https://doi.org/10.5664/jcsm.9438

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Assessment of self-reported and objective daytime sleepiness in adult-onset myotonic dystrophy type 1

Valeria A. Sansone, MD, PhD[1,2,*]; Paola Proserpio, MD[3,*]; Luca Mauro, CPM[2]; Andrea Lizio Biostat, PhD[2]; Erica Frezza, MD[4]; Andrea Lanza, Med Tech[3]; Paola Rogliani, MD[5]; Gabriella Pezzuto, MD[5]; Elisa Falcier, MD[2]; Carola Ferrari Aggradi, MD[2]; Alice Pirola, PT[2]; Fabrizio Rao, MD[2]; Elisabetta Roma, MD[2]; Claudia Galluzzi, PSY[4]; Matteo Spanetta, Med Tech[4]; Federica Cattaneo, Med Tech[3]; Annalisa Rubino, Med Tech[3]; Elio Clemente Agostoni, MD[3]; Federica Amico, Med Tech[3]; Alice Zanolini, MD[2]; Francesca Izzi, MD[4]; Giulia Greco, RN[4]; Andrea Romigi, MD[6]; Claudio Liguori, MD, PhD[4]; Lino Nobili, MD, PhD[7,8]; Fabio Placidi, MD, PhD[4]; Roberto Massa, MD, PhD[4]

[1]Neurorehabilitation Unit, University of Milan, Milan, Italy; [2]The NEMO Clinical Center, Milan, Italy; [3]Sleep Medicine Center, Dept. Neuroscience, Niguarda Hospital, Milan, Italy; [4]Department of Neurology, Tor Vergata University of Rome, Rome, Italy; [5]Department of Respiratory Diseases, Tor Vergata University of Rome, Rome, Italy; [6]IRCCS Neuromed Istituto Neurologico Mediterraneo, Pozzilli (IS), Rome, Italy; [7]Child Neuropsychiatry Unit, IRCCS Istituto G. Gaslini, Genoa, Italy; [8]Department of Neuroscience, DINOGMI, University of Genoa, Genoa, Italy; *Co-first authors

Study Objectives: Excessive daytime sleepiness (EDS) in myotonic dystrophy type 1 is mostly of central origin but it may coexist with sleep-related breathing disorders. However, there is no consensus on the sleep protocols to be used, assessments vary, and only a minority of patients are regularly tested or are on treatment for EDS. Our study presents data on self-reported and objective EDS in adult-onset myotonic dystrophy type 1.

Methods: Sixty-three patients with adult-onset DM1 were subjected to EDS-sleep assessments (polysomnography, Multiple Sleep Latency Test, Epworth Sleepiness Scale). Correlation coefficients were computed to assess the relationship between sleep and sleepiness test results, fatigue, and quality of life.

Results: 33% and 48% of patients had EDS based, respectively, on the Epworth Sleepiness Scale and the Multiple Sleep Latency Test, with a low concordance between these tests (k = 0.19). Thirteen patients (20%) displayed 2 or more sleep-onset rapid eye movement periods on Multiple Sleep Latency Test. Patients having EDS by Multiple Sleep Latency Test had a shorter disease duration ($P < .05$), higher total sleep time and sleep efficiency and lower wake after sleep onset on polysomnography. Patients with self-reported EDS reported significantly higher fatigue score compared with patients without EDS ($P < .05$). No other difference was found in demographic, clinical, and respiratory features.

Conclusions: EDS test results are contradictory, making treatment options difficult. Combining quantitative tests and self-reported scales may facilitate physicians in planning EDS care with patients and families.

Keywords: myotonic dystrophy type 1, excessive daytime sleepiness, Epworth Sleepiness Scale, Multiple Sleep Latency Test, polysomnography

Citation: Sansone VA, Proserpio P, Mauro L, et al. Assessment of self-reported and objective daytime sleepiness in adult-onset myotonic dystrophy type 1. *J Clin Sleep Med*. 2021;17(12):2383–2391.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Excessive daytime sleepiness (EDS) is among the most frequent complaints in myotonic dystrophy type 1, impacting patients and family lives. Despite this, there is no consensus on the sleep protocols to be used, assessments vary, and only a minority of patients are regularly tested or are on treatment for EDS. This study assesses EDS with self-reported and objective measures while describing demographic and clinical features of excessively sleepy and nonsleepy participants.

Study Impact: We describe the prevalence of EDS in a cohort of adult individuals with myotonic dystrophy type 1 using self-reported and objective tools. We conclude that there is no gold standard to test for EDS in myotonic dystrophy type 1 and that both self-reported and objective measures are useful and complementary.

INTRODUCTION

Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy of adults, affecting 1 in 2,500–8,000 worldwide according to the cohorts studied.[1–3] It is a multisystem disorder that impairs skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system. Excessive daytime sleepiness (EDS) is among the most frequent non-muscular symptoms and one of the most common complaint of patients with DM1.[1] In these patients, EDS can overlap with symptoms related to lack of motivation, depression, or apathy, as well as with symptoms of fatigue, both of central origin or related to the patient's motor disability. Although there may be an assessment bias related to the sensitivity of the tools used to determine it,[4,5] EDS reaches a prevalence of up to 88% in some studies.[6–9] It is also often reported as the presenting symptom of DM1, not infrequently, years preceding the diagnosis.[1,4–11]

EDS in patients with DM1 has specific features, being unaffected by naps and typically occurring in monotonous situations or when attention is not being held.[1,10–12] Although some sleep studies found some similarities with narcolepsy[7,9] (ie, reduced sleep latency associated with 2 or more sleep-onset rapid

eye movement periods [SOREMPs], at the Multiple Sleep Latency Test [MSLT]), typical attacks of sleepiness usually do not occur in patients with DM1 and the pathogenesis of EDS in DM1 is generally considered multifactorial. Several studies support the hypothesis of a central dysfunction of sleep regulation[12–17] Moreover, some studies suggest that, in some patients with DM1, EDS may also be related to a sleep fragmentation induced by a sleep-related breathing disorder[9,18,19] or it may be secondary to nocturnal hypoxemia and diurnal hypercapnia.[20] On the other hand, it is not infrequent to find patients with exceptionally high levels of daytime carbon dioxide (eg, 50 mmHg on at-rest morning pCO_2) not complaining of respiratory problems or of EDS.[21,22]

EDS can be approached with different treatment strategies, mainly depending on its cause. Noninvasive ventilation (NIV) is recommended to treat nocturnal hypoventilation related to chronic respiratory insufficiency.[20,22] However, the adherence of patients with DM1 to ventilatory treatment is poor and, even in those who are compliant to NIV, EDS may persist despite correction of the sleep-related breathing disorder.[19,22] Although off-label, modafinil—a drug used for EDS treatment in narcolepsy—has been reported to reduce EDS in a cohort of patients with DM1.[23,24] Despite these treatment options, in many centers, patients with DM1 are not routinely subjected to standardized diagnostic and management protocols for EDS (including respiratory and sleep studies), although this symptom has a significant deleterious impact on work, social life, and quality of life. The aim of this study is to describe the prevalence of EDS in a cohort of patients with adult-onset DM1 in Italy using different sleep assessment tools and investigating different demographic and clinical features possibly associated with self-reported or objective EDS.

METHODS

The study had ethical approval by the local institutional review board (protocol number 2016-000601-36; IRB approval code 66B-032016). All participants signed consent to the study.

Patient population

Patients were recruited from the NEMO (NEuroMuscular Omni-service) Center in Milan and the Neuromuscular Diseases Unit in Rome, Tor Vergata University Hospital. Patient demographic, clinical, and anthropometric details were collected at each site.

Inclusion criteria for the patients were the following: (1) molecular diagnosis of DM1, any range of cytosine-thymine-guanine (CTG) expansion size (≥ 50), adult-onset type; (2) age range 18–65 years; (3) NIV-naive patients or patients who had not been using NIV for at least 3 months prior to enrollment; (4) Raw Mini–Mental State Examination (MMSE) > 20; and (5) Trail Making Test A and B and the Color Word Stroop Test within normal range according to age and education. Patients taking drugs that could interfere with cognition, breathing, or sleep function were excluded (eg, steroids, antidepressants, benzodiazepines, taurine, antiepileptic drugs).

All patients were subjected to a complete battery of respiratory assessments to identify the presence of a possible chronic respiratory insufficiency requiring NIV. Sleep tests to assess the presence of EDS included polysomnography (PSG) followed by MSLT. The Epworth Sleepiness Scale (ESS) was used as the patient-reported measure of EDS. Neuromotor and cognitive assessments were also collected as well as measures of quality of life (QoL) perception.

Tests and procedures

A brief outline of the tests and procedures performed is given below.

Sleep tests

PSG

A standard overnight full PSG was performed with a portable device (Embla Polysomnography System, Respironics) in an unattended setting. In accordance with standard criteria[25,26] the recording included the following: electroencephalography (at least 6 channels), bilateral electro-oculography, chin and tibial electromyography, electrocardiography, oronasal airflow, chest and abdominal effort (recorded using respiratory inductance plethysmography), pulse oximetry, and sensor of body position. PSG traces were manually reviewed by a medical doctor expert in sleep medicine, certified by the Italian Association of Sleep Medicine and the European Sleep Research Society. Sleep was staged and respiratory and motor events scored according to standard criteria.[26] The following data were recorded: total sleep time, sleep efficiency, arousal index, percentage of sleep period for every sleep stage and wake (N1, N2, N3, rapid eye movement [REM], wake after sleep onset [WASO]), sleep latency, apnea-hypopnea index (AHI), oxygen desaturation index, mean oxygen saturation, minimal oxygen saturation, saturation time < 90%, periodic leg movement (PLM) index.

MLST

The test measures the propensity for falling asleep in a comfortable situation lying in bed in a dark and quiet room with the explicit permission to fall asleep. MSLT was conducted in the sleep laboratory the day after nocturnal PSG in accordance with a standardized protocol.[27] MSLT sessions took place at 9 and 11 AM and at 1, 3, and 5 PM. Patients, retired to a quiet, dark room and laying on a bed, were asked to try to fall asleep. EDS was defined when the mean sleep latency was ≤ 8 minutes. SOREMP was defined as the occurrence of 1 or more epochs of REM sleep within 15 minutes from sleep onset.

Sleep diary and 1-week actigraphy

Patients were encouraged to keep a regular sleep-wake schedule during the week before the MSLT, to limit the possibility that EDS could be induced by sleep deprivation. Specifically, adequate sleep was documented by a sleep diary the week before the MSLT and, when available, by an actigraphic recording for a period of 1 week. In particular, in a subgroup of patients, a watch-shaped unit (Actiwatch; Philips) was worn on the wrist of the non-dominant arm for 7 days. Data were recorded continuously and then analyzed using Actiware 6.02 software. In the analyses of records, the recommended algorithm for sleep scoring every

30-second epoch was used. Event markers determined the length of time spent in bed. In the case of missing event markers, sleep diary data were used. The extracted outcomes were total sleep time and sleep efficiency, time in bed, and time out of bed.

Respiratory assessments

Forced spirometry (forced vital capacity sitting and supine and the difference between these 2 measures) and respiratory muscle pressures (muscle inspiratory pressure, muscle expiratory pressure) assessments were performed according to the American Thoracic Society standards.[28] Peak cough expiratory flow was performed according to standard procedures.[29] The best value was recorded. The test was considered to be well performed and reliable when the difference between the measurements was not greater than 20 L/minute.

Fatigue and EDS assessments

To determine self-reported EDS and general fatigue, the Italian Version of ESS[30] and the Fatigue Sleepiness Scale (FSS) and Fatigue and Daytime Sleepiness Scale (FDSS)[5,31,32] were used. Patients scoring 11 or more on the ESS were considered to have self-reported EDS.

QoL perception

QoL perception was evaluated through the Italian version of the Short Form-36 Health Survey[33] and the Individualized Quality of Life (INQoL) questionnaire.[34]

Statistical analysis

Shapiro-Wilk test and Levene test were used for each variable included in the analysis, to assess the normality of the distribution and the homogeneity of variance, respectively.

Data were summarized using median and interquartile range for continuous variables and number and percentage for categorical ones.

Comparisons of demographic and clinical characteristics, disease characteristics, fatigue assessments, QoL perceptions, cognitive and behavioral aspects, and respiratory features between nonsleepy and sleepy patients in accordance with the ESS, and between nonsleepy and sleepy patients in accordance with the MSLT, were assessed using the Mann-Whitney test and the chi-square test as appropriate.

To test the degree of agreement between the ESS and the MSLT in classifying nonsleepy and sleepy patients, the Cohen's κ coefficient was used and was interpreted in accordance with McHugh.[35]

To test the ability of both MSLT and ESS to screen patients with respiratory abnormalities requiring NIV adaptation, the concepts of sensibility and negative predictive value were taken into account, arbitrarily considering as more appropriate the assessment that maximizes sensitivity and negative predicted value, giving greater importance to the potential screening purpose of MSLT and ESS.

To assess the difference in terms of total sleep time and sleep efficiency between patients with DM1 and a group of age- and sex-matched healthy controls using the actigraphy data, the Mann-Whitney test was used. Tests were 2-tailed, and a P value < 0.05 was considered statistically significant. All the analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patient population

Sixty-three patients with adult-onset DM1 were included (median age of 43.7 years [37.0–55.1], 30 men [48%], median CTG range of 184.0 [150.0–575.0]). All were ambulant, the majority with a Muscular Impairment Rating Scale of 2 (n = 16), 3 (n = 20), or 4 (n = 21). Only 4 patients had a Muscular Impairment Rating Scale of 1 and 2 of 5. Disease duration ranged from 7.2 years to 20.5 years, with a median disease duration of 12 years. In general, patients were slightly overweight (median body mass index, 25.1 kg/m^2; range, 22.7–27.9). None were hypothyroid. Ten patients were taking mexiletine as an antimyotonic agent.

Demographic and clinical details of the cohorts of patients with and without EDS determined either by MSLT or ESS are summarized in **Table 1**.

EDS

EDS was determined by ESS and MSLT in all participants. ESS was abnormal (ESS score > 10) in 21 of 63 (33.3%) patients, while MSLT proved to be abnormal (mean sleep latency ≤ 8 minutes) in 30 out of 63 (47.6%) patients screened. Concordance between abnormal ESS and MSLT results was present in 13 patients (20.6% of the overall population), while 25 (39.7%) patients proved to be abnormal in either one or the other (**Figure 1**). The degree of agreement between ESS and MSLT in terms of Cohen's κ coefficient resulted equal to 0.19 (−0.04 to 0.43]. Patients with objective EDS during MSLT displayed a shorter disease duration with respect to those without EDS (10 [6–17] vs 15 [11–22] years; $P < .05$). No other significant difference in the demographic and clinical characteristics was found between the cohorts with or without EDS as assessed by MSLT or by ESS.

Nine of the 30 patients with abnormal mean sleep latency at MSLT, had 2 or more sleep-onset REM periods (SOREMPs) during MSLT and/or PSG. Four additional patients without objective EDS had 2 or more SOREMPs (**Table 2**). The shortest sleep latency across MSLT naps was observed during the second nap both in patients with and without objective EDS (**Table 2**).

PSG results

Results for all 63 patients are summarized in **Table 3**. Forty-three patients (68%) displayed a sleep-related breathing disorder (AHI ≥ 5 events/h) that was mild in 16 patients (5 ≤ AHI < 15 events/h), moderate in 16 patients (15 ≤ AHI < 30 events/h), and severe in 7 patients (AHI ≥ 30 events/h). The PLM index was ≥ 15 in 7 patients (11.1%). Patients with objective EDS on MSLT showed a statistically significant increase in sleep efficiency (86.00% [79.80–92.10%] vs 81.60% [64.80–87.50%]; $P = .01$) and increase in total sleep time (428.00 [334.00–457.00] vs 346.00 [299.00–415.00] minutes; $P = .01$) and decrease in WASO (13.03 [6.70–18.37] vs 18.63 [10.30–31.10] minutes; $P = .04$) with respect to patients without objective EDS. Comparing PSG parameters in patients with or without self-reported EDS, the percentage of N1 was

Table 1—Demographic and clinical characteristics of the study cohort.

	Overall (n = 63)	MSLT Scores <8 (n = 30)	MSLT Scores ≥8 (n = 33)	ESS Scores >10 (n = 21)	ESS Scores ≤10 (n = 42)
Demographic and clinical features					
Age at screening, y	43.7 [37.0–55.6]	40.9 [33.0–51.5]	47.1 [39.6–58.6]	40.1 [36.3–51.3]	46.4 [38.2–55.6]
Male/female, n/n	30/33	13/17	17/16	9/12	21/21
BMI, kg/m^2	25.1 [22.7–27.9]	25.1 [22.1–28.2]	25.1 [23.7–27.7]	24.2 [22.0–27.4]	25.5 [23.7–28.4]
Disease characteristics					
MIRS, n (%)					
1	4 (6.3)	3 (10.0)	1 (3.0)	2 (9.5)	2 (4.8)
2	16 (25.4)	7 (23.3)	9 (27.3)	5 (23.8)	11 (26.2)
3	20 (31.7)	12 (40.0)	8 (24.2)	10 (47.6)	10 (23.8)
4	21 (33.3)	7 (23.3)	14 (42.4)	4 (19.0)	17 (40.5)
5	2 (3.2)	1 (3.3)	1 (3.0)	0 (0.0)	2 (4.8)
Disease duration, y	12.0 [7.2–20.5]	10.0 [6.0–17.0]*	15.0 [11.0–22.0]*	12.0 [7.0–18.0]	13.0 [8.0–21.0]
CTG range	184.0 [150.0–575.0]	150.0 [140.0–434.0]	250.0 [150.0–733.7]	150.0 [130.0–542.0]	250.0 [150.0–575.0]
Respiratory assessments					
% FVC seated	79.00 [65.00–90.00]	82.00 [73.00–90.00]	75.00 [63.00–89.00]	80.00 [67.50–98.00]	79.00 [65.00–89.00]
% FVC supine	74.00 [60.00–82.00]	77.00 [67.00–82.00]	69.00 [53.00–84.00]	75.00 [63.50–90.00]	73.50 [58.00–81.00]
MIP, cmH20	55.50 [39.00–75.00]	56.00 [44.00–66.00]	54.00 [37.00–78.00]	50.50 [38.00–69.00]	58.00 [44.00–78.00]
MEP, cmH20	54.00 [38.00–75.00]	50.00 [38.00–64.00]	54.00 [31.00–86.00]	55.00 [41.50–84.00]	54.00 [32.00 - 68.00]
PCEF, L/min	392.40 [330.00–480.60]	369.00 [297.60–528.00]	404.00 [333.60–469.80]	339.60 [272.40–412.00]	439.80 [349.80–514.20]
Fatigue					
FSS	40.00 [26.00–51.00]	42.00 [30.00–51.00]	39.00 [18.00–55.00]	49.00 [38.00–55.00]*	37.00 [20.00–50.00]*
FDSS	10.00 [6.00–13.00]	9.50 [7.00–12.00]	11.00 [5.00–13.00]	13.00 [10.00–16.00]*	8.00 [5.00–11.00]*
QoL perception					
INQoL total score	33.00 [17.20–47.20]	34.15 [21.70–41.70]	32.20 [17.20–51.70]	40.00 [28.30–47.20]	31.25 [15.60–40.00]
INQoL Fatigue	57.90 [42.10–68.40]	57.90 [47.40–68.40]	57.90 [36.80–68.40]	57.90 [57.90–73.70]	50.00 [31.60–63.20]
INQoL Activity	38.90 [16.70–52.80]	41.65 [19.40–52.80]	36.10 [10.20–58.30]	43.50 [30.60–52.80]	34.25 [13.90–53.50]
SF-36 Mental Component Summary score	52.00 [38.00–58.00]	52.00 [38.00–73.00]	47.00 [37.00–55.00]	44.00 [36.00–55.00]	52.00 [41.00–62.00]
SF-36 Physical Component Summary score	45.00 [33.00–56.00]	44.50 [33.00–63.00]	45.00 [34.00–55.00]	38.00 [33.00–55.00]	45.00 [36.00–56.00]

All data are represented as median and interquartile range, except where otherwise indicated. *Statistically significant comparison ($P < .05$). BMI = body mass index, CTG = cytosine-thymine-guanine, ESS = Epworth Sleepiness Scale, FDSS = Fatigue and Daytime Sleepiness Scale, FSS = Fatigue Severity Scale, FVC = forced vital capacity, INQoL = Individualized Neuromuscular Quality of Life questionnaire, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, MIRS = Muscular Impairment Rating Scale, MSLT = Multiple Sleep Latency Test, PCEF = peak cough efficacy flow, SF-36 = Short Form-36 Health Survey.

significantly lower in patients with EDS (3.26% [1.61–5.15%] vs 4.75% [3.45–7.60%]). No other significant difference was found in respiratory or limb movement PSG features between patients with or without objective or self-reported EDS. Two patients displayed SOREMPs during PSG recording. Both of them showed a mean sleep latency less than 8 minutes during MSLT but they did not report self-reported EDS (ESS ≤ 10).

Respiratory involvement

Of the 63 patients included in the study and subjected to respiratory screening protocols, 16 had an indication to use NIV at night (25%). Functional objective respiratory parameters (forced vital capacity, muscle inspiratory pressure, muscle expiratory pressure, and peak cough expiratory flow) did not differ between participants with DM1 with either self-reported or objective sleepiness (**Table 1**).

Actigraphy

Actigraphy was recorded in 23 of 30 patients having objective EDS on MSLT, based on the availability of the instruments. Results were compared with 17 age- and sex-matched historical controls from the Sleep Units in Milan and Rome. Patients with

DM1 showed a statistically significant increase in mean total sleep time with respect to controls (460.1 [426–502] vs 418.7 [379.8–438] minutes in controls; $P = .03$). Sleep efficiency was slightly decreased in patients with DM1 with respect to control participants (84.18% in patients with DM1 vs 88.47% in controls), yet this was not statistically significant ($P = .08$). There was a trend for patients to go to bed later (mean time into bed: DM1 = 01:18:00 vs controls = 00:26:08) and woke up in the morning later than controls (mean time out of bed: DM1 = 08:40:30 vs controls = 07:31:30), although this was not statistically significant ($P = .08$).

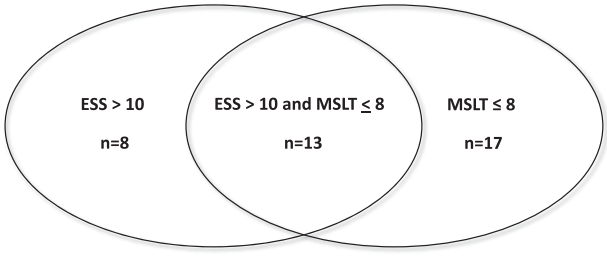
EDS and fatigue

No significant difference in terms of FSS and FDSS was found between patients with and without EDS assessed by MSLT. Considering EDS assessed by ESS, patients with EDS reported a significantly higher FSS and FDSS score compared with patients without EDS (49.00 [range, 38.00–55.00] vs 37.00 [range, 20.00–50.00], respectively; $P = .0286$ for FSS; 13.00 [range, 10.00–16.00] vs 8.00 [range, 5.00–11.00], respectively; $P < .01$ for FDSS) (**Table 1**).

QoL assessments

QoL perception as determined by the INQoL questionnaire (the higher the score the worse the perception) was the same irrespective of EDS assessed by MSLT and ESS ($P = .57$ and $P = .15$, respectively). In particular, neither the total score nor the scores on the subscales differed in the cohort with and without EDS as assessed by MSLT. The subscore Fatigue in the INQoL was higher in the patients reporting EDS on the ESS with respect to those without self-reported ESS (63.2 [57.9–73.7] vs 47.4 [34.2–43.5], respectively; $P = .042$). No difference was detected using the SF-36 mental and physical scores in patients with EDS measured by MSLT or ESS (**Table 1**).

Figure 1—Concordance between MSLT and ESS in the assessment of EDS.



EDS = excessive daytime sleepiness, ESS = Epworth Sleepiness Scale, MSLT = Multiple Sleep Latency Test.

DISCUSSION

This study confirms that EDS is a common complaint in patients with DM1, but the prevalence changes according to the test used. Indeed, between one-third and one-half of patients reported self-reported or objective EDS, respectively. Moreover, our results showed a low concordance between self-reported (ESS) or objective (MSLT) measures, in line with previous studies.[36,37] ESS has a major advantage over the MSLT in its very low cost and ease of administration; however, some authors underlined that this questionnaire may not be the most sensitive tool to assess daytime sleepiness in DM1.[5,38] Also, one may question the ability of patients with DM1 to be aware of their sleepiness and therefore fill in the questionnaire in a reliable way. In our study we included patients with scores on MMSE, the Trail Making Test, and the Colored Word Stroop Test within a normal range, thus reducing

Table 2—Multiple Sleep Latency Test features.

	MSLT ≤ 8	MSLT > 8
No. of SOREMPs, n (%)		
0	13 (43.33)	26 (78.79)
1	8 (26.67)	3 (9.09)
2*	5 (16.67)	4 (12.12)
3	1 (3.33)	0 (0.00)
4**	3 (10.00)	0 (0.00)
5	0 (0.00)	0 (0.00)
Mean sleep latency, median [IQR]		
Nap 1 (9 AM)	6.00 [3.75–9.00]	20.00 [10.25–20.00]
Nap 2 (11 AM)	4.00 [3.00–5.75]	10.50 [7.63–15.00]
Nap 3 (1 PM)	5.50 [4.13–7.75]	13.50 [10.00–18.00]
Nap 4 (3 PM)	6.00 [4.00–6.75]	11.50 [9.00–17.00]
Nap 5 (5 PM)	5.75 [4.63–8.00]	11.50 [9.00–14.00]

*Of the 4 patients having 2 SOREMPs, 1 had 1 SOREMP on PSG. **Of the 3 patients having 4 SOREMPs, 1 had 1 SOREMP on PSG. IQR = interquartile range, MSLT = Multiple Sleep Latency Test, PSG = polysomnography, SOREMP = sleep-onset rapid eye movement period.

Table 3—Descriptive analysis of the polysomnography data (n = 63).

	Overall (n = 63)	MSLT Scores < 8 (n = 30)	MSLT Scores ≥ 8 (n = 33)	ESS Scores > 10 (n = 21)	ESS Scores ≤ 10 (n = 42)
Sleep efficiency, %	84.65 [72.30–90.00]	86.00 [79.80–92.10]*	81.60 [64.80–87.50]*	84.75 [78.80–90.70]	84.65 [66.40–89.70]
Arousal index	12.50 [9.20–17.00]	11.80 [8.80–18.40]	12.95 [10.45–16.75]	13.10 [9.50–15.00]	12.40 [9.10–18.90]
TST, min	376.70 [312.50–447.00]	428.00 [334.00–457.00]*	346.00 [299.00–415.00]*	386.70 [312.75–460.50]	374.00 [312.50–431.70]
N1, % of sleep period	4.35 [2.69–6.20]	4.03 [2.69–5.60]	4.70 [3.45–9.40]	3.26 [1.61–5.15]*	4.75 [3.45–7.60]*
N2, % of sleep period	25.40 [21.00–32.90]	27.50 [22.41–33.67]	24.83 [17.96–32.26]	24.85 [21.50–35.22]	26.40 [18.40–32.40]
N3, % of sleep period	29.54 [21.87–35.87]	32.80 [25.10–37.02]	26.15 [20.70–33.42]	33.40 [21.39–38.60]	27.43 [22.60–33.60]
REM, % of sleep period	19.50 [14.70–25.83]	20.80 [16.42–26.20]	19.05 [11.97–24.00]	18.27 [13.42–23.47]	20.98 [14.80–26.50]
WASO, % of sleep period	15.36 [7.90–27.70]	13.03 [6.70–18.37]*	18.63 [10.30–31.10]*	14.24 [5.85–21.41]	15.61 [10.00–33.00]
Sleep latency, min					
N1	9.80 [3.50–21.30]	6.00 [3.60–17.00]	11.50 [3.50–29.80]	11.50 [3.50–22.30]	9.65 [3.40–21.30]
N2	16.55 [6.50–27.20]	17.25 [7.65–22.75]	16.30 [4.95–36.95]	14.40 [4.60–20.00]	17.00 [7.00–28.50]
N3	30.05 [17.95–60.60]	30.70 [18.95–53.50]	29.10 [15.30–70.00]	24.80 [12.90–65.50]	32.40 [19.00–58.80]
REM, min	87.75 [70.00–132.00]	90.25 [75.00–129.50]	81.00 [69.00–134.00]	120.00 [79.00–149.50]	81.50 [69.50–122.50]
< 15 minutes, n (%)	2 (3.33)	2 (7.14)	0 (0.00)	0 (0.00)	2 (4.88)
≥ 15 minutes, n (%)	58 (96.67)	26 (92.86)	32 (100.00)	19 (100.00)	39 (95.12)
AHI, events/h	10.80 [3.70–22.00]	8.65 [2.20–21.60]	14.70 [5.50–22.40]	7.30 [3.70–17.40]	14.20 [4.00–27.50]
≤ 5 events/h, n (%)	20 (31.75)	12 (40.00)	8 (24.24)	8 (38.10)	12 (28.57)
5–15 events/h, n (%)	16 (25.40)	7 (23.33)	9 (27.27)	6 (28.57)	10 (23.81)
15–30 events/h, n (%)	16 (25.40)	8 (26.67)	8 (24.24)	5 (23.81)	11 (26.19)
> 30 events/h, n (%)	11 (17.46)	3 (10.00)	8 (24.24)	2 (9.52)	9 (21.43)
ODI	9.80 [2.00–19.20]	7.35 [1.40–18.50]	13.50 [4.50–22.50]	4.30 [1.10–12.10]*	14.15 [3.30–22.60]*
Mean O_2 saturation, %	93.00 [91.00–95.10]	93.10 [92.00–95.70]	93.00 [90.00–95.00]	93.80 [92.30–95.20]	92.20 [89.00–95.00]
Minimal O_2 saturation, %	85.00 [74.00–88.00]	86.00 [74.00–90.00]	83.00 [73.00–88.00]	86.00 [78.00–89.00]	82.50 [73.00–88.00]
PLM index	2.50 [0.70–5.90]	2.35 [0.75–5.55]	2.50 [0.00–5.90]	1.45 [0.00–5.60]	3.20 [0.90–5.90]
< 15, n (%)	52 (88.14)	26 (92.86)	26 (83.87)	19 (95.00)	33 (84.62)
≥ 15, n (%)	7 (11.86)	2 (7.14)	5 (16.13)	1 (5.00)	6 (15.38)

All data are represented as median and interquartile range, except where otherwise indicated. *Statistically significant comparison. AHI = apnea-hypopnea index, ESS = Epworth Sleepiness Scale, MSLT = Multiple Sleep Latency Test, ODI = oxygen desaturation index, PLM = periodic limb movement, REM = rapid eye movement, TST = total sleep time, WASO = wake after sleep onset.

the risk of misunderstanding the questions on the ESS. Similarly, none of our patients were depressed or anxious based on the Hamilton Depression Scale and the Profile of Mood States (data not reported), again lowering the possibility that responses were biased by mood or behavioral abnormalities. Another explanation for the weak correlation between MSLT and ESS results could be related to the difficulty for the patients to self-reportedly discriminate between sleepiness and fatigue,[5,31,32] another common complaint in this population.[6,34] Consistently with this hypothesis, in our cohort, fatigue was similar in patients with and without EDS when this was objectively assessed with the MSLT; on the other hand, patients reporting EDS by self-reported assessments (ESS scores) had a higher perception of fatigue compared with those without EDS. Analogously, previous studies in patients with DM1 found higher levels of fatigue in patients with EDS, as measured by self-reported measures;[5,31,32] conversely, EDS was higher in patients with excessive fatigue. This emphasizes the importance of defining what is meant by EDS, specifically pointing to the need to distinguish it from fatigue,[39] and to address it as the patient's propensity to sleep across a variety of situations in normal life and specifically unrelated to physical disability.

From a clinical point of view, patients with DM1 frequently describe EDS features more similar to those reported by patients affected by SRDB than by patients with narcolepsy. Indeed, DM1-related EDS occurs prevalently in monotonous situations or when attention is not being held and is unaffected by naps; moreover "sleep attacks" are rarely reported. However, our sleep studies aimed at characterizing the nature of sleepiness frequently showed results that resembled those observed in patients with primary narcolepsy. Indeed, we found that 9 of the 30 patients with EDS at MSLT and 4 patients without objective EDS had 2 or

more SOREMPs during MSLT and/or PSG. These observations, in line with previous findings,[4,9,16,40] support an REM sleep dysregulation in these patients. Moreover, patients having EDS by MSLT displayed higher total sleep time and sleep efficiency and lower WASO on PSG with respect to patients without EDS. Thus, sleep deprivation seems not to be claimed as a possible cause of EDS in these patients. Other reports have already documented a longer habitual nocturnal sleep in patients with DM1 with respect to control participants.[7,16,41] Therefore, the association of long total sleep time, short sleep-onset latency, and multiple SOREMPs—highly suggestive for central hypersomnia—could suggest a "sleepy intrinsic phenotype," similar to that observed in other neurological disease, such as Parkinson's disease.[42]

We found that 68% of our patients was affected by SRDB (AHI >5 events/h). This prevalence is concordant with data from the literature, ranging from 15% to 86%.[8,19,43,44] The role of the presence of an SRDB in the pathogenesis of EDS in this specific population represents a highly debated topic. On one hand, recurrent respiratory and hypoxemia events could induce sleep fragmentation, thus favoring EDS.[18] However, different studies failed to reveal a direct correlation between sleepiness and SRDB[4,14,16,42] or between SRDB severity, daytime pulmonary function test results, and EDS in patients with DM1.[9,16,21] In our work, we did not find any difference in SRDB prevalence or in functional objective respiratory parameters between patients with or without self-reported or objective EDS, supporting the hypothesis that SRDB does not always explain EDS. Similarly to SRDB, PLMs are also frequently reported in patients with DM1, although the correlation between PLMs and EDS in DM1 is still controversial.[9] In our cohort we found a PLM index that was greater than 15 events/h only in 11.1% of patients and there was no difference between patients with or without self-reported or objective EDS, so that it is unlikely that PLMs caused significant sleep disruption to justify EDS.

To date, this is the first study applying actigraphy recording to evaluate sleep in a DM1 population, although actigraphy was recorded only in a minority of patients with DM1 with objective EDS. With respect to a control population, we showed an increase in total sleep time and a tendency to an increase in sleep efficiency in patients compared with control participants. These results seem to be in line with data of PSG already discussed. Moreover, there was a trend showing that patients tended to go to bed and wake up in the morning later than controls. This observation could suggest a possible alteration of the circadian rhythm as a further factor contributing to EDS pathogenesis.[45] As already observed by Bonanni and coworkers,[18] our patients with DM1 showed the lowest latency in the second session of the MSLT and not during the third or the fourth sessions as usually occurs in the general population according to the circadian sleep propensity. Thus, a sleep-wake rhythm disorder could also contribute to EDS in DM1 and should be further investigated.

Our study could not identify distinguishing demographic and clinical features among sleepy patients with DM1,[46] except for a shorter disease duration in patients with DM1 with objective EDS.

As patients included in our study had, in general, a relatively short CTG repeat expansion (median CTG = 184) our results might not be applicable to patients with DM1 with larger repeat-size expansions. On the other hand, choosing a less severe population may have reduced the risk of introducing additional EDS-promoting variables related to multiorgan impairment. Yet, despite the short expansion size, EDS was present in at least one-third of our patients and one-third of our patients had moderate–severe muscle weakness (21 patients with Muscular Impairment Rating Scale = 4 and 2 = 5). This suggests that, although progression of EDS over time has been reported to be modulated by CTG size, psychological distress, and body mass index,[46] its presence may be independent from muscle impairment and general disability, at least at baseline and in some patients.

Finally, it is worth underlining that the patients' perception of QoL was not affected by the presence or absence of EDS, supporting the hypothesis that QoL perception is multifactorial and cannot be related to 1 symptom, although predominant and of high impact.[34]

Many of our results replicated findings already reported in previous studies, although conducted in smaller cohorts of patients. Our study was partially limited by the complexity and number of procedures. From a technical point of view, we used unattended home portable PSG in order to give patients the opportunity to be registered in their natural environment. Moreover, with the aim of ensuring a high rate of adherence to the burden of procedures, we selected only adult patients without cognitive or psychiatric impairment. Therefore, given these inclusion criteria, our data may not be transferable to the whole population of patients with DM1.

In conclusion, our study provides some points of discussion that could be useful for designing a pharmacological trial on EDS in DM1. We can conclude that the ESS is easy to administer and low-cost and, if coupled to a quantitative sleep test like MSLT, it may reduce the possibility of excluding sleepy participants with either test. Also, our respiratory results seem to suggest that EDS is mostly of central origin. Anyway, we recommend always including respiratory function tests in the assessment of EDS to screen for patients having an indication for NIV. Finally, there seems to be no main significant difference in QoL perception, so that it is hard to conceive a way to monitor the impact of drugs acting on EDS from a QoL perception. Although actigraphy data did not differ between sleepy patients and controls, this cohort was too small to draw definitive conclusions. This technique is well tolerated and is a relatively low-cost procedure, which could be applied in a larger cohort of, maybe less selected, patients. The actigraphic studies, even associated with other tests (such as melatonin dosage), could be useful to investigate a possible circadian rhythm disorder. Moreover, actigraphy could be also applied to measure activity levels, an indirect indicator of social functioning. Thus, this technique may allow verifying whether changes with treatment, if any, are clinically meaningful to these patients who may potentially become more active and better functioning because they are less sleepy.

ABBREVIATIONS

AHI, apnea-hypopnea index
CTG, cytosine-thymine-guanine

DM1, myotonic dystrophy type 1
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
FDSS, Fatigue and Daytime Sleepiness Scale
FSS, Fatigue Sleepiness Scale
INQoL, Individualized Quality of Life
MSLT, Multiple Sleep Latency Test
NIV, noninvasive ventilation
PLM, periodic leg movement
PSG, polysomnography
QoL, quality of life
REM, rapid eye movement
SOREMP, sleep-onset rapid eye movement period
WASO, wake after sleep onset

REFERENCES

1. Harper HG. *Myotonic Dystrophy.* Philadelphia: WB Saunders; 2001.
2. Vanacore N, Rastelli E, Antonini G, et al. An age-standardized prevalence estimate and a sex and age distribution of myotonic dystrophy types 1 and 2 in the Rome Province, Italy. *Neuroepidemiology.* 2016;46(3):191–197.
3. Johnson NE. Myotonic muscular dystrophies. *Continuum (Minneap Minn).* 2019;25(6):1682–1695.
4. Yu H, Laberge L, Jaussent I, et al. Daytime sleepiness and REM sleep characteristics in myotonic dystrophy: a case-control study. *Sleep.* 2011;34(2):165–170.
5. 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(10):1403–1405.
6. Heatwole C, Bode R, Johnson N, et al. Patient-reported impact of symptoms in myotonic dystrophy type 1 (PRISM-1). *Neurology.* 2012;79(4):348–357.
7. Laberge L, Bégin P, Montplaisir J, Mathieu J. Sleep complaints in patients with myotonic dystrophy. *J Sleep Res.* 2004;13(1):95–100.
8. Romigi A, Izzi F, Pisani V, et al. Sleep disorders in adult-onset myotonic dystrophy type 1: a controlled polysomnographic study. *Eur J Neurol.* 2011;18(9):1139–1145.
9. Laberge L, Gagnon C, Dauvilliers Y. Daytime sleepiness and myotonic dystrophy. *Curr Neurol Neurosci Rep.* 2013;13(4):340–349.
10. Park JD, Radtke RA. Hypersomnolence in dystrophia myotonica. *J Neurol Neurosurg Psychiatry.* 1995;58(4):512–513.
11. Rubinsztein JS, Rubinsztein DC, Goodburn S, Holland AJ. Apathy and hypersomnia are common features of myotonic dystrophy. *J Neurol Neurosurg Psychiatry.* 1998;64(4):510–515.
12. Ashizawa T. Myotonic dystrophy as a brain disorder. *Arch Neurol.* 1998;55(3):291–293.
13. Kierkegaard M, Harms-Ringdahl K, Widén Holmqvist L, Tollbäck A. Perceived functioning and disability in adults with myotonic dystrophy type 1: a survey according to the International Classification of Functioning, Disability and Health. *J Rehabil Med.* 2009;41(7):512–520.
14. van der Meché FG, Bogaard JM, van der Sluys JC, Schimsheimer RJ, Ververs CC, Busch HF. Daytime sleep in myotonic dystrophy is not caused by sleep apnoea. *J Neurol Neurosurg Psychiatry.* 1994;57(5):626–628.
15. Bégin P, Mathieu J, Almirall J, Grassino A. Relationship between chronic hypercapnia and inspiratory-muscle weakness in myotonic dystrophy. *Am J Respir Crit Care Med.* 1997;156(1):133–139.
16. Phillips MF, Steer HM, Soldan JR, Wiles CM, Harper PS. Daytime somnolence in myotonic dystrophy. *J Neurol.* 1999;246(4):275–282.
17. Laberge L, Bégin P, Dauvilliers Y, et al. A polysomnographic study of daytime sleepiness in myotonic dystrophy type 1. *J Neurol Neurosurg Psychiatry.* 2009;80(6):642–646.
18. Bonanni E, Carnicelli L, Crapanzano D, et al. Disruption of sleep-wake continuum in myotonic dystrophy type 1: Beyond conventional sleep staging. *Neuromuscul Disord.* 2018;28(5):414–421.
19. West SD, Lochmüller H, Hughes J, et al. Sleepiness and sleep-related breathing disorders in myotonic dystrophy and responses to treatment: a prospective cohort study. *J Neuromuscul Dis.* 2016;3(4):529–537.
20. Spiesshoefer J, Runte M, Heidbreder A, et al. Sleep-disordered breathing and effects of non-invasive ventilation on objective sleep and nocturnal respiration in patients with myotonic dystrophy type I. *Neuromuscul Disord.* 2019;29(4):302–309.
21. Kiyan E, Okumus G, Cuhadaroglu C, Deymeer F. Sleep apnea in adult myotonic dystrophy patients who have no excessive daytime sleepiness. *Sleep Breath.* 2010;14(1):19–24.
22. Boentert M, Cao M, Mass D, et al. Consensus-based care recommendations for pulmonologists treating adults with myotonic dystrophy type 1. *Respiration.* 2020;99(4):360–368.
23. Annane D, Moore DH, Miller RG. Psychostimulants for hypersomnia (excessive daytime sleepiness) in myotonic dystrophy. *Cochrane Database Syst Rev.* 2006;(3):CD003218.
24. Hilton-Jones D, Bowler M, Lochmueller H, et al. Modafinil for excessive daytime sleepiness in myotonic dystrophy type 1–the patients' perspective. *Neuromuscul Disord.* 2012;22(7):597–603.
25. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep.* 2005;28(4):499–521.
26. Berry RB, Brooks R, Gamaldo CE, et al; for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*, Version 2.2. Darien, IL: American Academy of Sleep Medicine; 2015.
27. Littner MR, Kushida C, Wise M, et al; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep.* 2005;28(1):113–121.
28. American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med.* 2002;166(4):518–624.
29. Chatwin M, Toussaint M, Gonçalves MR, et al. Airway clearance techniques in neuromuscular disorders: a state of the art review. *Respir Med.* 2018;136:98–110.
30. Vignatelli L, Plazzi G, Barbato A, et al; GINSEN (Gruppo Italiano Narcolessia Studio Epidemiologico Nazionale. Italian version of the Epworth sleepiness scale: external validity. *Neurol Sci.* 2003;23(6):295–300.
31. Gallais B, Gagnon C, Forgues G, Côté I, Laberge L. Further evidence for the reliability and validity of the Fatigue and Daytime Sleepiness Scale. *J Neurol Sci.* 2017;375:23–26.
32. Hermans MC, Merkies IS, Laberge L, Blom EW, Tennant A, Faber CG. Fatigue and daytime sleepiness scale in myotonic dystrophy type 1. *Muscle Nerve.* 2013;47(1):89–95.
33. Ware JE Jr, Kosinski M, Gandek B, et al. The factor structure of the SF-36 Health Survey in 10 countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol.* 1998;51(11):1159–1165.
34. Sansone VA, Panzeri M, Montanari M, et al. Italian validation of INQoL, a quality of life questionnaire for adults with muscle diseases. *Eur J Neurol.* 2010;17(9):1178–1187.
35. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb).* 2012;22(3):276–282.
36. Chervin RD. The multiple sleep latency test and Epworth sleepiness scale in the assessment of daytime sleepiness. *J Sleep Res.* 2000;9(4):399–401.
37. Mehra R, Wang L, Andrews N, et al. Dissociation of objective and subjective daytime sleepiness and biomarkers of systemic inflammation in sleep-disordered breathing and systolic heart failure. *J Clin Sleep Med.* 2017;13(12):1411–1422.

38. Hilton-Jones D, Damian MS, Meola G. Somnolence and its management. In: Harper P, van Engelen B, Eymard B, Wilcox D, eds. *Myotonic Dystrophy: Present Management, Future Therapy.* Oxford, UK: Oxford University Press; 2004:1–7.
39. Laberge L, Dauvilliers Y, Bégin P, Richer L, Jean S, Mathieu J. Fatigue and daytime sleepiness in patients with myotonic dystrophy type 1: to lump or split? *Neuromuscul Disord.* 2009;19(6):397–402.
40. Dauvilliers YA, Laberge L. Myotonic dystrophy type 1, daytime sleepiness and REM sleep dysregulation. *Sleep Med Rev.* 2012;16(6):539–545.
41. 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(1):68–75.
42. Arnulf I, Leu-Semenescu S. Sleepiness in Parkinson's disease. *Parkinsonism Relat Disord.* 2009;15(Suppl 3):S101–S104.
43. Pincherle A, Patruno V, Raimondi P, et al. Sleep breathing disorders in 40 Italian patients with Myotonic dystrophy type 1. *Neuromuscul Disord.* 2012;22(3):219–224.
44. Bianchi MLE, Losurdo A, Di Blasi C, et al. Prevalence and clinical correlates of sleep disordered breathing in myotonic dystrophy types 1 and 2. *Sleep Breath.* 2014;18(3): 579–589.
45. Romigi A, Albanese M, Liguori C, Placidi F, Marciani MG, Massa R. Sleep-wake cycle and daytime sleepiness in the myotonic dystrophies. *J Neurodegener Dis.* 2013; 2013:692026.
46. Laberge L, Gallais B, Auclair J, Dauvilliers Y, Mathieu J, Gagnon C. Predicting daytime sleepiness and fatigue: a 9-year prospective study in myotonic dystrophy type 1. *J Neurol.* 2020;267(2):461–468.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December 31, 2020
Submitted in final revised form May 16, 2021
Accepted for publication May 17, 2021
Address correspondence to: Valeria A. Sansone, MD, PhD, Centro Clinico Nemo, Neurorehabilitation Unit, University of Milan, Piazza Ospedale Maggiore, 3, 20162 Milan, Italy; Tel: ++ 349 5607450; Email: valeria.sansone@centrocliniconemo.it; valeria.sansone@unimi.it

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The study was funded by a Telethon-UILDM (Italian Muscular Dystrophy Association) grant (GUP15004) given to V.A. Sansone. The authors report no conflicts of interest.