) workup excluding other plausible diagnoses; (3) at least one additional clinical sign/symptom (myoclonus, pyramidal/extrapyramidal signs, visual disturbances, cerebellar dysfunction, higher cortical dysfunction, or akinetic mutism)[2]; and (4) brain autopsy with evidence of definite CJD (analyzed at the National Prion Disease Pathology Surveillance Center [NPDPSC] at Case Western Reserve University).

### CSF, EEG, and MRI

All available CSF samples were sent to the NPDPSC for biomarker (total tau and 14-3-3) analysis as part of the diagnostic criteria for CJD. EEG records from clinical routine EEG studies were evaluated for the presence of periodic sharp wave complexes (PSWC) with a variability of < 500 msec or periodic generalized complexes (lasting 100–600 msec) that were biphasic or triphasic in morphology, as part of the diagnostic criteria for CJD. Patients without a contraindication underwent MRI with standard clinical T1-, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). Scans were evaluated for increased signal in the caudate nucleus, putamen, thalamus, or at least two cortical regions (temporal-parietal-occipital) either on DWI or FLAIR sequences, according to previously published diagnostic criteria.[19–21]

### Sleep Data

Sleep data included premorbid sleep diagnoses and sleep symptomatology at the time of evaluation, including self-reported hypersomnia, insomnia, restless legs, periodic limb movements (PLMs), and parasomnias such as confusional arousals, somniloquy, somnambulism, and dream enactment behavior. Hypersomnia was defined by excessive daytime sleepiness. Insomnia was characterized by difficulty falling or staying asleep resulting in daytime impairment. Restless leg syndrome (RLS) was clinically diagnosed using the International RLS study group criteria of (1) an urge to move limbs that is usually associated with paresthesias or dysesthesias, (2) symptoms that start or become worse with rest, (3) at least partial relief with physical activity, and (4) worsening of symptoms in the evening or night. Leg movements in sleep were defined as frequent stereotypic leg movements in sleep described by family members or seen on PSG. Parasomnias were defined by family members as complex behaviors in sleep such as talking, walking, goal-directed behaviors, or clear dream-enactment behaviors with dream recall. Confusional arousals were defined as episodes where patients appeared neither clearly awake nor asleep, were partially interactive for a period of time, and had no recall of the event the following day. A detailed sleep history was obtained by a board-certified sleep specialist in all cases. When participants were unable to provide a sleep history, it was collected from collateral sources and a review of the medical record.

PSG data were obtained in 14 of 28 subjects. Indications for PSG typically included suspicion for sleep-disordered breathing or other factors in the history that suggested untreated sleep disorders as a potential contributor toward morbidity (see example case). When PSG data were available, it was analyzed by one of two board-certified sleep medicine physicians in accordance with the American Academy of Sleep Medicine (AASM) 2007 criteria for the scoring of sleep and associated events. Standard PSG outcome measures included TST, periodic limb movement index (PLMI), presence of REM sleep without atonia according to visually scored AASM criteria using electromyography leads placed on the chin and the lower extremities, presence and severity of sleep-disordered breathing, sleep efficiency, percentage of different sleep stages and presence of EEG markers of sleep including sleep spindles, and K-complexes. PSG records were also evaluated for PSWC within the EEG and compared with findings from the routine EEG when available (**Table S2** in the supplemental material). Normative data for the human sleep cycle varies by age and has been well established.[22] For patients who underwent sleep study, neurologically active medications that may affect PSG findings were assessed at the clinical encounter associated with the PSG.

### Standard Protocol Approvals, Registrations, and Patient Consents

As all subjects were deceased, this study met the Washington University institutional review board criteria for exempt status.

## RESULTS

### Participant Characteristics and Clinical Findings

A total of 28 patients meeting inclusion criteria were identified and are summarized in **Table S1** in the supplemental material. Of these, two (7%) eventually received a diagnosis of E200K variant of familial CJD. One of 26 sporadic CJD cases received

**Table 1**—Polysomnography findings in our Creutzfeldt-Jakob disease cohort.

| Patient ID | Onset to PSG (d) | PSG to Death (d) | % Disease Duration at PSG | Sleep Efficiency (%) | SS/KC | % N3 | % REM | RSWA | AHI |
|---|---|---|---|---|---|---|---|---|---|
| 15[a] | 72 | 4 | 95 | 55 | SS−/KC− | 0 | 0 | N/A | 19.3 |
| 16 | 85 | 11 | 89 | 43 | SS−/KC+ | 0 | 5.5 | No | 17.3 |
| 17 | 214 | 78 | 73 | 44 | SS+/KC− | 0 | 0 | N/A | 0 |
| 18 | 104 | 29 | 78 | 20 | SS−/KC+ | 0.1 | 0 | N/A | 2.9 |
| 19 | 216 | 210 | 51 | 71 | SS+/KC+ | 3.8 | 0.3 | No | 9.4 |
| 20 | 155 | 21 | 88 | 83 | SS-/KC− | 0 | 0 | N/A | 9 |
| 21 | 252 | 127 | 66 | 65 | Not reported | 0 | 17.2 | Yes | 0.69[c] |
| 22 | 58 | 20 | 74 | 63 | SS−/KC− | 0 | 3.8 | No | 4.7 |
| 23 | 45 | 68 | 40 | 24 | SS+/KC+ | 0 | 0.4 | No | 6 |
| 24 | 150 | 124 | 55 | 62 | SS+/KC+ | 0 | 12 | No | 9.5 |
| 25 | 23 | 278 | 8 | 35 | SS+/KC+ | 0 | 0 | N/A | 49 |
| 26 | 222 | 44 | 83 | 67 | SS−/KC+ | 0 | 40.7 | Yes | 110.7 |
| 27[b] | 161 | 69 | 70 | 0 | SS−/KC− | N/A | N/A | N/A | N/A |
| 28 | 92 | 20 | 82 | 61 | SS−/KC− | 0 | 11.7 | Yes | 0[c] |

[a] In the absence of sleep spindles and K-complexes, the stages in this study were dichotomously scored as sleep (without substages N1, N2, N3) or wake. No rapid eye movements, sawtooth waves, or atonia was present to score REM. [b] No electrographic sleep recorded (see Discussion for full details). [c] Study done on positive pressure ventilation because of known premorbid sleep-disordered breathing (no baseline data post Creutzfeldt-Jakob disease diagnosis). AHI, apnea-hypopnea index; d, days; KC, K-complexes; N/A, not applicable; N3, Stage 3 non-REM sleep; REM, rapid eye movement sleep; RSWA, REM sleep without atonia; SS, sleep spindles.

a diagnosis of variable protease-sensitive prionopathy (VPSPr). Thirteen patients were women (46%). Cerebellar signs were present in 24 patients (86%). Pyramidal or extrapyramidal signs were seen in 25 patients (89%). Visual symptoms were present in 7 patients (25%). Myoclonus was present in 18 patients (64%). Eleven patients (39%) had cortical signs and 11 (39%) developed akinetic mutism.

## Diagnostic Testing

EEG testing for electrodiagnostic abnormalities revealed that PSWCs or triphasic waves were present in 10 of the available 27 EEGs (37%). Detection of PSWCs in the EEG from PSG studies was also used for evaluating PSWCs (see **Table S2** in the supplemental material). Two patients did not have MRI scans due to MRI-incompatible pacemakers. One patient underwent MRI at another institution and the results were not available for review. Of the remaining 25 patients, 23 (92%) showed abnormalities on MRI consistent with the diagnosis of CJD, including increased signal in the caudate nucleus, putamen, thalamus, or at least two cortical regions (temporal-parietal-occipital) either on DWI or FLAIR sequences. CSF analysis was not available in four patients. Of the remaining patients, 17 (71%) had a positive 14-3-3 antigen and the median total tau value was 3,253 (interquartile range [IQR] = 2,103–5,440) pg/mL. Total tau values > 1,200 pg/mL are strongly suggestive of CJD; 20 subjects (83%) showed total tau values > 1,200 pg/mL. CJD subtyping was conducted using Western blot analysis for protease resistant prion protein subtyping in combination with genotyping the codon 129 methionine(M)/valine(V) polymorphism of the prion protein gene. The most common molecular subtype was MM1 (11 patients [42%]), with MV1-2 the next most common (4 patients [15%]).

## Sleep Symptoms

Only 5 of 28 patients (18%) presented with premorbid sleep disorders at the time of evaluation, all of whom had obstructive sleep apnea (OSA), and one had comorbid RLS. However, during the clinical evaluation for their RPD, 25 of 28 patients (89%) reported symptoms of sleep dysfunction: Hypersomnia was reported in 11 patients (39%); insomnia was reported in 13 patients (46%). Restless legs or nocturnal limb movements were reported in seven patients (25%). Parasomnias were present in nine patients (32%).

## PSG Findings

PSG studies were obtained in half (14/28) of the patients, with findings summarized in **Tables 1** and **2**. In one of these patients, sleep was not identified at all during the overnight PSG (see Discussion). In the remaining 13 patients, 9 (69%) had absent or poorly formed sleep spindles and/or K-complexes, and 10 (77%) had sleep-disordered breathing. Of the eight patients who displayed REM sleep during the PSG, three (38%) met criteria for REM sleep without atonia (RSWA) based on visual scoring standards from the AASM. In two of the three cases of RSWA, dream-enactment behavior at home had been reported by collateral sources, thus meeting AASM diagnostic criteria for REM sleep behavior disorder (RBD). In one of these two cases (Patient 26), dream-enactment behavior characterized by shouting, talking and arm movements was also observed on video during REM sleep on PSG. Of the three subjects with PSG evidence of RSWA, one was receiving an antidepressant (nortriptyline in Patient 21) at the time of their PSG, a possible contributing variable given the association between RSWA and antidepressant use.[23] Median TST was 226 (IQR = 195–282) min. Median sleep efficiency

**Table 2**—Supplemental polysomnography findings in our Creutzfeldt-Jakob disease cohort.

| Patient ID | WASO (min) | % N1 [min] | % N2 [min] | REM Latency (min) | PLMI | SL | Neurologically Active Medications |
|---|---|---|---|---|---|---|---|
| 15[a] | 166 | N/A | N/A | N/A | 0 | 4 | Zolpidem; Propoxyphene/Acetaminophen |
| 16 | 119 | 2.7 [12.5] | 43.4 [204] | 128 | 0 | 146 | Fosphenytoin |
| 17 | 232 | 14.6 [66] | 30.3 [137] | N/A | 62.4 | 17 | Sertraline |
| 18 | 320 | 3.2 [12] | 26.2 [99] | N/A | 0 | 1 | None |
| 19 | 104 | 1.1 [6] | 66.2 [241] | 72 | 6.9 | 0 | None |
| 20 | 69 | N/A | N/A | N/A | 12.3 | 0 | Alprazolam; Trazodone |
| 21 | 122 | 4.8 [17.5] | 44.5 [161] | 58 | 0 | 2 | Cetirizine; fentanyl; gabapentin; ropinirole; oxycodone; clonazepam; nortriptyline |
| 22 | 167 | 2.7 [12.5] | 57.1 [261.5] | 8 | 42.4 | 0 | None |
| 23 | 271 | 9.1 [41] | 14.9 [67] | 335 | 78.5 | 70 | Quetiapine |
| 24 | 143 | 5.8 [24.5] | 52.4 [221] | 113 | 0 | 23 | Citalopram |
| 25 | 309 | 26.9 [128.5] | 9 [43] | N/A | 0 | 0 | Gabapentin; sertraline |
| 26 | 140 | 8.7 [25.5] | 50.5 [148] | 7 | 0 | 0 | Cetirizine |
| 27[b] | N/A | N/A | N/A | N/A | N/A | N/A | Clonazepam; diazepam; duloxetine |
| 28 | 174 | 51.3 [234] | 0 | 58 | 0 | 2 | None |

[a] In the absence of sleep spindles and K-complexes, the stages in this study were dichotomously scored as sleep (without sub-stages N1, N2, N3) or wake. No rapid eye movements, sawtooth waves, or atonia was present to score REM. [b] No electrographic sleep recorded (see Discussion for full details). SL, sleep latency; N1, Stage 1 non-REM sleep; N2, Stage 2 non-REM sleep; PLMI, periodic limb movement index; REM, rapid eye movement sleep; WASO, wake time after sleep onset.



was 58.5% (IQR = 41–65.5%). Median N3 sleep (absent in most patients) was zero (IQR = 0–0%). Median time in REM was 0.35% (IQR = 0–7.125%). Median PLMI was 0 per hour (IQR = 0–19.825) with periodic limb movements present in five patients (38%) on PSG.

### Case Vignette

A 42-year-old man (Patient 24) who was employed as a pilot presented with a 5-month history of progressive memory loss. His initial symptoms were lapses in short-term memory, emotional lability, and insomnia. The patient's initial diagnosis was depression, and he was started on citalopram. Two months later, jerking movements and a tremor in his right arm developed, followed by startle myoclonus. He also snored and on some nights his wife felt like he would "move nonstop" in his sleep. Results of inpatient diagnostic testing were consistent with probable CJD. An inpatient PSG demonstrated evidence of moderate obstructive sleep apnea but normal REM atonia, and he was started on continuous positive airway pressure (CPAP) treatment. One month later his nocturnal movements worsened, despite compliance with CPAP and more consolidated sleep. He started kicking his wife so hard that they could no longer share the same bed. The concurrent development of sleep walking, along with these violent nocturnal movements, made his wife extremely concerned that he would injure himself. Given the concern for parasomnia, low dose clonazepam (0.5–1 mg at bedtime) was prescribed and provided great benefit. They were able to return to sharing a bed, thereby allaying his wife's anxiety over his risk of self-injury. His sleep symptoms remained well controlled with the combination of CPAP and clonazepam for the remainder of his disease course. The patient died 10 months after symptom onset and definite sporadic CJD, VV1 subtype, was confirmed at autopsy.

## DISCUSSION

In this study, we present the signs and symptoms of sleep dysfunction present in 28 consecutive patients with autopsy-confirmed CJD. Furthermore, we present the PSG findings in 14 of these patients, making this study, to our knowledge, the largest collection of PSG data in a definite CJD population.

Our results demonstrate that sleep symptoms are extraordinarily common in patients with CJD. Although only five participants had an established sleep diagnosis, nearly 90% of participants had at least one sleep-related complaint at the time of their initial evaluation. Therefore, other than rapidly progressive dementia (by definition), this clinical finding was more prevalent than all other accepted clinical diagnostic criteria. Specific sleep signs/symptoms such as insomnia, hypersomnia, and parasomnias were as common or more common than half of the accepted clinical diagnostic features of CJD in our cohort, including visual signs, high cortical signs, and akinetic mutism. PSG analysis showed that abnormalities in sleep were common, though variable, in patients with CJD. The most frequently observed PSG aberrations were (1) loss of normal sleep EEG architecture and (2) the presence of sleep-disordered breathing. Variation in PSG findings may reflect the fact that each patient shows differential involvement of brain structures with prion pathology. Notably, the characteristics of our study population (i.e., proportion of familial CJD, clinical features, and results of diagnostic testing) was representative of what has been reported in other North American CJD

cohorts, and therefore supports a reasonable expectation of high external validity.[2] With these findings, we believe that routine screening of sleep symptoms should be considered in the evaluation of suspected CJD. Although not in the current clinical diagnostic criteria of CJD, given the high prevalence of sleep disturbances in definitive CJD, the inclusion of sleep symptoms in diagnostic criteria could be further evaluated in larger, longitudinal controlled studies.

A previous study by Wall and colleagues identified sleep symptoms in 62 of 126 patients (49%) with definite or probable CJD.[17] In contrast, we identified that 89% of our cohort had at least one sleep symptom. Insomnia was reported in 31 of 126 patients (24.6%) and hypersomnia was reported in 24 of 126 patients (19%) in their cohort. In comparison, our rates were 46% and 39%, respectively. These differences may be associated with the difference in inclusion criteria between studies (i.e., we only included autopsy-proven CJD). Furthermore, in the Wall et al. study,[17] it is not clear if a sleep specialist evaluated these patients, and therefore sleep signs/symptoms may have been missed or underreported. One caveat to our findings, however, is that clinical histories were obtained from collateral sources in the majority of patients in this study (due to profound cognitive impairment), and that it was not possible to blind the sleep clinicians evaluating these patients.

Comparing PSG findings to previous work is challenging. In the largest study of PSG findings in CJD to date, published by Landolt and colleagues,[18] the PSG findings of six patients showed universal absence of the EEG markers of normal sleep including sleep spindles, K-complexes, and vertex waves. They reported an average sleep efficiency of 16.5 ± 3%, non-REM sleep percentage of 15.6 ± 2.9% of total recording time, and 0.8 ± 0.3% of total recording time in REM sleep, but these periods of non-REM and REM sleep did not develop into consolidated periods of sleep and were typically interrupted by pseudoperiodic sharp waves and increased muscle tone. As in our study, their cohort was restricted to definite CJD. We obtained PSG data on 14 total patients (13 with EEG-defined sleep, and 1 without EEG-defined sleep). In contrast to this prior work, we found that poorly formed EEG markers of sleep are highly prevalent (69%), but not universal. Our median percentage of slow wave sleep was lower than this cohort at 0%, with stage 3 non-REM completely absent in 10 of 13 patients. Our median time in REM sleep was 0.35% (IQR 0–7.125%), comparable to previous findings.[18] This is strikingly low even when comparing against the normative values of the oldest aged cohort in population studies.[22] The prevalence of sleep-disordered breathing, RSWA, or PLMI has not been previously assessed in a similar group of CJD patients. In our cohort, we found that 10 (77%) had PSG evidence of sleep-disordered breathing, 3 of 8 (38%) had PSG evidence of RSWA, with two meeting criteria for RBD. The PLMI in our cohort was variable (range, 0–78.5) and five subjects demonstrated PLMs on PSG.

Previously published case reports have generated hypotheses that have not been studied in a systemic way. For example, Taratuto and colleagues[24] reported a case of E200K familial-CJD presenting with refractory insomnia, PSG showing absence of stage 3, 4 and REM sleep, and prominent neuropathologic involvement of the thalamus at autopsy. La Morgia and colleagues[25] also described a case of VV2 CJD with agrypnia excitata and PSG findings similar to FFI. Interestingly, one of our patients, also with the E200K variant (Patient 27) and with bilateral posterior medial thalamic involvement on MRI, had no EEG-based sleep identified on PSG. Behaviorally, this patient appeared to be asleep with occasional movements, but without changes in EEG morphology relative to the behaviorally awake state. This very unusual finding suggests either the presence of severe insomnia, or that there is an inability of the brain to generate sleep EEG features. It is unclear if there is an etiologic association of the E200K variant of familial CJD and severe insomnia, but this warrants further investigation.

Terzano and colleagues[26] published a case report of serial PSGs in a single patient with CJD, which suggested that loss of physiologic sleep patterns might be associated with disease progression. Whether characterization of sleep pathology in patients with RPD can aid in the diagnosis of CJD remains to be determined. It is also unclear if the presence of sleep abnormalities may correlate with spongiform changes in distinct regions in the brain or correlate with the disease progression. However, our study confirms that sleep pathology is prominent in CJD patients and we provide a case study demonstrating that the recognition and treatment of sleep pathology can have a dramatic effect on quality of life, for both patients and their caregivers. Future, larger scale studies could allow for a prospective comparison to normal control and disease control populations and aid in determining the diagnostic utility of sleep characterization.

Prior studies estimate that 45% of patients with AD also have sleep disturbances.[14] Sleep-related complaints in our CJD cohort were twice as common with 90% of patients having at least one sleep-related complaint at the time of presentation. Our observed prevalence (90%) is similar to other neurodegenerative disorders (e.g., PD), where sleep-related comorbidities sit among the most common non-motor manifestations of the disease.[5,6] Similar to our CJD cohort, the most common sleep-related signs/symptoms in the PD population include insomnia, hypersomnia, and parasomnias. Also similar to our findings in CJD, studies on AD and PD cohorts in the past have shown alterations in sleep spindles and K-complexes, and reductions in sleep efficiency, slow wave sleep (beyond that expected with normal aging) and REM sleep, along with increased wake after sleep onset. However, the reductions in TST and slow wave sleep in our CJD cohort are much greater than those reported in AD and PD populations. Seventy-seven percent of the CJD patients in our study that underwent PSG had evidence of a sleep-related breathing disorder (SRBD). Interestingly, studies in AD populations have estimated a SRBD prevalence of 40% to 70%. Follow-up studies suggest a direct correlation between the severity of the SRBD and the severity of the dementia,[14] and that the presence of SRBD is associated with an earlier age of AD-dementia onset.[13] Furthermore, randomized controlled trials have demonstrated that treatment of OSA in AD patients can improve sleep quality as well as cognitive performance.[27–29] Although the majority of our patients died soon after their studies were performed, a few subjects (and their caretakers) benefitted from treatment of their SRBD and RBD (example case).

RBD/RSWA is relatively uncommon in AD and there is a much stronger association with synucleinopathies, such as PD, dementia with Lewy bodies, and multiple system atrophy. Although our method of quantifying RBD/RSWA was based solely on clinical and visual polysomnographic criteria and therefore may not be directly comparable to research populations, our CJD cohort showed an RBD prevalence on par with figures reported in synucleinopathy populations. Estimated prevalence of RBD in synucleinopathies ranges from 40% (PSG confirmed) to 64% (probable) whereas patients with nonsynucleinopathy–related neurodegenerative disorders (including AD) had an RBD prevalence of between 0% (PSG confirmed) and 3% (probable).[9] Recent studies suggest a risk estimate of over 80% for eventual development of a synucleinopathy in patients with idiopathic RBD.[7,10] In fact, the association is so strong that in the setting of a comorbid neurodegenerative condition, many authors consider the presence of RBD as a predictor of an evolving synucleinopathy.[9] Our study suggests that RBD may be as common in CJD as it is in the synucleinopathy population. However, a major caveat is the potential difference in methodology used to assess RBD/RSWA across these different populations, and the possibility that the AASM method of visual scoring, with its poor sensitivity relative to other methods, may underestimate RSWA/RBD.[23,30] Furthermore, REM sleep was recorded in only 8 of 14 subjects; therefore, the opportunity to record RSWA was lost on those patients, potentially skewing prevalence results. Finally, without systematic sampling of dream enactment and other parasomnia behavior using validated questionnaires from the bed partner, the frequency of probable RBD and nonrapid eye movement parasomnias may have been underestimated.[31] Future prospective studies with larger cohorts are necessary to provide a more reliable estimate of the prevalence of RBD in CJD patients.

Strengths of the current study include fulfillment of diagnostic criteria for definite CJD in all patients. Probable CJD patients in our cohort, some of whom had PSGs performed, were not included but demonstrated a similar pattern of sleep pathology (data not shown). Additionally, our CJD population is representative of that typically seen in larger cohorts with respect to clinical, diagnostic, and molecular features.

However, our study also has several major limitations. (1) The retrospective, cross-sectional approach of the study prohibits definitive conclusions about causality. (2) Furthermore, it is not clear to what extent these patients had coexisting tau, amyloid, or synuclein pathology and, if present, whether these pathologies contributed to sleep disturbances. This is because cases of probable CJD at our hospital abide by a strict pathological protocol to limit the amount of specimen handling in order to minimize exposure risk for personnel. Given that all of the cases discussed herein were confirmed as definite CJD, no additional pathologic analysis was performed. (3) The use of validated sleep questionnaires in addition to the clinical sleep evaluation may also have helped to reduce recall bias. (4) Additionally, PSG data in this study was only available at a single time point. Sequential data would be invaluable in our understanding of sleep and the natural history of CJD. (5) Larger studies involving multiple centers may help to assess relationships between genotype, disease progression, and temporal presentation of sleep symptoms, as well as associations with specific sleep pathology on PSG. As noted previously, a matched control sample for comparison obtained during a prospective, longitudinal study would be valuable.

In summary, our study suggests that sleep pathology is extraordinarily common in CJD, and more common than symptoms that comprise the current diagnostic criteria for CJD (i.e., visual signs, high cortical signs, and akinetic mutism). PSG data may provide valuable information in caring for these patients. As such, clinicians should routinely screen for signs/symptoms of sleep pathology in patients with possible CJD. Early identification and treatment of sleep pathology may provide an intervenable target in this devastating neurodegenerative disease. Future studies should aim to map CJD sleep pathology against CSF biomarkers, neuroimaging findings, neuropathologic data, and clinical progression.

## ABBREVIATIONS

AD, Alzheimer disease
CJD, Creutzfeldt-Jakob disease
CSF, cerebrospinal fluid
DWI, diffusion-weighted imaging
EEG, electroencephalography
FFI, fatal familial insomnia
FLAIR, fluid-attenuated inversion recovery
IQR, interquartile range
MRI, magnetic resonance imaging
NPDPSC, National Prion Disease Pathology Surveillance Center
PD, Parkinson disease
PLMs, periodic limb movements
PLMI, periodic limb movement index
PSG, polysomnography
RBD, REM sleep behavior disorder
REM, rapid eye movement
RPD, rapidly progressive dementia
SRBD, sleep-related breathing disorder
TST, total sleep time
VPSPr, variable protease-sensitive prionopathy

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Address correspondence to: Miranda M. Lim, MD, PhD, 3710 SW US Veterans Hospital Road, Mailcode P3-RD42, Portland, OR 97221; Email: lmir@ohsu.edu or Robert C. Bucelli, MD, PhD, Campus Box 8111, 660 South Euclid Avenue, Saint Louis, MO 63110; Email: bucellir@neuro.wustl.edu

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