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Neuromuscular Disorders and Sleep in Critically Ill Patients

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Synopsis

Sleep-disordered breathing (SDB) is a frequent presenting manifestation of neuromuscular disorders and can lead to significant morbidity and mortality. If not promptly recognized and addressed early in the clinical course, SDB can lead to clinical deterioration with respiratory failure. In this article, we review the pathophysiologic basis of SDB in neuromuscular disorders, clinical features encountered in specific neuromuscular diseases, and diagnostic and management strategies for SDB in neuromuscular patients in the critical care setting. Non-invasive positive pressure ventilation (NIPV) has been a crucial advance in critical care management, improving sleep quality and often preventing or delaying mechanical ventilation and improving survival in neuromuscular patients.

Keywords

Neuromuscular disorders; Sleep; sleep disorders; Critical care; Intensive care unit; management

Neuromuscular disorders are frequently associated with sleep-disordered breathing (SDB) abnormalities, although the cumulative prevalence is not well known and probably underestimated. Between 27–62% of children (1–3) and 36–53% of adults (4) with neuromuscular disorders have SDB, depending on the type of neuromuscular disorder

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involved, definition of respiratory impairment, and tools used to measure SDB. Forty percent of patients followed at a Mexican neuromuscular clinic had sleep or SDB abnormalities (4). Sleep disordered breathing with or without nocturnal hypercapnic hypoventilation is a common complication of respiratory muscle weakness in childhood neuromuscular disorders. Sleep disordered breathing was found in 35/49 patients (71%), and 24 (49%) had sleep disordered breathing with nocturnal hypercapnic hypoventilation. (3) Patients suffering from neuromuscular disorders may present with impairment at the levels of the upper motor neuron, lower motor neuron, nerve roots, brachial plexus, peripheral nerve, neuromuscular junction, or muscle, causing weakness of respiratory muscles that may result in sleep-disordered breathing (SDB).

SDB often precedes daytime respiratory symptoms and may be the presenting manifestation in patients with neuromuscular disorders. Hence, untreated SDB may result in acute or chronic respiratory failure, the most common cause of morbidity and mortality in up to 80% of patients with neuromuscular diseases (5). The risk of respiratory infections is increased by impairment of cough due to respiratory muscle or bulbar weakness, and death is frequently due to respiratory failure. In addition to diaphragmatic and respiratory muscle weakness, several other factors mediate disturbed sleep in patients with neuromuscular disorders, including those summarized in Table 1 below.

During sleep, particularly in rapid eye movement (REM) sleep, upper airway resistance increases, while chemosensitivity and skeletal muscle tone decrease (with the exception of the diaphragm), resulting in hypoventilation leading to hypoxemic and hypercapnic failure. The most common form of SDB in patients with respiratory muscle weakness is hypoventilation due to reduced tidal volume, particularly during REM sleep, but nocturnal desaturation may occur due to nocturnal hypoventilation, periodic apneas and hypopneas, or ventilation/perfusion mismatching resulting from atelectasis in the supine posture. Secondary lung diseases such as aspiration from pharyngeal muscles impair deglutition and decrease cough reflex, predisposing to atelectasis and bronchiectasis, leading to long-term pulmonary fibrosis.

SDB leads to significant deterioration in both subjective and objective sleep quality, with specific common objective alterations in sleep architecture and polysomnographic parameters as outlined in Table 2 below. SDB is more likely to occur in patients with rib cage and spinal deformities, obesity, and craniofacial abnormalities. Because NMD are most vulnerable to oxygen desaturation during REM sleep, suppression of REM sleep may represent a compensatory mechanism. The risk of respiratory infections including pneumonia is also increased, due to impairment of cough and clearing of secretions given respiratory and/or bulbar weakness.

When there are clinical symptoms or signs or symptoms of sleep-related hypoventilation, polysomnographic evaluation and non-invasive positive pressure ventilation (NIPV) should be promptly considered. Typical signs of sleep-related hypoventilation include orthopnea, abdominal paradox in the supine position, daytime hypercapnia with $PaCO_2$ above 45 mg Hg, impairment of pulmonary function tests (FVC < 50%, maximal inspiratory pressure below 40 cm H_2O), waking oxyhemoglobin saturation below 91%, or SpO_2 saturation under

88% for 5 or more minutes (6). Paradoxical breathing while supine is not obvious until the diaphragmatic strength is less than 25% of normal. Other typical alterations in pulmonary function testing in neuromuscular patients that suggest the need for objective assessment for SDB are summarized in Table 3.

Symptoms of alveolar hypoventilation include: shortness of breath when sleeping supine or bending; nocturnal awakenings and difficulties to awaken in the morning hours; early morning or nocturnal headaches; decreased daytime stamina without change in weakness; shallow breathing or labored breathing, tachypnea or cyanosis while asleep; and red eyes due to conjunctival congestion. However, patients with neuromuscular disorders often fail to endorse symptoms of sleep/wake disturbance. In fact, sleep wake symptoms poorly predict patients with neuromuscular disorders who have SDB. Signs of alveolar hypoventilation include: paradoxical breathing and tachypnea in the supine position; rapid, shallow breathing and tachypnea while awake; use of accessory inspiratory respiratory muscles, and expiratory abdominal muscle to breath. Pulmonary predictors of sleep hypoventilation include: FVC <50% (< 60% if obese, pulmonary disease comorbidity, and/or kyphoscoliosis); supine paradoxical breathing and tachypnea; > 25% decrease in FVC from sitting to supine; awake oxyhemoglobin saturation < 91% on room air; daytime hypercapnia with $PaCO_2$ > 45; maximal inspiratory pressure < 40 cmH_2O.

Since nocturnal hypoxemia is caused by hypoventilation in neuromuscular weakness, oxygen should not be utilized without ventilatory support. Patients with chronic hypercapnia are dependent upon hypoxemic respiratory drive, and oxygen alone could further blunt the hypoxic drive to breathe, raising the risk for severe hypercapnia and respiratory failure.

Studies on sleep disorders in general and SDB in particular in neuromuscular patients hospitalized in the ICU are lacking. However, it is to be expected that the problems observed in less seriously ill neuromuscular patients will be magnified in those already exhibiting neuromuscular respiratory failure or critically ill because of intercurrent systemic disease. The pathophysiological concepts presented above should therefore be carefully kept in mind when caring for neuromuscular patients in the ICU, especially the risk of worsening respiratory failure during the night as patients lose respiratory muscle tone and develop more profound hypoventilation.

SDB Manifestations in Specific Neuromuscular Disorders

MOTOR NEURON DISORDERS

Amyotrophic lateral sclerosis (ALS)—Amyotrophic lateral sclerosis, also called motor neuron disease or Lou Gehrig's disease, is a fatal neurodegenerative disorder caused by fulminant degeneration of upper and lower motor neurons in motor cortex, brain stem, and spinal cord. ALS is characterized by progressive muscle weakness, atrophy, fasciculations, hyperreflexia, spasticity and bulbar symptoms. The major cause of morbidity and mortality in ALS is denervation weakness of respiratory muscles leading to respiratory failure. ALS exists in a sporadic form, which is most common, having onset in sixth and seventh decades, and a familial form, comprising 5–10% of cases and typically evolving at a younger age. (7) ALS most frequently begins asymmetrically in the limbs (60% of cases), although bulbar

variants (30%) are particularly devastating given their more rapidly progressive courses toward respiratory failure, and isolated involvement of the diaphragm and respiratory muscles also affects approximately 2% of cases at onset. (8) Nocturnal hypoventilation and oxyhemoglobin desaturation are the principal sleep-related abnormalities, and sleep apnea is most frequently described in bulbar involvement. (9)

Patients often experience frequent nocturnal awakenings, poor sleep quality often with daytime sleepiness, and morning headaches due to hypoventilation. The main cause of hypoxemia is REM sleep hypoventilation due to diaphragmatic weakness (10). Pulmonary function tests are prognostically valuable in monitoring disease progression (11). Respiratory insufficiency during sleep can be treated with non-invasive positive pressure ventilation (NIPV), bilevel positive airway pressure (BPAP), or tracheostomy ventilation (TV). Objective respiratory parameters signaling the need for consideration of NIPV are shown in Table 4 below (11,12).

NIPV improves nocturnal breathing, sleep quality, cognitive function (13), quality of life and median survival, especially in patients with normal or moderate bulbar impairment (13). There is no demonstrated effect on certain objective polysomnographic parameters such as sleep efficiency or arousal index (15). Mask intolerance may result from excessive sialorrhea or facial weakness, and remains a challenge and potential barrier to adequate adherence to NIPV. Excessive salivation can be reduced by tricyclic antidepressants, scopolamine patches, or botulinum injection (6). Diaphragmatic pacing stimulation to induce phrenic nerve function may delay chronic mechanical ventilation up to 24 months(16). Goals of care need to be clarified regarding invasive mechanical ventilation by tracheostomy, which is a resource intensive undertaking with a potentially high emotional toll. Air hunger in terminal stages is managed by palliative (hospice) care teams using morphine administration. In an epidemiological setting, ALS survival after tracheostomy was <1 year. (17)

Spinal muscular atrophy (SMA)/Kennedy's Disease (SMBA)—Spinal muscular atrophy (SMA) is characterized by deterioration of spinal cord anterior horn motor neurons and variable deterioration of bulbar cranial nerve nuclei. There are 4 subtypes according to age of onset. Kennedy's disease (Spinal Muscular Bulbar Atrophy, or SMBA) is an autosomal recessive neurodegenerative disorder associated with mutation of the androgen receptor gene. Patients may have intercostal and diaphragmatic muscle weakness with different degrees of bulbar symptoms, leading to respiratory dysfunction, hypoventilation, and SDB. Chest wall deformities and scoliosis may worsen ventilation, eventually leading to respiratory failure, especially in childhood onset forms. SDB in Kennedy's disease is characterized by obstructive sleep apnea/hypopnea, hypercapnia, and oxyhemoglobin desaturation during REM sleep. Sleep is disrupted by frequent arousals and sweating, morning headache, daytime sleepiness, and school performance difficulties in children and adolescents (18). NIPV can improve subjective and objective symptoms of SDB. OSA is the most common sleep disorder in SBMA. The sleep impairment could be induced both by OSA or/and the neurodegenerative processes involving crucial areas regulating the sleep-wake cycle. (19)

Post-polio syndrome (PPS)—Post-polio syndrome (PPS) may develop in patients with a history of remote acute poliomyelitis, most often occurring between 2 to 5 decades after the initial attack. (20) In primary acute poliomyelitis infection, poliovirus destroys spinal cord anterior horn motor neurons, causing denervation weakness. PPS is manifested by new weakness in previously involved and spared muscles. The process of ongoing chronic denervation due to aging-related motor neuron loss exceeds the capacity for reinnervation of the muscle by healthy neurons. Patients with bulbar forms may develop impaired respiration and swallowing. In the PSS, central respiratory control and peripheral respiratory function might be simultaneously affected, especially in sleep. PSG most often demonstrates obstructive sleep apnea, nocturnal hypoventilation, or a combination of both, with delayed REM sleep latency and reduced REM time (probably due to pontomedullary dysfunction in bulbar form), recurrent arousals, and sleep fragmentation. (21) SDB in the form of central or obstructive sleep apnea may lead to excessive daytime sleepiness, and ultimately respiratory insufficiency may occur. Patients with bulbar involvement have more frequent central sleep apnea, especially in NREM sleep, suggesting reduction in forebrain control of compromised bulbar respiratory centers during NREM sleep in post-polio syndrome. (22) Patients with kyphoscoliosis secondary to polio may develop restrictive respiratory dysfunction with thoracoabdominal and accessory muscle weakness (10, 23). Therapeutic options include introduction of NIV with pain control and physical therapy, and only rarely is tracheostomy with mechanical ventilation necessary. (20)

SPINAL CORD DISORDERS

Spinal cord injury—Sleep disruption in patients with spinal cord injury is multifactorial, caused by location of trauma, pain, spasms, bladder distention, incontinence, medication, and restless leg syndrome, requiring a highly collaborative and integrative multidisciplinary approach. Altered sleep-wake regulation may occur if spinal cord injury extends to the brain stem and affects reticular formation (RF) functioning. Concomitant traumatic brain injury accompanying spinal cord injury may cause central posttraumatic hypersomnia by affecting hypocretinergic projections. (24) Reduced plasma melatonin concentration may also occur in these patients, with consequences including shortened total sleep duration, repeated arousals, longer wakefulness periods, and reduced REM percentage. Obstructive sleep apnea is more common in patients with spinal cord injury than in the general population. (24) One series showed that 77% of spinal cord inured patients had SDB (AHI > 5 events/h), and that cervical spinal cord injured patients had decreased variability in minute ventilation and increased end tidal CO2 during sleep relative to thoracic spinal cord injured patients. (25) Sleep-related hypoventilation may occur given reduced activity of intercostal and respiratory accessory muscles, especially during REM sleep. Central sleep apnea may appear after cervical spinal cord injury with involvement of brain stem respiratory centers and syringobulbia.

Defective melatonin secretion can be treated with replacement by 2–6 mg dosed before bedtime and hypnotics can be used for insomnia (24). Excessive daytime sleepiness resulting from head injuries can be treated with modafinil (24). Treatment of sleep disordered breathing and central hypoventilation syndrome include conservative approaches like

positional control and minimizing respiratory suppressants, and more sophisticated strategies like NIPV, tracheostomy, and diaphragm pacing(16).

AUTOIMMUNE/INFLAMMATORY NEUROPATHIES

Acute Inflammatory Demyelinating Polyradiculoneuropathy (Guillain-Barre Syndrome, or GBS)—AIDP/GBS is an autoimmune process mediating rapid-onset weakness of the limbs, with varying involvement of bulbar and respiratory weakness and autonomic dysfunction. AIDP/GBS results from acute immune-mediated nerve dysfunction that is often triggered by an infectious process, especially Campylobacter Jejuni, mycoplasma, and viral processes such as CMV, EBV, and HIV. (26)

Progressive weakness of respiratory muscles leads to respiratory failure while bulbar weakness and ineffective cough predisposes to aspiration pneumonia and atelectasis.

Treatment includes IVIg or plasmapheresis with supportive measures. Serial NIF and FVC should be monitored with observation in ICU if Vital capacity < 1 L/min. Intubation is indicated in 30 % (27) cases of GBS usually secondary to respiratory muscles weakness. Dysautonomia can induce severe hypotension or cardiac arrhythmias associated with the use of sedatives.

Sleep disturbances in GBS include abnormal sleep onset latency, sleep fragmentation, reduced sleep duration. The severity of disruption correlates with anxiety, pain, paresthesia, and severity of immobility and degree of respiratory involvement. Sleep disturbances are frequent in GBS and impact over 50% patients; in one series, symptoms of insomnia were present in 13.3%, and 51.6% had symptoms of poor sleep quality on the Richard-Campbell Sleep Questionnaire. (28) Abnormal sleep onset latency, sleep fragmentation, and reduced sleep duration were reported in 35–46.6% of GBS patients. Symptoms of sleep disturbance were severe during the first week of hospitalization and significantly correlated with anxiety, pain, paresthesias, and severity of immobility, and symptoms improved after discharge. (28) NIPV is not a good option in patients with GBS because once these patients develop respiratory failure their respiratory muscle weakness will be prolonged. In addition, these patients can develop dangerous complications from dysautonomia while being treated with NIPV and particularly during emergency intubation following failure of NIPV (29). However, NIPV is a good option in recovering patients who can be extubated, but are still weak and need overnight support.

Bilateral Isolated Phrenic Neuropathies (BIPN)—Diaphragmatic palsy can develop in association with variety of disorders causing isolated injury to bilateral phrenic nerves, resulting in respiratory insufficiency. Unilateral diaphragmatic palsy is usually asymptomatic, unless there are other co-morbid restrictive or obstructive pulmonary factors impacting ventilation (i.e., obesity, chronic obstructive pulmonary disease), whereas insufficiency is frequent in the setting of bilateral phrenic neuropathies. (30)) Etiologies for diaphragmatic weakness, especially when bilateral, include inflammatory brachial neuritis (Parsonage-Turner syndrome, also known as neuralgic amyotrophy or immune brachial plexus neuropathy), or as part of a more diffuse systemic neuromuscular disorder with etiologies as diverse as diabetic polyradiculoneuropathy, the Guillain-Barre syndrome, large

artery vasculitis, von Recklinghausen disease (31), shrinking lung syndrome or iatrogenic causes (most cases in the ICU are encountered after thoracic surgery). The poorly understood entity of bilateral idiopathic isolated phrenic neuropathy (BIPN) is also recognized as a rare cause of acute or subacute unexplained dyspnea, with especially prominent orthopnea.(30,32) BIPN usually has an acute, painless onset, without antecedent trigger, leading to hypercapnic respiratory failure. Patients demonstrate orthopnea, use of accessory respiratory muscles, and thoracoabdominal paradox. Pulmonary function tests show an up to 50% decrease in vital capacity between the supine and upright positions (23). Chest x-rays show bilateral diaphragmatic elevation, electromyography demonstrates reduced or absent phrenic nerve conduction studies with active diaphragmatic denervation, and diaphragmatic ultrasound and fluoroscopy show reduced diaphragmatic excursion (32).

Patients with both bilateral and severe unilateral IPN with coexisting pulmonary pathology are at high risk of SDB. Severe nocturnal hypoventilation and desaturation during REM sleep can occur, obviating need for polysomnographic evaluation. Patients suffer from fragmented sleep and consequently fatigue, morning headaches, and hypersomnia. Patients with unilateral diaphragmatic paralysis and concurrent ipsilateral pulmonary pathology often demonstrate worsened severity of disordered breathing with more profound oxyhemoglobin desaturation when they are positioned with the functioning, healthy diaphragm in recumbency during lateral non-supine sleep positions, due to worsened ventilation perfusion mismatch as the more restricted lung parenchyma is upright. (30) A minor contribution could also be due to lateral sleep on the side of the “healthy diaphragm” restricting hemithoracic expansion of the “healthy side” and exacerbating the V/Q mismatch.

During reinnervation of the diaphragm which can be modest, partial, or complete, patients require NIPV to improve quality of life and prevent respiratory failure. NIPV often reduces sleep disruption and allows greater comfort and ease of resting in the recumbent position (32,33). Diaphragmatic function can also be sustained by functional electrical stimulation of the phrenic nerve if there has not been substantial axonal degeneration (34).

NEUROMUSCULAR JUNCTION DISORDERS

Myasthenia gravis—Myasthenia gravis (MG) is an autoimmune disease characterized by fatigable weakness with antibodies directed against components of neuromuscular junction, most often against the post-synaptic nicotinic acetyl choline receptor. Muscle specific tyrosine-kinase antibodies (MuSK) are also found in a subset of patients with MG. The majority of MG patients present with diplopia, ptosis, dysphagia, dysarthria, and weakness of limbs, neck extensors and flexors, and facial and bulbar musculature, with involvement of the diaphragm leading to respiratory failure in severe cases. MG symptoms fluctuate and typically worsen with repeated use, especially in the evening.

Respiratory and sleep disturbances can be detected by subjective symptoms such as nocturnal breathlessness, morning headache, fatigue, and daytime somnolence, or by objective testing demonstrating oxyhemoglobin desaturation or hypercapnia. SDB is especially prominent during REM sleep due to diaphragmatic weakness, with prominent obstructive, central, and mixed sleep apnea. OSA frequency is 15–20% higher in MG than in the normal population (35) due to oropharyngeal weakness. Daytime pulmonary function

tests are usually normal when MG is in remission, or if there are no risk factors for respiratory compromise such as older age, obesity, oropharyngeal weakness, or decreased total lung capacity (36).

While in stable disease there is no association with significant SDB (37), myasthenic or iatrogenic cholinergic crisis (the latter resulting from excessive pyridostigmine treatment) may lead to pronounced SDB, respiratory insufficiency, and eventual respiratory failure. MG patients suspected of myasthenic or cholinergic crises require ICU monitoring, with frequent serial FVC and NIF monitoring. Intubation is indicated for FVC < 20 ml/kg, NIF <−20, or rapid respiratory decline with signs such as brow sweating, tachypnea, or accessory respiratory muscle use.

NIPV with bilevel positive airway pressure (BPAP) can avert intubation and substantially decrease the duration of the hospitalization as compared to direct invasive ventilation (38). BPAP should be initiated early, ideally before the development of hypercapnia, to maximize its chances of success (38). As BPAP is being weaned off or after extubation, it is always safer to keep the patients on BPAP overnight, especially during the first 1–2 nights after daytime ventilation is removed.

Acute treatment for myasthenic crisis includes removing any precipitants (such as aggravating drugs, i.e., beta or calcium blocking antihypertensives, antiarrhythmics, certain antibiotics, or corticosteroids), IV cholinesterase inhibitor, plasma exchange, IVIg, NIPV and steroids (which must be administered with caution and careful monitoring given propensity for temporary acute worsening of MG).

When needed, SDB is symptomatically treated by introduction of nasal CPAP or NIPV. Nocturnal hypoventilation and sleep apnea may be severe and occasionally require assisted ventilation.

Lambert-Eaton Myasthenic Syndrome and Botulism—SDB in LEMS and botulism is much less frequent than in MG (23). Significant muscle weakness can lead to severe respiratory impairment that may require assisted ventilation. Frequent clinic evaluation of the bulbar and cervical muscles can help identify segmental weakness that may assist in predicting diaphragmatic weakness and the need for NIPV or mechanical ventilation.

MYOPATHIES

Dystrophies

Duchenne Muscular dystrophy—Duchenne muscular dystrophy (DMD) is a recessive X-linked muscle disease caused by mutation in dystrophin gene encoding the protein dystrophin. Clinical manifestations appear between 3–5 years of age, with progressive muscular weakness involving respiratory muscles ultimately causing respiratory failure, the most common cause of death (in 80%) by the third decade of life. Earlier in the course, especially in younger boys during the later first decade of life, obstructive sleep apnea occurs commonly due to involvement of upper airway dilator muscles, and tonsillectomy alone is often sufficiently effective treatment. Progression of muscular weakness leads to

musculoskeletal deformities of the rib cage in children 10). As DMD advances, patients suffer from marked REM-related hypoventilation with profound oxyhemoglobin desaturations despite normal awake ventilation due to progressive weakness and kyphoscoliosis, especially when a state of wheel chair dependence is reached. Daytime predictors of sleep related hypoventilation include a $PaCO_2$ > 45 mm Hg and daytime symptoms of excessive sleepiness, morning headaches, and fatigue caused by sleep fragmentation and REM sleep deprivation (5).

In patients suffering from sleep-related hypoventilation and daytime symptoms, polysomnography and NIPV should be considered. NIPV can improve sleep and quality of life, and decrease daytime sleepiness, while improving pulmonary function and daytime gas exchange, and increasing survival (39,40). Significant nocturnal and later daytime respiratory insufficiency and ineffective coughing occur as weakness progresses, leading to complications such as atelectasis and aspiration pneumonia, requiring 24-hour ventilatory support. Tracheostomy is indicated in patients with recurrent respiratory infections when direct airway suctioning is necessary, and in severely compromised chest wall compliance (10). Steroid use in children can slow progression of scoliosis and delay spinal corrective surgery.

Myotonic dystrophy—Myotonic dystrophy (DM) is an autosomal dominant multisystem disorder affecting skeletal and cardiac muscle as well as the eye, endocrine functioning, and central nervous system. DM is divided into 2 subtypes. Myotonic dystrophy type 1 (Steinert disease, DM1) is caused by CTG trinucleotide repeat expansion of protein kinase (DMPK) gene (41). DM 1 is characterized by genetic anticipation, which results in increasingly severe phenotypic expression in successive generations. Myotonic dystrophy type 2 (DM 2, proximal myotonic myopathy, or PROM) results from CCTG repeat expansion within the zinc finger protein 9 (ZNF9) gene. DM2 is usually a milder phenotype with onset in middle adulthood, but may involve a different spectrum of sleep disturbances, including prominent restless legs syndrome (41, 42).

Myotonic dystrophy is characterized by muscle weakness and myotonia but may be associated with a wide variety of sleep disturbances (,41,42,43) Interestingly, recent evidence shows extensive central nervous system white matter involvement in DM 1 and 2, while grey matter decrease (cortical areas, thalamus, putamen) was restricted to DM 1 (44). In moderately advanced DM, hypersomia, apathy, and mental decline have been linked to dysfunction of the dorsomedial thalamic nucleus (10).

Sleep disturbances in DM may include prominent SDB with obstructive or central sleep apnea and sleep- related hypoventilation, central hypersomnia resembling narcolepsy or idiopathic hypersomnia, fatigue, insomnia, restless leg syndrome, and periodic limb movement disorder (6,10,41,41,42,44,45). Due to severe diaphragmatic, intercostal, upper airway, and tongue muscle weakness, patients may demonstrate significant alveolar hypoventilation with hypoxemia and hypercapnia, especially during REM sleep. Pulmonary function tests and arterial blood gases may underestimate the degree of nocturnal respiratory compromise, especially in DM1 where severe sleep hypoventilation may occur despite normal PFTs and arterial blood gases while awake (6).

In addition to prominent SDB, polysomnography in DM patients may show frequent arousals (caused by muscle pain/stiffness), decreased sleep efficiency, and frequent periodic leg movements. Central hypersomnia is especially frequent and prominent in DM 1, and has also been noted in DM 2, and may result from decreased hypothalamic hypocretinergic and brainstem raphe serotonergic functioning, and reduction of medullary reticular catecholaminergic neurons (10). DM1 patients have been shown to demonstrate abnormal central REM sleep regulation with frequent sleep onset REM periods, increased REM density, and increased daytime and nighttime REM sleep propensity. (46)

Early PSG to evaluate for SDB may enable timely implementation of nocturnal CPAP for sleep apnea, or NIPV for sleep-related hypoventilation. If daytime somnolence persists in spite of effective therapy, then CNS stimulant drugs (e.g. modafinil, methylphenidate, or dexamphetamine) may be considered (10,43) and for significant restless legs symptoms, pharmacotherapy with a dopamine agonist drug (i.e., pramipexole, ropinirole, rotigotine), or non-dopaminergic agents (gabapentin, pregabalin, tramadol) may be considered.

Facioscapulohumeral muscular dystrophy (FSHD)—Fascioscapulohumeral dystrophy (FSHD) is a slowly progressing myopathy resulting from macrosatellite repeat D4Z4 contraction on chromosome 4q35. (47) Polysomnography data suggest that FSHD patients are at risk for developing SDB due to pharyngeal muscle weakness, though respiratory muscles are spared. The risk is not dependent on the severity of disease, but is higher in the presence of weight gain, increased neck circumference, and kyphoscoliosis resulting from asymmetrical involvement of the trunk and scapular muscles (47,48) Reduced nocturnal mobility also leads to poor sleep quality. Polysomnography shows longer sleep latency, frequent spontaneous arousals, reduced overall sleep time, and shortened REM sleep time (47).

Limb-girdle muscular dystrophy (LGMD)—LGMD is a descriptive term, reserved for childhood- or adult-onset muscular dystrophy characterized by proximal skeletal muscle weakness and atrophy, with relative sparing of the bulbar muscles in most cases. Onset, progression, and distribution vary considerably among individuals and genetic subtypes, but overall LGMD is similar to Duchenne and Becker muscular dystrophy in sleep manifestations. SDB appears due to both central sleep apnea on account of failure of respiratory control, and obstructive sleep apnea due to upper airway muscles weakness (49). LGMD patients with SDB should be treated with nocturnal NIPV, and tracheostomy ventilation is rarely required.

Congenital muscular dystrophies (CMD)—Congenital muscular dystrophy (CMD) is a clinically and genetically heterogeneous group of inherited muscle disorders with presentation between birth and early infancy, including laminin-α2–deficient CMD, Ullrich CMD and muscle-eye-brain disease. Sleep is disrupted by central sleep apnea/hypopnea due to a central ventilatory control disorder, or by obstructive sleep apnea/hypopnea resulting from upper airway muscle weakness (49). Respiratory muscle atonia during REM sleep may cause nocturnal desaturation and hypoventilation. Early identification of SDB may prevent respiratory failure, so screening with polysomnography is recommended early in the course (49).

Metabolic myopathies—Metabolic myopathies are heterogeneous conditions that have common abnormalities of muscle energy metabolism, resuting in skeletal muscle dysfunction. The best known and most common example resulting in respirátory insufficiency is acid maltase deficiency (AMD), also known as Pompe's disease, which is characterized by excessive accumulation of glycogen due to absence of acid maltase. The failure of diaphragmatic muscle function is most pronounced during REM sleep, resulting in sleep-disordered breathing characterized by profound and long duration periods of sleep-related hypoventilation, substantial oxyhemoglobin desaturation, and hypercapnea. SDB and sleep-related hypoventilation may be predicted by diurnal pulmonary function tests.(50) In order to improve quality of life and prevent early respiratory failure, NIPV should be promptly instituted (50,51,52). Recombinanat enzyme replacment may improve survival and delay mechanical ventilation. (52)

Mitochondrial myopathies—Mitochondrial encephalomyopathies are characterized by respiratory chain oxidative phosphorylation defects. These disorders result in reduced energy metabolism affecting the most energy demanding tissues, primarily the muscles and brain. Prominent fatigue is typical, and various forms of nocturnal respiratory compromise have been reported (6, 51).

Inflammatory myopathies—Inflammatory myopathies include dermatomyositis (DM), polymyositis (PM), and inclusion-body myositis (IBM). These disorders lead to mobility impairment, loss of muscle tone, weakness of respiratory muscles (particularly oropharyngeal muscles), leading to obstructive sleep apnea and respiratory compromise (53). PM is also associated with interstitial lung disease causing hypoxemia due to gas exchange abnormality(53).

Critical Illness Neuromyopathy—Critical illness neuromyopathy (CINM) is increasingly recognized complication of sepsis and multiorgan failure. Also known by the generic term ICU acquired weakness, this condition can affect peripheral nerves (critical illness polyneuropathy) and muscles (critical illness myopathy). Often the disease manifests combined signs of polyneuropathy and myopathy. Polyneuropathy is characterized by predominant motor nerve involvement while the myopathy is the product of myosin loss and occurs more commonly in patients treated with high dose steroids and neuromuscular blocking (44). CINM usually presents as unexplained, persistent diffuse weakness after respiratory support or neuromuscular paralysis, delaying weaning from mechanical ventilation. (45)

Preventive measures consist of early mobilization and reducing exposure to prolonged high dose steroids and neuromuscular blocking agents. There is no specific treatment. Prolonged invasive ventilatory support is required given the diaphragmatic involvement. Duration of weaning can be increased 2 to 7 times, with continued supportive measures (45). Full recovery has been reported in over 50% of patients, although incomplete recovery remains unfortunately frequent in severe cases and it is more common in patients with severe neuropathic involvement (45).

Diagnostic Assessment and Approach to the Patient with Neuromuscular Disease and Sleep-Disordered Breathing

Assessment of sleep complaints is crucial in patients with neuromuscular disease for consideration of polysomnographic evaluation for OSA, CSA, or hypoventilation. A careful sleep history includes questioning about disruptive snoring, snort or gasp arousals, witnessed pauses in breathing, and regular symptoms of morning headache, dry mouth, or sore throat. Inquiring about restless legs symptoms (uncomfortable urge to move the legs, rest onset/worsening, relief upon movement or getting up to walk, and evening predominance) is also important, especially in DM patients (42,43). However, some neuromuscular patients may still have significant SDB despite a paucity of clinical symptoms, so initial unattended screening studies such as portable oximetry should be considered to complement the history and physical examination.(4356,57)

Pulmonary function tests (PFT) may assist in evaluating for the likelihood of SDB, especially sleep-related hypoventilation and may have prognostic value (11). The most important PFT measures for prediction of SDB in neuromuscular patients are vital capacity (VC) in the upright and supine positions and maximal inspiratory and expiratory pressures. A decline in the VC between the sitting and supine positions by more than 20% is highly suggestive of diaphragmatic weakness and probable SDB and nocturnal hypoventilation. VC less than 50% and history of recurrent respiratory tract infections are frequent in patients with neuromuscular disease having nocturnal hypoventilation. Neuromuscular junction disorders such as myasthenia gravis or Lambert-Eaton syndrome lead to fluctuation of muscle weakness and VC, so caution in technique and interpretation is necessary and declining or stable trends may be more reliable than single values. Sleep hypoventilation is especially likely when VC is less than 50% of the predicted value, or if a 20% or greater decline in VC between the upright and supine positions is seen. In such cases, polysomnography with prompt triage toward NIPV should be strongly considered.

Supine vital capacity nasal inspiratory pressure (SNIP) measures inspiratory muscle function, especially diaphragmatic functioning. SNIP > 70 cm H_2O (in men) or > 60 cm H_2O (in women) essentially exclude significant respiratory muscle weakness. SNIP well predicts nocturnal hypoventilation and respiratory failure in ALS (58), and NIPV should be initiated when SNIP < 40 cm H_2O(59). Mouth pressures (MIP, MEP, aka bugle pressures) assess inspiratory and expiratory muscle functioning. Bugle pressure trends are very helpful in following respiratory functioning at the bedside in hospitalized neuromuscular patients, although caution is necessary in interpretation in patients with substantial facial muscle weakness, as this may lead to insufficient mouth sealing and consequently spuriously low measurements. Arterial blood gas (ABG) values remain normal range during wakefulness until later in the course of neuromuscular respiratory failure, and abnormal ABG values indicate significantly weak respiratory muscles, most often showing chronic, compensated respiratory acidosis with elevated $PaCO_2$ and bicarbonate and normal or slightly reduced pH. Nocturnal hypoventilation is diagnosed by nighttime oxyhemoglobin desaturation (SpO_2 < 88%) for five or more consecutive minutes, together with a morning ABG demonstrating

daytime hypercapnia ($PaCO_2$ > 45mm Hg) with raised pH values and bicarbonate (6). When nocturnal hypoventilation is found, NIPV should be promptly initiated.

Portable screening devices are not very sensitive and are able to detect only moderate to severe obstructive sleep apnea. (60) Polysomnography provides the most sensitive and specific assessment of sleep in patients with neuromuscular disorders, and provide polygraphic data not only concerning respiratory function, but also movement and sleep architecture. Absent REM sleep appears to correlate with a poor prognosis neuromuscular disorders, and suggests impending respiratory failure.

Management of Sleep-Disordered Breathing in Neuromuscular Diseases

Prompt recognition and treatment of SDB in neuromuscular patients can significantly improve patient quality of life and survival. SDB may be the initial manifestation of impaired respiratory functions in neuromuscular patients. Optimizing lifestyle with weight loss for obese patients, sufficient nutrition, exercise and rehabilitation of respiratory muscles, and ensuring adequate sleep hygiene with a regular sleep schedule and avoidance of caffeine, alcohol, or sedative drugs that may disturb sleep and suppress breathing is recommended for all patients. In acutely unstable hospital inpatients, respiratory failure can rapidly emerge, especially in AIDP/GBS, myasthenia, and high-level spinal cord injury.

For acutely deteriorating neuromuscular patients, invasive ventilation should be initiated in an intensive care unit to avoid respiratory arrest. In most cases, endotracheal intubation with positive pressure ventilation is the preferred initial approach, although discussion concerning comorbidities, quality of life after extubation, and the patient's wishes must be rapidly considered. NIPV with BPAP is instead preferred in myasthenic crisis except in patients who have already developed severe hypercapnia, have excessive secretions (most myasthenic patients have increased respiratory secretions as a consequence of the use of pyridostigmine, but still the majority do well with the BPAP mask) or have such a degree of weakness and fatigue that demands controlled ventilation. Rapidly progressive bulbar and generalized muscle weakness, VC < 20 ml/kg, MIP > −30 cm H_2O, or MEP < 40 cm H_2O predict impending respiratory failure and the need for invasive ventilation (61) in ALS. These numbers are sometimes extrapolated to other neuromuscular conditions, but their discriminatory value in these cases is less certain. Tracheostomy should be considered after 7–10 days of mechanical ventilation using endotracheal intubation because it permits better pulmonary toileting, is more comfortable to patients, reduces the risk of local complications (such as mucosal erosion and vocal cord stenosis), and might diminish the risk of infections (62). Tracheostomy should also be considered in chronically treated neuromuscular patients when NIPV is failing, usually when bulbar muscle weakness or scoliosis progresses, for increasing patient safety when unable to clear secretions, and for prolonging survival (12,63). Mechanical ventilation through the tracheostomy then provides positive pressure to reduce atelectasis and improves gas exchange to treat the hypercapnia from the ongoing hypoventilation. Tracheostomy impairs communication and swallowing, so is usually considered as a last resort and requires careful discussion and advance planning with patients and their families.

NIPV is the preferred initial treatment of SDB and daytime ventilatory support in chronic, more stable neuromuscular patients. Two types of NIPV to consider are continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP). BPAP is a device that delivers a higher inspiratory than expiratory pressure that may increase tidal volume and improve alveolar ventilation, and a back-up respiratory rate can be set in a BPAP Spontaneous-Timed (ST) mode device for patients with impaired respiratory drive or neuromuscular disease. BPAP is typically more effective for treatment of nocturnal hypoventilation, so CPAP should only be initiated only when nocturnal ventilation is normal to avoid increasing burden on weak respiratory muscles. NIPV can be applied through a variety of interfaces including nasal pillows or mask, or a full face Interface. NIPV may prevent declining lung function and improve sleep quality and quality of life (61,64,65). NIPV should be initiated when patients become symptomatic from SDB or when FVC < 50% predicted, SNIP < 40 cm H_2O, PaCO2>45 mm Hg, or when nocturnal oxyhemoglobin saturation < 88% for at least five minutes (62,63,66). NIPV improves symptoms such as daytime sleepiness, fatigue, and morning headaches, and helps sleep quality, daytime gas exchange, and nighttime oxygen saturation. It may also be used in palliative care settings when tracheostomy is not desired or is no longer needed (1).

According to AASM guidelines for NIPV, bilevel IPAP/EPAP titration should begin at 8/4 cm H_2O and titrated to a maximum of 30/20 cm H_2O (6). NIPV success requires excellent patient adherence/compliance, as well as interface comfort, fit, and seal. The earlier NIPV is initiated, the better tolerance may be achieved (66). Barriers to NIPV efficacy include inability to clear secretions and neuromuscular weakness progression, Oxygen therapy can improve hypoxemia but could blunt hypoxic breathing drive if there is chronic hypercapnia, potentially leading to acute respiratory failure. Therefore, oxygen should only be used with NIPV.

Diaphragmatic pacing may replace long term mechanical ventilation in some neuromuscular patients with intact phrenic nerve segments to stimulate the diaphragm, usually in the context of neuromuscular lesions involving failure of respiratory control centers in the brain stem, or malfunction of respiratory upper motor neurons, such as may be seen in spinal cord injury above C3 and in ALS. For ALS patients, diaphragmatic pacing may delay chronic NIPV or tracheostomy by up to 24 months (67). Laparoscopic mapping of the diaphragm to identify optimal contractible motor points and daily diaphragmatic conditioning of weak or atrophic fibers is necessary prior to weaning of ventilatory support (67).

CONCLUSIONS

Sleep problems, especially sleep-disordered breathing (SDB) are frequent in neuromuscular patients, and contribute significantly to morbidity and mortality. SDB usually manifests before any daytime respiratory symptoms evolve in patients with neuromuscular disorders. Nocturnal hypoventilation is particularly common, and obstructive sleep apnea (OSA) and central sleep apnea (CSA) are also common co-morbidities in neuromuscular patients. During REM sleep, respiration depends on diaphragmatic effort, and REM-related hypoventilation and SDB are early manifestations in neuromuscular patients with evolving diaphragmatic weakness. Typical daytime symptoms of SDB include sleepiness, morning

headaches, and orthopnea. Polysomnography should be considered when these symptoms emerge, or when supine abdominal paradox, daytime $PaCO_2$ > 45 mg Hg, or impaired pulmonary function tests (VC < 50% or maximal inspiratory pressure < 40 cm H_2O) are seen. Non-invasive positive pressure ventilation (NIPV) should then be promptly initiated since it may improve quality of life and delay mortality. In addition, other sleep problems in neuromuscular problems may include central hypersomnia disorders similar to narcolepsy or restless legs syndrome in myotonic dystrophy and other neuromuscular disorders, which may benefit from pharmacotherapy with stimulants or symptomatic therapies, respectively. A team approach involving critical care and sleep physicians is necessary to promptly identify and effectively treat SDB problems in patients with neuromuscular disorders.

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Key Points

- Sleep problems, especially sleep-disordered breathing (SDB) are frequent in neuromuscular patients, and contribute significantly to morbidity and mortality.
- SDB usually manifests before any daytime respiratory symptoms evolve in patients with neuromuscular disorders.
- Nocturnal hypoventilation is particularly common, and obstructive sleep apnea (OSA) and central sleep apnea (CSA) are also common co-morbidities in neuromuscular patients.
- During REM sleep, respiration depends on diaphragmatic effort, and REM-related hypoventilation and SDB are early manifestations in neuromuscular patients with evolving diaphragmatic weakness.

Table 1

Factors causing sleep-related difficulties in neuromuscular patients

Factors Causing sleep disruption
a) Diaphragmatic and respiratory muscle weakness
b) Upper airway & craniofacial weakness
c) Difficulty with secretion clearance
d) Impairment of cough mechanism
e) Limitation of posture/discomfort due to weakness
f) Diminished ventilatory drive

Table 2

Common alterations in objective sleep parameters in neuromuscular patients.

	Alterations in sleep structure in neuromuscular patients
1	↓ total sleep time
2	↓ sleep efficiency
3	↑ sleep fragmentation
4	↑ arousals
5	↑ stage 1 sleep
6	↓ REM sleep

Table 3

Pulmonary function and lung volume alterations accompanying neuromuscular weakness

Pulmonary function/Lung volume	**Effect**
Residual Volume (RV)	↑ (with expiratory muscle weakness
Vital Capacity (VC)	Initially normal, ↓after max pressures ↓50%
Total lung Capacity(TLC)	↓ (inspiratory weakness)
Functional Residual Capacity (FRC)	↓ (inspiratory weakness)
FEV1/FVC	Normal (proportional ↓ FEV1 & FVC in inspiratory weakness)
Residual Volume (RV)	↑ (with expiratory muscle weakness)
Peak Expiratory Flow (PEF) Maximum Voluntary ventilation (MVV)	↓ (NM weakness or effort)
Diffusing Capacity (DLco)	Normal (unless infiltrative/parenchymal process)
Maximal Inspiratory Pressure MIP	↓ (more than MEP in diaphragmatic weakness, effort)
Maximal Expiratory Pressure MEP	↓ (NM weakness, effort)

Table 4

Objective respiratory parameter thresholds suggestive of need for NIPV in ALS.

Indicators for NIPV initiation (7, 9)
FVC < 50% (possibly even earlier)
MIP > −60 CWP
Sniff nasal inspiratory pressure (SNIP) < 40 CWP
O2 sat of ≤ 88%, 5 min
$PaCO_2$ > 45 mm Hg

Table 5

Predictors for intubation and mechanical ventilation in AIDP/GBS.

Predictors of Mechanical Ventilation in AIDP/GBS	**Indications for intubation in AIDP/GBS**
Rapidly progressive motor weakness	Vital capacity < 12 to 15 ml/kg or with rapid decline
Involvement of limb and the axial muscles	Negative inspiratory force (NIF) < 25 cm H_2O
Ineffective cough	Hypoxemia: Pao_2 < 80 mm Hg
Bulbar muscle weakness	Difficulty with secretions
Rapid decrease in vital capacity	