Sleep-wake disturbances in sporadic Creutzfeldt-Jakob disease

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Abstract—*Background:* The prevalence and characteristics of sleep-wake disturbances in sporadic Creutzfeldt-Jakob disease (sCJD) are poorly understood. *Methods:* Seven consecutive patients with definite sCJD underwent a systematic assessment of sleep-wake disturbances, including clinical history, video-polysomnography, and actigraphy. Extent and distribution of neurodegeneration was estimated by brain autopsy in six patients. Western blot analyses enabling classification and quantification of the protease-resistant isoform of the prion protein, PrP^{Sc}, in thalamus and occipital cortex was available in four patients. *Results:* Sleep-wake symptoms were observed in all patients, and were prominent in four of them. All patients had severe sleep EEG abnormalities with loss of sleep spindles, very low sleep efficiency, and virtual absence of REM sleep. The correlation between different methods to assess sleep-wake functions (history, polysomnography, actigraphy, videography) was generally poor. Brain autopsy revealed prominent changes in cortical areas, but only mild changes in the thalamus. No mutation of the *PRNP* gene was found. *Conclusions:* This study demonstrates in sporadic Creutzfeldt-Jakob disease, first, the existence of sleep-wake disturbances similar to those reported in fatal familial insomnia in the absence of prominent and isolated thalamic neuronal loss, and second, the need of a multimodal approach for the unambiguous assessment of sleep-wake functions in these patients.

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Fatal familial insomnia (FFI) is a rare, usually inherited form of Creutzfeldt-Jakob disease (CJD).[1-5] The prominent thalamic neurodegeneration[6,7] in FFI is thought to lead to sleep-wake disturbances and sleep EEG changes.[8,9] This is in accordance with the hypothesized role of the thalamus in generating the EEG oscillations typical for sleep.[10-14]

The pathology of FFI is associated with an aspartic acid to asparagine mutation at codon 178 of the *PRNP* gene.[15] A highly common polymorphism at codon 129 (C129) seems to determine the phenotypic expression into either FFI or familial CJD^{178}.[7,16] FFI patients with a rapid clinical course (7 to 9 months) show severe sleep disruption (≤100 minutes of total sleep time [TST] per 24 hours), with near complete absence of non-REM sleep, while short episodes of REM sleep may still occur.[1,9,17] FFI patients with long clinical courses (>12 months) are characterized by a more gradual development of insomnia, with progressive reduction in TST and sleep spindles, and disappearance of REM sleep in the late course of the disease.[9,17]

Inherited forms of CJD account for only 10 to 15% of human prion diseases. Patients with sporadic CJD (sCJD) typically have rapidly progressing dementia, myoclonus, cerebellar, pyramidal, extrapyramidal, visual or oculomotor, and sensory symptoms.[18,19] Periodic sharp wave complexes in the waking EEG, elevated 14-3-3 protein in CSF, and diffusion-weighed and T2-weighted MRI abnormalities in striatum and cortex support the diagnosis of sCJD.[18-21] Sleep-wake disturbances were not traditionally considered to be characteristic of sCJD,[18] and the histopathologic lesions and PrP^{Sc} deposition are usually more diffuse than in FFI.[22] These clinical and neuropathologic differences between FFI and sCJD formed the basis for hypotheses concerning the role of thalamic neurodegeneration, sleep-wake symptoms, sleep EEG changes, and *PRNP* gene mutation in FFI.[6,8,23]

A recent study of 153 patients with sCJD reported that sleep disturbances are present in up to 45% of patients.[19] Moreover, prominent sleep EEG changes were reported at an early stage of the disease[24,25] and in single-case studies.[26-28] Based also on our own observations,[29] we investigated the hypothesis that patients with sCJD may present with clinical and sleep EEG changes similar to those described in FFI.

Methods. *Patients and controls.* Seven patients (five men, two women; mean age: 65.8 ± 3.8 years) consecutively seen by the senior author (C.L.B.) with definite, that is autopsy (n = 6) or

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Table 1 *Demographics and clinical findings in seven patients with sCJD*

Patient	Age, y/sex	Onset symptoms and signs	Symptoms and signs in the course	Sleep-wake symptoms	Duration	EEG; CSF 14-3-3	Genotype; PrPSc type
1	50/M	Leg paresthesias, depression, apathy	Dementia, gait ataxia, myoclonus	Prominent insomnia (month 1), visual hallucinations	10 wk	Typical; positive	No mutation; −/−
2	64/M	Leg paresthesias, dysarthria, apathy, irritability	Gait ataxia, dementia, myoclonus	Prominent hypersomnia (month 1)	5 wk	Typical; positive	No mutation; −/−
3	60/M	Gait ataxia	Dementia, myoclonus, leg paresthesias, polyneuropathy	Hypersomnia (month 9, mild)	52 wk	Typical; positive	No mutation; MV2
4	77/M	Confusional state	Dementia, gait ataxia, myoclonus	Prominent insomnia (month 3), visual and acoustic hallucinations	20 wk	Typical; positive	No mutation; MM1*
5	73/F	Speech difficulties, apathy	Dementia, gait ataxia, myoclonus	Hypersomnia (month 2), acoustic hallucinations	10 wk	Typical; positive	No mutation; MM1
6	68/M	Gait ataxia, apathy	Dementia, anxiety, polyneuropathy	Hypersomnia (month 1)	10 wk	Atypical; positive	No mutation; VV2
7	58/F	Amnesia	Dementia, myoclonus, depression	Prominent hypersomnia (month 1), insomnia	13 wk	Typical; positive	No mutation; MM1

Duration refers to disease duration between the onset of symptoms and death. Indices of time indicate the time after the onset of symptoms. Prominent sleep-wake symptoms were present in Patients 1, 2, 4, and 7 (see text).

* The prominent PrP^{Sc}-type as assessed by Western blotting of CNS tissue originating from the thalamus is compatible with a PrP^{Sc} type 2. Considering the fact that patients may harbor more than one PrP^{Sc} type in the CNS[48] in conjunction with clinical and histologic data of this individual, we nevertheless decided to assign this patient to MM1.

sCJD = sporadic Creutzfeldt-Jakob disease.

biopsy (n = 1) proven, sCJD (table 1) were studied. Eight healthy middle-aged male subjects (62.0 ± 3.8 years) served as controls. Informed consent for all procedures was obtained from all control subjects and from the sCJD patients' next of kindreds. Clinical assessment included specific questions about sleep-wake and neurologic symptoms in the course of the disease and a detailed clinical examination. Patients, and in case of incomplete or unreliable information, relatives or caregivers, were also interviewed. Conventional MRI examinations were performed in five patients.

The sleep and sleep EEG data of controls were reported in previous publications.[30,31] The patient recordings were made in the Departments of Neurology at the University Hospital-Inselspital in Bern (Patients 1 and 2), the University Hospital in Zürich (Patients 3 through 6; the two last recordings in Patient 3 were conducted in a private nursing home), and the Kantonsspital in Winterthur (Patient 7). The protocol was approved by the local ethics committees for research on human subjects. All nocturnal recordings in the patients started between 7 and 9 PM, and lasted for a minimum of 376.3 minutes and a maximum of 763.0 minutes (table 2). A total of 17 patient recordings was collected (1 to 5 recordings per patient). Patient 6 removed the electrodes 2 minutes after initiation of the recording. Further polysomnographic studies were refused by his family. Control subjects slept in the completely dark bedrooms of the sleep laboratory from 11 PM to 7 AM (n = 7) or from 12 midnight to 8 AM (n = 1).

Video-polysomnography. The EEG (data from the C3A2- or the C4A1-derivation are reported as indicated), submental electromyogram (EMG), electrooculogram (EOG, differential recording), and electrocardiogram (ECG) were recorded by a portable polygraphic amplifier (PS1, Institute of Pharmacology and Toxicology, University of Zürich, Switzerland). The signals were digitized, transmitted via fiber-optic cables to a notebook computer with a digital signal processor board, conditioned, and analyzed as in previous studies.[32] The behavior of Patients 3 through 7 during polysomnographic recordings was monitored by a portable infrared camera. Because of profound EEG alterations, the vigilance states wakefulness, non-REM sleep, and REM sleep could not be scored in the sCJD patients according to the criteria of Rechtschaffen and Kales.[33] Consecutive 20-s epochs of wake-, non-REM sleep-, and REM sleep-like states were defined in accordance with previous reports of sleep in patients with FFI and sCJD that specified the EEG, EOG, and EMG criteria for discriminating between waking and sleep.[8,9,28] We defined stage W ("wakefulness") by the presence of pseudo-periodic, 1-Hz EEG sharp wave discharges over a diffuse delta/theta background rhythm, and a normal or elevated EMG tone (figure 1A). Stage N ("non-REM sleep") was scored when the periodic sharp-wave complexes were attenuated or suppressed, rhythmic delta/theta activity (3 to 8 Hz) was present, and muscle tone was reduced compared with stage W. Stage R ("REM sleep") was defined by EEG characteristics similar to those of stage N coinciding with submental muscle atonia and occurrence of REM.

Wrist-actigraphy. All patients wore a small rest-activity monitor on the wrist of their left or right arm over at least 2 weeks. This unit (Actiwatch, Cambridge Technology, UK) measures motor activity by a piezoelectric element. The activity counts were accumulated in 1-minute epochs, and estimates of sleep and wakefulness were automatically extracted with the Sleepwatch software.

Neuropathology. Detection of PrP^{Sc} and protein analysis. Western blot analysis was carried out as described previously.[34] In brief, brain tissue homogenates (10% w/v) were prepared in 100 mM NaCl, 10 mM EDTA, 100 mM Tris HCl, 0.5% NP40, 0.5% NaDoc, pH = 6.9 using a RiboLyser (Hybaid, Ashford, UK) and stored at −80 °C until use. Samples containing 25 μg protein (according to a BCA-assay) were digested with Proteinase K (PK recombinant PCR grade solution, Roche, Switzerland) for 30 minutes at 37 °C with a concentration of 0.03 U per sample. Proteinase K was stored at −80 °C in storage buffer (50% glycerol, 10 mM Tris, pH = 7.5, 2.9 mg/mL $CaCl_2$). Proteins were separated in a 12% SDS-PAGE (Bio-Rad, Hercules) and then transferred to a nitrocellulose membrane in a wet-blotting system (Bio-Rad). Membranes were incubated overnight with the monoclonal antibody 3F4[35] (Signet, Denham) at a dilution of 1:2,000. After washing, HRP conjugated rabbit-anti-mouse-IgG-γ (Zymed, San Francisco, CA) served as the secondary antibody at a dilution of 1:20,000.

Table 2 *Sleep architecture in patients with sCJD*

		Polysomnography				Actigraphy		
Patient	TRT (min)	TST (min)	Sl-Eff (%)	St. N (%)	St. R (%)	"TST" (min)	"Sl-Eff" (%)	Time of recording
1	483.0	61.3	12.7	12.4	0.2			8/2
2	376.3	71.0	18.9	18.8	0.1			4/1
3	714.3	87.0	12.2	10.7	1.5	384	55.7	45/7
	717.3	67.0	9.3	7.9	1.5	421	59.0	47/5
	735.3	51.0	6.9	6.1	0.8	730	99.2	49/3
	735.0	157.0	21.4	19.9	1.5	724	98.5	51/1
4	746.7	33.3	4.5	4.5	0.0	744	99.6	13/7
	749.3	64.7	8.6	8.6	0.0	746	99.6	15/5
	748.9	82.3	11.0	11.0	0.0	743	99.2	16/4
	712.7	90.3	12.7	12.6	0.1	709	99.4	17/3
5	730.0	148.0	20.3	17.4	2.9	494	68.1	5/5
	729.7	84.3	11.6	10.6	0.9	709	97.1	7/3
	732.7	105.7	14.4	13.4	1.0	650	88.7	9/1
6	—	—	—	—	—	667	91.9	6/4
7	763.0	225.0	29.5	29.5	0.0	712	93.2	8/5
	720.7	222.3	30.9	27.6	3.2	756	99.6	12/1

sCJD = sporadic Creutzfeldt-Jakob disease; TRT = total recording time; TST = total sleep time (stages N and R); Sl-Eff = sleep efficiency (TST/TRT × 100); St. N = stage N; St. R = stage R; "TST" and "Sl_Eff" = total sleep time and sleep efficiency as derived from motor actigraphy data (quotation marks indicate the distinction from the similarly named sleep EEG-derived values); Time of recording = weeks after symptom onset/weeks before death; — = no polysomnography available in this patient.

The signal was visualized by enhanced chemoluminescence using a Versa Doc 5,000 imaging station. Five cases were PrP^{Sc}-typed according to the size of the protease-resistant core PrP fragment[36] and to the prevalence of glycoforms.[37,38]

Genetic analysis. Genomic DNA was extracted in most cases from blood, in some cases from other frozen tissues. PCR and analysis of the entire coding region of *PRNP* were performed using standard techniques and software (SeqScape, Applied Biosystems, Foster City, CA).[39]

Histologic analysis. Tissue was fixed with 4% buffered formalin, inactivated for 1 hour with 98% formic acid, and embedded in paraffin. Sections (3 μm) were subjected to conventional staining and immunostaining for glial fibrillary acidic protein (GFAP, Dako) and PrP (3F4) upon hydrolytic autoclaving employing published protocols.[40] The degree of spongiosis, gliosis, and PrP^{Sc} deposition was assessed semi-quantitatively by two researchers blind to the C129 genotype, PrP biochemistry, and clinical features.

Results. *Demographic characteristics and clinical findings.* The demographic characteristics of the patients and the main clinical findings are summarized in table 1. Neuropsychiatric symptoms (2 patients), cognitive changes (2), gait difficulties or ataxia (2), and painful or burning leg paresthesias (2) were initial symptoms in the studied cohort. Apathy was observed or reported in the initial phases of the disease in four patients. Dementia appeared in the

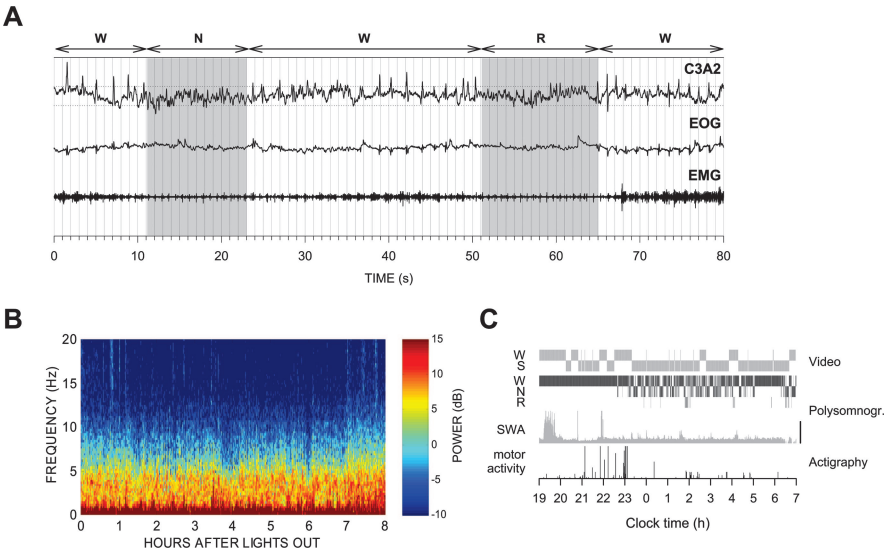

Figure 1. (A) Eighty-second tracings of EEG (C3A2 derivation), electrooculogram (EOG), and electromyogram (EMG) in Patient 5 (female, 73 years, C129 Met/Met). Episodes of stages W, N, and R are indicated by arrows on top; stages N and R are highlighted by shading. Dashed horizontal lines below and above the EEG trace indicate 75 μV. (B) Time course of EEG power between 0 and 20 Hz during 8 hours after lights-out (22.08 hours) in Patient 3 (male, 59 years, C129 Met/Val). Color-coded absolute power values are plotted on a logarithmic scale (C3A2 derivation). 0 dB = 1 μV^2/0.25-Hz. (C) Periods of wakefulness and sleep in the same night as in B as estimated from video recordings, polysomnographically defined sleep stages, slow-wave activity (SWA, power within 0.75 and 4.5 Hz), and motor activity. For scoring criteria of the polysomnographic recordings of EEG, EOG, and EMG, see text. SWA values were smoothed by a three-point moving average; the calibration bar indicates 1,000 μV^2. W, wakefulness; S, sleep; N, stage N; R, stage R. Note the overestimation of sleep derived from video and motor activity recordings when compared with polysomnographically defined sleep.

course of the disease in all patients. In the early stage of the disease, myoclonus and motor hyperactivity were found in all but one patient, whereas in late stages akinetic mutism appeared in all patients. Excluding the terminal phase of the illness, autonomic changes were clinically noted in four patients in form of tachycardia (Patient 1), tachycardia and increased sweating (Patient 7), initial weight loss despite good appetite and normal eating behavior (Patients 3 and 5). Sensorimotor polyneuropathy was observed clinically and electrophysiologically early in the course of the illness in Patients 3 and 6. The waking EEG showed periodic sharp wave complexes ("typical EEG") in all but Patient 6, whereas elevation of the 14-3-3 protein in the CSF was detected in all patients. A brain MRI was performed in five patients and revealed signal hyperintensities in the T2-weighted MRI in three patients (Patients 2 and 5: in basal ganglia bilaterally; Patient 7: nucleus caudatus on the right side, mesiotemporal regions bilaterally). An old lacunar stroke in the caudate nucleus was found in Patient 1 and an old stroke in the frontal lobe in Patient 7. The disease duration after symptom onset ranged from a minimum of 5 weeks to a maximum of 52 weeks.

Sleep-wake symptoms (see table 1) were reported or observed in all patients in form of difficulties initiating or maintaining sleep (i.e., insomnia, three patients), increased sleep need over 24 hours with or without subjective feeling of excessive daytime sleepiness (i.e., hypersomnia, five patients), and visual or acoustic hallucinations with dream-reality confusion (three patients). Insomnia was a prominent symptom in Patients 1 and 4. Patient 1 developed major difficulties falling asleep and maintaining sleep, with excessive motor activity while asleep within the first 4 weeks after disease onset. Patient 4 developed severe sleep maintenance insomnia 3 months after disease onset with episodes of dream-reality confusion and frightening hallucinations, during which he would speak and gesticulate incoherently. Similar nocturnal ("oneiric") behaviors were reported also in Patient 7. Hypersomnia was a prominent symptom in Patients 2 and 7. Patient 2 presented a dramatic increase in his sleep need from about 8 to 12 to 13 hours sleep per day within the first 3 weeks after disease onset. Patient 7 developed an unusual excessive daytime sleepiness (with episodes of dozing off in monotonous situations and also while eating) and restless nighttime sleep (during which the patient left her bed repeatedly for unclear reasons) within the first 4 weeks after disease onset.

Video-polysomnography. Studies were obtained within 4 and 45 weeks after onset of neurologic symptoms (see table 2). At least one study was performed during the last 3 weeks of life in all patients (the single sleep recording of Patient 6 could not be analyzed).

The mean duration of nocturnal recordings was 632.3 ± 66.3 minutes (SEM). Based upon the neurophysiologic data, all patients spent most of the time in stage W characterized by frequent, pseudo-periodic 1- to 2-Hz sharp-wave EEG irregularities together with diffuse delta/theta rhythmic activity (see figure 1A). Brief episodes of "sleep" without sharp-wave discharges and reduced muscle tone lasting between 10 s and a few minutes interrupted stage W at irregular intervals. Nevertheless, the EEG hallmarks of normal sleep such as sleep spindles, K-complexes, or vertex sharp waves were absent in all patients. Moreover, the stages N (no rapid eye movements) and R (rapid eye movements) never developed into consolidated sleep periods. Typically, pseudo-periodic sharp waves and increased muscle tone suddenly reappeared after 12 to 20 s. The combined stages N and R on average comprised 104.5 ± 25.0 minutes ("sleep efficiency": 16.5 ± 3.0% of recording time), whereas 98.6 ± 23.4 minutes (15.6 ± 2.9% of recording time) were spent in stage N and 5.8 ± 2.4 (0.8 ± 0.3%) in stage R (see table 2).

Figure 1B is a representative example illustrating the profound EEG alterations in sCJC. The typical sleep-cycle-related EEG power modulation in middle-aged men[30,31] was absent in the patient. In contrast, sustained high power in the low delta range (<2 Hz) was prominent, whereas no declining trend of slow-wave activity (1 to 4 Hz) and a complete loss of sleep spindles (no activity between 12 and 14 Hz) were evident. Similar sleep EEG changes were consistently observed in all patients. Moreover, no gradual change across multiple polysomnographic recordings was evident.

Actigraphy. Continuous wrist-actigraphy monitoring was initiated in Patients 3 to 7 on average 14.6 ± 7.7 weeks (range 4 to 45 weeks) after onset of symptoms. A high level of motor activity in the initial phase of hospitalization was evident. Although the patients were in bed during most of the time, their mean "time awake" (moving time) per 24 hours during the first 3 days of recording was 38.9 ± 4.7% (range: 31.0 to 57.0%). In the following days and weeks time awake rapidly decreased in all patients, with time asleep ranging from 56 to 100% during nighttime sleep recordings (see table 2).

Multimodal assessment of sleep-wake function. To further study the apparent discrepancy between EEG and motor activity-derived estimates of sleep, actigraphy in Patient 3 was compared with video monitoring and polysomnography during three nocturnal recordings performed at 2-week intervals during the final 5 weeks of illness. This multimodal investigation revealed major discrepancies between behaviorally and electroencephalographically defined waking and sleep. Wakefulness and sleep based on behavioral signs were estimated by inspection of the videotapes. In periods scored as wakefulness the patient's eyes were open, he exhibited gross movements, interacted with the environment, ate, and talked to visitors or the nursing staff. Episodes of sleep were defined as periods with eyes closed, reduced motor activity, and no obvious interaction with the environment. Although prolonged episodes of wakefulness were always present, periods of video-defined sleep predominated in all nocturnal recordings. In nights 1 to 3, 379 minutes (58% of recording time), 440 minutes (61%), and 481 (67%) minutes were classified as "sleep." In contrast, only short periods were scored as sleep (stages N and R) according to the polygraphic criteria (sleep efficiency: 9, 7, and 21%; see table 2). Moreover, no gradual changes were evident in any "sleep variable" in the course of the illness. It is interesting to note that stage R was still present 1 week prior to death in this patient (see figure 1C), while the ultradian modulation in EEG slow-wave activity or sleep periods with high values of slow-wave activity (other than artifacts in stage W) were absent in all recordings.

Table 3 *Neuropathology in patients with sCJD*

		Cortex				Nucleus					Nucleus	Thalamic nuclei			
Patient	NP/PrP	Frontal	Parietal	Temporal	Occipital	caudatus	Pallidum	Putamen	Pons	Cerebellum	olivaris	Ant.-vent.	Dors.-med.	Vent.-lat.	Pulvinar
1	Spongiosis	2	2	3	3	3	1	2	1	1	—	—	2	—	—
	Gliosis	2	2	2	2	2	1	2	1	1	—	—	1	—	—
	PrP	1s	0	3ps	0	0	0	0	0	1s	—	—	0	—	—
2	Spongiosis	3	2	1	1	3	1	1	0	1	1	—	—	—	—
	Gliosis	2	2	1	1	2	1	1	0	1	2	—	—	—	—
	PrP	2s	0	1s	0	0	0	0	0	0	0	—	—	—	—
3*	Spongiosis	3	—	—	—	—	—	—	—	—	—	—	—	—	—
	Gliosis	3	—	—	—	—	—	—	—	—	—	—	—	—	—
	PrP	WB+	—	—	—	—	—	—	—	—	—	—	—	—	—
4	Spongiosis	4	3	3	3	—	1	2	1	2	1	2	1	1	2
	Gliosis	4	4	3	3	—	1	1	1	2	1	2	3	2	3
	PrP	4ps	2ps	3ps	3ps	—	1ps	1ps	1s	2s	0	3p	2p	0	2p
5	Spongiosis	3	2	2	3	2	1	2	1	2	0	2	1	1	1
	Gliosis	3	3	2	2	2	1	1	1	2	1	2	0	1	2
	PrP	2s	3s	1s	3s	—	1s	1s	1s	2s	0	0	0	0	0
6	Spongiosis	1	3	2	1	—	2	3	1	3	0	2	2	2	2
	Gliosis	2	3	2	2	—	1	2	1	3	1	2	1	1	3
	PrP	2ps	2s	3ps	1ps	—	1ps	1ps	1ps	3ps	0	0	1p	0	1p
7	Spongiosis	3	3	2	4	—	1	1	2	3	0	2	1	1	3
	Gliosis	3	2	1	3	—	1	1	1	2	1	2	2	1	3
	PrP	3s	3ps	3ps	3ps	—	1p	2p	1s	2s	0	1p	1p	0	3p

*No autopsy was available; accumulation of PrP^{Sc} in biopsy material.

sCJD = sporadic Creutzfeldt-Jakob disease; ant.-vent. = antero-ventral; dors.-med. = dorso-medial; vent.-lat. = ventro-lateral; 0–4 = degree of involvement (0, none; 1, little; 2, mild; 3, moderate; 4, severe); – = No autopsy material available from this brain region; WB+ = confirmed by Western blot; s = synaptic; p = patchy-like.

Neuropathology. The neuropathologic findings are presented in table 3. Blinded investigation revealed that all patients showed the typical neuropathology of sCJD, including mostly severe spongiform degeneration, gliosis, and pathologic deposition of PrP^{Sc} in frontal, parietal, temporal, and occipital areas. In most other regions including striatum (caudate, pallidum, putamen), brainstem pons, and cerebellum, postmortem autopsy revealed little to mild neuronal loss, spongiosis, and gliosis. The degree of neuropathologic involvement of distinct thalamic nuclei could be assessed in Patients 4 to 7. Spongiosis, gliosis, and the deposit of PrP^{Sc} were mild to moderate in antero-ventral, dorso-medial, ventro-lateral, and pulvinar thalamic nuclei. Although not assessed in quantitative manner, visual inspection revealed no prominent neuronal loss in these nuclei. In no patient severe or isolated neuropathologic degeneration was found in the antero-ventral and dorso-medial thalamic nuclei. Moreover, in all but one patient, the nucleus olivaris was either not or only little affected (mild changes in Patient 2).

Distribution of PrP^{Sc} and PRNP genotype. The distribution of PrP^{Sc} in a cortical region (occipital cortex) and thalamus was investigated in detail in four of seven patients. This analysis revealed that three patients harbored slightly higher amounts of PrP^{Sc} in the occipital cortex when compared to thalamus, whereas one patient showed only minute amounts of PrP^{Sc} in the occipital cortex (figure 2).

No patient had mutations in the coding region of the *PRNP* gene (see table 1). At codon 129, Patients 4, 5, and 7 were methionine homozygous, Patient 6 valine homozygous, and Patient 3 methionine/valine heterozygous. The PrP^{Sc} glycotypes were as follows: Type 1 in Patients 4, 5, and 7 (type MM1), Type 2 in Patients 3 (MV2) and 6 (VV2). The codon 129 genotype and the PrP glycotype could not be determined in Patients 1 and 2.

Discussion. In this systematic prospective study of seven patients with definite sCJD a high fre-

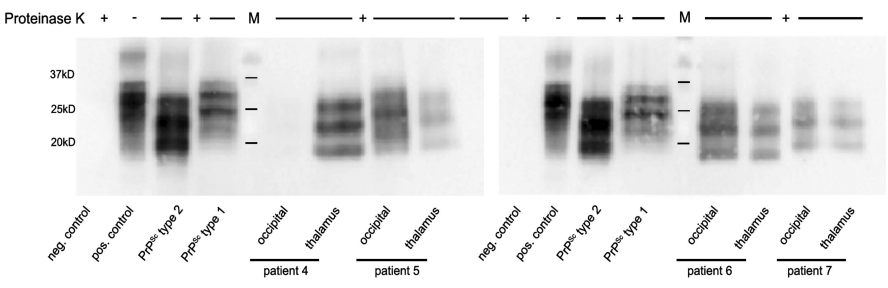

Figure 2. Western blots illustrating the PrP^{Sc} content in occipital cortex and thalamus in Patients 4 through 7. Controls include PrP^{Sc} type 1 and 2, and a sample of an individual without prion disease. Digestions with proteinase K are indicated above the respective lanes (+). Molecular weight markers were run on the fifth lane of each blot (M).

quency of sleep-wake symptoms and profound sleep EEG changes was observed. These findings might be somewhat surprising when considering the literature. The apparent discrepancy, however, could be related to the prospective nature of our study, which is in contrast to most previous studies and surveys. We think that sleep-wake symptoms are often neglected or obscured by other neurologic symptoms and signs if not specifically assessed or searched for. Nevertheless, a variety of sleep-wake symptoms including daytime drowsiness, disorders of vigilance, hypersomnia, increased sleep need, insomnia, and disappearance of consolidated sleep episodes were previously reported to occur in sCJD, sometimes even early in the course of the disease.[19,25,28]

Profound sleep EEG changes were present as early as 4 weeks after the onset of clinical symptoms. All-night polysomnographic recordings demonstrated in all patients a dramatic reduction of sleep efficiency, virtual absence of REM sleep, and complete loss of sleep spindles. In contrast, EEG delta- and theta-frequency activity (0.5 to 8 Hz) was increased compared to middle-aged healthy men. This increase, however, was unspecific and not indicative of physiologic, deep (slow wave) sleep (the detailed sleep and waking EEG spectra will be presented elsewhere). The lack of normal sleep was also evident from the absence of the usual ultradian modulation (non-REM/REM sleep cycles) and gradual decline of low-frequency activity throughout the course of the nights. In agreement with our findings, an early disappearance of physiologic sleep EEG characteristics was previously reported in patients with sCJD.[24-28]

The complete absence of sleep spindles and K-complexes and enhanced slow activity in the waking EEG precluded the unambiguous differentiation between waking and sleep periods based on conventional polysomnographic criteria. In addition, our multimodal approach (clinical assessment, video-polysomnography, and wrist-actigraphy) revealed major discrepancies among clinically, behaviorally, and electrophysiologically defined wakefulness and sleep. Although patients' reports, clinical observations (e.g., on the wards), and actigraphy suggested excessive amounts of sleep (hypersomnia) rather than insomnia in most of our patients, polysomnographic recordings demonstrated the loss of normal sleep (insomnia) in all patients. This discrepancy might underlie the inconsistent terminology used by different authors to describe sleep-wake disturbances in patients with sCJD. Besides the scientific implications of this finding, it also suggests that a multimodal assessment of sleep-wake disturbances is probably more appropriate in directing the symptomatic treatment of such disturbances with either hypnotics or stimulants.

It is interesting to note that the first reported patient with CJD restricted to the thalamus was reported as being drowsy.[41] The fact that we detected significant amounts of PrP^{Sc} in the thalamus in all investigated individuals is consistent with a significant involvement of this structure in the sleep-wake disturbances associated with the disease. In accordance with this view, sleep disturbances in FFI and sporadic fatal insomnia (sFI) were previously attributed to distinct pathologic changes of specific thalamic nuclei.[42] Nevertheless, considering the presence of severe sleep-wake disturbances including the disappearance of EEG spindle frequency activity in sCJD, it is important to note that no prominent neurodegeneration was found in the antero-ventral and medio-dorsal thalamic nuclei in those patients whose data were available. This finding challenges the clinical-pathologic correlation suggested by others.[1,8,9,42] It might be noteworthy to point out that those patients with less PrP^{Sc} deposition in thalamus than in occipital cortex (Patients 5 through 7) showed hypersomnia rather than insomnia as early sleep-wake symptoms (see table 3).

The observed sleep-wake symptoms (including prominent insomnia in two patients) indicate a remarkable clinical overlap between sCJD and FFI. Similar to the reported findings in progressed stages of FFI,[1,8,9,17,43] the EEG during waking was characterized by diffuse theta-alpha activity, while pseudo-periodic sharp wave complexes at 1 Hz were present in the majority of patients. Also, the inability of all patients to produce the electrophysiologic signs of non-REM sleep and non-REM/REM sleep cycles was reminiscent of the findings in FFI.[1,8,9,17,43] Based on EEG, EOG, and EMG polysomnographic criteria, all our patients spent most of their time in a "non-wake-non-sleep" sub-wakefulness state previously described in FFI.[17] This pattern was interrupted at irregular intervals by short episodes of muscular atonia with or without presence of REM. Some authors consider these "sleep periods" to reflect abortive REM sleep in short-duration FFI.[1,9] We discriminated between stages N (without REM) and R (with REM), and found a polysomnographically defined "sleep efficiency" below 20% with less than 1% stage R. These values are very similar to those obtained by nocturnal polysomnographic recordings in a patient with FFI[43] and in a presumed case of sFI.[44] Furthermore, reminiscent of the increased motor activity and lack of a circadian rest-activity pattern observed in a patient with FFI,[45] the 24-hour rest-activity pattern in our patients was severely disrupted with initially prominent motor activity and loss of distinct diurnal modulation. Finally, as reported before in FFI and sCJD,[19] we also found that heterozygosity at C129 (PrP^{Sc} type: MV2) is associated with the longest disease course. Taken together, our observations suggest that profound sleep-wake disturbances in patients with sCJD may reflect a similar underlying mechanism in sCJD and FFI, which does not depend on a selective neuronal loss in antero-ventral and dorso-medial thalamic nuclei and a specific *PRNP* mutation. This hypothesis is also supported by the observation of similar sleep-wake symptoms or sleep EEG changes in stroke patients

with thalamo-mesencephalic lesions[11] and hemispheric lesions sparing the thalamus.[46]

While our detailed clinical and neurophysiologic investigations in genetically and neuropathologically well-characterized patients with sCJD suggest a prominent overlap with the disease phenotype of FFI,[42] some limitations of our study need to be considered. Although the relative frequency of the molecular features of C129 (MM1, MV2, VV2 variants) in our patients is fairly representative of what has been reported in large series of patients with sCJD,[37] the absence of a molecular characterization of C129 in two patients limits the generalization of our results. Moreover, the presence in these two patients of a sporadic form of fatal insomnia[42,44] cannot be formally excluded. No patient with FFI could be studied for direct comparison, no objective measures allowed to test for the presence of circadian dysautonomia typical for FFI, and no patient with an early diagnosis and long survival time could be investigated. Moreover, it cannot be excluded that the patients' medication influenced some of our findings. Nevertheless, while most patients received a benzodiazepine to alleviate myoclonus or sleep problems, these substances are well-known to attenuate low-frequency EEG activity and enhance sleep spindles.[47]

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