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Review

The clinical management of neuromuscular disorders in intensive care

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Abstract

Life-threatening neuromuscular disorders affect a small, but growing group of patients in the intensive care unit who present special management problems, as well as great therapeutic opportunities. In inflammatory conditions, a cure is often possible, and for chronic, genetic or degenerative conditions, achieving the previous level of function is the target. Neuromuscular experts and intensivists need to cooperate closely to achieve the best possible outcomes. They need to acquire a very specific set of skills, including both a thorough understanding of the mechanics of ventilation as well as familiarity with the diagnostic categories of genetic and of autoimmune diseases. This review of the clinical management of adult neuromuscular disease in the ICU aims to provide an overview of the most important conditions encountered in the ICU and a practical approach to their diagnosis, monitoring, and treatment.

Keywords: Neuromuscular respiratory mechanics; Guillain Barré syndrome; Myasthenic crisis; Myopathy with early respiratory failure; Rhabdomyolysis; ICU acquired weakness.

1. Introduction

Neuromuscular conditions are the primary cause for admission in less than 0.5% of cases referred to the intensive care unit (ICU) [1], consisting of either severe, newly acquired neuromuscular diseases, or complications of a pre-existing disorder requiring organ support. New onset acquired neuromuscular conditions are associated with long stays in the ICU, but their ultimate prognosis is good compared with other neurological disorders. ICU-acquired weakness secondary to critical illness is very common, and can be a major cause for disability in survivors of critical illness. With chronic neuromuscular disease, intensive care physicians need to understand the particular situation of individuals who have always lived with muscular dystrophy, have little or no cognitive limitations, and who have often created an independent life for themselves where environmental control systems are increasingly compensating for physical disability.

Overall, our knowledge of the field remains incomplete and there has been a telling paucity of treatment trials - surprising particularly because it is a major health problem which may increase with increasing longevity and successful critical care management. Some useful recommendations can be given, even though they are mostly based on empiricism and keen observation of experts over many years, and the authors aim to provide an overview of current understanding of neuromuscular disease seen in the ICU.

2. The patient with an acute neuromuscular emergency

Intensive care of the neuromuscular case begins when an acutely deteriorating patient in the Emergency Department or on the ward is assessed for admission to the ICU. Neuromuscular emergencies may present with rapidly worsening weakness, respiratory failure and infection; oropharyngeal weakness and aspiration; cardiac failure, or cardiac dysrhythmia; dysautonomia; or acute rhabdomyolysis. The initial diagnostic consideration is whether the problem of truly new onset, or whether there is an underlying chronic neuromuscular condition, indicated by developmental delay or disability, pre-existing respiratory or cardiac problems or a relevant family history. Toxins or neuromuscular depressant drugs must be excluded. The examiner looks for contractures (suggesting particularly Emery–Dreifus or

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Bethlem myopathy), cataracts (myotonic dystrophy), or special constitutional features (congenital myopathies), and signs of systemic involvement. Areflexia, dysautonomia and flaccid tone may suggest a neurogenic disorder; preserved reflexes are more likely in acute myopathy or disorders of the neuromuscular junction. The pattern of muscle weakness and atrophy may suggest a specific genetic myopathy. Fatiguing weakness in diseases of the neuromuscular junction may only be apparent when sustained innervation is tested and is often overlooked. Assessment of respiratory mechanics and oropharyngeal function has priority to determine triage to monitoring in the intensive care or to immediate intervention. Respiratory assistance in most situations involves endotracheal intubation and positive pressure ventilation but some marginally affected patients could benefit from non-invasive measures; NIV may be the main option when invasive ventilation is not desired, as frequently the case in ALS. A general recommendation would be to err on the side of caution and admit patients to an ICU – even for 24 h. Monitoring on the ward is fraught with danger and rapid response teams are often called in. Arguably, emergency intubation of a cyanotic hypoxemic patient, or in a patient who has already developed significant hypercapnia generally indicates inadequate monitoring. Such situations can be avoided with a clear institutional protocol for ICU transfer that takes into account the patient's background and specifies when monitoring in the high dependency unit, and when interventions such as intubation, are appropriate.

The assessment of respiratory and oropharyngeal function takes in the patient's clarity of voice; counting to 20 in one breath; ability to lie flat; strength of swallow, cough and head flexion, tachypnea, orthopnea and use of auxiliary respiratory muscles. Normal breathing is largely accomplished by contraction of the diaphragm, responsible for most of the inspiratory effort [2]. Once insufficient, inspiration is automatically supported by external intercostals, scalene, and sterno-cleidomastoid muscles. Abdominal wall muscles play an important role – not in the respiration cycle but when a forceful cough is needed. Clearing secretions in a patient with oropharyngeal weakness therefore may be quite dependent on this muscle group forming an effective "belly band". Failure of the diaphragm to provide a solid inspiratory force will lead to hypoventilation and failure of alveoli deployment leading to shutdown, oxygen shunting and hypoxia. Furthermore, poor gas exchange in turn leading to tachypnoea and later hypercapnia. Tachypnoea is a consequence of signals to the respiratory centre from the abnormal respiratory muscles. $PaCO_2$ will decrease due to this rapid breathing; but when respiratory muscle strength declines, $PaCO_2$ will increase again. This subtle rise or falsely normal PaCO2 will indicate to the physician that systems are beginning to fail. Paradoxical breathing, also known as thoracoabdominal asynchrony, showing inward abdomen movement and little chest expansion only occurs with severe respiratory weakness. Such a clinical finding will be immediately urgent in acute settings but likely compensated for in more chronic conditions. Patients with chronic disorders such as motor neurone disease/ALS, Duchenne Muscular Dystrophy, or Myotonic Dystrophy may lapse into respiratory failure with very few of these symptoms, and indicators of chronic hypoventilation be lacking.

Detailed pulmonary function tests complete the assessment. Patients with diaphragmatic weakness show a fall in the forced vital capacity tested with the patient supine but definition of an abnormal test is not clear in many acute neurologic conditions. A high maximal inspiratory pressure (MIP) > 80 cmH_2O, particularly in combination with normal vital capacity (VC), makes a neuromuscular respiratory failure unlikely. In more slowly progressive neurologic disorders these pulmonary function tests are also important because – for example – a normal MIP in ALS means that the patient may be spared mechanical ventilation in 6 months. Peak expiratory cough flow (PECF) directly measures the strength of airway clearance and a PECF > 160 L/min (or 60 L/min at the endotracheal tube) correlates with extubation success [3]. A maximal expiratory pressure (MEP) > 60 cmH_2O may also predict the ability to cough in patients with neuromuscular disease and in one study in ALS, a MEP > 70 cmH_2O also was correlated with a > 50% predictive value of tracheostomy free survival. "Sniff pressures" can be used if there is facial or palatal weakness that precludes accurate mouth pressure measurement. Overnight pulse oximetry is an essential tool because nocturnal hypoventilation indicates respiratory muscle weakness in this setting. Transcutaneous capnography is not yet widely used in the acute setting.

Our clinical experience has taught us that it remains very difficult to be completely certain whether the patient is oxygenating well and not struggling. Pulmonary function tests can be unreliable not only due to poor patient effort but also poor coaching. The degree of limb weakness does not always coincide with involvement of the diaphragm, a discrepancy particularly common in Pompe disease, Bethlem myopathy, HMERF and ALS. In addition, respiratory tests that typically count the best measurement out of 5 attempts may not appreciate muscle fatiguing accurately, which may be misleading in myasthenia gravis (MG); repeated tests are essential. In Guillain Barré syndrome (GBS) we have found that critical values to consider intubation are VC < 20 ml/kg body weight, MIP < −30 H_20, and maximum expiratory pressure < 40 cm H_20 ("*20/30/40 rule*") [4].

Mechanical ventilatory support is often short term in MG, prolonged in GBS [5], and permanent in genetic or degenerative muscle disorders. In ventilated patients with a treatable neuromuscular disorder, improved strength will need a plan for weaning from the ventilator, which may include a plan to institute non-invasive nocturnal ventilation as a permanent or bridging measure. Weaning methods may vary. Patients can be switched to continuous positive airway pressure (CPAP) with pressure support ventilation (PSV) and the level decreased 1–3 cm H_2O each day. Reducing intermittent mandatory ventilation rate or reducing pressure support level can be used as weaning approaches, at the discretion of the treating physician. Novel techniques may

improve weaning, but there is no published experience in neuromuscular patients yet [6].

3. Newly acquired neuromuscular disorders in the ICU

Newly acquired neuromuscular disorders may be admitted to the ICU at presentation or during the early course include: Guillain Barré syndrome and other severe neuropathies or the "acute flaccid paralysis syndrome; myasthenic crisis and other disorders of neuromuscular transmission; and acute inflammatory or toxic muscle disease. Undiagnosed chronic, often genetic, muscle disease may present to ICU as a seemingly new acquired disorder, through respiratory infections or other factors, when longstanding asymptomatic weakness decompensates; these are discussed in section II.

3.1. Guillain Barré syndrome (GBS; acute inflammatory demyelinating polyneuropathy) in the ICU

GBS is the polyneuropathy most often seen in the ICU, with up to 30% of patients requiring respiratory support [7]. Weakness and areflexia commonly develop in an ascending pattern over 1–2 weeks and are preceded by a gastrointestinal or respiratory infection. Its incidence has remained stable to 1–2 cases per 100,000 people over several decades. Depending on the definition, dysautonomia occurs in up to 70% of patients in the ICU, manifesting as arrhythmias, tachycardia, diaphoresis, labile blood pressures, urinary retention, or adynamic ileus. Reasons for admission to the ICU are respiratory compromise, oropharyngeal weakness, and, rarely, severe dysautonomia.

For differential diagnoses of GBS we refer the reader to the standard literature. Confounders that may present directly to intensive care include vasculitic neuropathy, which can be suspected if there is evidence for a mononeuritis multiplex course, systemic or skin features, or relevant serology; paraneoplastic neuropathy, which is often combined with non-neurological or non-neuromuscular neurological features and a poor response to treatment. Infections and toxic neuropathies caused by environmental agents or drugs need to be excluded, and neoplastic infiltration or intravascular lymphoma occasionally cause severe progressive neuropathy requiring histological diagnosis (Fig. 1). The term „acute flaccid paralysis syndrome" is used in connection with acute anterior horn cell disease (West Nile Virus, Polio) and viral acute myelitis "plus" syndromes predominantly caused by Enterovirus D68/E71, Zika, Hepatitis E, which are increasing in some geographical regions.

Once the patient is mechanically ventilated, a prolonged ICU stay is anticipated, and in our experience, if the patient cannot be extubated within a few day, ventilatory support is likely to be prolonged so there is no benefit from deferring tracheotomy beyond the first week. A high number of patients will need tracheostomy despite early treatment with plasma exchange (PLEX) or intravenous immunoglobulins (IVIg); IVIg is more readily available, but significantly more expensive in most countries. Some have suggested that

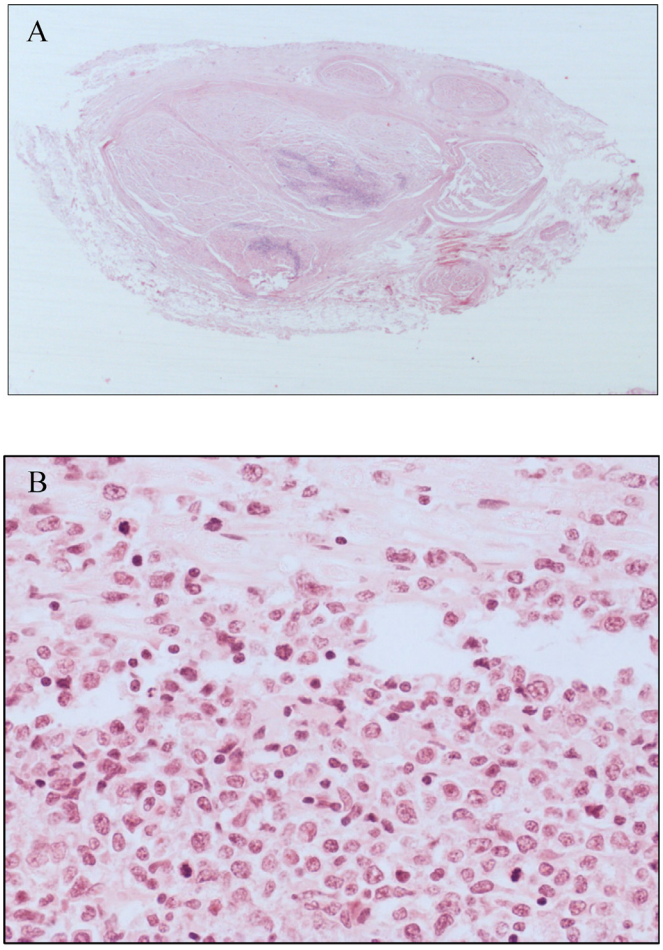

Fig. 1. Diffuse lymphomatous infiltration of peripheral nerves causing subacute neuropathy with 1 month accelerated progression to respiratory failure and death. Diagnosed as Guillain Barre Syndrome but refractory to two courses of IVIG and PLEX. (A) HE stain of left ulnar nerve at autopsy showing endoneurial infiltration. (B) HE x40 showing malignant lymphoreticular infiltrate.

patients whose IgG fails to rise after the initial course of IVIg might benefit from repeat treatment [8] but this measurement has not found a way into clinical practice. Currently, there is no clear evidence for superiority of either method over the other [9–11]. We suspect many neurologists would use combinations of treatment or additional courses of IVIG or PLEX.

Autonomic dysfunction includes orthostatic hypotension, diabetes insipidus, sensitivity to drugs, and cardiac dysrythmia. It is uncertain how to predict when moderate tachycardia and absence of heart rate variability will progress into a life-threatening complication such as the brady/tachycardia syndrome or asystole, which may occur in up to 20% and cannot be predicted by standard autonomic tests. Vagal spells with bronchorrhea, bradycardia and hypotension may be triggered by invasive procedures and cholinergic drugs, and SIADH may cause hyponatremia. Hypertension and persistent tachycardia affect over 50% of ventilated GBS patients [10]. The posterior reversible encephalopathy syndrome (PRES) may occur as a central

autonomic disturbance in GBS, affecting mainly women over 55y [11]. Neurogenic (Takotsubo) cardiomyopathy in GBS may be related to autonomic dysfunction [12].

The most severely affected patients with GBS may develop a locked in state where signaling has fully disappeared. This is mostly seen in an axonal variant and when symptoms progress in a matter of days. Recovery of these patients is very protracted with often more than 6 months of ventilatory support, and often incomplete.

With modern analgo-sedation patient comfort and tube tolerance can be ensured while allowing regular neurological assessment, and without deep sedation. Weaning from mechanical ventilation should be undertaken as early as possible because of the number of complications related to prolonged intubation. In GBS, diaphragmatic weakness may reverse before extremity weakness; thus, the timing of weaning should not be gauged solely by recovery of extremity muscle strength [13]. Mechanically ventilated patients have the ability to walk independently, which occurs in about 75% of the patients, and this may even extend up to two years after onset. Nonetheless, patients may show clinically significant improvement beyond 1–2 years, therefore aggressive rehabilitation is warranted. Mortality in GBS has been estimated at 3%, but doubles in long-term mechanically ventilated patients and may even approach 10–20% in patients with very significant co-morbidity, where pulmonary infections and sepsis are the leading causes of death, and urinary tract infections a further risk. [14]. Better ICU care and respiratory rehabilitation have much improved these percentages, and since 2/3 of deaths occur after ICU discharge, the quality of step-down care is crucial [1].

3.2. Myasthenia gravis (MG) in the ICU

MG is caused by an immune attack against nicotinic acetylycholine receptors (AchR) and related proteins (Muscle-Specific Kinase = MuSK; Low density lipoprotein receptor-related protein = LRP4) leading to a defective neuromuscular junction and fatigable focal or generalized weakness. Onset may be at any age but tends to be earlier in females (mean 28 years) than in males (mean 42 years), with an overall incidence of 0.5–5 cases per 100,000.

Myasthenic crisis occurs in 10–60% of MG patients [15], and is often understood as MG complicated by respiratory failure or oropharyngeal weakness requiring intubation and/or mechanical ventilation for more than 24 h. Patients with oropharyngeal and neck weakness often also have failure of respiratory muscles, and both neck flexion and extension need to be tested. Patients with overdose of cholinergic drugs may present with massive secretions and diarrhea but this rarely leads to respiratory weakness. Usually the need for ventilatory support in MG follows weakness of diaphragmatic or accessory respiratory muscles, but mechanical ventilation also may become necessary because of airway collapse from oropharyngeal muscle weakness, stridor from vocal cord weakness [16], or the inability to clear secretions. Large series have reported that a third of the patients may have recurrent myasthenic crisis, pointing towards some individual predisposition.

Precipitating causes include mundane viral or bacterial infection in 48% (pneumonia, respiratory infection, or sepsis), aspiration in 10%, pyridostigmine dosing errors or incautious initiation of high dose IV corticosteroids, which may adversely affect neuromuscular transmission and diminish the effect of pyridostigmine [17], although this remains controversial and the exact reason is still unclear. Other precipitating factors are surgical procedures (particularly extensive thoracic or abdominal surgeries), pregnancy, emotional stress, or exposure to drugs with neuromuscular blocking action such as aminoglycosides, or, occasionally, botulinum toxin [18].

The experienced clinician can often recognise impending myasthenic crisis early enough to ward off full crisis through rescue treatment with IVIg or PLEX. Many experts feel that PLEX has a more rapid effect than IVIg, thought the evidence is limited. Regularly testing (and clearly documenting) fatigability, respiratory function, cough and swallowing in a deteriorating patient is key. A number of factors can make respiratory failure in MG difficult to recognize, foremost, its variability and more erratic course than GBS. Bedside observations can be misleading: in many cases, clinical features of respiratory failure such as tachypnoea, use of auxiliary respiratory muscles, and paradoxical breathing may not be observed in early stages; supraclavicular retraction and retraction of intercostal spaces are often a late sign and can signify a bronchus plug. Weak auxiliary muscles can further mask increased respiratory effort. Counting in one breath can useful to observe deterioration in an individual patient, but has not been standardised, and depending on whether counting is metronomic or “as fast as possible”, patients with normal VC may count as little as 10 or as much as 50. Priority is given to securing airways; and the patient should be intubated if in doubt. Medications that impair neuromuscular transmission should be avoided as far as possible, such as betablockers or aminoglycosides. Patients may have been overdosed with cholinesterase inhibitors and may have excessive salivation and sweating, abdominal cramps and urinary urgency. Pyridostigmine is discontinued at the start of mechanical ventilation to reduce bronchial secretions, and when it is reintroduced for weaning intravenous dose equivalents must be observed if given parenterally: intravenous pyridostigmine is approximately 30 times, and intravenous neostigmine 60 times as potent as the oral dose of pyridostigmine. It is feasible to start steroids in high doses such as 1 g intravenously, then 100 mg oral, similar to other acute autoimmune disorders in a ventilated patient, as an initial adverse effect on the neuromuscular junction is irrelevant. Thymectomy has a significant effect on outcome, after much controversy finally proven by the Thymectomy trial [19], but its benefit only becomes significant after months and the intervention is not commonly performed during myasthenic crisis; the situation may be different if there is a (possibly occult) thymoma with recurrent or refractory crises. MG associated with muscle specific tyrosine kinase (MuSK)

antibodies features prominent oculobulbar weakness, although generalized weakness eventually develops. Pyridostigmine is ineffective in MuSK positive MG and may even enhance synaptic dysfunction [20]; therefore, early PLEX and escalation of immunosuppressive treatment are advised, for instance to second line steroid sparing agents such as Rituximab or Tacrolimus. Antibodies associated with thymoma include anti-striational antibodies such as anti-Titin, anti-Ryanodine receptor and anti-Kv1.4 antibodies. Anti-Kv1.4 may also be associated with myocarditis [21].

The mortality rate for myasthenic crisis has declined from a nearly always fatal outcome in the 1920s to less than 5% in the 21th century. However, data from specialised centres may not reflect wider practice, and mortality in UK ICUs overall was found to be 8.7%, with acute hospital mortality from myasthenic crisis even reaching 22% [1]. The prognosis of myasthenia gravis may also depend on the presence of acute diaphragmatic failure and on timely therapy with higher mortality where PLEX was delayed. Other deaths can be attributed to belated admission to the ICU (suggesting shortcomings of ward-based monitoring, in particular of respiratory function with reliance on arterial blood gas measurements rather than lung function tests); inappropriate transfer from ITU to the general ward, and recurrent crises being refused re-admission. Cardiac failure can be observed in some patients, with neurogenic stunned myocardium possibly related to stress caused by MG crisis [22,23].

An initial trial of non-invasive ventilation using positive inspiratory pressure support or bilevel positive airway pressure (BiPAP) may reduce ventilator days [24], and early tracheotomy is unnecessary, as recovery from myasthenic crisis can be rapid. Before even attempting to wean the patient with MG from the ventilator, one priority is to have satisfactory treatment of the myasthenic symptoms. The patient should have no major pulmonary problem and no evidence of atelectasis, plural effusion, or marked difficulty handling secretions. Secretion volume, whether the patient is comfortable with a T-piece trial, and a completely normal chest x-ray, have a good predictive value for successful extubation. Pulmonary function tests can predict, in some sense, weaning but are far from reliable. It is important to reintroduce cholinesterase inhibitors before extubation trials are initiated.An optimal dose of pyridostigmine needs to be found and patients will not be able to be liberated from the ventilator without adequate treatment despite multiple courses of IVIg or plasma exchanges. The weaning process can be initiated once VC reaches 25 mL/kg and spontaneous tidal volumes of 10–12 mL/kg are attained. PI max exceeding –50 cm H_2O and VC improvement by 4 mL/kg from pre-intubation to pre-extubation are associated with successful extubation. There is still a relatively high risk of reintubation [25]; successful extubation is particularly hard to predict in MG, where fatigability can develop rapidly in a patient who hours before seemed safe. Repeated extubation failure is not predictive of outcome and does not imply "futility" of further intensive care treatment.

Generally speaking, onset of myasthenia gravis in middle age has less severe manifestations, low probability of full remission and higher mortality when compared with early onset myasthenia. The worse outcome can be expected in patients with malignant thymoma but only if the tumor has breached the capsule and caused metastasis. Ultimate quality of life is largely determined by the severity of muscle weakness (which may include weakness of neck muscles and constant head drop), dysphagia and chewing problems, ptosis, diplopia, speech impediment, and the secondary effects of immunosuppressive therapy, which may include recurrent infections, osteoporosis, cataract, or malignancy in patient under immunosuppression for many years [26,27].

Myasthenic patients who undergo surgery should have well planned perioperative management with input from their myasthenia specialist clinic; they should be stabilized as well as possible prior to surgery, and preoperative IVIg or PLEX can be useful. Anticholinesterase medications should be taken with the minimal interruption using intravenous equivalent doses. Prednisolone should remain unchanged and for major surgery hydrocortisone perioperative stress cover may be considered, for example 50 mg hydrocortisone at induction, and postoperatively 25 mg three times daily. Sugammadex can reverse neuromuscular blockade through vecuronium. The clinician must set the frequency for monitoring of postoperative FVCs according to each patient's requirements, and myasthenia scores can be used to motor function and fatiguability [28,29].

3.3. Acute inflammatory myopathies in the ICU

The classification of inflammatory myopathies goes back to Peter and Bohan [30] and was updated by the European Neuromuscular Centres workshop 119 [31]. There are still difficulties in separating dermatomyositis from polymyositis, with considerable immunological and clinical overlap and ongoing controversy whether polymyositis constitutes a real entity. Myositis-specific or myositis-associated antibodies can help differentiate clinico-serological spectra, and identify overlap syndromes, in which connective tissue disorders such as Sjogren's disease or rheumatoid arthritis are associated with inflammatory muscle disease [32]. Inclusion body myositis is generally seen as a separate entity and is rarely seen in the ICU, if so in advanced stages with complications of dysphagia and aspiration.

Acute inflammatory myopathy may require ICU admission through severe weakness, lung involvement (severe interstitial lung disease associated with antisynthetase syndromes) or cardiac complications (pulmonary hypertension, inflammation of the heart muscle or coronary vessels). Major cardiac pathology is rare, but significantly worsens prognosis. Diastolic dysfunction appears to be relatively common. Antimitochondrial antibodies may be particularly associated with severe cardiac disease [33]. ECG changes are seen in up to a third of cases, and should prompt a thorough cardiac workup; often they remain of uncertain significance, and in the authors' view do not then warrant prolonged

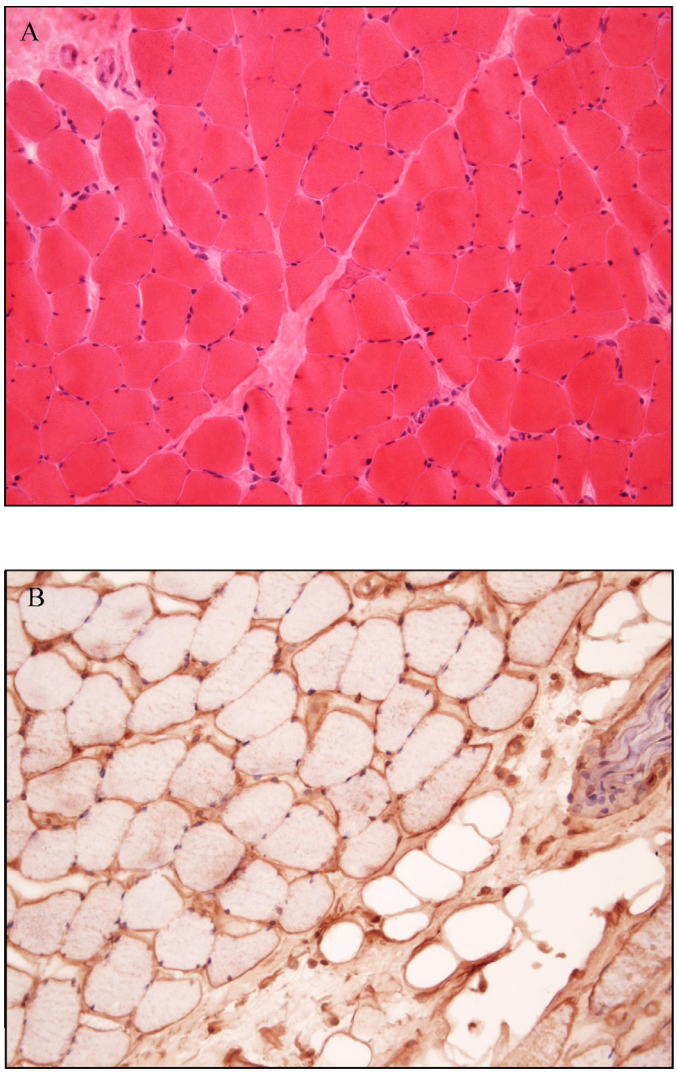

Fig. 2. 20 year old student, 6 weeks rash, dysphagia. 2 weeks limb weakness. 0.5 g/kg prednisolone/d given for 4 weeks prior to admission to ITU with respiratory failure (i.e. this patient was under-dosed prior to admission). (A) Normal routine histology with HE stain. (B) Upregulated MHC class 1 indication inflammatory disease despite normal HE stain.

ICU monitoring. In the authors' experience, inflammatory myopathies in the dermatomyositis spectrum, often associated with malignancy, and in the necrotizing spectrum ("immune-mediated necrotizing myopathy", IMNM) with anti-SRP and anti-HMGCR antibodies are most often seen in the ICU. It is important to request a muscle biopsy including specialist immune-histochemical antibody studies, because the immune-mediated nature of the condition may not be apparent in routine histological stains (Fig. 2). However, treatment should not be delayed while awaiting biopsy, complex histology or antibody tests. Intermittent pulse steroid regimens are increasingly used rather than conventional daily steroids (i.e. repeated 3 day IV methylprednisolone 1000 mg pulse treatments, or oral Dexametasone 40 mg on 4 consecutive days every 4 weeks) [34]. Additional immunomodulation is added according to the clinical response and antibody profile: immune-mediated necrotizing myopathy (IMNM) associated with anti-SRP antibody often presents as a rapidly progressive proximal myopathy, and most cases will need a second line immunosuppressant such as Rituximab [35–39]. In any inflammatory myopathy the ICU team must be reassured that there is a high chance of good recovery, even with severe prolonged weakness. Immunomodulation will take time, and mobility improves after months, so that skilled physiotherapy is needed from the start to prevent disabling contractures that delay rehabilitation and may even require surgery in patients who are often frail and elderly.

3.4. Acute rhabdomyolysis

Rhabdomyolysis is not well defined. By convention the term is understood as very high creatine kinase (CK) potentially causing renal failure and can be due to muscle ischemia, excessive physical exertion, toxicity including malignant hyperthermia [38] and serotonin syndrome [39], metabolic, endocrine disorders or paraneoplastic myopathy. Inflammatory myopathy can cause rhabdomyolysis; anti-MAS or anti-SRP antibodies are most often recognised. An increasing number of cases triggered by exertion or particular stresses in previously healthy patients are found to have a genetic cause or predisposition [40–45] (Table 1). Rhabdomyolysis is self-limiting and ICU treatment focuses on removing all potential causes of toxicity, adequate hydration, and sometimes a period of renal replacement. Muscle biopsy is unrewarding in the initial 4 weeks after acute rhabdomyolysis, and once toxic and environmental causes have been excluded, Next Generation Sequencing using a "rhabdomyolysis panel" is often a rapid and cost-effective way to achieve a diagnosis [46]. However, expertise is needed to avoid over-interpreting equivocal results, particularly due to the high frequency of atypical phenotypes.

3.5. Neuromuscular disease arising during treatment in the ICU

Patients in the general ICU without pre-existing neuromuscular disease who fail to wean from mechanical ventilation appropriately need to be screened for acute cerebral and spinal disorders, toxicity of many drugs used in the ICU (Table 2), and immunological derangements (Graft-versus-Host disease; side effects of immune checkpoint inhibitors) [47]. After these have been excluded, patients with symmetric weakness, often sparing facial and ocular muscles, often have a combination of critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) now termed "ICU-acquired weakness (ICU-AW)". ICU-AW affects about one third of patients who are ventilated for over 7 days, particularly those treated for sepsis and multiple organ failure. Electromyography does not separate CIP from CIM well [48], and muscle biopsies can show variably acute myosin-loss myopathy, necrotizing myopathy, or diffuse Type 2 fibre atrophy [49]. Acute myosin-loss myopathy is associated with steroid treatment and neuromuscular blocking agents in treatment for severe sepsis; inflammation, abnormal

Table 1
Genetic causes of rhabdomyolysis.

Categories of muscle disease	Mutations implicated	Triggers for rhabdomyolysis
Glycogenoses	PYGM, PFKM, ALDOA, ENO3, PGAM2, PGK1	Exercise (early), with cramps
Mitochondrial myopathies	POLG1, CO1, CO2, CO3, DGUOK	Prolonged exercise, toxicity
Fatty acid oxygenation disorders	CPT2, ACADVL, ETFDH	Prolonged exercise, fasting, fever, drugs, cold
Calcium trafficking disorders	RYR1, HOKPP	Dehydration,
Muscular dystrophies	ANO5, DMD, BMD, DYSF, FKRP, LIPN1, SIL1	Strenuous exercise

Table 2
Drugs commonly used in the ICU reported to cause severe myopathy. Note: this list is not exhaustive, and many reports rely on individual cases of multimorbid patients.

Drug category	Typical agents implicated
Anaesthetics	Halothane and other volatile agents, Fentanyl
Antiarrythmics	Amiodarone, especially combined with statins
Antiasthmatics	Terbutaline, Theophylline
Antidepressants	Trycyclics and selective serotonin antagonists (SSRIs)
Antimicrobials	Amphotericin B, Cotrimoxazole, Isoniazide, Levofloxacin, Linezolide Meropenem, Voriconazole
Antineoplastics	Cytarabine, Lenalidomide, Bortezomib, others
Antipsychotics	Phenothiazines, Haloperidol, Olanzapine, Quetiapine, Lithium
Cholesterol-lowering agents	Statins (particularly also drug interaction) and Fibrates
Corticosteroids	Dexamethasone
Diuretics	Furosemide
Immunosuppressants	Ciclosporin, Tacrolimus, Cyclophosphamide
Muscle relaxants	Succinylcholine (malignant hyperthermia), non-depolarising agents (acute myopathy)
Sedatives	Barbiturates (high doses) Propofol, Ketamine (mainly abuse)
Various	Vasopressin, Sodium valproate

protein metabolism, and deranged insulin metabolism may play a role [50–52]. Muscle biopsy rarely leads to specific treatment unless there is evidence of pre-existing neuromuscular weakness or antibody tests indicate anti-SRP, anti–HMGCR or other IMNM. One half of patients with ICU-AW recover fully with supportive treatment only. The combination of myopathy with significant neuropathy may worsen prognosis. ICU-AW remains poorly defined, but since it has been recognised as a major problem, coordinated research efforts are beginning to improve our understanding of its mechanisms and may lead to better prevention [53].

4. Pre-existing neuromuscular disease in the ICU

This section deals with chronic disorders in which ICU admission most often occurs during the later course, although the diagnosis has been made. These conditions are often genetic, although the majority of cases of ALS are non-hereditary.

4.1. Neurogenic disorders

Chronic neuropathies rarely cause admission to the ICU. Painful crises may complicate ICU treatment in patients with a neuropathy admitted for other reasons. Respiratory failure, not common in Charcot Marie Tooth (CMT) 1A, may be prominent in some variants of CMT. CMT2A (MFN2 mutations) and CMT2C (TRPV4) feature stridor and diaphragmatic failure; in CMT4A (GDAP1); CMT4B1 (MTMR2); and HMN6-SMARD1 (IGHMBP2) respiratory problems are well documented. Occasionally, acute intermittent porphyria may present as an acute neuromuscular disorder [54,55].

Amyotrophic lateral sclerosis (ALS) always progresses to respiratory failure, but 10% may present with respiratory symptoms. Admission to an ICU is often not part of the intended pathway, but this happens quite frequently due to acute decompensation over an infection precipitating respiratory distress earlier than anticipated, even despite careful follow up. The problem then arises that patients may not have made an advanced directive regarding their treatment preferences, and decisions are left to the next of kin and the ICU team. This situation can be avoided by timely multidisciplinary care and a discussion that allows an informed patient decision about the preferred priorities of treatment [56,57]. The rapid progression of weakness means that the level of function at the end of ICU care is almost always worse than on admission, in contrast with very chronic genetic diseases, where the previous levels of function can often be restored. Non-invasive home ventilation prolongs survival and improves quality of life [58,59]. The acceptance of invasive ventilation and tracheotomy, when NIV is no longer feasible, differs between countries: in Japan and in Italy, a substantial proportion of patients with ALS proceed to tracheotomy [60,61], but this seems to be less common in France and Switzerland [62] and is rare in the UK. Whereas the American Academy of Neurology provides guidance on the indications for invasive ventilation [63], the British National Institute of Clinical Excellence guideline from 2016 does not mention it as an option [64]. Independent of ethical controversy, it is clear that ventilator support places a significant burden on family, carers and community resources,

and it is often complicated by fronto-temporal syndrome in ALS patients [65]. Rarely, neurogenic cardiomyopathy in ALS causes dyspnoea and chest discomfort in the absence of coronary obstruction [66,67].

X-linked Spino-bulbar Muscular Atrophy (SBMA; Kennedy's disease).

This is the most common adult onset SMA with a prevalence of 20 per million population, causing bulbar, facial and symmetric limb weakness from the fourth decade of life, as well as gynecomastia due to an androgen receptor gene mutation. Respiratory failure, laryngospasm, dysphagia, or aspiration pneumonia may cause admission to the ICU [68]. Owing to its extremely slow progression, the considerations around ICU treatment resemble those of a progressive muscular dystrophy (see below) rather than ALS.

4.2. Genetic disorders of the neuromuscular junction

Congenital myasthenic syndromes (CMS) typically present in early childhood with ptosis, variable ophthalmoplegia, and often respiratory weakness. Some forms such as CMS 6 (Choline acetyltransferase – ChAT), CMS 11 (Rapsyn), CMS16 (SCN4A), and mutations in the δ subunit of the acetylcholine receptor gene (E381K) are associated with episodic respiratory arrest and require home apnoea monitors. Respiratory arrest becomes less frequent in adolescence, so ICU admission is rarely needed in adult life. Pyridostigmine helps in some, but not all cases; alternatives include 3,4-diaminopyridine (DAP), salbutamol, ephedrine and selective serotonin reuptake inhibitors, and an exact genetic diagnosis may aid the choice of medication [69]. The benefits of such treatment may be delayed but are worth exploring in aid of weaning, and there are reports that these medications may also provide benefit in congenital myopathies such as Dynamin2 (DNM2) and Myotubularin (MTM1) related congenital myopathies where neuromuscular junction abnormalities play a role [70,71].

4.3. Chronic myopathies in the ICU

The genetic conditions which can present with a pattern of respiratory failure in the absence of severe muscular symptoms or preceding disability, form a distinctive group. Naddaf and Milone found the most common diagnoses associated with early respiratory failure prior to loss of ambulation to be Pompe disease, myofibrillar myopathy, multi-minicore myopathy, and myotonic dystrophy [72], and this is a growing group.

Adults with Pompe disease (Acid Maltase deficiency or Glycogen storage disease type 2 – GSD2) suffer gradually progressive respiratory (especially diaphragmatic) failure and weakness. The onset may seem abrupt when precipitated by infection or other precipitants. Exercise intolerance with cramps, muscle pain, and mildly elevated creatine kinase may be longstanding as well as underbreathing during sleep. Diagnostic testing today is simplified with enzyme activity primarily tested in a dried blood spot and confirmed by a mutation analysis. It is important to think of this diagnosis as enzyme replacement treatment (ERT) with recombinant alglucosidase alpha is available [73]. Uncertainty remains about long term cost effectiveness, the patients' immune response to ERT, and emergence of new phenotypes under treatment [74].

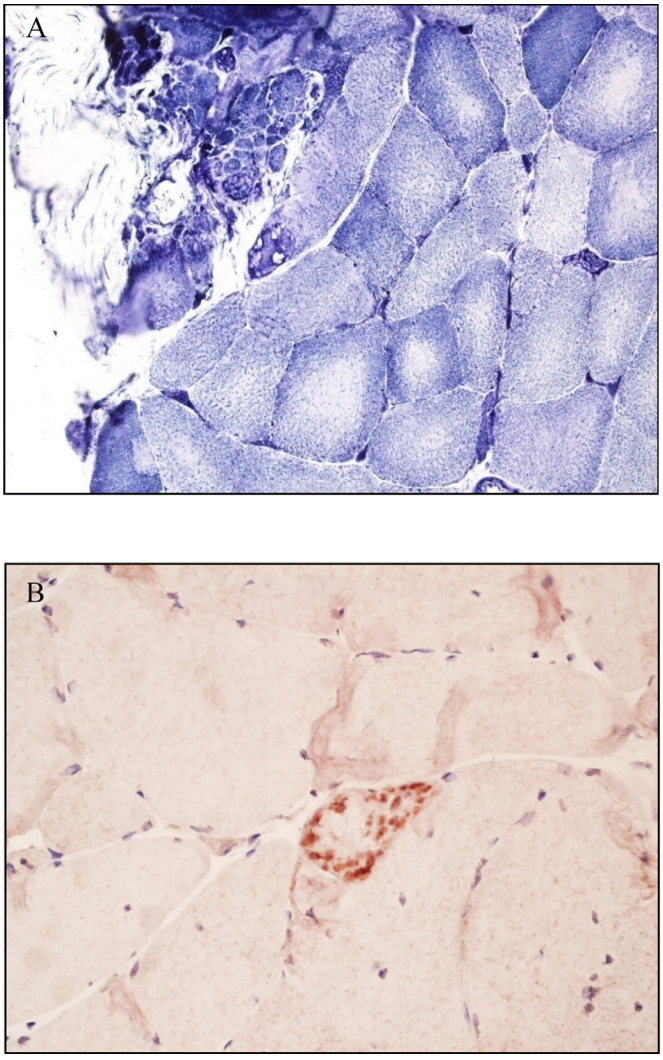

Fig. 3. A 58-year-old male, hiking at high altitude, developed increasing shortness of breath, acute respiratory failure. He was intubated, diagnosed with GBS and treated with IVIg; muscle biopsy was later performed as his delayed EMG appeared myopathic. Successful weaning from tracheotomy after 2 months to continued nocturnal non-invasive ventilation. Molecular analysis confirms a mutation in the FN3 119 domain of the Titin gene (Molecular analysis: Dr. Bjarne Udd, Tampere, Finland). (A) NAH-TR stain showing numerous "wiped-out" areas of disordered sarcomeric structure. (B) Myotilin stain showing aggregation of sarcomeric proteins.

Hereditary Myopathy with Early Respiratory Failure (HMERF) is typically due to mutations in the FN3 119 domain of exon 343 in the Titin gene (TTN) [75–77], combining prominent respiratory failure with proximal or distal weakness with or without cardiac involvement (Fig. 3). Other myofibrillar myopathies with various genetic backgrounds can also cause prominent respiratory failure and/or cardiac failure [78–80]. Myopathies in which

Table 3
Muscular dystrophies in which cardiomyopathy can be a prominent feature.

Myopathy (gene mutation)	Comments
Dystrophinopathy	Duchenne/Becker muscular dystrophy, including late onset Becker; some asymptomatic carriers
Myotilinopathy	LGMD1a and myofibrillar myopathy (MFM3); variable reports of cardiomyopathy, late feature [81,82]
Laminopathy (laminopathy)	LGMD 1B and EDMD 2 and 3 with tendency to conduction defects and ventricular fibrillation; allelic congenital cardiomyopathy syndromes
Desminopathy	LGMD 1E and myofibrillar myopathy (MFM1); majority of cases, can be presenting feature
LGMD 2C-F (sarcoglycanopathies)	<20% develop cardiomyopathy [83]
LGMD2I (Fukutin-related muscular dystrophy, FKRP)	A majority of cases develop cardiomyopathy; can be presenting feature. Arrhythmia less common [84]
Fukuyama congenital muscular dystrophy	Allelic familial cardiomyopathy CMD1X; late feature; less arrhythmia [85]
Myofibrillar myopathies	[82]

respiratory failure may occur disproportionately to limb weakness include late onset variants of structural myopathies, particularly myotubular myopathies (MTM1 mutations); centronuclear and cap myopathies; and nemaline rod myopathy (late cases with ACTA1 or Myopallidin = MYPN gene mutations). "Sporadic Late Onset Nemaline Myopathy" (SLONM) has no known genetic background but can be related to monoclonal gammopathy or HIV infection [86]; it can be successfully treated with chemotherapy /immunotherapy [87]. Rarely, muscular dystrophies including oculopharyngodistal muscular dystrophy, Bethlem myopathy, and some cases of limb girdle muscular dystrophy, especially Calpainopathy-LGMD2A or FKRP-LGMD2I), may cause respiratory failure, before severe limb weakness. Severe respiratory failure in congenital myopathies most often manifests in infancy, but can develop later in life, particularly in SEPN1, TPM3, ACTA1, NEB and DNM2 mutations [70].

Cardiac failure and arrhythmia may be the presenting symptom of otherwise minimal muscle disease. Particularly young patients with oligosymptomatic myotonic dystrophy may suffer cardiac arrest in the context of physical exertion [88,89]; rare cases present with fulminant cardiac failure. Muscular dystrophies commonly featuring cardiomyopathy are presented in Table 3; there is overlap with genetic cardiomyopathies, a number of which feature muscle weakness (e.g. Barth syndrome, Danon disease). Genetic classification can indicate appropriate cardiac treatment: patients with Emery Dreifus muscular dystrophy type 2 (Lamin A/C mutations) require implanted cardioverter/defibrillators [90] due to risk of ventricular fibrillation, whereas Emery Dreifus type 1 (Emerin mutations) need only pacemakers.

Patients with mitochondrial myopathies may be admitted to the ICU for severe weakness, aspiration and respiratory failure, which are essentially managed in the same way as other myopathies. Heart block is prominent in the Kearns–Sayre syndrome, and cardiomyopathy in a number of mitochondrial disorders, such as the A3243G (MELAS) mutation. In addition, mitochondrial diseases are often multisystemic with involvement of the central nervous system, in which seizures, status epilepticus and stroke-like episodes may be the leading problems. Metabolic derangements may be the cause of admission, or be triggered during treatment. Lactic acidosis is prominent, presumably caused by failure of the respiratory chain and aerobic metabolism. Whether elevated lactate itself can be toxic, or just a marker of metabolic failure, is unclear, but the key treatment for non-hypoxic (type B) lactic acidosis is minimising causative factors [91]. It is important to avoid medications with potential mitochondrial toxicity, and maintain good glycemic control and adequate perfusion. Medications with mitochondrial toxicity are a concern: sodium valproate can clearly cause hepatic injury in patients with Polymerase Gamma (POLG) mutations and should be avoided in mitochondrial disease [92,93]; antibiotics such as trimethoprim and linezolid can cause lactic acidosis and the latter has been reported to worsen mitochondrial disorders [94]; metformin and nucleoside analog reverse transcriptase inhibitors also cause hyperlacticemia. Importantly, propofol has been implicated as mitochondrion-toxic and the risk of propofol infusion syndrome may be increased in these patients [95]. Medication aimed at improving mitochondrial function is not of proven effectiveness in the ICU, but it is our practice to combine dietary measures [96] and treatment with Ubiquinone (400–600 mg per day), Riboflavine (400 mg per day), and Carnitine (3 g per day) empirically. Idebenone, a Ubiquinone analog that is now licenced for treating respiratory weakness in Duchenne Muscular Dystrophy may be considered, but as with other proposed therapies such as L-Arginine and Dichloracetate, our experience is limited.

4.4. Critical care in advanced chronic neuromuscular disease

Coordinated multidisciplinary care and timely interventions have vastly improved quality of life in patients with severe muscular dystrophy and doubled life expectancy for patients with Duchenne Muscular Dystrophy (DMD) [97], so the potential benefit for DMD patients from life-saving critical care treatment is today relatively greater. Patients can make informed decisions on their treatment preferences, including ceilings of care, if there has been a timely discussion. Weaning from the ventilator is invariably prolonged, but in experienced respiratory centres there is a high chance that patients will be liberated from the ventilator, and even that tracheotomy can be reversed. It must be clear that the disease trajectory is so slow that a level of function near the pre-ICU baseline can be achieved at the end of

weaning; advanced assistive support and environmental control systems have changed the perception of quality of life for people with severe paralysis [98,99]. Many features that influence recovery are determined by the quality of care in the community, for instance cardiac monitoring and timely provision of percutaneous gastrostomy or cough-assist devices. Home ventilation has banished the spectre that patients could remain "stranded" in the ICU with nowhere to go (at least in high income societies).

Patients with cardiomyopathy on the basis of a genetic muscle disease clearly can benefit from transplantation. Patients with Becker Muscular Dystrophy constitute approximately one half of muscular dystrophy patients who undergo cardiac transplantation. Provided that transplantation is not deferred until late complications reduce the chances of success, they achieve outcomes comparable to controls [100]. Cardiac assist devices may be considered as bridging to transplantation in frail patient, and the authors have had good experience with this strategy even in patients requiring a course of extracorporeal membrane oxygenation. Using cardiac assist devices as destination therapy remains controversial [101].

Anaesthetic complications in patients with severe, chronic myopathies include intraoperative heart failure, inhaled anaesthetic- and succinylcholine-related rhabdomyolysis and a malignant hyperthermia-like syndrome [102], but complex surgical procedures such as scoliosis correction are now better tolerated with growing experience.

5. Conclusion

Neuromuscular problems play an important part in neurological critical care. Neuromuscular specialists should provide guidance to intensivists and their role includes optimizing pre-ICU care and monitoring, understanding respiratory and cardiac complications, and identifying risks for the patient in the ICU and after step down. They should guide diagnostic procedures with a minimum of delay and as little invasive procedures as possible to start specific treatment. Understanding the priorities of ICU management and the specific risks encountered in the ICU is crucial for efficient cooperation.

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