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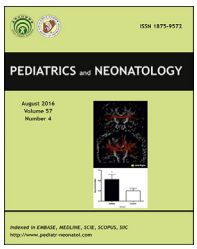

Review Article

Respiratory phenotypes of neuromuscular diseases: A challenging issue for pediatricians

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Abstract Neuromuscular disease (NMDs) encompass a heterogeneous group of genetic disorders, with respiratory problems of variable intensity and progression described at any pediatric age, from infancy to adolescence, and they are largely associated with significant lifelong morbidity and high mortality. Restriction of breathing, impaired gas exchange, decline of lung function and sleep disordered breathing progressively develop because of muscular weakness and culminate in respiratory failure. Depending on the disease progression, airways manifestations can take weeks to months or even years to evolve, thus depicting two major respiratory phenotypes, characterized by rapid or slow progression to respiratory failure. Assessing type and age at onset of airways problems and their evolution over time can support pediatricians in the diagnostic assessment of NMD. In addition, knowing the characteristics of patients' respiratory phenotype can increase the level of awareness among neonatologists, geneticists, neurologists, pulmonologists, nutritionists, and chest therapists, supporting them in the challenging task of the multidisciplinary medical care of patients. In this review we examine the issues related to the pediatric respiratory phenotypes of NMD and present a novel algorithm that can act as a guide for the diagnostic agenda and the key preventive or therapeutic interventions of airways manifestations. With prolonged survival of children with NMD, the advent of neuromuscular respiratory medicine, including accurate assessment of the respiratory

Abbreviations: NMD, Neuromuscular disease; FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; SDB, Sleep disordered breathing; OSA, Obstructive sleep apnea; SMA, Spinal muscular atrophy; SMARD, Spinal muscular atrophy with respiratory distress; MD, Myotonic dystrophy; PD, Pompe disease; ERT, Enzyme replacement therapy; MM, Mitochondrial myopathy; CM, Congenital myopathy; EEG, Electroencephalogram; DMD, Duchenne muscular dystrophy; LGMDs, Limb-girdle muscular dystrophies; LOPD, Late-onset Pompe disease; ACTs, Airway clearance techniques; NIV, Noninvasive ventilation; HFNC, High-flow nasal cannula; MIP, Maximum inspiratory pressure; MEP, Maximum expiratory pressure; RRI, Recurrent respiratory infections.

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phenotype, will help physicians to determine patients' prognoses and to design studies for the evaluation of new therapies.

1. Introduction

Neuromuscular diseases (NMDs) are characterized by respiratory muscle weakness with multifaceted manifestations, including restricted breathing, impaired gas exchange, and lung function decline, eventually reducing patients' lifespans. In addition, cough progressively weakens and becomes ineffective with time.[1]

In NMD patients, airways are intrinsically normal but are secondarily affected. Limitation of breathing efforts, combined with the inability to clear secretions, predisposes patients to recurrent pneumonia and atelectasis, reducing lung compliance and increasing airway resistance.

Lung function tends to deteriorate, showing progressively low forced expiratory volume in 1s (FEV_1) and low forced vital capacity (FVC), and a normal or high FEV_1/FVC. Total lung capacity also reduces because of muscle weakness (mainly, diaphragm). Patients breathelow tidal volumes, and any further decrease in expiratory muscles force leads to air trapping with increased residual volume, which leads to respiratory failure. This significantly affects morbidity and mortality among NMD patients.[2]

In most NMDs, sleep disordered breathing (SDB) including patterns of sleep hypoventilation, obstructive sleep apnea (OSA) and central sleep apnea contributes to respiratory failure. In normal subjects, during the rapid eye movement sleep, when tidal volume and respiratory rate decrease, the tone of respiratory muscles is lower and the ventilator response to hypoxia and hypercapnia reduces. These events are more evident in the presence of muscle weakness. Other features that are typically observed in NMD patients, such as bulbar muscles dysfunction and macroglossia, largely predispose to OSA.[3] Central or pseudocentral apnea was also reported.[4] In most NMDs, nocturnal hypoventilation and impaired gas exchange are prognostic indicators of irreversible respiratory compromise. In addition, the risk of respiratory failure is increased by vertebral scoliosis, which reduces chest wall and lung compliance and favors pulmonary hypertension and *cor pulmonale*.[5]

Taken together, these events explain the disease progression toward respiratory failure and its dramatic outcome for most NMDs.

2. Major respiratory phenotypes of NMD

Main breathing problems of NMD include shortness of breath, dyspnea, pooling of upper tract secretions, ineffective cough, recurrent-to-persistent airways infections, and aspiration phenomena.[1] As sleep is a vulnerable time for NMD subjects, difficulty in initiating and maintaining sleep, awakenings with dyspnea, morning or continuous headaches, diurnal hypersomnolence and difficulty concentrating are reported.[3,6]

The first steps in the approach to NMD are clinical, with straightforward history and thorough physical examination. Muscle deterioration may have a different timing of presentation or be more or less pronounced based on the segmental muscle weakness.[7] Depending on weakness progression, respiratory symptoms can take weeks to months or even years to evolve. Assessing type, age at onset and rapidity of evolution of airways problems can support pediatricians in the challenging differential diagnosis of NMD.[8] Based on the developed clinical problems, two major respiratory phenotypes are identified, both at risk of acute failure (Table 1). We herein examine the main respiratory features exhibited by patients with NMDs.

2.1. Rapidly progressive respiratory failure phenotype

This phenotype can be recognized among the youngest and oldest patients. When respiratory symptoms and signs develop early and worsen rapidly, the decision-making process should be quick to delay the risk of respiratory failure. Some NMDs present with the "floppy baby syndrome" which is often associated with a rapidly deteriorating clinical course and imposes fast therapeutic choices.

- **Spinal muscular atrophy (SMA),** a disorder of the anterior horn cell, caused by mutation of the survival motor neuron gene 1, is responsible for rapidly progressing respiratory failure. The most severe phenotype is reported in SMA 0, which is characterized by prenatal onset witnessed by decreased fetal movement *in utero*, joint contractures, respiratory failure at birth and death in a few weeks. In **SMA 1** (Werdnig-Hoffman disease), intercostal muscle weakness is responsible for paradoxical inward rib cage movement at each inspiration with a bell-shaped chest, while the diaphragm is relatively spared. Different subtypes of SMA 1, named 1A, 1B and 1C, are described according to the age of symptoms onset (as early as the first two weeks, or the first trimester, or between three and six months of life, respectively).[9] The SMA 1A, the most severe type, is characterized by marked muscular weakness at birth, severe difficulty swallowing, respiratory failure and early death. In SMA 1B and 1C, swallowing disorders and aspiration phenomena dominate the clinical scenario. Studies of SDB document initial marked thoraco-abdominal asynchrony which is followed by central

Table 1 Respiratory phenotypes of hereditary neuromuscular disorders at different pediatric ages.

Age	Condition	Progression of respiratory disease		Major respiratory manifestations		
		Rapid	Slow	Ineffective cough	RRI	SDB
Newborns	SMA0/SMA 1	Common		Marked	Common	Possible
	SMARD 1	Common		Marked	Common	Unknown
	Congenital myasthenic syndromes	Common		During crisis (sudden apnea)	Possible	Unknown
	Congenital myotonic dystrophy	Common		Common	Common	Possible
	Congenital myopathies (very severe form)	Common		Common	Common	Unknown
	Glycogenosis Type V	Common		Common	Common	Unknown
	Charcot-Marie-Tooth disease (severe early onset)	Common		Common	Common	Possible
Infants	Congenital-hypomyelinating neuropathy	Common		Common	Common	Possible
	Dejerine—Sottas syndrome	Common		Common	Common	Possible
	Pompe disease (early onset/ infantile disease)	Common		Common	Common	Common
	Mitochondrial disease (Leigh Syndrome)	Common		Common	Common	Possible
Preschool-school age children	SMA 2		Common	Possible	Possible	Possible
	Rigid spine with muscular dystrophy		Common	Possible	Uncommon	Possible
	Childhood-onset myotonic dystrophy		Common	Common	Common	Possible
	Facio-scapulo-humeral muscular dystrophy		Common	Possible	Possible	Possible
Adolescents	SMA 3		Common	Rare	Rare	Possible
	Duchenne muscular dystrophy		Common	Common	Common	Common
	Becker muscular dystrophy		Common	Rare	Possible	Possible
	Limb-girdle muscular dystrophy		Common	Common	Common	Possible
	Ullrich congenital muscular dystrophy		Common	Possible	Rare	Possible
	Myotonic dystrophy type 1		Common	Common	Common	Common
	Nemaline myopathy		Common	Possible	Possible	Possible
	Multiminicore myopathy		Common	Possible	Possible	Possible
	Late-onset Pompe disease		Common	Common	Common	Common

Abbreviations: Recurrent Respiratory Infections, RRI; Sleep Disordered Breathing, SDB.

apnea and OSA. Prognosis is poor, with 95% of infants dying if intensive intervention is delayed. Children with SMA may also be classified into "non-sitters," "sitters," and "walkers".[9] Respiratory evaluation of non-sitters includes pulse oximetry, capnography and sleep study to confirm hypoventilation.[10] In sitters or non-sitters, the assessment should be performed at least every six months, or initially every three months and then every six months, respectively.[10] Sleep studies are routinely recommended in non-sitters and sitters but not in walkers, unless overt symptoms occur.[10] The **SMA** with respiratory distress type 1 (SMARD1) is an autosomal recessive NMD caused by mutation in IGHMBP2 gene and is clinically characterized by progressive motor and respiratory decline manifesting from birth. Infants with SMARD look like those with SMA, and severe respiratory insufficiency due to neurogenic diaphragmatic palsy with normal-shaped thorax may develop after a symptom-free interval following birth. Prognosis is poor, with early death unless mechanical ventilation is provided.[11] Recently, patients with a SMARD phenotype non-carrying mutations in IGHMBP2 gene, have shown pathogenic variants in the LAS1L gene on chromosome X.[12]

- **Myotonic dystrophy (MD)** is an autosomal dominant NMD caused by an expansion of DNA 8 tandem repeats in the DMPK gene (type I, Steinert disease) or the CNBP (ZNF9) gene (type 2 MD).

Both forms are characterized by failure of muscle relaxation after activation, with diverse clinical presentation at different ages.[13] DM1 is divided into three types: (1) congenital, (2) mild, and (3) classic. The congenital type is considered when an affected mother delivers a floppy infant. Severe respiratory difficulty is reported in 50% of cases and it is responsible for death in approximately 30% of these.[14]

- **Congenital myasthenic syndromes**, which are disorders of the neuromuscular junction, are characterized by weakness of ocular, bulbar, and limb muscles with onset at or shortly after birth or in early childhood.[15] Respiratory insufficiency with sudden apnea and sometimes stridor are important clues to the disease.
- The **glycogenosis type II (Pompe disease, PD)** is caused by absence of functional acid alpha-1,4-glucosidase, and in the early onset form infants show hypotonia, failure-to-thrive and respiratory difficulty. Severe cardiomyopathy may lead to lobar atelectasis secondary to bronchial compression, and infants, when untreated, may die from cardiorespiratory failure and recurrent-to-persistent airways infection before the age of 2 years.[16] A milder subtype with less severe or absent cardiomyopathy but showing life-threatening respiratory insufficiency has been described.[17] Despite the frequency of OSA occurrence, few SBD studies are available. A study performed before and after enzyme replacement therapy (ERT) found no statistically significant difference in polysomnography although a trend towards improvement was demonstrated.[18] While muscle weakness mostly contributes to respiratory insufficiency, bulbar motoneurons dysfunction due to central nervous system glycogen accumulation may cause sleep apnea. Provided that the recombinant enzyme does not cross the blood—brain-barrier, this could explain why ERT may not result in significantly improved polysomnography.[18] The infantile form of another muscular glycogenosis, the **type V**, due to muscle glycogen phosphorylase deficiency, is characterized by progressive weakness and respiratory distress at or shortly after birth.[19]
- The **Charcot-Marie-Tooth disease is** a heterogeneous group of peripheral nerve disorders disorders 12 associated with distal muscle weakness and atrophy with reduced nerve conduction velocity.[20]

Infants with very severe neuropathy may also present early, rapidly evolving respiratory involvement.[20] However, genetic neuropathies including the Dejerine-Sottas syndrome and the congenital hypomyelinating neuropathy should always be considered in the differential diagnosis of floppy infants.

- **Mitochondrial Myopathy (MM)** typically develops during: Please check->pediatric age and includes several rare conditions.

Although muscle involvement is a hallmark of all pediatric onset MM, pulmonary function typically declines later. An exception is Leigh syndrome, a disorder of defective mitochondrial energy generation, in which respiratory decline may be rapidly progressive in infancy.[21]

- The **congenital myopathies** (CM) are a group of heterogeneous muscle disorders, including a) nemaline myopathy; b) core myopathy (subtypes: central core and multiminicore myopathy); c) centronuclear myopathy (subtypes: myotubular myopathy and autosomal centronuclear myopathy); d) congenital fiber-type disproportion myopathy and e) myosin storage myopathy.[22] In particular, multiminicore disease and congenital fiber-type disproportion myopathy are caused by mutation in the SELENON gene.[23] In recent years, the spectrum of **selenoprotein-related myopathies** has extended and currently includes multiple clinical phenotypes such as congenital muscular dystrophy with rigid spine and some types of desmin-related myopathy with Mallory body-like inclusions, which are negative for desmin mutations.[24,25] Clinical course of CM may be rapidly or slowly progressive. In core myopathy, the extremely severe lethal neonatal form can be rapidly progressive and require mechanical ventilation.[26] Also in nemaline myopathy, respiratory involvement is the main prognostic factor since survival depends on the severity of neonatal respiratory disease.[26] Patients with core myopathy have a fairly benign disease, and lung function is generally preserved with the exception of neonatal-onset cases.[22] Among the centronuclear myopathies, respiratory problems are a common cause of morbidity and some patients at birth or in early infancy require invasive ventilation or die prematurely.

2.2. Slowly progressive respiratory failure phenotype

This phenotype is characterized by development and worsening of symptoms and signs over years or decades.[8] Of all NMD, it is by far the most common course of respiratory disease either among the youngest or oldest patients.

- **SMA 2**, which includes 30% of all SMA cases, presents with muscle weakness by 6—18 months of life.[9] SMA 2 is distinguished into subtypes 2A and 2B according to the age of acquisition of the sitting position (after or before 8 months of life, respectively). No significant differences in respiratory disease ore need for ventilatory support have been reported between the two subtypes.[27] Respiratory insufficiency and dysphagia are common findings.[9] Lung function decline starts by school-age, and it slowly progresses after puberty. Recurrent respiratory infections and decreasing FVC are associated with increased risk of SDB and assisted ventilation need.[10,28,29] In these patients, SDB isharacterized by reduced EEG arousability and decreased number of sleep stage shifts/hour. Long-term non-invasive ventilation results in only small sleep microstructure changes.[30]
- Patients with **SMA 3** (15% of all cases of SMA) are able to achieve autonomous walking; however, motor manifestations, especially proximal muscle weakness of the lower limbs, progressively appear, at around the 18th month of life.[31,32] Early SDB and slow pulmonary function decline are typically reported.[33]
- In **Duchenne Muscular Dystrophy (DMD),** a X-linked recessive disorder, abnormal gait, frequent falls, and difficulty climbing steps become evident in affected boys at two to four years of age.

Events like respiratory muscle fatigue, pneumonia, atelectasis and respiratory failure largely affect morbidity. In the early phases of DMD, lung function may be normal

and the onset of increasing respiratory problems coincides with loss of ambulation; thus patients are distinguished into ambulatory or non-ambulatory ones. Adolescents develop a pulmonary restrictive pattern because of slowly progressive muscle weakness and contractures, spinal deformity, vertebra-costal joint ankylosis and obesity.[34] Monitoring lung function is critical from school-age because spirometry rapidly worsens even in the absence of dyspnea, with FVC providing guidance for treatment as indicator of survival.[35] A drawback to spirometry is the difficulty to perform it due to the fatigue induced by repeated maximal maneuvers. Furthermore, spirometry does not provide information on rib cage, diaphragm and abdominal muscles impairment.[34] Conversely, sleep studies may be necessary during the ambulatory stage, especially in individuals with weight gain due to steroids and/or overt SBD. The first sign of respiratory failure in DMD is nocturnal hypoventilation, especially in the first decade of life. A study found that 63.6% of DMD steroid-treated boys developed OSA, which was positively related with body mass index, while central sleep apnea or nocturnal hypoventilation was found in 33.6% and 17% of cases, respectively.[36] **Becker muscular dystrophy** is significantly less severe than DMD, with limb-girdle weakness and calf hypertrophy presenting by ten years. Typically, spirometry does not decline with aging.[37]

- **Myotonic dystrophy type 1** (DM1), an autosomal dominant NMD caused by expansion of CGT triplet repeat in the 3′ UTR region of the myotonin protein kinase gene, may manifest between one and ten years (childhood onset) or later in adolescence or adulthood (classic type).

The infantile form is characterized by muscle hypotonia, growth retardation, abdominal symptoms and intellectual disability. A common symptom is chronic fatigue, largely due to SDB.[38] The combined effects of SDB, increased abdominal adipose tissue, and muscle weakness are responsible for slowly progressing respiratory impairment with a restrictive pattern.

- **Limb-girdle muscular dystrophies (LGMDs) are a group of rare and heterogeneous conditions characterized by progressive weakness of proximal limb girdle muscles (pelvic and shoulder muscles), with age at onset of symptoms varying from early childhood to late adulthood.**[39]

To date, more than 30 genetic forms of LGMDs, either dominant (LGMD1) or recessive (LGMD2), are recognized including recessive calpainopathy (LGMD 2A/R1), dysferlinopathy (LGMD 2B/R2), sarcoglycanopathy (LGMD 2C—2F/R3-R6) types and the dominant type due to TPNO3 variants, transportinopathy (LGMD 1F/D2). The current classification of LGMDs was introduced following the 229th ENMC International Workshop 2017; however, the nomenclature remains a significant problem with the increased speed at which new disease genes are being discovered.[39,40] Symptoms can start from childhood to adulthood, with some school-age children presenting a progressive DMD-like evolution with loss of ambulation and reduced survival because of cardiopulmonary involvement.[41] Patients with 2C and 2D LGMD may have more respiratory impairment than others. There are few data about LGMD sleep studies although SDB was reported.[41]

- **Facio-scapulo-humeral muscular dystrophy** is a muscular dystrophy with disease onset from childhood to late adulthood with typical involvement of facial, shoulder girdle, and distal or proximal lower extremities muscles.

Because of nocturnal hypoventilation, shortness of breath, daytime fatigue and sleepiness may develop, and patients may benefit from mechanical ventilation.[42]

- **Collagen VI myopathies**, caused by defects in genes encoding collagen VI, a muscular extracellular matrix protein, include the Bethlem myopathy and the Ullrich muscular dystrophy. Patients with Ullrich dystrophy can exhibit loss of ambulation, scoliosis and progressive lung function decline. In Bethlem myopathy, a milder disorder with proximal weakness and distal joint contractures, respiratory muscle involvement requiring ventilatory support is rarely described.[43]
- **Late-onset Pompe disease** (LOPD) indicates glycogenosis type II with late-infantile, childhood, juvenile, or adult disease manifestations. The late-infantile, juvenile and adult forms present with slowly progressive dysfunction of the limb-girdle and trunk muscles and diaphragm, and less severe cardiac involvement.[44] Respiratory muscle weakness manifests first as nocturnal hypoventilation, followed by sleep disruption, morning headache, fatigue, and excessive daytime sleepiness. Macroglossia and upper airway collapse increase the risk of SDB (Fig. 1).[44] Respiratory decline is due to progressive lung function decline and predictors of poor respiratory outcome include male sex, disease duration, and neurological compromise.[44]
- Patients with **congenital myopathies** (CM), described more deeply in the previous section, can have a slowly progressive or quite stable clinical course. In particular, in core myopathy, less severe diseases with later onset and the milder clinical forms with relative stability until adulthood are reported.[26] In myosin storage myopathy, the clinical course is slowly progressive, with scoliosis largely contributing to respiratory insufficiency.

3. Diagnostic approach

Assessing airway impairment is mandatory when children, in the absence of overt respiratory symptoms, are diagnosed with NMDs. The main reasons are the prevention and early treatment of even minimal clinical problems, which, if neglected, could progress towards respiratory failure.[8] A detailed medical history and a thorough physical examination must precede patient referral to a multidisciplinary clinic for extensive workup. When planning investigations, a detailed knowledge of the pathophysiological mechanisms underlying respiratory impairment is imperative.[1] Lung function monitoring, blood gas exchange, muscle strength and sleep quality must be performed at a pediatric

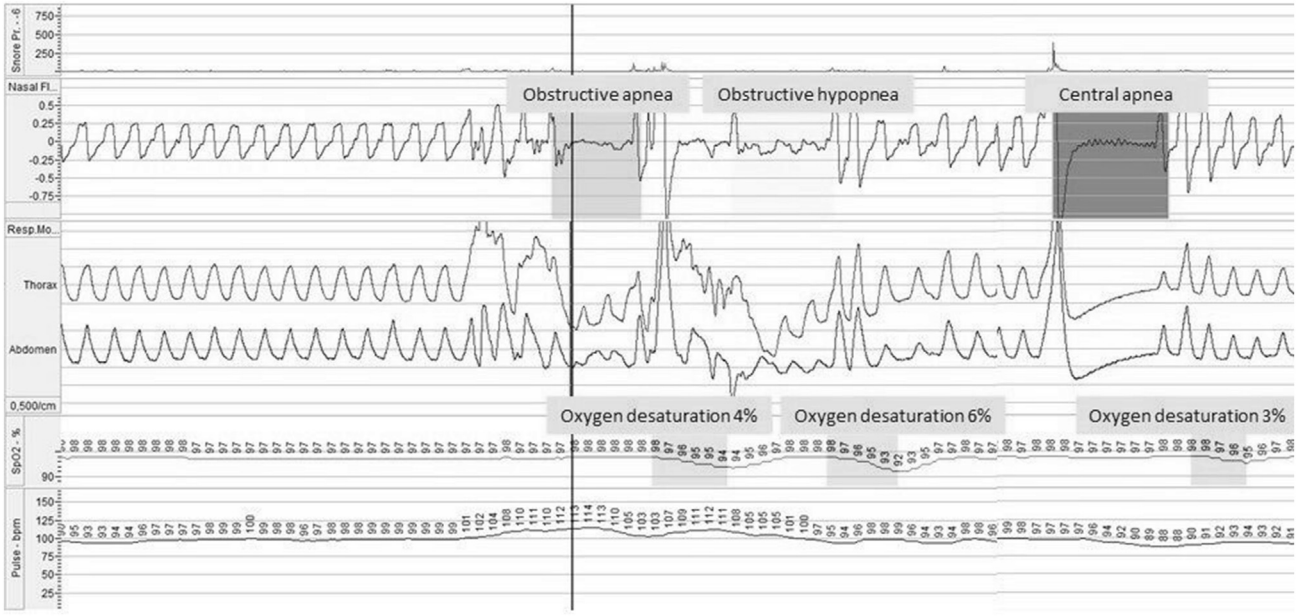

Figure 1 Respiratory polygraphy of a 9-year-old male with acid maltase deficiency (late onset Pompe disease). The cardiorespiratory monitoring used sensors to detect airflow (nasal air pressure transducer), respiratory effort (inductance plethysmography), blood oxygen (pulse oximetry) and pulse rate. This monitoring showed: central apnea characterized by fall in amplitude of the nasal pressure >90% and absent inspiratory effort; obstructive apnea and hypopnea characterized by fall in amplitude of the nasal pressure >90% and >30%, respectively, and increase of respiratory effort with paradox; and oxygen desaturation >3%.

pulmonology center considering patients' age, level of cooperation, and clinical symptoms. The agenda includes an initial assessment *plus* close follow-up visits scheduled according to muscle dysfunction evolution, with special attention to floppy infants who may require fast therapeutic decisions. Some investigations should be repeated at least annually in low-risk patients (having favorable genotype and/or lacking overt clinical symptoms), or more often in high-risk patients (suffering from recurrent respiratory symptoms). In addition to pediatric pulmonologists, the team should include other specialists, namely gastroenterologists for swallowing or aspiration studies, radiologists for chest and spinal imaging, otolaryngologists for the upper airways, orthopedists for spinal deformities, speech therapists for voice disorders, and nutritionists for growth and nutrition assessment (Table 2).

4. Respiratory therapeutic strategies

In the last two decades, practice guidelines focused on patients' respiratory care have been developed to facilitate the management of SMA, DMD and PD.[9,45–47] In absence of guidelines for each NMD, prevention or treatment of respiratory manifestations can be adapted to other patients, although with more unpredictable outcomes. Unfortunately, the frequency of respiratory assessment and the use of assistive devices among NMD patients are lower than recommended. Therefore, collaboration of all professional figures should be encouraged to ensure access to the full spectrum of respiratory interventions, supporting the family/patient decisions on issues such as long-term ventilation.

When NMD is diagnosed in children or adolescents, a major target is to impact the course of respiratory disease by organizing a comprehensive therapeutic program. Although respiratory complications remain the major cause of morbidity and mortality, an aggressive, supportive therapeutic approach has the potential to significantly impact the outcome. The cornerstones of respiratory treatment are mobilization of secretions, prevention and treatment of airway infections, and ventilation support (Table 3). Core interventionsclude.

a) Daily application of airway clearance techniques (ACTs) to improve the ability to clear secretions and preventing pneumonia and atelectasis, such as a series of manual maneuvers (e.g., glossopharyngeal breathing and air stacking, or forcing expiration by hand compression on abdomen and chest wall) or mechanical devices [e.g., insufflator-exsufflator, or positive expiratory pressure mask, cough assistance machine, high-frequency chest-wall compressor and intrapulmonary percussive ventilator). Rehabilitation programs may also include manual chest physiotherapy with clapping or mechanical percussion and vibration, postural drainage, and autogenic drainage. Airway clearance can be supported by oronasal suctioning of upper airways secretions, especially in non-cooperating patients. Home treatment by a medical professional is encouraged to meet caregivers' and patients' needs.[8]
b) Prevention and therapy of airway infections, through seasonal vaccines or palivizumab, and early institution of antibiotic treatment[35,48,49]: Generally, pathogens colonization of airways increases the risk of infectious exacerbations, which can further impair respiratory

Table 2 Pathway for respiratory assessment of children with hereditary neuromuscular diseases.

MEDICAL HISTORY
Major issues to be addressed
• Age at onset of symptoms and signs of muscle weakness
• Progression of muscle weakness, degree of ambulation and muscle fatigability
• Age at onset of symptoms and signs of any respiratory manifestation
• Coughing or choking with foods, difficulties with chewing or in clearing secretions
• Frequency and management of respiratory infections
• Strength of voice and cough
• Headache, nausea, dyspnea, tachycardia, sweating, peripheral vasoconstriction or vasodilation, fatigue, and anxiety (suggesting daytime hypoventilation)
• Disturbed sleep, morning headache, morning anorexia or nausea, daytime sleepiness, fatigue, and poor concentration (suggesting nocturnal hypoventilation)
• Snoring, breathing effort and arousal (suggesting obstructive sleep apnea syndrome)
CLINICAL EXAMINATION
• Vital signs, body weight, height, or ulna length/arms span
• Growth and nutritional status
• Posture, seating and evidence of rib cage or spine deformities
INVESTIGATIONS
• Pulmonary function tests
- Spirometry **in** cooperating patients; impulse oscillometry in noncooperating patients
- Tests of **respiratory** muscle strength:
1. Noninvasive tests: Maximum inspiratory pressure; Maximal expiratory pressure; Sniff nasal inspiratory pressure; Cough peak flow; Crying mouth pressure
2. Invasive tests: Breathing pattern with esophageal pressure and gastric pressure measurement; esophageal pressure and transdiaphragmatic pressure measurement during maximal sniff; gastric pressure measurement during a maximal cough; transdiaphragmatic pressure during crying
• Measurement of daytime arterial blood gases
• Overnight sleep monitoring: pulse oximetry; capnography; polygraphy/polysomnography
• Swallowing/aspiration studies (video fluoroscopy swallow study; fiberoptic endoscopic evaluation of swallowing; airways endoscopy with bronchoalveolar lavage)
• Lung and chest or spine imaging (X-ray; lung ultrasound; computed tomography; magnetic resonance)
• Bacteria or virus identification on upper respiratory tract sample (sputum or deep oropharyngeal aspirate or nasopharyngeal swab)

muscle function. Most available NMD guidelines recommend that the threshold to treat infections is kept low, with early and aggressive administration of antibiotics, possibly targeted on known or suspected pathogens at culture.[9,46,47]

Table 3 **Key preventive** and therapeutic interventions for respiratory manifestations of hereditary neuromuscular disorders.

- **Mobilization of secretions through daily airway clearance techniques and pulmonary rehabilitation programs**
Manual maneuvers: lung volume recruitment (glossopharyngeal breathing; air stacking; hand compression on abdomen/chest wall)
Mechanical devices (insufflator-exsufflator; positive expiratory pressure mask; cough assisted machine; high-frequency chest-wall compressor; intrapulmonary percussive ventilator)
Chest physiotherapy
Oronasal suctioning of upper airways secretions–
- **Prevention and therapy of airway infections**
Seasonal influenza and pneumococcal vaccines, and palivizumab for respiratory syncytial virus prophylaxis
Early administration of antibiotics (targeted on results of airways culture)
- **Assisted mechanical support**
Noninvasive nocturnal or daytime ventilation (continuous or bilevel positive airway pressure ventilators, volume ventilators)
Invasive ventilation (positive pressure via endotracheal tube or tracheostomy)

c) Supporting ventilation to reduce morbidity and mortality, and improve patients' quality of life[7,50]: Guidelines suggest a supportive respiratory care for all patients with respiratory fatigue and/or lung function abnormalities or evidence of hypoventilation with nocturnal decreasing PaO_2 and increasing $PaCO_2$.[50] Benefits include stabilization of vital capacity, improvement of gas exchange, correction of SDB, prevention or treatment of *cor pulmonale*, and promotion of growth.[7] Occasionally, symptoms occurring during infectious exacerbations or surgical procedure may require prompt ventilator support.[8] Although invasive mechanical ventilation is commonly employed, there has been a huge increase in noninvasive (NIV) support options, including high-flow nasal cannula oxygen therapy (HFNC), continuous positive airway pressure, and bi-level positive airway pressure. HFNC uses "high flow" rates (greater than minute ventilation and with heated and humidified air) to avoid complications and improve patient comfort.[51] It is recommended to first propose NIV support, well-tolerated by patients, using spontaneous or controlled ventilation mode devices equipped with nasal, oronasal, or oral interfaces. Ventilatory assistance may be initially restricted to nighttime, but, as respiratory function worsens, patients may extend the support to daytime.[1] Ventilation efficacy, including gas exchange monitoring, should be assessed both initially and at follow-up. Even infants can be effectively treated with NIV, either in the hospital or at home after discharge.[52] With a tailored and adequate respiratory management, a good quality of life and lifespan into adulthood is expected for some NMD.[9] However, in case of failure of oxygenation, positive pressure ventilation via

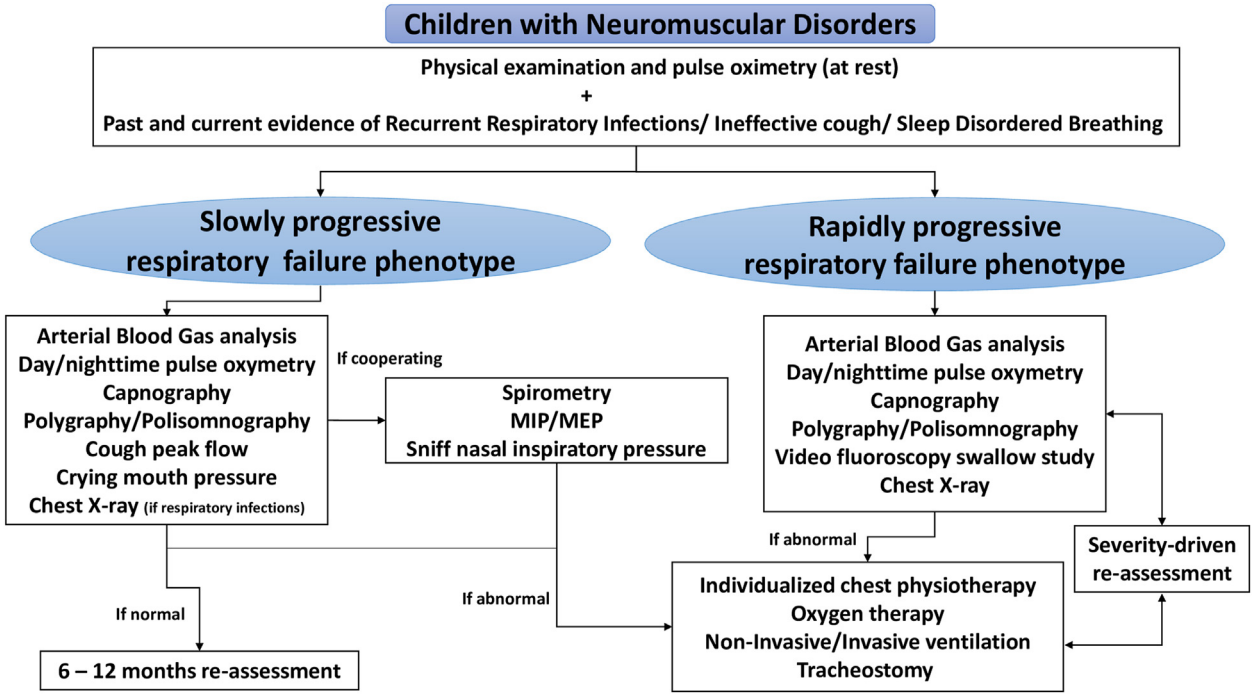

Figure 2 Algorithm for the evaluation and surveillance of respiratory manifestations in pediatric patients with neuromuscular disorders differentiated between those with slowly or rapidly progressive respiratory symptoms and signs. MIP, Maximum Inspiratory Pressure; MEP, Maximum Expiratory Pressure.

endotracheal tube or tracheostomy is mandatory, notwithstanding several risks of potential complications.[1]

Swallowing disorders require prompt nasogastric or gastrostomy tube feeding for preventing aspiration phenomena and treating the failure-to-thrive. Finally, steroids administered to DMD patients at early ambulatory stage has proven efficacy in preserving pulmonary function and in delaying the shift towards the non-ambulatory stage.[35]

Recent advances in molecular genetic mechanisms of NMDs have enabled impressive progress in the development of new therapies which, if administered early enough, might significantly change disease progression. Neuromuscular respiratory medicine now also includes the assessment of lung function or other respiratory outcomes to measure effectiveness of emerging therapies. Recent publications mostly concern subjects with SMA or DMD or PD.[18,53–64] Not all emerging drugs have obtained the approval from regulatory agencies, and some clinical trials are still ongoing. Unfortunately, few therapeutic interventions of NMD appear to modify the respiratory course significantly, with the phenotypic variability being a bias for treatment efficacy, thus hampering a straightforward evaluation of emerging therapies.

5. Conclusions

Most patients with NMD experience respiratory manifestations of variable intensity and rate of evolution throughout their life. Generally, the respiratory impairment of NMD is associated with significant lifelong morbidity and a high mortality rate.[65] The respiratory phenotype of NMD depends mainly on the muscular impairment evolution, on changes of the rib cage and spinal column, and on the inability to protect airways from swallowing disorders. Ultimately, SDB can dramatically accelerate the decline towards respiratory failure. At any age, the primary goals of the management of NMD respiratory manifestations are to prevent respiratory decline, to suppress airway infections minimizing exacerbations, to reduce morbidity and mortality and improving quality of life. Importantly, the prompt recognition of the respiratory phenotypes of NMD can help physicians establish the management of patients and improve the knowledge of the disease's natural history. Due to the severe complaints that some patients may experience, we propose a novel synthetic algorithm (Fig. 2), based on the evidence from literature review, which may be helpful in the management of slowly- or rapidly progressive respiratory failure phenotypes. Like all algorithms, it is not meant to replace clinical judgment, but it should drive clinicians dealing with NMD to adopt a systematic approach to respiratory disease in affected children and adolescents.

Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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