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Respiratory assessment in centronuclear myopathies

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Abstract

The centronuclear myopathies (CNMs) are a group of inherited neuromuscular disorders classified as congenital myopathies. While several causative genes have been identified, some patients do not harbor any of the currently known mutations. These diverse disorders have common histological features, which include a high proportion of centrally-nucleated muscle fibers, and clinical attributes of muscle weakness and respiratory insufficiency. Respiratory problems in CNMs may manifest initially during sleep, but daytime symptoms, ineffective airway clearance, and hypoventilation predominate as more severe respiratory muscle dysfunction evolves. Respiratory muscle capacity can be evaluated using a variety of clinical tests selected with consideration for the age and baseline motor function of the patient. Similar clinical tests of respiratory function can also be incorporated into preclinical CNM canine models to offer insight for clinical trials. Since respiratory problems account for significant morbidity in patients, routine assessments of respiratory muscle function are discussed.

Keywords

myopathy; respiratory assessment; canine; muscle disease; genetics

Introduction

Centronuclear myopathies (CNMs) are part of a wide spectrum of genetic neuromuscular disorders termed congenital myopathies (CMs). They have variable clinicopathological features[1] that most often present in childhood but occasionally in adulthood[2] and follow a progressive clinical course. Most patients succumb to respiratory failure. Infants may present as “floppy” and hypotonic. While no pathognomonic clinical features associate with any individual CM, some clinical findings associate frequently. These include proximal muscle weakness, atrophy, hypotonia, and elongated facies with a high arched palate in young children[2]. Because of the overlap between clinicopathological features associated with individual gene mutations in CMs, classification of these disorders (Table 1) has been

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based on the appearance of abnormal structures on muscle biopsies examined under the light microscope. Further classification of CMs was based on the appearance of centrally located nuclei (central nuclear myopathies), rod-like structures, and other distinguishing features of organelles. Thus "structured" CMs include central core disease (CCD), multi-minicore disease (MMD), centronuclear myopathies, nemaline myopathies, actin aggregate myopathy, desminopathy, and hyaline body myopathy. In contrast, "unstructured" CMs include congenital fiber type disproportion (CFTD), a non-progressive childhood neuromuscular disorder without prominent accumulation of abnormal structures visible under the light microscope. While these characteristic features provide some distinguishing characteristics that help differentiate congenital myopathies from metabolic myopathies and muscular dystrophies, such structural features are not informative about the underlying pathophysiology or genetic mutations associated with each disease.

Genetic abnormalities in the CNMs give rise to characteristic pathological changes within the sarcomere, the contractile apparatus of the myofiber. Examples of such changes include aberrant calcium handling and alterations of the normal excitation-contraction coupling machinery leading to inefficient muscle contraction. In contrast to muscular dystrophies where recurring cycles of myofiber degeneration and regeneration occur, in congenital myopathies the myofibers do not undergo recurring degeneration/regeneration. Replacement of contractile tissues with non-contractile connective tissue or fat in muscular dystrophies or accumulation of glycogen depots in metabolic myopathies is usually not a typical feature of congenital myopathies.

Clinical features of CNMs

The congenital myopathies classified as CNMs are distinguished histologically by a characteristic high prevalence of centrally-nucleated muscle fibers. Thus far, 6 genetic mutations have been linked to CNM. However, more gene defects exist, and up to 30% of patients with CNM have a variant not linked to any of the known mutations.[3] The clinical presentation of these disorders is diverse and typically non-progressive,[4] and it may range from severe disease in newborns to mild symptoms presenting in adolescence or adulthood. Despite the clinical heterogeneity of the CNMs, some degree of neuromuscular weakness and respiratory insufficiency is prevalent.

The most severe form of CNM is a non-progressive, X-linked myotubular myopathy (XLMTM) that usually presents in infancy as hypotonia, diffuse weakness, and early respiratory failure.[5] Most newborns with XLMTM require immediate external respiratory support. While a small portion of children recover some independent breathing as the respiratory control system matures, approximately 80–85% of surviving boys require part- or full-time mechanical ventilation.[6,7] Frequently, the presence of dysphagia and pharyngeal hypotonia requires a feeding tube, and children have a high rate of extraocular muscle weakness and ptosis. XLMTM is associated with a high rate of mortality in the first year of life.[6] A small proportion of boys with XLMTM have relatively preserved function and remain ambulatory into adulthood.[8]

CNM linked to mutations of dynamin-2 (*DNM2*) are autosomal-dominant inheritance and occur in approximately in 50% of the CNMs.[3] Affected individuals present as a diverse

clinical phenotype, which may range from a severe, infantile onset[9] to a more commonly observed mild disease presenting in adolescence or adulthood.[10] Symptoms include facial weakness, ptosis, opthalmoplegia, and peripheral muscle weakness. Distal muscle involvement is particularly prominent in mild disease[11] and can be distinguished with noninvasive muscle imaging.[12] Restrictive ventilatory defects and reduced cough effectiveness have been reported,[11] particularly in infantile-onset disease.[13] However, mechanical ventilator dependence is uncommon.[14]

Cases of autosomal-recessive inheritance have been reported due to mutations of the amphiphysin 2 (*BIN1*) gene.[15,16] The mutation is less common than *XLMTM* and *DNM2* and not well understood. Patients with *BIN1*-related CNM have a large variability in clinical presentation,[17] and the severity appears intermediate between XLMTM and DNM2.[15] Early childhood onset cases have been reported, marked by loss of developmental milestones, progressive generalized weakness, and higher preponderance of respiratory involvement. In these patients, respiratory insufficiency is more severe and may necessitate assisted ventilation support.[18]

More recently, an autosomal dominant mutation of the ryanodine receptor 1 (*RYR1*) was reported.[3] Affected individuals have early onset of proximal muscle weakness, bulbar involvement, ptosis, and respiratory insufficiency.[19] Early onset disease tends to correspond to more severe generalized weakness and higher ocular and bulbar muscle involvement.[20] *RYR1* mutations can result in other congenital myopathies; approximately one-quarter of patients with *RYR1* recessive mutations have CNM histological features.[21]

While the other genetic mutations known to result in CNM encode proteins related to excitation-contraction coupling and the sarcomplasmic reticulum triad, the most recently reported CNM-related mutation encodes the protein for titin (*TTN*), essential to regulation of elasticity and passive tension in the muscle sarcomere.[22] *TTN*-related CNM was reported in 5 of 29 patients without mutations in any of the genes previously associated with CNM.[23] The range of symptoms reported in *TTN*-related CNM appears heterogeneous in age of onset, pattern of weakness, and severity of respiratory muscle involvement. It may range from severe infantile-onset disease with respiratory failure to a pediatric presentation with mild involvement. Despite the more recent discoveries of causative genes of CNM, a large proportion of individuals with CNM do not have a genetic mutation linked to 1 of the known gene defects. [24] It is hoped that more integrative diagnostic approaches may identify other causative genes in the future.[25]

Respiratory Manifestations of CNM

Despite the clinical heterogeneity of age of onset, severity, and pattern of skeletal muscle weakness in CNM, many patients have some degree of respiratory muscle involvement. Dysfunction of the respiratory muscles may be compounded by mechanical constraints that increase the respiratory load, including low lung compliance, musculoskeletal restrictive defects in the chest wall, and kyphoscoliosis.[26] Additionally, weak pharyngeal musculature places patients at a higher risk of dysphagia and aspiration. Respiratory problems are a common cause of morbidity.[4] Functional manifestations of respiratory muscle insufficiency may include sleep disturbances, fatigue, ineffective cough, and hypoventilation.

Mild respiratory weakness may initially manifest only during sleep, when a low central respiratory drive combines with higher mechanical load. Sleep-related muscle dysfunction in neuromuscular disease may cause airway obstruction, hypoventilation, or both. Overnight polysomnography (PSG) is the recommended test for diagnosing the presence and source of sleep dysfunction.[27,28] Many children with CNM also have weakness and hypotonia of the pharyngeal muscles. This can lead to partial or complete obstruction of the upper airway, particularly during rapid eye movement (REM) sleep when extra-diaphragmatic muscular activity is inhibited. Diaphragm inspiratory efforts accompanied by ineffective or absent contractions of the tongue and pharyngeal dilator muscles will result in narrowing or obstruction of the upper airway. Obstructive events can be detected by PSG, when the absence of nasal airflow occurs despite evidence of respiratory efforts using inductive plethysmography bands. Short obstructive events elicit periods of desaturation and rises in end-tidal CO2. Continued obstruction may result in arousal and awakening. Overnight oximetry is subject to movement artifact and has a low sensitivity for sleep disordered breathing, [27] since periodic desaturation may occur with either obstructive apnea or hypoventilation.

Hypoventilation can also accompany REM sleep in the presence of inspiratory muscle weakness. With more extensive respiratory muscle involvement, patients may not snore or exhibit outward symptoms of labored breathing. Inspiratory pressures generated by the weakened respiratory pump may only partially obstruct the airway, resulting in hypoventilation. PSG tests detect hypoventilation as periods of reduced airflow with continued efforts detected by respiratory bands. Persistent hypoventilation can also be detected by sustained periods of elevated end-tidal CO_2. However, an absence of hypoxemia has been reported during some nighttime hypercapnic episodes in children with sleep disordered breathing who use external support.[29] Over the long term, chronic hypoventilation during sleep can result in blunted hypercapnic and hypoxic ventilatory responses and reduced respiratory drive.[30] Daytime symptoms of sleep-disordered breathing may include orthopnea, morning headaches, poor appetite, and fatigue, but clinical signs may be difficult to recognize in the presence of other symptoms and manifestations of CNM. Thus, daytime blood gases and symptoms have largely been ineffective predictors of sleep problems.[31,32] Consensus statements for other neuromuscular diseases in children recommend PSG to evaluate sleep disordered breathing whenever possible and to use the most detailed alternative when PSG is not feasible.[33]

In addition to sleep problems, individuals with clinically significant pharyngeal or respiratory muscle weakness frequently have reduced cough efficacy. Ineffective airway defensive reflexes increase the risk for aspiration, which can result in recurrent aspiration pneumonias and progressive fibrosis.[34] In the presence of CNM and other neuromuscular diseases, children may exhibit poor coordination of the timing of cough, reduced cough inspiratory volume, incomplete glottis closure, or decreased peak cough airflow. Patients with neuromuscular disease and peak cough flow <270 L/min are prone to increased respiratory morbidity, which can be reduced by mechanical and/or manual augmentation of cough.[35] A cough peak flow of 160L/min is the minimum recommended for clearance of secretions and successful extubation.[36] A weak cough can become catastrophic in the presence of a common cold, when inability to clear mucus may predispose children to

further infection or need for assisted ventilation. There is clear evidence that cough assistance can enhance cough function[37] to reduce acute respiratory morbidity in patients with chronic neuromuscular disease and respiratory insufficiency.[38,39]

Severe respiratory muscle weakness manifests as resting dyspnea and daytime hypoventilation. The clinical signs of daytime hypoventilation may include progressive fatigue and lethargy, difficulty feeding, and poor growth. The presence of daytime hypercapnia indicates a need for positive-pressure ventilatory support. In the US, non-invasive ventilation (NIV) is indicated for adults with restrictive respiratory disease in the presence of a vital capacity <50% of predicted, maximal inspiratory pressure <60 cm H_2O, or daytime arterial CO_2 >45 mmHg.[40] Threshold hypoxemia and hypercapnia values are not as clearly defined in children, but evidence of daytime disturbance indicates a need for external assistance. It has been suggested that whenever possible, time should be dedicated prior to institution of non-invasive ventilation, particularly in children, to acclimate the patient to an interface (e.g. facemask, helmet) identify the most comfortable settings, and positively reinforce compliance.[41,42]

Proactive use of NIV can stabilize acute respiratory decompensation and avoid tracheal intubation,[43,44] but invasive mechanical ventilation is necessary in the presence of severe bulbar dysfunction or when hypercapnia and/or hypoxemia persist despite high levels of non-invasive support. In the majority of children with XLMTM mutations, this may present early in the first year of life, while significant hypoventilation in other CNMs may not develop until later. In either case, home mechanical ventilation has been described as the most complicated medical intervention provided outside of an in institutional setting.[45] Families and their providers will need to weigh the life-saving function of chronic mechanical ventilation with its associated risks of complications and burden of care. [46] The prevalence of chronic home mechanical ventilation varies regionally, and essential requirements include appropriate funding, equipment, care providers, care coordination, and respite for families.[47] Providers may perceive the value and level of comfort with newer mechanical ventilation technologies differently from families.[48] The limited evidence of quality of life in ventilator-dependent neuromuscular disease indicates that some adolescents and young adults report greater life satisfaction than their medical providers may otherwise assume.[49] A study of younger children with chronic ventilator dependence found that several factors influenced the patient's quality of life, including social isolation, importance of a routine, availability of quality services, and effective communication.[50] We are not aware of any systematic study of quality of life focused exclusively on ventilator-dependent children with CNM.

Respiratory Muscle Assessments in Patients with CNM

The high prevalence of respiratory muscle involvement and risk for morbidity necessitates regular respiratory muscle evaluations for individuals with CNM. Respiratory motor involvement may include the inspiratory, expiratory, and bulbar muscles, and function can be evaluated through volitional or non-voluntary assessments using methods that can either be invasive or non-invasive. The number and type of tests will depend upon the age and cognitive function of the patient as well as the presence of respiratory-related symptoms and

dependence upon mechanical ventilation. Non-invasive, voluntary measurements, including spirometry and maximal respiratory pressures, are reported frequently in neuromuscular disorders, because they require little physical space, use relatively inexpensive equipment, are quick to administer, and tend to correlate with both more invasive respiratory muscle tests and with respiratory morbidities. For example, in Duchenne muscular dystrophy (DMD) and spinal muscular atrophy, forced vital capacity (FVC) and maximum respiratory pressures have been used extensively to track the rate of disease progression and determine product efficacy in clinical trials.[51–53]

Vital capacity is the maximum volume of air exhaled after an inhalation to total lung capacity and is a useful technique to monitor respiratory muscle function longitudinally. Changes in vital capacity may reflect respiratory muscle weakness and reduced pulmonary and chest wall compliance. FVC was found to correlate with presence of nocturnal hypoventilation in children with progressive neuromuscular diseases, but the threshold value for clinical significance varied with age and diagnosis.[54,55] Others have found that pulmonary function does not predict sleep problems.[32,56] Reductions of both FVC and forced expiratory volume in one second (FEV1) reflect a restrictive disease pattern. Further reductions of these measures in the supine position can indicate diaphragmatic weakness in neuromuscular disease.[57] However, respiratory muscle strength may decrease by >30% before appreciable changes in vital capacity are detected.[58] Children younger than 5 years may have difficulty achieving reproducible maximal efforts, although many preschool-aged children can perform a technically-acceptable test with repetition and an experienced tester.[59] Modifications to VC test procedures may be required due to bulbar weakness; the use of a facemask for vital capacity tests has been useful in congenital muscular dystrophies.[60]

Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) tests are non-invasive clinical estimates of the strength of the muscles of respiration. Much like a manual muscle test of the limb muscles, respiratory pressure tests calculate the best-effort tension the inspiratory or expiratory muscles can generate statically. They can be used to diagnose and track the course of respiratory muscle weakness. In the clinic, pressure is most often measured non-invasively at the airway opening (mouth, endotracheal tube). A flange mouthpiece is recommended, particularly for patients with facial weakness. Alternatively, invasive pressure catheters can be placed into the esophagus and stomach to yield the pressure produced by the diaphragm (maximal transdiaphragmatic pressure, Pdimax).[61] Since the tension exerted by the respiratory muscles differs according to muscle length, maximum respiratory pressures are volume-dependent.[62] Adult and pediatric reference values are available for ranges of ages and ethnicities.[63,64] Non-invasive tests, like MIP and MEP, are generally lower in children with neuromuscular disorders who require NIV when they are compared with children who have no ventilatory requirements.[65] These tests require cooperation from the patient and maximal effort, which may be difficult for young children.

Since only ~60% of young children with neuromuscular disorders may be able to complete effort-based maneuvers such as FVC and MIP,[66] additional tests may offer a more comprehensive picture of respiratory muscle involvement, particular in younger children. Nicot[66] conducted invasive measures of diaphragm muscle function during volitional and

non-volitional tests of pulmonary function in pediatric inherited neuromuscular disorders, Children as young as age 2 years were included, as well as 13 subjects with mild CM. Children with CM were an average 7.6 years of age, and none required positive pressure ventilation. In addition to MIP and FVC, children completed maximum voluntary sniff and cough maneuvers. Using invasive pressure manometry, the authors identified moderate respiratory insufficiency related to diaphragm weakness in the sample. While invasive pressure manometry is not clinically practical in most instances, importantly, all of the younger subjects could complete the sniff and cough maneuvers reliably,[66] suggesting the maneuvers could offer insight into respiratory muscle function in younger children with CM.

Sniff nasal inspiratory pressure (SNIP) is a voluntary, noninvasive test of the peak negative pressure generated during a maximal sniff maneuver, as measured from a manometer occluding the opposite nostril. In a longitudinal study, SNIP began to decrease in boys with Duchenne muscular dystrophy an average of 2 years before FVC, suggesting it was an earlier indicator of respiratory muscle decline.[67] Anderson[56] also found that young children could complete SNIP assessments succesfully; the sample included a small number of children with CM. The test is typically well tolerated, and pediatric SNIP reference values are available.[68] SNIP was found to correlate significantly with MIP and FVC in pediatric neuromuscular disease, but it does not predict desaturation or hypoventilation during sleep consistently.[56,32] While SNIP is a more natural maneuver than MIP, it may underestimate inspiratory muscle strength in patients with severe ventilatory insufficiency.[69]

Much like a sniff, cough is a natural respiratory maneuver that may be easier for small children to complete. A cough consists of an inspiration of a larger than normal volume of air, followed by glottis closure. With the glottis closed, the abdominal muscles then contract to generate high abdominal and thoracic pressures. Following the period of compression, the glottis opens, and the abdominal muscles remain in a contracted state, forcing expulsion of air at a high velocity. Cough efficacy can be reported noninvasively using peak cough flow, or invasively by cough gastric pressure obtained through invasive manometry. Cough gastric pressure is reduced markedly in children who require some breathing assistance,[65] but the invasive pressure catheters may be difficult to place and are tolerated poorly in small children. Cough peak flow is more feasible for clinically tracking indications for augmentation of airway clearance. Results will be influenced by the strength of the inspiratory and expiratory muscles, inspiratory capacity, and stiffness of the chest wall. Cough peak flow increases with age and height, and reference values are available for children and adolescents.[70] Older children with peak cough flows <160L/min are at increased risk for respiratory infections,[71] but clinically meaningful threshold values have not been validated for children younger than age 10 years. More work is needed to understand the value of a low cough peak flow in a small child.

Non-volitional or invasive tests, including inspiratory occlusion pressure (P0.1) ventilatory response to CO_2, transdiaphragmatic pressure during breathing and maximal respiratory pressure maneuvers, magnetic stimulation of the phrenic nerves, and gastric cough pressure, offer additional value for evaluation of respiratory muscle fatigue and weakness,[65] but the required equipment and procedures are more difficult to complete in a clinical setting.[65] In

addition, these tests may be distressing for young children. For these reasons, we recommend that these invasive, non-volitional maneuvers be reserved for research purposes.

Special Considerations for Ventilator Dependent Patients

Children with mild CNM have been included in a few published reports of quantitative respiratory function,[56,66] but less is understood about the respiratory muscle function of ventilator-dependent individuals with CNM. This is a particularly important consideration for XLMTM, because most affected individuals require external ventilatory assistance. With severe paresis, traditional measures of FVC, MIP and MEP may be technically difficult or impossible to obtain in a reproducible fashion. Our group employs an alternate method for MIP and MEP that has been validated in the pediatric intensive care unit setting[72] and can provide valuable insight into the capacity of the respiratory muscles and the control of breathing in ventilator-dependent CNM.

A modified MIP technique has been developed and validated for mechanically-ventilated adults in the ICU.[73] The test is applicable to patients with stable cardiovascular function and an intact respiratory drive. In the modified MIP maneuver, patients are disconnected from the ventilator circuit, and then a pressure sensor and one-way valve are attached to the end of the patient's airway tube. The one-way valve permits exhalation, but occludes during inspiration. This has two effects: operational lung volumes will lower, resulting in a more favorable length-tension orientation for the diaphragm.[74] In addition, mechanoreceptor feedback results in a rapid escalation of inspiratory drive.[75] As a result, patients generate progressively more negative inspiratory pressure, with a plateau pressure typically achieved within 20–25 seconds. In children, the negative inspiratory pressures typically plateau in 15–20 seconds.[72] We found that ventilator-dependent infants and children with NMD, including CNM, Pompe disease, and nemaline myopathy can complete MIP in a reliable fashion and with stable cardiovascular function.[76,77] Figure 1 illustrates the inspiratory pressure generated by a boy with XLMTM during a 20-second inspiratory occlusion.

Voluntary and reflexive cough function has been another valuable tool in the ICU to identify small yet important changes in respiratory muscle function. The coordination of cough differs with invasive ventilation. With a patent artificial airway, patients cannot close the glottis. Without a compressive phase of cough, patients cannot accumulate positive pressure, which results in a lower cough peak gastric pressure/expiratory flow and reduces cough effectiveness.[78] To calculate cough in the ICU, patients must be disconnected briefly from the ventilator. The patient can be instructed to cough voluntarily, or a mechanical stimulation can be applied to the trachea. Quantitative cough peak expiratory flow can be measured directly by a pneumotachometer or clinical flowmeter connected to the airway tube. In ICU patients with acute ventilatory failure, poor cough peak expiratory flow measurements correlate with MIP and can predict the outcome of extubation.[79,78] Cough peak flow has also been a significant predictor of weaning success in neuromuscular disease[36] and should be considered in the perioperative management of children with neuromuscular diseases.[80,33,60] However, the validity of MIP and cough function measures have not been evaluated formally in children with CMN, and threshold cough peak flow

values associated with ventilator weaning have not been reported in children <age12 years.[33]

Breathing pattern assessments can provide information about the effectiveness of the ventilator settings and the control of breathing under different conditions. Tidal breathing patterns can be conducted during wakefulness or sleep. A sleep study on ventilated patients with CM not only removes conscious influences on the breathing pattern, it can evaluate adequacy of the prescribed ventilator settings.[28] Besides mechanically ventilated individuals, infants and toddlers tolerate tidal breathing measurements well. An additional advantage of breathing pattern evaluation is that many of the respiratory tests can be simulated in the canine. We compare the resting breathing pattern on the patient's typical level of ventilatory support to a period of reduced support or unassisted breathing, depending upon the patient's respiratory reserve. Our group uses a pneumotachometer and differential pressure transducer to calculate the timing of the inspiratory and expiratory phases of respiration, as well as flow, volume, and pressure during each phase. Observations of a patient's breathing pattern may assist with clinical decision making regarding the most suitable mode and level of ventilatory support. In addition, evaluations of tidal breathing patterns can be advantageous for evaluation of ventilatory reserve in preclinical models of CNM in anticipation of future therapeutic trials.

There are several important reasons to evaluate respiratory muscle function and the level of external assistance systematically. For example, children may transiently require periods of acutely increased ventilator support during times of respiratory infections or distress. In the absence of pulmonary injury, external support should ideally be titrated toward the prior ventilator settings as children stabilize to reduce the potential for complications of long-term high levels of positive pressure.[81] Evaluations may also identify when children require additional support due to progression of musculoskeletal deformities and growth. Ventilator-dependent children will require careful evaluation of their level of ventilatory support and airway clearance regimen in preparation for surgical procedures. Finally, evaluations will become more necessary in the future to determine the efficacy of emerging regenerative therapies to treat genetic diseases.

Ventilatory muscle assessments: Lessons from animal models

It is the long-term goal of our group and others to provide safe and effective clinical interventions to improve ventilatory function in patients with CNMs. To address this issue, breathing control and performance are active areas of research in both animal models of CNM and in human subjects. While rodents are the most commonly used animal models of CNMs, the small size of mice prohibits the use of the measures of pulmonary function or respiratory muscle kinematics (movement) used in patients. Moreover, while diaphragm and other ventilatory function measures have been studied in murine models of Pompe disease, Duchenne muscular dystrophy, and other neuromuscular models[82–84], to our knowledge, similar studies have not been reported in animal models of CNMs. Recently, a larger, intermediate-sized animal model of CNM was established in dogs that allow for clinically relevant respiratory assessment. X-Linked myotubular myopathy, was identified in Labrador retrievers as a missense mutation in the *MTM1* gene on the short arm of the X

chromosome [85]. Male XLMTM-affected dogs display temporal muscle mass loss, "dropped jaw" appearance [85], hind-limb muscle atrophy, contracture of hind distal and middle phalanges, a shortened, choppy and stilted gait, and difficulty walking as the disease progresses. Hind limb strength in affected dogs decreases to about 10% of normal by age 4 months[86]. Puppies appear clinically normal at birth but develop subtle signs of disease starting at age 8–10 weeks. Female carrier dogs do not display any of the clinical signs observed in affected males.

All animals are cared for according to institutional animal care and use committee (ACUC) guidelines. Despite intensive veterinary care, hand feeding and other support, affected dogs develop progressive respiratory weakness that can lead to aspiration pneumonitis, analogous to human patients. Affected dogs are generally euthanized before age 6 months due to the lack of intensive supportive care available for affected humans. The dogs do not receive intubation for respiratory support or gastrotomy tube feedings for nutritional support. This differs from human XLMTM in which the myopathy is relatively non-progressive despite being severe at birth [85]. In this canine model of XLMTM, respiratory dysfunction appears clearly illustrated by airflow exchange rates and respiratory muscle kinematic measures analogous to measures observed in human patients.[87] Parameters such as peak inspiratory flow are currently under study in response to experimental gene replacement in the canine XLMTM model as a preclinical measure of respiratory function.

In both human and canine XLMTM, insufficient motor capacity leads to decreases in tidal volume and inspiratory time with a concomitant increase in elastic load and decreased length-tension advantage at higher lung volumes. The functional result, a rapid, shallow breathing pattern, is an ineffective strategy to sustain minute ventilation over the long term and is associated with ventilator dependence.[88] Figure 2 illustrates respiratory compensatory responses in canines exposed to the respiratory stimulant doxapram. Both the resting and doxapram-stimulated breathing pattern in canine XLMTM, was evaluated recently in a preclinical study of gene replacement therapy.[89] Peak flow rates increase in response to doxapram in a dose-dependent manner (Figure 2a), where peak inspiratory flow rates are 112.0 ±9.1, 199.3 ± 8.0, 279.5 ± 31.4 and 389.3 ± 33.2 mL/s and peak expiratory flow rates are 394.9 ±4.4, 371.8 ± 5.9, 374.6 ± 20.3 and 380.2 ± 22.0 mL/s after 0, 0.5, 1.0 and 2.0 mg/kg doxapram respectively. Inspiratory time (Figure 2b) remains relatively constant despite doxapram administration: 1326.2 ± 50.1, 1235.0 ± 63.0, 1124.3 ± 73.5 and 11.64.3 ± 65.0 sec after each stepwise doxapram dose. However, expiratory time is reduced in a dose-dependent manner: 2207.6 ± 127.6 sec prior to doxapram and 1528.5 ± 119.3, 1513.5 ± 67.1 and 1273.8 ± 15.0 sec following 0.5, 1.0 and 2.0mg/kg doxapram. Respiratory rate shows little change: 27.6 ± 1.7, 26. ±1.7, 22.8± 0.4 and 24.9 ± 0.8 bpm at 0, 0.5, 1.0 and 2.0mg/kg doxapram but tidal volume increases, and each respective dose produced 9.9 ± 1.1, 15.7 ± 0.8, 18.0 ± 1.8 and 23.6 ± 1.5 mL/kg. Taken together, these data indicate a pattern of respiratory responses in myotubularin-deficient canine muscles that might be useful to model effects of gene replacement therapy on the respiratory response pattern in patients.

The pattern of respiratory muscle involvement in XLMTM patients or canines can be measured non-invasively. Displacement of the chest and abdominal cavities can be detected with strain gauges or inductive plethysmography bands placed around the chest and

abdomen.[87] When respiratory-inductive plethysmography bands are used alone, qualitative data can be appreciated regarding synchrony of thoracic and abdominal expansion and the presence of paradoxical movements of the chest or abdomen during inspiration (Figure 3), termed thoraco-abdominal asynchrony (paradoxical breathing). When combined with a pneumotachometer, the relative thoracic and abdominal contributions to volume can be calculated. With this information, investigators can make inferences about the preservation of function in the diaphragm or intercostal muscles.[90] This information could be particularly valuable when planning and evaluating the efficacy of tissue-specific therapies such as local intramuscular gene therapy approaches.[91]

Ventilatory muscle research assessments: translation to children with CNM

Since the control and output of the ventilatory muscles is less understood in the CNMs, the evaluation of ventilatory function in this group of children is largely based upon a growing understanding from preclinical animal models. Respiratory-inductive plethysmography bands are well tolerated in children who may have difficulty cooperating with spirometry or with using a facemask and/or mouthpiece. [92] Figure 4 shows the chest and abdominal displacement obtained from a child with XLMTM and 11-year history of ventilator dependence. When baseline MV support was compared to the lowest tolerated level of mechanical ventilation, the respiratory bands were displaced more frequently, which corresponded to more frequent spontaneous breathing during reduced ventilator support. Additionally, the emergence of thoraco-abdominal asynchrony and a thoracic inspiratory paradox could be observed during the patient's spontaneous breaths, as the work of breathing increased (Figure 4, B, arrows). Paradoxical movements of the chest wall can be related to greater relative weakness of the intercostals than the diaphragm, to significant abdominal wall compliance secondary to expiratory muscle weakness, to poor compliance of the rib cage, or to a combination of any of these factors. Evaluations with respiratory inductive plethysmography bands require specialized equipment and thus may not offer added clinical value beyond traditional assessments of respiratory muscle function. However, these studies and others in the canine XLMTM model may direct researchers to potential muscular candidates for local or regionally delivered regenerative therapies. Further study is needed.

Summary of Respiratory Assessments in CNM

Consensus guidelines have been defined for other pediatric neuromuscular conditions, including DMD,[93] congenital muscular dystrophies,[60] and spinal muscular atrophy.[94] The guidelines recommend routine assessments of respiratory function at diagnosis and follow-up approximately every 6 months to include pulse oximetry, spirometry, maximum respiratory pressures, and peak cough flow.[93,94,39] In addition, annual chest X-ray, capnography, and laboratory studies (e.g. CBC, serum bicarbonate) are recommended. Evidence of dysphagia, aspiration, or sleep-disordered breathing should be referred to specialists for further management, and children who require assistance should be evaluated more frequently. A European Neuromuscular Consortium (ENMC) workshop on respiratory care in congenital myopathies, congenital muscular dystrophies, congenital myotonic dystrophy, and SMA type II[95] similarly recommended routine, coordinated evaluations at

least annually. It should be noted that, while existing consensus statements advocate overnight pulse oximetry to evaluate sleep-disordered breathing, PSG is indicated to distinguish obstructive apnea from hypoventilation.[28,27] Assessments addressed lung function, nighttime ventilation, cough efficacy, and respiratory-related symptoms. Table 2 summarizes the recommended respiratory assessments derived from these consensus statements.

Despite the relatively high prevalence of respiratory-related symptoms in CNM, respiratory function has been descriptively defined historically as mild, moderate, or severe.[7,6] As a key component of clinical trial readiness, quantitative studies are required to better characterize the clinical heterogeneity, use of adaptive aids, occurrence of adverse events, and rate of progression in the CNMs. While the CNMs are thought to be non-progressive, restrictive spinal and thoracic skeletal deformities can be progressive, and the pattern of respiratory muscle involvement is not well defined. An understanding of these factors is needed to further elucidate respiratory control and function in CNM and to establish a baseline for future therapeutic trials.

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Abbreviations

CNM	Centronuclear myopathy
CM	Congenital myopathy
DMD	Duchenne muscular dystrophy
ETCO2	End-tidal carbon dioxide
FEV1	Forced expired volume in one second
FVC	Forced vital capacity
MEP	Maximum expiratory pressure
MIP	Maximum inspiratory pressure
PSG	Polysomnography
SNIP	Sniff nasal inspiratory pressure
XLMTM	X-linked myotubular myopathy

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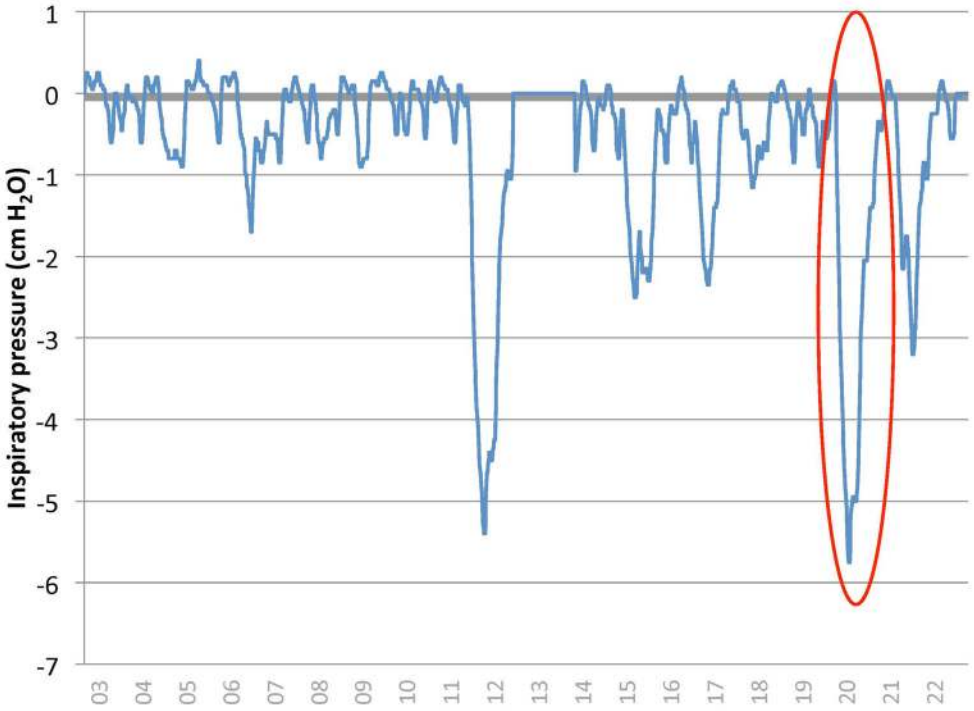

Figure 1.

Maximum inspiratory pressure in a tracheostomized, mechanically ventilated child with XLMTM. The patient was briefly removed from the ventilator, and a one-way valve was placed over the tracheostomy opening. Negative pressure deflections indicate inspiratory efforts, while exhalation was unobstructed. The most negative pressure in 20 seconds (circled) was the maximum inspiratory pressure.

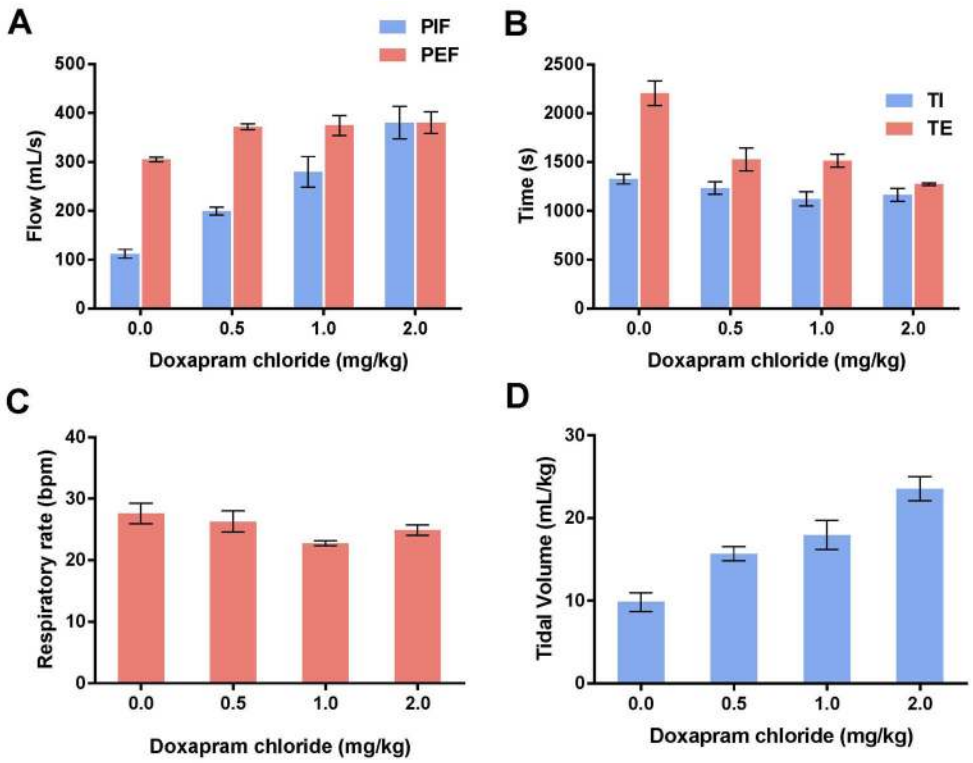

Figure 2.

Breathing pattern compensation in dogs with XLMTM. **A.** Peak inspiratory (PIF) and expiratory (PEF) flow increase in response to a respiratory stimulant, doxapram chloride. **B.** Inspiratory time (TI) and expiratory time (TE) in response to doxapram. XLMTM dogs maintain their respiratory rate (C), while they increase tidal volume (D) in response to respiratory stimulation with doxapram.

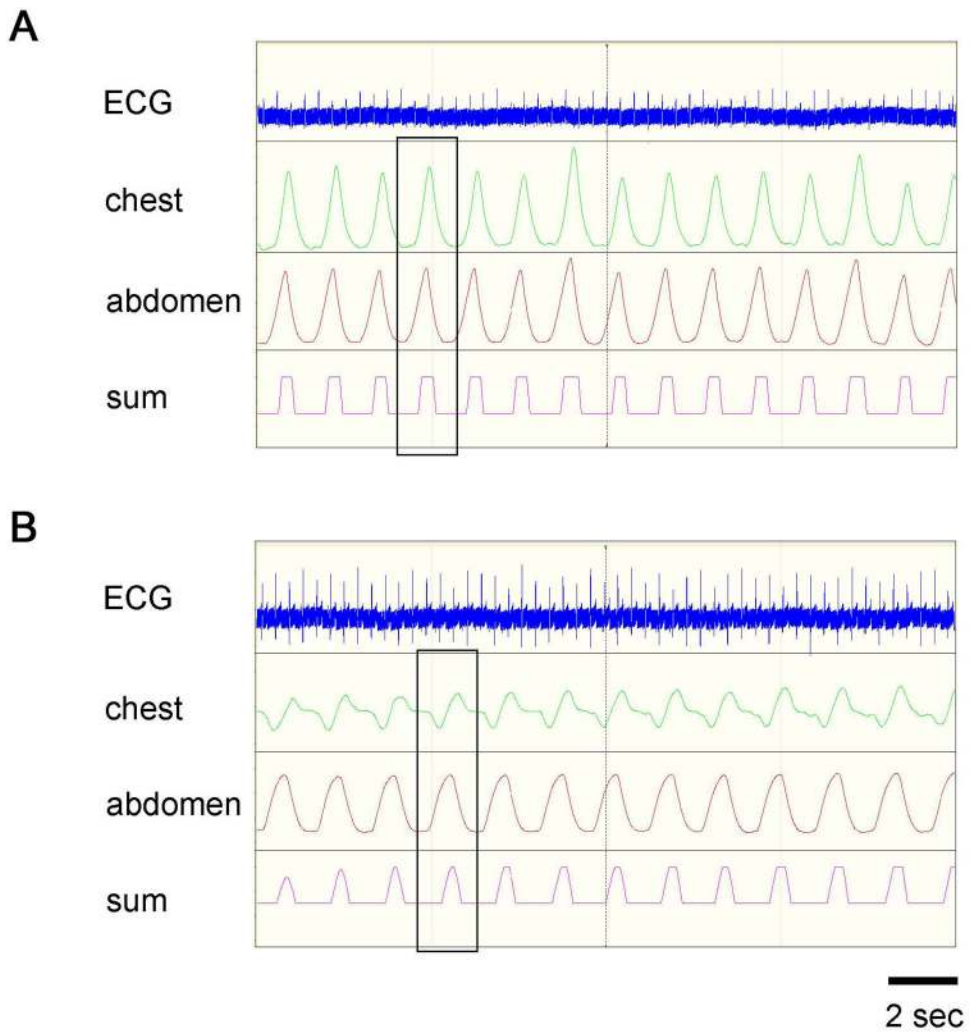

Figure 3.

Thoracoabdominal motion in an anesthetized **A**. normal and **B** XLMTM dog 45s after stimulation with doxapram chloride (1.0mg/kg). While thoracic and abdominal motion are synchronous in the normal dog (boxed area in A), paradoxical thoracic motion (boxed area in B) was detected during stimulation in the XLMTM dog. Note also the difference in the thoracic (green) waveform in panel B vs. panel A.

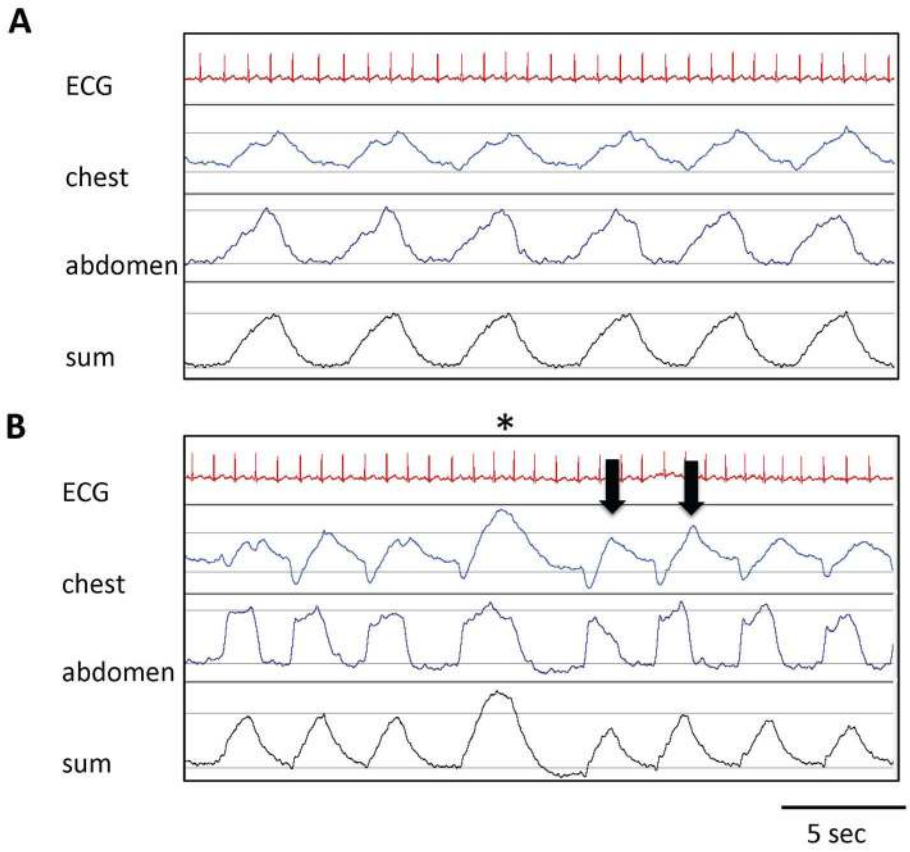

Figure 4.

Qualitative thoracoabdominal motion in a mechanically-ventilated boy with XLMTM, showing relative displacements of the thoracic and abdominal bands coinciding with breathing. **A.** On resting support, thoracic and abdominal displacement was coordinated, with a slow, regular respiratory pattern. **B.** At the lowest level of support, paradoxical thoracic motion (arrows) was detected during inspiratory efforts (* = sigh breath delivered by the ventilator).

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Table 1

Congenital myopathies: predominant features, genetics and mammalian models.

Structural Features	Type	Inheritance	Gene	Locus	Protein	Mammalian models
Congenital Myopathies with central nuclei	Myotubular myopathy	X-linked	*MTM1*	Xq28	Myotubularin	*Mtm1* KO mouse[96] R69C mouse[97] XLMTM dog[98]
	Centronuclear myopathy	AD	*DNM2*	19p13	Dynamin 2	R465W mouse[99]
		AR	*PTPLA*	Canine only	Protein tyrosine phosphatase-like member A	PTPLA dog[100]
		AR	*BIN1*	2q14	Amphiphysin	shRNA-Bin1 knockdown in mice[101] IMGD dog[102]
		AD	*RYR1*	19q13	Ryanodine receptor	*Ryr1I4895T/wt* (IT/+) mouse[103]
		AR	*TTN*	2q31	Titin	Ttn(mdm)mouse[104]
Congenital Myopathies with cores	Central core disease	AD, AR	*RYR1*	19q13	Ryanodine receptor	
	Multiminicore disease	AR	*SEPN1*	1p36	Selenoprotein N1	Sepn1-KO mouse[105]
	Congenital myopathy	AR	*TTN*	2q31	Titin	
Congenital Myopathies with fiber size variation		AD, AR	*TPM3*	1q21.2	Tropomyosin-3 Nebulin	
		AR	*NEB*			
		AD	*ACTA1*	2q22	Actin α1	
		AD	*TPM2*			
		AR	*TNNT1*			
		AD	*?*			
		AR	*CFL2*			
Congenital Myopathies with protein accumulation	NM1	AD, AR	*TPM3*	1q21.2	Tropomyosin-3 Nebulin	αTm_{slow}(M9R) mouse[106]
	NM2	AR	*NEB*	2q22	Actin α1, skeletal muscle Tropomyosin Troponin T type 1, skeletal muscle	Neb(DeltaExon55) mouse[107 107]
	NM3	AD, AR	*ACTA1*	1q42.1		
	NM4	AD	*TPM2*	9p13		
	NM5	AR	*TNNT1*	19q13		
	NM6	AD	*?*	15q21-q24	Coflin 2, muscle	
	NM7	AR	*CFL2*	14q12		

Table 2

Respiratory Assessments, based upon consensus guidelines for DMD and SMA and an ENMC workshop on respiratory function in congenital myopathies.

Routine Respiratory Neuromuscular Assessments
Respiratory Strength
Spirometry
Maximal Respiratory Pressures or SNIP
Sleep Dysfunction
Overnight pulse oximetry
Airway Clearance
Peak Cough Flow *
Ancillary Studies
Chest X-ray
Laboratories (CBC, serum bicarbonate)
Capnography
Symptoms
Miscellaneous As Needed
Polysomnography
Clinical swallow studies
Lung Volumes
Blood gases