Review

Sleep Disorders in Neuromuscular Diseases: A Narrative Review

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Abstract: Neuromuscular disorders (NMDs) encompass a highly diverse group of conditions that affect the skeletal muscles, peripheral nervous system, or motor endplate. Depending on the underlying disease, common characteristics include progressive muscle weakness and sensory disturbances, both of which can contribute to sleep disruption. Disorders of sleep are extremely frequent in NMDs and substantially co-determine overall morbidity, quality of life, and survival. As many NMDs currently lack a cure, supportive therapy is mandatory and includes appropriate management of sleep-related symptoms. Specific sleep disorders that may arise in NMDs include insomnia due to pain or leg muscle cramps, restless legs syndrome, and sleep-disordered breathing, notably obstructive sleep apnea and hypoventilation. This review article aims to comprehensively outline the clinical spectrum of sleep disorders and sleep properties associated with NMDs.

Keywords: sleep-related breathing; neuropathy; motor neuron disease; myopathy; hypoventilation; sleep apnea; noninvasive ventilation

1. Introduction

In a strict sense, sleep research aims at extending knowledge on sleep (patho-)physiology, and sleep medicine is about patient care. In this narrative review, both aspects shall be covered in regard to the large and heterogenous group of neuromuscular disorders (NMDs). These are diseases affecting the skeletal muscles, the motor endplate, anterior horn cells, or the peripheral nervous system (Table 1). The majority of NMDs can be considered as rare (having a prevalence <50/100,000) [1], but the cumulative prevalence of NMDs in industrialized countries may reach >160:100,000 [2]. Among many other neurological conditions that are not sleep disorders themselves, NMDs are frequently associated with a plethora of sleep-related symptoms. These may ostensibly arise from any kind of motor impairment that simply interferes with the ability to move during sleep. The latter is a prerequisite of healthy sleep, which seems trivial at a first glance but may be perceived as an unsurmountable obstacle by patients who are incapable of changing body position, adjusting bed linen, scratching themselves, or independently frequenting the lavatory. Depending on the individual pattern of muscle weakness, breathing, coughing, and swallowing may also be compromised. In good health, all these functions are nothing we must worry about at nighttime, as they properly operate during both wakefulness and sleep. In contrast, sleep-related symptoms may be both torturous and life-threatening for people with NMDs. Apart from muscle weakness, sleep disturbances in NMDs may be associated with spontaneous motor phenomena (e.g., muscle cramps and spasticity), pain and sensory symptoms that may arise from immobility or, more directly, from peripheral nervous system involvement. Sleep-related symptoms are frequently reported by people with NMDs [3–7] and may substantially add to the burden of disease as they multiply fatigue, exercise intolerance, and overall daytime dysfunctions which already arise from disease-related motor handicaps alone. Finally, in advanced stages or genuinely fatal conditions, the sequelae of tetraplegia and respiratory muscle failure almost inevitably lead to premature death. Accordingly, early recognition of sleep disturbances and appropriate
treatment, including initiation of ventilatory support, can improve both quality of life and survival [8–11].

Table 1. Classification of neuromuscular diseases according to etiology and the primary anatomical level (or structures) involved: HIV, human immunodeficiency virus; NMJ, neuromuscular junction.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Anatomical Origin</th>
<th>Peripheral Nerve and Neuromuscular Junction</th>
<th>Anterior Horn Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory</td>
<td>Poly-/Dermatomyositis, Necrotizing Myositis, Sporadic Inclusion Body Myositis</td>
<td>Guillain–Barré Syndrome, Chronic Inflammatory Neuropathy, Demyelinating Neuropathy, Multifocal Motor Neuropathy, Systemic vasculitis; NMJ; Ocular myasthenia, Myasthenia gravis</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Infectious</td>
<td>Streptococci, Trichinosis, HIV, Influenza A/B, Epstein-Barr Virus</td>
<td>Lyme Disease, Leprosy</td>
<td>Lyme Disease, Leprosy</td>
</tr>
<tr>
<td>Toxic</td>
<td>Ethanol, Statins, Fibrates, Steroids, Critical Illness Myopathy</td>
<td>Ethanol, Chemotherapeutics, Critical Illness Neuropathy, Renal Failure, Liver Disease, Chloroquine, D-penicillamine, Gentamicin, Quinidine, Botulinum Toxin</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Vitamin D Deficiency, Hypokalemia, Hyperkalemia</td>
<td>Vitamin deficiencies (B1, B6, B12, Folic acid)</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypothyroidism, Hyperparathyroidism, Hypercortisolism</td>
<td>Hypothyroidism, Diabetes Mellitus</td>
<td>Diabetic Radiculopathy or Plexopathy</td>
</tr>
<tr>
<td>Degenerative</td>
<td>Inclusion Body Myositis (Sporadic)</td>
<td>Idiopathic Polyneuropathy</td>
<td>Amyotrophic Lateral Sclerosis</td>
</tr>
<tr>
<td>Hereditary</td>
<td>Muscular dystrophies, Congenital Myopathies, Metabolic Myopathies, Mitochondrial Myopathies, Myotonic myopathies, Hereditary Inclusion Body Myositis</td>
<td>Charcot–Marie–Tooth Disease, Fabry’s Disease, Transthyretin Familial Amyloid Neuropathy; NMJ; Congenital Myasthenic Syndromes</td>
<td>Spinal Muscular Atrophy, Bulbar and Spinal Muscular Atrophy (Kennedy’s Disease), Amyotrophic Lateral Sclerosis (Familial)</td>
</tr>
</tbody>
</table>

The following article aims to outline the clinical spectrum of sleep disturbances in adult patients with NMDs, focusing on both fatal and nonfatal conditions, and collecting the current evidence regarding distinct diseases in which certain sleep-related issues may be particularly common or relevant. Secondly, recommendable approaches to symptomatic treatment will be listed, considering the vast majority of NMDs are chronic, progressive, and still incurable. The latter holds true despite major therapeutic breakthroughs having been achieved during the last two decades that promise to substantially modify both the clinical course and overall prognosis of genetic conditions in particular. Lastly, this article aims to summarize the current knowledge on genuine changes in sleep properties that may be encountered in NMDs that have been sufficiently investigated to enhance our general understanding of sleep pathophysiology in these conditions.

2. Materials and Methods

This article is based on own practical experience, clinical research in the respective field, and a recent Medline search that was specifically tailored to distinct neuromuscular conditions intending to gather current evidence on sleep symptomatology, alterations in objective sleep outcomes, clinical impact of sleep-related issues, and specific therapies. Apart from distinct disease names, search terms included “sleep”, “sleep quality”,...
“sleep architecture”, “sleep-disordered breathing”, “sleep apnea”, “restless legs syndrome”, “muscle cramps”, “hypersomnia”, “daytime sleepiness”, “non-invasive ventilation”, “prognosis”, and “quality of life”. Unlike previous articles on the topic [12,13], the present review takes a primarily symptom-oriented perspective and is structured according to the symptomatology of sleep disorders rather than that of NMDs, as it is depicted in Table 1. This approach accounts for the fact that most sleep-related symptoms, as well as nosologically distinct sleep disorders, can occur in various neuromuscular conditions and, notably, may coincide in a single patient. Thus, the following chapters focus on different causes of insomnia as well as sleep-disordered breathing (SDB), before only amyotrophic lateral sclerosis (ALS) and myotonic dystrophy type 2 (DM2) are specifically discussed in separate chapters. For these two conditions, both scientific evidence and clinical knowledge have progressed the furthest, and the complexity of sleep-related disease aspects is immense.

3. Burden of Symptoms

Systematic studies on sleep-related symptoms have been conducted on various NMDs. The prevalence of self-reported insomnia has been found to be 50% or more in motor neuron diseases [4], myasthenia gravis [14], genetic muscular dystrophies [15,16], and Charcot–Marie–Tooth disease (CMT) [5]. The association of reduced sleep quality with daytime hypersomnia is particularly relevant in myotonic dystrophy type 1 (DM1), with symptom burden paralleling disease progression [17]. In other conditions, insomnia may be statistically related to fatigue rather than excessive daytime sleepiness (EDS) [5,14,18], reflecting that the formal absence of EDS is not sensitive enough to rule out the need for further diagnostic work [19].

The impact of sleep disturbances on quality of life (QoL) in NMDs cannot be overestimated. One population-based study found sleep quality to be among the most significant predictors of QoL in a large cohort of patients with various NMDs [20]. Of note, objective sleep quality may be improved by correction of SDB through ventilatory support [21] but may still remain a major issue in stable patients on long-term ventilation, as pain, helplessness, anxiety, and patient–ventilator asynchrony may be ongoing factors that potentially disrupt sleep [22–24]. Regarding the comprehensive evaluation of patient-reported outcomes, numerous studies have been published focussing on people with spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), Duchenne’s muscular dystrophy (DMD), and myotonic dystrophy type 1 (DM1). New tools have been developed for the assessment of relevant domains that are not fully addressed by standard measures of motor function or sleep quality [25]. Validation of these instruments in distinct diagnostic cohorts allows for long-term monitoring of meaningful change in response to therapeutic interventions such as NIV, professional caregiving, and modern pharmacological treatments [26,27].

With increasing muscle weakness, helplessness, and vulnerability, disease-related morbidity may not only bother affected patients themselves but also family caregivers [28]. This holds particularly true if frequent interventions are necessary during the night. In a recent study on ALS, disturbed sleep was among the various predictors of caregivers’ depression [29].

Table 2 depicts prevalence numbers for clinically important NMDs, giving an impression of the overall epidemiological burden of disease when distinct conditions are pooled. Figure 1 visualizes the main associations between different classes of NMDs and distinct sleep disorders.
Table 2. Prevalence of clinically important neuromuscular diseases, grouped according to their anatomical origin [2,30–32]. Neuromuscular diseases are arranged according to their anatomical origin. DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; FSHD, facio-scapulo-humeral muscular dystrophy; LGMD, limb–girdle muscular dystrophy; NMJ, neuromuscular junction; MG, myasthenia gravis; LEMS, Lambert–Eaton myasthenic syndrome; CMS, congenital myasthenic syndromes; MG, myasthenia gravis; CMT, Charcot–Marie–Tooth disease; CIDP, chronic inflammatory demyelinating polyneuropathy; ALS, amyotrophic lateral sclerosis; SMA, spinal muscular atrophy.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (Range or Estimate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td></td>
</tr>
<tr>
<td>DMD</td>
<td>0.70–4.70</td>
</tr>
<tr>
<td>BMD</td>
<td>0.07–3.65</td>
</tr>
<tr>
<td>Myotonic dystrophies</td>
<td>7.1–26.5</td>
</tr>
<tr>
<td>FSHD</td>
<td>2.03–6.8</td>
</tr>
<tr>
<td>LGMD</td>
<td>0.81–6.9</td>
</tr>
<tr>
<td>Pompe disease</td>
<td>0.28–0.35</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>3.45–9.7</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>1.97–21.42</td>
</tr>
<tr>
<td>MG</td>
<td>5.35–35.0</td>
</tr>
<tr>
<td>LEMS</td>
<td>0.23–0.40</td>
</tr>
<tr>
<td>Peripheral nerve and NMJ</td>
<td>2.22 (per 100,000 children)</td>
</tr>
<tr>
<td>CMS</td>
<td>3.10–82.30</td>
</tr>
<tr>
<td>CIDP</td>
<td>0.67–8.90</td>
</tr>
<tr>
<td>ALS</td>
<td>1.07–11.31</td>
</tr>
<tr>
<td>SMA</td>
<td>1.30–3.20</td>
</tr>
</tbody>
</table>

Figure 1. Main associations between subclasses of neuromuscular diseases and distinct sleep disorders; the latter are categorized as sleep-related breathing and (other causes of) insomnia. Arrows visualize common or specifically important associations and do not exclude the possibility of rare or unusual disease manifestations, e.g., RLS in a patient with myasthenia gravis or spasticity in a subject with Charcot–Marie–Tooth disease and pyramidal tract involvement. Dark grey arrows
indicate which sleep disorders can potentially be encountered in any neuromuscular disease. Light grey arrows (right side of the panel) depict synergistic effects of different causes of insomnia on sleep disruption. CSA, central sleep apnea; NMJ, neuromuscular junction; OSA, obstructive sleep apnea; RLS, restless legs syndrome; (1), mitochondrial myopathies with cerebral white matter lesions; (2), myotonic dystrophies; (3), sensory and sensorimotor neuropathies; (4), amyotrophic lateral sclerosis, primary lateral sclerosis, and hereditary spastic paraplegia.

4. Muscle Cramps, Spasticity, and Pain

Sleep-related muscle cramps comprise painful and involuntary contractions of the muscles in the thigh, lower leg, or feet but may also affect other muscle groups [33]. Patients with motor neuron disease and motor neuropathies are particularly prone to nocturnal muscle cramps. Exact prevalence numbers of nocturnal muscle cramps in NMDs are scarce. One study focusing on anti-myelin-associated glycoprotein antibody neuropathy reported sleep disruption by muscle cramps in 60% of patients [34]. A large survey revealed that muscle cramps are reported by 92% of patients with ALS, being the presenting symptom in many cases, but nocturnal occurrence of cramps was not specifically considered [35]. Muscle cramps can be aggravated by metabolic conditions (e.g., electrolyte imbalance and dehydration) but also due to medications such as diuretics, sympathomimetics, and statins. Medical treatment is based on the clearance of trigger factors and probatory use of calcium channel blockers or anticonvulsants, although specific evidence is insufficient [36]. Supplementation with magnesium or calcium may be considered for patients with low serum electrolyte levels. Quinine has shown moderate effectiveness but bears the risk of severe long-term side effects [37,38]. In ALS, mexiletine at a dose of 150 mg twice daily has been proven effective in a RCT but is off-label [39].

NMDs that may cause muscle stiffness and spasticity include amyotrophic and primary lateral sclerosis, hereditary spastic paraplegia (HSP) and, rarely genetic neuropathies with pyramidal signs. Insomnia due to spasticity has specifically been found to be common in HSP [40]. Albeit many patients with upper motor predominant ALS experience augmented spasticity at night, systematic studies are still lacking. Regarding therapy, no NMD-specific, evidence-based recommendations are available for certain compounds or nonpharmacological measures [41]. Baclofen, tizanidine, diazepam, or tolperisone may be used as oral medications, weighing individual benefits and systemic side effects [42]. Cannabinoids, for which evidence is also still insufficient and ambiguous, can be attempted. Localized spasticity is the domain of intramuscular botulinum toxin therapy.

Nocturnal pain in NMDs may arise from muscle cramps, spasticity, contractures, or mechanical tissue damage due to immobilization. Usually, these types of pain are localized and clearly nociceptive. In contrast, neuropathic pain is diffuse and indicates dysfunction of somatosensory pathways. It mostly relates to sensory or sensorimotor neuropathies [43–45] but may also be reported by patients with motor neuron disease [46]. A third etiology of pain is central sensitization, which is characterized by abnormal and sustained enhancement of nociceptive responses within the central nervous system [47]. Pain and insomnia frequently coincide in patients with NMDs, substantially impacting quality of life [48,49]. Regarding distinct NMDs, reported prevalence numbers for pain vary between different conditions. For ALS, a recent meta-analysis showed that pain has a pooled prevalence of 60% and mostly arises from cramps and spasticity [48], whereas in myogenic conditions, genuine myalgias are vastly predominant [49,50]. The prevalence of chronic pain exceeds 40% in limb–girdle muscular dystrophies (LGMD), DMD, and facioscapulohumeral dystrophy (FSHD) [50–52]. In DM1, pain has been shown to be even more frequent (65% of affected subjects), with evidence for both peripheral and central mechanisms [53]. Neuropathic pain is especially common in CMT, with predominant distal and symmetric location [54]. The relationship between neuropathic pain and insomnia has specifically been investigated in diabetic neuropathy and cryptogenic sensory polyneuropathy [43–45]. Of note, neuropathic pain shows a diurnal pattern, with exacerbation in the evening and at night [55]. Thus, common conditions such as symptomatic diabetic
neuropathy or nerve entrapment syndromes (e.g., carpal tunnel syndrome) often get more bothersome during the night and may cause significant sleep disruption [45,56].

Management of pain should primarily address treatable causes. For alleviation of mechanical triggers, optimized provision of assistive technology devices is essential. Daytime physiotherapy may also help prevent nighttime pain. For pharmacological treatment, nonsteroidal anti-inflammatory drugs, metamizole, or acetaminophen can be administered on-demand or regularly, if appropriate. In poly- and dermatomyositis, myalgias are an immanent symptom and can be alleviated by immunosuppressive therapy with corticosteroids or steroid-sparing compounds. For severe or persistent pain, opioids may be considered. In advanced stages of fatal NMDs, opioids should be considered, particularly if intractable pain comes together with dyspnea that cannot be relieved by mechanical ventilation. For treatment of neuropathic or central pain, gabapentin, pregabalin, or tricyclic antidepressants should be considered in accordance with current guidelines [57]. Cannabis-based compounds may be used to mitigate pain, while also providing anxiolytic, sedating, and appetizing effects [58]. Neuropathic pain may respond to topical application of high-concentration capsaicine [59] or physical measures, such as hot and cold applications, diathermy, and low-frequency currents truncutaneous electrical nerve stimulation [60].

5. Restless Legs Syndrome and Periodic Limb Movements in Sleep

Diagnosis of restless legs syndrome (RLS) may be particularly difficult in patients with NMDs, as distinction from other sensations—including cramps, paraesthesias, neuropathic pain, and venous stasis—can be challenging. Moreover, each of these conditions may coincide and mingle with “true” RLS in the same patient. Whereas reduced mobility per se is likely to cause, unmask, or aggravate RLS in any patient with NMD, peripheral neuropathies may specifically induce RLS due to nerve damage, abnormal sensory input, and altered signaling. Whereas RLS prevalence has been reported to range between 4.5% (men) and 7.2% (women) in the general population [61], it is much more common in patients with peripheral neuropathies, motor neuron disease, and distinct myopathies. Specifically, high prevalence numbers have been reported for hereditary neuropathies, including Charcot–Marie–Tooth disease type 1 (CMT1) [62], CMT2 [63], familial amyloid neuropathy [64], and hereditary sensory and autonomous neuropathies [65]. The prevalence of RLS is also increased in acquired sensory or mixed neuropathies, including diabetic, toxic, and cryoglobulinaemic polyneuropathies [65–68]. Finally, patients with ALS and myotonic dystrophy type 2 have been found to frequently complain of RLS symptoms [69,70]. Causative treatment of an underlying neuropathy, if applicable, may alleviate RLS symptoms. Iron supplementation may be considered if iron deficiency is identified as a contributing factor, and rational pharmacological treatment should be implemented according to standard recommendations [71].

Only a few studies specifically investigated periodic limb movements in sleep (PLMS) in distinct NMDs, such as DM1 [72], ALS [73], and bulbar and spinal muscular atrophy [74]. While PLMS may be more prevalent in NMD patients than in healthy subjects, it remains unclear whether PLMS that do not cause arousals from sleep are relevant at all.

6. Sleep-Disordered Breathing

Sleep-disordered breathing (SDB) encompasses obstructive sleep apnea (OSA), central sleep apnea (CSA), and sleep-related—or nocturnal—hypoventilation (NH) [33]. In patients with NMD, both OSA and NH frequently develop and may often coincide. The definition of sleep apnea syndromes is usually based on an apnea hypopnea index ≥ 5 per hour of total sleep time [75].

6.1. Obstructive Sleep Apnea

The pathophysiology of OSA may be multifactorial in NMDs. Upper airway patency during inspiration depends on pharyngeal muscle tone and width, as determined by individual anatomical features [76]. Both neurogenic and myogenic conditions may
hamper preinspiratory tonization of the pharyngeal dilators, and in muscular dystrophies or metabolic myopathies, macroglossia potentially adds to the risk of upper airway collapse [77]. As skeletal muscle tone is physiologically reduced during REM sleep, patients with NMDs are particularly prone to REM-related obstructive events [78]. Several studies have demonstrated that in people with NMDs, OSA risk is associated with overall motor impairment rather than age or body mass index [62,79]. In the general population, OSA affects 3–7% of men and 2–5% of women [80]. Much higher prevalence rates have been reported in different NMDs (Table 3), but respective case–control studies were possibly limited by a selection bias, as most patients had initially presented to sleep laboratories. However, OSA risk should be considered high in each patient with a known NMD who complains of sleep-related symptoms. As screening tools, the Epworth Sleepiness Scale, the STOP-BANG, or the Berlin questionnaire may be used.

Table 3. Prevalence rates of obstructive sleep apnea (OSA) in selected neuromuscular diseases, taken from disease-specific case–control studies: MG, myasthenia gravis; CMT1, Charcot–Marie–Tooth disease type 1; ALS, amyotrophic lateral sclerosis; DM1, myotonic dystrophy type 1; FSHD, facio-scapulo-humeral muscular dystrophy; DMD, Duchenne muscular dystrophy; SBMA, spinal and bulbar muscular atrophy. In all referenced studies, OSA was defined by an apnea–hypopnea index ≥ 5/h.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MG</td>
<td>36% [81]</td>
</tr>
<tr>
<td>CMT1</td>
<td>38% [62]</td>
</tr>
<tr>
<td>ALS</td>
<td>43.6% [82]</td>
</tr>
<tr>
<td>SBMA</td>
<td>61% [74]</td>
</tr>
<tr>
<td>DM1</td>
<td>41–60% [79,83,84]</td>
</tr>
<tr>
<td>FSHD</td>
<td>55%; 25% [16,85]</td>
</tr>
<tr>
<td>DMD</td>
<td>16.6%; 18% [78,86]</td>
</tr>
</tbody>
</table>

Continuous positive airway pressure (CPAP) therapy is usually the standard for first-line therapy of OSA [87]. This holds also true for patients with NMDs. As CPAP does not provide inspiratory support, it is unsuitable in case of coincident hypoventilation. Thus, long-term CPAP therapy is only appropriate if significant diaphragm weakness and NH have been ruled out. Otherwise, bilevel ventilatory support, i.e., noninvasive positive pressure ventilation, is indicated.

6.2. Central Sleep Apnea

Central sleep apneas may be observed in NMDs that also involve the central nervous system, e.g., mitochondrial disease and DM1 in which cerebral white matter lesions and altered regulation of breathing have been described [79,88]. In pure CSA, cranial imaging is indicated to identify structural brain abnormalities, and treatment should be established using nocturnal bilevel ventilation [89].

Central apneas with periodic breathing or Cheyne–Stokes respiration (CSA–CSR) may be encountered in any patient with comorbid heart failure with reduced ejection fraction [90]. Notably, cardiac involvement may immanently occur in distinct genetic myopathies or muscular dystrophies [91], rendering these conditions a risk factor of CSA–CSR. Interestingly, this aspect has not yet been specifically addressed by systematic studies, and treatment options have only been evaluated for patients with CSA–CSR and all-cause heart failure [92]. As the SERVE-HF study showed increased mortality in response to adaptive servoventilation (ASV) in patients with symptomatic heart failure, ejection fraction ≤ 45%, AHI > 15/h, and predominant CSA, ASV therapy is currently not recommended for this patient population. However, a recent meta-analysis showed positive effects on cardiac function for both CPAP and ASV [93], leaving optimal treatment strategies for CSA–CSR in patients with heart failure still under debate. Regarding subjects with NMDs and clinically relevant cardiomyopathy, treatment decisions require individual assessment of
sleep-related breathing, including evaluation of nocturnal gas exchange as noninvasive ventilation (NIV) might be indicated independent of sleep apnea.

6.3. Nocturnal Hypoventilation

Sleep-related hypoventilation in NMDs results from weakness of the inspiratory muscles that mainly comprise the diaphragm and external intercostal muscles. Respiratory muscle dysfunction is a prominent feature in motor neuron diseases and numerous myopathies or muscular dystrophies, eventually leading to type II respiratory failure. Slowly progressive phrenic nerve involvement has also been reported in patients with rare or severe CMT subtypes [94]. Acquired neuropathies that potentially cause (sub)acute bilateral phrenic nerve palsy include acute inflammatory demyelinating polyneuropathy (Guillain–Barré syndrome) and idiopathic phrenic nerve palsy, which may rarely occur with or without coincident Parsonage–Turner syndrome (i.e., neuralgic shoulder amyotrophy) that is thought to reflect aseptic inflammation of the brachial plexus [95].

Inspiratory muscle weakness and hypoventilation first manifest during the night, because respiratory drive is physiologically reduced during sleep. Furthermore, respiratory mechanics worsen in the supine position. Hypoventilation usually starts during REM sleep, when skeletal muscle tone is physiologically suppressed, with only the diaphragm being spared [96]. As diaphragmatic weakness progresses, hypoventilation extends to other sleep stages and eventually results in diurnal respiratory failure. Definitions of sleep-related hypoventilation are based on either carbon dioxide tension or peripheral oxygen saturation [97]. The latter is less sensitive than continuous capnometry, as according to the oxygen–hemoglobin dissociation curve, a moderate decrease in oxygen tension does not cause significant desaturation. In fact, NH has been shown to go undetected by pulse oximetry alone in about 30% of cases [82,98]. However, capnographic definition of NH is still inconsistent. The 2012 AASM definition (maximum pCO$_2$ ≥ 55 mmHg for ≥10 min or pCO$_2$ ≥ 50 mmHg with an increase of ≥10 mmHg from the awake baseline value) has recently been adopted by the American College of Chest Physicians [99,100], whereas the respective German guideline postulates a transcutaneous pCO$_2$ ≥ 50 mmHg for ≥30 min or an increase of ≥ 10 mmHg from the baseline value [101]. Chronic hypercapnic respiratory failure is consistently defined by a daytime arterial pCO$_2$ > 45 mmHg. Transcutaneous pCO$_2$ levels may gradually increase during the night, reflecting exhaustion of the inspiratory muscles. With disease progression, hypercapnia and hypoxemia may disproportionately worsen due to reduced lung volumes and atelectasis of lower lung segments that result in even more ventilation–perfusion mismatch [102].

Clinical symptoms of NH encompass sudden arousals from sleep, nonrestorative sleep, and headaches or drowsiness after awakening. Symptoms of respiratory muscle weakness comprise dyspnea during exertion or at rest, exercise intolerance, orthopnea, and impaired cough. Clinical signs may include tachypnea, speech dyspnea, hypophonia, and paradoxical breathing in the recumbent position. Inspiratory capacity should be assessed using a set of tests that combines spirometry and respiratory muscle strength testing [103]. Namely, forced vital capacity (FVC), measured in the upright and supine position, maximum inspiratory mouth occlusion pressure (MIP), and sniff nasal inspiratory pressure (SNIP) can be recommended. While FVC is widely in use, it also depends on lung compliance and airway resistance, probably rendering MIP and SNIP more direct measures of inspiratory muscle force. AnFVC < 60% of the predicted value indicates considerable diaphragm weakness and NH in subjects with NMDs [104,105]. Without suitable equipment, e.g., in telephone or video calls, the single-breath count test can be used as a substitute for spirometry and manometry [106]. All these tests are volitional, yielding variable results and being potentially unfeasible in patients with severe motor or bulbar impairment. For nonvolitional assessment of inspiratory muscle strength, transdiaphragmatic pressure changes in response to cervical magnetic stimulation of the phrenic nerves may be helpful [107]. However, the procedure is invasive and not suitable for routine use. In contrast, ultrasound is widely available and has been shown to yield valuable information...
on diaphragm morphology and function, including prediction of NH [105,108]. Magnetic resonance imaging of the diaphragm may also be applied but has not yet been evaluated regarding its predictive value [109].

For assessment of SDB, either full polysomnography or cardiorespiratory polygraphy are recommended [110]. Noninvasive carbon dioxide monitoring should be included in sleep studies when NH is specifically suspected. Continuous transcutaneous capnometry has been validated against arterial CO\textsubscript{2} measurements [111], is substantially more sensitive for detection of NH than pulse oximetry (see above) and allows for early diagnosis of REM-related hypoventilation if combined with polysomnography. Early-morning blood gas analysis helps to verify nocturnal hypercapnia if compensatory renal bicarbonate retention is evident.

7. Noninvasive Ventilation

Noninvasive positive pressure ventilation (NIV or NPPV, respectively) is indicated for treatment of CSA and NH but is also a recognized therapeutic option for OSA if CPAP is not tolerated or fails to be effective [89,100,112]. Several criteria have been introduced for indication of NIV in patients with NMDs or thoracic wall disease, all including the presence of NH-related complaints or clinical symptoms of respiratory muscle weakness [100,101,113–115]. Substantial variability between different guideline recommendations exists regarding the cut-off value for FVC, the role of MIP testing, and the significance of overnight capnometry. Whereas several guidelines specifically focus on ALS [114,115], others cover NMDs and restrictive lung disorders in general [100,101]. Special consideration of ALS in this context seems indeed appropriate, as it is inevitably fatal and typically progresses faster than most other NMDs. At the same time, numerous studies have confirmed positive effects of NIV on survival in ALS, rendering early initiation of ventilatory particularly important for affected patients [8,11,116]. Of note, potential survival benefits will not be fully achieved if NIV is only initiated when FVC has already dropped below 70% or even 50% of the predicted value [11,117]. Apart from ALS, beneficial effects of NIV on survival have been confirmed for various other NMDs, including DM1 [118], DMD [119], and SMA [120]. In addition, several studies have shown that in NMD patients with SDB, NIV rapidly improves objective sleep outcomes and self-reported sleep quality [121–123]. Improvement of sleep architecture may remain stable even when respirator dependency increases with time [21,123]. However, various aspects of mechanical ventilation potentially decrease sleep quality and promote unsatisfactory treatment adherence. Obvious problems may arise from insufficient mask fitting, leakage of air, or xerostomia. Furthermore, ventilator settings must be optimally synchronized with the patient’s demands to prevent patient–ventilator asynchrony (PVA) and sleep disruption [124]. Causes of PVA encompass ineffective or untimely triggering by the patient or autotriggering that may result from hiccups, cough, or inappropriate ventilator settings. Different ventilation modes have been evaluated, with some evidence favoring spontaneous-timed bilevel pressure support [125], but no clear advantage of targeted tidal volumes [126]. Notably, PVA does not necessarily result in ineffective gas exchange [127] or overt patient discomfort [128], and its true significance in patients with NMDs has yet to be evaluated [129]. In helpless patients, NIV itself may be stressful and can only be successfully established when caregivers can reliably deliver on-demand support.

After initiation of NIV, regular and thorough follow-up is essential. The ventilator’s internal memory provides data on adherence, air leaks, and pressure/flow curves that indicate intermittent upper airway obstruction during NIV. Modification of ventilator settings or switching to an alternative mask may be adequate in this case [130]. Poly(somno)graphy combined with noninvasive capnometry is mandatory to assess whether respiratory muscle weakness has worsened, and minute volume or pressure settings must be increased to achieve sustained normocapnia, normoxia, and AHI normalization, which all impact survival in ventilated NMD patients [131–133].
Tracheostomy-invasive ventilation (TIV) may be indicated if alveolar hypoventilation cannot be corrected any more despite maximum utilization of NIV, or if NIV is no longer tolerated. Furthermore, TIV should also be considered when noninvasive management of secretions has failed, or in patients in whom severe dysphagia requires cannulation independent of respiratory failure. Tracheostomy potentially prolongs life expectancy, even in patients with advanced motor neuron or muscle disease, but it also has major impact on homecare requirements and the situation of caregivers. In fatal conditions, it is mechanical ventilation that makes late stages of the disease experienceable, eventually shifting the focus to the personal will and preferences of affected individuals. In this context, advanced care planning includes individual consideration of whether elective tracheostomy is desired in the case of long-term NIV failure. Moreover, patients face the decision of whether orotracheal intubation and subsequent, often unavoidable, tracheostomy should be advocated for in the event of acute respiratory deterioration.

8. Weakness of Cough

Weakness of cough may promote mucus retention and potentially lead to dyspnea, lower respiratory tract infections, and secondary sleep disturbances. Cough effectiveness depends on expiratory muscle strength and inspiratory capacity. In addition, closure of the glottis is essential for intrathoracic pressure build-up but is frequently impaired in patients with bulbar dysfunction. Thus, management of cough and secretions is highly relevant for patients with NMDs, and appropriate measures must be taken if either excess secretions or significant respiratory muscle weakness evolve. Peak cough flow (PCF) can easily be measured using a bedside peak flow meter and helps steer individualized therapeutic strategies. These may comprise techniques that enhance lung inflation and augment cough, such as lung volume recruitment, manually assisted coughing, and mechanical insufflation–exsufflation [134]. Current evidence confirms the general clinical utility of these measures [135], but the strength of clinical recommendations is hampered, as large prospective studies are still lacking.

9. Important Aspects in Selected NMDs

9.1. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disorder that involves the pyramidal tract and anterior horn cells. It is inevitably progressive and eventually leads to generalized muscle weakness and premature death. Sleep disturbances are highly frequent in patients with ALS and substantially add to the disease burden for both patients and caregivers. Sleep disruption may be caused by muscle cramps, reduced mobility, pain, spasticity, RLS, mucus retention, and SDB. Furthermore, as in other fatal conditions, depression and existential fears should be recognized as potential causes of insomnia.

Overall, prognosis is overshadowed by the prospect of chronic respiratory failure that evolves in most patients, also being the most common cause of death by far [136]. NH may be detectable long before patients complain of sleep disruption or daytime dyspnea [137]. Several measures that indicate respiratory muscle dysfunction or sleep-disordered breathing have been reported to predict shorter survival, including FVC reduction, amplitudes of phrenic nerve compound muscle action potentials, maximum expiratory mouth pressure, SNIP, and duration of nocturnal oxygen desaturation [138–142].

Central sleep apnea is rare in ALS, but OSA has been reported to be much more frequent than in the normal population [82]. Of note, OSA is less common in patients with bulbar dysfunction, possibly reflecting the impact of tongue atrophy on the upper airway.

Direct effects of SDB on sleep architecture have been investigated in ALS much more comprehensively than in most other NMDs. Sleep may be severely disrupted by hypercapnia, hypoxemia, or OSA itself. In nonventilated patients, SDB relates to a reduction in sleep duration, sleep efficiency, slow-wave sleep, and REM sleep. In patients with preserved diaphragm function, periodic desaturations have been found independent of upper airway obstruction, possibly indicating altered central respiratory drive [143]. Patients without
perceived sleep disruption showed reduction in sleep efficiency, REM sleep, and N3 sleep, along with signs of autonomous nervous system dysregulation in the absence of significant SDB [144]. Few studies have investigated whether patients with ALS exhibit REM sleep behavioral disorder (RBD) [73,145]. Current evidence suggests that RBD may be found in a small subset of patients only. Whereas RBD has mainly been related to α-synucleinopathies, it might rarely occur in other neurodegenerative disorders, including ALS, possibly indicating atypical involvement of pathways that regulate muscle tone during REM sleep. To further elucidate this finding, hypocretin levels in cerebrospinal fluid (CSF) samples of patients with ALS were investigated, but no abnormalities were found [146].

9.2. Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 (DM1) is a multisystem disorder with dominant inheritance, characterized by progressive muscular dystrophy and myotonic symptoms but also by bilateral cataract, endocrine abnormalities, cardiac involvement, and cerebral white matter lesions [147]. Muscle weakness affects the face and distal limbs, and proximal muscles are often involved in advanced stages. Disease severity is mainly determined by the length of a pathological repeat extension within the causative gene. A broad spectrum of sleep disorders may evolve in patients with DM1, including all types of SDB (including ataxic breathing in a recent case report [148]), secondary causes of insomnia, and daytime hypersomnolence, which is basically independent of nocturnal sleep. Daytime sleepiness is among the earliest symptoms patients recall and may even predominate muscular complaints in early disease stages. The severity of hypersomnolence is weakly associated with overall motor impairment, apparently suggesting its relationship to physical fatigue and SDB. However, patients with DM1 may show clinical and polysomnographic characteristics of idiopathic hypersomnia and even narcolepsy. Polysomnographic evaluation shows dysregulation of REM sleep and sleep-onset REM in a subset of patients [149,150]. Narcolepsy-like findings in the multiple sleep latency test were found in up to 25.6% of patients with DM1 and EDS [151]. Regarding CSF hypocretin levels in patients with DM1, current evidence is ambiguous [152,153]. Apart from alterations of nocturnal sleep patterns, circadian rhythm dysregulation possibly adds to sleep-related symptoms in the daytime [154].

Regarding NIV in DM1 patients with NH or more complex SDB, direct treatment benefits may be difficult to confirm, since adherence to NIV is low in a substantial number of subjects. This has been considered a distinct feature of DM1 that could be attributed to several reasons: First, improvement of daytime sleepiness may be perceived as insufficient, since hypersomnolence is likely to have more than one etiology. Second, adherence may be hampered by reduced perception of respiratory symptoms or general apathy that potentially relates to cognitive impairment [155]. Treatment decisions should be based on individual considerations that thoroughly acknowledge disease severity, sleep study results, subjective symptoms, perceived benefits from therapeutic interventions, and the delicate interrelation of EDS and fatigue that plays an eminent role in DM1 [17,156]. Regarding pharmacological treatment, modafinil may be prescribed off-label for alleviation of hypersomnolence, but the respective evidence is inconsistent [157,158].

10. Conclusions

Sleep disturbances are frequent in NMDs and substantially contribute to the overall burden of disease for patients and caregivers. Depending on the underlying condition, progressive muscle weakness, muscle cramps, or nociceptive or neuropathic pain, RLS or SDB may add to sleep disruption, daytime sleepiness, and fatigue. Appropriate pharmacological therapy and provision of assistive technologies is indicated for treatable symptoms or problems that ostensibly interfere with sleep. Sleep studies should encompass poly(somno)graphy along with noninvasive nocturnal CO₂ monitoring that is obligatory if diaphragm weakness is suspected or has already been confirmed. Type II respiratory failure and OSA may coincide in a broad range of neurogenic or myogenic conditions. In the case
of NH, home ventilatory support should be initiated and regularly followed-up. Long-term treatment with nocturnal CPAP is only indicated for isolated OSA if diaphragm weakness and hypoventilation have reliably been excluded. Chronic hypercapnic respiratory failure eventually develops in numerous NMDs and critically determines lifespan in ALS, DMD, and early-onset SMA but also in patients severely affected by muscular dystrophies or other genetic myopathies. Myotonic dystrophy type 1 is specifically associated with all types of SDB, as well as daytime hypersomnolence, including additional aspects such as altered sleep regulation, circadian rhythmicity, and cognitive function. In ALS and DMD, both survival and quality of life can meaningfully be improved by early initiation of NIV. Regarding other NMDs, the same has not been specifically investigated but can reasonably be assumed for patients with significant respiratory muscle weakness. Apart from mechanical ventilation, adequate respiratory care includes management of secretions, cough assistance, and appropriate immunizations to prevent lower respiratory tract infections. Although respiratory issues tend to dominate somnological care for patients with NMDs, constant awareness for nonrespiratory sleep complaints is necessary. Future studies are needed to better identify and characterize sleep-related issues in rare NMDs that have been investigated in small case series only. For the assessment of symptom prevalence and treatment responses, prospective studies are desirable that systematically combine sleep study results with validated patient-reported outcomes measures. Finally, further effort should be made to both describe and improve structural conditions for patients with NMDs and sleep disorders in different healthcare systems.

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**Abbreviations**

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
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<tr>
<td>AHl</td>
<td>Apnea hypopnea index</td>
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<td>ALS</td>
<td>Amyotrophic lateral sclerosis</td>
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<tr>
<td>BMD</td>
<td>Becker muscular dystrophy</td>
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<tr>
<td>CIDP</td>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
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<tr>
<td>CMT</td>
<td>Charcot–Marie–Tooth disease</td>
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<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<tr>
<td>CSA</td>
<td>Central sleep apnea</td>
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<tr>
<td>CSA-CRR</td>
<td>Central sleep apnea with Cheyne–Stokes respiration</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
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<td>DM1</td>
<td>Myotonic dystrophy type 1</td>
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<tr>
<td>DMD</td>
<td>Duchenne muscular dystrophy</td>
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<tr>
<td>EDS</td>
<td>Excessive daytime sleepiness</td>
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<td>FVC</td>
<td>Forced vital capacity</td>
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<td>FSHD</td>
<td>Facio-scalpulohumeral muscular dystrophy</td>
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<td>HSP</td>
<td>Hereditary spastic paraplegia</td>
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<td>LEMS</td>
<td>Lambert–Eaton myasthenic syndrome</td>
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<tr>
<td>LGMD</td>
<td>Limb–girdle muscular dystrophies</td>
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<td>MIP</td>
<td>Maximum inspiratory pressure</td>
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<td>N3</td>
<td>Slow-wave sleep</td>
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<td>NH</td>
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<td>NMD</td>
<td>Neuromuscular disorders</td>
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