CHAPTER 10

Sleep and Neuromuscular Disease

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Neuromuscular diseases (NMD) by definition involve the muscle, neuromuscular junction, nerve, plexus, nerve root, or anterior horn cells. Depending on the pathophysiologic mechanism, neuromuscular diseases may involve the corticospinal tracts, upper motor neurons, and other aspects of the central nervous system (CNS).

An incomplete summary of NMD is included in Table 10.1. These are a heterogeneous group, ranging from acute-onset conditions to chronic, slowly progressive disorders. They may appear at birth, in childhood, or later in life. Their etiologies vary, and include developmental, degenerative, metabolic, immune-mediated, infectious, traumatic, and toxic causes. Some are treatable, while others are irreversible. Weakness may be intermittent, fluctuating, static, or progressive.

**TABLE 10.1** Differential of Neuromuscular Diseases

<table>
<thead>
<tr>
<th>Muscle</th>
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<tbody>
<tr>
<td>Polymyositis</td>
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<td>Dermatomyositis</td>
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<td>Inclusion body myositis</td>
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<td>Duchenne muscular dystrophy</td>
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<td>Becker muscular dystrophy</td>
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<td>Nemaline myopathy</td>
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<td>Critical illness myopathy</td>
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<td>Statin myopathy</td>
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<td>McArdle disease</td>
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<td>Pompe disease</td>
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<tr>
<td>Neuromuscular junction</td>
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<tr>
<td>Myasthenia gravis</td>
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<tr>
<td>Lambert–Eaton myasthenic syndrome</td>
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<td>Congenital myasthenic syndrome</td>
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<tr>
<td>Botulinum toxicity</td>
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<tr>
<td>Nerve</td>
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<tr>
<td>Guillain–Barre syndrome</td>
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<tr>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
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<tr>
<td>Inherited neuropathy (Charcot–Marie–Tooth)</td>
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<tr>
<td>Phrenic neuropathy (traumatic, diabetic, etc.)</td>
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<tr>
<td>Vasculitic neuropathy</td>
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<td>Critical illness polyneuropathy</td>
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<td>Plexus</td>
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<td>Parsonage–Turner syndrome</td>
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<td>Diabetic amyotrophy</td>
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<tr>
<td>Tumor infiltration</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Root, anterior horn cell, cord</td>
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<tr>
<td>Amyotrophic lateral sclerosis</td>
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<tr>
<td>Spinobulbar muscular atrophy</td>
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<tr>
<td>Spinal muscular atrophy</td>
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<tr>
<td>Poliomyelitis and enterovirus-related syndromes</td>
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<td>Spinal cord injury</td>
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It is important to note that essentially any process causing respiratory muscle weakness can cause sleep-disordered breathing.

Evaluation for these conditions begins with a thorough general, neurological, and neuromuscular examination. Based on this evaluation, further testing may be indicated, such as serum laboratory evaluations (e.g., creatine kinase, acetylcholine receptor antibodies), electromyography and nerve conduction studies, muscle and nerve biopsy, brain and lung imaging, and genetic testing.

THE PHYSIOLOGY OF NORMAL BREATHING

The major muscle of inspiration is the diaphragm, a large band of muscle with a central fibrous tendon positioned between the xiphoid, costal margins, rib cage, and upper lumbar vertebrae. It is innervated by the phrenic nerve, which arises from the C3–C5 nerve roots. Inspiration also involves external intercostal muscles (supplied by the intercostal nerves that arise from corresponding thoracic roots), and the scalene and sternocleidomastoid “accessory” muscles, which are innervated by the C3–C6 nerve roots and spinal accessory nerve (cranial nerve XI), respectively.

Exhalation is typically mediated by the passive elastic recoil of the thoracic wall and rib cage. The internal intercostal muscles (innervated by the intercostal nerves), rectus abdominus (innervated by the thoracoabdominal nerves), and other abdominal musculature also play a role, particularly when forceful exhalation is required for a cough.

Patency of the upper airway is necessary to allow for adequate intake of oxygenated air. The upper airway structures include the lips, tongue, soft palate, epiglottis and larynx, supplied by cranial nerves VII, IX, X, and XII. During inspiration, the diaphragm contracts and moves downward, pushing the abdominal contents downward and outward and creating negative intrathoracic pressure. Air travels through the upper airway to fill this vacuum. During exhalation, the diaphragm relaxes, and elastic recoil of the lungs and chest wall forces air outward. Control of respiratory function is largely automatic and driven by brainstem centers. Impulses are relayed from medullary respiratory neurons to lower motor neurons of the phrenic and intercostal nerves.

Adjustments to the respiratory drive are mediated, in part, by the central and peripheral chemoreceptors in the brainstem and carotid sinus, respectively. The central chemoreceptors in the ventral medulla stimulate ventilation in response to reductions in cerebrospinal fluid (CSF) pH caused by hypercapnia. The peripheral chemoreceptors in the carotid and aortic bodies similarly respond to reductions in pH and elevations in CO₂, as well as changes in the partial pressure of O₂ in arterial blood. The CNS plays an important role in regulating ventilation, particularly in patients with chronic NMD.

MECHANISMS OF SLEEP DISTURBANCES IN NEUROMUSCULAR DISEASE

NMDs affect sleep in a number of ways:

- restrictive pattern of ventilation due to inspiratory muscle weakness
- airway obstruction due to pharyngeal weakness
• secondary central hypoventilation syndrome due to chronic hypercapnia
• primary central disturbances of sleep regulation
• restless legs syndrome (RLS)
• neuropathic pain

Hypoventilation due to Compromise of the Respiratory Pump

When neuromuscular weakness involves the respiratory musculature, reduced ventilation results in inadequate delivery of oxygen to lung capillaries (hypoxemia) and inadequate clearance of carbon dioxide (hypercapnia). Hypoventilation occurs in two ways:

• “Obstruction” of air flow is caused by weakness in the upper airway.
• “Restriction” of air flow is caused by reduced diaphragm and chest wall excursion due to muscle weakness or fibrosis.

Patients are more vulnerable to the effects of neuromuscular weakness during sleep for several reasons:

• In the recumbent position, diaphragmatic excursion is not aided by gravity, resulting in decreased inspiration.
• In rapid eye movement (REM) sleep, atonia of the respiratory accessory muscles further reduces inspiratory effort.
• Weakness and hypotonia of the upper airway increase the risk of airway obstruction.
• In sleep, there is less central chemoreceptor sensitivity and less response to hypoxemia and hypercapnia than there is during wakefulness.

In patients with neuromuscular ventilatory insufficiency and disrupted sleep, hypoxemia and hypercapnia intermittently trigger increases in respiratory effort. This results in arousals from sleep and a majority of the sleep period spent in stage 1 and 2 non-REM (NREM) sleep. Patients or their sleep partners may not be aware of these involuntary arousals; instead, patients may endorse symptoms of daytime fatigue and sleepiness, morning headaches, and cognitive difficulties.

As noted previously, several factors result in more shallow breathing during sleep, typically before wakeful breathing is affected. As such, nocturnal hypoventilation often precedes daytime hypoventilation. In disorders that primarily affect the diaphragm, sleep-related hypoventilation may be the only sign of neuromuscular impairment. The sleep clinician thus may be the first to identify respiratory muscle involvement by a NMD.

Other Structural Changes that Affect the Respiratory Pump

Congenital or early-onset NMDs are often associated with deformities of craniofacial structures due to weakness during development. Examination reveals a high, narrow palate, narrow face, and micrognathia (Fig. 10.1). Conditions such as Pompe disease and Duchenne muscular dystrophy (DMD) are associated with macroglossia. These changes may in turn contribute to upper airway obstruction.

These patients are also prone to paraspinal muscle dysfunction, resulting in thoracic cage deformities (pectus excavatum or pectus carinatum) and scoliosis (Fig. 10.2). This chronic remodeling limits chest wall mobility and may contribute to ventilatory restriction. Reduced
chest wall mobility can also occur in late-onset diseases such as amyotrophic lateral sclerosis (ALS), where chronic respiratory weakness can lead to reduced chest wall compliance.

Truncal obesity and increased abdominal content (e.g., due to constipation, aerophagia, or organomegaly) occur in conditions such as Duchenne muscular dystrophy. This further predisposes patients to reduced vital capacity via restrictive mechanisms.\(^5\)
ASSESSMENTS OF HYPOVENTILATION AND SLEEP DISTURBANCE IN NEUROMUSCULAR DISEASE

The astute clinician can identify this complication during the routine neurological history and examination, even before sleep studies are performed.

Symptoms

The symptoms of nocturnal hypoventilation in sleep are listed in Table 10.2. Patients will often dismiss these symptoms as normal. More severe neuromuscular respiratory weakness may result in overt dyspnea or orthopnea during activities of daily living.

A number of clinical scales can be used to screen for poor sleep quality and ventilatory impairment. These include the Epworth sleepiness scale (ESS), the Borg dyspnea scale, and the Fatigue and Daytime Sleepiness Scale (FDSS).

Clinical Signs

Proximal weakness often correlates with respiratory muscle weakness. Neck flexion strength is most accurately tested with the patient in the supine position. One can also observe for orthopnea, accessory muscle use, and paradoxical breathing. Paradoxical breathing (or thoracoabdominal asynchrony) takes two forms:

- Inward movement of the abdominal wall on inspiration due to diaphragm weakness, which is common in neuromuscular disorders.
- Inward movement of the chest wall on inspiration due to poor thoracic cage elasticity. This is seen in children with spinal muscular atrophy (SMA), where intercostal weakness exceeds diaphragm weakness.

A thorough neuromuscular exam should include evaluation of ocular and bulbar function, proximal and distal strength, reflexes, sensation, and gait, screening for muscle fatigability, myotonia, atrophy, fasciculations, craniofacial deformities including temporal wasting, and

TABLE 10.2 Symptoms of Nocturnal Hypoventilation

<table>
<thead>
<tr>
<th>Daytime symptoms</th>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Excessive daytime sleepiness</td>
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<tr>
<td>Morning headaches</td>
</tr>
<tr>
<td>Fatigue upon awakening</td>
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<tr>
<td>Reliance on an alarm</td>
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<tr>
<td>Sleeping in on weekends</td>
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<table>
<thead>
<tr>
<th>Nighttime symptoms</th>
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<tbody>
<tr>
<td>Snoring</td>
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<tr>
<td>Apneas</td>
</tr>
<tr>
<td>Restlessness</td>
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<tr>
<td>Frequent awakenings</td>
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<tr>
<td>Nocturia</td>
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other musculoskeletal abnormalities. Disease-specific nonmusculoskeletal features may include frontal balding, neurofibromas, cataracts, hypogonadism, and gynecomastia.

As a proxy measure of vital capacity, patients may be asked to count out loud to the highest number possible in one exhalation, enunciating at a standardized rate of two numbers each second. The forced vital capacity (FVC) is approximately 100 mL for each number counted, and a proposed normal cutoff is 25 numbers. In individuals with nasopharyngeal weakness, the nostrils should be closed with a clip during this assessment to improve its accuracy.

Tongue and pharyngeal weakness can contribute to upper airway obstruction and collapse. Symptoms of bulbar dysfunction may include difficulty chewing and swallowing, ineffective cough due to poor glottal closure, trouble managing secretions, and reduced speech volume and rapidity. The examination should include an assessment of speech quality (nasal or spastic speech), tongue strength and speed, palatal elevation, gag reflex, and ability to swallow and cough.

**Laboratory Testing**

In addition to the exam, patients should undergo basic vital signs including respiratory rate, pulse oximetry, and, when possible, end-tidal CO\(_2\) (though this may underestimate arterial pCO\(_2\)). These measures serve as a gross screen for significant respiratory dysfunction. It should be emphasized again that signs of nocturnal hypercapnia will often precede such markers of daytime hypercapnia.

Patients with neuromuscular disorders should also undergo pulmonary function tests (PFTs), even in the absence of sleep symptoms or daytime hypoventilation. Abnormalities on these measures may predict nocturnal desaturations and hypercapnia, and provide a useful measure of disease progression or response to treatment. Basic PFTs include forced vital capacity (FVC), slow vital capacity (SVC), and forced expiratory volume in the first minute (FEV\(_1\)). Maximum inspiratory and expiratory pressures (MIP and MEP) and sniff nasal inspiratory pressure (SNIP) also measure inspiratory and expiratory muscle strength. Note that all PFTs can be confounded by the presence of bulbar or pseudobulbar weakness or limited patient effort.

In many patients with neuromuscular disorders, a polysomnogram (PSG) is not required for initiation of noninvasive ventilation (NIV). Any patient with a neuromuscular diagnosis and FVC <50% of predicted, MIP <60 cm H\(_2\)O, or PaCO\(_2\) >45 mmHg will meet current Medicare criteria for use of nocturnal NIV without a diagnostic PSG (Table 10.3). On the other hand, PSG remains an essential diagnostic tool in patients without daytime hypoventilation, as criteria for NIV also include O\(_2\) saturation <88% for greater than five consecutive minutes while asleep. PSG is also valuable to optimize fittings and settings for all neuromuscular patients who require nocturnal NIV. Lastly, despite the Medicare criteria, PSG is often required to support the clinician’s decision to implement NIV.

**TABLE 10.3** Medicare Criteria for Coverage of Noninvasive Ventilation in Patients with Neuromuscular Disease

One of the following:
- FVC <50% predicted FVC
- MIP <60 cm H\(_2\)O
- PaCO\(_2\) >45 mmHg
- SaO\(_2\) <88% for >5 consecutive minutes on PSG
There are several findings on PSG that may be identified in patients with NMDs. Obstructive apneas appear when upper airway collapse results in reduced airflow despite normal respiratory effort. Nonobstructive apneas occur when limited chest wall movement results in poor airflow and hypoxia, without observable obstruction. This limited movement is due to muscle weakness, contracture of the thoracic cage, or severe upper airway collapse. Note that this finding may be termed a “central apnea.” A diagnostic pitfall occurs when nonobstructive apneas are incorrectly attributed to a primary deficit in the central respiratory drive, leading to unnecessary investigations for CNS diseases, such as brainstem stroke or PHOX2B mutations. Thus, more accurate terms are “nonobstructive” or “pseudocentral” apneas. Lastly, paradoxical chest and abdominal wall movements may also confound identification of obstructive or central apneas. To avoid misdiagnosis, NMD should be considered in the differential for all patients with a significant number of nonobstructive apneas (more than 5 per hour) during sleep.

Imaging such as chest X-ray and sniff fluoroscopy (SNIF) can evaluate for diaphragmatic weakness. On chest X-ray, the paralyzed diaphragm may be abnormally elevated. During the inspiratory phase of SNIF testing, the muscle does not demonstrate normal downward excursion, and can even have paradoxical elevation. These imaging studies are well suited for detection of hemidiaphragmatic weakness (as seen in cases of phrenic nerve paralyses due to trauma, tumor invasion, diabetic nerve palsies, and brachial plexitis). However, in most NMD the diaphragm weakness is bilateral, causing the chest X-ray and SNIF to appear “pseudo-normal” due to the symmetric diaphragm appearance.

The phrenic nerve conduction study is being explored in the research setting as a direct marker of cervical motor neuron, phrenic nerve, and diaphragm function in patients with ALS and Charcot–Marie–Tooth disease (CMT). This noninvasive test is not confounded by the low patient effort and bulbar weakness that can affect traditional PFTs. Ultrasound of the phrenic nerve and diaphragm are also being explored to measure neuromuscular structure and function. Phrenic nerve enlargement has been demonstrated in some forms of CMT.

**TREATMENT OF NEUROMUSCULAR HYPOVENTILATION**

The mainstay of treatment is the use of NIV to maintain adequate air exchange while keeping the upper airway patent. This intervention compensates for multiple mechanisms of neuromuscular weakness. NIV options include pressure-based devices, such as bilevel positive airway pressure, and advanced devices that offer volume-targeted modes to maintain adequate minute ventilation, such as average volume assured pressure support (AVAPS). A backup rate may be utilized if there is evidence of reduced ventilatory drive or if the patient is unable to maintain adequate respiratory effort.

The choice of device is often made in conjunction with a neuromuscular specialist and pulmonologist. Pressure-based devices allow for easier detection of air leaks, but volume-based devices may be more effective due to guaranteed volume delivery. This has been demonstrated in the ALS population, though aerophagia contributes to lower tolerance. For insurance purposes, NIV is divided into two categories: respiratory assist devices and portable
ventilators, based on the sophistication of the device. Disease severity often affects what type of equipment is authorized by the insurance provider.

Continuous positive airway pressure (CPAP) is commonly used to treat obstructive sleep apnea in the general population. In neuromuscular patients with impaired expiratory strength, CPAP can impede exhalation and reduce tidal volume, thereby exaggerating hypoventilation and hypoxemia. As a result, bilevel and AVAPS are preferable and likely safer. CPAP is occasionally used in neuromuscular patients who have obstructive apneas due to isolated pharyngeal weakness, but have preserved inspiratory and expiratory muscle function. Outside of this scenario, CPAP is not considered a respiratory assist device in this population.

The interface for NIV is chosen based on the patient’s comfort and degree of handicap. Options include the nasal mask, nasal pillows, and full-face mask interfaces (Fig. 10.3). The input of respiratory and occupational therapists can be invaluable, especially in patients with coexistent hand weakness who have trouble applying or removing their NIV device.

NIV settings are typically based on calculation of tidal volume (using ideal body weight) and patient tolerance, and later adjusted based on the degree of ventilatory impairment or gas exchange abnormalities. Device titration can be optimized with in-laboratory titration PSG. However, patients with neuromuscular weakness may not be able to undergo reliable overnight PSG testing due to logistical challenges. In those cases, home titration of portable ventilators by respiratory therapists may be an acceptable alternative.

NIV can be utilized in any situation where nocturnal hypoventilation is impacting sleep, regardless of disease duration. This includes reversible or episodic conditions [i.e., Guillain–Barre syndrome (GBS), myasthenia gravis] and progressive diseases (i.e., ALS, Duchenne muscular dystrophy). This is especially true in myasthenia gravis, where acute to subacute onset of nocturnal hypoventilation can result in sleep deprivation and exaggerated daytime fatigue, both of which can be remedied quickly with NIV while awaiting the drug response of immunomodulatory treatment.
Phrenic Nerve Stimulation and Diaphragmatic Conditioning

Patients with high spinal cord injury or a congenital central hypoventilation syndrome (PHOX2B mutation) have intact neuromuscular structures, including phrenic nerves, diaphragm, and intercostal muscles. Phrenic nerve and diaphragm stimulators utilize electrical stimulation to directly generate a normal respiratory rate and volume, allowing some patients to wean off of invasive mechanical ventilation, despite the loss of CNS input.\(^{20}\)

In patients with ALS, a device to condition the denervated diaphragm and potentially improve muscle resilience has been explored. This diaphragm stimulator provides low intensity current to the muscle, without the effect of simulating typical respiration rate and volume. Although there has been suggestion of improvement in some measures of sleep, reports of improved survival have not yet been validated.\(^ {21}\) Investigators in one randomized controlled trial found increased mortality in the implanted group, and recommended against its use; additional trials are ongoing.\(^ {22}\)

Other Measures to Minimize Hypoventilation

Daytime measures that improve vital capacity, improve cough, and clear secretions may also have positive impacts on nocturnal ventilation. These include:

- daytime use of NIV
- mechanical insufflator–exsufflator (CoughAssist), a device to aid in airway clearance
- chest percussion devices to loosen secretions
- nebulizer treatments and other forms of pulmonary toilette.\(^ {23}\)

CENTRAL HYPOVENTILATION SYNDROME DUE TO CHRONIC HYPERCAPNIA

Patients with longstanding neuromuscular weakness and chronic hypoventilation often develop chronic hypercapnia. The central chemoreceptors become desensitized to elevated CO\(_2\) and the ventilatory drive becomes dependent on hypoxemia alone. This is termed “central hypoventilation,” as the central respiratory effort does not increase to manage the rising CO\(_2\). It bears reminding that this “central” process develops due to peripheral neuromuscular weakness; as such, it is treated by using NIV to correct hypoventilation.

In the awake patient, the presence of hypercapnia on end-tidal CO\(_2\), pulse CO\(_2\), or blood gas indicates chronic hypercapnia. Other symptoms are described previously (Table 10.2). More severe hypercapnia may result in cognitive slowing or obtundation. In sleep, the ventilatory drive is naturally depressed, further increasing hypercapnia. This becomes even more apparent during REM sleep, when skeletal muscle tone is suppressed and the accessory muscles of respiration are not activated to assist the diaphragm.

The PSG may be difficult to interpret when there is primary weakness and secondary central hypoventilation. The underlying obstructive and/or restrictive neuromuscular process leads to apneic events. These may be detected as obstructive or nonobstructive apneas (“pseudocentral,” in that reduced ventilatory effort due to muscle weakness is misinterpreted as poor central respiratory drive). True central apneas due to CNS desensitization
to hypercapnia may also be present, but are difficult to distinguish on routine PSG.\textsuperscript{24} If the chronic hypercapnia is not taken into account, then a congenital or acquired central hypventilation syndrome (i.e., brainstem stroke, \textit{PHOX2B} mutation) may be incorrectly diagnosed while the underlying NMD is overlooked. Thus, PSG findings should always be interpreted in the context of clinical findings and tests of respiratory function.\textsuperscript{25}

Oxygen supplementation is occasionally initiated during the PSG to correct persistent hypoxemia, often when the clinician or technician is unaware of the underlying diagnosis. In the setting of chronic hypoventilation, correction of hypoxemia results in further depression of respiratory function. In this instance oxygen supplementation can reduce respiratory drive, heighten hypercapnia and paradoxically result in greater hypoxemia. For these reasons, oxygen supplementation is not recommended during the routine assessment of central hypoventilation syndrome due to the risk of producing an exaggerated respiratory depression.

**Treatment of Central Nocturnal Hypoventilation**

The sleep clinician may be the first to recognize the effects of chronic hypercapnia and initiate investigations for underlying neuromuscular respiratory weakness. NIV is used to treat the primary obstructive and/or restrictive airway disease causing the cascade of hypoventilation, chronic hypercapnia, and central respiratory depression.

While oxygen supplementation in the absence of ventilatory support can be harmful, oxygen is occasionally used in conjunction with NIV when hypoxemia is severe. It is essential that the underlying disease physiology is recognized and managed, and hypoxemia is not treated in isolation.

**CENTRAL SLEEP DYSFUNCTION IN NEUROMUSCULAR DISEASE**

Some NMD are associated with central sleep disturbances that appear independent of respiratory weakness. In addition, it is postulated that sleep architecture in neuromuscular patients naturally evolves to reduce REM-associated hypoventilation, resulting in reduced time spent in REM, and loss of REM atonia (also termed EMG augmentation).\textsuperscript{24}

**Myotonic Dystrophy**

Myotonic dystrophy types 1 (DM1) and 2 (DM2) are autosomal dominant disorders associated with myotonia (delayed muscle relaxation), bulbar and limb weakness.\textsuperscript{26} In DM1 in particular, widespread effects on splicing regulation result in CNS, endocrine, and other systemic manifestations.

Multiple peripheral and central mechanisms converge to cause sleep disturbances in DM1. These manifest as excessive daytime sleepiness, nocturnal hypoventilation, sleep-onset REM periods, sleep fragmentation, and periodic limb movements of sleep (PLMS).\textsuperscript{27} Excessive daytime sleepiness appears early and is out of proportion to the degree of respiratory muscle and craniofacial weakness.\textsuperscript{28,29} This implies other regulatory processes in the sleep-wake cycle, including the loss of serotonergic neurons in the brainstem raphe nuclei,\textsuperscript{30} disturbances in growth hormone secretion,\textsuperscript{31} and persistence of neonatal patterns of sleep due to alternative
splicing in CNS circuits. In DM2, alternative splicing in dopaminergic and other pathways has been proposed as a mechanism for the increased incidence of RLS in these patients. The hypothalamic neurotransmitter hypocretin (also known as orexin) may be involved in the pathophysiology of DM1. Central regulation of sleep is mediated in part by hypocretin signaling, and reduced levels have been associated with narcolepsy. A small group of patients with DM1 were found to have a significant decrease in CSF hypocretin-1, whereas a larger group did not display significant abnormalities. Thus the contribution of hypocretin deficiency to hypersomnia in DM1 is not yet clear.

In addition to PSG, the Rasch-built FDSS is being explored as a tool for the evaluation of sleep in DM1.

Guillain–Barre Syndrome

This acute-onset, immune-mediated polyradiculoneuropathy often occurs in the context of Campylobacter jejuni infection. Symptoms may include neuropathic weakness, sensory changes, and autonomic instability. In addition, many patients report fatigue, and disordered sleep has been described with sleep-onset REM and loss of REM atonia. In some patients with GBS, CSF studies have revealed absence of hypocretin, similar to what is seen in narcolepsy; patients may experience persistent sleep disturbances months after the onset of GBS. This raises the possibility of immune-mediated hypothalamic dysfunction and subsequent hypocretin deficiency leading to chronic sleep-related disturbances and fatigue. Interestingly, a small group of patients with a related condition, chronic inflammatory demyelinating polyneuropathy (CIDP), were not found to have reduced CSF hypocretin levels.

UPPER MOTOR NEURON DYSFUNCTION

Involvement of the upper motor neurons (also known as corticospinal or pyramidal dysfunction) is predominant in a number of neurological diseases, including primary lateral sclerosis and hereditary spastic paraparesis. Primary CNS impairment of the respiratory drive in sleep has been postulated in such patients where muscle weakness is minimal, but sleep-disordered breathing is significant. The precise mechanism is unknown.

RESTLESS LEGS SYNDROME IN NEUROMUSCULAR DISEASE

RLS, or Willis–Ekbom disease, is defined by an unpleasant urge to move the legs and/or arms, relief with movement, and a predominance of symptoms during evening hours and during periods of inactivity. The etiology is complex and likely multifactorial. Postulated mechanisms include genetic predisposition, decreased iron stores, thalamic dysfunction, and dysregulation of dopamine and other neurotransmitters. PLMS may also be present. Peripheral neuropathies are associated with an increased incidence of RLS and PLMS. These include diabetic polyneuropathy, inherited polyneuropathies (CMT), and CIDP. The pathophysiology may be related to axonal dysfunction or lack of spinal inhibitory input. Frequent symptoms may require daily use of dopamine agonists or calcium channel alpha-2-delta ligands, such as gabapentin. Serum ferritin should always be checked and levels
<50 should be treated with iron and vitamin C supplementation. It should be noted that all of the medications used in the treatment of RLS may exacerbate excessive daytime sleepiness in patients with neuromuscular hypoventilation. Opiates, including methadone, should be avoided in these patients as they can exacerbate sleep disordered breathing and nocturnal hypoventilation. For a complete review of RLS and its treatment, the reader is directed to the movement disorders chapter in this text.

PAIN SECONDARY TO NEUROMUSCULAR DISEASE

Pain is common in NMD; the causes may include neuropathic pain from sensory neuropathy, muscle pain from myositis, and other musculoskeletal pain due to weakness, inability to move, and orthopedic problems. These symptoms should be discussed at each visit. The mainstay of pharmacologic treatment is neuropathic pain medications (i.e., gabapentin, pregabalin, nortriptyline) in low doses. While not as sedating as opiates, the patient should still be queried on follow up visits for any symptoms of respiratory depression. Difficulties in positioning may be addressed with a hospital bed or alternating pressure mattress cover. An occupational therapist can provide valuable input on equipment.

EVIDENCE FOR TREATMENT OF SLEEP DISTURBANCES IN NEUROMUSCULAR DISEASE

As a general rule, treatment with NIV is recommended in any patient with NMD and nocturnal hypoventilation. In many conditions, NIV is associated with improved quality of life and even extended duration of life.

Amyotrophic Lateral Sclerosis

ALS is characterized by progressive degeneration of the upper and lower motor neurons. Respiratory failure is common, and typically results in death within 3–5 years of disease onset. Sleep-disordered breathing is a common feature due to weakness of the respiratory musculature. A number of studies have demonstrated that NIV improves sleep architecture, nocturnal hypoxia, and hypercapnia, even in patients with bulbar weakness (in whom mask fit and titration are assumed to be more challenging). The benefit of NIV in ALS goes beyond sleep because it unequivocally prolongs survival. In a randomized controlled trial of 41 ALS patients with either orthopnea and MIP <60 cm H₂O, or with symptomatic daytime hypercapnia, patients with moderate or no bulbar dysfunction who used NIV had prolonged survival by 205 days, and also reported large benefits in quality of life on several indices. The sleep clinician may be an important advocate in helping ALS patients avail themselves of this life-altering treatment.

Myotonic Dystrophy

As in other NMDs, the use of NIV in DM improves nocturnal hypoventilation on PSG and symptoms of daytime sleepiness. In addition, there is limited data to support the use of
stimulant medications for symptomatic treatment of excessive daytime sleepiness in patients with DM1. In a small crossover trial, methylphenidate 20 mg daily significantly reduced excessive daytime sleepiness as measured by ESS. However, a small randomized controlled trial of modafinil 300 mg daily was ineffective in improving results on maintenance of wakefulness test scores or self-reports of sleepiness as measured by a global self-assessment scale. Of note, in a nonrandomized observational study of 145 patients, many patients and caregivers reported meaningful benefit from modafinil on open-ended surveys (the ESS and other measures were not used). Further stimulant trials are ongoing.

**Duchenne Muscular Dystrophy**

Duchenne Muscular Dystrophy (DMD) is an X-linked disorder that results in mutations to the dystrophin gene, which is essential to muscle membrane and cytoskeleton stability. In early childhood, boys manifest proximal greater than distal weakness and Gower’s sign, a maneuver in which the arms are used to push up to a standing position. Over time, restrictive ventilatory disease develops due to thoracic wall weakness and scoliosis. Standard of care includes corticosteroids to slow disease progression; however, these medications can result in obesity and further impact respiratory function. Disease-associated cardiomyopathy also compounds efforts to improve sleep-related breathing, and it is important to recognize that untreated ventilatory insufficiency can contribute to cardiac disease.

PSG in DMD reveals obstructive and restrictive components. As in other NMDs, morning headaches and daytime fatigue may precede frank respiratory symptoms. Predictors of sleep-disordered breathing include a higher body mass index (BMI) and decreased abdominal wall strength. Since the oral and pharyngeal musculature is less affected than truncal, ventilatory, and limb musculature in Duchenne patients, NIV can typically be used well into the course of the disease without resorting to tracheostomy to maintain adequate daytime and nighttime ventilation.

In DMD, the use of NIV improves quality of sleep, quality of life, and survival. DMD-specific guidelines support nocturnal NIV if the following abnormalities are noted:

- signs or symptoms of hypoventilation,
- awake baseline SpO$_2$ <95% and/or blood or end-tidal CO$_2$ >45 mmHg,
- apnea–hypopnea index (AHI) >10 per hour; or four or more episodes of SpO$_2$ <92%; or desaturations of at least 4% per hour of sleep during PSG.

**Spinal Muscular Atrophy**

Mutations in the survival motor neuron 1 (SMN1) gene result in this autosomal recessive anterior horn cell disease. Residual function of the SMN2 gene allows for some modulation of disease severity. Patients develop proximal greater than distal weakness with lower motor neuron features. Onset ranges from childhood to adulthood, and earlier symptoms are associated with a more severe and potentially fatal course.

Restrictive lung disease is common, in large part due to intercostal muscle weakness, although the diaphragm is also involved to a lesser degree. As a result, contrary to what is seen
in other NMDs, patients with SMA often breathe better when recumbent than when upright. Paradoxical breathing is common, with inward movement of the chest wall during inspiration. Nocturnal hypoventilation has been well documented in the infant SMA population, and certainly occurs in adult patients with SMA. Daytime fatigue due to increasing nocturnal hypoventilation might be erroneously attributed to disease progression in the skeletal muscles, when in fact the worsening hypoventilation is quite treatable. Treatment with NIV significantly improves the subjective and objective quality of sleep in infants and children, and incontrovertibly improves survival. There is limited evidence to suggest that a CNS process in infants with SMA may reduce arousal thresholds during sleep. If so, this may further impact the quality of sleep, independent of nocturnal hypoventilation.

**Pompe Disease**

This autosomal recessive metabolic disorder is caused by mutations in lysosomal acid alpha-glucosidase (acid maltase), leading to pathologic intracellular accumulations of glycogen and exaggerated lysosomal function. Ultimately, the disease manifests in infants as severe hypotonia and cardiomyopathy, or presents later in life with progressive skeletal myopathy and hypoventilation. The diaphragm is often involved. Respiratory muscle weakness and nocturnal hypoventilation are significant in both infantile- and adult-onset forms of the disease. Treatment with NIV improves gas exchange during sleep and reduces symptoms of daytime sleepiness and fatigue. There is evidence that respiratory muscle training improves strength during inspiration and expiration, and also improves performance on PFT parameters; this could theoretically improve nocturnal hypoventilation as well. Enzyme replacement therapy may also stabilize the progression of sleep disturbances.

**CONCLUSIONS**

NMDs affect sleep via several mechanisms. Respiratory and bulbar weakness and abnormal skeletal anatomy result in hypoventilation. Over time, secondary hypercapnia results in desensitization of central chemoreceptors and diminished respiratory drive. In certain conditions, additional central changes in sleep patterns can occur independent of respiratory weakness. PSG may reveal obstructive and nonobstructive (pseudocentral) apneas, and hypoventilation can become severe during REM sleep. NIV is the mainstay of treatment of hypoventilation. Supplemental oxygen should be used with extreme caution, if at all. Stimulants and other treatments may be used in certain conditions.

The astute sleep clinician may be the first to recognize hypoventilation and respiratory muscle weakness due to NMD. Early and ongoing treatment of these patients can significantly improve sleep, quality of life, and survival.

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References


16. SLEEp aND NEUrOmUScULar DISEaSE
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