Original Article

Characterization of the sleep disorder of anti-IgLON5 disease

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Abstract

Study Objective: To characterize the sleep disorder of anti-IgLON5 disease.

Methods: We reviewed 27 video-polysomnographies (V-PSG), 6 multiple sleep latency tests (MSLT), 2 videsomnoscopies with dexmedetomidine, and 10 actigraphies recorded during the disease course of five patients. Due to severe sleep architecture abnormalities, we used a novel modified sleep scoring system combining conventional stages with a descriptive approach in which two additional stages were identified: undifferentiated-NREM (UN-NREM) and poorly structured N2 (P-SN2) sleep that were characterized by abnormal motor activation and absence or sparse elements of conventional NREM sleep.

Results: Sleep-related vocalizations, movements, behaviors, and respiratory abnormalities were reported by bed-partners. In all patients, NREM sleep onset and sleep reentering after an awakening occurred as UN-NREM (median: 29.8% of total sleep time [TST]) and P-SN2 sleep (14.5% TST) associated with vocalizations and simple and quasi-purposeful movements. Sleep initiation was normalized in one patient with a high dose of steroids, but NREM sleep abnormalities reappeared in subsequent V-PSG. In all patients, if sleep continued uninterrupted, there was a progressive normalization with normal N2 (11.7% TST) and N3 (22.3% TST) sleep but stridor and obstructive apnea emerged. REM sleep behavior disorder (RBD) occurred in four patients. Sleep initiation was also altered in MSLT and dexmedetomidine-induced sleep. Actigraphy showed a 10-fold increase of nocturnal activity compared with controls. Sleep abnormalities remained stable during the disease.

Conclusions: The sleep disorder of anti-IgLON5 disease presents as a complex sleep pattern characterized by abnormal sleep initiation with undifferentiated NREM sleep, RBD, periods of normal NREM sleep, stridor, and obstructive apnea.

Statement of Significance

To assess the complex sleep disorder of anti-IgLON5 disease, we used a new modified scoring system that combined conventional staging with a descriptive approach for periods of abnormal sleep architecture. This method better characterized the disorganized sleep architecture in anti-IgLON5 disease and could be useful to assess sleep in other neurological diseases in which conventional scoring system cannot be applied. Patients with the anti-IgLON5 disease showed abnormalities in NREM sleep initiation that may be due to the involvement of neural areas that induce sleep onset. Recently, a GABAergic NREM sleep inducing center in the medulla of rats, the parafacial zone, has been identified. Impairment of an analogous area in anti-IgLON5 disease is possible as pathological abnormalities are maximal in the medulla.

Introduction

The anti-IgLON5 disease is a recently described disorder associated with antibodies against IgLON5, a neuronal cell adhesion protein of unknown function. The disease is clinically characterized by a sleep disorder, symptoms of brainstem dysfunction (mainly dysphagia, dysarthria, and oculomotor abnormalities), gait dysequilibrium, chorea, and cognitive impairment [1–4]. Postmortem examination of patients with anti-IgLON5 disease suggests a novel tauopathy with neuronal loss and deposits of tau aggregates mainly localized in the tegmentum of the brainstem and hypothalamus [1, 5]. Whether the primary underlying pathophysiology of anti-IgLON5 disease is degenerative or autoimmune is unclear, as is the role of IgLON5 antibodies. The absence of complete response to immunotherapy in most cases and the neuropathological findings favors a primary degenerative disorder. In contrast, the strong association with specific HLA alleles (the DRB1*1001 and DQB1*0501) and the presence of an antibody against a neuronal surface antigen suggests that the disease is autoimmune [4].

The sleep disorder in anti-IgLON5 disease is characterized by a complex parasomnia involving both NREM and REM sleep with a sleep breathing disorder [1, 4]. An accurate characterization of this distinctive sleep disorder is important as it appears to be unique to the disease. Identification of the sleep disorder in a patient can raise suspicion for the condition and lead to testing for the presence of anti-IgLON5 antibodies. Some features of the sleep disorder in anti-IgLON5 disease have previously been described [1, 6]. Herein, we describe in detail the clinical and video-polysomnography (V-PSG) features of this sleep disorder and their evolution over the course of the disease, emphasizing aspects that have only been scantly delineated or were previously unknown. In addition, to optimally assess the complex sleep disorder of anti-IgLON5 disease, we developed a novel modified sleep scoring system that combines conventional staging with a descriptive approach.

Methods

Study participants

We studied five patients with anti-IgLON5 disease attending the Multidisciplinary Sleep Disorders Unit of the Hospital Clinic of Barcelona. They were three males and two females, with a median age at first visit of 59 (range: 53–76) years (Supplementary Table S1). Their clinical features have previously been described [1, 4]. Sleep disturbances were present at disease onset in all five patients, and in three they were the main symptom leading to medical consultation. Median follow-up at our institution was 58 (range: 6–84) months. Three patients have died, all of them suddenly during sleep. Postmortem neuropathological findings have previously been reported in two (patients 2 and 4) [1, 5].

Sleep history and sleep studies

A comprehensive semi-structured clinical interview focusing on sleep complaints was conducted in all patients and bed partners. All sleep studies recorded in our center during the disease course were reviewed and included: (1) Twenty-seven nocturnal V-PSG recorded in the five patients, (2) six multiple sleep latency test (MSLT) in four patients (patients 1–3 and 5),

(3) two dexmedetomidine-induced sleep with V-PSG recording and nasal endoscopy in two cases (patients 3 and 5), and (4) 10 actigraphic studies (90–150 days) in four patients (patients 1–3 and 5). All five patients underwent laryngoscopy during wakefulness. In three patients (patients 2–4), hypocretin-1 levels in cerebrospinal fluid (CSF) were determined with a commercially available radioimmunoassay kit (Phoenix Pharmaceuticals) [7].

V-PSGs and MSLTs were recorded at different points through the disease course (Supplementary Table S2). Fourteen V-PSG studies were performed when the patients not taking CNS active drugs (e.g. antidepressants, hypnotics) and seven were done after immunotherapy (e.g. intravenous steroids, cyclophosphamide, immunoglobulins, or rituximab). In three patients with a previous diagnosis of obstructive sleep apnea syndrome (OSAS) (patients 1–3) all but one V-PSG were performed with the patients wearing their positive airway pressure (PAP; continuous-PAP [CPAP] or Bi-level PAP) mask, and the remaining V-PSG study was performed without PAP therapy. In patient 4, V-PSGs were done without CPAP, and the last study with a tracheostomy. In patient 5, the initial study was done without CPAP, in the second CPAP was titrated, and the last study was conducted with the patient wearing the CPAP mask. Five actigraphies were recorded during periods in which immunological therapy was administered, including 3–30 days before and 30–120 days after treatment.

Video-polysomnographic evaluations

V-PSGs were recorded with the Deltamed system (Coherence version 6, France) following the American Academy of Sleep Medicine (AASM) recommendations [8] and included electrooculogram (EOG), electroencephalogram (EEG) (F3, F4, C3, C4, O1, and O2, referred to combined mastoids), submental electromyogram (EMG), and surface bilateral EMG of the anterior tibialis. In 23 out of 27 studies, additional muscles were recorded, including the flexor digitorum superficialis ($n = 22$) or the biceps brachii ($n = 1$) in the upper limbs, and the extensor digitorum brevis in the lower limbs ($n = 9$). Electrocardiography, nasal and oral airflow measured with cannula and thermistor, thoracic and abdominal movements, and oxyhemoglobin saturation were also recorded. Five-nap MSLT were performed according to recommended guidelines [9]. All studies had synchronized audiovisual recording.

Scoring of sleep stages and events

Sleep in patients with anti-IgLON5 disease was characterized by periods of extremely abnormal sleep architecture that alternated with periods of normal sleep. When sleep architecture was normal, sleep stages were scored according to the AASM criteria [8]. In periods of disorganized sleep architecture, however, conventional sleep scoring was difficult to apply and produced inconsistent results. To overcome this problem, we applied different metrics [1, 10] using information not only from the routine EEG, EOG and submental EMG signals, but also analyzing the synchronized audiovisual recording (e.g. assessing the state of the eyes—open or closed, body posture, vocalizations and movements, interaction with the environment and external stimuli, and presence of snoring or stridor), the graphic display of the EEG power spectrum over time (density spectral array), and respiratory variables (from the airflow sensors, respiratory bands,

and pulse oximetry). Since periods of normal and abnormal sleep architecture alternated throughout the night, scoring an isolated 30-s epoch was difficult in some cases and it was necessary to take into account information from the preceding and subsequent epochs.

Each 30-s epoch was first classified as wakefulness or sleep, based on all of the above information. If sleep was identified (mainly because of the disappearance of the patient's characteristic awake alpha rhythm recorded during clear behavioral awake periods while the patient was with the eyes closed— Figure 1A), we then decided if it was REM or NREM sleep, with information from the 6-channel EEG providing the most important reference. REM sleep was scored, even in the presence of increased EMG activity in the submentalis muscle, whenever the EEG was characteristic (low amplitude with mixed frequencies) and the EOG demonstrated definite and recurrent rapid eye movements. NREM sleep was scored whenever the characteristic EEG/EOG pattern of REM sleep was absent. In epochs with typical EEG markers of NREM sleep (vertex waves, K-complexes, sleep spindles, and high amplitude delta slowing) the standard scoring system including stages N1, N2, or N3 was used [8].

Sleep not corresponding to REM sleep and without the characteristic elements of NREM sleep (vertex waves, K-complexes, sleep spindles, and high amplitude delta slowing) was scored as *Undifferentiated NREM* (UN-NREM) sleep. In anti-IgLON5 disease, UN-NREM sleep was characterized by consecutive epochs of sleep with diffuse irregular theta EEG activity of 4–7 Hz and moderate amplitude (20–50 μV) usually associated with excessive mentalis and limb EMG activation linked to frequent vocalizations and movements in the absence of vertex waves, K complexes, sleep spindles, and delta slowing (Figure 1B–D). We also defined the stage *poorly structured N2* (P-S N2) sleep in those epochs with occasional identifiable K complexes or sleep spindles associated with abnormal behavioral manifestations (typically vocalizations and limb movements) (Figure 2A and B). This stage was distinguished from epochs of normal NREM N2 sleep that could also appear in the same recording and were characterized by absence of motor activation and the occurrence of frequent well-formed K complexes and sleep spindles (Figure 2C). In P-S N2 sleep, K complexes and sleep spindles were scant and sometimes very difficult to distinguish due to the high amount of EMG activity and movement artifacts in the EEG channels.
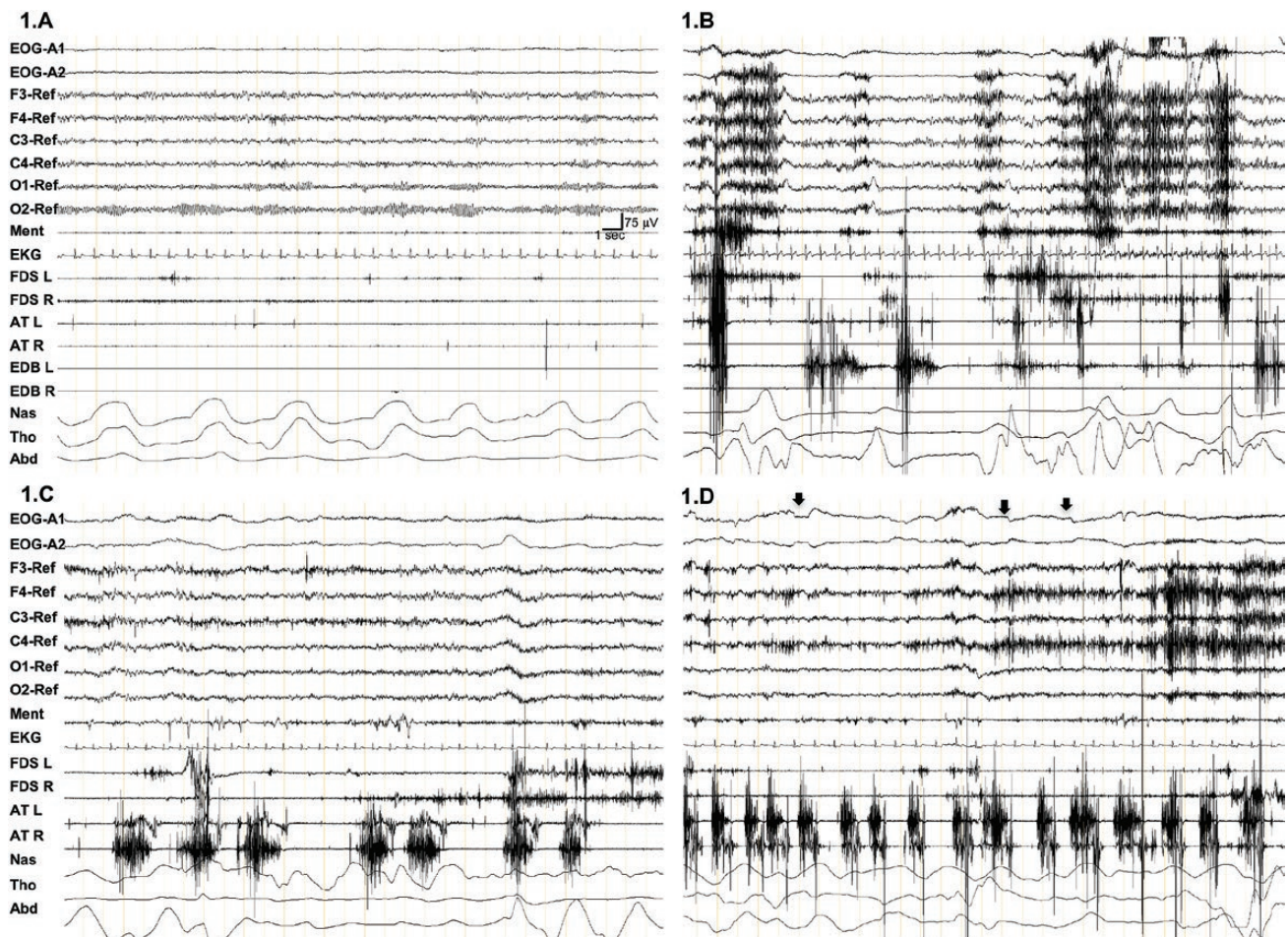

Figure 1. Sleep onset as undifferentiated NREM sleep. (A) Quiet wakefulness with normal posterior alpha rhythm at 10 Hz; (B) sleep onset with undifferentiated NREM sleep characterized by diffuse theta activity with intense EMG activation that correlates with vocalizations and quasi-purposeful movements; (C) undifferentiated NREM sleep with rapid periodic leg movements recorded in AT EMG channels; (D) undifferentiated NREM sleep with low amplitude semi-rapid eye movements (arrows) and rapid periodic leg movements in AT EMG channels. EMG = electromyogram; EOG = electrooculogram; Ment = electromyography of mentalis muscle; EKG = electrocardiogram; FDS = flexor digitorum superficialis muscle left (L) and right (R); EDB = extensor digitorum brevis muscle left (L) and right (R); AT = anterior tibialis left (L) and right (R); NAS = nasal air flow; THO = thoracic respiratory movement; ABD = abdominal respiratory movement. Note the calibration mark for time / EEG voltage (panel A). All pictures represent a 30-s epoch. REF: EEG electrodes were referenced to both ears.
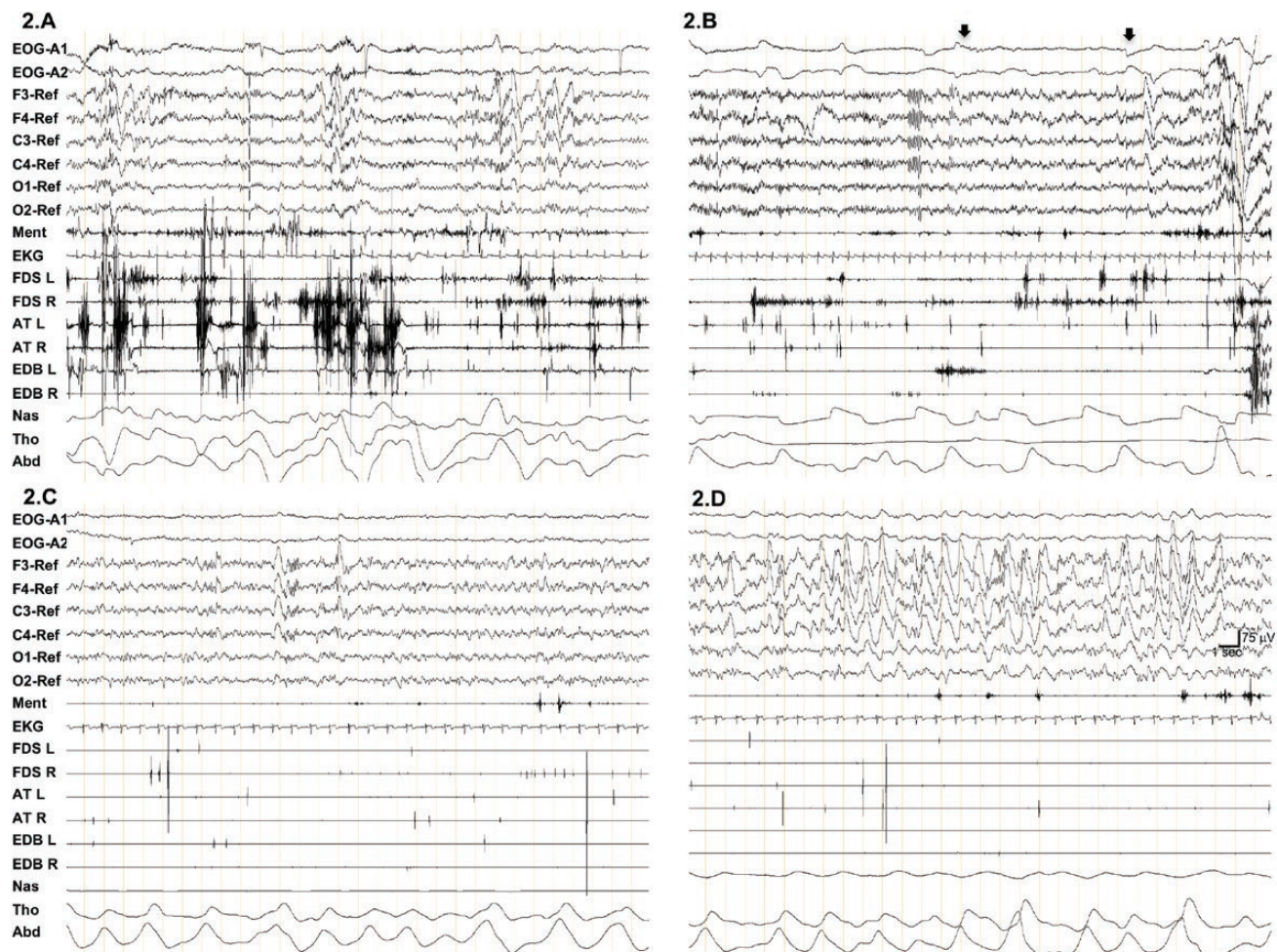
Figure 2. Poorly structured N2, normal N2 and N3 sleep. (A) Poorly structured N2 with K complexes with frequent muscle activity in EMG of the limbs that correlates with quasi-purposeful movements; (B) poorly-structured N2 with well-defined sleep spindles at 12–14 Hz and K complexes with EMG activation and low amplitude semi-rapid eye movements (arrows) with a movement artifact at the end of the epoch; (C) normal stage N2 without motor activation; (D) normal stage N3 without motor activation. EMG = electromyogram; EOG = electrooculogram; Ment = electromyography of mentalis muscle; EKG = electrocardiogram; FDS = flexor digitorum superficialis muscle left (L) and right (R); EDB = extensor digitorum brevis muscle left (L) and right (R); AT = anterior tibialis left (L) and right (R); NAS = nasal air flow; THO = thoracic respiratory movement; ABD = abdominal respiratory movement. Note the calibration mark for time / EEG voltage (panel D). All pictures represent a 30-s epoch. REF: EEG electrodes were referenced to both ears.

REM sleep behavior disorder (RBD) was defined by the occurrence during REM sleep of excessive tonic and/or phasic muscle activity in the submental and/or limb EMG associated with typical jerky movements (Figure 3).

To assess the validity of our new system to score sleep stages that combined conventional scoring with a descriptive approach, we examined the intra- and inter-rater agreement. Two sleep medicine experts (CG and JS) scored sleep stages of two V-PSG studies from two patients. In addition, each rater scored one of the studies one more time, with at least 1 month between scorings. In total, 1884 epochs were scored by each rater. For inter-rater variability, agreement was obtained in 77.4% of epochs, with Cohen's kappa coefficient showing substantial agreement between the two observers ($k = 0.705$). For intra-rater variability, agreement was obtained in 79.4% of epochs, with substantial agreement in the Cohen's kappa coefficient ($k = 0.729$). These inter- and intra-scorer agreements were similar to those reported with conventional sleep staging in non-neurological patients [11, 12]. Most disagreements between different scorers or within the same scorer resulted from categorizing UN-NREM

sleep as wakefulness and less frequently as P-S N2 sleep, or from scoring normal stage N2 as N3 or vice versa.

Scoring of additional sleep events

Arousals, apneas, and periodic limb movements during sleep (PLMS) were scored according to the AASM criteria [8, 13]. We also scored previously undescribed events that we termed *rapid periodic leg movements* (RPLM) and *atypical isolated rapid eye movements in NREM sleep*. RPLM were defined as repetitive lower limb movements that did not fulfill criteria for classical PLMS [13] because of a short interval between movements of less than 5 s. These RPLM were repetitive, quasi-periodic, brief, unilateral or bilateral, asynchronous, stereotyped extension of the toes and flexion of the ankle with an interval between movements usually ranging from 2 to 5 s (Figure 1C and D) [1]. *Atypical isolated rapid eye movements in NREM sleep* were defined as occasional irregular semi-rapid eye movements in the EOG. These conjugate eye movements had an initial deflection lasting ≥250 ms or <250 ms but with lower amplitude and frequency than those
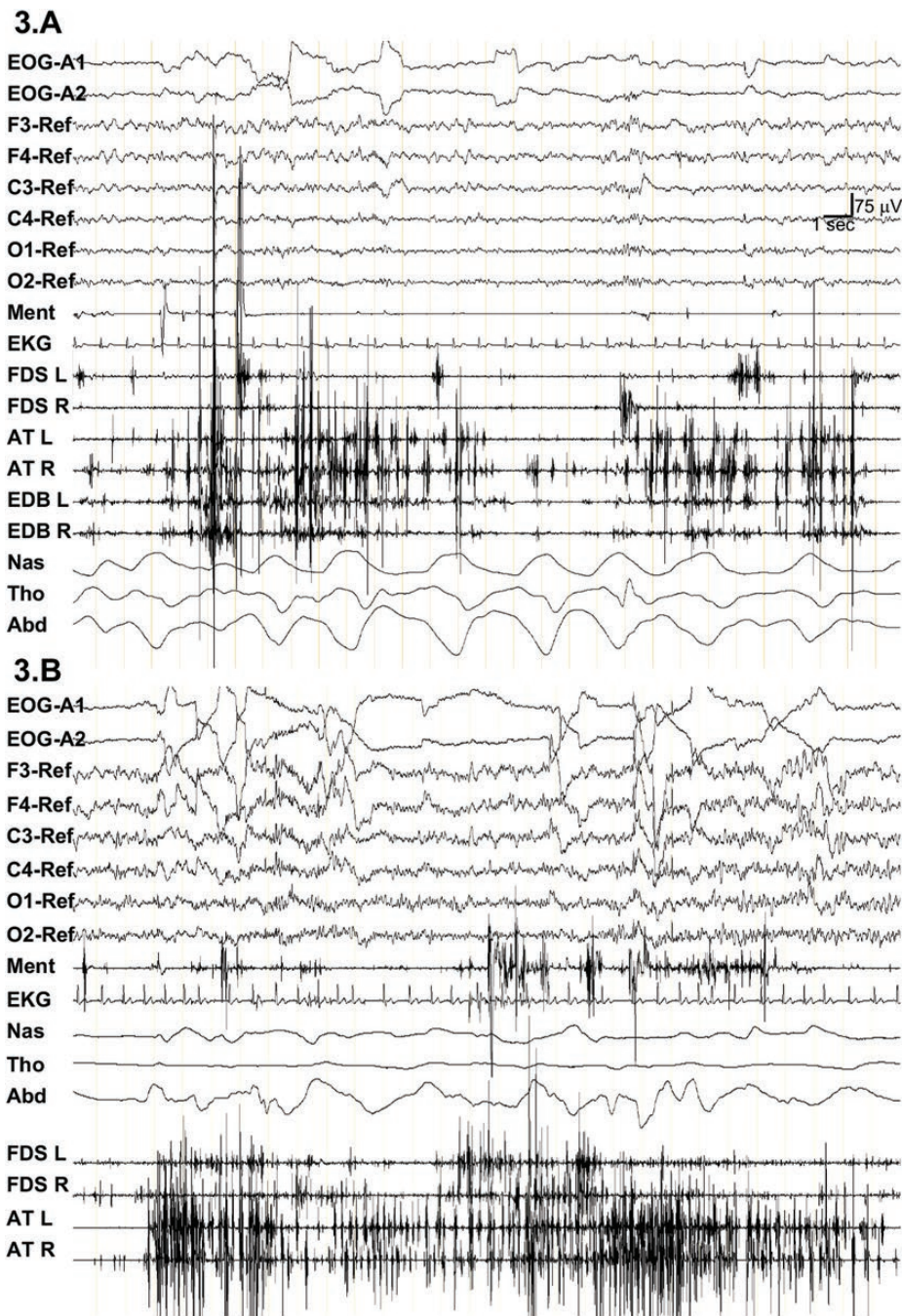
Figure 3. REM sleep behavior disorder. (A and B) REM sleep with typical rapid eye movements and EEG features but with excessive phasic and tonic muscle activity associated with body jerks typical of REM sleep behavior disorder. In (A), there is normal muscle atonia in the mentalis muscle. In (B), the mentalis muscle shows phasic bursts of EMG activity and minimal tonic EMG activation. EMG = electromyogram; EOG = electrooculogram; Ment = electromyography of mentalis muscle; EKG = electrocardiogram; FDS = flexor digitorum superficialis muscle left (L) and right (R); EDB = extensor digitorum brevis muscle left (L) and right (R); AT = anterior tibialis left (L) and right (R); NAS = nasal air flow; THO = thoracic respiratory movement; ABD = abdominal respiratory movement. Note the calibration mark for time / EEG voltage (panel A). All pictures represent a 30-s epoch. REF: EEG electrodes were referenced to both ears.

typically seen in periods of REM sleep in the same patient, and occurred during NREM sleep (Figures 1D and 2B). Epochs containing *atypical isolated rapid eye movements* were not scored as REM sleep because (1) the EEG was characterized by diffuse theta activity of moderate voltage similar to the epochs of UN-NREM sleep without isolated rapid eye movements and clearly different from the low amplitude with mixed frequencies typical of REM sleep, (2) the EEG often contained typical markers of NREM sleep (e.g., sleep spindles or K-complexes in P-S N2), and (3) the

rapid eye movements were not as frequent, recurrent and large in amplitude as those typically recorded in REM sleep (Figure 3).

Sleep-related vocalizations and motor events

Synchronized audiovisual recordings were reviewed to evaluate the presence or absence of vocalizations and movements during sleep in each 30-s epoch. Vocalizations were classified as simple (e.g. murmuring, whispering, groaning) and complex (e.g. talking,

shouting, laughing, crying). Motor events were classified as jerks (sudden contractions of a single or several muscle groups), simple movements (e.g. raising the arms, kicking, punching), or quasi-purposeful (i.e. "finalistic" or elaborated movements or gestures that followed a complex pattern that clearly resembled an identifiable activity of daily life, such as eating, drinking, or manipulating objects). When more than one type of vocalization or movement was present within the same epoch, the more complex event was selected to categorize the epoch (e.g. complex prevailed over simple vocalizations and quasi-purposeful over simple and jerky movements). PLMS and RPLM in the anterior tibialis were scored separately from jerks or simple and quasi-purposeful movements.

Dexmedetomidine-induced sleep with polysomnography and nasal endoscopy

Sleep was induced with dexmedetomidine during daytime and recorded via V-PSG to visualize the levels of obstruction in the upper airway. The process was conducted in an operating room after 8 h of fasting. After premedication with midazolam 0.5 mg intravenously, dexmedetomidine was administered intravenously with a loading dose of 1 mcg/kg for 15 min, followed by 0.4 mcg/kg/h. Systolic and diastolic arterial pressure, heart and respiratory frequency, and oxyhemoglobin saturation were monitored. While sleep was induced for 30–45 min, the upper airway was evaluated through nasal endoscopy by an ENT specialist (IV).

Circadian rest–activity cycle measurements

Rest–activity cycles were measured by wrist actimetry using the Actiwatch AW7 (CamNtech Ltd., UK) that was worn on the nondominant wrist while the patients continued their daily activities and sleep–wake rhythms in their environment. Nine age-matched healthy control participants without sleep complaints (age range: 51–70 years) were recruited to compare the long-term circadian rest–activity cycle recordings with the anti-IgLON5 disease patients. Actimetry data were analyzed by the Sleep and Activity Analysis Software 7.23V (Cambridge Neurotechnology Ltd, UK). Nonparametric circadian rhythm analysis was carried out on continuous days with complete data. This analysis yields circadian characteristics of the rest–activity cycle such as the relative amplitude, the interdaily stability index, and intradaily variability. The relative amplitude was calculated from the ratio of the most active 10-h period to the least active 5-h period across the averaged 24-h profile. The interdaily stability index quantifies the day-to-day stability, that is, the strength of the coupling of the rhythm to supposedly stable environmental zeitgebers while the intradaily variability gives an indication of the fragmentation of the rhythm. In addition, spectral analysis of time series on the 1-min activity values ranging from 10 to 114 days in four patients and age-matched nine control volunteers were performed (PROC spectra, SAS 9.4).

Results

Sleep symptomatology

Bed-partners reported that all patients had frequent sleep-related vocalizations, movements, and complex behaviors and made loud respiratory noise (described as a "*very noisy and heavy snoring*"). The bed partners also reported that they had witnessed apneas during sleep (Table 1). Reported vocalizations included mumbling, whispering, and groaning, and less often talking, shouting, crying, and laughing. Movements and behaviors encompassed jerking, raising the arms, knocking, kicking, and gesticulating as if arguing, discussing, and commanding. All of these behaviors took place in the bed. Violent behaviors were infrequent, and punching or grabbing the bed partner by the neck or hair were not reported. Two patients had fallen out of the bed several times, and in one, this resulted in a mild facial contusion. Bed partners were not injured but their sleep was markedly disrupted, and two decided to sleep in a separate room because of patients' sleep-related vocalizations, movements, and respiratory noise. Three patients had occasional episodes of nocturnal confusion in which they were disoriented, got out of the bed and behaved oddly; for example, they used the toilet unsuitably, opened the windows or doors without any clear purpose, or got dressed in the middle of the night. In two patients, the frequency and intensity of these episodes clearly increased when they took tricyclic antidepressants such as amitriptyline.

All patients were unaware of their sleep vocalizations, movements, and behaviors. Bed-partners often had the impression that the patient was acting out their dreams but nightmares or dream mentation was not recalled by the patients. Four patients complained of fragmented, unrefreshing, and poor quality sleep (Table 1). The remaining patient did not complain of sleep problems and considered her sleep to be of good quality. Symptoms of restless legs syndrome were absent, but three patients reported a continuous inner feeling of restlessness resembling akathisia. This restlessness was not focused in the lower limbs (in two patient it was centered in the abdomen), occurred during the whole day without significant nocturnal worsening, and failed to improve with dopaminergic agonists. Excessive daytime sleepiness (EDS) was present in the four patients complaining of poor sleep quality. EDS was intense with sudden episodes of unintended sleep even in active situations (e.g. walking, eating, or working). EDS significantly improved in all four patients with CPAP therapy although mild sleepiness reappeared occasionally in passive situations.

Three patients were initially evaluated in other sleep centers. For all three, sleep studies were done without video recording and showed frequent obstructive apnea. They were initially diagnosed as having OSAS, without a parasomnia or sleep-related movement disorder. A CPAP device eliminated the loud respiratory noise and apnea/hypopnea but vocalizations, movements, and behaviors during sleep persisted, and for this reason, they were referred to our multidisciplinary sleep center. In the remaining two patients, sleep problems were present at disease onset, and both consulted their general medicine physician but specific sleep evaluation was not requested.

Polysomnographic features

Nocturnal V-PSG showed moderate reduction in total sleep time and sleep efficiency with sleep fragmentation and frequent awakenings with increased wakefulness after sleep onset (Table 2). V-PSG showed the following main features of the sleep disorder: (1) in all patients sleep initiation was characterized by abnormal NREM sleep architecture associated with intense motor activation with vocalizations and simple and quasi-purposeful movements, (2) if sleep was uninterrupted by an awakening,

Table 1. Sleep disturbances reported by bed partners and patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Bed-partner's report					
°Sleep vocalizations, movements, and behaviors	Yes	Yes	Yes	Yes	Yes
°Loud respiratory noise and apnea during sleep	Yes	Yes	Yes	Yes	Yes
Patient's complaints					
°Fragmented sleep	Yes	Yes	Yes	No	Yes
°Unrefreshing and poor quality sleep	Yes	Yes	Yes	No	Yes
°Sleep onset insomnia	No	No	No	No	Yes
°Nightmares or dream mentation	No	No	No	No	No
°Awareness of sleep vocalizations, movements, and behaviors	No	No	No	No	No
°Excessive daytime sleepiness	Yes	Yes	Yes	No	Yes
Other sleep-related problems	Occasional episodes of nocturnal confusion	Occasional episodes of nocturnal confusion Nocturnal enuresis	Occasional episodes of nocturnal confusion	No	No
Previous sleep consultation	In a sleep center, PSG: AHI 81, OSAS diagnosed	In a sleep center, respiratory polygraphy: AHI 59, OSAS diagnosed	In a sleep center, PSG: AHI 33, OSAS diagnosed	To family doctor	To family doctor. Lorazepam introduced

PSG = polysomnography without video; AHI = apnea–hypopnea Index; OSAS = obstructive sleep apnea syndrome.

there was a progressive normalization of NREM sleep in which conventional sleep spindles, K complexes and delta slowing of stages N2 and N3 were discernible, (3) four out of five patients had RBD, and (4) all patients had a sleep breathing disorder with stridor and obstructive apnea.

Altered sleep initiation
In all patients, wakefulness was characterized by normal posterior alpha rhythm; no theta or delta slowing was recorded. In all patients sleep initiation, either at sleep onset or following an awakening after sleep onset, was abnormal and consisted of UN-NREM sleep and P-S N2 sleep with continuous EMG activation associated with frequent vocalizations and simple and quasi-purposeful movements (Supplementary Videos 1–3). In 25 out of the 27 V-PSGs, sleep onset at the beginning of the night was characterized by prolonged periods of UN-NREM sleep followed by P-S N2 sleep (Figure 4). In these 25 studies, episodes of sleep reentering after awakenings during the night also occurred as UN-NREM followed by P-S N2, or less often straight to P-S N2 sleep. Normal sleep reentering as normal stage N1 or N2 without EMG activation, vocalizations or movements were rarely recorded at sleep initiation.

In patient 4, this abnormal pattern of sleep initiation as UN-NREM followed by P-S N2 sleep differed in two V-PSG studies. The first V-PSG was recorded in the intensive care unit (ICU) and showed the typical abnormal sleep initiation with UN-NREM and P-S N2 sleep. The second V-PSG, recorded 22 days later in the sleep laboratory following treatment with high-dose intravenous steroids, showed normal sleep onset and reentering of sleep with normal stages N1 or N2 without vocalizations and simple and quasi-purposeful movements (Supplementary Figure S1). Despite additional immunotherapy with cyclophosphamide, there was a marked reemergence of sleep initiation abnormalities in a third study recorded 3 months later. Although periods of UN-NREM sleep were absent, sleep onset and most

episodes of sleep reentering in this study occurred in P-S N2 sleep with frequent vocalizations and motor events.

UN-NREM sleep represented a significant proportion of the TST (median: 29.8%), although this varied widely from one patient to another and within the same patient on different nights (Table 2). Periods of UN-NREM sleep often lasted more than 10 min, and sometimes longer periods of up to 230 min were recorded (Figure 4). Periods of UN-NREM sleep were larger at sleep onset in the first half of the night and were fragmented by frequent arousals and awakenings, and occasionally contained one or two intermixed epochs of P-S N2.

As sleep progressed, UN-NREM sleep was replaced by epochs of P-S N2 with sparse K complexes or sleep spindles, continuous EMG activation, and vocalizations and movements (Figure 2A and B). If sleep continued uninterrupted, K complexes and spindles rapidly increased in number, with a simultaneous decrease in EMG activation, vocalizations, and movements until they disappeared and NREM sleep became normal. Periods of P-S N2 sleep represented a median of 14.5% of TST and lasted for a median of 5 min until NREM sleep was normalized (Table 2). P-S N2 sleep was also fragmented by frequent arousals and awakenings, sometimes with intermixed epochs of UN-NREM sleep.

The total amount of normal stage N1 was reduced. Stage N1 was absent at sleep onset at the beginning of the night, was exceptional during reentering of sleep after an awakening, and occurred only as one or two epochs following brief arousals from normal stages N2 or N3. During the awakenings emerging from UN-NREM or P-S N2 sleep, the patients were oriented, behaved normally, and their normal occipital alpha rhythm reappeared in the EEG. Four patients showed *atypical isolated rapid eye movements in NREM sleep*, clearly different in amplitude and frequency from those seen in REM sleep in the same subject (Figures 1D and 2B). Up to 80% of isolated rapid eye movements occurred during UN-NREM sleep, and less frequently in P-S N2 sleep.

Table 2. Video-polysomnographic findings

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Total
Number of V-PSGs recorded	6	5	10	3	3	27
TST (min)	254.5 (204.5–315.5)	318.5 (254–408)	272.5 (144–342)	371 (104–402)*	191.5 (183–284)	280.7 (104–408)
Sleep efficiency (%)	56 (44–68)	72 (67–87)	61.5 (29–72)	88 (26–89)*	41 (36–65)	67 (26–89)
Sleep-onset latency (min)[†]	13 (3–24.5)	24.5 (4–25.5)	22.2 (2–74.5)	4 (3.5–26.5)	51.5 (38.5–156)	22.5 (2–156)
Wakefulness after sleep onset (min)	184.7 (142.5–243)	92.5 (51–102.5)	155.7 (45–291)	48.5 (47.5–275)	172 (99.5–237)	128 (45–291)
Awakenings (n)[‡]	15.5 (14–21)	13 (4–14)	13 (9–25)	15 (7–21)	1 (0–20)	14 (0–25)
Arousal index (n/h)	50.1 (45–63.1)	54.4 (17.9–78.9)	38.3 (20–55.4)	47.6 (28.6–76.7)	35.7 (33–40.9)	45.5 (17.9–78.9)
Number of V-PSGs with abnormal sleep onset and sleep reentering	6 of 6	5 of 5	10 of 10	2 of 3[§]	3 of 3	26 of 27
Normal stage N1						
Number of V-PSGs with periods of stage N1	6 of 6	5 of 5	8 of 10	3 of 3	3 of 3	25 of 27
Percentage of TST (%)	2.6 (0.2–7.1)	1.4 (0.8–4.1)	0.5 (0–1.4)	6 (3.4–7.2)	0.5 (0.3–1.7)	1.3 (0–7.2)
Stage UN-NREM						
Number of V-PSGs with periods of UN-NREM	6 of 6	5 of 5	10 of 10	1 of 3[§]	3 of 3	25 of 27
Percentage of TST (%)	40 (27.6–67.2)	36.2 (11.5–43.5)	21.6 (11.8–58)	0 (0–51)	2.6 (2.4–21.2)	29.8 (0–67.2)
Duration of the first episode of UN-NREM after sleep onset (min)[‖]	77.2 (15.5–208.5)	29 (7.5–79.5)	23.2 (10–233.5)	17 (—)	4.5 (4.5–8)	29 (4.5–233.5)
Number of episodes of UN-NREM sleep[¶]	6 (4–9)	5 (3–7)	9 (7–13)	8 (0–19)	7 (1–9)	7 (0–19)
Stage P-S N2						
Number of V-PSGs with periods of P-S N2 sleep	6 of 6	5 of 5	10 of 10	2 of 3[§]	3 of 3	26 of 27
Percentage of TST (%)	5.9 (5.4–6.8)	15.4 (4.5–39.1)	25.5 (12.1–52.9)	30.5 (0–41.8)	9.2 (4.4–25.8)	14.5 (0–52.9)
Latency from sleep onset (min)	27.2 (15.5–208.5)	12 (9–22.5)	16 (10–233.5)	5.75 (0–11.5)	1.5 (1.5–4.5)	15.5 (0–233.5)
Duration of the first episode of P-S N2 (min)[#]	4.5 (2–6)	3.5 (2–6)	5.7 (2–16)	34.2 (6–62.5)	10.5 (9–12.5)	5 (2–62.5)
Normal stage N2						
Number of V-PSGs with periods of normal N2 sleep	6 of 6	4 of 5	10 of 10	2 of 3[§]	3 of 3	25 of 27
Percentage of TST (%)	13.7 (7.1–19.8)	10.3 (0–29.7)	10.6 (0.3–33)	16.7 (0–54.2)	67.4 (16.4–71.9)	11.7 (0–71.9)
Normal stage N3						
Number of V-PSGs with periods of stage N3	6 of 6	4 of 5	10 of 10	2 of 3[§]	3 of 3	25 of 27
Percentage of TST (%)	26.7 (8.2–42.5)	19.3 (0–36.1)	22.3 (8.2–34.5)	39.2 (0–40.3)	20.7 (19–28.7)	22.3 (0–42.5)
Number of V-PSGs with motor activation in epochs of stage N3	2 of 6	2 of 4	10 of 10	1 of 2	1 of 3	16 of 25
Percentage of epochs of N3 with motor activation (%)	0 (0–11.5)	0.2 (0–1)	10.8 (2.5–71.4)	2.8 (0–5.7)	0 (0–12.7)	1 (0–71.4)
Number of episodes of normal NREM sleep**	5.5 (3–7)	4 (0–6)	5 (2–11)	7 (0–20)	3 (1–4)	5 (0–20)
Latency from sleep onset (min)	98.7 (21–225)	68 (23.5–118.5)	47.5 (16.5–250)	64.5 (—)	13.5 (12.5–53.5)	61.5 (12.5–250)
Duration of the first episode (min)	18.7 (6–32.5)	24 (19–108)	19 (9–65)	11 (—)	105 (7–170.5)	19.5 (6–170.5)
Stage REM						
Number of V-PSGs with periods of REM sleep	4 of 6	5 of 5	9 of 10	2 of 3[§]	1 of 3	21 of 27
Percentage of TST (%)	4 (0–17.8)	10.1 (1.6–27.2)	10.5 (0–15.4)	0.6 (0–9.2)	0 (0–7.6)	8.4 (0–27.2)
Latency from sleep onset (min)	234 (181–332.5)	16 (6–225)	107 (54–251.5)	105.2 (87–123.5)	42 (—)	100.7 (6–332.5)
Episodes of REM (n)[††]	1 (0–6)	6 (2–8)	2 (0–7)	1 (0–7)	0 (0–1)	2 (0–8)
REM sleep behavior disorder	Yes	Yes	Yes	Yes	No	4 of 5

Results are presented as median and range. Note that the total percentage of all sleep stages is not 100% as the results are presented as the median.

V-PSGs = video-polysomnographies; TST = total sleep time; min = minutes; *n* = number; Arousal index = number of arousals per hour of sleep; UN-NREM = undifferentiated NREM; P-S N2 = poorly structured N2; RBD = REM sleep behavior disorder.

*The lowest TST and sleep efficiency correspond to the first study which was performed a day after weaning from ventilation in the ICU where there was continuous stimulation by noise, light, and nurses.

[†]Defined as the time from lights out to first epoch of any stage of sleep.

[‡]Awakenings longer than 1 min.

[§]Sleep onset and reentering of sleep occurred as UN-NREM sleep followed by P-S N2 in the first V-PSG. In this initial sleep study, conducted in the ICU with low sleep efficiency, normal stages N2 and N3 were not recorded. In the second sleep study of patient 4, sleep initiation was normalized. In the third study, sleep onset and reentering of sleep were again abnormal but occurred directly as stage P-S N2. In this last study, UN-NREM sleep was not recorded.

[‖]Duration of the first episode of UN-NREM at sleep onset until more than 3 consecutive epochs of another stage of sleep occurred.

[¶]Number of episodes of UN-NREM sleep followed or not by P-S N2. Episodes separated by periods of normal NREM sleep, REM sleep or by more than 15 min of wakefulness were considered as different episodes.

[#]Defined as more than 3 consecutive epochs of P-S N2 after sleep onset.

**Established NREM sleep was defined as 5 or more minutes of consecutive normal N2 or N3.

[††]Two episodes of REM sleep were considered to be the same REM period if they were separated by 15 or less minutes.

Overall, only 14% of epochs of UN-NREM sleep and 7% of epochs of P-S N2 contained *isolated rapid eye movements* that usually occurred in conjunction with limb movements and vocalizations.

Normalization of NREM sleep

In all patients, if sleep continued uninterrupted, there was a progressive normalization of NREM sleep with the appearance of normal stages N2 and N3 without abnormal motor activation, vocalizations and movements (Figure 2C and D). Normal stages N2 (median: 11.7% of the TST) and N3 (median: 22.3% of the TST) were present at some point in all patients and in 25 of the 27 V-PSGs (Table 2). Two V-PSGs had no normal NREM sleep: one was the study recorded in the ICU (patient 4) that showed low sleep efficiency, and the other was the first study performed in patient 2 that showed UN-NREM sleep and P-S N2 sleep that alternated with periods of REM sleep (Supplementary Figure S1).
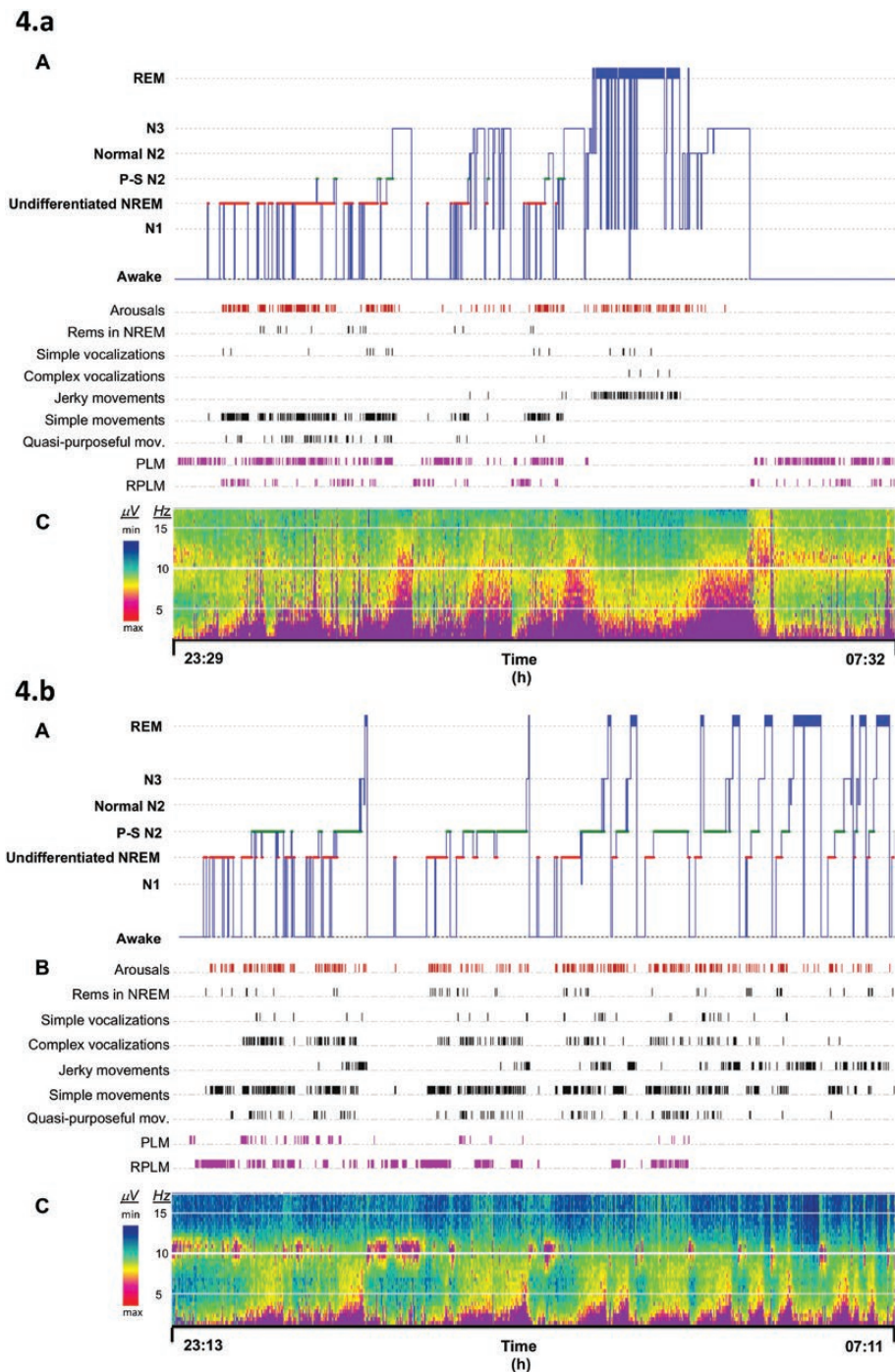
Figure 4. Hypnograms with arousals, vocalizations, movements, and EEG density spectral arrays. (A) Polysomnography number 3 in patient 1; (B) polysomnography number 1 in patient 3. (A) hypnogram; (B) arousals, atypical isolated rapid eye movements in NREM sleep, vocalizations (simple and complex), motor events (jerks, simple, and quasi-purposeful movements) and periodic leg movements and rapid periodic leg movements; (C) density spectral array showing the power spectrum of electroencephalographic frequencies (0–17 Hz) in electrode C3 referenced to electrode O2. Warmer colors indicate higher power in the corresponding frequency (please note the color bar). P-S N2 = poorly structured N2 sleep; REMs = atypical rapid eye movements in NREM sleep; PLM = periodic limb movements; RPLM = rapid periodic leg movements.

Normal NREM sleep usually appeared as a short period (usually less than 3 min) of normal stage N2 followed by a longer episode (normally more than 10 min) of stage N3, or as direct transition from P-S N2 to normal stage N3 (Table 2). Episodes of normal NREM sleep tended to occur and were longer in the second half of the night. Epochs of stage N3 were characterized by abundant sleep spindles in addition to typical delta activity with high amplitude. All patients had occasional isolated epochs of stage N3 containing motor activation with jerks. Vocalizations and simple or quasi-purposeful movements were rarely present in stage N3. Awakenings emerging from NREM sleep were normal and episodes of altered arousal from NREM sleep, such

as confusional arousals, sleepwalking or sleep terrors, were not recorded.

REM sleep behavior disorder

REM sleep was present in all patients and recorded in 21 of the 27 V-PSGs (Table 2). REM sleep was absent in three sleep studies with reduced sleep efficiency (<40%) and in one study done without the patient wearing CPAP where frequent obstructive apnea with marked sleep fragmentation occurred (Supplementary Figure S2). The remaining two studies without REM sleep were recorded with benzodiazepines but not antidepressants. Episodes of REM sleep usually occurred in the second half of the night. Four subjects had RBD showing excessive tonic and phasic muscular activity in the mentalis and all four limbs associated with face, neck, limb, or body jerks (Supplementary Video 4), and less frequently vocalizations and simple or quasi-purposeful movements and vigorous behaviors. REM sleep was normal with preserved muscle atonia and without vocalizations or movements in one patient (patient 5, in the only V-PSG in which 14.5 min of REM sleep were recorded).

Sleep breathing disorder

Stridor and obstructive apneas during sleep were present in all five patients (Table 3; Supplementary Figure S2). Stridor during sleep was intense and frequent in four patients and mild and intermittent in one. Stridor was particularly continuous and loud during stage N3 (Supplementary Video 5), while during UN-NREM sleep and P-S N2 sleep, it was intermittent and less intense. Stridor persisted during REM sleep in three patients (REM sleep was not recorded in the V-PSG without CPAP in the remaining two patients).Central apnea was infrequent. Stridor and obstructive apnea were eliminated in four patients by CPAP and in one patient with tracheostomy. In one case (patient 3), however, stridor and apnea reappeared despite increasing the CPAP pressure.

Laryngoscopy during wakefulness demonstrated bilateral or unilateral vocal cord paresis in four patients (Supplementary Video 5). In two patients, the upper airway was studied with dexmedetomidine-induced sleep (patients 3 and 5, Table 3). Obstruction at multiple levels in the oro-and hypopharynx was seen in both patients. Patient 3 had bilateral vocal cord paresis and posterior epiglottis collapse. Due to these abnormalities and the lack of control of stridor and apnea despite increasing CPAP pressure, this patient was placed on Bi-level PAP that successfully eliminated the stridor and apnea. In patient 5, intense snoring was recorded in the videosomnoscopy, but stridor and vocal cord palsy were absent even though these had been detected some months earlier by V-PSG and laryngoscopy, respectively. In this patient, the videosomnoscopy was performed after immunotherapy with rituximab that had resulted in significant clinical improvement in other neurological symptoms including cognitive impairment.

Vocalizations and movements during sleep

In all five patients, vocalizations and movements were frequent during sleep and occurred mostly in stages UN-NREM, P-S N2, and REM (Supplementary Tables S3 and S4). Only a minority of 30-s epochs of UN-NREM, P-S N2, and REM sleep did not contain vocalizations and movements (Supplementary Table S5). Most movements during UN-NREM and P-S N2 sleep were simple or quasi-purposeful. In contrast, during RBD a different pattern emerged, with predominant limb and body jerks. Vocalizations and movements were absent in normal N1 and N2 sleep, and occurred infrequently in epochs of stage N3, usually as isolated limb and body jerks.

Simple vocalizations were slightly more frequent than complex ones. Vocalizations usually occurred during UN-NREM sleep and less frequently in P-S N2 sleep (Supplementary Table S3, Supplementary Videos 1 and 2). They were infrequent in RBD and very rare in stage N3. Most frequent simple vocalizations were whispering and groaning. Talking was the most usual complex vocalization. Talking was usually unintelligible, although a few words could occasionally be understood. Shouting, swearing, crying, or laughing occurred but were infrequent. Episodes of vocalizations usually lasted less than 10 s.

The most frequent movements were simple followed by jerks, while quasi-purposeful movements were the least common (Supplementary Table S4, Supplementary Videos 1, 3, and 4). Jerks usually occurred during RBD and P-S N2 sleep, and less commonly during stages N3 and UN-NREM. Jerks usually appeared isolated or in 1–2 s episodes of repeated sudden movements that could involve one or several limbs, the face, neck, trunk, or whole body. Their intensity varied from mild twitches to violent jerks. Most simple and quasi-purposeful movements occurred during UN-NREM sleep, and less frequently in P-S N2 sleep. They were rare during REM sleep, and exceptional in stage N3. Simple movements consisted in head elevation or turning (sometimes the patient seemed to be looking around but with the eyes closed), limb raising, flexion or extension, or finger tapping, grasping, handling, scratching or twirling, sometimes involving the bed sheet, the electrode wires or the CPAP equipment without a clear purpose. Quasi-purposeful movements included gesticulations (e.g. pointing, greeting, grabbing) or mimicking daytime activities (e.g. eating, drinking, writing or handling and manipulating an imaginary object, seemingly a cable, a hammer or a screwdriver) (Supplementary Video 3). Some of these quasi-purposeful movements resembled tasks regularly performed by the patients (e.g. a patient who worked as an electrician seemed to be manipulating wires and making a knot). Quasi-purposeful movements usually lasted between 5 and 30 s. Violent and vigorous behaviors such as punching or kicking occurred rarely, usually during REM sleep.

Simple movements occurred while the patient was asleep with the eyes closed in stages UN-NREM or P-S N2. Simple and complex vocalizations and quasi-purposeful movements often overlapped with simple movements. The combination of vocalizations together with body and limb movements and gesticulations often gave the impression that the patient was acting out a dream as he or she was chatting, discussing, arguing or calling someone, or performing an activity of their daily life such as working or doing a home task. From this state, patients could be awakened easily with reappearance of their normal occipital alpha rhythm. Just upon awakening, patients were oriented and behaved normally, although they were totally unaware of their precedent sleep vocalizations and movements and did not report any related mental activity.

RPLM were present in three patients (patients 1–3; Supplementary Video 1 segment 5). RPLM appeared during relaxed wakefulness and persisted after sleep onset (Figure 1C and D). RPLM were very frequent during UN-NREM sleep, but

Table 3. Sleep breathing disorder

	Patient 1*	Patient 2*	Patient 3*	Patient 4†	Patient 5‡
Stridor during sleep	Continuous and intense	Continuous and intense	Continuous and intense	Continuous and intense	Intermittent and mild
Stridor during wakefulness	Absent	Absent	Absent	Absent	Absent
Laryngoscopy during wakefulness	Unilateral vocal cord partial abduction restriction	Normal	Bilateral vocal cord partial abduction restriction	Bilateral vocal cord partial abduction restriction	Unilateral vocal cord partial abduction restriction
Upper airway evaluation with flexible fiber endoscopy during dexmedetomidine-induced sleep	Not done	Not done	Stridor combined with snoring. Multilevel obstruction at soft palate, oropharynx, hypopharynx and posterior epiglottis. Bilateral vocal cord partial abduction restriction	Not done	Snoring (no stridor). Multilevel obstruction: soft palate, oropharynx and hypopharynx. Normal vocal cord motility§
Polysomnography					
AHI (n/h)	37.8	20	43.8	23	44.1
Obstructive apnea index (n/h)	11.1	0	1.4	0	0
Obstructive hypopnea index (n/h)	26.5	20	40.3	23	44.1
Central apnea index (n/h)	0.2	0	2.1	0	0
Oxyhemoglobin de-saturation nadir	88%	88%	85%	81%	82%
Oxyhemoglobin CT < 90%	5%	2%	15%	45%	8%
Treatment	CPAP 12 cm H_2O	CPAP 12 cm H_2O	CPAP 13 cm H_2O Bi-level PAP (IP: 12 cm H_2O, EP: 4 cm H_2O)‖	Tracheostomy	CPAP 11 cm H_2O

AHI = apnea–hypopnea index, number of apneas and hypopneas per hour of sleep; CT = cumulative time spent below an arterial oxyhemglobin saturation of 90%; CPAP = continuous positive airway pressure; PAP = positive airway pressure; IP = inspiratory pressure; EP = expiratory pressure.

*Patients 1–3 had only one V-PSG recorded without CPAP (Supplementary Table S2).

†Data from the second V-PSG in patient 4. The first study was recorded in the ICU with reduced sleep efficiency, obstructive hypopnea was frequent (AHI = 31 per hour), but stridor was not recorded. The third study was recorded with tracheotomy and stridor and obstructive apnea were absent (AHI = 1.4 per hour), however, when the tracheotomy was closed in the second half of the night, stridor was present without significant apnea (AHI = 4.1 per hour).

‡Data from the first V-PSG in patient 5. The second V-PSG was recorded while CPAP titration and the third V-PSG was done with CPAP.

§Upper airway evaluation with flexible fiber endoscopy during dexmedetomidine-induced sleep was performed following immunotherapy with subsequent improvement in cognitive status and resolution of vocal cord palsy and stridor.

‖The CPAP was switched to Bi-level PAP because stridor and apnea reappeared.

disappeared as sleep progressed to stage P-S N2. Conventional PLMS occurred in all five patients (in 25 out of 27 V-PSGs; median PLMS index: 59.8 movements per hour; range: 0–148.5).

Distribution of sleep abnormalities throughout the night

In 16 out of 27 V-PSGs, there was a characteristic distribution of sleep abnormalities over the course of the night. In these studies, periods of UN-NREM sleep and P-S N2 sleep predominated and were of longer duration at sleep onset and in the first half of the night. In contrast, periods of normal stages N2 and N3 tended to occur and were longer in the second half of the night (Figure 4). In seven studies, periods of UN-NREM sleep, P-S N2 sleep or normal NREM sleep were distributed similarly throughout the night. In three studies, UN-NREM sleep and P-S N2 sleep predominated in the second half of the night, while stage N3 occurred in the first half. The remaining study was that of patient

4, in which NREM sleep was normalized after high dose of intravenous steroids. In 16 out of the 21 studies in which REM sleep was recorded, this sleep stage predominated in the second half of the night. REM sleep took place in the first half of the night in three studies and was distributed similarly throughout the night in two studies.

Longitudinal follow-up of NREM and REM sleep abnormalities over the course of the disease

NREM and REM sleep abnormalities remained stable during the course of the disease, particularly in patients 1, 2, and 3 who had follow-up ranging from 3 to 7 years. The V-PSG studies were done while the patients were taking clonazepam and melatonin, or following different immunotherapies, and did not show any substantial modification in the sleep architecture and abnormal behavioral manifestations. This was in line with bed-partners' perception who reported no improvement in abnormal sleep

movements and behaviors with these treatments. An exception, as mentioned previously, occurred in patient 4, whose sleep study after high dose intravenous steroids showed normal NREM sleep initiation but with the persistence of sleep breathing abnormalities and RBD. In this patient, NREM sleep abnormalities (particularly stage P-S N2) reappeared in a study performed 3 months after immunotherapy. In all patients, sleep efficiency, percentages of each sleep stage or amount of vocalizations and movements during UN-NREM sleep or P-S N2 sleep were variable in different studies recorded during the course of the disease (Figure 5 and Supplementary Figure S3). In patient 3, who developed oculomotor abnormalities during follow-up, rapid eye movements in REM sleep and *atypical isolated rapid eye movements in NREM sleep* decreased progressively and were very infrequent in his last five V-PSG studies (Supplementary Figure S4).

Circadian rest–activity cycles (actigraphy)

Visual inspection of the 24-h profiles of rest–activity cycles in four patients (patients 1–3 and 5) yielded discernible diurnal changes in wrist activity during the recording days with increasingly frequent abnormal motor activity during the night. Thus, the activity at night reported by the bed partners could be clearly picked up by actigraphy. In patient 1, a total of 114 continuous days were recorded and showed a decrease of the abnormal nocturnal activity over the recording period immediately following treatment with high dose intravenous steroids (Figure 6). In the other patients with fewer recording days such a change was not discernible. The control volunteers showed normal circadian rest–activity cycles (i.e. high activity during the day and low activity during the night). In comparison to the healthy control group, the four patients had almost 10-fold higher activity counts at night, while these differences were not present during the day (Figure 7). This was confirmed by nonparametric circadian analysis showing a clear increase in activity during the last five active hours in patients compared with controls, which was absent during the 10 most active hours. This resulted in much lower relative amplitudes in patients than in controls. Other circadian indices, such as the inter-daily stability, the intra-daily variability, the onset time of the five last active periods and the onset time of the 10 most active periods did not differ between patients and controls. Spectral analysis of the time series of activity counts per volunteer revealed, as expected, robust peaks in the 24-h component and its harmonic at 12 h for the controls. Such a stable 24-h peak, was only observable in two patients, while for the other two patients the 24-h components and its
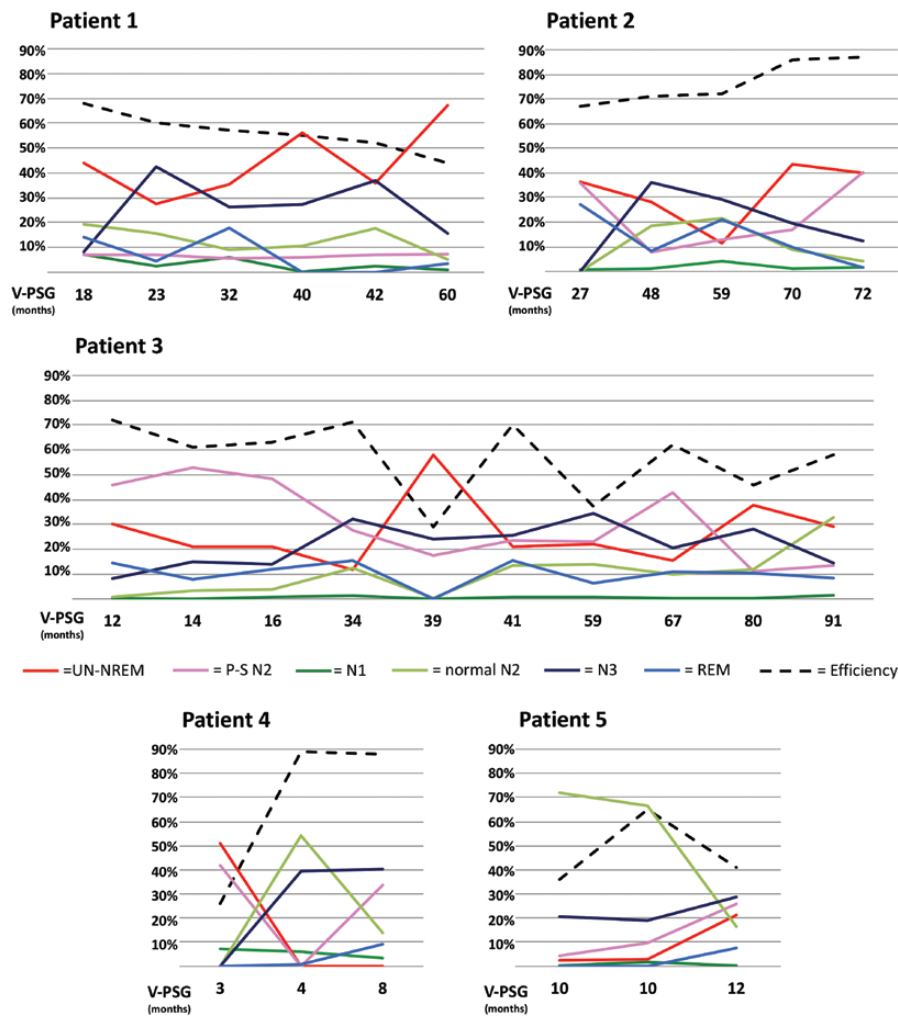

Figure 5. Percentages of each stage of sleep and sleep efficiency during the course of the disease. V-PSG (months) = video-polysomnography, months recorded after symptoms onset; UN-NREM = undifferentiated NREM sleep; P-S N2 = stage poorly structured N2.
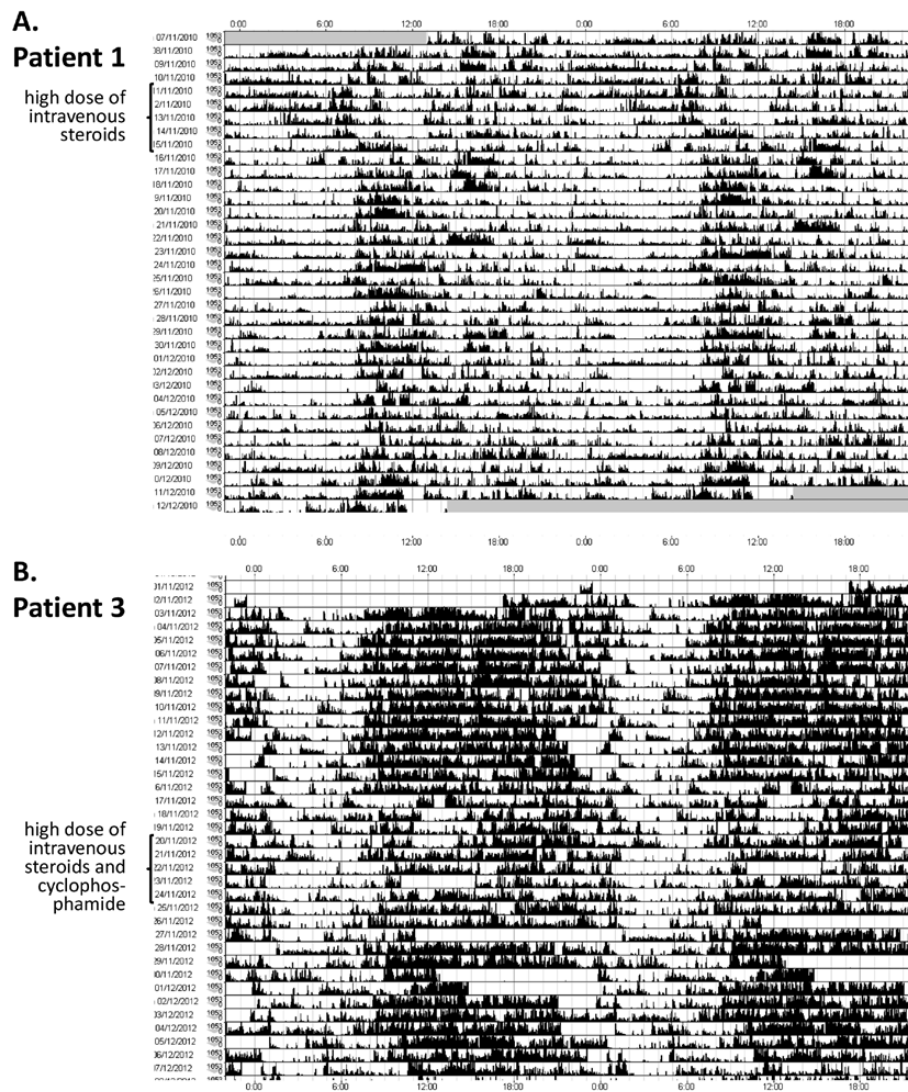
Figure 6. Actigraphic recording in two patients during treatment with high dose of intravenous steroids. (A) Patient 1 showed a transient decrease of the abnormal nocturnal motor activity during the week following treatment with high dose intravenous steroids. (B) Patient 3 showed incessant abnormal nocturnal motor activity, even after immunotherapy.

harmonic were absent and replaced by a prominent peak at 20.6 h in one patient, and by two prominent peaks at 8 and about 16 h (Figure 7).

Other sleep and laboratory studies

The abnormal pattern of sleep initiation as UN-NREM sleep and P-S N2 sleep also occurred in daytime sleep episodes in the MSLT or in sleep induced by dexmedetomidine. Mean sleep latency was normal (>10 min) in the six MSLTs recorded in four patients (Supplementary Table S6). Sleep was recorded in 13 out of the 30 naps of the MSLT. Sleep onset was abnormal and consisted in isolated UN-NREM sleep in 10 naps or as UN-NREM sleep followed by P-S N2 sleep in three naps (in all instances with vocalizations and simple and quasi-purposeful movements). REM sleep was recorded in two naps in the same patient but the overall sleep latency onset was normal, not reproducing the narcoleptic pattern. Sleep latency in videosomnoscopy with

dexmedetomidine was 1 min in one case and 14 min in another. In both cases, sleep was initiated as UN-NREM sleep followed by P-S N2 sleep with frequent vocalizations and movements in the operating room. These periods of UN-NREM sleep and P-S N2 sleep lasted 5 and 31 min, respectively. Normal NREM sleep with dexmedetomidine induced-sleep occurred in only one patient with latency from sleep onset of five min and lasted 25 min. Hypocretin-1 CSF levels were normal in three patients (Supplementary Table S1).

Discussion

In this study, we comprehensively describe the sleep disorder of five patients with anti-IgLON5 disease. Our results show that anti-IgLON5 disease is associated with a prominent sleep disorder characterized by abnormal NREM sleep initiation and motor activation associated with frequent vocalizations and movements. In all patients, as sleep continued, motor activity,
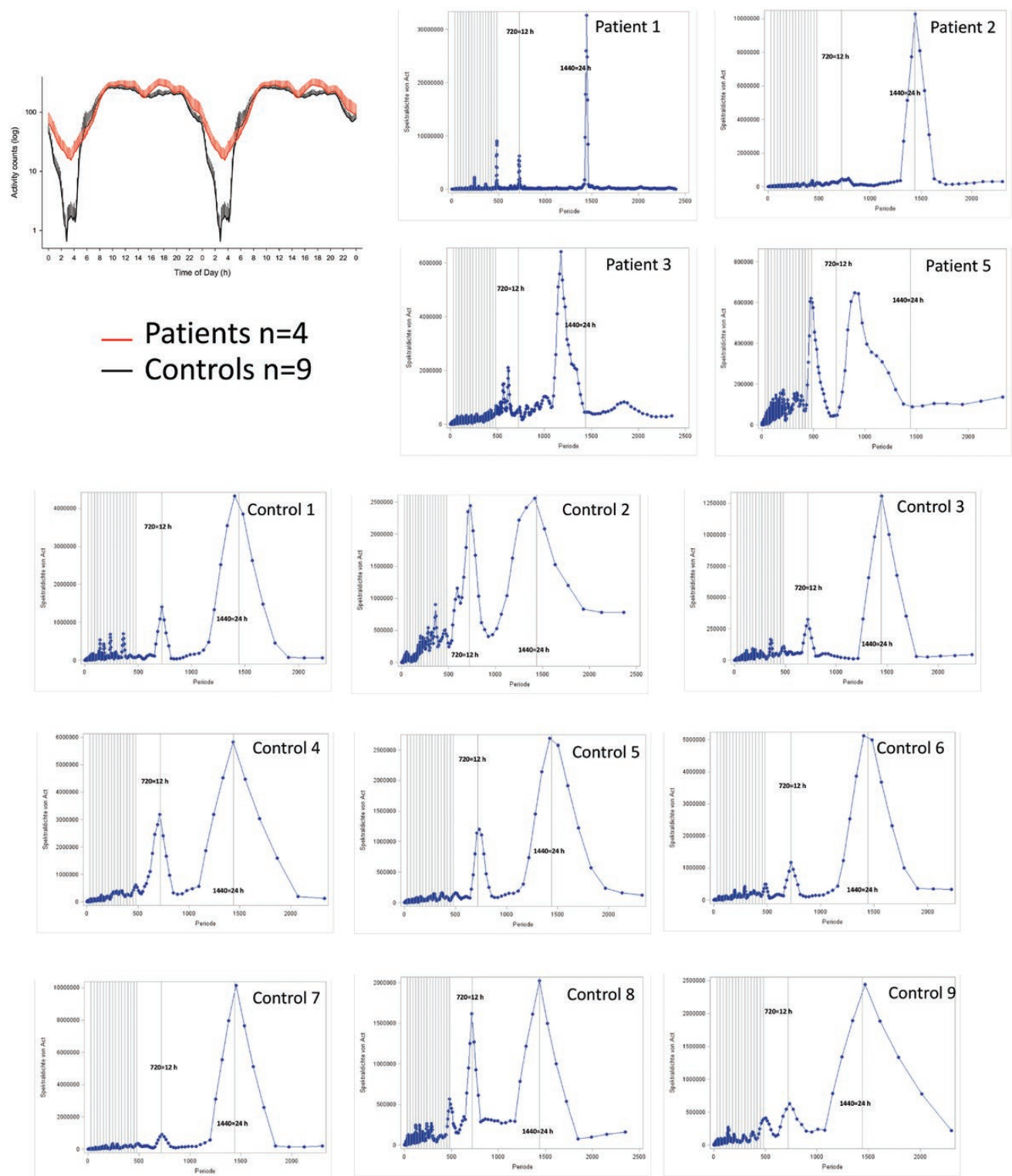
Figure 7. Actigraphic periodograms of patients and controls. Upper left panel: Wrist activity profiles over 24 h (activity counts per 10-min bins, double-plotted over 48 h on a log scale for better visualization) was averaged from data collected from patients (red; n = 4) and controls (black; n = 9); mean values + SEM. Patients showed higher activity counts during the night than controls resulting in a reduced diurnal modulation of the rest–activity cycle. This came mostly about a more irregular circadian rest–activity pattern in patients than in controls as quantified by periodogram analyses for each individual (remaining panels in the figure). All controls showed the main peak at 24 h (1440 minutes =24 h) reflecting good entrainment to the 24-h day, with a strong harmonic at 12 h, which was the second highest peak in the spectral density of the activity counts (y-axis) for all controls. In contrast, only two out of the four patients showed a prominent peak at 24 h with no (patient 2) or a small 12 h component. Patients 3 and 5 showed peaks clearly different from 24 and 12 h. Thus, based on the periodogram analyses we have evidence that the patients showed attenuated entrainment to the 24-h day.

vocalizations, and movements gradually disappeared and normal sleep spindles and K complexes became more frequent, leading to a normalization of NREM sleep while sleep breathing disorder with stridor increased or emerged. RBD occurred in four out of the five patients. Most vocalizations and quasi-purposeful movements occurred during UN-NREM sleep and P-S N2 sleep and were more prominent and common than in the setting of RBD. In patients with RBD, limb and body jerks were prominent whereas violent behaviors were infrequent.

Sleep-related vocalizations, movements, and respiratory difficulties during sleep were only noticed by the bed partners. Patients were unaware of them and did not report dreams or any other type of mentation. They complained of sleep fragmentation with unrefreshing and poor quality sleep and EDS. Sleep breathing abnormalities had a prominent role in the occurrence of EDS as this symptom was markedly improved after CPAP therapy. In this sense, three patients were initially misdiagnosed with isolated OSAS because a comprehensive sleep evaluation including V-PSG was not performed. CPAP therapy eliminated sleep-breathing difficulties but vocalizations and movements persisted. As often occurs in other neurological diseases, the sleep disorder in anti-IgLON5 disease can be easily overlooked, as occurred in the remaining two patients, likely as a result of (1) other neurological symptoms, such as gait instability, bulbar dysfunction or cognitive impairment being more prominent than the sleep symptoms, (2) patients and bed partners not spontaneously reporting sleep problems to the doctors, or (3) doctors not inquiring about sleep difficulties. It is important to specifically ask about sleep problems, in particular, vocalizations and motor behaviors, when anti-IgLON5 disease is being considered [4].

Sleep abnormalities with motor activation were present in all five anti-IgLON5 patients and occurred every night. This is supported by the V-PSG studies and the patients' actigraphy data that showed motor activity about 10 times higher than in healthy controls. The absence of 24-h peaks in the activity spectrum in two patients hints an involvement of a potential circadian sleep–wake rhythm disturbance. However, the remaining two patients showed clear diurnal patterns of lower activity at night and higher activity during the day. Thus, whether the sleep disorder of anti-IgLON5 disease affects the circadian regulation of sleep–wake rhythms is unclear and would need confirmation by the measurement of endogenous circadian melatonin rhythms.

Periods of UN-NREM sleep and P-S N2 sleep represented up to 40%–45% of the TST and tended to be more frequent and prolonged in the first half of the night. In contrast, stage N3 was preserved or even increased during the second part of the night, suggesting that sleep pressure accumulates during UN-NREM and P-S N2 sleep. In this sense, the finding that stridor and obstructive apnea were more frequent and intense during normal stages N2 and N3 than in UN-NREM and P-S N2 sleep, suggests that these abnormal stages of NREM sleep may represent a lighter sleep associated with increased muscle tone of the upper airway and preserved respiratory control.

During the course of the disease, the NREM and REM sleep abnormalities did not change with time and did not improve following immunotherapy. One exception was the patient who had normalization of NREM sleep abnormalities after high dose of intravenous steroids administered early in the course of the disease. Sleep breathing disorder and RBD, however, persisted,

and NREM sleep abnormalities reappeared despite additional immunotherapy. Other exceptions were seen in the patient in whom abnormal motor activity in the actigraphy was transiently reduced after high dose intravenous steroids, and the patient showing improvement in stridor and vocal cord palsy after immunotherapy with rituximab. The precise role of the immune system in the etiopathogenesis of anti-IgLON5 disease is still unclear, and whether adequate immunotherapy can modify the sleep disorder has to be addressed in future studies.

Because of the complexity of this sleep disorder, we designed a novel modified scoring system with different metrics. Conventional sleep stage scoring were applied whenever possible, such as when epochs of stage N1, N2, N3, or REM sleep were clearly identifiable in parts of the V-PSG, but for other parts of the recording, had to be combined with a more elementary descriptive approach based mainly in the EEG and the behavior displayed in the audiovisual recording. The validity and consistency of this modified scoring system for sleep staging was supported by our substantial intra- and inter-rater agreement. This descriptive approach led us to identify an additional nonconventional sleep stage that we termed as UN-NREM sleep. Instead of forcing the categorization of these periods of sleep into one of the conventional NREM sleep stages (N1, N2, and N3) we decided to use the term UN-NREM sleep to describe epochs with EEG and EOG features different from those of REM sleep and without the typical elements of well-differentiated NREM stages. In anti-IgLON5 disease, UN-NREM sleep was characterized by diffuse irregular theta activity, clearly different from the posterior alpha rhythm of wakefulness, without vertex waves, sleep spindles or K-complexes, and without the typical frequent rapid eye movements seen in REM sleep, although occasional low amplitude semi-rapid eye movements could be present. UN-NREM sleep was associated with intense and widespread EMG activation with frequent vocalizations, movements, and complex behaviors while the patient had the eyes closed. In addition, epochs with EMG activation, vocalizations, and movements showing occasional but clearly identifiable K-complexes or sleep spindles were scored as P-S N2 sleep to emphasize the difference from other epochs of conventional normal stage N2 with frequent K-complexes and spindles without abnormal vocal and motor manifestations.

UN-NREM sleep was different from stage N1 because: (1) UN-NREM sleep usually occurred in prolonged periods, often lasting more than 10 min (and up to 4 h in some studies), which is unusual for a normal transition from wakefulness to stage N2; (2) during normal stage N1, there is partial consciousness with some perception of the environment and a partial response to external stimuli [14], whereas anti-IgLON5 disease patients were unaware of what they were doing during UN-NREM sleep; (3) vertex sharp waves, the most typical EEG marker of stage N1, were not recorded; and (4) patients had abnormal motor activation with frequent vocalizations, simple movements, and purposeful-looking behaviors.

UN-NREM sleep is mainly defined as those periods of sleep different from REM sleep but lacking the typical elements that allow the identification of the conventional stages of NREM sleep. UN-NREM sleep is not exclusive to anti-IgLON5 disease and can also occur in other neurological diseases such as dementia with Lewy bodies [15]. Some specific features of UN-NREM sleep, however, can vary depending on the disease. For example, in anti-IgLON5 disease UN-NREM sleep is characterized by theta

activity in the EEG and is usually associated with excessive EMG activation linked to vocalizations and abnormal behaviors. In contrast, UN-NREM sleep in dementia with Lewy bodies is characterized by delta–theta frequencies in the EEG while EMG activation with vocalizations or movements is infrequent [15]. Future studies should delineate the frequency and features of UN-NREM sleep in other neurological disorders.

We considered that describing epochs of UN-NREM sleep as "dissociated REM sleep" "ambiguous sleep" or "REM intrusions in NREM," or to label the whole sleep–wake pattern as "status dissociatus" was unhelpful, because these terms oversimplified the variety and wide range of clinical and V-PSG findings and prevented detailed analyses that could lead to alternative explanations. For example, the rapid eye movements in UN-NREM sleep could be the ocular counterpart of the same purposeful-looking limb movements that the patient was displaying simultaneously. For example, if the patient is acting as if trying to pick up an item with their hand, maybe their gaze would be directed toward the item, rather than the gaze being an expression of the neurophysiological brainstem changes occurring in REM sleep. This is supported by a study that described exploratory gaze shifts in conjunction with other complex behaviors by stimulation of the motor cortex of monkeys [16].

The features of the anti-IgLON5 sleep disorder are clearly different from other parasomnias, such as RBD, disorders of arousal from NREM sleep (e.g. somnambulism, sleep terrors, and confusional arousals), overlap parasomnia (the association of RBD with a disorder of arousal from NREM sleep), agrypnia excitata, or status dissociatus. Agrypnia excitata occurs in patients with fatal familial insomnia, Morvan syndrome, and delirium tremens. It is characterized by a prominent sleep disorder with abnormal motor activation with dream enactment behaviors and extremely reduced sleep efficiency with disorganized sleep structure in the absence or severe reduction of K complexes, spindles and slow wave activity of stage N3 [17]. Oneiric stupor is the typical motor behavior of agrypnia excitata characterized by complex gestures and movements reminiscent of routine daytime activities and conveying the content of dream-like mentation that patients are able to recall. Oneiric stupor episodes may occur with opened or closed eyes and may last up to 1–2 min. They can occur in any part of the night and the day, and at times, if the patient is left alone, these behaviors may invade wakefulness or arise from an unusual sleep state that has been defined as the concomitant occurrence of stage N1 intermixed with REM sleep with and without muscle atonia (stage N1–REM) [17, 18]. Although quasi-purposeful behaviors in anti-IgLON5 disease have similarities to oneiric stupor [19], the accompanying polysomnographic pattern differed since quasi-purposeful behaviors could occur, apart from UN-NREM sleep, during periods containing clear elements of stage N2 such as K complexes and sleep spindles. In addition, the behaviors seen in anti-IgLON5 disease occurred in periods of sleep, always with the eyes closed, and never invaded daytime wakefulness. In contrast to agrypnia excitata, dream mentation in relation to quasi-purposeful movements is not reported in anti-IgLON5 disease, sleep efficiency was only slightly reduced and there were established periods of normal NREM sleep including delta slowing of stage N3.

Sleep-related vocalizations and movements in anti-IgLON5 disease patients may resemble status dissociatus. Status dissociatus is an extreme form of sleep–wake state dissociation [20, 21] in which patients have sleep-related motor agitation with frequent limb movements and vocalizations. These manifestations are associated with disorganized sleep with abnormally mixed polysomnographic elements, mainly, EEG with fast and slow activity and mixtures of slow and rapid eye movements without spindles, K complexes, delta slowing, or identifiable stages of NREM or REM sleep. Status dissociatus has been described in the setting of a variety of disorders such as narcolepsy, severe dementia, multiple system atrophy, brainstem lesions, or treatment with psychoactive medications [20–22]. Thus, the presence of identifiable stages N2, N3, and REM distinguishes the anti-IgLON5 sleep disorder from status dissociatus.

The anti-IgLON5 sleep disorder appears to be unique. We have found only one other patient with a similar sleep disorder who was reported before our initial identification of the disease [23]. This patient was a 55-year-old woman who presented with progressive dementia associated with a sleep disorder characterized by continuous sleep-related motor agitation with vocalizations and complex purposeful-looking movements during NREM sleep stages N1 and N2 with spindles and K complexes and moderate hypopnea. Stage N3 and REM sleep were not recorded and stridor was absent. These sleep findings are compatible with IgLON5 sleep disorder. Since the initial description of anti-IgLON5 disease, more than 70 patients have been reported [24]. In most, sleep-related movements and behaviors were present by clinical history and NREM and REM sleep parasomnia with disordered sleep breathing were usually found in sleep studies with audiovisual recording [2–4, 6, 25–27].

The neuropathology of anti-IgLON5 disease is characterized by neuronal loss with accumulation of hyperphosphorylated tau predominantly in the hypothalamus and tegmentum of the brainstem including the areas and nuclei that regulate NREM and REM sleep and control vocal cord motility and respiration during sleep [1, 5]. The characteristic difficulty in entering sleep in anti-IgLON5 disease could be explained by involvement of two brain regions, the hypothalamus and medulla. Neuropathological abnormalities with tau deposition in the hypothalamus are severe in the posterior area, particularly in the dorsomedialis and ventromedialis nuclei, but milder in the anterior region including the nucleus supraopticus [5], which has a prominent role in sleep initiation. Hypocretin-1 levels in CSF are normal in anti-IgLON5 disease, indicating that hypocretin deficiency does not have a major role in the pathogenesis of the condition. Recently, a GABAergic NREM sleep inducing center in the brainstem, at the level of the medulla, has been described in rats [28–30]. This GABAergic center, the parafacial zone, appears to have an important role in sleep initiation, in contrast to the hypothalamic ventrolateral preoptic nucleus that would stabilize sleep [29]. Lesions of the parafacial zone in rats increase the wake time, mainly at the expense of NREM sleep [28]. Since pathological abnormalities in the brainstem of patients with anti-IgLON5 disease are maximal at the level of the medulla [1, 5], we speculate that an analogous area of the parafacial zone could be damaged in the patients, preventing the normal onset of sleep, and that only after the accumulation of enough homeostatic sleep pressure could normal NREM sleep finally appear. Finally neuronal loss and tau aggregates involving the nucleus magnocellularis in the medulla may account for RBD given that the subcoeruleous nucleus was not damaged [31]. Nocturnal stridor and obstructive sleep apnea can be explained by medullary pathology involving the nucleus ambiguus, which could

impair the motor control of the vocal cords and affect the sensitivity to hypoxemia or hypercapnia [32].

It has been suggested that "oneiric stupor" and sleep abnormalities in agrypnia excitata are secondary to the thalamic dysfunction encountered in fatal familial insomnia, Morvan syndrome, or delirium tremens [17, 18]. The thalamus, however, is spared in anti-IgLON5 disease [1, 5], and this accounts for the preservation of sleep spindles and the presence of periods of normal stages N2 and N3. An alternative explanation for the excessive motor activation resembling daytime activities in anti-IgLON5 disease could be abnormal sleep-related hippocampal reactivation of the motor patterns displayed during wakefulness [33, 34]. During sleep, fast rewinding of diurnal experiences takes place in the hippocampus to transfer memories from hippocampal to neocortical control. It is believed that during sleep the neural firing patterns representing memories and events are replayed 5–20 times faster than their behavioral rate. In anti-IgLON5 disease this mechanism could be disinhibited or potentiated as a consequence of damage of the hippocampus and its afferents from the brainstem [1, 5], contributing to the emergence of the quasi-purposeful movements resembling daytime activities. Interestingly, administration of low-dose of dexmedetomidine in our patients also induced UN-NREM sleep and P-S N2 sleep with vocalizations and quasi-purposeful movements. Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist that produces dose-dependent sedation. It has been hypothesized that dexmedetomidine administered in low-dose induces sedation that may be homologous to NREM sleep since it can be easily reversed with verbal stimuli and generates EEG slowing with frequent spindle-like activity resembling stage N2 [35]. It has also been suggested that dexmedetomidine exerts its effects via normal sleep-promoting pathways [36]. In anti-IgLON5 disease, dexmedetomidine could induce NREM sleep by activating the damaged neural structures, reproducing the abnormal pattern of entering into sleep.

A major limitation of our study is that only five patients were evaluated. It is possible that some distinctive features of the sleep disorder in anti-IgLON5 disease (e.g. NREM sleep parasomnia, RBD, or the sleep breathing disorder) could be different in severity or even be absent in some patients. It appears that anti-IgLON5 disease is clinically more heterogeneous that initially thought and different clinical phenotypes have been reported [4, 37]. Some patients reported with the disorder (confirmed by the presence of anti-IgLON5 antibodies), had no significant sleep problems or lacked some features of the distinctive sleep disorder, such as NREM parasomnia, RBD, and stridor [4, 6, 38]. In fact, one of our patients had no RBD.

Further studies including a larger number of patients with anti-IgLON5 disease are necessary to better delineate this complex sleep disorder. As the severe sleep architecture abnormalities of the disorder makes it difficult to apply conventional sleep stage scoring, for optimal assessment we developed a modified scoring system. This system combines conventional staging with a descriptive approach using information from the EEG, EOG, submental EMG, the behaviors displayed in synchronized audiovisual recording and the respiratory pattern. This modified descriptive approach could be useful to evaluate the severe sleep abnormalities occurring in other neurological diseases (e.g. degenerative or autoimmune) in which conventional scoring systems are not optimal.

Disclosure

Dr Dalmau receives royalties from Athena Diagnostics for the use of Ma2 as autoantibody tests and from Euroimmun for the use of NMDA receptor, GABAB receptor, DPPX, GABAA receptor, and IgLON5 as autoantibody tests. Dr Graus receives royalties from Euroimmun for the use of IgLON5 as an autoantibody test. The rest of the authors report no disclosures.
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