Hypoventilation syndrome in neuromuscular disorders

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Purpose of review
Hypoventilation syndrome in neuromuscular disorders (NMDs) is primarily due to respiratory muscle weakness and results in increased morbidity and mortality. This article highlights current aspects of neuromuscular hypoventilation syndrome, including pathophysiology, clinical symptoms, assessment, respiratory involvement in various NMD, and causal and symptomatic treatments with an emphasis on recent research and advances.

Recent findings and Summary
New therapeutic agents have been developed within the last years, proving a positive effect on respiratory system. Symptomatic therapies, including mechanical ventilation and cough assistance approaches, are important in NMD and respiratory muscle training may have benefit in strengthening respiratory muscles and should be offered patients with respiratory muscle weakness the same way as physiotherapy. Correct respiratory assessments and their correct interpretation are hallmarks for early diagnosis of hypoventilation syndrome and treatment.

Keywords
neuromuscular hypoventilation, pathophysiology, respiratory muscle training, respiratory muscle weakness

INTRODUCTION

Neuromuscular disorders (NMDs) comprise a heterogeneous group of chronic-progressive diseases, characterized by involvement of the central and/or the peripheral nervous system, neuromuscular junction, or muscle. Ventilatory insufficiency in NMD is caused by inspiratory muscle weakness especially the diaphragm, thoracic restriction, and/or upper airway obstruction. In some multisystemic NMD, impaired respiratory drive may be present due to central involvement. Generally, the lung tissue is not affected, though with disease progression and ventilatory insufficiency, collapse, or closure of small or larger lung compartments may occur (dys- and atelectasis) and compromise pulmonary gas exchange.

PATHOPHYSIOLOGY

Central neurons generate breathing rhythm and depth. Their activity is influenced by the sensory integration of chemical and mechanical feedback from peripheral and central receptors. The diaphragm and external intercostals are the primary inspiratory muscles, whereas the sternocleidomastoid and scalenes are accessory muscles of inspiration. Expiration is largely passive due to elastic recoil though forced expiration during exercise or coughing is dependent on the internal intercostal and abdominal muscles. Afferent neurological inputs to the diaphragm originate from the phrenic nerves arising bilaterally from the third, fourth, and fifth cervical nerves, and thoracic nerves are responsible for the innervation of intercostal and abdominal muscles [1]. Therefore, respiratory dysfunction may occur at four different levels or their combinations:

(1) Central breathing irregularities and sleep-disordered breathing (SDB) are frequent findings in patients with NMD [2], but underlying mechanisms are not fully understood. Skeletal muscle hypotonia during sleep adds to a disease-related muscle weakness and causes decreased ventilatory output, resulting in chronic hypoventilation and

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KEY POINTS

- Hypoventilation syndrome is primarily due to respiratory muscle weakness and is an important cause of morbidity and mortality in NMD.
- Routine assessment of respiratory function is critical for early diagnosis of hypoventilation syndrome and treatment.
- There has been recent development of new therapeutic agents which have a positive effect respiratory function.
- Symptomatic therapies including mechanical ventilation, respiratory muscle training, and cough assistance approaches are increasingly important in NMD.

hypercapnia. In addition, chronic hypercapnia causes decreased respiratory drive which leads to impaired CO_2 responsiveness. Starting with episodes of rapid eye movement (REM) sleep hypopnea, respiratory muscle weakness (RMW) develops to REM sleep-associated hypoventilation and continuous nocturnal hypoventilation at later stages.

(2) During sleep, oropharyngeal muscle activity decreases in healthy persons, but additional weakness in NMD may contribute to upper airway obstruction and result in periods of apnea and hypercapnia (obstructive sleep apnea, OSA). OSA occurs independently of central breathing disorders and those arising from RMW.

(3) RMW may be associated with neurogenic, myogenic, and/or neuromuscular junction disorders. Inspiratory muscle weakness causes a reduction in alveolar ventilation (hypoventilation) and produces an increase in the arterial partial pressure of carbon dioxide ($PaCO_2$) and a corresponding reduction in PaO_2. Typically, both inspiratory and expiratory muscles are affected though patterns and distribution of weakness vary.

(4) Skeletal deformities: Severe thoracic deformities contribute to insufficient compliance, resulting in ineffective thoracic expansion during inspiration. Typically, NMD with severe skeletal deformities of the spine (severe scoliosis or lordosis) or ribs present with a stable restrictive respiratory pattern.

CLINICAL SYMPTOMS

Initial hypoventilation symptoms are nonspecific in most patients and include morning headache, daytime sleepiness, concentration difficulties, depression, and fatigue [3,4▪,5,6]. Reduced oropharyngeal muscle activity combined with upper airway muscle weakness in some NMD causes OSA, resulting in nocturnal snoring and apnea. In these patients, unrestful sleep, daytime sleepiness, and morning headache represent the most important symptoms [7]. With deteriorating RMW, exercise dyspnea and orthopnea in a supine position become present. At this stage, paradoxical ventilation with abdominal flattening during the inspiratory phase is typical. Shortness of breath, speech, and resting dyspnea with activation of accessory respiratory muscles indicate severe RMW. Weakness of expiratory muscles results in cough inadequacy, increasing the risk of respiratory tract infections. Epworth Sleepiness Scale [8] or the Medical Research Council Breathlessness Scale [9] may help to identify patients with hypoventilation syndrome, but was not specifically designed for NMD patients [10]. Therefore, interviewing patients for specific and nonspecific symptoms should be done regularly.

ASSESSMENT OF RESPIRATORY FUNCTION AND SLEEP BREATHING

Although a variety of techniques are available, assessment of respiratory function with volitional noninvasive spiromanometric assessments is the standard of care in NMD (Fig. 1). Considering the impact of RMW on morbidity and mortality in NMD, respiratory function must be assessed and monitored regularly. Overall, respiratory function in NMD should be assessed with diverse tests which assess lung volumes and pressures rather than single isolated measures.

RMW may lead to decreased vital capacity in many patients with NMD and spirometric measurement of vital capacity is the most commonly performed assessment of respiratory function in NMD. However, it is important to note that vital capacity is an indirect measure of respiratory muscle strength that assesses inspiratory and expiratory function, as well as structural aspects of the chest wall, airway, and lungs. A variety of approaches are used to obtain vital capacity including the slow vital capacity and the forced vital capacity (SVC and FVC). Though both are generally equivalent, there has been increased interest in the use of SVC to measure vital capacity in NMD due to the SVC being more comfortable to perform [11]. Although typically obtained in an upright position, upright and supine vital capacity measurements are recommended in NMD as a $>20\%$ drop from upright to supine implicates substantial diaphragmatic weakness [12–14]. As a part of spirometry, maximum voluntary ventilation is used for the evaluation of respiratory capacity and the measurement of workload. However, as

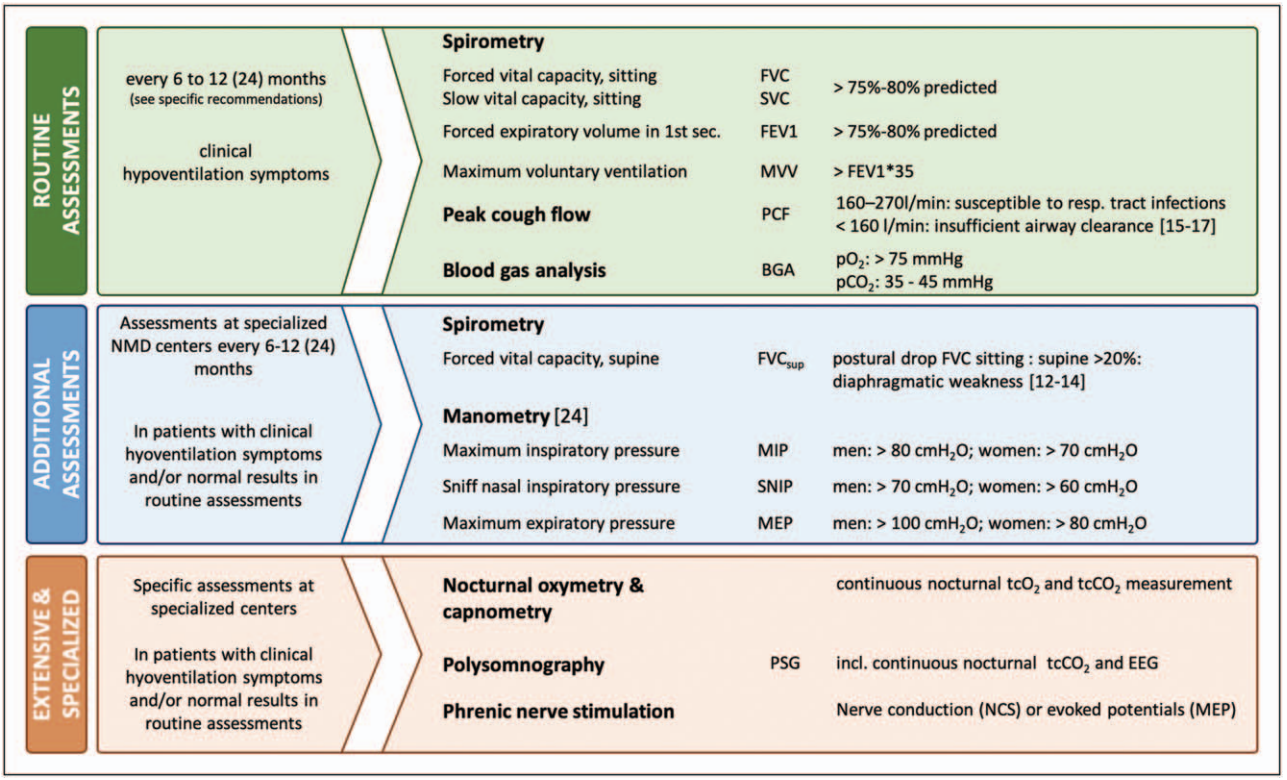

FIGURE 1. Assessment of respiratory function and sleep breathing in neuromuscular disorders. cmH_2O, centimeters of water; EEG, electroencephalogram; l/min, liters per minute; mmHg, millimeters of mercury; NMD, neuromuscular disorders; PCO_2, partial pressure of carbon dioxide; pCO_2, partial pressure of oxygen; $tcCO_2$, transcutaneous carbon dioxide; tcO_2, transcutaneous oxygen.

this assessment may be exhausting, patients with NMD and RMW might not be able to perform this test sufficiently.

RMW leads to an inadequate cough in many NMD. Cough adequacy can be assessed with spirometric measurement of peak cough flow (PCF) during volitional cough production. In NMD, PCF < 160 L/min is associated with an ineffective cough [15,16], whereas PCF values between 160 and 270 L/min are associated with increased risk of respiratory morbidity [17].

Manometric measures of maximum inspiratory pressure and maximum expiratory pressure (MIP, MEP) allow direct measurement of inspiratory and expiratory muscle strength noninvasively at the oral opening, respectively. Due to the curvilinear relationship between lung volumes and pressures [18,19], MIP and MIP are more sensitive to changes in respiratory muscle strength than spirometry measures such as FVC [20,21]. For example, in amyotrophic lateral sclerosis (ALS), MIP is more frequently affected at diagnosis than spirometric measures of lung volumes and therefore such measures may underdiagnose respiratory dysfunction [22,23]. Updated American Thoracic Society/European Respiratory Society guidelines for measurement of MIP/MEP provide guidance for methodological issues (e.g., use of flanged mouthpieces, manual assistance in the event of oral leak, five versus three repeated efforts for each maneuver), as well as improved normative data to guide interpretation [24]. Sniff nasal inspiratory pressure (SNIP) is a complementary approach to MIP in the assessment of inspiratory muscle strength and may be useful when bulbar weakness causes an inadequate labial seal. Compared to MIP, SNIP may also be easier and more intuitive to perform as the maneuver is performed from functional residual capacity rather than residual volume. One challenge to measurement and interpretation of SNIP is variability in the exact methodology in terms of whether the contralateral nostril should be open or closed during testing. SNIP with the contralateral nostril occluded versus unoccluded results in higher values that are more strongly correlated with MIP [25].

A variety of other approaches are available to assess respiratory function, but their clinical utility is limited by availability and/or their invasive nature including phrenic nerve stimulation with gastroesophageal manometry and diaphragm ultrasound. In neurogenic disorders, phrenic nerve conduction studies may have utility.

Polysomnography may be used to assess SDB in NMD to classify respiratory events, identify SDB triggered by noninvasive ventilation, and to establish an effective positive airway pressure titration [26]. Nocturnal hypercapnia may emerge before oxygen desaturation which requires assessment with transcutaneous capnometry [27,28].

RESPIRATORY INVOLVEMENT IN NEUROMUSCULAR DISORDERS

Overview

Slowly progressive RMW is common in muscular dystrophies and some limb-girdle-muscular dystrophies (LGMD) and also occurs frequently in myotonic dystrophy type 1 (DM1), congenital myotonic dystrophy, and some metabolic myopathies, congenital myopathies, and motorneuron diseases. However, a rapid deterioration of respiratory function may be seen in every patient with RMW due to respiratory tract infection associated with dysphagia and/or an inadequate cough. In acquired inflammatory myopathies and neuropathies, respiratory involvement is often acute or subacute, including exacerbation in myasthenic syndromes (Fig. 2).

Inherited neuromuscular diseases with hypoventilation syndrome

Muscular dystrophies

In x-linked dystrophinopathy Duchenne muscular dystrophy (DMD), FVC declines by approximately 8% annually and RMW becomes apparent at around age 10, resulting in mechanical ventilation at age 15 to 20 [29,30]. Becker muscular dystrophy (BMD) is a milder phenotype with later age of onset and slower disease progression. Although RMW is rare, OSA and inadequate cough may occur. Of note, cardiac involvement is frequent in BMD and cardiomyopathy may result in respiratory decompensation due to lung edema.

Research on respiratory involvement in autosomal-dominant DM1 emphasizes, as this form typically presents with a more severe phenotype [31]. DM1 is associated with early central apnea and OSA [6,32]. With disease progression, RMW becomes more prominent. Frequency of hypoventilation syndrome in DM2 is lower, but central apnea, OSA, and, more rarely, RMW may evolve [33]. For DM1, an annual decline in FVC of 0.73% is estimated [34]. In contrast to other NMD, expiratory muscle weakness is more severe and occurs earlier, resulting in inadequate cough and increased risk for respiratory morbidity early in the disease course [21,35]. As daytime sleepiness, fatigue, and concentration difficulties are part of the multisystemic involvement of myotonic dystrophies, hypoventilation symptoms may overlap and thus may be overlooked, so frequent assessments of respiratory function, including polysomnography, are recommended [33,36]. A short questionnaire assessing hypoventilation symptoms in DM1 was introduced in 2015 and was recently validated [36,37].

Oropharyngeal and RMW are present in about 50% of newborns with congenital muscular dystrophy (CMD) and is the main cause of dramatically reduced survival with an increased mortality rate of 30–40% [38]. Invasive ventilation is unavoidable in most patients. For all forms of autosomal-dominant muscular dystrophy, no specific therapy exists up to date.

Although clinical presentation and disease course in patients with autosomal dominant facioscapulohumeral muscular dystrophy (FSHD) is highly variable, up to 38% of patients may develop hypoventilation at later stages [39]. OSA and SDB are found in a high proportion of patients [5,6]. Both the inspiratory and expiratory muscles are involved, and in patients with early onset disease, skeletal deformities also contribute to a restrictive ventilatory pattern. Disease severity and D4Z4 fragment length correlate inversely with respiratory involvement [6,39].

Metabolic myopathies

This heterogeneous group of inherited myopathies encompasses glycogen storage diseases, lipid storage diseases, and mitochondrial diseases with defects in glycogen, lipid, or energy metabolism. Of those, glycogen storage disease type 2 (Pompe disease) with an autosomal recessive defect in the GAA gene causes progressive RMW. Onset of symptoms and disease progression depends on residual lysosomal enzyme activity. RMW is one of the most important clinical manifestations and occurs in all infants, all severely affected children, and in about 2/3 of adults. Despite the availability of enzyme replacement therapy (ERT), respiratory decline is seen in about 2/3 of adults with an annual decline of 2.3% in FVC and 3.2% in MIP [40,41]. PCF is also decreased, particularly those with the infantile-onset form although abnormal PCF is also present in up to 70% of those with juvenile- or adult-onset Pompe disease [42▪]. Although glycogen deposits were found in spinal cord and phrenic motor neurons in animal studies [43], a (contributing) neurogenic damage could not be confirmed in a recent clinical study [44].

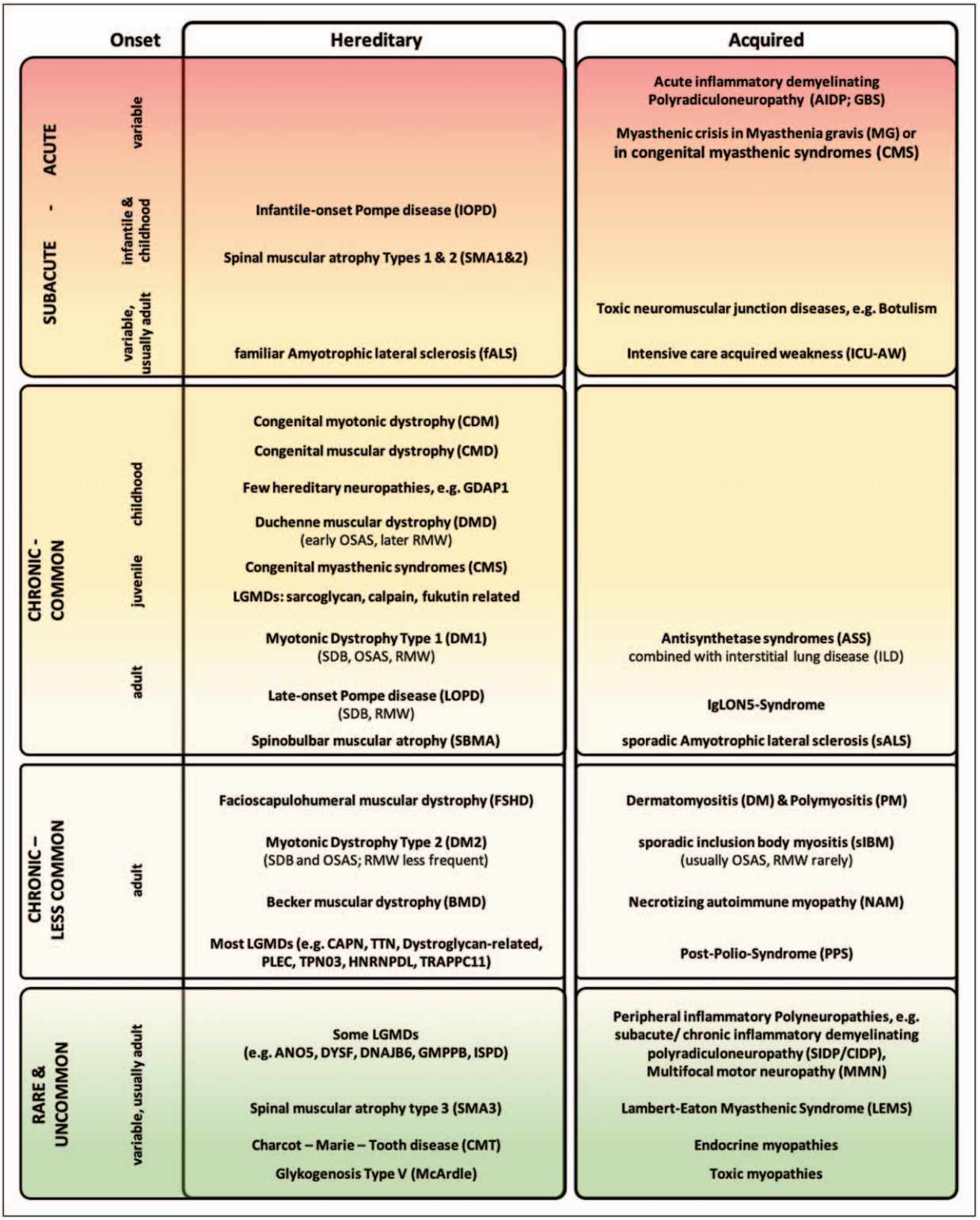

FIGURE 2. Overview of respiratory involvement in neuromuscular disorders. OSAS, obstructive sleep apnea syndrome; RMW, respiratory muscle weakness; SDB, sleep-disordered breathing.

Motorneuron diseases

Autosomal recessive deletions or loss-of-function mutations in the SMN1 gene cause spinal muscular atrophy (SMA). Onset and disease severity are determined by the number of SMN2 copies and the current classification comprises four clinical types [1–3,4▪,45]. Respiratory involvement is common in SMA types 1 and 2, and rare in type 3 [21,46].

While the diaphragm in SMA is relatively preserved, intercostal weakness affecting inspiration and expiration is frequent. Moreover, early paraspinal muscle involvement, especially in SMA types 1 and 2, leads to underdevelopment of the lung and chest-wall with severe deformities, resulting in reduced chest-wall compliance and restrictive respiratory pattern [46].

10–15% of ALS cases are familial ALS (fALS) [47]. Due to advances in molecular genetic technology, several genes have been identified with the most common mutations in C9ORF72, SOD1, transactive response DNA binding protein, and fused in sarcoma in Europe [48–50]. Both upper and lower motor neurons are affected, leading to progressive muscle weakness, atrophy, and spasticity of locomotor, oropharyngeal, and respiratory muscles. RMW and/or bulbar involvement occur in almost every patient within 2–5 after diagnosis and are primary causes for a dramatically increased morbidity and mortality [47]. RMW is also reported as the first symptom in some cases.

Congenital myasthenic syndrome

Congenital myasthenic syndrome is caused by gene mutations responsible for the function and organization of the presynaptic, synaptic, and/or postsynaptic neuromuscular junction. Clinical presentation is heterogeneous, comprising abnormal fatigability, reduced exercise endurance, and/or transient or permanent skeletal muscle weakness including respiratory and oropharyngeal muscles. RMW is common and comprises early-onset weakness of respiratory and oropharyngeal muscles, as well as musculoskeletal deformities. Respiratory failure is common in patients with dysphagia [51–53].

Congenital myopathy

Clinical hallmarks of heterogeneous autosomal recessive and dominant congenital myopathies (CMs) are persistent muscle hypotonia, delayed motor milestones, early-onset skeletal deformities, limb-girdle, and/or axial weakness. Restrictive respiratory insufficiency due to RMW and chest wall deformities is prominent in about 30% of neonatal and infant patients [54]. In contrast to other inherited myopathies, locomotor and RMW progress slowly or even remains stable for many years [55].

Limb-girdle muscular dystrophy

Core clinical feature of the more than 30 types of autosomal dominant and autosomal recessive limb-girdle muscular dystrophy (LGMD) [56] is limb-girdle and axial weakness. Hypoventilation due to RMW is frequent in sarcoglycanopathies (LGMDR2-R6), calpainopathy (LGMDR1), and fukutinopathy (LGMDR9), but may evolve at later stages in many other types of LGMD, including OSA [57].

Acquired neuromuscular disorders with hypoventilation syndrome

Motor neuron diseases

Sporadic amyotrophic lateral sclerosis accounts for about 75–80% of ALS cases. The clinical spectrum corresponds to those of fALS with high variability in age of onset and disease course. FVC is a significant predictor of survival, as faster disease progression in patients with FVC < 75% of predicted at baseline indicates higher mortality [58]. PCF has been shown to decrease rapidly by 124.8 L/min annually in ALS [59] and a decline of 50 L/min increases the risk of death by 1.31 [23].

Postpolio syndrome follows an acute infection in childhood with the polio virus causing poliomyelitis. Distribution of muscle weakness is highly variable, including locomotor and respiratory muscles. After acute infection, weakness improves variably over a long duration but may deteriorate with age. In 15–80%, muscle strength declines decades after acute infection. In those patients with childhood respiratory involvement, RMW may occur with age in about 25–35% [60].

Idiopathic inflammatory myopathies

Idiopathic inflammatory myopathies (IIMs) are a group of chronic, autoimmune NMD encompassing dermatomyositis, polymyositis, necrotizing autoimmune myopathy, antisynthetase syndromes, and sporadic inclusion body myositis (sIBM). An acute or subacute weakness of limb-girdle and axial muscles is characteristic and may be accompanied by myalgia, reduced exercise endurance, and increased fatigability [61]. Hypoventilation syndrome due to RMW or OSA may emerge except for sIBM where RMW is uncommon [62]. Of note, lung tissue may be affected in IIM, contributing to impaired respiratory function [63].

Inflammatory neuropathies

Acute inflammatory demyelinating poly (radiculo-)neuropathy (guillain-barré-syndrome [GBS]) and its variants and intensive-care acquired weakness (ICU-acquired weakness) are commonly associated with acute respiratory failure (ARF) due to RMW, whereas hypoventilation syndrome in subacute and chronic forms is rare [64]. Up to 1/3 of GBS patients and 2/3 of ICU-acquired weakness patients require mechanical ventilation [65,66]. Based on a large observational study, increased limb muscle weakness is associated with a poorer outcome requiring

prolonged mechanical ventilation in GBS [66]. Invasive ventilation is necessary in most patients with dysphagia [67].

Myasthenic syndromes

Common autoantibodies against postsynaptic membrane receptors include the nicotinic acetylcholine receptors, muscle-specific kinase, and lipoprotein-related protein 4. They typically cause fluctuating, exercise-induced muscle weakness, and fatigability. Respiratory and/or bulbar muscles are commonly involved and hypoventilation may be the first clinical sign in some patients [68,69]. With adequate therapy, most patients remain asymptomatic or stable with only minimal clinical signs, but myasthenic crisis requiring mechanical ventilation due to infections, concomitant medications, or drugs may occur in 15% to 20% [70▪▪]. Severity of the disease is assessed by Quantitative Myasthenia Gravis score and Besinger Score including FVC. However, abnormalities in MIP and PCF are more likely to indicate respiratory dysfunction earlier than changes in FVC in these patients [71].

TREATMENT OF RESPIRATORY MUSCLE WEAKNESS

Causal/specific therapies

Glucocorticoid therapy for DMD has been a mainstay treatment for DMD for many years, attenuating disease progression and postponing noninvasive ventilation. In a clinical trial assessing the efficacy of Eteplirsen, a significant slowing of respiratory decline was observed for both ambulatory and nonambulatory patients [72].

ERT is available since 2006 for all forms of Pompe disease, slowing disease progression and stabilizing respiratory function for at least 2–5 years in more than 2/3 of patients [41,73–75,76▪▪,77–79]. Clinical trials are being conducted on the efficacy of AAV gene-based therapy in Pompe disease.

For the treatment of SMA, three therapeutic agents have been approved recently and overall, they show promising results regarding respiratory system. Antisense oligonukleotide Nusinersen received European approval for all types of SMA in 2017. AAV9-delivered SMN1 gene replacement therapy with onasemnogene abeparvovec-xioi was approved in 2019 in Europe for all 5q-SMA forms with a maximum of three SNM2 copies or the phenotypical SMA1 presentation. The survival of motor neuron two-directed RNA splicing modifier Risdiplam was approved in 2020 for 5q-SMA types 1–3 or 1–4 SMN2 copies and ≥ 2 months of age. Efficacy comparison of the three agents is difficult due to different respiratory outcome assessments and various phenotypes among the different cohorts. In 17 infants with SMA1, ventilation status did not change significantly after 2 years of therapy with nusinersen [80]. A total of 12 patients with SMA2 compared to 14 controls significantly improved in FVC and SNIP after six nusinersen injections [45]. In contrast, 12 pediatric SMA2 and three patients treated with nusinersen did not show a significant improvement in respiratory function after 300 days [81]. A significant change in respiratory function was found in 17 SMA3 patients after 10 months based on PCF, but not in FVC [82▪▪]. In the pivotal trial of onasemnogene abeparvovec-xioi, all patients with SMA1 remained ventilator-free after 20 months compared to 8% in natural history studies [83]. And 21 infants with SMA1 treated with Risdiplam were ventilator-free at 12 months, which would not be expected in the natural disease course [84].

Tofersen, an antisense oligonucleotide for patients with fALS with SOD1 mutations, showed promising results by slowing disease progression measured by ALSFRS-R score [85].

Currently, no specific treatment is available for muscular dystrophies, congenital myopathies, or sporadic motorneuron diseases, but many clinical trials are being conducted, like tideglusib in CMD or losmapimod in FSHD.

Symptomatic therapies

Mechanical ventilation

Mechanical ventilation is the mainstay to support insufficient respiratory muscles to prevent chronic hypoventilation and ARF. Mechanical ventilation is typically established by noninvasive ventilation (NIV) by face or nasal mask, depending on the disease severity, prognosis, and facial anatomy. In patients with ARF, dysphagia, and inadequate cough, tracheostomy invasive ventilation (TIV) may be unavoidable [86,87]. In most patients with acquired NMD on adequate treatment, mechanical ventilation is temporarily [67,70▪▪,88]. On the contrary, even though specific treatment may attenuate respiratory decline in some NMD, RMW is typically chronic and progressive and the only sufficient treatment for hypoventilation syndrome is home mechanical ventilation (HMV). In these patients, intermittent NIV is initiated during the night for several hours. In patients with early onset, increasing ventilation times exceeding 20 h/day, and/or recurrent respiratory tract infections, TIV may

become necessary. Recommendations to initiate mechanical ventilation vary across different countries and medical disciplines, but overall, they comprise a combination of a reduced FVC (<70% to < 75%), an increased $PaCO_2$ at night or even during the day, decreased PaO_2, and/or clinical symptoms suggestive of hypoventilation syndrome [87,89–92]. A nocturnal peak ≥49 mmHg in transcutaneous capno-oximetry (TCO_2) was the best predictor of HMV initiation in different NMD [93]. The benefit of HMV has been demonstrated in many studies in various NMD resulting in improved sleep quality, quality of life, and prolonged survival [94–96]. Some discussion exists about the optimal time to initiate HMV. An improved survival was found in ALS when NIV was initiated early with only mild decreased FVC [97–100]. For DM1, reports on mechanical ventilation adherence show a high variability in different cohorts and poor compliance seems to be associated with a higher risk of pulmonary adverse events [101,102,103▪]. Highest survival rates were found for mechanical ventilation > 7 h/day, whereas < 4 h/day was associated with increased mortality [103▪]. Except for central core myopathy, a progressive decline in pulmonary function is unpreventable in most NMD, demanding an individual approach regarding initiation of and adherence to HMV.

Respiratory muscle training

Respiratory muscle training (RMT) to target inspiratory and/or expiratory muscle weakness in NMD has also been explored. Early studies investigated the effects of RMT in a variety of populations including DMD and SMA and the results suggest that RMT may increase respiratory muscle strength [104,105]. More recently, the role of RMT in children [106,107] and adults with Pompe disease has received considerable attention [108–112,113▪,114]. Although these relatively small studies differ considerably in their methods and outcomes, the results in adults with Pompe disease suggest that RMT is safe, well tolerated, and generally increases MIP by about 15–20%. However, in the only randomized controlled trial of RMT in late-onset Pompe disease (LOPD), despite a 17% increase in MIP and a 23% increase in MEP, the treatment group did not statistically outperform the control group for increases in inspiratory and expiratory muscle strength. Time to climb four steps and daytime sleepiness measured with the epworth sleepiness scale did improve significantly [113▪]. Although further trials are needed, the use of RMT in adults with Pompe has been advocated especially in those with progressive respiratory muscle weakness [110]. RMT focusing on the expiratory muscles (expiratory muscle training, EMT) has been explored in ALS including a recent RCT which showed EMT to be well tolerated, increase MEP, and improve aspects of swallowing performance [115▪,116].

Cough assistance and techniques

In patients with weak expiratory muscles, impaired airway clearance may lead to recurrent respiratory infections. Even though respiratory tract infection may cause ARF, they also cause atelectasis of lung tissue, following a reduced ability of oxygenation. Cough assistance is generally recommended once PCF drops below 270 L/min and is strongly indicated in patients with PCF < 160 L/min [117]. The manual insufflation-exsufflation technique is not associated with relevant side effects and should be performed with a peak pressure of 40 cmH_2O for adults, followed by exsufflation. Best expiratory flow depends on the patient's compliance and disease severity, but overall an expiratory flow of 10–25% of peak inspiratory flow is considered as safe and effective [118,119]. Such symptomatic coughing therapy can be augmented by physiotherapeutic breathing and coughing techniques [120].

CONCLUSION

Hypoventilation syndrome is frequent in NMD. As specific therapy is currently available only for a minority of inherited NMD, early diagnosis and treatment are hallmarks for improving quality of life and reduce mortality.

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Conflicts of interest

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- ■■ of outstanding interest

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