REVIEW ARTICLE

Pulmonary Involvement in Neuromuscular Diseases

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Ghamartaj KHANBABAEE[1],
Parvaneh KARIM ZADEH[2,3],
Mohammad Mahdi NASEHI[2,3]
Seyed Ahmad TABATABAII[1],
Matin POURGHASEM[1],
Fariba ALAEI[4],
Saeed SADR[1],
Nazanin FARAHBAKHSH[1],
Seyedeh Zalfa MODARRESI[5],
Fatemeh KHAZAII[1],
Maedeh SOFLAEE[1],
Abdolhamid TAGHIZADEH BEHBAHANI[1],
Nafiseh FADAVI[6],
Mahsa POURGHASEM[7]

1.Department of Pediatric Pulmonology, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Pediatric Neurology Research Center , Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3.Pediatric Neurology Department, Mofid Children Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
4.Pediatric Cardiology

Abstract

Neuromuscular diseases (NMDs) affect muscle function directly or indirectly by affecting nerves or neuromuscular junctions. One of the leading causes of death in patients with NMD is respiratory muscle weakness (RMW). Respiratory involvement in patients with NMD can manifest widely, from mild failure that may initially affect only sleep to severe failure that can be life-threatening. Care approaches include arranged and precise clinical follow-ups of signs of sleep-disordered breathing, daytime hypoventilation, coughing, and swallowing disturbances**.** This manuscript will review the mechanisms and abnormalities of respiratory function in patients with NMD and help optimize NMD management.

Keywords: Neuromuscular diseases; Respiratory muscle weakness; Respiratory involvement

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Introduction

Neuromuscular diseases (NMDs) are heterologous neurological disorders affecting several neural structures, such as motor nerves, neuromuscular junctions, or muscles (1, 2). Most NMDs are determined by progressive muscle disturbances leading to loss of movement, wheelchair-boundness, dysphagia, respiratory muscle weakness (RMW), and death due to respiratory failure (3-5). The term "neuromuscular" is used for inherited or acquired disorders that primarily manifest with motor dysfunction. From the standpoint of a pulmonologist, all NMDs appear with a prevalent feature: impaired ventilatory function (6). This disorder is caused by protective reflexes, compromising airway patency, or reducing the efficiency of the respiratory pump (7, 8). These pathophysiological mechanisms cause sleep-disordered breathing followed by daily hypoventilation in the

Department, Mofid Children Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5.Children Growth Disorder Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
6.Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.
7.Department of Pharmacy, Islamic Azad University, Pharmaceutical Sciences Branch (IAUPS), Tehran, Iran.
Corresponding Author
Modarresi SZ. MD
Children Growth Disorder Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

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later stages of the disease. Moreover, patients with NMD are prone to other respiratory complications, including infections, aspiration syndromes, and atelectasis (9, 10). Due to the gradual inspiratory muscle weakness and increasing elastic load induced by reduced lung and thorax compliance, patients with NMDs suffer from a progressive decline in vital capacity (VC) and an increased work of breathing (11, 12).

Dyspnea typically appears late in the course of the disease, causing patients to have difficulty moving; therefore, it is imperative to monitor lung and respiratory muscle function early on because they are both thought to be the most significant prognostic indicators in patients with NMD (13, 14). Conditions that appear with the gradual onset of respiratory failure due to degenerative muscle diseases require careful follow-up and long-term treatment (15). Rapid shallow breathing, using accessory muscles, decreased chest expansion, diminished breath sounds, abdominal paradox, weak coughing, and sniffling are all clinical indicators of RMW. Deformities of the chest that resemble bells and chest paradox are indications of intercostal muscular weakening with maintained diaphragmatic function. Scoliosis may be evident in NMD with childhood-onset, sometimes with signs of surgical correction. Central cyanosis, coarse tremor, dilated veins, bounding pulse, papilloedema, confusion, and sleepiness are indications of respiratory failure (5, 16, 17). Early identification of clinical signs of respiratory failure in patients with NMD significantly helps to diagnose these patients. This review article aims to understand the mechanisms and abnormalities of respiratory function in NMD patients and help better manage these patients.

Pulmonary function in NMD patients

The three groups of respiratory muscles include expiratory, inspiratory, and upper airway muscles. Dysfunction of these muscle groups can manifest as three distinct types of failure: (1) upper airway failure and swallowing disorder (upper airway muscle dysfunction), (2) respiratory pump failure (respiratory muscle dysfunction), and (3) Cough failure (3, 7). The air-breathing pump moves air in and out of the lungs. When the respiratory pump works against an increased workload or if

the respiratory muscles cannot generate sufficient force, the respiratory pump loses its function. This condition causes respiratory muscle fatigue, described as the inability to retain contractile force versus a constant workload (6, 18).

patients with NMD have inspiratory and expiratory muscle dysfunction, and chest wall compliance is reduced due to scoliosis and tightening of tendons and ligaments of the chest. The reduction of lung compliance is due to frequent aspiration, micro atelectasis, and respiratory congestion caused by heart disorders (19). In addition, upper airway obstruction and decreased blood pressure increase airflow resistance, which increases the respiratory pump's workload (20). An increase in the respiratory drive is the preliminary physiological response to these mechanisms, but it is insufficient to retain alveolar ventilation, and finally, hypoventilation happens (21, 22). Furthermore, failure of the upper airway muscles causes swallowing disorders and airway protection disorders, leading to frequent aspiration and pneumonia episodes (3, 23).

Pulmonary function testing in NMD patients

A baseline test with criteria that included lung volume, diffusion capacity, spirometry, arterialized veins, arterial capacity, or capillary blood-gas testing was considered to establish a baseline and rule out other associated pulmonary disorders. RMW causes a restricted pattern described by a decrease in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) with a preserved ratio (24). Generally, patients present these signs. On the other hand, individuals suffering from bulbar weakness may be unable to shape a mouth seal and have false low measures. Subtle abnormalities may be observed, such as a rapid decline in expiratory flow and a disproportionate drop in peak expiratory flow. Despite growth in residual volume, total lung capacity will decline. If vital capacity decreases, diffusion capacity may be recorded at a low or normal level. Hypoventilation is characterized by an arterial or capillary carbon dioxide level of over 45 mmHg (15).

Sniff nasal inspiratory pressure assessment can have a better prognostic value than FVC. Thus, assessing FVC in the supine position is a supplementary experiment for RMW detection (25). Diaphragm weakness is indicated by more than a 20%-30% reduction(26). In addition, less than –30 cmH2O Inspiratory mouth pressure and more than 40 cmH2O expiratory mouth pressure depict weakness. These tests may often represent indefinite findings below the lower limit of normal but do not distinctly illustrate RMW. Significant RMW is characterized by less than 270 L/min, compared to less than 160 L/ min, which is considered severe cough (25, 27).

Sleep and breathing in patients with NMDs

During non-rapid eye movement (NREM) sleep, ventilation suddenly decreases and is accompanied by a faster, shallower, and more regular breathing pattern, leading to an increase in the partial pressure of CO2 (3). After sleep is established, ventilation shows only a slight further decrease (28). Contrary to ventilation, the upper airway resistance increases suddenly at the onset of sleep due to the decrease in the activity of the pharyngeal dilator muscles and the increase in delta activity in the electroencephalogram during slow-wave sleep (29). People with tracheostomy have similar sleep patterns as normal people. Therefore, changes in ventilation during sleep are most likely related to reduced ventilatory drive with blunted chemosensitivity (30). Increased genioglossus activity during NREM sleep, after an initial decrease at sleep onset, may play an essential

role in maintaining airway patency (3). During sleep, exceptionally rapid eye movement (REM) sleep, RMW can lead to hypoventilation, apnea, and hypopnea with sleep disturbance. Symptoms include restless sleep, vivid dreams, daytime sleepiness, lethargy, poor concentration, and mood disorders. However, other problems can disrupt sleep, including pain, choking on secretions, anxiety, and depression (31, 32). Hypercapnia usually does not develop until RMW is severe and becomes more apparent overnight. Symptoms include a headache that worsens upon awakening, poor appetite, confusion, and drowsiness. Weakness of the bulbar muscle can cause problems with speech, swallowing, frequent aspiration, recurrent lower respiratory tract infections, and a weak cough. When inspiratory and expiratory muscles are weak, airway clearance is more compromised (5, 33).

Assessing the cough in patients with NMD

Assessing cough efficiency requires the measurement of cough flow variables. The most important are cough volume acceleration (CVA) and peak expiratory cough flow (PECF). Asthmatic patients use a typical hand-held peak flow meter or an office spirometer to compute cough flow. Nonetheless, remarkable differences have been observed between peak flow meter assessments and pneumotachograph assessments (34).

However, an ineffective cough is determined by lower inspiratory flow, lower PECF, and a more prolonged compression phase (35). CVA is obtained by dividing PECF by the time required to reach its value (peak expiratory flow rise time, PEFRT) (35). The highest cough flow achieved after teaching the patient to take a deep breath and force cough is PECF. A PECF of less than 160 L/min is related to ineffective secretion clearance and failure of tracheostomy decannulation for adults and older children (36). Furthermore, a PECF of less than 270 L/min is associated with a high risk of acute respiratory failure and severe respiratory complications during an episode of minor respiratory tract infection (37, 38). It has been reported that compared to PECF and PEFRT, CVA is the most reliable predictor of aspiration in patients with amyotrophic lateral sclerosis (ALS) (34).

Scoliosis and treatment indication

Spinal deformity is a common and often severe musculoskeletal condition in children with pre-existing neurological or myopathic disorders (39). Scoliosis is a predominantly coronal plane deformity, the most common curve pattern in patients with neuromuscular conditions (39, 40). Severe curvature of the vertebral column causes difficulties in mobility and seating posture (41). The neuromuscular spinal deformities, in many cases, progress, and this progression often continues into adulthood. Patients with neuromuscular conditions may suffer from the spinal deformity's long-term disabling effects, including loss of the ability to sit, a decrease in overall function, and adverse effects on cardiopulmonary function (40, 41). The Scoliosis Research Society has classified neuromuscular spinal deformities into neuropathic and myopathic conditions (40, 42). The neuropathic conditions have been subdivided into those with upper- and lower-motor-neuron lesions. The group with upper-motor-neuron lesions includes diseases such as cerebral palsy, Friedrich ataxia, syringomyelia, and spinal cord injury; the group with lower-motor-neuron lesions includes poliomyelitis, myelomeningocele, and spinal muscular atrophy. The myopathic conditions include Duchenne's muscular dystrophy, arthrogryposis, muscular

dystrophy, and other forms of myopathy (40, 42). Bracing neuromuscular curves is not the definitive treatment, and the natural history of scoliosis cannot be affected by it (43, 44). The mainstay of treatment for neuromuscular scoliosis is surgical stabilization. Indications for surgical intervention for patients with neuromuscular scoliosis differ based on the disease etiology and individual and clinical circumstances of each patient (45). However, the two main indications for surgery are curvature progression and deterioration in sitting ability (40). Despite the advantages of operation, the risks of complications in patients with neuromuscular scoliosis after surgical intervention are high, so the patients' families should be involved in all decision-making stages (46). The most common complications are respiratory problems (post-operative pneumonia due to some degree of pre-existing intercostal paralysis and a poor cough reflex), ileus, nutritional problems, hip problems (hip subluxation, dislocation, and contracture), and crankshaft phenomenon (46).

Respiratory management and treatment of patients with NMD

Patients suffering from NMD might develop restrictive lung disease due to RMW (chest wall, diaphragm, and abdominal muscles), hypotonia of bulbar muscles, coexisting anatomical abnormalities (such as rigid spine or scoliosis), and decreased central respiratory drive (47, 48). These patients may have difficulty inhaling and exhaling, as well as coughing. Chronic neuromuscular respiratory failure could be a poor prognostic indicator in patients with patients with NMD. It could predispose them to severe respiratory system infections and cause disability due to dyspnea and sleep disruption (47, 48). Thus, recognizing the presence of neuromuscular respiratory failure is essential for initiating timely and supportive care and management in patients with NMD.

Several available therapies have improved these patients' quality of life and survival. Therefore, it is recommended to identify RMW at its early stages (48). Pulmonary function tests should routinely be performed in these patients, and their results (including maximal inspiratory and expiratory pressure and FVC) should be closely monitored. Maximal inspiratory pressure is indicative of ventilatory ability and diaphragm strength. Maximum expiratory pressure reflects the strength of the chest wall and abdominal muscles and the ability to cough and bring up secretions. The other measurement that should be monitored is the peak cough flow, which indicates the amount of pressure generated by a patient during a volitional cough (48, 49). Hypoventilation leading to hypercapnia is a significant problem in patients with NMD (48), for which periodic measurements of arterial blood gases or end-tidal carbon dioxide levels are recommended. Performing a thorough review of systems is of great importance in these patients. Nocturnal hypoventilation-induced hypercapnia causes morning headaches, poor sleep quality due to nightmares and nocturnal restlessness, and daytime somnolence (48). Moreover, probable lung damage at later stages of the disease could lead to insufficient respiration with hypoxia (48).

Noninvasive ventilation (NIV) could prolong survival and improve quality of life. The advantages of a multidisciplinary symptom management approach include decreased hospitalization rates and improved quality of life for these patients (50). The criteria for initiation of NIV include the presence of symptoms suggestive of hypoventilation and any of the following: daytime arterial blood gas CO2

levels of ≥ 45 mmHg, oxygen saturation (SpO2) of ≤ 88% for at least five minutes during sleep, P_{Imax} ≥ -60 cmH2O, or FVC < 50% of predicted FVC performed in the upright or supine position (50). The preferred modality of assisted ventilation in patient with NMD is bimodal positive airway pressure (BiPAP) which is similar to the older technology, continuous positive airway pressure (CPAP), used for treating sleep apnea (47, 48).

Poor cough in patients with NMD causes difficulty clearing and bringing up the secretions. As mentioned above, the peak cough flow measures the cough effectivity. A peak cough flow of <160 L/min is suggestive of a severely compromised and ineffective cough for clearance of the airway. The peak cough flow could be increased with the assistance of cough augmentation techniques (51), such as mechanical cough augmentation, breath-stacking, or manual chest and abdominal compression (51, 52). A hand-held resuscitator with a 1-way valve is utilized in sequential breath-stacking for lung volume recruitment. The increased lung volume and chest wall range of motion prevent basal atelectasis and maintain the chest wall's flexibility, respectively (52-54). These factors help reduce breathing work and improve cough strength and effectiveness in patients with NMD.

In Conclusion

Patients with NMD are highly prone to respiratory complications during the disease. Early and timely diagnosis of respiratory disorders is a multidisciplinary and necessary approach that must be adopted to provide optimal treatment. Noninvasive positive pressure ventilation and cough management strategies are the gold standards of care for neuromuscular disorders because they improve survival, sleep, and quality of life in these patients.

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Author's contribution

Gh Kh.& P K. conceived of the presented idea and supervised the findings of this work; MM N. & SA T contributions to conception and design and discussed the results,; F A., S S., N F., prepared the first draft of the paper; M P., SZ M., & N F., searched for relevant articles and edited the manuscript. F Kh., M S., A TB., & M P contributed to writing the manuscript, participated in revising. All authors participated in revising, and gave final approval of the version to be submitted.

Conflicts of interest

The authors declare no conflicts of interest.

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