Restless legs syndrome and daytime sleepiness are prominent in myotonic dystrophy type 2

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ABSTRACT

Objectives: Although sleep disturbances are common in myotonic dystrophy type 1 (DM1), sleep disturbances in myotonic dystrophy type 2 (DM2) have not been well-characterized. We aimed to determine the frequency of sleep disturbances in DM2.

Methods: We conducted a case-control study of 54 genetically confirmed DM2 subjects and 104 medical controls without DM1 or DM2, and surveyed common sleep disturbances, including symptoms of probable restless legs syndrome (RLS), excessive daytime sleepiness (EDS), sleep quality, fatigue, obstructive sleep apnea (OSA), probable REM sleep behavior disorder (pRBD), and pain. Thirty patients with DM2 and 43 controls responded to the survey. Group comparisons with parametric statistical tests and multiple linear and logistic regression analyses were conducted for the dependent variables of EDS and poor sleep quality.

Results: The mean ages of patients with DM2 and controls were 63.8 and 64.5 years, respectively. Significant sleep disturbances in patients with DM2 compared to controls included probable RLS (60.0% vs 14.0%, $p < 0.0001$), EDS ($p < 0.001$), sleep quality ($p = 0.02$), and fatigue ($p < 0.0001$). EDS and fatigue symptoms were independently associated with DM2 diagnosis ($p < 0.01$) after controlling for age, sex, RLS, and pain scores. There were no group differences in OSA ($p = 0.87$) or pRBD ($p = 0.12$) scores.

Conclusions: RLS, EDS, and fatigue are frequent sleep disturbances in patients with DM2, while OSA and pRBD symptoms are not. EDS was independently associated with DM2 diagnosis, suggesting possible primary CNS hypersomnia mechanisms. Further studies utilizing objective sleep measures are needed to better characterize sleep comorbidities in DM2. *Neurology*® 2013;81:157-164

GLOSSARY

DM1 = myotonic dystrophy type 1; **DM2** = myotonic dystrophy type 2; **DSS** = Daytime Sleepiness Scale; **EDS** = excessive daytime sleepiness; **ESS** = Epworth Sleepiness Scale; **FSS** = Fatigue Severity Scale; **MSQ** = Mayo Sleep Questionnaire; **OSA** = obstructive sleep apnea; **pRBD** = probable REM sleep behavior disorder; **PSQI** = Pittsburgh Sleep Quality Index; **RBD** = REM sleep behavior disorder; **RLS** = restless legs syndrome; **SA-SDQ** = Sleep Apnea scale of the Sleep Disorders Questionnaire.

Myotonic dystrophy type 1 (DM1) and type 2 (DM2) are genetically distinct, autosomal dominantly inherited, progressive, multisystem disorders that share several common features, including muscle weakness, myotonia, premature cataracts, cardiac dysrhythmias, and endocrine abnormalities.^{1,2}

Despite these commonalities, differences in clinical phenotypes are often sufficient to target confirmatory gene analysis. While DM1 is characterized by distal weakness, DM2 typically results in proximal weakness and myalgia.^{1,3} Myotonia is often more evident in DM1 than in DM2.² The extraskeletal muscle abnormalities are similar in both diseases, although cardiac arrhythmia may be more prevalent and severe in DM1.^{1,3}

Sleep disturbances are frequent in DM1, especially fatigue, excessive daytime sleepiness (EDS), and sleep-disordered breathing, including obstructive or central sleep apnea and sleep-related hypoventilation.⁴⁻⁶ Restless legs syndrome (RLS) and primary CNS hypersomnia including narcolepsy-like symptoms may also occur in DM1.^{5,7}

Supplemental data at
www.neurology.org

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Considerably less is known about sleep disturbances in DM2. Our recent retrospective case series suggested that RLS symptoms may be frequent in patients with DM2, and previous reports conflict on whether other sleep disturbances are as prominent in DM2 as in DM1.^{8–10} Further prospective studies characterizing sleep disturbances in DM2 are needed, and could aid in clinical distinction of myotonic dystrophy subtypes and improve recognition of comorbid sleep problems in this patient population. Our aim was to determine the frequency of sleep disturbances in patients with genetically proven DM2 in comparison to age- and sex-matched controls. The primary outcomes were group differences in RLS symptoms, EDS, fatigue, and sleep quality ratings.

METHODS **Standard protocol approvals, registrations, and patient consents.** This study was approved by the Mayo Clinic Institutional Review Board. Written informed consent was received from all participants.

Participants. Cases were 54 patients with genetically confirmed DM2 seen at Mayo Clinic, Rochester, Minnesota, from 2001 to 2011. Controls were drawn from general medical preventive clinics during 2011, and matched for age and sex to DM2 cases 2:1, although 4 controls were excluded (1 had died and 3 had unretrievable addresses), leaving 104 age- and sex-matched controls without a history of myotonic dystrophy. All subjects were mailed survey-based questionnaires. Patients were selected without knowledge of any sleep disorders or symptoms. Thirty patients with DM2 and 43 controls returned completed surveys, while the remainder declined or failed to return surveys. See figure 1 for derivation of included subjects.

Questionnaires. Sleep quality. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a validated questionnaire measuring sleep quality. The PSQI includes 19 self-rated items, which are grouped to derive 7 components each scored 0–3, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction, yielding a global maximum score of 21.¹¹ A global score of greater than 5 is indicative of poor sleep quality.¹¹

Restless legs syndrome. RLS symptoms were assessed using the well-validated Cambridge-Hopkins Questionnaire for Ascertainment of RLS as shown in appendix e-1 on the *Neurology*[®] Web site at www.neurology.org.¹² Subjects who responded to all items in a manner consistent with RLS were considered to have RLS symptoms.

Excessive daytime sleepiness. The Epworth Sleepiness Scale (ESS) was used to assess for EDS.¹³ Eight items are summed to assess the respondent's likelihood of dozing in situations typically encountered on a daily basis, with each item rated 0–3 (0 indicating no chance and 3 a high chance for dozing). ESS scores >10 indicate EDS, although a previous study suggested that the ESS may be insensitive toward EDS assessment in DM1.¹⁴

EDS was also assessed by the Daytime Sleepiness Scale (DSS), an alternative measure developed specifically for patients with DM,¹⁴ consisting of a 5-item questionnaire posing several questions appropriate to identify EDS in a more sedentary and socially isolated neuromuscular population (as shown in appendix e-2). The DSS has been previously validated with retest reliability in DM1.⁴ Scores of 7 or greater are indicative of EDS.⁴

Fatigue. The Fatigue Severity Scale (FSS) is a 9-item questionnaire that measures daytime fatigue in medical and neurologic patients.¹⁵ Statements addressing severity of fatigue symptoms are rated 1–7, with lower ratings indicating lesser and higher scores indicating stronger endorsement of fatigue symptoms. Individual items are summed to yield total FSS scores, which are then divided by 9. Resulting scores of 4 or greater suggest problematic fatigue symptoms.¹⁵

Obstructive sleep apnea. The Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ, freely available on the

Figure 1 An illustration of survey response rates in DM2 patient and control groups

Sixty subjects with myotonic dystrophy type 2 (DM2) were seen over a decade span at our institution, with 54 of these subjects surveyed, of whom 30 (55.6%) responded. A total of 104 age- and sex-matched medical controls were also surveyed, of whom 43 (41.3%) responded.

Web at http://www.commondataelements.ninds.nih.gov/PD.aspx#tab=Data_Standards) is a validated screening tool for sleep-disordered breathing, adapted from the Sleep Questionnaire and Assessment of Wakefulness of Stanford University.¹⁶ The 12-item SA-SDQ questionnaire rates frequency of obstructive sleep apnea (OSA) symptoms, and also includes scores for weight, body mass index, smoking, and age. Unlike other OSA screening tools, the SA-SDQ does not assess EDS symptoms, which could lead to overestimation of OSA in inherently sleepy subjects. Each item is scored 0–5, with higher scores representing increased OSA propensity. The maximum score possible is 60. We utilized the established general population OSA cutoffs of 36 for men and 32 for women,¹⁶ an accepted and consistent measure, although alternative cutoffs have been established in certain patient populations, such as those with epilepsy.¹⁷

REM sleep behavior disorder. Probable REM sleep behavior disorder (pRBD) was identified by a history of dream enactment behavior using the Mayo Sleep Questionnaire (MSQ, freely available on the Web at <http://www.mayoclinic.org/pdfs/MSQ-copyrightfinal.pdf>) without polysomnography confirmation of loss of muscle atonia during REM sleep. The MSQ includes a primary question on REM sleep behavior disorder (RBD) addressing recurrent dream enactment answered by the patient's bed partner, identifying pRBD with high sensitivity and reasonable specificity.¹⁸

Pain. Our pain scale included 3 items addressing pain, modified from the Medical Outcomes Study Short Form Health Survey.¹⁹ Higher scores indicate more severe pain.

Comorbidities and medication use. We reviewed the medical records of patients with DM2 and controls for medical and psychiatric comorbidities (cataracts; diabetes; hypertension; chronic obstructive pulmonary disease; prior cancer; cardiovascular, cerebrovascular, thyroid, or renal disease; peripheral neuropathy; and depression and anxiety diagnoses by a psychiatrist) and centrally active medications (narcotics; benzodiazepines and other hypnotics; antidepressants; and other CNS-active drugs).

Statistical analysis. Statistical calculations were carried out using JMP version 9 (SAS Inc., Cary, NC). Qualitative data were reported as relative frequencies. Quantitative data were reported as means, standard deviation, and range. Group differences between patients with DM2 and controls were compared with Student *t* test for continuous variables and χ^2 tests for categorical variables. Associations between continuous variables were analyzed with one-way analysis of variance and mixed model linear regression analysis. If a participant failed to complete a questionnaire, they were excluded from that group comparison. Multiple mixed model logistic regression analyses were conducted for the primary dependent outcome variables of sleepiness (for DSS ≥ 7), fatigue (for FSS ≥ 4), and poor sleep quality (for PSQI > 5), entering relevant age, demographic, group, and pain, sleep apnea, and RLS outcomes to identify independent associations. Significance level was set at an α of $p < 0.05$.

RESULTS Demographic data. Thirty of 54 (55.6%) patients with DM2 and 43 of 104 (41.3%) controls responded to the survey ($p = 0.09$), with the remainder declining or failing to return surveys. Neuromuscular symptom duration, available for 29 of 30 patients with DM2, had a mean of 16.5 years. Twenty-one (70%) patients with DM2 and 32 (74%) controls were women ($p = 0.68$). Mean ages in DM2 patient and control groups were 63.8 and 64.5 years, respectively ($p = 0.59$). The groups were

also similar in mean body mass index ($p = 0.85$) and smoking history ($p = 0.66$). See the table for additional group difference statistics.

Comorbidities and medication use. As expected, there was a higher frequency of diabetes ($p = 0.046$) in DM2 than controls, but there were no significant differences in frequency of other comorbidities or use of CNS-active drugs (see table).

Sleep disturbances. Restless legs syndrome. RLS symptom frequency was higher in patients with DM2 than controls ($p < 0.0001$, figure 2). However, among patients with RLS symptoms, severity (distress or symptom frequency) did not differ between groups, and RLS status was not associated with age or symptom duration in DM2.

Three of 6 patients with DM2 with recorded testing had serum ferritin < 50 $\mu\text{g/mL}$, each reporting RLS symptoms.

Sleep quality. Three controls did not complete the PSQI. Mean PSQI score was higher in DM2 than control patients ($\chi^2 = 5.39$, $p = 0.02$). PSQI scores were associated with RLS symptoms ($\chi^2 = 9.56$, $p < 0.01$), fatigue severity ($\chi^2 = 4.30$, $p = 0.038$), and pain ($F = 19.9$, $p < 0.0001$), but not OSA ($\chi^2 = 0.81$, $p = 0.37$). PSQI scores were not associated with age, DM2 symptom duration, depression or anxiety, or use of centrally active drugs.

RLS was an independent predictor for poor sleep quality after controlling for age, sex, and pain scores ($\chi^2 = 6.00$, $p = 0.014$).

Excessive daytime sleepiness. Mean DSS scores were higher in patients with DM2 than control patients ($p < 0.001$), and a higher percentage of patients with DM2 than controls had DSS scores ≥ 7 ($p < 0.001$). However, mean ESS scores were similar between groups ($p = 0.086$). Neither DSS nor ESS scores were associated with age, DM2 symptom duration, or depression in the DM2 or control groups. Patients with RLS symptoms had higher DSS scores ($\chi^2 = 6.84$, $p < 0.01$) than those without RLS. PSQI scores were positively correlated with DSS scores ($F = 5.39$, $p = 0.023$).

EDS as indicated by a DSS score ≥ 7 was independently associated with DM2 diagnosis ($\chi^2 = 8.46$, $p < 0.01$) after controlling for age, sex, RLS, and pain scores. Within each group alone, however, DSS was unassociated with other measured variables.

Fatigue. One patient with DM2 did not complete the FSS. Fatigue (FSS ≥ 4) was more common in DM2 than controls ($\chi^2 = 18.46$, $p < 0.001$), and mean FSS scores were higher in patients with DM2 than control patients ($\chi^2 = 13.97$, $p < 0.0001$). After controlling for age, sex, OSA, and RLS, FSS scores were associated with DM2 diagnosis ($\chi^2 = 6.85$, $p < 0.01$) and pain scores ($\chi^2 = 5.84$, $p = 0.016$).

Table Demographic, comorbidity, medication, and questionnaire data			
Demographics	DM2	Controls	p Value
Participants, n	30	43	—
Female, %	70.0	74.4	0.68
Age, y, mean (SD); range	63.83 (9.94); 42-84	64.53 (8.05); 42-80	0.59
BMI, kg/m ² , mean (SD); range	27.14 (5.12); 18.1-38.4	27.53 (5.53); 18.0-42.7	0.85
Smoking history, %	36.7	41.9	0.66
Smoking currently, %	3.3	0	0.23
Years smoking, mean (SD); range	4.61 (9.80); 0-30	5.71 (9.84); 0-35	0.5
Comorbidities, %			
Hypertension	40.0	37.2	0.81
Cardiovascular disease	23.2	20.9	0.81
Cerebrovascular disease	3.3	4.7	0.78
COPD	0	0	1.00
Diabetes	23.3	7.0	0.046
Thyroid disease	26.7	18.6	0.41
Renal disease	0	4.7	0.23
Cancer	30.0	37.2	0.52
Depression	13.3	18.6	0.55
Anxiety	3.3	9.3	0.59
Peripheral neuropathy	13.3	9.3	0.59
Cataracts	60.0	41.9	0.13
Medication use, %			
Narcotic use	6.7	9.3	0.69
Hypnotic use	13.3	14.0	0.94
Antidepressant use	16.7	30.2	0.19
Other CNS-active drug use	20.0	9.3	0.19
Questionnaires			
ESS score, mean (SD); range	7.87 (5.09); 0-17	5.62 (3.80); 0-16	0.086
ESS >10, %	30.0	14.0	0.095
DSS score, mean (SD); range	6.03 (2.97); 1-11	3.51 (2.20); 0-9	<0.001
DSS score ≥7, %	43.3	7.0	<0.001
FSS score, mean (SD); range	4.44 (1.73); 1.00-7.00	2.59 (1.31); 1.00-5.33	<0.0001
FSS ≥4, %	58.6	16.3	<0.001
PSQI score, mean (SD); range	7.97 (4.05); 0-18	5.78 (3.85); 1-18	0.021
PSQI >5, %	66.7	47.5	0.11
SA-SDQ score, mean (SD); range	27.19 (5.48); 18-36	27.37 (6.00); 14-39	0.87
Clinically significant SA-SDQ score, %	11.1	14.0	0.77
RBD from MSQ, %	4.8	19.4	0.12
CH-RLSq RLS, %	60.0	14.0	<0.0001
Pain score, mean (SD); range	6.93 (5.02); 0-18	5.15 (3.87); 0-18	0.18

Abbreviations: BMI = body mass index; CH-RLSq = Cambridge-Hopkins Questionnaire for Ascertainment of RLS; COPD = chronic obstructive pulmonary disease; DM2 = myotonic dystrophy type 2; DSS = Daytime Sleepiness Scale; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; MSQ = Mayo Sleep Questionnaire; PSQI = Pittsburgh Sleep Quality Index; RBD = REM sleep behavior disorder; SA-SDQ = Sleep Apnea scale of the Sleep Disorders Questionnaire.

Figure 2 Sleep disturbances in patients with DM2 and controls

Comparisons between patients with myotonic dystrophy type 2 (DM2) and controls in percent with reported restless legs syndrome (RLS) symptoms (A), Pittsburgh Sleep Quality Index (PSQI) scores (B), Daytime Sleepiness Scale (DSS) scores (C), Fatigue Severity Scale (FSS) scores (D), Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) scores (E), and percent with probable REM sleep behavior disorder (pRBD) (F).

OSA. Four patients with DM2 did not complete the SA-SDQ. There were no group differences in mean SA-SDQ scores ($\chi^2 = 0.03$, $p = 0.87$) or SA-SDQ scores above sex-specified OSA cutoffs ($\chi^2 = 0.08$, $p = 0.77$).

pRBD. Twenty-one (70%) patients with DM2 and 36 (83%) controls completed the MSQ for pRBD ($\chi^2 = 1.94$, $p = 0.16$), and pRBD status was similar in patients with DM2 and controls ($\chi^2 = 2.37$, $p = 0.12$).

Pain. Modified pain scale ratings were similar between DM2 and control groups ($\chi^2 = 1.79$, $p = 0.18$).

DISCUSSION Similar to patients with DM1, patients with DM2 have a high frequency of comorbid sleep disturbances, especially RLS symptoms, confirming our previous study that found RLS diagnoses in half of genetically confirmed patients with DM2 seen in a small sleep clinic-based series.¹⁰ RLS symptoms were even more frequent in the present larger series of patients with DM2, who were not specifically selected for sleep complaints.

A previous study reported that 22.5% of patients with DM1 had RLS,⁷ although RLS was absent in controls, suggesting reduced population prevalence of RLS that could have led to an underestimate of RLS frequency in DM1. Future studies comparing RLS frequency in DM1 and DM2 are necessary to determine whether RLS phenotype

may aid in discrimination between the myotonic dystrophies.

The prominence of RLS symptoms in DM2 is striking and of uncertain cause. One possible hypothesis for the prominent pain and RLS symptoms seen in DM2 would be RNA toxicity and spliceopathy mediating dysfunction of the dopaminergic hypothalamic A11 pathway.^{20,21} Other possible factors affecting DM2-associated RLS could include dysfunctional iron or calcium homeostasis. A recently described RLS risk haplotype, MEIS1, leads to decreased MEIS1 mRNA and protein expression and is associated with altered brain tissue ferritin expression caused by RNA interference.^{22,23} DM2-induced spliceopathy could potentially mediate RLS symptoms via RNA interference with the transcription or translation of the *MEIS1* gene or its products. Alternatively, calcium channel dysfunction could generate DM2-related RLS symptoms; calcium channels may in part mediate RLS symptoms since presynaptic voltage-gated calcium channel α -2- δ subunit receptor agonists (e.g., gabapentin) effectively treat RLS symptoms.²⁴ Recent evidence suggests DM-splicing defects alter calcium homeostasis in skeletal and cardiac muscle in DM2.^{25–29} Three of our patients (out of 6 with recorded laboratories) also had low serum ferritin, implicated as an aggravator of RLS,²⁹ suggesting that iron deficiency should be evaluated prospectively in DM2.

We also found a high frequency of EDS in DM2, especially by the DSS instrument, and that EDS was independently associated with DM2 diagnosis when controlling for age, sex, RLS symptoms, and pain scores. Previous studies had yielded conflicting findings concerning sleepiness in DM2. One study found poor sleep quality and excessive fatigue in DM2, but, in contrast to DM1, daytime sleepiness was not prominent in DM2.⁸ However, EDS was frequently present in all 6 genetically confirmed or clinically suspected patients with DM2 in one recent series,⁹ and symptoms of sleepiness were seen in 75% and fatigue in 50% of our recent series of 8 genetically confirmed patients with DM2 with sleep disturbance.¹⁰ Identifying sleepiness in relatively sedentary, socially isolated patient populations with neuromuscular conditions may require alternative sleepiness rating scales such as the DSS to identify symptoms of sleepiness. Interestingly, our study found significantly increased sleepiness in patients with DM2 by report of the DSS, but no significant difference in sleepiness from controls when utilizing the ESS.

Consistent with previous DM2 series,^{8,10} fatigue was common in our DM2 patient group. In contrast to DM1, our patients with DM2 had symptoms of OSA no more frequently than controls, suggesting that sleepiness in DM1 and DM2 may have different causes. In DM1, hypersomnia is often caused by OSA, a frequent comorbidity in this group.^{4,6} Our results suggest that sleepiness, fatigue, and poor sleep quality in DM2 are not linked to OSA. This could imply that hypersomnia may be intrinsic in DM2, similar to the primary CNS hypersomnia seen in some patients with DM1.^{4,30–32} However, our investigation of sleep apnea was limited to survey symptom reports rather than the gold standard of polysomnography. Future prospective studies of patients with DM2 utilizing objective, quantitative sleep measures including polysomnography, multiple sleep latency testing, and actigraphy monitoring are necessary to determine the true frequency of disordered breathing, primary CNS hypersomnia, and circadian and sleep disturbances including RLS in this patient population. If primary CNS hypersomnia appears to be a feature of CNS involvement in DM2 similar to that seen in DM1, psychostimulant therapies may also be of potential benefit in treating hypersomnia symptoms in the DM2 patient population.³³

Our series of patients with DM2 also reported frequent reduction in sleep quality as measured by the PSQI, which has been previously observed in this patient population.⁸ However, in the previous Dutch DM2 patient series, poor sleep quality was instead associated with pain while RLS symptoms were not specifically analyzed.⁸ In contrast to that study, we found that PSQI scores were independently

associated with RLS symptoms but not depression, pain, or sleep apnea symptoms. Further prospective research is necessary to determine the most prominent determinants of poor sleep quality in patients with DM2 so as to identify strategies to improve patient well-being and functioning.

Whereas a recent case report described RBD in a patient with DM2,³⁴ our series instead suggests that RBD is no more frequent in DM2 than in controls. The frequency of pRBD in our patients with DM2 (4.8%) does not appear to be higher than that expected for similarly aged patients within the general population, given that mean age of RBD diagnosis is in the seventh decade.³⁵ A recent study found a 6.8% rate of pRBD in a 70- to 89-year-old population-based sample using the MSQ, the same pRBD instrument used in this study.³⁶ Although it should be noted that the MSQ is not entirely specific for RBD (specificity was found to be around 70% in a validation study),³⁷ the relatively higher rate of pRBD in our control group (19.4%) was unanticipated. While there was no statistically significant difference in antidepressant use between patients with DM2 and controls, the relatively higher frequencies of depression, anxiety, and antidepressant use in the control group (which are well-known factors associated with RBD) may have in part explained the relatively higher frequency of pRBD in our controls.^{35,38}

A strength of our study is its large, systematic, and comprehensive survey of sleep disturbances with an acceptable return rate, comparing a representative, naturalistic clinical practice sample of genetically confirmed patients with DM2 to age- and sex-matched medical controls. Our data expand understanding of the range of sleep disturbances in patients with DM2, particularly regarding the prominence of RLS symptoms and their impact on sleep quality, and further clarify the frequency of EDS symptoms in DM2 as identified by a sensitive, disease-specific screening measure.

However, our study has several notable limitations. As a survey of subjective sleep outcomes from a single tertiary care center, we may have been unable to identify and control for potential confounding referral and sampling biases, so our findings may not be generalizable to all patients with DM2. In addition, neither RLS nor RBD symptoms were confirmed by interviews, and OSA was not evaluated by polysomnography. Future prospective studies will be necessary to address these methodologic problems inherent in survey-based research and to determine the impact of sleep disturbances on quality of life in patients with DM2.

Our study suggests that RLS, hypersomnia and fatigue symptoms, and poor sleep quality are frequent in DM2. However, DM2 does not appear to be more frequently associated with OSA or RBD than in the general population. Future studies of larger samples

of patients with genetically confirmed DM1 and DM2 utilizing subjective survey and objective sleep measures such as polysomnography, multiple sleep latency tests, and actigraphy are necessary to better define the characteristics of comorbid sleep disturbance in the myotonic dystrophies.

AUTHOR CONTRIBUTIONS

Dr. Lam: study design, acquisition of data, analysis and interpretation, and critical revision of the manuscript for important intellectual content. Mr. Shepard: acquisition of data, analysis, and authoring of manuscript. Dr. St. Louis: study concept and design, acquisition of data, data analysis and interpretation, authorship and critical revision of the manuscript, and study supervision. Mr. Dueffert: acquisition of data, critical revision of the manuscript for important intellectual content. Ms. Slocumb: acquisition of data, critical revision of the manuscript for important intellectual content. Mr. McCarter: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Silber: critical revision of the manuscript for important intellectual content. Dr. Boeve: critical revision of the manuscript for important intellectual content. Dr. Olson: critical revision of the manuscript for important intellectual content. Dr. Somers: critical revision of the manuscript for important intellectual content. Dr. Milone: critical revision of the manuscript for important intellectual content.

STUDY FUNDING

Supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant 1 UL1 RR024150-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

DISCLOSURE

E. Lam and P. Shepard report no disclosures. E. St. Louis reports that he receives research support from the Mayo Clinic Center for Translational Science Activities (CTSA), supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant 1 UL1 RR024150-01. L. Dueffert, N. Slocumb, S. McCarter, and M. Silber report no disclosures. B. Boeve reports that he is an investigator in clinical trials sponsored by Cephalon, Inc., Allon Pharmaceuticals, and GE Healthcare. He has received honoraria from the American Academy of Neurology. He receives research support from the National Institute on Aging and the Mangurian Foundation. E. Olson, V. Somers, and M. Milone report no disclosures. Go to Neurology.org for full disclosures.

Received December 20, 2012. Accepted in final form March 14, 2013.

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