Neuromuscular disorders are progressive conditions that affect some part of the neuromuscular system. In a normal person, neurons (nerve cells) in the brain (upper motor neurons) send messages to neurons in the brain stem and spinal cord (lower motor neurons), and from there the messages are sent to the corresponding muscles. In neuromuscular disorders, these neurons that control essential muscle activity (walking, speaking, breathing and swallowing) become destroyed, and communication to muscles is reduced or lost. The affected muscles begin to weaken and atrophy (waste away). Damage and weakness of the muscles can lead to uncontrollable muscle twitching (fasciculations), cramping, aches, pain, and joint and movement problems; and can affect cardiovascular and respiratory function. Parts of the neuromuscular system that may be affected include:

- Muscles
- Peripheral motor nerves of the arms, legs, neck and face
- Neuromuscular junction (point where nerves and muscles connect)
- Motor neurons in the spinal cord that control muscles

More than one million people in the U.S. are affected by a neuromuscular disorder, and more than 40 percent of these are under the age of 18, although all ages are affected. Many neuromuscular disorders are genetic (inherited), some are caused by an immune system disorder (acquired), and some have no known cause. There are no cures for most neuromuscular disorders; therefore, treatment involves taking measures to improve length and quality of life. Prognosis varies depending on the form of neuromuscular disorder and the person’s age at disease onset. Neuromuscular disorders such as spinal muscular atrophy and amyotrophic lateral sclerosis are fatal. Life expectancy varies across neuromuscular disorders from very short to normal, and the cause of death is often a result of heart and respiratory problems, which are secondary to muscle wasting.

Many forms of neuromuscular disorders exist. The following are examples:

- Motor neuron diseases
- Multiple sclerosis
- Neuromuscular junction disorders
- Polyneuropathies and diseases of peripheral nerve
- Myopathies

Motor neuron diseases are progressive and destroy cells that control the muscles of speaking, walking, breathing and swallowing. In adults, symptoms usually appear after age 40; and in children, symptoms appear at birth or before the child begins to walk. These diseases can be inherited or acquired; but in many cases, the cause of the disease is unknown. There are no cures or standard treatments for motor neuron diseases; however, physical, speech and occupational therapy as well as rehabilitation may improve some symptoms. Common forms of motor neuron diseases include amyotrophic lateral sclerosis, primary lateral sclerosis, spinal muscular atrophy and post-polio syndrome. Prognosis depends on the type of motor neuron disease, the age of onset and the rate of progression. Some progress slowly and are not fatal, such as primary lateral sclerosis; others (i.e., amyotrophic lateral sclerosis and some forms of spinal muscular atrophy) may progress rapidly and are fatal.

Amyotrophic lateral sclerosis (ALS), or Lou Gehrig’s disease, is rapidly progressive and attacks neurons responsible for controlling voluntary muscles, which gradually weaken and atrophy; eventually, all control of voluntary movement can be lost. The ability to move arms, legs and body diminishes; however, the person’s thinking and cognition are unaffected. As the disease progresses, muscles in the diaphragm and chest wall fail, and the patient will need ventilatory support. Most patients die within 3-5 years due to respiratory failure; but some may live for more than 10 years.

Spinal muscular atrophy (SMA) mainly affects infants and children, and it includes several hereditary types that cause weakness and atrophy of voluntary muscles in the arms and legs. Lower motor neurons in the spine degenerate and die due to loss of a gene called the survival motor neuron gene (SMN1). No cure exists for SMA, and treatment consists of managing symptoms and preventing complications.

Associated Sleep Disorders

The earliest signs of breathing abnormalities in ALS may present during sleep. People with ALS may experience sleep problems due to arousals from periodic limb movements and sleep disordered breathing (SDB). As ALS progresses, the phrenic nerve is affected, and the diaphragm becomes paralyzed, which significantly intensifies hypoventilation and oxygen desaturations during rapid eye movement (REM) sleep. Poor sleep quality and disrupted architecture can occur early in the course of ALS, with apneas and hypopneas associated with hypoxemia being the most common finding.

In spinal muscular atrophy, SDB may be an early sign of respiratory muscle failure. SDB is reported to range from REM-related hypopnea to severe hypoventilation. Spinal muscular atrophies are associated with hypoventilation especially during sleep, which worsens as the disease progresses.

Multiple Sclerosis

Multiple sclerosis (MS) is a disease of the central nervous system that usually manifests between the ages of 20 and 40. Myelin, which insulates nerves, is attacked, disrupting communi-
cation between the brain and the rest of the body. Effects of MS can range from mild dysfunction to devastating disability. An initial symptom may be blurred or double vision, or even blindness in one eye. Other common symptoms include muscle weakness, pain, numbness, and tingling in extremities; and problems with cognition, speech, coordination and balance. In the worst cases, MS may even cause total paralysis.

Associated Sleep Disorders
MS is commonly associated with sleep disorders, and MS patients are coincidentally genetically susceptible to narcolepsy. Common complaints include chronic fatigue, difficulty falling asleep, restless sleep, nonrestorative sleep, and early morning awakenings. Polysomnography studies in patients with MS reveal reduced sleep efficiency and more awakenings during sleep.\(^7\)

NEUROMUSCULAR JUNCTION DISORDERS
Neuromuscular junction disorders are characterized by weakness and fatigability with exercise. These diseases may be acquired or inherited and may result from an autoimmune disorder, toxin, or congenital disorder. Myasthenia gravis is the most common disorder affecting the neuromuscular junction.\(^8\) It is a chronic autoimmune disorder involving weakness and fatigue of skeletal muscles. Muscle weakness increases during activity and improves during rest. Muscles in the face are often involved, and muscles of respiration may be affected. This disorder is caused by a defect in the transmission of nerve impulses to muscles. With treatment, patients with myasthenia gravis usually lead normal or nearly normal lives.\(^3\)

Associated Sleep Disorders
Sleep-disordered breathing is a common finding in patients with myasthenia gravis. It is associated with peripheral respiratory muscle weakness, primarily weakness of the diaphragm.\(^4\) Typical risk factors include older age, high body mass index and daytime alveolar hypoventilation.\(^3\)

POLYNEUROPATHIES & DISEASES OF PERIPHERAL NERVE
Polyneuropathies are inherited or acquired, and are characterized by degeneration of peripheral nerves and nerve roots. This results in muscle atrophy, which begins distally in the feet and legs and progressively involves more proximal muscles. Symptoms depend on the types of nerves that are damaged, which include motor, sensory or autonomic. Symptoms may include numbness, tingling, muscle weakness, sensitivity to touch, burning pain, paralysis, or organ or gland dysfunction.\(^3\) Progression and prognosis is variable in peripheral neuropathies.

Charcot-Marie-Tooth disease is a polyneuropathy and is one of the most common inherited neurological disorders.\(^3\) This disease is caused by gene mutations that affect the normal function of peripheral nerves. Onset is most often adolescence or early adulthood. The disease is typically characterized by weakness of the foot and lower leg muscles, and foot and lower leg deformities. As the disease progresses, weakness and muscle atrophy may occur in the hands.

Disrupted sleep architecture and gas-exchange abnormalities occur in more than 80 percent of patients with neuromuscular disorders."

MYOPATHIES
Myopathies adversely affect muscle function and are characterized by skeletal muscle weakness. Less commonly, myopathies may affect smooth, ventilatory or cardiac muscles. Myopathies can be inherited (i.e., muscular dystrophy) or acquired (i.e., common muscle cramps). Other symptoms may include muscle cramps, stiffness and muscle spasms. Most myopathies are lifelong conditions that progress slowly or remain essentially static.

Muscular dystrophies are genetic myopathies and affect all ages. Thirty types exist and are characterized by progressive weakness and degeneration of the skeletal muscles that control movement. Myotonic dystrophy is the most common form of muscular dystrophy in adults, and it manifests with myopathy, myotonia, baldness, cataracts, cardiac arrhythmias and endocrine dysfunction.\(^4\) Some forms of muscular dystrophy progress very slowly over a normal lifespan, while others progress quickly and may cause functional disability and even death.

Associated Sleep Disorders
Myopathies may cause chest wall deformities and restrictive lung disease, which contribute to sleep dysfunction including sleep fragmentation, respiratory problems, frequent arousal and sleep state changes, hypercapnia and hypoxemia.\(^9\) Patients with other types of myopathies are at risk for alveolar hypoventilation and SDB, including central and obstructive apneas and hypopneas.\(^7\)

Muscular dystrophies are associated with hypoventilation especially during sleep, which worsens as the disease progresses. Hypoventilation symptoms include daytime sleepiness, increasing nocturnal awakenings and morning headache.\(^6\) Patients are also at risk for SDB, particularly upper airway obstruction.

A wide variety of sleep disorders manifest in myotonic dystrophy, including SDB, nocturnal desaturation, hypercapnia, hypersomnolence, increased apnea/hypopnea index and abnormal sleep architecture.\(^8\) Excessive daytime sleepiness is common

Associated Sleep Disorders
Sleep problems are common in patients with painful neuropathies.\(^5\) Charcot-Marie-Tooth disease is the most common polyneuropathy associated with SDB. In these patients, SDB is a result of upper airway obstruction or diaphragm dysfunction due to pharyngeal neuropathy.\(^9\) Charcot-Marie-Tooth disease can be associated with restrictive pulmonary impairment, sleep apnea and restless legs. Insomnia may result from pain and discomfort during sleep. Obstructive sleep apnea (OSA) and nonhypocapnic central apnea can occur and may be due to pharyngeal neuropathy. Restrictive pulmonary impairment is associated with phrenic nerve dysfunction, thoracic cage abnormalities and diaphragm dysfunction. Central sleep apnea and hypercapnia also may be associated with Charcot-Marie-Tooth disease.\(^10\)

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in patients with myotonic dystrophy, which may even present before deterioration of the respiratory muscles. Hypersomnia is associated with dysfunction of the thalamus and hypothalamus.\(^6\)

### EVALUATION OF SLEEP

Patients with neuromuscular disorders are especially vulnerable to sleep disorders, which are influenced by the severity and type of neuromuscular disorder. Disrupted sleep architecture and gas-exchange abnormalities occur in more than 80 percent of patients with neuromuscular disorders. Sleep-disordered breathing, including apneas, hypopneas, hypoventilation, upper airway resistance, and frequent arousals due to respiratory effort, has a high prevalence in patients with neuromuscular disorders.\(^5\)

The most common form of SDB found in patients with neuromuscular disorders is hypoventilation, particularly during REM sleep. All people experience hypoventilation during sleep, but in neuromuscular disorders, this is exacerbated by the suppression of the intercostal and accessory respiratory muscles and diaphragm dysfunction.\(^9\) OSA may exacerbate the already existing hypoventilation/hypoxemia during sleep in patients with neuromuscular disorders. Pharyngeal dilator muscles in the upper airway may become weakened in neuromuscular disorders and contribute to increased upper airway resistance, particularly during REM when these muscles are atonic.\(^11\)

Sleep-related disorders should be assessed routinely in patients with neuromuscular disorders because treatment can help improve symptoms and quality of life. Evaluation will vary according to the type of neuromuscular disorder and the degree of the patient’s disability. A detailed evaluation of sleep history is needed to identify the severity and type of sleep-related dysfunction. Assessments should include an evaluation of the degree of pain and discomfort during sleep, whether or not the patient experiences urinary or digestive dysfunction during wake and sleep, and evaluation of autonomic dysfunction suspected during sleep. Diagnostic tests may include a disability index scale, sleep disorder questionnaire, actigraphy or sleep log. Pulmonary function and gas exchange measures are routinely performed, and it is suggested that polysomnography be performed when these measures indicate a risk for sleep hypoventilation.

Polysomnography is accepted as standard practice for the evaluation of neuromuscular disorders according to the American Academy of Sleep Medicine.\(^12\) Overnight polysomnography in a laboratory is key for documenting behavioral changes, anoxic seizures and parasomnias in these patients. Polysomnography with a measurement of transcutaneous CO\(_2\), evaluating overall ventilation during sleep, can even provide a guide to ventilation assistance during sleep.\(^7\) The following may be considerations for determining when to perform polysomnography: \(^6\)

1. Perform overnight polysomnography early in the course of the neuromuscular disease to provide a baseline recording for comparison.
2. Repeat polysomnography periodically to evaluate effects of various therapies.
3. Follow-up polysomnography may be repeated to allow detection and correction of poor treatment (i.e., ventilation inadequacies).

The major muscle of respiration during wake and sleep (especially REM sleep) is the diaphragm. When the diaphragm is affected, as in myopathy, significant changes are expected in breathing and oxygenation. Breathing abnormalities during sleep in these patients may include central apneas, obstructive apneas and prolonged hypventilation, which contribute to frequent arousals, reduced sleep time and sleep deprivation.\(^7\) Neuromuscular disorders may affect patients psychologically, which can lead to secondary sleep-onset insomnia as well as anxiety and depression.\(^9\)

Sleep worsens the disability of patients with neuromuscular disorders, and overlooking the sleep-related hypoventilation caused by neuromuscular disorders may lead to patient death. Daytime impairments secondary to abnormal sleep, such as fatigue and daytime sleepiness, further decrease quality of life.\(^9\) Several sleep-related factors may predispose patients with neuromuscular diseases to sleep disorders, including: \(^5,9\)

1. Movement and posture limitations due to weakness, pain, discomfort, spasticity and rigidity
2. Autonomic dysfunction
3. Poor sphincter control
4. Abnormal movements and behaviors during sleep
5. REM-related hypoventilation
6. Diaphragm weakness
7. Increase in upper airway resistance
8. Pulmonary restriction and secretion clearance problems
9. Impaired respiratory chemosensitivity
10. Involvement of the central nervous system

Adult patient complaints of increased tiredness, fatigue or nocturnal sleep problems may be the first signs of the onset of a neuromuscular disease; however, the mechanisms of sleep problems may be under recognized or ignored because clinicians may simply attribute the sleep problems to the neurologic problem. The added-on sleep dysfunction further complicates patients’ neurologic issues and worsens quality of life.\(^7\)

The International Classification of Sleep Disorders diagnostic criteria for sleep-related hypoventilation/hypoxemia due to neuromuscular and chest wall disorders are: \(^13\)

A. A neuromuscular or chest wall disorder is present and believed to be the primary cause of hypoxemia.
B. Polysomnography or sleeping arterial blood gas determination shows at least one of the following:
   i. An SpO\(_2\) during sleep of less than 90% for more than five minutes with a nadir of at least 85%
   ii. More than 30% of total sleep time at an SpO\(_2\) of less than 90%
   iii. Sleeping arterial blood gas with PaCO\(_2\) that is abnor-
mally high or disproportionately increased relative to levels during wakefulness.

C. The disorder is not better explained by another current sleep disorder, another medical or neurological disorder, medication use, or substance use disorder.

TREATMENTS AND OUTCOMES

Overall, goals of treating sleep dysfunction in patients with neuromuscular disorders include improving sleep, daytime function and quality of life by restoring normal sleep architecture.

Initial polysomnography should be used as a basis for treatment of SDB, and follow-up also should include polysomnographic studies. Treatment planning varies according to the type of neuromuscular disorder, the type of sleep disorder present, and whether or not other sleep abnormalities are present.

Several forms of ventilation assistance may be used, including phrenic nerve pacing, cuirass ventilation, nasal continuous positive airway pressure (CPAP), and nasal intermittent positive-pressure ventilation. Bi-level PAP is also effective in the treatment of several neuromuscular disorders and may be as effective as a conventional ventilator in early disease stages. Noninvasive ventilation (NIV) is a major advance in the management of SDB and respiratory muscle weakness associated with neuromuscular disorders. Many studies reveal that the use of NIV as well as other treatments for sleep-related dysfunction in patients with neuromuscular disorders improves symptoms and quality of life.

REFERENCES


