Sleep dysfunction in neuromuscular disorders

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Summary

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There is an increasing awareness of sleep dysfunction in neuromuscular disorders. Most of the sleep disturbances in neuromuscular disorders are secondary to sleep disordered breathing. Sleep-disordered breathing in neuromuscular disorders is commonly associated with a slowly developing chronic respiratory failure, particularly in the advanced stages, but the condition often remains unrecognized and untreated. The most common sleep-disordered breathing in neuromuscular disorders is sleep-related hypoventilation which initially manifests during REM sleep and later as the disease advances, it is also noted during non-REM sleep and even during daytime. In addition to the hypoventilation, central and upper airway obstructive apneas as well as hypopneas occur. Hypoventilation during sleep gives rise to hypoxemia and hypercapnea causing chronic respiratory failure. The abnormal blood gases may later persist during the daytime. Some patients may, however, have sleep onset or maintenance insomnia as a result of associated pain, muscle immobility, contractures, joint pains and muscle cramps as well as anxiety and depression. The commonest complaint in patients with neuromuscular disorders associated with sleep-disordered breathing is excessive daytime somnolence as a result of repeated arousals and sleep fragmentation due to sleep hypoventilation and transient nocturnal hypoxemia. Sleep-disordered breathing causing sleep disturbance is well known in patients with poliomyelitis, postpolio syndrome, amyotrophic lateral sclerosis, also known as motor neuron disease, primary muscle disorders including muscular dystrophies and myotonic dystrophy, congenital or acquired myopathies, neuromuscular junctional disorders and polyneuropathies. All of these conditions may cause weakness of the diaphragm, the intercostal and accessory muscles of respiration causing breathlessness and other respiratory dysrhythmias. As a result of the respiratory and upper airway muscle weakness, the normal sleep-related respiratory physiologic vulnerability becomes pathological in these patients with neuromuscular disorders causing hypoventilation or central and upper airway obstructive apneas during sleep. Multiple factors are responsible for sleep-disordered breathing in neuromuscular disorders causing sleep hypoventilation and other respiratory dysrhythmias, and these include: impaired chest bellows, increased work of breathing, hyporesponsive respiratory chemoreceptors, increased upper airway resistance, decreased minute and alveolar ventilation, REM-related marked hypotonia or atonia of the respiratory muscles except the diaphragm, respiratory muscle fatigue and kyphoscoliosis secondary to neuromuscular disorders causing extrapulmonary restriction of the lungs.

Nocturnal hypoventilation and chronic respiratory failure in neuromuscular disorders may present insidiously and initially may remain asymptomatic. A high index of clinical suspicion is needed. Clinical clues suggesting sleep-disordered breathing include daytime hypersomnolence, breathlessness, disturbed nocturnal sleep and unexplained leg edema. If the clinical clues strongly suggest sleep-disordered breathing, a physical examination must be directed to uncover bulbar and respiratory muscle weakness. Patients with neuromuscular disorders showing these clinical features must be investigated to uncover nocturnal hypoventilation to prevent serious consequences of chronic respira-

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tory failure such as pulmonary hypertension, congestive heart failure and cardiac arrhythmias. The single most important laboratory test in patients with hypersomnia and nocturnal sleep disturbance is an overnight polysomnographic recording. The definitive test for alveolar hypoventilation is an analysis of arterial blood gases showing hypercapnea and hypoxemia. In the early stages, however, arterial blood gases remain normal during wakefulness, but in advanced stages with chronic respiratory failure these values will be abnormal. Polysomnographic study including finger oxymetry is most important to show the presence of nocturnal hypoxemia during sleep as well as sleep-related respiratory dysfunction and sleep disruption. Pulmonary function tests should also be performed to assess respiratory and ventilatory muscle functions. A significant reduction of forced vital capacity from upright to supine position is indicative of diaphragmatic weakness. The objective of treatment of sleep-disordered breathing in neuromuscular disorders is to improve arterial blood gases, eliminate daytime symptoms, improve quality of life and prevent serious consequences of chronic respiratory failure. The contemporary standard of management for chronic respiratory failure is noninvasive intermittent positive pressure ventilation using a nasal mask or prongs. In patients with upper airway obstructive sleep apnea continuous positive airway pressure is the ideal treatment. Long-term follow-up studies of patients using noninvasive intermittent positive pressure ventilation have shown improvement in quality of life, daytime somnolence and arterial blood gases as well as a reduction in the need for prolonged hospitalization and increased longevity. Further studies are needed to identify daytime predictors for identification of those patients who will develop sleep-disordered breathing and nocturnal hypoventilation at an early stage. Many critical questions regarding the ideal method of treatment, physiological mechanisms, whom to treat, and when to treat remain unanswered.

Keywords: sleep-disordered breathing; sleep hypoventilation; chronic respiratory failure; neuromuscular disorders; hypersomnolence; overnight polysomnography; noninvasive intermittent positive pressure ventilation; tracheostomy

Introduction

Since Sarnoff at al. [1] directed our attention to hypoventilation in poliomyelitis patients, and Benaim and Worster-Drought [2] in 1954 first described alveolar hypoventilation in myotonic dystrophy, medical community began to be aware of sleep dysfunction in neuromuscular disorders. Most of the sleep disturbances in neuromuscular disorders are secondary to sleep-disordered breathing. This is most commonly associated with a slowly developing chronic respiratory failure. In this review, I will briefly describe sleep dysfunction and sleep-disordered breathing in a variety of neuromuscular disorders, such as poliomyelitis and postpolio syndrome, amyotrophic lateral sclerosis, muscular dystrophy, myotonic dystrophy, acid maltase deficiency, congenital or acquired metabolic myopathies, polymyositis, mitochondrial myopathies, myasthenia gravis and myasthenic syndrome as well as polyneuropathies including Guillain-Barré syndrome.

Sleep-related respiratory dysfunction is the cause of the sleep disturbance in most neuromuscular disorders. Disordered breathing in neuromuscular disorders often is evident in sleep. However, pain, muscle immobility, contractures, joint pains and muscle cramps as well as anxiety and depression may all contribute to sleep dysfunction causing sleep onset or maintenance insomnia in many of these patients. Sleep-disordered breathing in neuromuscular disorders is commonly associated with chronic respiratory failure, particularly in the advance stages, but the condition is often unrecognized and untreated [3–6]. It is, however, sometimes the initial presentation of certain disorders such as motor neuron disease and acid maltase deficiency.

The types of sleep-disordered breathing in neuromuscular disorders

The most common sleep-disordered breathing in neuromuscular disorders is sleep-related hypoventilation, which initially manifests during REM sleep and later as the disease advances, it is also noted during non-REM sleep, and even during daytime. In addition to the hypoventilation, central and upper airway obstructive apneas as well as hypopneas occur. Hypoventilation during sleep gives rise to hypoxemia and hypercapnea causing chronic respiratory failure. The abnormal blood gases may later persist during the daytime. Respiratory failure can be defined as an inability of the lungs to effectively exchange gas and maintain normal acid base balance, resulting in an arterial oxygen tension (PaO_2) of less than 60 mm Hg or a carbon dioxide tension (PaO_2) greater than 50 mm Hg. In addition to REM-related hypoventilation as a result of reduction in tidal volume, the patient also may have central apneas. Finally, some patients

may have paradoxical breathing (movements of the thorax and abdomen in opposite directions) suggesting upper airway obstructive sleep apnea or upper airway resistance syndrome.

Clinical manifestations of sleep dysfunction in neuromuscular disorders

Sleep disturbances in neuromuscular disorders are secondary to involvement of the respiratory pump, which includes upper airway muscles (genioglossus, palatal, pharyngeal, laryngeal, hyoid and masseter muscles), intercostal and other accessory muscles of respiration, and diaphragm as a result of affection of the motor neurons, the phrenic and intercostals nerves or the neuromuscular junctions of the respiratory and oropharyngeal muscles. The commonest complaint is excessive daytime somnolence as a result of repeated arousals and sleep fragmentation due to sleep hypoventilation and transient nocturnal hypoxemia.

Sleep-disordered breathing causing sleep disturbance is well known in patients during the acute and convalescent stage of poliomyelitis. Sleep disorders, however, in postpolio syndrome are less known and such patients may present with sleep-related hypoventilation or sleep apnea causing excessive daytime somnolence. Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), may cause daytime hypersomnolence as a result of nocturnal hypoventilation, repeated sleep apneas-hypopneas, hypoxemias, hypercapneas and sleep fragmentation. Some patients may complain of insomnia. In ALS, sleep-disordered breathing may result from weakness of the upper airway, diaphragmatic and intercostal muscles due to involvement of the bulbar, phrenic and intercostal motor nuclei. In addition, degeneration of the central respiratory neurons may occur causing central and upper airway obstruction sleep apneas.

Primary muscle disorders or myopathies present with symmetric proximal limb muscle weakness and wasting without sensory impairment or fasciculations, and result from a defect in the muscle membrane or the contractile elements, which is not secondary to a dysfunction of the lower or upper motor neurons. Respiratory disturbances are generally noted in the advanced stage of the illness, but sometimes respiratory failure appears in the early stage. Sleep complaints and sleep-related respiratory dysrhythmias are common in Duchenne and limb girdle muscular dystrophies, myopathies associated with acid maltase deficiency, and may also occur in other congenital or acquired myopathies, mitochondrial encephalomyopathy and polymyositis.

Since the early description of alveolar hypoventilation in myotonic dystrophy, many patients with this condition have been described with central, mixed and upper airway obstructive sleep apneas, alveolar hypoventilation, daytime fatigue and excessive somnolence. Nocturnal oxygen desaturation accompanies alveolar hypoventilation and apneas, and becomes worse during REM sleep.

Sleep-disordered breathing in myotonic dystrophy may have resulted from weakness and myotonia of the respiratory and upper airway muscles as well as an inherent abnormality of the central control of ventilation [7]. Snoring and sleep dysfunction have also been reported in patients with recently described proximal myotonic myopathy (PROMM) [7], also called DM2. This condition is an inherited myotonic disorder that is differentiated from myotonic dystrophy by absence of the chromosome 19 CTG trinucleotide repeat that is associated with classic myotonic dystrophy. Sleep disturbance in PROMM includes difficulty initiating sleep, excessive daytime somnolence, snoring, and frequent awakenings.

In polyneuropathies, involvement of the nerves supplying the diaphragm and the intercostal and accessory muscles of respiration may cause breathlessness on exertion and other respiratory dysrhythmias. This may worsen during sleep causing sleep fragmentation and daytime hypersomnolence. Painful polyneuropathy patients may have insomnia.

Neuromuscular junctional disorders (e.g. myasthenia gravis, myasthenic syndrome, botulism and tick paralysis) are characterized by easy fatigability of the muscles including the bulbar and other respiratory muscles as a result of failure of transmission of the nerve impulses at the neuromuscular junctions. Respiratory failure in these conditions, particularly in myasthenia gravis, may be mild during wakefulness, but deteriorates during sleep. Patients with myasthenia gravis may have central, obstructive, mixed apneas and hypopneas accompanied by oxygen desaturation. A sensation of breathlessness on awakening in the middle of the night and early morning hours may indicate respiratory dysfunction. The older myasthenic patients and those with increased body mass index, abnormal pulmonary function results and abnormal daytime blood gas values are at particular risk for sleep-related respiratory dysrhythmias. Sleep-related hypoventilation and sleep apneas-hypopneas in neuromuscular junctional disorders may be severe enough to require assisted ventilation.

Mechanism of sleep-disordered breathing in neuromuscular disorders

Regardless of causes, patients with weak respiratory muscles may present with more severe breathing difficulties during sleep than during wakefulness. In wakeful state, both voluntary and metabolic respiratory control systems are intact. The central respiratory neurons increase the rate of firing or recruit additional respiratory neurons to drive weak respiratory muscles in neuromuscular disorders to maintain ventilation adequately. However, during sleep respiration is entirely dependent on the metabolic controlling system and thus respiration is vulnerable during sleep aggravating the ventilatory problems causing more severe hypoventilation and even apneas and hypopneas. In addition, functional impairment of the sensitivity of the central respiratory neurons causing decreased metabolic respiratory control may also cause apnea-hypopnea during both REM and non-REM sleep. The upper airway muscle weakness coupled with REM-related hypotonia or atonia of the muscles contributes to possible upper airway obstructive sleep apnea. Multiple factors are responsible for sleep-disordered breathing in neuromuscular disorders causing sleep-related hypoventilation and other respiratory dysrhythmias [3, 5–8]. These factors are summarized as follows:

1 Impaired chest bellows (weakness of the respiratory and chest wall muscles);
2 increased work of breathing due to altered chest mechanics and reduced forced vital capacity caused by weakness of the chest wall muscles and diaphragm so that breathing is less efficient;
3 hyporesponsive respiratory chemoreceptors which may be secondarily acquired or related to altered afferent inputs from skeletal muscle spindles causing functional alteration of the metabolic respiratory neurons;
4 increased upper airway resistance due to weakness of the upper airway muscles;
5 decreased minute and alveolar ventilation during sleep;
6 REM-related marked hypotonia or atonia of all the respiratory muscles except the diaphragm causing increased diaphragmatic workload;
7 respiratory muscle fatigue due to increasing demand on the respiratory muscles during sleep, particularly during REM sleep; and
8 kyphoscoliosis secondary to neuromuscular disorders causing extrapulmonary restriction of the lungs with impairment of pulmonary functions, breathlessness, sleep apnea, and hypoventilation.

All of the above factors may lead to chronic respiratory failure. In the advanced stage of the illness, respiratory failure may be present during daytime as a result of alveolar hypoventilation, ventilation-perfusion mismatching, hypoxemia and hypercapnea.

Clinical approach to diagnosis

Clinical diagnosis of acute respiratory failure as may be seen in patients with acute inflammatory demyelinating polineuropathy (Guillain-Barré syndrome), myasthenic crisis and acute poliomyelitis is quite obvious. Patients may have rapid or shallow breathing, intermittent cessation of breathing and cyanosis. Nocturnal hypoventilation and chronic respiratory failure, however, in neuromuscular disorders may present insidiously and initially may remain asymptomatic. Therefore, a high index of clinical suspicion is needed. Initial approach in patients with sleep-disordered breathing and neuromuscular disorders is therefore clinical. Clinical clues strongly suggesting sleep-disordered breathing include the presence of excessive daytime somnolence, daytime fatigue, breathlessness, morning headache in some patients, restless and disturbed nocturnal sleep, intellectual deterioration and unexplained leg edema. If the clinical clues strongly suggest sleep-disordered breathing, physical examination must be directed to uncover bulbar and respiratory muscle weakness, in addition to detailed neurological and general medical examination to exclude other cause of sleep-disordered breathing including nocturnal hypoventilation. Patients with neuromuscular disorders showing these clinical features deserve to be investigated to uncover nocturnal hypoventilation in order to prevent serious consequences of chronic respiratory failure, such as pulmonary hypertension, congestive heart failure and occasionally cardiac arrhythmia.

Laboratory investigations

Laboratory tests are simply an extension of the history and physical examination. Therefore, in patients with sleep disturbances associated with neuromuscular disorders, a careful history, including present and past sleep history, family, drug-alcohol, medical and psychiatric histories, is essential.

The single most important laboratory test in patients with hypersomnia and nocturnal sleep disturbances is an overnight polysomnographic

recording. This must be performed in all patients with excessive daytime somnolence unless the patient is so severely impaired by the neurological conditions that the diagnosis and treatment of sleep problems will not alter the outcome. Polysomnographic findings in myopathies including Duchenne and other muscular dystrophies, and myotonic dystrophy may include the following: increased number of awakenings, sleep fragmentation and disorganization; reduced total sleep time; central, mixed and upper airway obstructive sleep apneas and hypopneas associated with oxygen desaturation; and non-apenic oxygen desaturation becoming worse during REM sleep. Similar findings may be noted in polyneuropathies, neuromuscular junctional disorders, and motor neuron disease. Additionally, in painful polyneuropathy and those neuromuscular conditions associated with muscle pain and cramps, polysomnographic recording may show sleep onset, maintenance insomnia and reduced sleep efficiency.

The definitive test for alveolar hypoventilation is an analysis of arterial blood gases showing hypercapnea and hypoxemia [3, 5, 6]. In the early stages of neuromuscular disorders, arterial blood gas (ABG) values remain normal during wakefulness but in advanced stages with chronic respiratory failure these values will be abnormal. An indwelling arterial catheter is required throughout the night to detect abnormal nocturnal ABG, but this is invasive and impractical, and does not continuously monitor blood gases throughout the night. Finger oxymetry is, of course, always included in the polysomnographic recording to detect oxygen desaturation throughout the night. Some investigators also recommend noninvasive monitoring of carbon dioxide tension in addition to finger oxymetry to detect hypoventilation. There are, however, pitfalls. The usefulness of finger oxymetry alone is limited because this may show mild oxygen desaturation in the presence of significant hypoventilation and reduced arterial oxygen tension. The noninvasive end-tidal and transcutaneous carbon dioxide tension measurements are unreliable correlating poorly with actual arterial carbon dioxide tension. Polysomnographic recording, however, is the most important test to evaluate patients with sleep-disordered breathing and sleep disruption.

To document the presence and severity of daytime sleepiness and to diagnose associated narcolepsy, multiple sleep latency test (MSLT) may be performed. A mean sleep onset latency of less than five minutes is consistent with pathologic sleepiness and additional presence of sleep-onset REM in two or more of the 4–5 nap recordings suggests a diagnosis of associated narcolepsy in patients with neuromuscular disorders.

Pulmonary function tests including lung volume (total lung capacity, functional residual capacity, expiratory reserve volume and residual volume), expiratory flow (forced expiratory volume for one second-FEV_1, forced vital capacity including inspiratory vital capacity, FEV_1/VC ratio), maximum static inspiratory (MIP) and expiratory (MEP) pressures, and arterial blood gases (PaO_2 and $PaCO_2$) assess ventilation and respiratory muscle functions. Patients suspected to have diaphragmatic paralysis should have chest fluoroscopy and measurement of transdiaphragmatic pressure using esophageal and gastric balloons. Vital capacity measurement is the simplest and quickest way to determine respiratory muscle weakness. A significant reduction of forced vital capacity from upright to supine position is indicative of diaphragmatic weakness.

EMG and nerve conduction may be necessary in patients with respiratory failure due to affection of the diaphragm, intercostal and other accessory muscles of respirations. In selected patients, EMG of the diaphragm and intercostal muscles may be indicated. Phrenic and intercostal nerve conduction studies may help diagnose phrenic and intercostal neuropathy in some of these patients. Needle EMG of the diaphragm may reveal diaphragmatic denervation which would suggest neurogenic dysfunction of the diaphragm.

Principles of treatment of sleep dysfunction in neuromuscular disorders

Treatment should first be directed toward the primary neurologic condition. In many, however, there is no specific treatment and only symptomatic measures are available. The objective of treatment of sleep disturbances related to sleep-disordered breathing is to improve arterial blood gases, eliminate daytime symptoms, improve quality of life, and prevent occurrence of serious consequences of chronic respiratory failure such as pulmonary hypertension and congestive cardiac failure [3, 5–8]. The major thrust of treatment in the past was invasive ventilation through a tracheostomy, but this has now been replaced by noninvasive method of ventilation. Noninvasive ventilatory supports for patients with sleep-disordered breathing including hypoventilation consist of negative and positive pressure ventilators. Iron lung or tank respirator and the cuirass are the two principal negative pressure ventilators. The tank respirator is bulky limiting the patient's accep-

tance. In addition, the negative pressure ventilator may be associated with upper airway obstructive sleep apnea and oxygen desaturation in patients with neuromuscular disorders. The contemporary standard of management for chronic respiratory failure in neuromuscular disorders is noninvasive intermittent positive pressure ventilation using a nasal mask or prongs. Positive pressure ventilation includes continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) and intermittent positive pressure ventilation (IPPV). CPAP is the ideal treatment for patients with upper airway obstructive sleep apnea. In some patients, high pressure during both inspiration and expiration while using CPAP may not be tolerable and they may be able to tolerate BiPAP using higher inspiratory than expiratory positive airway pressure. The standard method of treating chronic respiratory failure in neuromuscular disorder is noninvasive IPPV.

Long-term follow-up studies of patients using noninvasive IPPV through a nasal mask for six to eight hours during sleep have shown improvement in quality of life, improvement in daytime somnolence and arterial blood gases, a reduction in the need for prolonged hospitalization and increased longevity [6, 9]. The complications of IPPV are similar to those of CPAP. A recent consensus conference outlined criteria for noninvasive positive pressure ventilation for patients with neuromuscular disorders [10]. The diagnosis, however, must first be established by history and physical examination followed by appropriate diagnostic tests. The patient also must receive treatment for associated or underlying conditions. There have been some recent attempts to undertake diagnostic tests to predict which neuromuscular patients will develop sleep-disordered breathing. In one such study [11] inspiratory vital capacity and maximum inspiratory muscle pressure have the highest predictive values for onset of sleep-disordered breathing in such patients. However, further studies are needed to definitely identify daytime predictors for those patients who will develop sleep-disordered breathing and nocturnal hypoventilation at an early stage.

The role of supplemental oxygen therapy using low-flow (1 to 2 liters per minute) oxygen in treatment of sleep-disordered breathing in neuromuscular disorders remains controversial. Supplemental oxygen treatment is mostly ineffective in patients with neuromuscular disorders and may even be dangerous, leading to marked carbon dioxide retention.

Tracheostomy remains the only effective emergency measure for those patients with marked respiratory failure with severe hypoxemia and those with sudden respiratory arrest after resuscitation by intubation. Tracheostomy may also be beneficial for those patients who fail noninvasive IPPV treatment or who cannot cooperate with such treatment. However, a decision about tracheostomy should be carefully weighed in many of these neuromuscular disorders with relentless progression and an overall unfavorable prognosis.

Patients who complain of insomnia should follow general sleep hygiene measures, such as regular sleep-wake schedule, avoidance of alcohol and caffeine in the evening and other measures [7]. Analgesics may be prescribed for pain; occasionally patients may need hypnotics, which should be used judiciously, with low doses not more than two to three nights a week.

In conclusion, patients with neuromuscular disorders with sleep difficulties and sleep-disordered breathing often remain unrecognized, but it is important to have a high index of clinical suspicion so that appropriate diagnostic tests may be designed to diagnose nocturnal hypoventilation and other sleep-related breathing disorders in the early stage of the illness. Noninvasive positive pressure ventilation may improve the quality of life for many of these patients without always altering the natural history of the illness. Many critical questions regarding the ideal method of treatment, physiological mechanisms, whom to treat and when to treat, however, remain unanswered.

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