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SLEEP (M THORPY AND M BILLIARD, SECTION EDITORS)

Comparative Sleep Disturbances in Myotonic Dystrophy Types 1 and 2

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Abstract

Purpose of Review To update current knowledge regarding sleep disturbances and myotonic dystrophies so as to better understand if sleep symptoms may help in the early recognition of the two genetic subtypes: myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2).

Recent Findings Sleep-disordered breathing (SDB), restless legs syndrome, periodic limb movements in sleep, hypersomnia, and REM sleep dysregulation are frequently described in DM1 patients. SDB does not always explain hypersomnia, but a central dysregulation of sleep–wake modulation is reported mainly in DM1. Sleep apnea, restless legs syndrome, and REM sleep without atonia have been reported in single case reports and small case series of DM2.

Summary DM2 is less prevalent and more recently described than DM1, with a milder phenotype than DM1. The most frequent sleep disorders in DM1 are hypersomnia, SDB, periodic limb movements, and a narcoleptic-like phenotype, whereas restless legs syndrome, SDB, and REM sleep without atonia seem to be the most frequent sleep disorders in DM2. Comparative sleep studies are strongly required to delineate the sleep phenotype of myotonic dystrophies.

Keywords Myotonic dystrophy type 1 · Myotonic dystrophy type 2 · Excessive daytime somnolence · Fatigue · Sleep · Sleep-disordered breathing

Introduction

Myotonic dystrophies are autosomal dominant genetic disorders characterized by progressive and multisystemic involvement, including myopathy, myotonia, cardiomyopathy, endocrine abnormalities, and neuropsychological deficits [1]. Myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2) are the two clinical, histopathological, and genetic forms of myotonic dystrophy, although these entities show an overlap in the clinical features [2]. Sleep disorders are highly reported in neuromuscular diseases as probable causes of death and morbidity [3•]. Persistent and transient sleep hypoxemia due to sleep-disordered breathing (SDB) may induce cardiovascular and pulmonary failure. Furthermore, sleep fragmentation and diurnal somnolence may impair frailty and affect psychiatric and cognitive functioning [3•]. Sleep disorders and hypersomnia are described mainly in DM1 [4]. Hypersomnia has been mentioned in some anecdotal reports of myotonic dystrophy, and this condition was usually considered secondary to hypercapnia [5–7]. The most represented sleep disorders in DM1 are obstructive sleep apnea associated with sleep hypoxia and hypercapnia and central hypersomnia, rapid eye movement (REM) sleep dysregulation (i.e., narcoleptic-like phenotype), and periodic limb movements in sleep (PLMS) [8–11]. Sleep–wake cycle circuits may be modulated in DM1 as shown by the reduced cerebrospinal fluid (CSF) levels of orexin A and the reduction of serotoninergic neurons of dorsal raphe nucleus [12–14, 15•]. Also, the severity of SDB, fatigue, and REM sleep alterations seem to be unrelated to somnolence, whereas central sleep–wake dysfunction may explain these findings [8–10, 16]. Data regarding sleep disorders in patients with DM2 are scarce, mainly because of its recent genetic definition and its

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low prevalence in some countries [17]. SDB, sleepiness [8, 18, 19, 20•], restless legs syndrome (RLS) [21, 22], and REM sleep disorders [9, 18] were further described also in DM2, although few polysomnographic studies are available. DM1 and DM2 are characterized by a significant clinical variability of muscular and nonmuscular manifestations, although several symptoms may be comparable [23]. In this narrative review, we highlight current knowledge regarding sleep disturbances and myotonic dystrophies to better understand if sleep symptoms may help to recognize and diagnose both subtypes at an early stage.

Genetic Features of DM 1 and DM2

DM1 was first described by Steinert in 1909, while the gene encoding myotonic dystrophy protein kinase (*DMPK*) that is responsible for DM1 was discovered in 1992 [24, 25]. DM1 is associated with an expansion of a CTG trinucleotide repeat in the *DMPK* gene on chromosome band 19q13.3. In 1994 an autosomal dominant myotonia with prevalent proximal weakness, muscle pain, stiffness, multisystemic involvement (cognitive dysfunction, hypersomnia, tremor, and hearing loss), and early cataracts without a CGT repeat in the *DMPK* gene was firstly described [26, 27]. In 2002 a new mutation of the zinc finger protein 9 gene (*CNBP*) mapped to 3q21.3 was observed in DM2 [28–30]. A CCTG repeat expansion in the *CNBP* gene, located on chromosome band 3q21.3 and encoding a ubiquitous protein, has been identified in DM2 [28, 29, 31]. Mutations of *DMPK* and *CNBP* induce the formation of transcript aggregates in the nucleus, which interfere with proteins involved in RNA metabolism. Sequestration or inappropriate phosphorylation of these proteins leads to misplacement of several downstream effector genes and causes loss of function of genes, including those encoding insulin receptor, the chloride channel, and cardiac troponin T [2]. This phenomenon is potentially a significant player in DM1/DM2 pathological mechanisms, and it leads to the multiorgan involvement/multisystemic phenotype [2, 23]. The severity of the disease differs by the number of CTG repeats. In particular, the *DMPK* gene of healthy individuals contains between 5 and 38 CTG repeats, whereas genes harboring between 39 and 50 repeats are considered premutation alleles. Severely affected individuals have a *DMPK* gene with 50 to several thousand repeats. In line with this, disease severity increases and the age of onset decreases with increasing number of repeats [2, 23]. Unlike in DM1, in DM2 the number of repeats is not associated with disease severity and does not show anticipation [1, 2, 23]. Crude prevalence estimates of molecularly defined DM1 range between 0.43 and 158 per 100,000 in different populations, with the Taiwanese lying at the lower end of this range and French Canadians of northeastern Quebec at the higher end of it; in the latter population a founder effect appears to have played a role in increasing the frequency of mutant alleles. The recent characterization and difficulty in diagnosing DM2 explain the paucity of data on the prevalence of this neglected disorder. A recent study reported DM1 and DM2 age-standardized prevalences of 9.65 per 100,000 and 0.99 per 100,000, respectively [32••]. DM2 prevalence rates are tenfold lower than those of DM1. Later onset of symptoms and less evident clinical presentation may somewhat explain this difference, leading to a greater diagnostic delay for DM2.

Clinical Features of DM 1 and DM2

The primary clinical manifestations of DM1 are facial and distal muscle weakness and wasting, together with grip and percussion myotonia. Conduction abnormalities, arrhythmias, and conduction blocks are the main cardiac manifestations and increase morbidity and mortality associated with DM1 [33–35]. Furthermore, several patients develop posterior subcapsular cataracts. Cognitive deficits and obsessive–compulsive and passive–aggressive personality traits have also been reported [36, 37]. Obstructive and central sleep apnea and diurnal drowsiness are frequently described in DM1. Gastrointestinal tract involvement includes irritable bowel syndrome, symptomatic gallstones, and γ-glutamyltransferase level elevations. Endocrine manifestations (i.e., testicular atrophy, adrenal insufficiency, insulin resistance, type 2 diabetes, thyroid dysfunction, and vitamin D deficiency) have been reported [23]. Although DM1 and DM2 are similar in molecular pathological features, the clinical entities are quite different. Distinctive clinical features of DM2 include less severity, proximal weakness, and lack of prominent muscle wasting. Moreover, common clinical symptoms of DM1 such as facial weakness, respiratory insufficiency, and a congenital form are not described in DM2 [38]. However, differential diagnosis between DM1 and DM2 is frequently challenging, and a genetic test is mandatory to clarify the diagnosis [1, 23, 29, 39].

Fatigue and Sleepiness: Two Sides of the Same Coin in Myotonic Dystrophies?

The third edition of the *International Classification of Sleep Disorders* [40] defines sleepiness as the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep. On the other hand, fatigue is also defined as a reversible decline in motor and cognitive capacities associated with decreased motivation and increased need to rest [41]. Although these two definitions may seem different, when you ask a sleepy or a fatigued person how he or she feels, both will likely say "I am tired." "Fatigue" and

"sleepiness" may be interchangeable in common language but also in the medical literature. Sleepiness, sleep disorders, and fatigue are common clinical features of several neurological and neuromuscular diseases, including myotonic dystrophies. Fatigue and excessive daytime sleepiness (EDS) are common clinical symptoms of DM1, and occur in 62.5% and 30–39% of patients, respectively [42–44, 45•]. These manifestations may account for social isolation, depression, and low quality of life (QoL) [45•, 46–48]. Fatigue is evident as a subjective deficiency of physical and/or mental energy, and is more frequent in DM1 than in other neuromuscular disorders [49]. SDB, chronic hypercapnia, and depression slightly explain EDS [45•, 48, 50–52]. Yet, fatigue and EDS share common, overlapping features frequently associated with DM1 [44, 49]. In a large DM1-patient-reported survey, the prevalence of fatigue was 90.2% and that of EDS was 87.9% [53]. Although DM2 is less severe than DM1, fatigue seems to be highly reported. A large survey of DM2 patients by Heatwole et al. [54•] reported fatigue in 89.2% of the DM2 patients and sleep disturbances or daytime drowsiness in 77% of the DM2 patients. They found the highest life impact scores for sleepiness and fatigue. Also, women with DM2 were more severely affected by impaired sleep or daytime sleepiness and fatigue, even though the study might be biased by registry-based design, a higher female prevalence, and the lack of information regarding treatment that may modulate the main clinical symptoms of DM2 (i.e., pain, fatigue, and EDS). Recently, the incidence of diurnal somnolence, as measured through the Daytime Sleepiness Scale, was significantly higher in DM1 patients (50%) than in DM2 patients (27%), and the incidence of fatigue was higher in DM1 patients (65.9%) than in DM2 patients (47.8%) without reaching statistical significance [55•]. Also, EDS was recently related to disease-specific QoL measures in childhood-onset DM1 [56]. These findings confirm previous data [57] obtained with SF-36, a not-disease-specific QoL questionnaire. Impairment of QoL was evident in both DM1 and DM2 patients compared with healthy controls although DM2 patient scores did not differ from DM1 patient scores. In the DM2 group, the severity of pain was significantly correlated with QoL scores for pain. Fatigue was significantly correlated with the SF-36 scores for physical functioning, general health, and vitality [57]. Low levels of interleukin-6 were described in DM1 patients [58]; interleukin-6 may modulate fatigue in neuromuscular disease and sleep disorders[59, 60, 61••]. Patients with myotonic dystrophies possibly experienced fatigue, which may be referred to as EDS.

SDB in DM1 and DM2

Hypoventilation and obstructive and central sleep apneas have been repeatedly described in myotonic dystrophies [7, 10, 16, 62–64]. SDB may be explained by the weakness and myotonia of respiratory muscles and the altered central control of ventilation. Although this hypothesis is not completely clarified, earlier studies suggest that reduced respiratory muscle strength itself does not account for the presence of SDB in myotonic dystrophies [8, 9]. A different pathogenesis is supported by neuropathology studies that reported a severe neuronal loss in medullary nuclei associated with breathing function in DM1 patients with alveolar hypoventilation [66] (see Fig. 1). Furthermore, EDS and hypercapnia do not seem to be linked, because DM1 patients with sleepiness may exhibit normal CO_2 levels [62, 63]. Inversely, abatement of alveolar hypoventilation occasionally induces elimination of EDS [6, 7]. SDB in DM1 patients has long been documented and is a key feature of the clinical picture, with prevalence in DM1 ranging from 15% to 86% [10, 64, 67–70]. Their clinical impact should not be overlooked, considering that the severity of obstructive sleep apnea has been correlated with frontal–subcortical modifications (anatomical or functional), decreased psychomotor speed, and executive dysfunction in DM1 [70] similarly to the general population [71]. Daytime somnolence is a puzzling issue in myotonic dystrophies. Recurrent and brief hypoxemias may account for sleep fragmentation, high arousability, increased cyclic alternating pattern, and overall "sleep instability" that may affect sleep resilience [65, 72••, 73•]. Nevertheless, several authors failed to demonstrate a direct correlation between sleepiness and SDB [8, 9, 16, 52, 74] or between the severity of SDB, daytime pulmonary function test results, and EDS in DM1 [16, 51, 62,

Fig. 1 Factors predisposing patients with myotonic dystrophies to sleep-disordered breathing (SDB) [65]

63, 75]. Less sleep time and lower sleep efficiency, an increase of wakefulness after sleep onset, and an increase of REM sleep latency were also shown in DM1 patients with SDB compared with DM1 patients with PLMS [Periodic Limb Movement Index (PLMI) greater than 5/h] or no sleep disorders [10]. In a sample of 43 DM1 patients without selection bias, low mean sleep latencies as shown by the Multiple Sleep Latency Test (MSLT) were correlated to the higher severity of diurnal hypercapnia, breathing muscle weakness, and lung volume restriction [16]. Also, SDB severity was statistically related to lung and vital capacity, even though these pulmonary measurements accounted for low variability of the apnea–hypopnea index (AHI; 16%) [16]. Recently, a prospective uncontrolled study in a large sample of DM1 patients with sleepiness (Epworth Sleepiness Scale score greater than 9) showed EDS in the DM1 group with obstructive sleep apnea (21 of 120 participants), in the daytime respiratory failure group (33 of 120 participants), and also in the normal sleep group (36 of 120 participants) even though EDS was evaluated only by the Epworth Sleepiness Scale, which is not considered an adequate tool [45•, 76]. Since DM2 was recently recognized, few polysomnographic studies have been performed, and the real magnitude of SDB in DM2 patients is not well documented. However, DM2 patients exhibited EDS, poor sleep quality, decreased sleep efficiency, SDB, and diaphragmatic weakness [8, 18, 20•, 67]. Patients with DM2 also had lower respiratory volumes and pressures, abnormalities in the arterial gas analysis results, night oxygen desaturation, and higher end-tidal CO_2 pressure [21] but they were less pronounced than in the DM1 population [20•]. Sleep apnea defined as AHI greater than 5/h [77] was reported in 6 of 16 DM2 patients (38%) [20•], 6 of 14 DM2 patients (42.8%) [67], 7 of 12 DM2 patients (58%) [18], and 3 of 5 DM2 patients (60%) [19] and was mainly due to obstructive apnea without evidence of sleep-related hypoxia suggestive of clinically significant hypoventilation [18, 19, 20•, 67]. Therefore few data are available regarding the impact of SDB in DM2. Firstly, SDB and diurnal tiredness were highly reported in a small sample of patients with DM2. Phrenic compound motor action potential amplitudes, an indicator of diaphragm weakness, below normal values were found in DM2 patients and correlated with respiratory functions and sleep quality [20•]. Very recently, Banach et al. [78] described a correlation between SDB and peripheral neuropathy where the amplitude of the ulnar sensory nerve action potential (SNAP) was related to nocturnal mean arterial oxygen saturation in both DM1 and DM2, and the median sensory nerve action potential was related to AHI in DM1 and mean oxygen saturation in DM2. They proposed a possible role of neuropathy inducing SBD by muscle weakness [78]. Although DM2 was poorly evaluated and hypoventilation was not detected, sleep studies should be performed to confirm the high prevalence of SDB in DM2 and its role in sleepiness and sleep fragmentation. Comparative sleep studies in DM1 and DM2 are summarized in Table 1.

RLS and PLMS in DM1 and DM2

RLS and PLMS were described in both DM1 and DM2 [8]. Laberge et al. [43] found no significant differences between DM1 patients with and DM1 patients without

Table 1 Comparative studies on sleep disorders in myotonic dystrophies

Sleep disorder	DM1	DM2	Reference	Tool
Fatigue	90.2%	89.2%	[53, 54•]	Interview, C (DM1 vs HS; DM2 vs HS)
	65.9%	47.8%	[55•]	DSS, FSS, In-QoL, C (DM2, DM1)
EDS	87.9%	77%	[53, 54•]	Interview, C (DM1 vs HS; DM2 vs HS)
	50%	27%	[55•]	DSS, FSS, In-QoL, C (DM2, DM1)
	44.8%	6.9%	[79]	PSQI, ESS (DM1, DM2, HS)
	16.6%	33%	[18]	PSG, MSLT, PSQI, DSS, C (DM1, DM2, HS)
	60%	45%	[20•]	PSG, interview, C (DM1, DM2, HS)
	21.1%	14.3%	[67]	HST, ESS, C (DM1, DM2)
SDB	69%	43%	[67]	HST, ESS, C (DM1, DM2)
	27.7%	58%	[18]	PSG, MSLT, PSQI, DSS C (DM1, DM2, HS)
	61%	38%	[20•]	PSG, interview C (DM1, DM2, HS)
PLMS	25%	11.1%	[18]	PSG, MSLT, PSQI, DSS, C (DM1, DM2, HS)
RBD and/or RSWA	0%	50%	[18]	PSG, MSLT, PSQI, DSS, C (DM1, DM2, HS)

C controlled study, *DM1* myotonic dystrophy type 1, *DM2* myotonic dystrophy type 1, *HS* Healthy Subjects, *DSS* Daytime Sleepiness Scale, *EDS* excessive daytime somnolence, *ESS* Epworth Sleepiness Scale, *FSS* Krupp's Fatigue Severity Scale, *HS*, *HST* home sleep test, *In-QoL* Individualized Neuromuscular Quality of Life Questionnaire, *MSLT* Multiple Sleep Latency Test, *PLMS* periodic limb movements in sleep, *PSG* polysomnography, *PSQI* Pittsburgh Sleep Quality Index, *RBD* REM sleep behavior disorders, *RSWA* REM sleep without atonia, *SDB* sleep-disordered breathing

control for RLS. In childhood-onset DM1, 38% of DM1 patients (8/21) had a PLMI greater than 5/h (mean PLMI 15.5/h) [80]. More than half of DM1 patients had a PLMI greater than 5/h, and 40% had a PLMI greater than 10/h; an association between DM1 and RLS was found in 22.5% of DM1 patients versus none in the control group [9]. Also, DM1 patients with RLS had the highest PLMI [9]. PLMI greater than 5/h was found in 61.1% of DM1 patients [10], suggesting that higher PLMI may represent a polysomnographic marker in adult-onset DM1 [8–10] as well as in childhood-onset DM1 [80]. Nevertheless, similarly to SDB, a relationship between RLS, PLMS with or without arousals, and subjective EDS (Epworth Sleepiness Scale, Daytime Sleepiness Scale) and objective EDS (MSLT) was not reported. Lastly, PLMS were frequently found in DM1, but their clinical consequences are still uncertain, with a negligible potential effect on EDS. Although the high frequency of PLMS should be confirmed with the most recent cut-off (PLMI greater than 15/h), PLMS should be suspected since this sleep-related movement disorder may increase cardiovascular risk because of nocturnal periodic-limb-movement-induced autonomic activation [81••, 82••]. On the other hand, RLS and PLMS were not prominent in a DM1 patient with sleepiness [14], where the mean PLMI was 7.2/h, with all patients having a PLMI below 21/h. No patients with RLS were reported, and sleepiness and REM sleep dysregulation were not correlated with reduced CSF orexin levels [14]. Although RLS and primary CNS hypersomnia, including narcolepsy-like symptoms, have been described in DM1, few data have been reported regarding DM2. Shepard et al. [19] firstly described RLS in DM2 in a small uncontrolled series. Four of eight DM2 patients had RLS, and low ferritin levels were found in two of the four patients. Three of the four patients with RLS had a mean PLMI of 19/h (range 8–32/h). Therefore two of the eight DM2 patients (25%) had primary RLS. The mean age of this group was high (62 years; range 43–82 years); therefore RLS *prevalence* was higher than the expected prevalence in the general elderly population [83]. Besides, DM2 patients may report having *RLS mimics* (i.e., myalgias, chronic pain, fibromyalgia) [23], which may bias the results from this study. After this first report, the same group published an observational questionnaire-based study [21]. They evaluated 30 DM2 patients (mean age 63 years) and 44 age-and sex-matched healthy controls by a comprehensive battery of subjective scales for sleep quality (Pittsburgh Sleep Quality Index), sleepiness (Epworth Sleepiness Scale, Daytime Sleepiness Scale), sleep apnea (sleep apnea scale of the Sleep Disorders Questionnaire), RLS (Cambridge-Hopkins diagnostic questionnaire for RLS); fatigue (Krupp's Fatigue Severity Scale), and REM sleep behavior disorders (Mayo Sleep Questionnaire). They found a higher significant RLS prevalence in DM2 patients (60%, 18/32) compared with healthy controls (14%, 6/43). They highlighted that RLS was the most relevant sleep disorder in DM2, more so than obstructive sleep apnea, which would be represented in DM2 similarly as in healthy controls. However, this study was biased by the lack of polysomnographic data and a probable underrating of SDB in DM2 patients [21, 22, 84]. The lack of studies comparing RLS prevalence in DM1 and DM2 does not allow one to conclude that there is higher RLS prevalence in DM2; also, two polysomnography-controlled studies did not report RLS in small samples of DM1 and DM2 patients [18, 20•].

REM Sleep Alterations and Other Polysomnographic Abnormalities in Myotonic Dystrophies

REM sleep alterations are frequent findings in DM1 patients [8, 9, 11, 16]. Several authors showed the appearance of sleep-onset REM periods (SOREMPs) during night polysomnography and the MSLT in DM1 patients and pathological mean sleep latencies, describing a *narcoleptic-like* phenotype and orexin (hypocretin) CSF deficiency [13, 14, 73•, 85]. The presence of at least two SOREMPs was similar in DM1 patients with EDS (33–60%) [13, 74, 85] and in DM1 patients not selected for EDS (25–50%) [9, 14, 16]. Also, the number and the presence of SOREMPs were related to younger age, less diurnal sleep, lower nocturnal REM sleep latencies, milder oxygen desaturation, and worse muscular involvement [9, 14]. Diurnal somnolence and SOREMPs were common features of DM1 and narcolepsy where low CSF orexin levels were observed. Previous studies reported reduced CSF orexin levels also in DM1 patients, but the results are inconsistent [13, 14, 86]. In a first study, low CSF orexin levels in DM1 patients were found [13], but this finding was not confirmed in a second CSF study in DM1 patients [14]. Very recently a moderate decrease of CSF orexin levels was reported in a small retrospective cohort of DM1 patients (17 patients with ESD) compared with patients with narcolepsy and idiopathic hypersomnia [15•]. The detection limits for orexin were arbitrarily defined as low (110 pg/mL or less), intermediate (more than 110 pg/mL to 200 pg/mL or less), or normal (more than 200 pg/mL). Four DM1 patients had undetectable orexin levels, whereas three DM1 patients had intermediate levels. The remaining ten DM1 patients (58%) had normal values. Further REM sleep alterations were described in DM1. High REM density (a twofold increase compared with controls), REM sleep without atonia (RSWA), and REM sleep phasic EMG activity in the absence of

Table 2 Sleep disorders and myotonic dystrophy type 2 (DM2)

Sleep findings	Study design	Participants	Reference	Tool
EDS: 6.9% of DM2 patients, 44.8% of DM1 patients, 6.2% of controls Poor sleep quality: 66% of DM2 patients, 45% of DM1 patients, 26% of controls	P, C, subjective scales	29 DM2 patients, 29 DM1 patients, 65 controls	[79]	Subjective scales
RSWA with dream-enacting behavior in OSA patients after CPAP[a]	Single case report, sleep disorder, DM2	1 DM2 patient	[88]	Video PSG
EDS: 75% (6/8) Insomnia: 62.5% (5/8) Excessive fatigue 50% (4/8) OSA: 60% (3/5) RLS: 50% (4/8)	R, U, sleep disorders, DM2	8 DM2 patients (5/8 PSG)	[19]	PSG study
EDS: 100% (6/6); 66.7% (4/6) low MSL, no SOREMPs Insomnia: 33.3% (2/6) Snoring: 66.7% (4/6) OSA: 66.7% (4/6) RSWA with dream-enacting behavior in OSA patients after CPAP: 16.7% (1/6)[a] Paradoxical breathing in REM sleep: 33.3% (2/6) RSWA: 16.7% (1/6) Low sleep efficiency—alpha–delta sleep: 33.3% (2/6)	P, U, sleep disorders, DM2	6 DM2 patients (6/6 PSG)	[65]	PSG study
RLS: 60% of DM2 patients (18/30) vs 14% of controls (6/43) (S) EDS (DSS): 13/30 43.3% of DM2 patients vs 7% of controls (3/43) (S) Poor sleep quality (PSQI): 66.7% of DM2 patients (20/30) vs 46.5% of controls (20/43) (NS) OSA (Sa-SDQ): 13.3% of DM2 patients (4/30) vs 14% of controls (6/43) (NS)	P, C, DM2 patients vs controls	30 DM2 patients, 43 controls	[21]	Interview, subjective scales
Pain-related sleep disturbance (PSQI): 58.3% of DM2 patients (7/12) EDS (subjective scales): 16.7% of DM2 patients (2/12); MSLT 33.3% of DM2 patients (4/12) no SOREMPs Snoring: 16.7% of DM2 patients (2/12) Low sleep efficiency (PSG): 100% of DM2 patients OSA: 58.3% of DM2 patients (7/12) PLMS (PLMI > 15/h): 25% of DM2 patients (3/12) RSWA with dream-enacting behavior in severe OSA: 8.3% of DM2 patients (1/12) Paradoxical breathing in REM sleep: 8.3% of DM2 patients (1/12) RSWA: 50% of DM2 patients (6/12)	P, C, DM2 patients vs DM1 patients and controls	12 DM2 patients, 18 DM1 patients, 12 controls	[18]	PSG and subjective scales
OSA: 69% of DM1 patients (49/71), 42.9% of DM2 patients (6/14) Poor sleep quality (PSQI): 42.9% of DM2 patients (6/14), 47.9% of DM1 patients (34/71) EDS (ESS score >9): 14.3% of DM2 patients (2/14), 21.1% of patients DM1 (15/71)	P, U, DM2 patients vs DM1 patients	14 DM2 patients, 71 DM1 patients	[67]	HST and subjective scales (PSQI, ESS)
OSA: 59.2% of DM1 patients (16/27), 37.5% of DM2 patients (6/16)	P, C, DM2 patients and DM1 patients vs controls	16 DM2 patients, 27 DM1 patients, 16 healthy controls	[20•]	PSG, phrenic motor nerve conduction studies

C controlled, *CPAP* continuous positive airway pressure, *DM1* myotonic dystrophy type 1, *DSS* Daytime Sleepiness Scale, *EDS* excessive daytime somnolence; *ESS* Epworth Sleepiness Scale, *HST* home sleep test, *MSLT* Multiple Sleep Latency Test, *MSL* mean sleep latency at MSLT, *OSA* obstructive sleep apnea; *PLMI* Periodic Limb Movement Index, *PLMS* periodic limbs movements in sleep, *PSQI* Pittsburgh Sleep Quality Index, *P* prospective, *PSG* polysomnography, *R* retrospective, *RLS* restless legs syndrome, *RSWA* REM sleep without atonia, *Sa-SDQ* sleep apnea scale of the Sleep Disorders Questionnaire, *SOREMPs* sleep-onset REM periods, *U* uncontrolled

[a] Probably the same patient

clinically confirmed REM sleep behavior disorder were noted [9]. Although all these results did not clarify the clinical significance of REM sleep alterations, they may support the suggestion of a "central" REM sleep dysregulation in DM1 [11, 16]. REM sleep dysregulation was also described in DM2. Small case series [87] and single case reports [88] described RSWA with dream-enacting behavior in obstructive sleep apnea patients after continuous positive airway pressure (16.7%, 1/6) and RSWA (16.7%, 1/6). The first controlled polysomnographic study reported a high prevalence of RSWA in DM2 patients (50%, 6/12; one of the six patients had RSWA with dream-enacting behavior associated with severe obstructive sleep apnea, and three of the six patients had RSWA associated with mild to moderate obstructive sleep apnea) versus zero prevalence in DM1 patients [10]. The pathogenesis of RSWA in DM2 patients may only be speculated. RSWA may represent a compensatory and protective mechanism against sleep apnea as suggested by Huang et al. [89]. We can also hypothesize that brainstem and diencephalon involvement (i.e., pedunculopontine and laterodorsal tegmental nuclei) may play a role inducing activated behavioral states during REM sleep [90]. Very recently Cheung et al. [91•] found an increase of EEG nocturnal theta relative power in DM1 patients during sleep stage N2 and increased theta/beta and theta/alpha power spectral ratios compared with healthy individuals during all sleep stages without any REM sleep dysregulation. They suggested that these quantitative EEG changes may reflect disease-specific alterations of the sleep modulatory networks [91•]. On the other hand, Bonanni et al. [73•] confirmed central sleep dysregulation. They found REM sleep alterations as expressed by SOREMPs and increased nocturnal REM sleep duration but they also found an increase of sleep instability as shown by high cyclic alternating pattern and slower delta power nocturnal dissipation [73•].

Conclusion

DM1 and DM2 are quite different: DM2 is less prevalent and more recently described than DM1 and has a milder and more varied phenotype than DM1. The most frequent sleep disorders are hypersomnia, SDB, PLMS, REM sleep alterations (i.e., SOREMP, increased REM sleep duration, high REM density; narcoleptic-like phenotype) in DM1 [8–11], whereas RLS, SDB, and RSWA seem to be the most frequent sleep disorders in DM2 [18, 21, 22, 67]. However, very few polysomnographic data are available regarding sleep and DM2 (see Table 2), and larger comparative sleep studies regarding DM1 and DM2 are strongly required to delineate the clinical phenotype of myotonic dystrophies better.

Compliance with Ethical Standards

Conflict of Interest AR has received personal fees from Eisai, Sandoz and UCB Pharma outside the submitted work. GV has received personal fees from Fidia Farmaceutici outside the submitted work. VF, FP, CL, ER, DC, and RM declare that they have no competing interests.

Human and Animal Rights This article does not contain any studies with humans or animals performed by any of the authors.

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