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Mechanisms of Neuromuscular Dysfunction in Critical Illness

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Abstract

The development of neuromuscular dysfunction (NMD) during critical illness is increasingly recognized as a cause of failure to wean from mechanical ventilation and is associated with significant morbidity and mortality. At times it is difficult to identify the presence of NMD and distinguish the etiology of the weakness in patients with critical illness, but subtle clinical findings and bedside electrophysiological testing are helpful in establishing the diagnosis. The purpose of this review is to describe the clinical spectrum of acquired neuromuscular weakness in the setting of critical illness, provide an approach to diagnosis, and to discuss its pathogenesis. Finally, we propose defective sodium channel regulation as a unifying mechanism underlying NMD in critically ill patients.

Keywords

acquired paresis; critical illness myopathy; critical illness polyneuropathy; inexcitability; sodium channel; weakness; paralysis; acute quadriplegic myopathy; sepsis; neuromyopathy

Introduction

It has been three decades since the first description of acquired neuromuscular dysfunction (NMD) in the setting of critical illness. In the first case report, myopathy developed in a patient treated for status asthmaticus [1]. Since that time there have been many reports of debilitating myopathy that develop in various ICU settings [2–4]. The acquired myopathy has been identified as a cause of prolonged weakness and is termed critical illness myopathy (CIM), among which there are several variants including acute quadriplegic myopathy, thick filament myopathy, or acute myopathy of critical illness [5]. The second principal cause of acquired weakness in critical illness, critical illness polyneuropathy (CIP), is a generalized neuropathy that was first described two decades ago in the setting of sepsis and multi-organ failure [6]. In the initial report the authors identified five patients with sepsis and multi-organ dysfunction who developed an axonal sensorimotor polyneuropathy during the acute illness.

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Incidence of Acquired Neuromuscular Dysfunction in the ICU

Acquired neuromuscular dysfunction (NMD) is a comprehensive designation incorporating both CIM and CIP. Alternate terms include ICU-acquired paresis, critical illness neuromyopathy, and critical illness neuromuscular abnormalities. CIM has been reported in at least one third of ICU patients treated for status asthmaticus [8] and studies of critically ill patients suggest incidence rates between 12–35% [9–12]. Prospective studies suggest that CIP may occur in up to 50–70% of patients admitted to the ICU with a diagnosis of systemic inflammatory response syndrome (SIRS) [13–15]. In a recent systematic review of 24 studies reporting data for 1421 patients, the overall median prevalence of NMD was 46% (95% confidence interval 43–49%) in adult subjects with either sepsis, multi-organ failure, or prolonged mechanical ventilation (median duration, 7 days) [7]. Further study is needed to define the incidence of NMD in critically ill populations without multi-organ dysfunction or mechanical ventilation and whether distinct risk factors accurately predict CIM and CIP.

It is difficult to determine the true prevalence of NMD associated with critical illness given the heterogeneity of populations studied, the variability in applied diagnostic criteria, and the limited descriptive detail of clinical syndromes in many published studies. Early studies of CIP revealed a high frequency of concurrent myopathic changes suggesting that, at least in some patients, CIP may occur concomitantly with CIM [16]. It was later suggested that neuropathy and myopathy might be acquired in tandem during critical illness [17]. Multiple prospective studies subsequently reported combined myopathic and neuropathic findings in individual patients on the basis of either electrophysiologic or biopsy specimens [12,18,19]. Data allowing for specific classification of NMD revealed similar proportions of patients diagnosed with CIM (49/144, 34%), CIP (51/144, 35%), and combined CIM/CIP (44/144, 30.6%) [7]. Although the finding of coexisting CIM and CIP may simply reflect an inability to discriminate between two distinct processes due to the inherent difficulties in assessing peripheral nervous system function in the ICU setting, an alternative hypothesis is that these entities simply reflect different manifestations of a single syndrome (see below).

Although continuous use of paralytics to aid mechanical ventilation during critical illness has become less common in recent years, prolonged neuromuscular blockade must be considered in addition to CIM and CIP when evaluating a weak patient. The presence of concomitant renal or hepatic dysfunction may significantly increase neuromuscular blocker half-life and prolong weakness. Drug-drug interactions may also interfere with the metabolism of the paralytics and cause similar effects [20].

Risk factors for acquired neuromuscular weakness

Sepsis and SIRS has been associated with NMD in a number of prospective studies [14,15, 21–23]. Severity of critical illness and organ dysfunction scores predicts NMD in multivariable analyses. A large prospective single-center study of 98 mechanically ventilated patients found that higher APACHE III scores as well as the presence of SIRS at the time of study entry (day 4 of mechanical ventilation) predicted NMD [10]. In that study, the probability of developing NMD by thirty days was 72% for those with APACHE III scores >85 and SIRS, whereas those with an APACHE III score of ≤70 and no SIRS had a risk of only 8%. A prospective multi-center study of 95 patients mechanically ventilated for 7 or more days reported that the number of days with organ dysfunction of ≥2 organs significantly predicted NMD in multivariable analysis [21]. Duration of SIRS and severity of organ dysfunction also predict NMD: approximately 86% of NMD subjects had >3 days with SIRS) and cumulative 1-weeks SOFA score >45 [9].

Associations between selected pharmacological agents such as neuromuscular blockers and corticosteroids with NMD have been inconsistent. Early reports of patients with CIM noted an

association with exposure to either neuromuscular blocking agents or to systemic corticosteroids, leading investigators to postulate that these agents may be involved in the pathogenesis of this syndrome [2–4]. These studies, however, did not adjust for confounding variables that might associate with the development of NMD and, in fact, many of these same patients with ICU weakness had sepsis, multi-organ dysfunction (MOD), or organ rejection. Further prospective studies subsequently found no association between NMD and either steroids or neuromuscular blockade [9,10,24], although in one report corticosteroid administration was associated with NMD in multivariate analysis (OR 14.9, 95% CI 3.2–69.8, $p < 0.001$) [21].

Increased risk of acquired NMD related to elevated plasma glucose levels has been reported by a number of prospective studies [21,25,26]. Interestingly, recent reports from randomized controlled studies document that intensive insulin therapy can decrease the incidence of NMD [26,27]. Further study of plasma glucose levels, insulin therapy, and corticosteroid administration are needed, particularly given recent trends regarding the administration of steroids in sepsis and the impact of corticosteroids on glycemic control.

Approach to the Diagnosis of NMD in the Intensive Care Unit

Bedside Examination

NMD is typically heralded by difficulty in weaning from mechanical ventilation or by the presence of diffuse weakness in a cooperative patient. Early signs of development of NMD are non-specific and may simply include a reduction in spontaneous movement of the limbs. In many cases establishing the presence of NMD in critically ill patients and then distinguishing CIM from CIP is limited by the ability of the clinician to obtain an adequate history and physical examination due to factors such as endotracheal intubation, administration of sedatives and analgesics, or delirium. Clinically, patients with CIM and CIP appear similar; both have a flaccid quadriparesis or quadriplegia. The cranial nerves, including extraocular movements, typically remain intact. Facial weakness, if present, is mild. A distinguishing feature may be muscle stretch reflexes. The muscle stretch reflexes are usually present in CIM and absent in CIP. Sensation to primary modalities such as light touch, vibration, proprioception, and temperature remain intact in CIM, though detailed sensory testing is commonly limited in ICU setting. The sole indication of preserved sensation may be the observation of a facial grimace in response to noxious stimulation to an extremity without the simultaneous withdrawal of the extremity suggesting CIM. In contrast to CIM, in CIP sensation to pain and proprioception is reduced in the distal extremities such that patients do not grimace in response to a noxious stimulus in the extremity.

Laboratory assessment of patients with NMD, including serum creatine kinase (CK), is usually unrevealing. Abnormalities typically reflect the systemic illness and do not alert the clinician to the presence of myopathy or neuropathy. However, when present, elevated CK levels should raise the possibility of a toxic or inflammatory myopathy.

Electrodiagnosis of NMD

Recognizing the inherent limitations to a detailed neuromuscular examination in the ICU setting, the diagnosis of NMD traditionally relies upon the use of nerve conduction studies and electromyography. Such electrophysiologic testing entails simple procedures, which may easily be performed at the bedside and can definitively localize the cause of weakness to peripheral nervous system, thereby excluding the possibility of central nervous system dysfunction as well as non-neurological etiologies for diffuse weakness (e.g., malnutrition or deconditioning).

Although some of the electrophysiologic features of CIM and CIP overlap, testing in a cooperative patient not only identifies NMD, but also can reliably distinguish CIM from CIP. In CIM, nerve conduction studies are either normal or have reduced amplitudes of compound motor action potentials (CMAPs) with preservation of sensory nerve action potentials (SNAPs). On needle examination (EMG), fibrillations may or may not be present, but the presence of small, polyphasic motor unit potentials (MUPs) with an early recruitment pattern is a consistent finding. Reduction of CMAP amplitudes on nerve conduction studies and fibrillations may also be seen in CIP, but CIP is distinguishable by the amplitude reduction or absence of SNAPs and the presence of normal or large MUPs that display a reduced recruitment pattern. In CIP, only axonal loss is identified and primary demyelinating features (conduction block, temporal dispersion, conduction velocity slowing) are not present. Nerve conduction study of the phrenic nerve may show reduced or absent responses and EMG of the diaphragm reveals acute denervation (fibrillations) [28].

Not infrequently, electrodiagnostic testing may be technically limited during an acute illness by the presence of wound dressings, intravenous and intra-arterial lines, which preclude the accurate placement of recording electrodes or the application of an electrical stimulus over a particular motor or sensory nerve. It is important to note that examinations performed in the presence of significant peripheral edema can produce low amplitude or absent sensory nerve evoked responses in the absence of pathology, and must be interpreted cautiously. In this setting, low amplitude or absent sensory responses may be incorrectly used as support for the presence of CIP. Although needle electromyography allows for the objective discrimination between myopathic and neurogenic pathology based upon observed motor unit action potential morphology and pattern of recruitment with voluntary activation, EMG may be difficult to interpret if the patient is either unable to cooperate with the examiner or to volitionally activate muscles. Furthermore, recordings of evoked potentials from nerve and muscle may be altered by interference from electrical equipment commonly found in the intensive care unit environment, such as intravenous pumps, monitors and beds.

When standard electrodiagnostic testing is limited by circumstances that commonly arise in the setting of critical illness, another electrophysiologic technique, direct muscle stimulation, may be beneficial. This electrophysiologic technique is based upon the comparison of the motor response amplitude obtained by directly stimulating muscle with the response obtained by stimulating nerve and relies on the finding that skeletal muscle is electrically inexcitable in CIM [29,30]. Direct muscle stimulation is most useful early in the course of illness when the traditional MUP assessment on EMG is not possible due to delirium or sedation. In the presence of severe weakness and very reduced CMAP amplitudes (less than 1 mV), this technique may allow for distinction of myopathy from neuropathy [30].

Electrophysiologic testing can also confirm a clinical suspicion of neuromuscular blockade. Slow repetitive nerve stimulation (3–5 Hz) produces the prototypical decremental motor response that occurs when postsynaptic neuromuscular blockade is present. It should be noted, however, that in patients with severe weakness, the motor response may be entirely abolished and thus repetitive stimulation may not be possible. Once the clinical suspicion of neuromuscular blockade is confirmed, the offending agent should be discontinued and supportive care should be maintained until the neuromuscular blockade has resolved. If weakness persists beyond several days, repetitive nerve stimulation should be repeated and other etiologies of the weakness should be considered.

Muscle and Nerve Biopsy

Definitive diagnosis of CIM is made by nerve and muscle biopsy, but such invasive procedures are not routinely indicated. Even if a biopsy is taken, diagnosis can be difficult as the pathologic features of CIM are quite variable [31,32]. Type II fiber atrophy is often reported (a nonspecific

finding), but type I fiber atrophy and muscle fiber necrosis are occasionally described. One consistent finding among many studies using immunohistochemistry and electron microscopy is the loss of myosin thick filaments. In patients with CIP, nerve biopsies show primary axonal loss greater in the terminal segments compared to proximal segments without evidence of inflammation [6,16].

Prognosis of ICU-acquired NMD

Prospective studies in patients ventilated for over seven days have reported increased hospital mortality associated with NMD [13,15,24]. In fact, the development of NMD early in the course of critical illness may predict mortality. In a prospective cohort of 48 patients with severe sepsis, it was found that abnormal nerve conduction studies obtained within 72 hours of ICU admission predicted hospital mortality (55% versus 0%, $p < 0.001$) [19]. The presence of NMD is also associated with clinically significant short and long-term morbidity. Both CIM and CIP are associated with prolonged duration of mechanical ventilation and increased length of hospital and ICU stay [13,15,35]. Thus the presence of acquired paresis can inform the clinical decision to pursue early tracheostomy and arrange for long-term care after hospital discharge.

In addition to these short term outcomes, NMD is reported as a major cause of functional limitation and reduced health-related quality of life in survivors of critical illness. In a prospective study of 109 survivors of acute respiratory distress syndrome (ARDS), it was found that survivors commonly reported complaints of muscle weakness and fatigue and physical function measured by distance walked in 6 minutes remained abnormal at 12 months [36]. Much of the available data regarding long-term functional prognosis after the development of NMD during sepsis is based upon patients with CIP. A high prevalence of long-term functional limitations was reported in ICU survivors with CIP [37]. In the first prospective study of CIP, sepsis survivors with mild-to-moderately severe neuropathy recovered over a period of months, while patients with severe neuropathy had more protracted clinical deficits or no recovery [14]. It might be expected that functional outcome in CIP would be determined by the extent of axonal degeneration: recovery of strength is dependent upon axonal regeneration so recovery would be expected to occur in proximal muscle groups before distal muscle groups [33]. In a prospective community ICU study including patients with > 7 days of mechanical ventilation, it was found that although sensory and motor deficits associated with CIP improved with time, severe functional deficits persisted at one year after ICU discharge in 22% of all 1-year survivors [13]. In another study of patients who survived longer than 4 weeks of critical illness, some continued to have evidence of clinical weakness and electrophysiologic evidence of neuropathy up to 4 years after hospitalization [34].

Less is known about the long-term outcome of CIM. In theory patients with CIM should have a better prognosis and recover faster than patients with CIP since muscle, unlike nerve, regenerates relatively rapidly. However, a retrospective study of 92 patients who underwent electrophysiologic testing while in the ICU, reported similar functional outcomes for CIM and CIP at 4 months - only 48% with CIM and 44% with CIP were ambulatory at follow-up [31]; however these results were limited by the presence of medical and neurological co-morbidities that may have contributed to the poor recovery of many of the patients diagnosed with CIM.

Mechanisms Underlying Acquired Paresis in CIM

There are at least three factors that contribute to weakness in patients with CIM – atrophy of muscle fibers, loss of myosin, and muscle inexcitability [3,38]. Atrophy and loss of myosin both cause weakness due to loss of force generation following muscle fiber action potentials. The causes of muscle atrophy and loss of myosin are complex and are still poorly understood [5,39] and while very important, will not be discussed further. The third factor is loss of the ability of muscle fibers to generate action potentials, which results in electrical inexcitability

of muscle [29,30,40]. Atrophy and loss of myosin are likely more important in chronic weakness of patients with CIM, whereas loss of muscle excitability may be more important in the acute setting.

Investigation into the causes of muscle inexcitability has been carried out in a rat model of CIM that was established 20 years ago [41,42]. In that model the muscles in one leg are denervated by cutting the sciatic nerve to mimic neuromuscular blocking agents, and this is followed by 7–10 days of high dose corticosteroids. Steroid-treated, denervated rat muscle (SD muscle) has the same histopathologic loss of myosin ATPase staining [42] and a similar loss of muscle fiber excitability to that seen in tissues from critically ill patients [43] suggesting that this model is reflective of patients with classical CIM. Moreover, the rat model of CIM has provided detailed analysis into the etiology of the loss of muscle electrical excitability, a process affected by numerous parameters, including the following:

1) The resting membrane potential of SD muscle is more depolarized (hyperpolarized) than muscle from control rats [43,44]. Depolarization of resting membrane potential of SD muscle inactivates sodium channels so that they are unable to open and participate in generating muscle fiber action potentials. If too many sodium channels are inactivated, muscle fibers fail to generate an action potential and become inexcitable. Denervation without steroid treatment causes hyperpolarization of the resting membrane potential that is similar to that seen in SD muscle [45,46] whereas steroid treatment alone does not [43]. It is important to note, however, that hyperpolarization of resting potential following denervation without steroid exposure does not, in and of itself, lead to widespread loss of electrical excitability. The vast majority of denervated muscle fibers from rats not treated with corticosteroids retain excitability despite depolarized resting potentials [43,47]. Thus the cause of hyperpolarization in resting potential of SD muscle appears to be denervation rather than steroid treatment, and the loss of excitability results from the coexistence of denervation and steroid treatment.

It appears that the denervation associated change in resting potential is primarily due to muscle inactivity [48,49]. Evidence for this comes from experiments in which restoring muscle activity of denervated muscle prevented loss of resting potential [50,51]. This is important clinically because it suggests that depolarization of resting potential will occur whenever muscle is inactive. This may explain why immobility may be a risk factor for development of ICU acquired weakness [52]. Loss of muscle activity occurs both when patients are treated with neuromuscular blocking agents and when they are heavily sedated in the absence of neuromuscular blockade. One implication is that the practice of limiting exposure to neuromuscular blocking agents by increasing sedation in the ICU may not reduce the incidence of CIM.

Surprisingly, despite a great deal of research on muscle, the mechanism underlying the depolarization of inactive muscle is not well established (for a detailed discussion see [53]). It has been suggested that increased activity of a furosemide-sensitive chloride transporter following denervation plays a central role in the change in resting potential [54,55], but this has never been tested in vivo. Although it has never been proven that CIM muscle fibers from patients are more depolarized than normal muscle, understanding why resting potential depolarizes following loss of muscle activity is likely to be valuable in developing treatments for CIM.

2) There is an approximately two-fold decrease in the density of sodium channels in SD muscle [43,44]. A decrease in sodium channel density affects excitability by reducing the number of sodium channels available to participate in action potential initiation. However, the reduction in sodium channel density does not appear to be the most important factor in loss of excitability

since the density does not correlate with the severity of the reduction in excitability of individual SD fibers [44].

3) The voltage dependence of sodium channel activation (channel opening during an action potential) and inactivation (long-term channel closing following an action potential) are shifted toward more negative potentials [40]. This means that the normal function of the sodium channel occurs at more negative (hyperpolarized) membrane potentials in inexcitable SD muscle compared with control muscle. Not all muscle fibers are equally affected by SD treatment. Some SD fibers retain excitability while others become inexcitable. In excitable SD fibers there is no change in the regulation of sodium channel activation or inactivation relative to control muscle fibers. In inexcitable fibers, however, activation and inactivation of sodium channels occurs at more negative, (hyperpolarized) membrane potentials [44,47]. This shift in the voltage dependence of sodium channel regulation, combined with the depolarized resting potential present in inexcitable SD fibers, resulted in the inactivation of more than 99% of sodium channels. Thus paralysis in this animal model of CIM is due primarily to failure of action potential generation because of altered function of sodium channels.

Inexcitability of SD muscle is due to abnormal regulation of Nav1.4 sodium channel inactivation

There are two ways in which the shift in sodium channel regulation toward more hyperpolarized membrane potentials could be induced in SD fibers. The first is through the novel expression of different types of sodium channels that inactivate more readily at the depolarized resting potential found in SD muscle. The second is through modification of the sodium channels that were already present in the muscle membrane. In normal mature skeletal muscle only the Nav1.4 sodium channel is present. Following denervation or steroid treatment, however, the Nav1.5 sodium channel is also expressed [56,57]. It has been found in tissue culture that Nav1.5 sodium channels inactivate at more hyperpolarized membrane potentials than Nav1.4 sodium channels [58,59]. The net result is that at the depolarized resting potential of SD muscle, a higher percentage of Nav1.5 sodium channels than Nav1.4 sodium channels are inactivated. Thus upregulation of Nav1.5 sodium channels could explain the presence of more inactivated sodium channels and hence reduced action potential generation, inexcitability and the clinical manifestation of weakness. However, although Nav1.5 sodium channels were present in SD muscle, they do not account for the alteration in sodium channel regulation [43,60]. This finding demonstrated that the primary cause of the loss of excitability of SD fibers is an alteration in the regulation of Nav1.4 sodium channels instead of the new expression of Nav1.5 channels. Future studies will be aimed at determining the cause of the abnormal regulation of Nav1.4 in animal models of CIM.

To date, the majority of studies on sodium channel gating, the cycle of activation, inactivation and reactivation, have been performed on the rat SD model of CIM. However, many patients with CIM and electrical inexcitability of muscle have not been exposed to neuromuscular blockade or corticosteroids [11], and the relationship between these factors CIM is not firmly established. A recent study examined whether chronic sepsis causes abnormal regulation of sodium channels in rat muscle [61], finding as in SD muscle, that the inactivation of the sodium channel was altered. Thus it appears likely that sepsis causes changes in Nav1.4 sodium channels similar to those seen in SD muscle.

Is there a syndrome of electrical inexcitability in critically ill patients?

As outlined above, it is generally thought that CIM and CIP are distinct entities that have different causes. However, recently it has been recognized that the two syndromes often coexist [9,18,19,62]. CIP and CIM could occur together either because they are distinct syndromes that are due to coexisting risk factors or because they represent different manifestations of a

single underlying disorder. For example, if a negative shift in sodium channel gating occurs in both nerve and muscle then both tissues might become inexcitable and cause neuropathy or myopathy respectively. It is now relatively well established that skeletal muscle becomes electrically inexcitable in septic patients [11,29,30,63]. There is also evidence of inexcitability of sensory nerves. In a study on septic patients with CIP who had reduced SNAPs, sural nerve biopsies from some patients were normal and the decrease in SNAPs was rapidly reversed, suggesting a functional rather than a structural change [62]. Although a technical problem such as tissue edema might explain the reduced SNAPs, the rapid recovery of amplitude and findings of normal nerve morphology suggested that reduced excitability of the nerve is also a possible explanation for the findings. Inexcitability of nerve could recover quickly (requiring only modification of sodium channel behavior rather than regrowth of axons) and would not be expected to result in an abnormal nerve morphology using standard tissue staining techniques. Further studies in an animal model of sepsis will be required to determine whether peripheral nerves become inexcitable in sepsis.

There is also evidence consistent with reduced excitability of the heart in septic patients. It has been shown that there is a reversible reduction of ECG amplitude in patients during periods of severe sepsis [64]; in this study pericardial effusion and pulmonary hyperinflation were ruled out such that the ECG amplitude reduction could not be ascribed to these technical issues. Decreases in ECG amplitude are also observed in patients given type 1 antiarrhythmic agents, which block cardiac sodium channels, raising the possibility that a reduction in cardiac sodium current underlies the reduction in ECG amplitude in septic patients. A reduction in cardiac sodium current might also contribute to the reduced cardiac contractility that is seen during sepsis.

We propose that available data is consistent with reduced excitability of peripheral nerve, skeletal muscle and cardiac muscle in septic patients. While there is no evidence indicating that excitability of central nervous system neurons is altered during sepsis, it is notable that many patients who have CIP also have septic encephalopathy [5]. The pathogenesis of septic encephalopathy has never been determined. In many patients, imaging studies are normal, as would be expected if the cause were functional (i.e. due to electrical inexcitability) rather than structural. Further study is needed to determine whether the syndrome of generalized loss of excitability that we propose exists in septic patients. This hypothesis suggests a unifying underlying mechanism to explain many of the clinical features observed in severe sepsis and septic shock, and indicates potential targets for future therapies of CIP and CIM.

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