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SLEEP AND NEUROLOGICAL CONDITIONS (A AVIDAN, SECTION EDITOR)

Sleep Disturbances in Patients with Disorders of the Nerve and Muscle Diseases

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Abstract

Purpose of Review Recognize sleep disorders associated with neuromuscular diseases.

Recent Findings Neuromuscular diseases can be associated with various sleep disorders. Diaphragmatic weakness, bulbar dysfunction, pharyngeal neuropathy, and central neurodegeneration cause sleep-disordered breathing. Spinal cord hyperexcitability, loss of inhibitory descending pathways, and neuropathy promote restless legs syndrome. Reduced cerebrospinal fluid (CSF) hypocretin, central dysfunction of sleep regulation, and degeneration of GABAergic intracortical circuits may contribute to central hypersomnia. Dysfunction of the nigrostriatal dopaminergic system, associated with neurodegenerative diseases and certain neuromuscular disorders, may be a common pathophysiologic mechanism responsible for the loss of rapid eye movement (REM) sleep muscle atonia and REM sleep behavior disorder (RBD).

Summary Different neuromuscular disorder may be more susceptible to specific sleep disturbances. A low threshold needs to be maintained for the diagnosis and treatment of sleep disorders in neuromuscular diseases, due to their high prevalence, lack of symptom specificity, and presence even in minimally symptomatic patients. However, loss of REM atonia may be protective against sleep-disordered breathing. There are reasonable pathophysiologic mechanisms such as respiratory muscle weakness, upper airway obstruction, and central dysfunction that explain the link between sleep disorders and neuromuscular diseases

Keywords Neuromuscular diseases · Sleep-disordered breathing · Restless legs syndrome · Periodic limb movements · Disorders of excessive somnolence

Introduction

Neuromuscular diseases (NMD) encompass a diverse group of acquired or inherited disorders affecting the nerves, muscles, and the neuromuscular junction. Central to NMD is muscle weakness, with variable involvement of the respiratory muscles, associated with significant compromise in quality of life and premature death.

In this context, breathing is most vulnerable during rapid eye movement (REM) sleep where it depends on diaphragmatic function, when all other respiratory muscles are atonic [1]. Thus, diaphragm weakness is a critical vulnerability associated with nocturnal alveolar hypoventilation, oxygen desaturations, sleep fragmentation, and reduced sleep efficiency.

Other sleep disorders such as the restless legs syndrome (RLS), periodic limb movement disorder (PLMD), hypersomnia, and loss of REM atonia are common in NMD with a prevalence that exceeds that expected in the general population or from confounding by sequelae of NMD, reflecting shared pathophysiologic mechanisms. This review will cover various sleep disturbances in NMD, highlighting recent findings in the literature.

This article is part of the Topical Collection on *Sleep and Neurological Conditions*

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Sleep-Disordered Breathing

Pseudo-central and Diaphragmatic Sleep-Disordered Breathing

The most common sleep-disordered breathing (SDB) in the setting of NMD is "pseudo-central" or diaphragmatic SDB

(Table 1, Fig. 1) [2, 3]. Pseudo-central SDB refers to non-obstructive and non-central reductions in airflow due to diaphragmatic and extra-diaphragmatic muscle weakness, with or without hypoventilation, generally timed to REM sleep [4]. During polysomnography, reduced or absent excursion in thoracic and abdominal belts from respiratory muscle weakness may incorrectly suggest a central origin, thus the term pseudo-central. Yet, monitoring of inspiratory EMG activity demonstrates inspiratory effort during these pseudo-central events [5].

Pseudo-central breathing is the earliest manifestation of SDB in many NMD. Characteristically, it first surfaces in REM sleep when breathing is almost exclusively dependent on diaphragmatic function due to REM sleep muscle atonia [6]. As respiratory muscle weakness progresses, hypoventilation is also observed during NREM sleep. One study of 33 patients with various primary myopathies illustrates the natural evolution to hypercapnic respiratory failure in NMD [7]. While SDB was present in 78% of patients, only 6 patients had obstructive sleep apnea (OSA) (Table 2). The predominant finding in all subjects (with a spectrum of mild to severe ventilatory restriction) was hypopneas (defined in the study as a discernible reduction in airflow or thoracoabdominal effort lasting > 10 s accompanied by > 3% oxyhemoglobin desaturation) that evolved in three distinct patterns: hypopneas only during REM sleep, REM hypopneas with hypoventilation, and in those with worse restriction, continuous REM and non-REM hypoventilation. This "hypoventilation march" reflects gradual weakening of respiratory muscles, the major determinant of ventilatory compromise in NMD [8, 9•]. The result is hypoventilation throughout sleep and wakefulness, the latter defining the advent of hypercapnic respiratory failure.

Table 1 Sleep disturbances and their representative neuromuscular conditions and proposed contributing mechanisms

Sleep disturbance	Representative neuromuscular conditions	Proposed contributing mechanisms
Diaphragmatic breathing/hypoventilation	Most NMDs: diaphragm paralysis, amyotrophic lateral sclerosis, Duchenne muscular dystrophy and acid maltase deficiency (bimodal: late hypoventilation), myotonic dystrophy, spinal muscular atrophy, post-polio syndrome, myasthenia gravis, spinal cord injury	Diaphragm and respiratory muscle weakness
Obstructive sleep apnea	DMD and AMD (bimodal: early OSA) Charcot-Marie-Tooth (esp. CMT1) Amyotrophic lateral sclerosis, myasthenia gravis, poliomyelitis, and spinal-bulbar muscular atrophy Spinal cord injury	Upper airway muscle hypotonia, macroglossia, obesity due to corticosteroids in DMD Pharyngeal neuropathy Bulbar dysfunction Passive upper airway collapsibility
Central sleep apnea		
Periodic breathing	Amyotrophic lateral sclerosis	Degeneration of upper motor neurons efferent to the phrenic nerve or of Bötzinger complex
	Spinal cord injury	Increased plant gain
Cheyne-Stokes breathing	Duchenne muscular dystrophy and other muscular dystrophies	Increased controller gain, lower awake/sleep CO_2, circulatory time delay
Cheyne-Stokes breathing	Duchenne muscular dystrophy and other muscular dystrophies	Increased controller gain, lower awake/sleep CO_2, circulatory time delay
Central hypersomnia	Myotonic dystrophy (esp. type 1)	Central dysfunction of sleep regulation vs. narcolepsy equivalent
	Amyotrophic lateral sclerosis	Degeneration of inhibitory GABAergic intracortical circuits
Restless legs syndrome/periodic limb movement disorder	Amyotrophic lateral sclerosis	Spinal cord hyperexcitability, loss of inhibitory descending pathways
	Charcot-Marie-Tooth (esp. CMT2)	Axonal loss/neuropathy
	Sequelae of poliomyelitis	Inflammatory/autoimmune/disruption of dopaminergic pathways
REM sleep without atonia (RSWA)	Amyotrophic lateral sclerosis, myotonic dystrophy (especially type 2?)	Dysfunction of the nigrostriatal dopaminergic system

NMD neuromuscular diseases, *OSA* obstructive sleep apnea, *DMD* Duchenne muscular dystrophy, *AMD* acid maltase deficiency, *CMT1* Charcot-Marie-Tooth type 1, *CMT2* Charcot-Marie-Tooth type 2

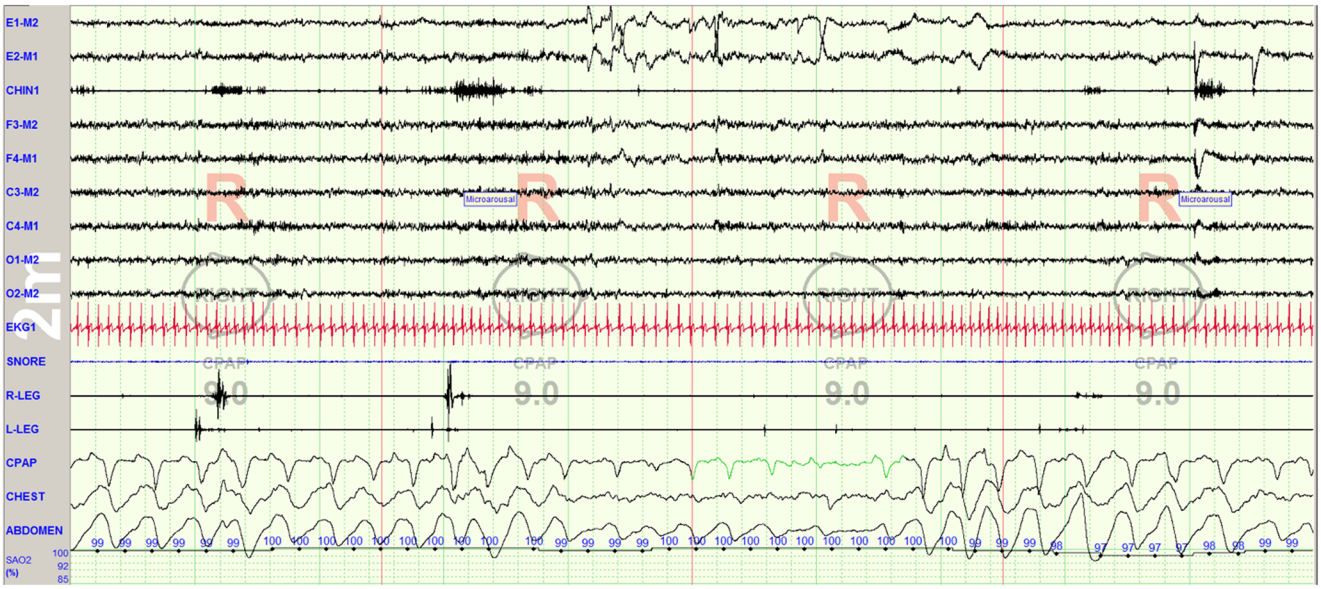

Fig. 1 A 57-year-old man with initial diagnosis of sleep apnea who underwent a CPAP titration study from which this 2-min epoch is extracted. He had been complaining of progressive upper extremity weakness, which led to a diagnosis of amyotrophic lateral sclerosis just 1 month after this titration. This epoch shows a reduction of chest wall excursion (CHEST channel) in the middle of the epoch, corresponding in onset and offset to sharp eye movements (E1-M2 and E2-M1 channels), raising concern for a neuromuscular etiology, especially given additional contexts of absence of snoring, absence of flow limitation, and absence of thoracoabdominal paradox with the event. Although his forced vital capacity was measured at 97% of predicted at the time of that sleep study, his respiratory function declined very rapidly and he died 1 year later

Obstructive Sleep Apnea

Nocturnal desaturation in neuromuscular disease is more likely to originate from diaphragmatic hypopneas and hypoventilation than upper airway obstruction. Assessing the true prevalence of OSA is complicated by the risk of event misclassification in the absence of diaphragmatic EMG or esophageal pressure monitoring, to ascertain the presence of inspiratory effort. Nevertheless, a combination of pathophysiological and structural features such as increased upper airway collapsibility due to reduced pharyngeal muscle tone, bulbar dysfunction, and pharyngeal neuropathy predispose specific neuromuscular disorders to obstructive events.

Certain primary myopathies, particularly Duchenne-type muscular dystrophy (DMD) and acid maltase deficiency (AMD), place patients with these conditions susceptible to developing obstructive respiratory disorders. In the case of DMD, OSA occurs in approximately 16 to 30% of patients [7, 10–12], perhaps due to reduced tone of the upper airway dilator muscles. Use of chronic corticosteroids contributes to central obesity, with studies supporting an association between the body mass index and the apnea hypopnea index (AHI) in DMD [13•], while one study found no correlation between truncal fat distribution, body mass index, and the AHI [14]. Nonetheless, effective treatment of SDB with positive airway pressure therapy may facilitate weight management [15]. Additionally, anatomical upper airway obstruction may be due to an enlarged tongue (macroglossia) in some individuals with DMD [16, 17]. Consequently, SDB in DMD is associated with poor sleep efficiency, increased REM sleep latency, and reduced REM sleep percentage [12]. As with many neuromuscular conditions, the earliest signs of respiratory failure appear during sleep, often before onset of daytime symptoms and hypercapnia [18].

The prevalence of OSA in DMD varies with age. Specifically, SDB in DMD has a bimodal distribution with susceptibility to obstructive events at a younger age and transition to hypoventilation later in life [11, 19]. For example, in a non-ambulatory cohort of patients with DMD [with a mean age of 15 years, (range 13–23)], 62% had nocturnal hypoxemia below 90% which consisted of obstructive (60%) and central (30%) events [19]. Ten of these patients had repeat sleep studies: while 90% had more frequent hypoxemic dips, in two patients, a dramatic fall in the proportion of obstructive apneas was observed within 3 years. Similarly, another study found that obstructive events are more prevalent at a younger age, whereas hypoventilation was more common in the second decade of life (median age 13) [11]. Correspondingly, in a small study of "older" individuals (mean age of 18 years), 4 out of 6 patients with DMD had symptoms suggestive of sleep-related respiratory disturbances, and although misclassification of pseudo-central events as central cannot be excluded, 85% of the apneas were categorized as central events [20].

AMD shares this bimodal age distribution. Several studies support a high prevalence of OSA, particularly in the most severe infantile-onset AMD. This is probably due to a combination of facial myopathy, tongue and bulbar weakness, and macroglossia, which together predispose to the downward

Table 2 Neuromuscular conditions and polysomnography observations

Condition	Characteristic sleep disturbances and prevalence
Mixed primary myopathies	Overall SDB prevalence 78%
	Progression from REM-associated hypopneas to hypoventilation correlates with worse ventilatory restriction
DMD	SDB prevalence 62%; OSA prevalence of 16 to 30%
	OSA is more common in younger patients, while hypoventilation is more common after the second decade of life
AMD	SDB prevalence of 41 to 50% in juvenile and adult-onset AMD
	OSA is more common in infantile-onset AMD with transition to hypoventilation later in life
Myotonic dystrophy	SDB prevalence from 15 to 85% in DM1 and from 38 to 65% in DM2
	Most studies report the predominant SDB being OSA, while others report a higher prevalence of central events
	PB prevalence of 12.5%
	RLS in 23% of DM1
	RSWA in 50% of DM2
Charcot-Marie-Tooth	OSA prevalence from 42 to 79% in CMT1
	RLS prevalence 10 to 41%
Amyotrophic lateral sclerosis	SDB prevalence up to 82%, predominantly pseudo-central breathing; OSA is considered rare
	CSA in > 25% of patients with preserved diaphragm function
	RLS prevalence is 25%; PLM is strongly associated with RLS in ALS
	RSWA in 9.7%
Spinal cord injury	Cervical cord injury: OSA 33%, CSA 63%, PB 88%
	Thoracic cord injury: OSA 25%, CSA 13%, PB 38%

SDB sleep-disordered breathing, *OSA* obstructive sleep apnea, *DMD* Duchenne muscular dystrophy, *AMD* acid maltase deficiency, *CMT1* Charcot-Marie-Tooth type 1, *DM* myotonic dystrophy, *RLS* restless leg syndrome, *PB* periodic breathing, *CSA* central sleep apnea, *RSWA* rapid eye movement sleep without atonia, *PLM* periodic limb movement

displacement of the tongue towards the pharynx (glossoptosis) [21•, 22]. Moreover, lysosomal glycogen that accumulates in the tongue may not respond to enzyme replacement therapy, as it does with other tissues in the body [23]. In 17 patients with predominantly classic infantile-onset AMD (mean age at time of polysomnography of 8 months), mild to moderate OSA on polysomnography was found in 41% of patients, potentially underestimated due to concurrent oxygen use in 4 patients, and hypoventilation in 37.5% [21]. In contrast, in 27 patients with later juvenile and adult-onset AMD, SDB was present in nearly half, but only 3 had polysomnographic findings compatible with OSA [24]. A small study disclosed REM and NREM sleep apneas and hypopneas in all four patients with childhood-onset AMD, including in one asymptomatic patient with no clinical evidence of muscle weakness [25].

Obstructive sleep events may also occur in patients with myotonic dystrophy (DM), possibly due to facial, jaw, pharyngeal, and laryngeal muscle weakness [26]. Others propose a role for peripheral neuropathy in inducing SDB [27•]. Several studies confirm a high prevalence of SDB in myotonic dystrophy type 1 (DM1), with a wide prevalence ranging from 15 to 85% [26, 28•], including in patients without excessive daytime sleepiness [29]. The prevalence of SDB in the milder form myotonic dystrophy type 2 (DM2) ranges between 38 and 65% [28, 30, 31]. In this context, most studies report that the predominant SDB in DM is OSA [26, 29, 31, 32]. However, objective measurement of inspiratory effort show that obstructive events represent the minority of SDB in myotonic dystrophy, found in only 3 of the 7 patients who had SDB and of those, only up to 15% of apnea events were obstructive [33]. Additional reports have similarly found a high or even predominant pattern of central apneas [31, 34].

In the most common subtype of the hereditary motor and sensory neuropathies, Charcot-Marie-Tooth (CMT) type 1 disease, the prevalence of OSA ranges between 42 and 79% [35–37]. For instance, SDB was found in 11 of 14 related individuals with familial CMT1, 9 of which had OSA, and only the 3 patients who lacked neuropathy were spared from sleep apnea [36]. A correlation between neuropathy severity and the severity of sleep apnea was seen in several studies perhaps mediated by pharyngeal neuropathy leading to upper airway dysfunction and increased airway collapsibility [35–37]. By means of repetitive hypoxic insults and mechanical trauma, OSA itself can also induce or aggravate

neurogenic pharyngeal changes which in turn may contribute to persistence of sleep apnea [38, 39].

OSA in amyotrophic lateral sclerosis (ALS) and other neuromuscular disorders is more controversial. The overall prevalence of SDB in ALS has been reported to be as high as 82% [40] and may be present even in patients with preserved respiratory function tests and phrenic nerve function [41]. ALS patients may be at increased risk of OSA due to the bulbar dysfunction that often accompanies the disease [42]. However, SDB events are generally more characteristically pseudo-central or diaphragmatic in ALS (Fig. 1) [6]. Hence, pure OSA in ALS is believed to be rare [43], including in patients with predominant bulbar symptoms [8]. The low prevalence of obstructive events is attributed to the inability to generate negative inspiratory pressures exceeding the upper airway critical closing pressure necessary to collapse the airway [44]. Weight loss and absent or minimal REM sleep in ALS with diaphragmatic dysfunction may also protect against obstructive events [45], therefore limiting the total time the patient spends in this vulnerable period.

Bulbar dysfunction may also be found in patients with post-polio syndrome, myasthenia gravis, spinal-bulbar muscular atrophy, and the Guillian-Barré syndrome, where it may also predispose to obstructive sleep events. Finally, OSA due to increased passive upper airway collapsibility has been documented in 33% and 25% of individuals with cervical and thoracic cord injury, respectively [46, 47].

Central Sleep Apnea, Periodic Breathing, and Cheyne-Stokes Breathing

There are two principal mechanisms of central sleep-disordered breathing in neuromuscular conditions: periodic breathing secondary to instability in the control of breathing, as a result of diaphragm weakness or as an intrinsic central manifestation of the disease, and Cheyne-Stokes breathing (CSB) secondary to heart failure, a common manifestation in certain NMD like the dystrophinopathies.

Although cardiac disease in ALS appears to be common [48], including recent reports of heart failure due to Takotsubo cardiomyopathy [49], dysfunction in the central control of breathing in ALS appears to be the major culprit of central SDB and abnormal breathing during sleep in ALS is common even in the absence of diaphragmatic dysfunction [41, 50, 51]. Specifically, studies have shown attenuated responses to breathing stimulus despite preserved lower phrenic nerve motor nucleus function, supporting a central impairment in the control of breathing. Potential mechanisms include involvement of the medullary respiratory premotor neurons efferent to the phrenic nerve spinal motor nuclei [52] or degeneration of the pre-Bötzinger complex interneurons [53•], with central sleep-disordered breathing found in at least a quarter of ALS patients with preserved diaphragm function [41, 54].

Similarly, a reduced ventilatory response to carbon dioxide in patients with DM was independent of lung function impairment and respiratory muscle weakness, suggesting a central cause of dysregulation [55••]. Periodic breathing was found in 5 of 40 patients with DM1, none of which had evidence of cardiac disease [26]. These patients had lower measurements of maximal inspiratory pressure, suggesting that periodic breathing may be triggered by a reduction in muscle strength due to increased instability of the respiratory system control. This mechanism also explains central SDB in cervical spinal cord injury, where the prevalence of central apneas and periodic breathing can be as high as 63% and 88%, respectively [56].

In DMD and other dystrophinopathies, the defective protein dystrophin has a fundamental role in stabilizing the cell membrane of both skeletal and cardiac myocytes [57]. Almost all patients with DMD will develop cardiomyopathy if they survive past 18 years of age [58]. In this context, SDB may be due to Cheyne-Stokes respiration with central apneas which may portend increased mortality from cardiomyopathy [59].

Diagnosis of Sleep-Disordered Breathing and Nocturnal Hypoventilation

A detailed and focused history and physical examination are essential in the assessment of nocturnal hypoventilation and other sleep disorders. Targeted diagnostic testing to detect nocturnal hypoventilation and other sleep disturbances may follow. Since breathing is critically dependent on diaphragmatic muscle function, REM sleep becomes a test of inspiratory function in itself [1] and should be a focus in the interpretation of polysomnography and nocturnal oximetry studies. While a polysomnography may not be always feasible in patients impacted by neuromuscular disease, practice guidelines endorse the routine use of polysomnography in such patients with otherwise clinically unexplained sleep-related symptoms [60]. Transcutaneous or end-tidal CO_2 monitoring to assess for nocturnal hypoventilation is an essential tool in patients with neuromuscular disease as well as expanded EMG montage for those with possible motor symptoms at night.

Several pitfalls in the interpretation of polysomnography contribute to misclassification of respiratory sleep events, with a bias towards labelling pseudo-central events as obstructive [2]. For instance, paradoxical chest wall movements due to weak chest wall muscles are often incorrectly interpreted as obstructive events [61]. In contrast, obstructive events may be mistaken for central events when patients have reduced respiratory effort due to weak respiratory muscles with limited thoracic effort against a narrowed or closed upper airway [3, 19, 62]. In effort to definite distinction between diaphragmatic breathing, central, and obstructive events, one requires measurement of transdiaphragmatic pressures or assessment of diaphragm electrical activity during polysomnography. Due to their more invasive nature, only selected studies have used esophageal balloon

manometry or diaphragm EMG to evaluate sleep in NMD [6, 33, 63]. Persistence of chest wall movement and evidence of abdominal and rib cage paradox could be useful surrogates of inspiratory effort [19], especially in younger patients in whom respiratory muscle strength may still be relatively well-preserved. Further, asymmetric greater decrease in the thoracic belt excursion relative to the abdominal belt occurring predominantly during phasic REM sleep should raise suspicion for diaphragmatic breathing and hypoventilation due to neuromuscular disease [4].

Nocturnal oximetry may be helpful for screening and routine monitoring. The characteristic episodic saw-tooth patterns of desaturations observed at 90- to 120-min intervals are suggestive but not exclusively diagnostic of REM-related nocturnal desaturations [2]. However, nocturnal oximetry is associated with a high occurrence of false-negative results, and polysomnography remains the gold standard to consider in a follow-up evaluation. Home sleep apnea testing has not been adequately validated in patients with neuromuscular diseases for the evaluation of sleep-disordered breathing other than OSA and is currently not indicated in this population.

Treatment

Treatment of SDB in neuromuscular disease generally consists of non-invasive ventilation which can improve sleep quality, quality of life, and survival [9•]. Non-invasive ventilation settings need to correct various types of SDB, address hypoventilation, and avoid patient-device dyssynchrony [9•, 40, 64, 65]. For instance, excessive pressure support and hyperventilation with non-invasive ventilation may trigger central apneas if the $PaCO_2$ is lowered below the hypocapnia apneic threshold [65]. In one study, a central apnea index greater than 5 was found in one-third of patients with ALS on non-invasive ventilation and was dramatically reduced after adjustment of the inspiratory support [64].

Restless Legs Syndrome and Periodic Leg Movements

Restless legs syndrome/Willis-Ekbom disease (RLS/WED) is defined by clinical features consisting of an urge to move due to an unpleasant limb sensation, with worsening in the evenings or during inactivity, and relieved with movement [66]. Periodic limb movements in sleep (PLMS) are defined by electromyographic features on polysomnography. About 80% of patients with RLS have PLMS, whereas PLMS may be isolated or occur in association with other sleep disorders. Cramps, pain, impairment in functional mobility, and positional discomfort in neuromuscular disease mimic and confound RLS [67], but common pathophysiologic mechanisms to NMD and RLS may reflect a true association.

In ALS, the prevalence of RLS is 25% compared to 8% in matched controls [68, 69]. As expected, an impairment in functional mobility from ALS is associated with RLS and can confound the presentation but does not explain the circadian pattern to the RLS symptoms in ALS [68]. There is a strong association of RLS in ALS with PLM, with all patients with ALS and RLS having a periodic limb movement index (PLMI) $\geq$ 15 in one study [69]. Spinal cord hyperexcitability or central loss of inhibitory descending pathways may be the pathogenetic mechanisms linking ALS with RLS and PLM [70, 68, 69, 71••].

There is an association between CMT and RLS. In a prospective study, RLS was found in 37% of CMT2 vs. 0% of CMT1 [72]. Cramps and paresthesia without circadian variations can confound RLS in this setting, but an expert assessment similarly documented a predominance of RLS in CMT2 compared to CMT1 (prevalence of 16% vs. 10% respectively) [73]. One study reported a high prevalence (41%) of RLS in CMT1 but may have selected patients with sleep symptoms [37]. On polysomnography, PLM were found in 2 of 3 CMT2 patients with RLS in one study [72] compared to none of 11 CMT1A in another study [36]. In contrast, a PLMI > 15/h is found equally frequently in CMT1 patient with RLS compared to those without RLS (40.0% and 41.7% respectively) [37]. The higher association of RLS and PLM with CMT2 relative to CMT1 may reflect the axonal loss in CMT2 (as opposed to demyelination in CMT1), with axonal pathology also reported as the most frequent type of nerve damage in primary RLS [74].

RLS is also present in 40% of patients with sequela of poliomyelitis (PM) in one study [75•]. Although the majority (75%) of those patients had the post-polio syndrome, there was no significant difference in the prevalence of RLS in PM patients with vs. without the post-polio syndrome (41% vs. 38%, $p = 0.87$) [75•]. Another study of patients with the post-polio syndrome found a similar prevalence of RLS (36%) but suggested that the onset of RLS coincided with symptoms of post-polio syndrome [76]. Finally, in a study which included age- and gender-matched controls, there was a 64% prevalence of RLS in the post-polio syndrome compared to 8% of controls [77]. The pathophysiologic link between sequelae of poliomyelitis and RLS needs to be elucidated with some suggesting inflammatory/autoimmune mechanisms or disruption of dopaminergic pathway at the anterior horn of the spinal cord [75•,76, 77].

RLS is also common in DM, found in 23% of patients with DM1 compared to none of the controls [78]. The PLMI is also elevated at 6.2–8.4/h in DM1, 7.42/h in DM2 compared to 0–2% in controls [30, 78].

There is a scarcity of information about movement disorders in DMD. One case reported significant emotional and physical stress in a patient with Duchenne and RLS augmented by amitriptyline [79].

Notwithstanding the common pathophysiologic mechanisms that link RLS and NMD, specific considerations impact the management decision. For instance, patients with CMT may have intact function scores despite RLS, and their PLM index may not correlate with sleep architecture parameters [37]. Patients with ALS and RLS do not appear to have significant difference in sleepiness, insomnia, or use of hypnotics or antidepressants compared to counterparts without RLS [68, 69]. Paradoxically, PLM in ALS may be associated with less sleepiness, and no or even fewer respiratory disturbance indices on polysomnography [71••, 80].

If a decision to treat RLS is made, opiates may not always be appropriate because of the potential for underlying sleep-disordered breathing. Neuropathic medications such as calcium channel ligands or carbamazepine may be preferred agents in the context of a neuropathy as may be present in CMT [81]. Dopaminergic agents have been shown to be effective in RLS associated with sequelae of polio [75•].

Central Disorders of Hypersomnia

Fatigue is found in 61–74% of patients with neuromuscular disorders [82], and up to 90% of those with ALS [83]. A central component has been implicated in ALS [84], and especially DM [85]. For instance, specific symptoms of sleepiness are particularly common in myotonic dystrophy, found in 33–40% of DM1 individuals [85, 86], compared to none of similarly disabled CMT controls [85]. The excessive daytime sleepiness of DM1 occurs in the absence of SDB [34, 85, 87] or persists after treatment of OSA [88]. Further, sleepiness in DM1 has features of narcolepsy including a reduced sleep latency, increased REM propensity, sleep onset REM periods in [78, 86, 87, 89, 90], cataplexy [32], hypnagogic hallucinations [86], and reduced CSF hypocretin levels [91, 92•].

However, doubt was raised about sleepiness in DM1 being related to dysfunction of the hypothalamic hypocretin system, the key mechanism of narcolepsy. For instance, one study showed no evidence of a defect in hypocretin production or hypocretin receptor [90], while another showed low hypocretin levels in DM1 that did not explain the excessive daytime sleepiness [92•]. There was no cataplexy or other features of narcolepsy in other studies [89, 90]. Further, neither excessive daytime sleepiness nor hypocretin levels correlated with the CTG expansion length [86, 90].

Alternative possibilities include a central dysfunction of sleep regulation in DM1 [78] with animal studies suggesting a disruption of the muscle blind-like protein 2 (MBNL2) mediated developmental splicing program [93]. In ALS, the central fatigue was attributed to degeneration of inhibitory GABAergic intracortical circuits [94]. As such, there is a role for the use of modafinil for treatment of excessive daytime sleepiness in both ALS [95] and myotonic dystrophy [96].

Loss of REM Atonia and Potentially Adaptive Mechanisms

Compensatory mechanisms to respiratory muscle weakness involve changes in accessory respiratory muscle activity during wakefulness and sleep, as well as modifications in sleep architecture. For instance, subjects with respiratory muscle weakness may contract the abdominal muscles to assist with expiration during wakefulness and NREM sleep in the semi-recumbent position, followed by abdominal muscle relaxation, which aids in diaphragmatic descent during inspiration [6]. Recruitment of accessory inspiratory muscles with increased inspiratory activity of the genioglossus, intercostal, and sternomastoid muscles during NREM may also maintain ventilation [6, 97].

In patients with ALS and diaphragmatic dysfunction, loss of normal REM atonia may be an acquired adaptive mechanism and may prolong total REM sleep [45]. REM without atonia was observed in 4 of 41 (9.7%) patients with ALS [71••], and in 6 of 12 (50%) patients with DM2 [30]. Loss of REM atonia is less common in DM1, found in none of 18 DM1 patients in one study [30], and in 2 of 40 (5%) DM1 patients in another study [78]. However, there was correlation in DM1 patients between the percentage of REM sleep without atonia and phasic burst of EMG activity during REM sleep [78]. This phenomenon is best illustrated by the remarkable conservation of inspiratory sternomastoid and genioglossus muscle activation during phasic or tonic REM in nearly 40% of patients with various neuromuscular conditions [5, 6], which may help protect against REM-associated hypoventilation and diaphragmatic breathing by assisting the weak diaphragm and augmenting alveolar ventilation [45]. Loss of REM atonia in neuromuscular disorders can be associated with dream enactment behavior [30, 98, 99]. Although the combination of REM without atonia and dream enactment behavior is consistent with REM sleep behavior disorder, the expected association with synucleinopathies has not been established in neuromuscular diseases, except perhaps for the confounding by extrapyramidal symptoms and cognitive impairment in the ALS-Plus syndrome. Central involvement by those various neuromuscular diseases is the likely pathophysiology with one study showing reduced presynaptic dopamine transporter in ALS-associated REM without atonia [71••].

Finally, near complete or complete suppression of REM has been reported in association with severe diaphragmatic weakness [6, 45], perhaps as a protective mechanism against recurrent oxygen desaturations and hypoventilation during this most vulnerable stage of sleep.

Conclusion

Disorders of sleep in neuromuscular disease include SDB, RLS, PLM, central hypersomnia, and loss of REM atonia. Of the SDB events, diaphragmatic/pseudo-central breathing

and nocturnal hypoventilation may be the most frequent. However, OSA is also commonly seen especially in certain myopathies such as DMD, AMD in association with upper airway muscle hypotonia and macroglossia, and in CMT1 possibly in association with pharyngeal neuropathy. Central events in the dystrophies are due to cardiac dysfunction, or in ALS in association with medullary upper motor neuron involvement possibly of premotor neurons connecting to the phrenic nerve, or interneurons of the pre-Bötzinger complex. Circadian patterns and pathophysiologic links may reflect a true association between RLS and certain neuromuscular disorders despite confounding by cramps, poor functional mobility, and positional discomfort. Central hypersomnia may be of concern in ALS and DM1. Finally, loss of REM atonia has been reported in ALS, DM2, and occasionally associated with dream enactment. Diagnostic and treatment options are generally the same as for sleep conditions in non-neuromuscular disease with some potential important differences. These include challenges in the correct identification of various SDB events in the context of NMD, appropriate use of non-invasive ventilation settings, and judicious use of pharmacologic options.

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Conflict of Interest Jorge L. Morales-Estrella declares no conflict of interest.

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- •• Of major importance

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