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REVIEW

Diagnosis of muscle diseases presenting with early respiratory failure

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Abstract Here we describe a clinical approach and differential diagnosis for chronic muscle diseases which include early respiratory failure as a prominent feature in their presentation (i.e. respiratory failure whilst still ambulant). These patients typically present to neurology or respiratory medicine out-patient clinics and a distinct differential diagnosis of neuromuscular aetiologies should be considered. Amyotrophic lateral sclerosis and myasthenia gravis are the important non-muscle diseases to consider, but once these have been excluded there remains a challenging differential diagnosis of muscle conditions, which will be the focus of this review. The key points in the diagnosis of these disorders are being aware of relevant symptoms, which are initially caused by nocturnal hypoventilation or diaphragmatic weakness; and identifying other features which direct further investigation. Important muscle diseases to identify, because their diagnosis has disease-specific management implications, include adult-onset Pompe disease, inflammatory myopathy, and sporadic adult-onset nemaline myopathy. Cases which are due to metabolic myopathy or muscular dystrophy are important to diagnose because of their implications for genetic counselling. Myopathy from sarcoidosis and colchicine each has a single reported case with this presentation, but should be considered because they are treatable. Disorders which have recently had their genetic aetiologies identified include hereditary myopathy with early respiratory failure (due to *TTN* mutations), the *FHL1*-related syndromes, and myofibrillar myopathy due to *BAG3* mutation. Recently described syndromes include oculopharyngodistal muscular dystrophy that awaits genetic characterisation.

Keywords Myopathy · Respiratory failure · Muscle · Neuromuscular · Respiratory

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Introduction

Respiratory muscle weakness occurs in a broad variety of muscle disorders, typically in the context of severe and diffuse muscle weakness, and manifests itself relatively late in the disease course. The clinical presentation of early neuromuscular chronic respiratory failure (ERF, i.e. chronic-onset respiratory muscle weakness whilst the patient is still ambulant) is rare, but represents a distinct diagnostic category requiring a different approach and differential diagnosis. In this clinical situation, the conditions which should be considered first include amyotrophic lateral sclerosis and myasthenia gravis, and these are the most common non-muscle diseases with this presentation. If these conditions are excluded in a patient, there remains a challenging differential diagnosis of several muscle conditions. This review will focus on a clinical approach to the diagnosis of chronic muscle diseases that present with ERF.

Mechanisms of chronic neuromuscular respiratory failure

ERF may occur in muscle disease due to the following mechanisms. Weakness of respiratory muscles (including diaphragm and/or intercostal muscles, or accessory respiratory muscles) can directly result in respiratory insufficiency due to respiratory pump failure. Weakness begins insidiously but becomes more severe, and hypoventilation ensues with rise in arterial carbon dioxide and consequent proportional fall in arterial oxygen. However, additional factors which may coexist in particular muscle diseases, such as kyphoscoliosis, and chest wall deformity which are associated with restrictive changes in pulmonary physiology or weakness of pharyngeal and laryngeal muscles which may additionally compromise airway clearance and predispose to aspiration and pneumonia. Muscle contractures or muscle fibrosis may also occur in respiratory muscles and limit chest movement, thus increasing the work required for adequate respiratory function. Some muscle diseases also have a contribution of abnormal central respiratory control (for example myotonic dystrophy type 1). Furthermore the innervation of respiratory muscles can be compromised, as in certain motor neuropathies (most commonly amyotrophic lateral sclerosis), or via abnormal neurotransmission (as in myasthenia gravis). Finally, all of the above can contribute to susceptibility to atelectasis or respiratory tract infection causing a disproportionate reduction in arterial partial pressure of oxygen (PaO_2).

Clinical presentation of early respiratory failure

Patients with ERF due to chronic muscle diseases will typically be referred to out-patient clinics in neurology or respiratory medicine for assessment of unexplained dyspnoea, orthopnoea, or sleepiness (Box 1). Typical sleep symptoms resemble those of obstructive sleep apnoea, and include sleep disruption, morning headache, and hypersomnolence [1]. These symptoms may result from fragmented sleep, nocturnal hypoventilation with consequent hypercapnia, or both. The nocturnal hypoventilation is most pronounced during REM sleep as muscle weakness is further aggravated by REM muscle atonia. In response individuals may become REM avoidant and less restorative, and stage 1 sleep will be increased [2]. Respiratory complaints may also predominate with symptoms due to diaphragmatic weakness such as orthopnoea, dyspnoea on bending forward, or dyspnoea on immersion into a pool. Dyspnoea on exertion is a variable finding which will depend on the level of exertion of an individual. First presentation with recurrent chest infections or choking episodes may point to laryngeal dysfunction or other impairment in airway clearance. The former can precipitate acute physiological decompensation, sometimes resulting in admission to intensive care. Physical signs of respiratory failure (RF) include tachypnoea, slow speech, use of accessory respiratory muscles at rest, and loss of chest-abdomen respiratory synchronisation/abdominal paradox where the abdomen moves out of phase with the rib cage [3]. An audibly ineffectual cough may also be present [4]. These symptoms are often very subtle and progress insidiously over months or years. The RF may be frequently misdiagnosed as obstructive sleep apnoea, asthma, or chronic obstructive lung disease (COPD). As a result, RF due to neuromuscular disease can go unrecognised for prolonged periods until it becomes advanced and presents acutely due to an exacerbating increase in respiratory demand such as an infection or pulmonary embolism. Eventually, chronic RF can result in severe disability, susceptibility to pulmonary and other medical complications, and death.

Diagnostic evaluation

In patients with the above symptoms, various diagnostic tests can confirm the presence of RF.

Sleep testing

Sleep testing may reveal sleep apnoea or nocturnal hypoventilation. Most causes of neuromuscular weakness will be associated with nocturnal hypoventilation once the vital capacity has fallen to 60 %. Obstructive sleep apnoea (OSA) may be evident if obesity is more prominent or if muscles of the upper airway are involved. Central sleep apnoea (CSA) will rarely be seen due to derangements in the control of ventilation more prominent in sleep than wakefulness, this is the case in myotonic dystrophy. In considering specific testing, overnight oximetry is often readily available and convenient for patients. It is likely to show prolonged periods of hypoxaemia if nocturnal hypoventilation is present or intermittent hypoxia if OSA or CSA is present. A pattern of periodic desaturation may suggest REM-related OSA or hypoventilation. The addition of transcutaneous PCO_2 monitoring, if available, will show a rise in CO_2 corresponding to the period of hypoventilation, but is not essential to diagnose ERF. A rise of 10 mmHg in the CO_2 or above a peak of 55 mmHg for 10 min is consistent with nocturnal hypoventilation. Home cardiorespiratory monitors will provide further details of the respiratory flow contour to differentiate between central and obstructive events but are not validated for use in diagnosis of neuromuscular disorders. These monitors may

include respiratory effort bands which may reveal abdominal paradox, and also contribute to differentiating central from obstructive apnoea. Full polysomnography (PSG) should be considered in patients with report of significant sleep disruption/insomnia or who are likely to fail home monitoring due to poor co-ordination related to muscle weakness. PSG provides additional information on sleep duration and sleep state allowing greater certainty of the diagnosis. PSG can also be used as a setting for initiation/titration of ventilator therapies [5]. Daytime arterial blood gas measurement will confirm decreased PaO_2 and elevated $PaCO_2$ in advanced disease. The pH will be low or normal, depending on the duration of hypercapnia. The latter may have gone unrecognised for some time, and occasionally, chronic hypercapnia may be suggested in retrospect by finding a previously elevated venous bicarbonate concentration [6].

Pulmonary function testing

Pulmonary function in respiratory muscle weakness characteristically shows a restrictive ventilatory defect, with a reduced vital capacity (VC) and normal ratio with the forced expiratory volume in 1 s (FEV1 to FVC >0.7). Due to the direct effect of expiratory weakness, peak expiratory flows are typically reduced, but the finding is nonspecific and any abnormal result should be followed by spirometry. Similarly reserve volume will be found to be increased due to weakness in expiratory muscles. Spirometry may have an egg-shaped appearance due to the lack of a sharp rise in expiratory flow and an abrupt end to the effort. Hypercapnic respiratory failure is particularly likely with a VC of less than 15 ml/kg, an absolute value of 1 l, 50 % of predicted and/or a decrease in VC of greater than 20–30 % whilst recumbent compared with the standing position [4, 7]. The latter is a characteristic of severe bilateral diaphragmatic weakness or paralysis and reflects the difficulty in displacing the abdominal contents without the aid of gravity when in the supine posture. Respiratory muscle function can be assessed directly by measuring maximum respiratory pressures during forceful voluntary manoeuvres with airway occlusion, with measurements made either statically at the mouth or in the nostril during a forceful sniff with the other nostril occluded. Levels suggestive of inspiratory muscle weakness are maximal inspiratory pressure less than -30 cmH_2O, maximal expiratory pressure of <40 cmH_2O, or a nasal sniff pressure of less than 32 % of predicted [1] whilst values greater than 80 cmH_2O for men, or 70 cmH_2O for women and sniff nasal inspiratory pressure greater than 70 cmH_2O for men, or 60 cmH_2O for women exclude neuromuscular weakness [8]. Further testing is required for patients in the indeterminate zone between these cut-offs. It should be noted that maximum pressures are, by definition, strictly effort dependent and therefore are not "fail safe"; it is essential to ensure maximal cooperation and effort, and several practice attempts may be required before achieving reproducible and valid results. Bulbar weakness preventing proper mouth seal can also falsely lower results. Maximum pressure measurements are generally more sensitive than VC to milder degrees of respiratory muscle weakness, but by the time hypercapnia develops, VC would be expected to be severely reduced to below 50 % of predicted. Recurrent infection or other evidence of a poor cough should prompt measurement of the peak cough flow (PCF). A peak cough flow of less than 270 l/min is suggestive that cough assist techniques should be implemented whilst at less than 160 l/min the aforementioned complications are likely. [4] Chest physiotherapy by techniques including cyclical breathing, huffing, or percussion may aid in secretion mobilisation but alone is likely to prove ineffective [4].

Pulmonary imaging

Chest radiography or CT scanning may demonstrate coexistent scoliosis which may contribute to RF, and may also be helpful to exclude coexistent pulmonary parenchymal disease. Dynamic imaging by ultrasound or fluoroscopy can be used to assess diaphragmatic motion and confirm diaphragmatic weakness [1, 7].

Finally, other causes of RF should also be ruled out as appropriate to the clinical situation and may entail further respiratory, cardiovascular, neurological, and toxicological investigations (Fig. 1).

Differential diagnosis of muscle diseases

Numerous neuromuscular diseases include RF as a component, although this is most frequent towards the end of the disease course, and a discussion of these is beyond the scope of this review. Of these, chronic neuromuscular disorders presenting with ERF are a distinct entity and the differential diagnosis for this group is summarised in Table 1. Of these, the most important conditions that are not primary muscle diseases are amyotrophic lateral sclerosis and myasthenia gravis. For both of these conditions, ERF as an initial presentation of the disorder is common (about 3 % of patients with ALS [9], and 14 % of patients with myasthenia gravis [10]). Because this work focuses on muscle diseases these conditions will not be reviewed in detail. It should also be noted that some of these conditions (namely myasthenia gravis) can also present with acute respiratory failure, and that any of these conditions may present acutely in combination with another illness (such as respiratory infection or drug toxicity).

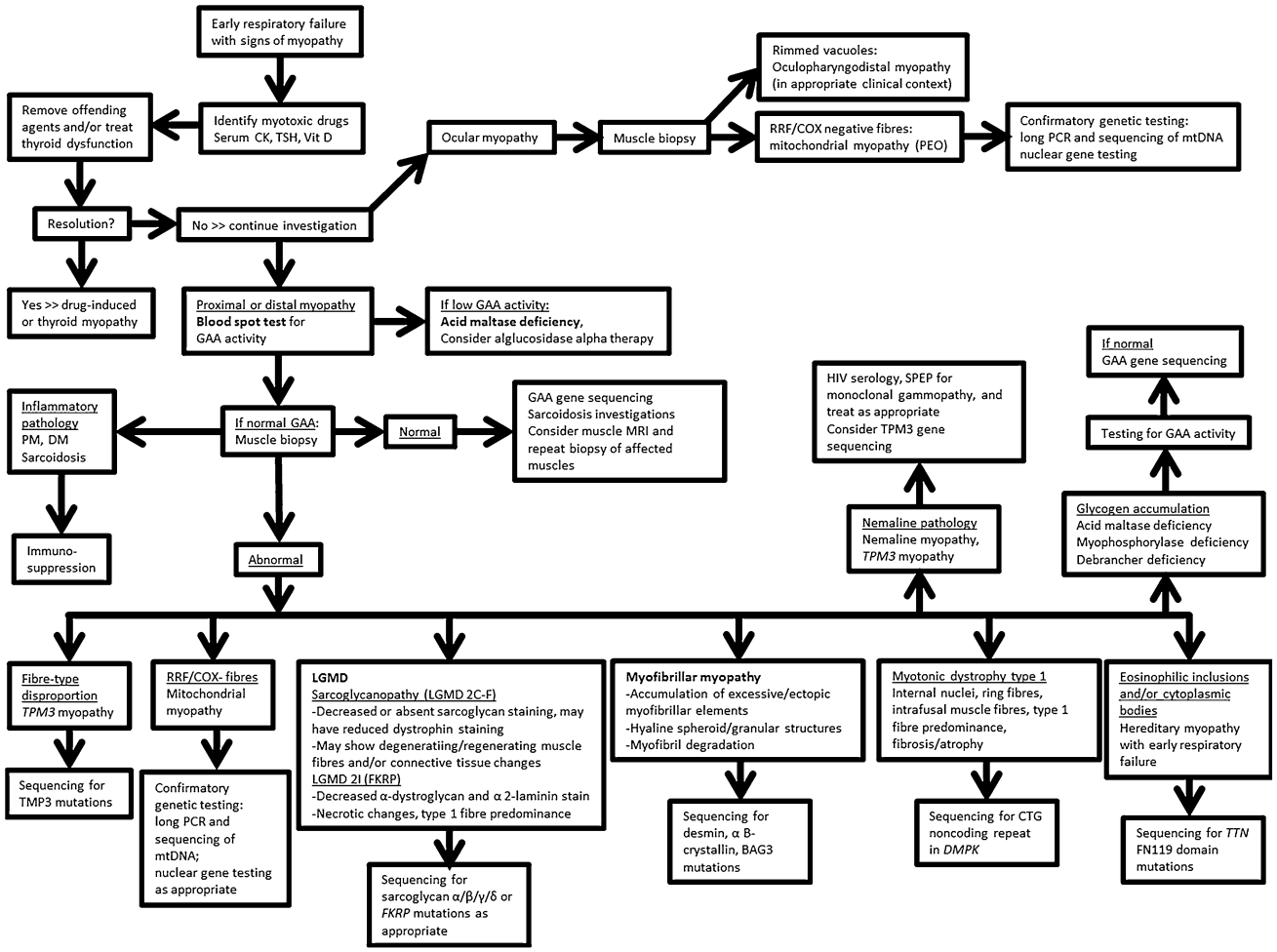

Fig. 1 Algorithm for diagnosis and treatment of chronic muscle disease presenting with early respiratory failure. *CK* creatine kinase, *GAA* acid α-glucosidase, *PM* polymyositis, *DM* dermatomyositis, *RRF* ragged red fibres, *COX* cytochrome *c* oxidase, *PCR* polymerase chain reaction, *mtDNA* mitochondrial DNA, *LGMD* limb-girdle muscular dystrophy, *HIV* human immunodeficiency virus, *SPEP* serum protein electrophoresis

Table 2 summarises those conditions which are muscle diseases, which will be the focus of this article, and for purposes of this review the conditions will be discussed in these broad aetiological categories. It is important to emphasise that for some of these conditions, ERF is a typical presentation of the disease, and we distinguish diseases that have ERF as a typical versus uncommon presentation, in Table 2. Although some of the conditions have only few reported cases with this clinical presentation, some of these have management implications and should still be considered in the initial differential diagnosis, and these have also been indicated in Table 2.

Conditions which we have not included are disorders presenting with acute neuromuscular respiratory failure (which have been reviewed in detail elsewhere), as well as muscle diseases that have respiratory muscle weakness late in the clinical presentation (e.g. several years after onset of the condition, or in patients who are no longer ambulant due to diffuse severe muscle weakness, or when muscle weakness does not predominate at any point in the clinical phenotype).

Hereditary muscle diseases causing early respiratory failure

Metabolic myopathies

Late-onset Pompe disease Also known as glycogen storage disease type II, this lysosomal storage disorder is caused by deficiency of acid α-glucosidase (GAA) and may present from infancy to late adulthood [11].

Late-onset Pompe disease (PD) is the prototype muscle disease which presents with ERF. The presentation of chronic respiratory muscle weakness in ambulant patients is one of the typical clinical presentations for PD [12], and respiratory failure is the most common cause of death [13].

Table 1 Chronic neuromuscular disorders which present with early respiratory failure

Disease category	Disease/syndrome	Comment
Lower motor neurone/anterior horn cell disorder	Amyotrophic lateral sclerosis	3 % of patients present with early respiratory failure [9]
	Toxic neuronopathy	
	Distal spinal muscular atrophy type I	Neonatal/infantile, or rarely juvenile onset. Due to mutations of IGHMBP2 gene [120]
Peripheral neuropathy (mainly: demyelinating and/or acquired, as opposed to axonal and/or hereditary)	Autoimmune neuropathy	
	Chronic inflammatory demyelinating polyradiculoneuropathy	
	Connective tissue diseases	
	Paraneoplastic	
	Sarcoidosis	
	Infiltrative neuropathy	
	Haematologic malignancy	
	Amyloidosis	
	Toxic neuropathy: lead	
	Multifocal motor neuropathy	Only a single case reported [121]
Neuromuscular junction disorder	Myasthenia gravis	Amongst myasthenia gravis patients with respiratory failure, 14 % had respiratory failure as their initial disease presentation in one series [10]
	Lambert–Eaton myasthenic syndrome	Rarely occurs, one series and few case reports have been published [122, 123]
	Congenital myasthenic syndromes	CHAT [124] and RAPSN [125] mutations; fluctuations with illness common
Myopathy	Refer to Table 2	

Neuromuscular disorders causing acute- or subacute-onset respiratory failure have a broader differential diagnosis which is beyond the scope of this review

Because this disease is potentially treatable with enzyme replacement therapy, reaching the diagnosis of PD is important. Unfortunately diagnosis is often delayed by several years on account of the rarity and phenotypic variability of this disease [14]. Recently, diagnostic guidelines for this condition were published [15]. To summarise, PD should be considered in patients with adult-onset proximal myopathy and/or respiratory muscle weakness. Testing for GAA enzyme activity is quickly and accurately achieved with dried blood spot testing and should be performed amongst the initial diagnostic tests [16]. The muscle biopsy classically demonstrates vacuolar glycogen accumulation, but can occasionally be normal [17]. Muscle tissue can also be used for GAA enzyme testing. When muscle pathology and enzyme activity are difficult to interpret, the diagnosis can be confirmed with *GAA* sequencing.

Treatment with alglucosidase alpha was evaluated in a placebo-controlled trial in adult-onset disease, significantly stabilising walking distance and pulmonary function [18]. The treatment was also demonstrated to be safe and effective in a 3-year observational study [19]. Since PD is progressive, treatment should be considered, though evidence for this treatment is recent, and long-term outcomes are unknown. Furthermore, patients may develop antibodies to the infusion [20], which leads to infusion-related reactions, and potentially decreased treatment efficacy [21], which requires further study in adult patients.

Other treatment options include nutrition and exercise programs designed to increase fatty acid utilisation by muscle, which may slow deterioration in this condition [22]. Prognosis in this condition is difficult to predict, since enzyme activity levels do not correlate with phenotype in late-onset PD. It has been suggested that respiratory dysfunction and low BMI are predictive of poor prognosis [23], although the latter claim has been disputed, suggesting that low BMI actually portended better response to treatment and thus better prognosis [24]. Another prognostic factor includes the presence of homozygous deletion polymorphism at intron 16 of the angiotensin converting enzyme gene (rs1799752), which is associated with poorer phenotype and prognosis [25]. It is likely that numerous genetic factors interact to produce the phenotype in individual patients, and as more of these are identified genomic medicine may identify individuals at higher risk for deterioration, and thus closer follow-up and intervention.

Table 2 Categories of muscle disease which may present with early respiratory failure

Disease category and specific disease	Early respiratory failure typical or atypical presentation	Management implications
Metabolic myopathy		
Adult-onset Pompe disease	Typical (prototypic)	Alglucosidase alpha enzyme replacement
Mitochondrial myopathy	Atypical	
Myophosphorylase deficiency	Single case report [46]	
Debrancher deficiency	Single case report [47] (although other features make it unclear whether this truly reflects ERF in this case)	
Hereditary myopathy or muscular dystrophy		
Myotonic dystrophy type I (*DMPK*)	Typical	
LGMD 2I, 2C-F	Typical	
Myofibrillar myopathy (desmin, α B-crystallin, *BAG3*)	Typical	
TPM3 myopathy	Typical	
Hereditary myopathy with early respiratory failure (*TTN*)	Typical	
Oculopharyngodistal muscular dystrophy	Typical	
Acquired myopathy (autoimmune, inflammatory, toxic)		
Inflammatory myopathy	Atypical	Immunosuppression for dermato/polymyositis and search for underlying causes
Dermatomyositis		
Polymyositis		
Inclusion body myositis		
Adult-onset nemaline myopathy	Atypical	Investigate for HIV status and monoclonal gammopathy
Sarcoidosis	Single case report [116]	Immunosuppression
Colchicine myopathy	Single case report [117]	Symptoms improved with cessation of colchicine therapy

Mitochondrial myopathy Mitochondrial myopathies are caused by primary dysfunction of the mitochondrial respiratory chain, and typically produce multisystem disease, on account of the fact that mitochondria are distributed throughout the body and required for energy production. Dysfunction is most likely to occur in tissues/organs with high energy requirements, therefore explaining that MM most often affects muscles (particularly extraocular muscle), and the nervous, cardiac, and endocrine systems. A detailed description of all mitochondrial myopathies, and their clinical characteristics, prognosis, diagnosis, and treatment is beyond the scope of this review, although this topic was recently reviewed in detail [26].

Clinically apparent respiratory dysfunction in mitochondrial myopathies appears to be an unusual finding: in recent series, respiratory dysfunction has similar prevalence to controls in patients with the m.3243A>G mutation [27], and was present in only one of 40 patients in a recent PEO series [28]. However, a recent study of 23 patients suggests that respiratory muscle weakness is common in PEO and is more likely to appear in patients with limb-girdle muscle weakness (although abnormalities of pulmonary function do not correspond to respiratory symptoms) [29]. In another study of 331 patients with unexplained dyspnoea, 28 (8.5 %) of these were diagnosed with respiratory muscle weakness due to mitochondrial myopathy [30]. This suggests that respiratory muscle weakness due to mitochondrial myopathy may be more common than that has been recognised. However, this study is limited due to the absence of genetic studies; therefore, misdiagnosis could have occurred depending on interpretation of the muscle pathology, which can be nonspecific. Referral bias may also have played a role.

Numerous case studies also report mitochondrial myopathy presenting initially with respiratory failure. Reports have identified families in which multiple individuals presented with respiratory failure, suggesting specificity of certain mutations for respiratory muscles. These families have mutations of tRNA genes at mitochondrial DNA (mtDNA) positions 3302 [31] and 3288

[32]. The other individual cases which have been genetically characterised are also due to tRNA gene mutations [33–35], and it is unclear why other types of mutations, or deletions, have not been described.

Other reports discuss patients who had presented with acute respiratory failure requiring ventilator support. In retrospect, they had experienced chronic respiratory symptoms which had been unrecognised, or had not come to medical attention [35–38]. In some instances, background respiratory dysfunction was worsened in the context of an acute illness or other metabolic stressors. As it is characteristic for metabolic stressors to expose subclinical metabolic diseases [39], mitochondrial myopathy should be considered in the differential diagnosis in these contexts.

It is important to mention that mitochondrial disorders also affect respiratory function via central mechanisms [40–43], that may be frequently symptomatic, or mimic the clinical presentation of respiratory muscle weakness (i.e. nocturnal symptoms of obstructive sleep apnoea [44, 45]).

Other causes Individual cases of myophosphorylase deficiency [46] and debrancher enzyme deficiency [47] have been reported with respiratory failure as an initial presenting feature.

Inherited muscle diseases

Muscular dystrophies *Myotonic dystrophy type 1*: Myotonic dystrophy type 1 (DM1) is the second most common muscular dystrophy and is a multisystem disorder caused by a noncoding CTG repeat expansion in the *DMPK* gene resulting in RNA hyperaggregation. The condition has autosomal dominant inheritance with high penetrance and variable expressivity, and maternal anticipation. Clinical features include frontal balding, atrophic facial muscles, distal myopathy with myotonia, and frequent involvement of the central nervous, ocular, endocrine, and cardiac systems.

The severity and likelihood of developing RF in DM1 correlate well with the severity of the phenotype [48]. Respiratory muscle weakness was demonstrated in one-third of 106 patients in one series, including some with only distal muscle weakness [48]. Uncommonly, DM1 patients develop overt RF whilst still ambulant, as the case for 3 patients (who had dyspnoea at rest) in one series [49]. Hypersomnolence is extremely common in DM1, affecting 69.8 % of patients in one recent series [50]; in some cases hypercapnia or sleep apnoea may contribute, but most evidence favours a neurological origin as the main cause in DM1 [51–53]. Sleep disorders are increasingly recognised in DM1 [51, 54]. Obstructive sleep apnoea, presumed due to weakness and hypotonia of upper airway muscles, is frequently found [50], particularly amongst those who are overweight and even without hypersomnolence [55].

Treatment for patients with symptomatic hypercapnia may include nocturnal non-invasive ventilation (NIV), although patients with DM1 tend to adapt less well to this form of therapy than those with respiratory failure due to other neuromuscular conditions [56]. There is insufficient evidence to recommend symptomatic treatment with stimulants for DM1 patients on the basis of randomised placebo-controlled data [57, 58].

Limb-girdle muscular dystrophy: Respiratory muscle involvement occurs in several muscular dystrophies, although as a rule this tends to occur late in the disease course, when there is generalised and severe muscle weakness. In limb-girdle muscular dystrophies (LGMD), respiratory failure is relatively uncommon for the majority of cases, and RF tends not to present even in advanced disease. The exceptions include LGMD2I (due to *FKRP* mutation) and LGMD 2C-F (sarcoglycanopathies) which commonly involve respiratory failure as a component of their disease course, and also may present with ERF in the context of limited limb muscle symptoms.

Mutations in the *FKRP* gene cause a broad disease spectrum which includes congenital myopathy (MDC1C), or proximal myopathy in childhood or adulthood (LGMD2I) [59]. Respiratory muscle weakness is a common complication in LGMD2I, affecting 10 of 16 patients in one series [60]. Respiratory failure may occur in patients whilst they are still ambulant, but, typically, this is after several years' disease duration [61, 62]. In another series, five patients requiring nocturnal ventilatory support were still ambulant [63]. Furthermore, results of this series suggested that respiratory muscle weakness was more likely to be a prominent feature in individuals with later-onset disease [63].

LGMD2C-F are due to mutations in the sarcoglycans, which are proteins demonstrated to be integral to the function of diaphragmatic muscle [64]. For the sarcoglycanopathies, the usual clinical presentation involves childhood onset with severe proximal and eventually distal muscle weakness, with a clinical course resembling Duchenne muscular dystrophy. All patients with sarcoglycanopathies (LGMD2C-F) are likely to have some degree of respiratory failure, though this would appear to be most significant with LGMD2C and 2D [65]. Of these, LGMD2D (due to α-sarcoglycan mutations) has been reported to present with respiratory failure [66].

Inherited myopathies with myofibrillar pathology *Myofibrillar myopathies*: Myofibrillar myopathies (MFM) are muscular dystrophies characterised by the pathological findings of Z-disc disorganisation and the abnormal accumulation of myofibrillar elements [67]. Respiratory muscle weakness is a common feature during the disease course of most MFM, including those caused by filamin [68], desmin

[69], α B-crystallin [70], BAG3 [71], and a minority caused by myotilin mutations [72]. Of these, there are cases reported of patients presenting with respiratory failure in MFM due to mutations in desmin [69], α B-crystallin [70], and *BAG3* [71]. The predilection for most of the MFM to affect the respiratory muscles (MFM caused by *ZASP* mutation has not been associated with respiratory muscle weakness) is not understood, although desmin has elevated expression in the diaphragm and may have a conformation particularly important to the function of this muscle [73].

Hereditary myopathy with early respiratory failure (HMERF): HMERF (OMIM #603689) is caused by mutations in the 119th fibronectin 3 domain of the giant sarcomeric gene titin (*TTN*) [74–76] and meets diagnostic criteria for MFM on muscle pathology [75, 76], as well as having similarities with other subtypes of MFM in clinical presentation and MRI abnormalities [77, 78]. The condition is common compared with other subtypes of MFM in the United Kingdom, probably owing to a founder effect [75], although another study of MFM patients in the United States found a similar prevalence [79], suggesting that the disease is internationally distributed and likely to be common in other populations as well. The original mutation associated with this condition is in the kinase domain of *TTN* [80] but appears to have also been associated with another mutation in the 119th fibronectin 3 domain [81], and further study will need to determine whether the kinase variant is pathogenic (it has also been found in normal controls and is listed as a low-frequency polymorphism in dbSNP: rs140319117). The condition typically presents with distal leg weakness and respiratory muscle weakness in mid-life, although broad phenotypic variability exists [77].

Inherited myopathies with other pathology *TPM3 myopathy*: The tropomyosin-3 (*TPM3*) gene encodes a muscle protein required for actin binding. Myopathy caused by *TPM3* mutations can be associated with a variety of disease phenotypes and muscle pathologies. Clinically, this disorder may present at any age from congenitally up into late adulthood. The phenotype includes hypotonia, muscle atrophy, and contractures in early-onset presentations [82, 83], and in adulthood, proximal myopathy often with respiratory failure [83]. Scoliosis and/or lumbar lordosis are commonly associated features, and can contribute to respiratory failure. This disease may show muscle pathology of congenital fibre-type disproportion myopathy [83], nemaline myopathy [84], or cap myopathy [85]. Inheritance may be autosomal recessive or dominant (potentially due to a dominant negative effect [86]). Respiratory failure as an early component of the disease, whilst patients are still ambulant, appears to be a typical presentation of this rare disease [83, 87]. *TPM3* myopathy should be considered in the differential diagnosis when any of the above nonspecific muscle pathology findings are present, but particularly for congenital fibre-type disproportion [88].

FHL1-related syndromes: There is a very broad spectrum of muscle disease phenotypes caused by mutations in *FHL1*. Amongst these are early-onset muscle diseases such as reducing body myopathy, or rigid spine syndrome, as well as adult-onset muscle diseases such as X-linked myopathy with postural muscle atrophy (XMPMA), a scapuloperoneal syndrome, or an Emery–Dreifuss muscular dystrophy phenotype [89]. Interestingly, there is also phenotypic variability between individuals sharing the same mutation and founder haplotype [90]. *FHL1* mutations can also present with the clinical and pathological features of MFM [91]. Amongst these phenotypes, XMPMA has been reported to have respiratory failure in ambulant patients [92, 93] and should be considered in adult-onset muscle disease having atrophy of postural muscles and hypertrophy of muscles with predominance of type II muscle fibres [93].

Oculopharyngodistal myopathy: This myopathy is characterised by ophthalmoparesis and ptosis, with pharyngeal and distal muscle weakness. Pathological changes include the presence of rimmed vacuoles, and inheritance pattern may be autosomal dominant [94] or recessive [95]. The genetic basis of this condition has not yet been discovered. In a recent study, 21 patients were studied with spirometry testing (18 of whom were still ambulant), and 13 had evidence of respiratory muscle involvement (8 of whom had daytime hypercapnia and 3 requiring nocturnal ventilatory support) [96]. The resemblance of this condition to PEO might present diagnostic confusion with mitochondrial myopathy, although distal muscle weakness is uncommon for mitochondrial disease, and muscle pathology markedly different.

Acquired myopathies presenting with early respiratory failure

Inflammatory myopathy

This category of disease includes polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM). All these diseases are associated with subclinical respiratory muscle dysfunction, with DM patients more frequently affected [97]. In one study of 156 PM/DM patients, 21.8 % had respiratory muscle weakness, although it was not specified how this was ascertained [98]; although in general the impression is that respiratory muscle weakness rarely causes respiratory failure in these

disorders [99]. Cases have been reported of PM presenting with respiratory failure: one in which respiratory failure was the first and predominant feature that progressed over three months [100]. In another case, the patient was admitted to intensive care and in retrospect probably had longstanding respiratory muscle weakness [101]. One case of antisynthetase syndrome had isolated respiratory muscle weakness [102] (although it should be emphasised that the more common cause of respiratory failure in these patients is interstitial lung disease). Other reports exist of patients having been admitted to the ICU for respiratory muscle weakness due to PM [103] or DM [104], (although it should be noted many of these presented acutely to hospital rather than with chronic ERF to ambulatory clinics); in the DM patients most of these were early in the course of their disease and the authors emphasise the high mortality for these patients [104]. There is also a case report of a patient with respiratory muscle weakness occurring 5 years after onset of limb symptoms in a patient with IBM [105]. All of these cases have in common that the consequences of respiratory muscle weakness in these conditions can be severe, and fortunately for PM and DM, treatment is available.

Sporadic adult-onset nemaline myopathy

Nemaline myopathy (NM) is a congenital myopathy which rarely presents in adulthood (6 out of 143 cases in the largest study of this disorder) [106]. It is defined by the presence of nemaline structures within muscle fibres on Gomori trichrome histochemistry and/or electron microscopy, within the context of a characteristic clinical picture.

Adult-onset nemaline myopathy (AONM) features several differences with the typical congenital form which presents neonatally or in early childhood. AONM is distinguished by late age of onset, and milder phenotype, which includes proximal myopathy, often with dysphagia, and respiratory muscle weakness [107]. Although numerous genetic causes exist for typical NM, and a family history is frequently present, the reported cases of AONM are most frequently sporadic, without genetic aetiology identified [106]. In these cases, the disorder may relate to other causes: AONM has been associated with HIV infection [108] as well as monoclonal gammopathy [107]. Furthermore, nemaline pathology is not a specific finding and has also been described in other inherited, endocrine, and inflammatory disorders [83, 109, 110].

Several cases of AONM presenting with respiratory failure have been reported [111–113], and respiratory failure is a recognised component of the disease course [107, 114]. Given the possibility of responsivity to immunomodulation [115], ruling out this diagnosis with muscle biopsy is important. Furthermore, identification of patients with nemaline pathology on muscle biopsy should prompt additional investigation with serum protein electrophoresis and HIV serology.

Other causes

Individual cases of sarcoid myopathy [116] and colchicine myopathy [117] have been reported and should be considered because of their management implications.

Management of chronic respiratory failure due to muscle diseases

In the absence of specific therapy to reverse or stabilise progressive muscle weakness, therapy is focussed on management of the respiratory complications. Sleep disordered breathing can be stabilised with introduction of non-invasive ventilation. Unloading of the respiratory system during the night improves ventilatory mechanics and can delay progression of respiratory impairment and ventilatory failure. Early involvement of pulmonary medicine specialists is recommended to plan for the introduction of NIV once vital capacity has fallen to $\sim$50 % of predicted, or earlier if low mouth pressures, symptoms of sleep disordered breathing, orthopnoea, or daytime hypercapnoea as described above is present. The goal of NIV is to completely take over the work of respiration during sleep [118]. The evidence to support the use of NIV in this context was generated in observational trials followed by randomised trials in ALS populations [119] which showed improvement in survival and quality of life. Comparison of historical cohorts of DMD patients has also shown that NIV has likely contributed to the substantial improvement in longevity in these diseases. Whilst longevity is likely only to be impacted if the disease is rapidly progressive, improvement in quality of life justifies the effort of introduction of NIV where bulbar function is preserved.

Poor peak cough flow, recurrent respiratory infection, or the presence of significant atelectasis should prompt the introduction of manual or mechanical cough assist. Use of manual cough assist should be considered for individuals with persistent glottis function and good hand strength. It involves the use of a bag valve mask to deliver stacked breaths to expand the lung closer to total lung capacity. The patient will then use an abdominal thrust to increase intra-abdominal pressure and forcefully exhale. For patients unable to co-ordinate their breathing mechanical in-exsufflation can be considered. These

devices deliver a positive pressure breath followed by negative pressure to suck out mobilised secretions. In addition to improving the efficiency of cough these techniques may improve lung compliance and decrease atelectasis [4]. Chest physiotherapy with percussion or other techniques to mobilise secretions may be considered if secretions are tenacious or purulent but alone are insufficient in this population [4].

Conclusion

Chronic muscle diseases presenting with ERF represent an uncommon clinical presentation. Recognising ERF and identifying the underlying condition can have important implications for patient care, particularly with the increasingly widespread availability of long-term domiciliary NIV, which is a highly effective form of treatment for many patients with symptomatic hypercapnic respiratory failure due to respiratory muscle weakness. These conditions have in common that they are mainly inherited metabolic diseases or muscular dystrophies. It is thus far unclear why these conditions involve the respiratory muscles at an early stage. As the molecular mechanism is discovered for more of these diseases, such as oculopharyngodistal muscular dystrophy, we may gain further insight on the differentiating features of respiratory muscle function compared with other skeletal muscles, and eventually design treatments targeted to respiratory muscle. These would have implications for the diseases listed above and potentially also for more common muscle diseases (such as Duchenne muscular dystrophy) which cause respiratory failure at other time-points in the disease course. This would be an important development in the treatment of muscle disease, since respiratory failure is one of the most important contributors to patient morbidity and mortality. The identification of the diseases discussed in this review are therefore important from a research point of view, to identify novel therapeutic targets which could be valuable for both rare and common muscle diseases with respiratory failure.

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Conflicts of interest The authors report no competing interests.

Box 1: Symptoms of chronic respiratory failure of neuromuscular origin

Nocturnal symptoms:

- Orthopnoea
- Sleep disruption
- Headache upon awakening

Daytime symptoms:

- Hypersomnolence
- Dyspnoea (positional, exertional, or otherwise unexplained)
- Tachypnoea
- Slow speech/dysarthria
- Weak cough
- Fatigue

References

1. Laghi F, Tobin MJ (2003) Disorders of the respiratory muscles. Am J Respir Crit Care Med 168(1):10–48
2. Bourke SC, Gibson GJ (2002) Sleep and breathing in neuromuscular disease. Eur Respir J 19(6):1194–1201
3. Rochester DF, Esau SA (1994) Assessment of ventilatory function in patients with neuromuscular disease. Clin Chest Med 15(4):751–763
4. Ambrosino N, Carpene N, Gherardi M (2009) Chronic respiratory care for neuromuscular diseases in adults. Eur Respir J 34(2):444–451
5. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK et al (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American academy of sleep medicine. J Clin Sleep Med 8(5):597–619
6. Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans AT (2007) Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. Sleep Breath 11(2):117–124
7. American Thoracic Society/European Respiratory Society (2002) ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med 166(4):518–624
8. Hutchinson D, Whyte K (2008) Neuromuscular disease and respiratory failure. Pract Neurol 8(4):229–237
9. Gautier G, Verschueren A, Monnier A, Attarian S, Salort-Campana E, Pouget J (2010) ALS with respiratory onset: clinical features and effects of non-invasive ventilation on the prognosis. Amyotroph Lateral Scler 11(4):379–382
10. Qureshi AI, Choundry MA, Mohammad Y, Chua HC, Yahia AM, Ulatowski JA et al (2004) Respiratory failure as a first presentation of myasthenia gravis. Med Sci Monit 10(12): CR684–CR689
11. Wang RY, Bodamer OA, Watson MS, Wilcox WR, ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases (2011) Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genet Med 13(5):457–484

12. Mellies U, Lofaso F (2009) Pompe disease: a neuromuscular disease with respiratory muscle involvement. Respir Med 103(4):477–484
13. Winkel LP, Hagemans ML, van Doorn PA, Loonen MC, Hop WJ, Reuser AJ et al (2005) The natural course of non-classic Pompe's disease; a review of 225 published cases. J Neurol 252(8):875–884
14. Muller-Felber W, Horvath R, Gempel K, Podskarbi T, Shin Y, Pongratz D et al (2007) Late onset Pompe disease: clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. Neuromuscul Disord 17(9–10): 698–706
15. American Association of Neuromuscular and Electrodiagnostic Medicine (2009) Diagnostic criteria for late-onset (childhood and adult) Pompe disease. Muscle Nerve 40(1):149–160
16. Goldstein JL, Young SP, Changela M, Dickerson GH, Zhang H, Dai J et al (2009) Screening for Pompe disease using a rapid dried blood spot method: experience of a clinical diagnostic laboratory. Muscle Nerve 40(1):32–36
17. Schoser BG, Muller-Hocker J, Horvath R, Gempel K, Pongratz D, Lochmuller H et al (2007) Adult-onset glycogen storage disease type 2: clinico-pathological phenotype revisited. Neuropathol Appl Neurobiol 33(5):544–559
18. van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ et al (2010) A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med 362(15):1396–1406
19. Bembi B, Pisa FE, Confalonieri M, Ciana G, Fiumara A, Parini R et al (2010) Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II. J Inherit Metab Dis 33(6):727–735
20. de Vries JM, van der Beek NA, Kroos MA, Ozkan L, van Doorn PA, Richards SM et al (2010) High antibody titer in an adult with Pompe disease affects treatment with alglucosidase alfa. Mol Genet Metab 101(4):338–345
21. Kishnani PS, Goldenberg PC, DeArmey SL, Heller J, Benjamin D, Young S et al (2010) Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. Mol Genet Metab 99(1):26–33
22. Slonim AE, Bulone L, Goldberg T, Minikes J, Slonim E, Galanko J et al (2007) Modification of the natural history of adult-onset acid maltase deficiency by nutrition and exercise therapy. Muscle Nerve 35(1):70–77
23. Kobayashi H, Shimada Y, Ikegami M, Kawai T, Sakurai K, Urashima T et al (2010) Prognostic factors for the late onset Pompe disease with enzyme replacement therapy: from our experience of 4 cases including an autopsy case. Mol Genet Metab 100(1):14–19
24. Ravaglia S, Carlucci A, Danesino C (2010) Prognostic factors for late-onset Pompe disease with enzyme replacement therapy: the two sides of low BMI. Mol Genet Metab 100(4):388
25. de Filippi P, Ravaglia S, Bembi B, Costa A, Moglia A, Piccolo G et al (2010) The angiotensin-converting enzyme insertion/deletion polymorphism modifies the clinical outcome in patients with Pompe disease. Genet Med 12(4):206–211
26. Pfeffer G, Chinnery PF (2013) Diagnosis and treatment of mitochondrial myopathies. Ann Med 45:4–16
27. Kaufmann P, Engelstad K, Wei Y, Kulikova R, Oskoui M, Battista V et al (2009) Protean phenotypic features of the A3243G mitochondrial DNA mutation. Arch Neurol 66(1):85–91
28. Pfeffer G, Sirrs S, Wade NK, Mezei MM (2011) Multisystem disorder in late-onset chronic progressive external ophthalmoplegia. Can J Neurol Sci 38(1):119–123
29. Smits BW, Heijdra YF, Cuppen FW, van Engelen BG (2011) Nature and frequency of respiratory involvement in chronic progressive external ophthalmoplegia. J Neurol 258(11): 2020–2025
30. Flaherty KR, Wald J, Weisman IM, Zeballos RJ, Schork MA, Blaivas M et al (2001) Unexplained exertional limitation: characterization of patients with a mitochondrial myopathy. Am J Respir Crit Care Med 164(3):425–432
31. Bindoff LA, Howell N, Poulton J, McCullough DA, Morten KJ, Lightowlers RN et al (1993) Abnormal RNA processing associated with a novel tRNA mutation in mitochondrial DNA. A potential disease mechanism. J Biol Chem 268(26):19559–19564
32. Hadjigeorgiou GM, Kim SH, Fischbeck KH, Andreu AL, Berry GT, Bingham P et al (1999) A new mitochondrial DNA mutation (A3288G) in the tRNA(leu(UUR)) gene associated with familial myopathy. J Neurol Sci 164(2):153–157
33. Yang CC, Hwang CC, Pang CY, Wei YH (1998) Mitochondrial myopathy with predominant respiratory dysfunction in a patient with A3243G mutation in the mitochondrial tRNA(-leu(UUR))gene. J Formos Med Assoc 97(10):715–719
34. Kleinle S, Schneider V, Moosmann P, Brandner S, Krahenbuhl S, Liechti-Gallati S (1998) A novel mitochondrial tRNA(phe) mutation inhibiting anticodon stem formation associated with a muscle disease. Biochem Biophys Res Commun 247(1): 112–115
35. Goto Y, Tojo M, Tohyama J, Horai S, Nonaka I (1992) A novel point mutation in the mitochondrial tRNA(leu)(UUR) gene in a family with mitochondrial myopathy. Ann Neurol 31(6): 672–675
36. Cros D, Palliyath S, DiMauro S, Ramirez C, Shamsnia M, Wizer B (1992) Respiratory failure revealing mitochondrial myopathy in adults. Chest 101(3):824–828
37. Desnuelle C, Pellissier JF, Serratrice G, Pouget J (1988) Chronic progressive external ophthalmoplegia (CPEO) associated with diaphragm paralysis: successful treatment with coenzyme Q (CoQ). Neurology 38(suppl):102
38. O'Brien A, Blaivas M, Albers J, Wald J, Watts C (1998) A case of respiratory muscle weakness due to cytochrome *c* oxidase enzyme deficiency. Eur Respir J 12(3):742–744
39. Baker SK, Vladutiu GD, Peltier WL, Isackson PJ, Tarnopolsky MA (2008) Metabolic myopathies discovered during investigations of statin myopathy. Can J Neurol Sci 35(1):94–97
40. Manni R, Piccolo G, Banfi P, Cerveri I, Bruschi C, Zoia C et al (1991) Respiratory patterns during sleep in mitochondrial myopathies with ophthalmoplegia. Eur Neurol 31(1):12–17
41. Carroll JE, Zwillich C, Weil JV, Brooke MH (1976) Depressed ventilatory response in oculocraniosomatic neuromuscular disease. Neurology 26(2):140–146
42. Barohn RJ, Clanton T, Sahenk Z, Mendell JR (1990) Recurrent respiratory insufficiency and depressed ventilatory drive complicating mitochondrial myopathies. Neurology 40(1):103–106
43. Feit H, Kirkpatrick J, Van Woert MH, Pandian G (1983) Myoclonus, ataxia, and hypoventilation: response to L-5-hydroxytryptophan. Neurology 33(1):109–112
44. Tatsumi C, Takahashi M, Yorifuji S, Nishikawa Y, Kitaguchi M, Hashimoto S et al (1988) Mitochondrial encephalomyopathy with sleep apnea. Eur Neurol 28(2):64–69
45. Sembrano E, Barthlen GM, Wallace S, Lamm C (1997) Polysomnographic findings in a patient with the mitochondrial encephalomyopathy NARP. Neurology 49(6):1714–1717
46. Voduc N, Webb KA, D'Arsigny C, McBride I, O'Donnell DE (2004) McArdle's disease presenting as unexplained dyspnea in a young woman. Can Respir J 11(2):163–167
47. Kiechl S, Willeit J, Vogel W, Kohlendorfer U, Poewe W (1999) Reversible severe myopathy of respiratory muscles due to adult-onset type III glycogenosis. Neuromuscul Disord 9(6–7):408–410

48. Kaminsky P, Poussel M, Pruna L, Deibener J, Chenuel B, Brembilla-Perrot B (2011) Organ dysfunction and muscular disability in myotonic dystrophy type 1. Medicine (Baltimore) 90(4):262–268
49. Jammes Y, Pouget J, Grimaud C, Serratrice G (1985) Pulmonary function and electromyographic study of respiratory muscles in myotonic dystrophy. Muscle Nerve 8(7):586–594
50. Laberge L, Begin P, Dauvilliers Y, Beaudry M, Laforte M, Jean S et al (2009) A polysomnographic study of daytime sleepiness in myotonic dystrophy type 1. J Neurol Neurosurg Psychiatry 80(6):642–646
51. Yu H, Laberge L, Jaussent I, Bayard S, Scholtz S, Raoul M et al (2011) Daytime sleepiness and REM sleep characteristics in myotonic dystrophy: a case–control study. Sleep 34(2):165–170
52. Giubilei F, Antonini G, Bastianello S, Morino S, Paolillo A, Fiorelli M et al (1999) Excessive daytime sleepiness in myotonic dystrophy. J Neurol Sci 164(1):60–63
53. van der Meche FG, Bogaard JM, van der Sluys JC, Schimsheimer RJ, Ververs CC, Busch HF (1994) Daytime sleep in myotonic dystrophy is not caused by sleep apnoea. J Neurol Neurosurg Psychiatry 57(5):626–628
54. Romigi A, Izzi F, Pisani V, Placidi F, Pisani LR, Marciani MG et al (2011) Sleep disorders in adult-onset myotonic dystrophy type 1: a controlled polysomnographic study. Eur J Neurol 18(9):1139–1145
55. Kiyan E, Okumus G, Cuhadaroglu C, Deymeer F (2010) Sleep apnea in adult myotonic dystrophy patients who have no excessive daytime sleepiness. Sleep Breath 14(1):19–24
56. Nugent AM, Smith IE, Shneerson JM (2002) Domiciliary-assisted ventilation in patients with myotonic dystrophy. Chest 121(2):459–464
57. Annane D, Moore DH, Barnes PR, Miller RG (2006) Psychostimulants for hypersomnia (excessive daytime sleepiness) in myotonic dystrophy. Cochrane Database Syst Rev 3:CD003218
58. Orlikowski D, Chevret S, Quera-Salva MA, Laforet P, Lofaso F, Verschueren A et al (2009) Modafinil for the treatment of hypersomnia associated with myotonic muscular dystrophy in adults: a multicenter, prospective, randomized, double-blind, placebo-controlled, 4-week trial. Clin Ther 31(8):1765–1773
59. Mercuri E, Brockington M, Straub V, Quijano-Roy S, Yuva Y, Herrmann R et al (2003) Phenotypic spectrum associated with mutations in the fukutin-related protein gene. Ann Neurol 53(4):537–542
60. Poppe M, Cree L, Bourke J, Eagle M, Anderson LV, Birchall D et al (2003) The phenotype of limb-girdle muscular dystrophy type 2I. Neurology 60(8):1246–1251
61. Bourteel H, Vermersch P, Cuisset JM, Maurage CA, Laforet P, Richard P et al (2009) Clinical and mutational spectrum of limb-girdle muscular dystrophy type 2I in 11 French patients. J Neurol Neurosurg Psychiatry 80(12):1405–1408
62. Boito CA, Melacini P, Vianello A, Prandini P, Gavassini BF, Bagattin A et al (2005) Clinical and molecular characterization of patients with limb-girdle muscular dystrophy type 2I. Arch Neurol 62(12):1894–1899
63. Poppe M, Bourke J, Eagle M, Frosk P, Wrogemann K, Greenberg C et al (2004) Cardiac and respiratory failure in limb-girdle muscular dystrophy 2I. Ann Neurol 56(5):738–741
64. Patel ND, Jannapureddy SR, Hwang W, Chaudhry I, Boriek AM (2003) Altered muscle force and stiffness of skeletal muscles in alpha-sarcoglycan-deficient mice. Am J Physiol Cell Physiol 284(4):C962–C968
65. Politano L, Nigro V, Passamano L, Petretta V, Comi LI, Papparella S et al (2001) Evaluation of cardiac and respiratory involvement in sarcoglycanopathies. Neuromuscul Disord 11(2):178–185
66. Walter MC, Dekomien G, Schlotter-Weigel B, Reilich P, Pongratz D, Muller-Felber W et al (2004) Respiratory insufficiency as a presenting symptom of LGMD2D in adulthood. Acta Myol 23(1):1–5
67. Selcen D (2011) Myofibrillar myopathies. Neuromuscul Disord 21(3):161–171
68. Kley RA, Hellenbroich Y, van der Ven PF, Furst DO, Huebner A, Bruchertseifer V et al (2007) Clinical and morphological phenotype of the filamin myopathy: a study of 31 german patients. Brain 130(Pt 12):3250–3264
69. Walter MC, Reilich P, Huebner A, Fischer D, Schroder R, Vorgerd M et al (2007) Scapuloperoneal syndrome type kaeser and a wide phenotypic spectrum of adult-onset, dominant myopathies are associated with the desmin mutation R350P. Brain 130(Pt 6):1485–1496
70. Selcen D, Engel AG (2003) Myofibrillar myopathy caused by novel dominant negative alpha B-crystallin mutations. Ann Neurol 54(6):804–810
71. Selcen D, Muntoni F, Burton BK, Pegoraro E, Sewry C, Bite AV et al (2009) Mutation in BAG3 causes severe dominant childhood muscular dystrophy. Ann Neurol 65(1):83–89
72. Olive M, Odgerel Z, Martinez A, Poza JJ, Bragado FG, Zabalza RJ et al (2011) Clinical and myopathological evaluation of early- and late-onset subtypes of myofibrillar myopathy. Neuromuscul Disord 21:533–542
73. Boriek AM, Capetanaki Y, Hwang W, Officer T, Badshah M, Rodarte J et al (2001) Desmin integrates the three-dimensional mechanical properties of muscles. Am J Physiol Cell Physiol 280(1):C46–C52
74. Palmio J, Evila A, Chapon F, Tasca G, Xiang F, Bradvik B et al (2013) Hereditary myopathy with early respiratory failure: occurrence in various populations. J Neurol Neurosurg Psychiatry 85(3):345–353
75. Pfeffer G, Barresi R, Wilson IJ, Hardy SA, Griffin H, Hudson J et al (2014) Titin founder mutation is a common cause of myofibrillar myopathy with early respiratory failure. J Neurol Neurosurg Psychiatry 85(3):331–338
76. Izumi R, Niihori T, Aoki Y, Suzuki N, Kato M, Warita H et al (2013) Exome sequencing identifies a novel TTN mutation in a family with hereditary myopathy with early respiratory failure. J Hum Genet 58(5):259–266
77. Pfeffer G, Elliott HR, Griffin H, Barresi R, Miller J, Marsh J et al (2012) Titin mutation segregates with hereditary myopathy with early respiratory failure. Brain 135(Pt 6):1695–1713
78. Ohlsson M, Hedberg C, Bradvik B, Lindberg C, Tajsharghi H, Danielsson O et al (2012) Hereditary myopathy with early respiratory failure associated with a mutation in A-band titin. Brain 135(Pt 6):1682–1694
79. Toro C, Olive M, Dalakas MC, Sivakumar K, Bilbao JM, Tyndel F et al (2013) Exome sequencing identifies titin mutations causing hereditary myopathy with early respiratory failure (HMERF) in families of diverse ethnic origins. BMC Neurol 13:29
80. Lange S, Xiang F, Yakovenko A, Vihola A, Hackman P, Rostkova E et al (2005) The kinase domain of titin controls muscle gene expression and protein turnover. Science 308(5728):1599–1603
81. Hedberg C, Melberg A, Dahlbom K, Oldfors A (2013) Hereditary myopathy with early respiratory failure is caused by mutations in the titin FN3 119 domain. Brain 137(Pt 4):e270
82. Lehtokari VL, Pelin K, Donner K, Voit T, Rudnik-Schoneborn S, Stoetter M et al (2008) Identification of a founder mutation in TPM3 in nemaline myopathy patients of turkish origin. Eur J Hum Genet 16(9):1055–1061
83. Clarke NF, Kolski H, Dye DE, Lim E, Smith RL, Patel R et al (2008) Mutations in TPM3 are a common cause of congenital fiber type disproportion. Ann Neurol 63(3):329–337
84. Laing NG, Wilton SD, Akkari PA, Dorosz S, Boundy K, Kneebone C et al (1995) A mutation in the alpha tropomyosin

gene TPM3 associated with autosomal dominant nemaline myopathy NEM1. Nat Genet 10(2):249
85. De Paula AM, Franques J, Fernandez C, Monnier N, Lunardi J, Pellissier JF et al (2009) A TPM3 mutation causing cap myopathy. Neuromuscul Disord 19(10):685–688
86. Waddell LB, Kreissl M, Kornberg A, Kennedy P, McLean C, Labarre-Vila A et al (2010) Evidence for a dominant negative disease mechanism in cap myopathy due to TPM3. Neuromuscul Disord 20(7):464–466
87. Munot P, Lashley D, Jungbluth H, Feng L, Pitt M, Robb SA et al (2010) Congenital fibre type disproportion associated with mutations in the tropomyosin 3 (TPM3) gene mimicking congenital myasthenia. Neuromuscul Disord 20(12):796–800
88. Lawlor MW, Dechene ET, Roumm E, Geggel AS, Moghadaszadeh B, Beggs AH (2010) Mutations of tropomyosin 3 (TPM3) are common and associated with type 1 myofiber hypotrophy in congenital fiber type disproportion. Hum Mutat 31(2):176–183
89. Cowling BS, Cottle DL, Wilding BR, D'Arcy CE, Mitchell CA, McGrath MJ (2011) Four and a half LIM protein 1 gene mutations cause four distinct human myopathies: a comprehensive review of the clinical, histological and pathological features. Neuromuscul Disord 21(4):237–251
90. Sarkozy A, Windpassinger C, Hudson J, Dougan CF, Lecky B, Hilton-Jones D et al (2011) Phenotypic heterogeneity in british patients with a founder mutation in the FHL1 gene. Eur J Hum Genet 19(10):1038–1044
91. Selcen D, Bromberg MB, Chin SS, Engel AG (2011) Reducing bodies and myofibrillar myopathy features in FHL1 muscular dystrophy. Neurology 77(22):1951–1959
92. Avram C, Angus R, Ford V, Ward K, Parker R (2011) XMPMA: acute on chronic ventilatory failure managed successfully with non-invasive ventilation. JRSM Short Rep 2(11):84
93. Windpassinger C, Schoser B, Straub V, Hochmeister S, Noor A, Lohberger B et al (2008) An X-linked myopathy with postural muscle atrophy and generalized hypertrophy, termed XMPMA, is caused by mutations in FHL1. Am J Hum Genet 82(1):88–99
94. Satoyoshi E, Kinoshita M (1977) Oculopharyngodistal myopathy. Arch Neurol 34(2):89–92
95. van der Sluijs BM, ter Laak HJ, Scheffer H, van der Maarel SM, van Engelen BG (2004) Autosomal recessive oculopharyngodistal myopathy: a distinct phenotypical, histological, and genetic entity. J Neurol Neurosurg Psychiatry 75(10):1499–1501
96. Durmus H, Laval SH, Deymeer F, Parman Y, Kiyan E, Gokyigiti M et al (2011) Oculopharyngodistal myopathy is a distinct entity: clinical and genetic features of 47 patients. Neurology 76(3):227–235
97. Teixeira A, Cherin P, Demoule A, Levy-Soussan M, Straus C, Verin E et al (2005) Diaphragmatic dysfunction in patients with idiopathic inflammatory myopathies. Neuromuscul Disord 15(1):32–39
98. Marie I, Hachulla E, Cherin P, Hellot MF, Herson S, Levesque H et al (2005) Opportunistic infections in polymyositis and dermatomyositis. Arthritis Rheum 53(2):155–165
99. Kalluri M, Oddis CV (2010) Pulmonary manifestations of the idiopathic inflammatory myopathies. Clin Chest Med 31(3):501–512
100. Blumbergs PC, Byrne E, Kakulas BA (1984) Polymyositis presenting with respiratory failure. J Neurol Sci 65(2):221–229
101. Sano M, Suzuki M, Sato M, Sakamoto T, Uchigata M (1994) Fatal respiratory failure due to polymyositis. Intern Med 33(3):185–187
102. Dejardin Botelho A, Perez T, Pouwels S, Wallaert B, Hachulla E, Tillie-Leblond I (2008) Inspiratory muscle myopathy and antisynthetase syndrome. Rev Med Intern 29(4):325–327
103. Selva-O'Callaghan A, Sanchez-Sitjes L, Munoz-Gall X, Mijares-Boeckh-Behrens T, Solans-Laque R, Angel Bosch-Gil J et al (2000) Respiratory failure due to muscle weakness in inflammatory myopathies: maintenance therapy with home mechanical ventilation. Rheumatology (Oxford) 39(8):914–916
104. Sherer Y, Shepshelovich D, Shalev T, Haviv Y, Segal E, Ehrenfeld M et al (2007) Outcome of patients having dermatomyositis admitted to the intensive care unit. Clin Rheumatol 26(11):1851–1855
105. Cohen R, Lipper S, Dantzker DR (1993) Inclusion body myositis as a cause of respiratory failure. Chest 104(3):975–977
106. Ryan MM, Schnell C, Strickland CD, Shield LK, Morgan G, Iannaccone ST et al (2001) Nemaline myopathy: a clinical study of 143 cases. Ann Neurol 50(3):312–320
107. Chahin N, Selcen D, Engel AG (2005) Sporadic late onset nemaline myopathy. Neurology 65(8):1158–1164
108. Dalakas MC, Pezeshkpour GH, Flaherty M (1987) Progressive nemaline (rod) myopathy associated with HIV infection. N Engl J Med 317(25):1602–1603
109. Pavlu J, Carey MP, Winer JB (2006) Hypothyroidism and nemaline myopathy in an adult. J Neurol Neurosurg Psychiatry 77(5):708–709
110. Gyure KA, Prayson RA, Estes ML (1997) Adult-onset nemaline myopathy: a case report and review of the literature. Arch Pathol Lab Med 121(11):1210–1213
111. Falga-Tirado C, Perez-Peman P, Ordi-Ros J, Bofill JM, Balcells E (1995) Adult onset of nemaline myopathy presenting as respiratory insufficiency. Respiration 62(6):353–354
112. Kudou M, Kobayashi Y, Yamashita K, Kita H, Yasuba H, Hamada K (2006) Two cases of nemaline myopathy diagnosed after episodes of respiratory failure. Nihon Kokyuki Gakkai Zasshi 44(6):474–478
113. Kelly E, Farrell MA, McElvaney NG (2008) Adult-onset nemaline myopathy presenting as respiratory failure. Respir Care 53(11):1490–1494
114. Jungbluth H, Sewry CA, Brown SC, Nowak KJ, Laing NG, Wallgren-Pettersson C et al (2001) Mild phenotype of nemaline myopathy with sleep hypoventilation due to a mutation in the skeletal muscle alpha-actin (ACTA1) gene. Neuromuscul Disord 11(1):35–40
115. de Sanctis JT, Cumbo-Nacheli G, Dobbie D, Baumgartner D (2008) HIV-associated nemaline rod myopathy: role of intravenous immunoglobulin therapy in two persons with HIV/AIDS. AIDS Read. 18(2):90–94
116. Dewberry RG, Schneider BF, Cale WF, Phillips LH 2nd (1993) Sarcoid myopathy presenting with diaphragm weakness. Muscle Nerve 16(8):832–835
117. Tanios MA, El Gamal H, Epstein SK, Hassoun PM (2004) Severe respiratory muscle weakness related to long-term colchicine therapy. Respir Care 49(2):189–191
118. Simonds AK (2006) Recent advances in respiratory care for neuromuscular disease. Chest 130(6):1879–1886
119. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ (2006) Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol 5(2):140–147
120. Guenther UP, Handoko L, Varon R, Stephani U, Tsao CY, Mendell JR et al (2009) Clinical variability in distal spinal muscular atrophy type 1 (DSMA1): determination of steady-state IGHMBP2 protein levels in five patients with infantile and juvenile disease. J Mol Med 87(1):31–41
121. Kyriakides T, Papacostas S, Papanicolaou E, Bagdades E, Papathanasiou ES (2011) Sleep hypoventilation syndrome and respiratory failure due to multifocal motor neuropathy with conduction block. Muscle Nerve 43(4):610–614
122. Gracey DR, Southorn PA (1987) Respiratory failure in lambert-eaton myasthenic syndrome. Chest 91(5):716–718

123. Nicolle MW, Stewart DJ, Remtulla H, Chen R, Bolton CF (1996) Lambert-eaton myasthenic syndrome presenting with severe respiratory failure. Muscle Nerve 19(10): 1328–1333
124. Ohno K, Tsujino A, Brengman JM, Harper CM, Bajzer Z, Udd B et al (2001) Choline acetyltransferase mutations cause myasthenic syndrome associated with episodic apnea in humans. Proc Natl Acad Sci USA 98(4):2017–2022
125. Milone M, Shen XM, Selcen D, Ohno K, Brengman J, Iannaccone ST et al (2009) Myasthenic syndrome due to defects in rapsyn: clinical and molecular findings in 39 patients. Neurology 73(3):228–235