Daytime Sleepiness and REM Sleep Characteristics in Myotonic Dystrophy: A Case-Control Study

Huan Yu, MD, PhD[1,2]; Luc Laberge, PhD[3]; Isabelle Jaussent, MSc[4]; Sophie Bayard, PhD[1,4,5]; Sabine Scholtz[1,5]; Raoul Morales, MD[1]; Michel Pages, MD[1]; Yves Dauvilliers, MD, PhD[1,4,5]

[1]Service de Neurologie, Hôpital Gui-de-Chauliac Montpellier, France; [2]Department of Neurology, Shanghai Huashan Hospital, Shanghai Fudan University, Shanghai, China; [3]Département des sciences de l'éducation et de psychologie, Université du Québec à Chicoutimi, Canada; [4]INSERM U888, Montpellier, France; Univ Montpellier 1, Montpellier, F-34000, France; [5]Centre de Référence National sur les Maladies Rares (Narcolepsie, Hypersomnie Idiopathique, Syndrome de Kleine-Levin), France

Study Objectives: Excessive daytime sleepiness (EDS) and high daytime REM sleep pressure are important sleep features of myotonic dystrophy (DM1). Small and uncontrolled studies have focused on EDS phenotype; none have focused on nocturnal REM sleep characteristics in DM1. Our objectives were to compare polysomnographic and multiple sleep latency test (MSLT) parameters, and both tonic and phasic components of REM sleep between DM1 and controls.

Design and Patients: Forty consecutive DM1 patients and 40 sex- and age-matched controls were included. All subjects underwent overnight polysomnography followed by a MSLT.

Results: About 80% of DM1 patients complained of EDS through clinical interview: 31.4% had Epworth scores > 10, and 12.5% had objective sleepiness (latency < 8 min). Higher apnea and central apnea indexes, and a greater proportion of subjects with severe apnea/hypopnea syndrome were found in DM1. The number of SOREMP differed between DM1 and controls, one and two SOREMPs being present in 47.5% and 32.5%, and one control had one SOREMP. Higher percentages of slow wave sleep and REM sleep were found in DM1. DM1 patients had significantly more PLMW, PLMS in both NREM and REM sleep, and PLMS-associated microarousals. Higher REM density was found in DM1 with similar tendencies for either REM sleep without atonia or phasic EMG activity.

Conclusions: This is the first case-control sleep study in DM1 to demonstrate higher frequency of daytime sleepiness and abnormalities in REM sleep regulation, with an increased daytime and nighttime REM sleep propensity, REM density, and PLMS. These data suggest a primary central sleep regulation dysfunction in DM1.

Keywords: Myotonic dystrophy, excessive daytime sleepiness, REM sleep, PLM, MSLT

Citation: Yu H; Laberge L; Jaussent I; Bayard S; Scholtz S; Morales R; Pages M; Dauvilliers Y. Daytime sleepiness and REM sleep characteristics in myotonic dystrophy: a case-control study. *SLEEP* 2011;34(2):165-170.

MYOTONIC DYSTROPHY (DM1) IS AN AUTOSOMAL DOMINANT DISORDER CHARACTERIZED MAINLY BY MYOTONIA, MUSCULAR DYSTROPHY, CATARACT, hypogonadism, and cardiac arrhythmias.[1,2] The genetic defect in DM1 results from an amplified trinucleotide CTG repeat in the 3-prime untranslated region of a protein kinase gene (*DMPK*) on chromosome 19.[3,4] The unstable nature of *DMPK* was thought to explain the characteristic variation in severity of the disease.[4]

DM1 has long been recognized for its sleep disturbances, with excessive daytime sleepiness (EDS) being one of the most frequent non-muscular symptom.[5-14] However, most of previous data reported the absence of good consistencies between the different methods used to assess EDS in DM1 population.[15] Although considered the gold standard in the general population, the Epworth Sleepiness Scale (ESS) appears to be a questionable measure of the complaint of EDS in DM1 population,[15,16] and self-report instruments have not

correlated with objective measurements.[9,11,14] Only small and/or uncontrolled studies have addressed the question of frequency and phenotype of EDS using objective methods of assessment.[9,11,14,17] Despite methodological limitations, previous reports have highlighted the frequent occurrence (up to 60% of cases) of sleep-onset rapid eye movement periods (SOREMPs) during daytime sleep episodes.[9,11,14,17] Although the pathogenesis of EDS in DM1 is unclear, hypersomnia associated with REM sleep dysregulation in DM1 is considered a consequence of primary CNS dysfunction.[11-17] To our knowledge, little is known on the characteristics of nocturnal REM sleep in DM1. As normal REM sleep is characterized by tonic and phasic features, and REM sleep seems dysregulated in DM1, investigation of REM sleep patterns including REM density and excessive tonic and phasic muscle activities is warranted. We were interested in evaluating the presence of EDS in 3 different ways: (1) clinically assessed EDS as the presence of frequent feeling of being excessively sleepy during the day, (2) evaluation using questionnaire (ESS), and (3) objective measurement using the multiple sleep latency test (MSLT).

The aims of the present study were: (1) to measure EDS through face-to-face clinical interview, questionnaire, and objective evaluation; (2) to compare polysomnographic (PSG) and MSLT parameters; and (3) to study the tonic and phasic components of REM sleep, of a prospective cohort of DM1 patients and sex- and age-matched normal controls.

PATIENTS AND METHODS

Subjects

Forty consecutive unrelated adult patients (16 men and 24 women; mean age 44.0 ± 9.6 years) with DM1 followed at the Department of Neurology (Montpellier, France) were included. Their diagnoses were based on clinical symptoms, family history, and molecular confirmation. Mean (SD) expansion of CTG was 633.7 ± 447.0 (range 90-1567). Patients were prospectively recruited without selection bias as regards sleepiness complaints, and no patient had ever been diagnosed with a sleep disorder. Forty healthy community-dwelling control subjects (15 men and 25 women; mean age 46.7 ± 21.8 years) matched for age, sex, and body mass index (BMI) were recruited from local associative networks (Montpellier, France). None of the subjects had any psychiatric disorder, based on DSM-IV criteria, and none was taking any medication known to influence sleep or muscle activity at the time of the sleep laboratory investigation. All subjects participated in a face-to-face standardized clinical interview to determine the age at onset, the complaint of EDS, fatigue, and snoring. We defined EDS a priori as the presence of frequent feeling of being excessively sleepy during the day, and fatigue as the presence of frequent feeling of being tired during the day. In addition to clinically assessed EDS, EDS was also evaluated using the ESS, with scores > 10 considered pathological.[16] The presence of hypnagogic hallucinations, sleep paralysis, cataplexy, clinically assessed REM sleep behavior disorder (RBD) (defined as the presence of elaborate motor activity associated with dream mentation), and restless legs syndrome (RLS)[18] was diagnosed by experienced physicians on the basis of standard criteria.

All subjects gave informed consent to take part in the study, which was approved by the local research ethics committee.

Polysomnographic Recordings

All subjects underwent one night of audio-video-polysomnography (PSG) recording in the sleep laboratory. Lights out time was based on the subject's routine sleeping hours, mainly 23:00 to 06:00. Sleep recording included 3 EEG leads (C3, C4, and O2), 2 electroculograms (EOG), one chin electromyogram (EMG), and electrocardiogram (EKG). Airflow was measured using a nasal cannula and mouth thermocouple. Thoracoabdominal movement was measured by inductance plethysmogram, and arterial oxygen saturation (SpO_2) by finger pulse oximetry. Sleep was stage manually according to standard criteria,[19] with the exception that REM sleep was scored on the basis of EEG and EOG only. The occurrence of the first REM epoch was used to determine the onset of a REM sleep period. The termination of REM sleep periods was identified by the occurrence of an EEG feature indicative of another stage (K complex, sleep spindle, or EEG sign of arousal) or by the absence of rapid eye movements during 6 consecutive 30-sec epochs. The same method was used to score REM sleep in DM1 and controls.

Tonic and phasic components of REM sleep were scored using a method previously described.[20] Each 30-sec epoch was either scored as tonic or atonic, depending on whether tonic chin EMG activity was present for ≥ 50% or < 50% in a given epoch. After baseline EMG signal for atonia was determined for each subject, any EMG signal that was twice the amplitude measured during atonia and > 10 μV was considered tonic (REM sleep without atonia). Two types of REM sleep phasic activities were scored: (1) REM density defined as the percentage of 2-sec mini-epochs of REM sleep containing at least one rapid eye movement, and (2) phasic EMG density scored from the submental EMG recording and characterized by the percentage of 2-sec mini-epochs containing phasic EMG events lasting from 0.3 to 5 sec with amplitude exceeding 4 times the baseline EMG signal.[20]

Respiratory events were scored according to AASM guidelines.[19] Obstructive sleep apneas were defined as complete cessation of airflow > 10 sec associated with thoracoabdominal movements. Central sleep apneas were defined by the absence of airflow and thoracoabdominal movements > 10 sec. Hypopneas were defined as a reduction ≥ 50% in airflow plus ≥ 3% drop in SpO_2 and/or a micro-arousal. Apnea-hypopnea index (AHI) was calculated as the number of events per hour of sleep: an index 5-14.9 was considered mild, 15-30 was moderate, and an index > 30 was severe.

Surface EMG electrodes placed 3 cm apart on the right and left anterior tibialis muscles were used to record periodic limb movement during sleep (PLMS). PLMS were scored following standard criteria.[21] Movements lasting 0.5-10 sec, separated by intervals of 5-90 sec, and occurring in a series of ≥ 4 consecutive movements were counted. The amplitude criterion for detecting leg movements was an increase in EMG to ≥ 8 μV above the resting baseline for the onset of the movement and a decrease in EMG to < 2 μV above the resting level for the offset of movement. Microarousals (MAs) were scored according to standard criteria.[19] Indices of PLM were calculated as PLMW (PLM during wake), PLMS, PLMS in REM and in NREM sleep, and PLM-MAs (PLM associated with microarousals).

Multiple Sleep Latency Tests

All subjects had an MSLT the day after PSG. It consisted of 5 naps scheduled at 2-h intervals between 09:00 to 17:00.[22] For each recording, the patient was allowed 20 min to fall asleep. If they did fall asleep, they were allowed to sleep for an additional 15 min and were then awakened. Sleep latency was determined by the time from lights out to either 3 consecutive epochs of stage 1 sleep or the first epoch of any other stage of sleep. The absence of sleep on a nap opportunity was calculated as a sleep latency of 20 min. Mean sleep latency (MSL) from the 5 naps was computed for each subject, with MSL ≤ 8 min being considered pathological. SOREMPs were defined by the onset of REM sleep within 15 min of sleep onset.

Statistical Analysis

Characteristics of DM1 patients and controls were described using median values and ranges for quantitative variables, and proportions for categorical variables. For continuous variables, the distributions were tested with the Shapiro-Wilk test and were mostly skewed. We therefore used nonparametric tests. Chi square or Fisher tests and Mann-Whitney tests were respectively utilized for between-group comparisons of categorical and continuous variables. Spearman rank order correlations were used to measure the associations between 2 continues variables. For all comparisons, significance was set at P < 0.05.

Table 1—Demographic and clinical data of myotonic dystrophy (DM1) patients and control subjects

	DM1 patients (n = 40)	Controls (n = 40)	P
Demographic data			
Sex, M/F	16/24	15/25	0.82
Age, y	43 (30-65)	60.5 (20-71)	0.49
Clinical data			
BMI, kg/m^2	24.2 (17.6-38.1)	22.6 (17.2-30.8)	0.19
Daytime sleepiness complaint, %*	79.5	17.1	< 0.0001
ESS, score	9 (0-23)	6 (0-13)	0.002
ESS ≥ 11, %	31.4	17.1	0.16
Fatigue, %*	62.2	17.1	< 0.0001
Snoring, %	40.5	27.7	0.18
RLS, %	22.5	0	0.002

BMI, body mass index; ESS, Epworth Sleepiness Scales; RLS, restless leg syndrome. Data are expressed as median (min-max). *Assessed through structured clinical interview.

Table 2—Polysomnographic MSLT parameters of patients with myotonic dystrophy (DM1) and control subjects

	DM1 patients (n = 40)	Controls (n = 40)	P
Polysomnographic data			
Total sleep time, min	370 (147.5-504)	371.5 (256.5-474)	0.88
Sleep efficiency, %	82.0 (32.3-95.8)	79.3 (51-94.5)	0.44
Sleep latency, min	19.3 (2-128)	16.8 (6-86)	0.71
REM sleep latency, min	79.5 (0-398)	97.5 (4.9-277.5)	0.091
Stage 1, %	9.7 (2.4-26.5)	7.3 (1.9-55.4)	0.051
Stage 2, %	45.0 (18.4-83.7)	57.9 (23.5-81.9)	< 0.0001
SWS, %	22.9 (0-51.4)	14.3 (1.2-46.5)	0.0031
REM sleep, %	22.1 (0-42.8)	16.6 (0.7-27.6)	0.027
Microarousal index, n/h	15.2 (3.3-43.9)	7.0 (0-18.1)	< 0.0001
Multiple sleep latency test			
Mean sleep latency, min	14.2 (2.8-20)	14.2 (8.2-20)	0.54
SOREMP: 0 or 1, %	67.5	100	< 0.0001
SOREMPs: 2 or more, %	32.5	0	< 0.0001

SOREMP(s), sleep onset REM period(s); SWS, slow wave sleep. Data are expressed as median (min-max).

Statistical analysis were performed using SAS software, version 9.1 (SAS Institute, NC, USA).

RESULTS

Demographic and Clinical Characteristics

Table 1 presents demographic and clinical characteristics of DM1 patients and controls. Between-group comparison revealed a higher prevalence of complaints of both EDS and fatigue, as assessed by a structured clinical interview in DM1 patients. EDS evaluated by questionnaire was also higher in DM1 patients; however, pathological scores of ESS did not differ between patients and controls (Table 1). Of the DM1 patients, 22.5% were diagnosed with RLS, and none in the control group. Finally, neither patients nor controls reported hypnagogic hallucinations, sleep paralysis, cataplexy, or clinically assessed RBD, or had abnormal behaviors during REM sleep in the sleep laboratory.

Nocturnal Sleep Structure and Sleep Disordered Breathing

PSG data of patients with DM1 and controls are shown in Table 2. We noted higher percentages of slow wave sleep and REM sleep in DM1 together with a decrease in percentage of stage 2 NREM sleep. In contrast, the microarousal index was increased in DM1. No between-group difference was noted regarding sleep and REM sleep latency. We found a negative correlation between REM sleep latency at night and the percentage of REM sleep in DM1 patients (r = −0.51, P < 0.001).

Table 3 indicates that DM1 patients exhibited a higher apnea index, central apnea index, and AHI during NREM sleep compared to controls. The proportion of subjects with mild, moderate, and severe AHI differed between DM1 patients and controls, with a greater proportion of DM1 patients having severe AHI (27.5% vs. 7.5%). Among the 11 DM1 patients with

Table 3—Sleep disordered breathing findings in patients with myotonic dystrophy (DM1) and control subjects

	DM1 patients (n = 40)	Controls (n = 40)	P
Apnea index, n/h	2.28 (0-68)	0.35 (0-26.8)	0.001
Hypopnea index, n/h	5.6 (0-49.6)	5.4 (0-24.9)	0.65
Central apnea index, n/h	1.4 (0-43)	0 (0-5.1)	< 0.0001
Obstructive apnea index, n/h	0.45 (0-28.0)	0 (0-25.8)	0.16
Mixed apnea index, n/h	0 (0-38)	0 (0-95)	0.025
Apnea/hypopnea index, n/h	10.4 (0.5-92)	5.3 (0-36.5)	0.062
AHI during REM sleep, n/h	3.7 (0-60.5)	4.0 (0-59.3)	0.52
AHI during NREM sleep, n/h	12.4 (0.2-102.5)	5.2 (0-43.2)	0.013
AHI, n/h			
< 5, %	27.5	42.5	0.0114*
[5-15], %	30.0	15.0	
[15-30], %	15.0	35.0	
≥ 30, %	27.5	7.5	
Mean SpO$_2$, %	92.8 (82-97)	95.9 (86-98.3)	< 0.0001
Minimal SpO$_2$%	80 (55-91)	88 (76-93)	< 0.0001
Sleep time with SpO$_2$ < 90%, %	7.05 (0-99.4)	0 (0-34.6)	< 0.0001

AHI, apnea hypopnea index; SpO$_2$, O2 saturation. Data are expressed as median (min-max). *Chi-square test (used to compare the repartitions of AHI between cases and controls).

severe AHI, 9 presented central apneas (mean central apnea index 22.9/h). Mean and minimal SpO$_2$, and percentage of sleep time spent with SpO$_2$ > 90% were lower in DM1 patients.

Periodic Leg Movements

Table 4 shows that patients with DM1 had more PLMS and PLMW than controls. A higher proportion of DM1 patients

had a PLMS index > 5 (54.3% *vs.* 15.4%) and > 10 (40.0% *vs.* 10.3%). Indexes of PLMS were higher in both NREM and REM sleep in DM1 patients. PLMS associated with MAs were more frequent in DM1 with a greater proportion of patients having PLMS-MAs index > 5.

REM Sleep Characteristics

Figure 1 illustrates the distribution of REM density, REM sleep without muscle atonia, and REM phasic EMG activity in DM1 patients and in controls. Table 4 shows that DM1 patients had a 2-fold greater REM density than controls. One may note a similar tendency for REM sleep without muscle atonia and REM sleep phasic EMG activity in DM1 patients. A positive correlation was observed in DM1 patients between percentage of REM sleep without muscle atonia and REM phasic EMG activity ($r = 0.81$, $P < 0.0001$). However, based on the 20% pathological threshold for the percentage of REM sleep muscle atonia,[23,24] only 2 subjects were considered abnormal in DM1 and none in controls. In contrast, neither

patients nor controls achieved the REM phasic EMG pathological threshold of 15.[24]

Objective Daytime Sleepiness and Sleep Onset REM Periods

MSL on the MSLT did not differ between DM1 and controls (Table 2). However, pathological MSL was exclusively present in DM1 patients (12.5%; $P = 0.001$). Of 5 patients with abnormal MSL, only one had an ESS > 10. We found no difference between DM1 patients with and without objective EDS in demographic or clinical characteristics (age, gender, BMI, RLS) or PSG findings (nocturnal sleep parameters, REM sleep characteristics, SDB, SpO_2, and PLMS).

The number of SOREMPs on the MSLT was higher in DM1 patients ($P < 0.0001$). More precisely, at least one SOREMP was present in 19 patients with DM1 (47.5%), including 13 (32.5%) with at least 2 SOREMPs (4, 7, and 2 patients with respectively 2, 3, and 4 SOREMPs), in contrast to one control with 1 SOREMP and none with several ($P < 0.0001$; Table 2). The number of SOREMPs varied either with demographic characteristics or with PSG findings in DM1 patients. Hence, longer latencies were observed on the MSLT in presence of 0-1 SOREMP than in the presence of 2 or more SOREMPs (15.8 min [2.8-20.0] vs 10.2 min [6.0-17.4], $P < 0.01$). REM sleep latency at night also differed between groups, with longer latencies in the 0-1 SOREMP condition (88 min [19-398] vs 62 min [0-114], $P = 0.0085$), with similar tendency for sleep latency at night (22 min [2-128] vs 11.5 min [4-46.5], $P = 0.0996$). Finally patients were older in presence of 0-1 SOREMP (45 years [31-65] vs 36 years [30-60], $P = 0.026$), and more hypoxemic (minimal SpO_2: 78.5% [55-89] vs 83% [67-91], $P = 0.044$).

DISCUSSION

The present study shows that patients with DM1 have a higher frequency of complaints of daytime sleepiness and fatigue, apnea index, SOREMPs, REM sleep, REM density, PLMW, and PLMS compared to sex- and age-matched normal controls.

EDS was present in 80% of DM1 patients, as assessed by structured clinical interview, and in 31.4% and 12.5% evaluated, respectively, by questionnaire (ESS > 10) and MSLT; all these frequencies were greater than in controls. However, the

Table 4—Periodic leg movements and REM sleep characteristics of DM1 patients and control subjects

	DM1 patients (*n* = 40)	Controls (*n* = 40)	P
Periodic leg movements			
PLMs, n/h	6.2 (0-93.7)	0 (0-27.7)	< 0.0001
PLMw, n/h	28.5 (0-112.2)	12.6 (0-49.7)	0.0057
PLM-MAs, n/h	1.3 (0-36.0)	0 (0-1)	< 0.0001
PLM-REM, n/h	0.6 (0-44.0)	0 (0-13)	< 0.0001
PLM-NREM, n/h	7.2 (0-110.2)	0 (0-4)	< 0.0001
PLMS ≥ 5, %	54.3	15.4	0.0004
PLMS ≥ 10, %	40.0	10.3	0.0029
PLM-MAs ≥ 5, %	25.7	0	< 0.0001
REM sleep characteristics			
REM density, %	27.2 (10.7-57.9)	15.6 (6.3-34.8)	< 0.0001
REM sleep without atonia, %	1.3 (0-20.6)	0.43 (0-15.4)	0.06
Phasic EMG activity, %	2.14 (0-14.03)	1.64 (0.14-5.03)	0.053

PLMS, periodic leg movements in sleep; PLMW, periodic leg movements in wake; MA, microarousals. Data are expressed as median (min-max).
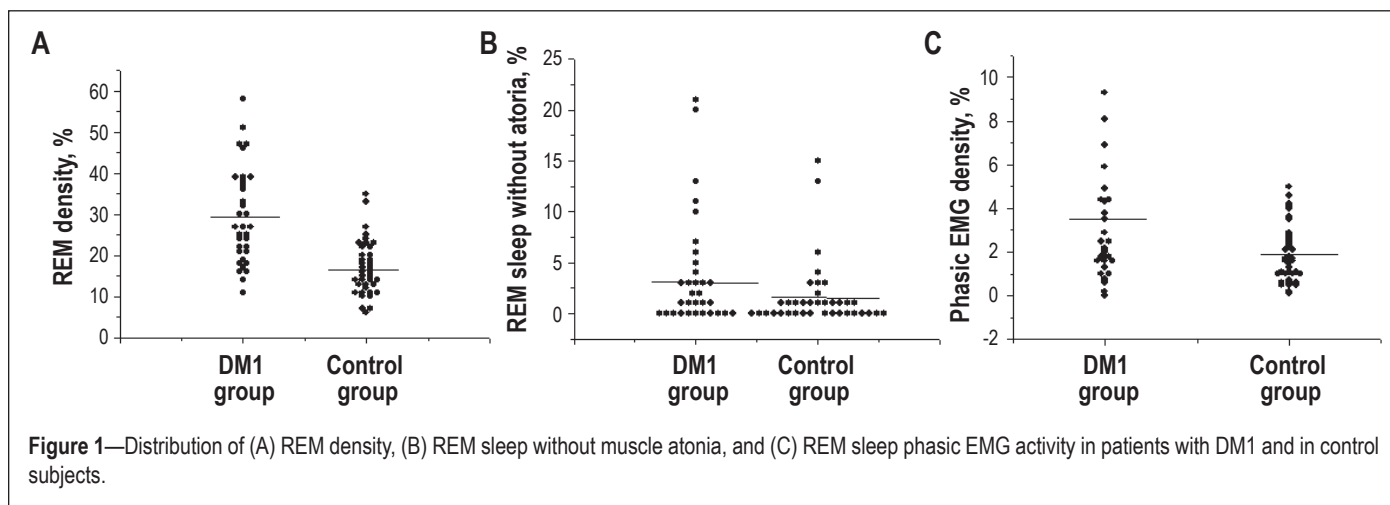

Figure 1—Distribution of (A) REM density, (B) REM sleep without muscle atonia, and (C) REM sleep phasic EMG activity in patients with DM1 and in control subjects.

frequency of EDS in our population remained lower than previous studies, with some methodological limitations.[9,11,14,15,17,25] In a different series of 43 French Canadian DM1 patients without selection or referral bias regarding EDS complaints (Saguenay, Québec), 44.2% had objective daytime sleepiness as assessed by the MSLT.[11] Even if unexplained discrepancies exist between these two populations with objective sleepiness underrepresented in our present sample, EDS reported by patients through clinical interview and ESS are prominent.

In agreement with most previous studies,[11,26-28] we pinpointed higher apnea and central apnea indices and a higher proportion of DM1 patients with severe AHI compared to controls. However, we failed to report any relationship between clinical characteristics, PSG abnormalities, SDB, and objective EDS. Previous studies reported that adequate treatment of SDB with improved blood gases only inconsistently improved EDS in DM1.[28]

The presence of SOREMPs on the MSLT is another frequent finding in DM1.[9,11,12,14] The present case-control study demonstrated that a majority of DM1 patients had one SOREMP and that about one third had ≥ 2 SOREMPs. Previous uncontrolled studies reported that DM1 patients recruited on the basis of EDS complaints presented ≥ 2 SOREMPs in 33% to 60% of cases.[9,11,14] We reported in a different cohort of French Canadian DM1 patients (Saguenay, Québec) that those with ≥ 2 SOREMPs had higher muscular impairment and lower MSL than patients with 0-1 SOREMP.[11] Unfortunately, no standardized quantification of muscular impairment was available at time of our study. We demonstrated here that DM1 patients with several SOREMPs were younger, had lower daytime sleep and nighttime REM sleep latencies, and less often presented a hypoxemic condition. Similar relationships in the occurrence of several SOREMPs, shorter nighttime REM latency, and reduced MSL on the MSLT were found in the general population.[29] Our study showed that REM sleep percentage was higher in DM1, correlated with nighttime REM sleep latency, with a tendency for a shorter REM sleep latency. High percentage of REM sleep (mean at 30.5%) has been previously reported in DM1,[14] but without a control group for comparison. All of these findings suggest both nocturnal and diurnal REM sleep dysregulation in DM1.

The present study reports for the first time a higher REM density in DM1 patients with a two-fold increase compared to controls. Although similar tendencies were noted for both REM sleep without atonia and REM sleep phasic EMG activity, pathological cutoffs of 80% and 15% were respectively fulfilled by only two patients in the former condition and by none in the latter. Moreover, REM sleep motor activity may be not clinically significant, since no patient reported a clinical history of RBD or had abnormal behaviors during REM sleep in the laboratory. We may add that none of patients reported hypnagogic hallucinations, sleep paralysis, or cataplexy.

This study is the first to demonstrate that DM1 patients have higher PLMS in both NREM and REM sleep, PLMS associated with microarousals, and PLMW indices than controls, with high proportions of patients having PLMS index above 5 and 10 (54.3% and 40%, respectively). Previous uncontrolled studies in DM1 reported major discrepancies regarding the level of PLMS indexes.[10,11,14] To our knowledge, this study provides the first definitive observation of an association between RLS and DM1; full diagnosis criteria of RLS were present in 22.5%, with RLS-DM1 patients having the highest PLMS indexes. We failed to report any relationship between PLMW, PLMS with or without MAs, and objective EDS. Although the significance of PLMS remains clinically unclear in DM1, their presence requires further attention, since DM1 was classically associated with cardiovascular abnormalities with concomitant increased risks of PLMS-related autonomic activation during sleep.[30]

All these data add credence to the hypothesis of a motor dyscontrol in DM1 in both wake and sleep, and especially in REM sleep with high PLMS and REM density indexes. While the eye movements of REM sleep are generated by premotor neurons of the reticular formation, phasic EMG activity in REM sleep is the result of a phasic depolarization of alpha motoneurons via the activation of both reticular and pyramidal neurons. Different brainstem regions and pathways are involved in REM sleep atonia, namely the subcoeruleus region. Our results suggest damage in brainstem regions responsible for a global motor disinhibition of REM sleep patterns in DM1 as reported in narcolepsy.[24] As multiple SOREMPs and reduced MSL are reported in narcolepsy and DM1, previous studies looked for a dysregulation of hypocretin neurotransmission in DM1. However, CSF hypocretin-1 levels[13,14,31,32] and splicing of hypocretin receptors mRNAs in postmortem temporal cortex samples[14] did not differ between DM1 and controls.

The pathogenesis of EDS remains unclear in DM1. Available clinical, neurophysiological, and histopathological results support the hypothesis that EDS and REM sleep dysregulation rely on a primary CNS disturbance in DM1 that may include circadian and ultradian timing abnormalities,[17] metabolic-endocrine dysfunctions,[33] and neuronal loss and gliosis.[34] However, the mechanism by which the expanded CTG repeat in the *DMPK* gene leads to these features is unclear. Several evidences support a model in which nuclear accumulation of RNA from the expanded allele contributes to the pathogenesis through a transdominant toxic effect of CUG-repeat RNA on RNA processing in altering the function of CUG-binding proteins.[35,36] One may thus posit that sleep regulatory dysfunction in DM1 may result from a toxicity of CNS expanded *DMPK* mRNA on alternative splicing outside the hypocretin genes.

In summary, this is the first case-control study in DM1 to demonstrate a higher frequency of daytime sleepiness and abnormalities in REM sleep regulation with an increased in both daytime and nighttime REM sleep propensity, REM density, and PLMS. An intrinsic CNS defect input to brainstem structures may contribute to high REM sleep pressure and REM sleep motor dyscontrol.

DISCLOSURE STATEMENT

REFERENCES

1. Mathieu J, Allard P, Potvin L, Prevost C, Begin P. A 10-year study of mortality in a cohort of patients with myotonic dystrophy. Neurology 1999;52:1658-62.
2. Harper PS. Myotonic dystrophy, 3rd ed. Philadelphia: W.B. Saunders, 2001.

3. Brook JD, McCurrach ME, Harley HG, et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. Cell 1992;68:799-808.

4. Fu YH, Pizzuti A, Fenwick RG Jr, et al. An unstable triplet repeat in a gene related to myotonic muscular dystrophy. Science 1992;255:1256-8.

5. Phemister JC, Small JM. Hypersomnia in dystrophia myotonica. J Neurol Neurosurg Psychiatry 1961;24:173-5.

6. Rubinsztein JS, Rubinsztein DC, Goodburn S, Holland AJ. Apathy and hypersomnia are common features of myotonic dystrophy. J Neurol Neurosurg Psychiatry 1998;64:510-5.

7. Manni R, Zucca C, Martinetti M, Ottolini A, Lanzi G, Tartara A. Hypersomnia in dystrophia myotonica: a neurophysiological and immunogenetic study. Acta Neurol Scand 1991;84:498-502.

8. Giubilei F, Antonini G, Bastianello S, et al. Excessive daytime sleepiness in myotonic dystrophy. J Neurol Sci 1999;164:60-3.

9. Gibbs JW III, Ciafaloni E, Radtke RA. Excessive daytime somnolence and increased rapid eye movement pressure in myotonic dystrophy. Sleep 2002;25:662-5.

10. Quera Salva MA, Blumen M, Jacquette A, et al. Sleep disorders in childhood-onset myotonic dystrophy type 1. Neuromuscul Disord 2006;16:564-70.

11. Laberge L, Begin P, Dauvilliers Y, et al. A polysomnographic study of daytime sleepiness in myotonic dystrophy type 1. J Neurol Neurosurg Psychiatry 2009;80:642-6.

12. Park JD, Radtke RA. Hypersomnolence in myotonic dystrophy: demonstration of sleep onset REM sleep. J Neurol Neurosurg Psychiatry 1995;58:512-3.

13. Martinez-Rodriguez JE, Lin L, Iranzo A, et al. Decreased hypocretin-1 (Orexin-A) levels in the cerebrospinal fluid of patients with myotonic dystrophy and excessive daytime sleepiness. Sleep 2003;26:287-90.

14. Ciafaloni E, Mignot E, Sansone V, et al. The hypocretin neurotransmission system in myotonic dystrophy type 1. Neurology 2008;70:226-30.

15. Laberge L, Gagnon C, Jean S, Mathieu J. Fatigue and daytime sleepiness rating scales in myotonic dystrophy: a study of reliability. J Neurol Neurosurg Psychiatry. 2005;76:1403-5

16. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.

17. van Hilten JJ, Kerkhof GA, van Dijk JG, Dunnewold R, Wintzen AR. Disruption of sleep-wake rhythmicity and daytime sleepiness in myotonic dystrophy. J Neurol Sci 1993;114:68-75.

18. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101-19.

19. Iber C, Ancoli-Israel S, Chesson A, Quan S, for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events; rules, terminology and technical specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine, 2007.

20. Lapierre O, Montplaisir J. Polysomnogrpahic features of REM sleep behavior disorder: development of a scoring method. Neurology 1992;42:1371-4.

21. Zucconi M, Ferri R, Allen R, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). Sleep Med 2006;7:175-83.

22. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep 2005;28:113-21.

23. Gagnon JF, Bedard MA, Fantini ML, et al. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 2002;59:585-9.

24. Dauvilliers Y, Rompre S, Gagnon JF, Vendette M, Petit D, Montplaisir J. REM sleep characteristics in narcolepsy and REM sleep behavior disorder. Sleep 2007;30:844-9.

25. Phillips MF, Steer HM, Soldan JR, Wiles CM, Harper PS. Daytime somnolence in myotonic dystrophy. J Neurol 1999;246:275-82.

26. Guilleminault C, Cummiskey J, Motta J, Lynne-Davies P. Respiratory and hemodynamic study during wakefulness and sleep in myotonic dystrophy. Sleep 1978;1:19-31.

27. Cirignotta F, Mondini S, Zucconi M, et al. Sleep-related breathing impairment in myotonic dystrophy. J Neurol 1987;235:80-5.

28. Guilleminault C, Philip P, Robinson A. Sleep and neuromuscular disease: bilevel positive airway pressure by nasal mask as a treatment for sleep disordered breathing in patients with neuromuscular disease. J Neurol Neurosurg Psychiatry 1998;65:225-32.

29. Mignot E, Lin L, Finn L, et al. Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults. Brain 2006;129:1609-23.

30. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi P. Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology 2007;68:1213-8

31. Dauvilliers Y, Baumann CR, Carlander B, et al. CSF hypocretin-1 levels in narcolepsy, Kleine-Levin syndrome, and other hypersomnias and neurological conditions. J Neurol Neurosurg Psychiatry 2003;74:1667-73.

32. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59:1553-62.

33. Culebras A, Podolski S, Leopold NA. Absence of sleep-related growth hormone elevations in myotonic dystrophy. Neurology 1977;27:165-7.

34. Ono S, Takahashi K, Jinnai K, et al. Loss of catecholaminergic neurons in the medullary reticular formation in myotonic dystrophy. Neurology 1998;51:1121-4.

35. Timchenko LT. Myotonic dystrophy: the role of RNA CUG triplet repeats. Am J Hum Genet 1999;64:360-4.

36. Jiang H, Mankodi A, Swanson MS, Moxley RT, Thornton CA. Myotonic dystrophy type 1 is associated with nuclear foci of mutant RNA, sequestration of muscle blind proteins and deregulated alternative splicing in neurons. Hum Mol Genet 2004;13:3079-88.