REVIEW ARTICLE

Neuromuscular Causes of Weakness in Critically Ill Patients
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INTRODUCTION

Critically ill patients in the intensive care unit (ICU) are exposed to multiple risk factors that increase the likelihood of damage to their motor unit. Fluid and electrolyte disturbances, catabolic stressors, nutritional deficiency, and medications collectively increase the risk for neuromuscular damage, consequently prolonging hospital stay, delaying recovery, and increasing morbidity and mortality.¹ The most common causes of neuromuscular weakness in the ICU patients are critical illness neuropathy and critical illness myopathy, which usually present as failure to wean off from the ventilator and decreased limb movements.² The incidence rate for acquiring weakness from critical illness neuropathy (CIN) and critical illness myopathy (CIM) has drastically increased, and it is twice as common as primary neuromuscular causes, such as Guillain-Barre syndrome (GBS) and motor neuron diseases.² Early diagnosis and prompt treatment are necessary as complications, such as ventilatory failure and aspiration pneumonia significantly increase morbidity and mortality.

CLASSIFICATION

Although there are multiple causes for generalized weakness in an ICU patient, motor weakness can be broadly classified as due to:

- Preexisting neuromuscular disorders
- Neuromuscular complications of critical illness

Motor weakness can be further localized to the anatomical site of involvement of a disease process (Table 1).

PREEXISTING NEUROMUSCULAR DISORDERSS

Spinal cord disorders
Motor weakness due to spinal cord disorders can be further classified into compressive and non-compressive myelopathy. The most common cause for non-compressive myelopathy is transverse myelitis. Transverse myelitis is mostly idiopathic or post-infectious secondary to an infection with a virus (cytomegalovirus, herpes simplex virus, Coxsackie), or bacteria (Mycoplasma, Legionella). Other causes include: multiple sclerosis, Devic’s disease, and collagen vascular disease.³

Transverse myelitis can be diagnosed upon a high clinical suspicion as it characteristically presents with bilateral signs and symptoms, and a clearly demarcated sensory level with progression period ranging...
Table 1. Causes of generalized weakness in ICU and their anatomical localization

<table>
<thead>
<tr>
<th>Localization</th>
<th>Preexisting Neuromuscular Disorder</th>
<th>Complication of Critical illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>Trauma Infarction Transverse myelitis</td>
<td>Unknown</td>
</tr>
<tr>
<td>Anterior horn cell</td>
<td>Amyotrophic lateral sclerosis (ALS) Poliomyelitis</td>
<td>Hopkins syndrome</td>
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<tr>
<td>Peripheral nerve</td>
<td>GBS Chronic inflammatory demyelinating polyneuropathy</td>
<td>Critical illness polyneuropathy</td>
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<tr>
<td>Neuromuscular junction</td>
<td>Myasthenia gravis Lambert-Eaton syndrome Botulism</td>
<td>Prolonged neuromuscular blockade</td>
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<tr>
<td>Muscle</td>
<td>Muscular dystrophy Polymyositis Metabolic/congenital Mitochondrial</td>
<td>Critical illness myopathy</td>
</tr>
</tbody>
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Cerebrospinal fluid (CSF) shows characteristic pleocytosis or high immunoglobulin levels, and an MRI shows increased segmental contrast enhancement.

Spinal cord infarction is a known complication of: aorto-iliac occlusion, aortic dissection, and aortic surgeries. It can also be secondary to cardiac arrest and global hypotension.

The standard care of treatment for transverse myelitis includes intravenous corticosteroids, such as methyl prednisone or dexamethasone, which helps in reducing spinal cord swelling and inflammation. Plasma exchange can be tried in refractory cases.

Anterior Horn Cell Disorders

Amongst anterior horn cell disorders, amyotrophic lateral sclerosis (ALS) is a well-known culprit causing respiratory weakness due to primary phrenic motor neuron involvement. Most common presenting symptoms include weakness, atrophy, fasciculations, difficulty swallowing, and slurred speech. The disease is usually relentlessly progressive with death occurring in 50% of cases within 3 years and in 80% of cases within 5 years. The most common complication encountered in ALS patients in the ICU is aspiration pneumonia secondary to respiratory failure, which almost always requires tracheostomy and/or percutaneous endoscopic gastrostomy (PEG) tube placement. Electrophysiological study is the preferred method of investigation and reveals widespread denervation on electromyography (EMG).

Peripheral Nerve Disorders

Amid the peripheral nerve disorders, GBS is well known to cause weakness. GBS usually occurs weeks after a flu-like or diarrheal illness caused by infectious agents, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes Simplex virus (HSV), Mycoplasma, Chlamydia and/or...
Campylobacter. Weakness follows a characteristic pattern of a rapidly progressive ascending motor and sensory paralysis, which later progress to respiratory weakness and bulbar involvement. Also commonly seen is the autonomic involvement that presents as postural hypotension, fluctuation in blood pressure and cardiac dysrhythmias.

Respiratory paralysis is the most common indication for an ICU admission. The characteristic lab finding in GBS is CSF albuminocytological dissociation, which usually occurs 48 hrs after onset of the illness. Electrodiagnostic studies show slowing of nerve conduction velocity. Management of GBS in an ICU setting is governed by two parameters: vital capacity (VC) and arterial blood gas (ABG). Intubation is recommended in patients with: VC <12-15 ml/kg, falling VC, and retained secretions. The recommended treatment options are intravenous immunoglobulin (IVIG) or plasma exchange. Plasmapheresis is usually recommended in patients unable to ambulate, worsening forced vital capacity, bulbar muscle involvement, and in those requiring intubation and ventilation. Five sessions of plasma exchange over 10-14 days is recommended with exchange of a total of 200 mL of plasma/ kg of body weight.

IVIG in dose of 2 g/kg divided over 5 consecutive days is the recommended treatment. Combination therapy of IVIG and plasma exchange is not recommended and has no added benefits over individual treatment. Steroids are not helpful in treatment of GBS in ICU patients.

Neuromuscular Junction Disorders
The most common myasthenic syndrome encountered in an ICU includes myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome. The underlying defect in myasthenia gravis is a decreased number of available acetylcholine receptors (AChRs) at the neuromuscular junction, secondary to an antibody mediated immune destruction, which compromises the neuromuscular conduction and presents as motor weakness. The distribution of muscle weakness has a characteristic involvement of extraocular, facial, bulbar and later respiratory muscles, which usually presents as diplopia, dysphagia, and dysarthria.

Myasthenic crisis is the most common reason for an ICU admission in patients with MG. Myasthenia crisis is associated with respiratory compromise. It presents as respiratory muscle insufficiency, and/or inability to handle excessive oral and respiratory secretions that require intubation and mechanical ventilation.

The most common precipitants of an MG crisis include intercurrent infections, aspiration, sepsis, surgical procedures, medications, and pregnancy. About 30-70% of seronegative myasthenic patients may have an antibody directed against Muscle specific tyrosine kinase (MuSK). Such patients tend to have severe disease and high frequency of respiratory crises compared to an AChR antibody positive patients.

A vital capacity of less than 1 liter (or <20-25 ml/kg), or a negative inspiratory factor (NIF) <20 cm of H2O, indicates significant respiratory weakness; both measurements are commonly used to define myasthenic crisis. Between 66%-90% of patients with an MG crisis require intubation, mechanical ventilation, and ICU management of the complications. IVIG and plasma exchange are the mainstay of treatment in crisis patients. A typical course of IVIG is 400 mg/kg daily for 5 days. Five rounds of plasma exchange every alternative day for 10 days is the standardized therapy. Prednisone can also be used in conjunction with IVIG and plasma exchange.

High rate rapid nerve stimulation studies and PQ type anti-voltage gated calcium channel antibodies are the standard...
investigations for diagnosis of Lambert Eaton syndrome that responds well to IVIG. Botulism and tick paralysis are amongst the uncommon neuromuscular junction disorders encountered in an ICU. Botulism presents with flaccid paralysis, areflexia, and autonomic disturbances. Early diagnosis is imperative as early antitoxin therapy is associated with decreased hospital stay, morbidity, and mortality. Mechanical ventilation is the mainstay of treatment. Tick paralysis is associated with areflexia, ascending motor paralysis and preserved sensations; a careful search and removal of the tick aids in rapid resolution of symptoms.

**Muscle Disorders**

Inflammatory myopathies commonly encountered in the ICU are dermatomyositis and polymyositis. Both present with proximal muscle weakness and pain. Dermatomyositis has characteristic skin lesions, such as purplish periorbital (heliotrope) rash that spreads to the back, the neck - Shawl sign, and over the knuckles - Gottron’s sign. Dermatomyositis is also more commonly associated with malignancies. The initial investigation for

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**NEUROMUSCULAR COMPLICATIONS OF CRITICAL ILLNESS**

ICU acquired neuromuscular weakness is a major cause of morbidity in critically ill patients. It significantly affects the overall prognosis and increases the length of hospitalization. The three most common causes of an acquired neuromuscular weakness in the ICU patients are: critical illness polyneuropathy (CIP), critical illness myopathy (CIM), and prolonged neuromuscular blockade. Both, CIP and CIM, present as symmetrical, diffuse, flaccid muscle weakness affecting extremities and diaphragm with a relative sparing of the cranial nerves. Multiple possible factors play a role in the development of neuromuscular weakness in critically ill patients. The major ones are: systemic inflammatory response syndrome (SIRS), corticosteroid use, and neuromuscular blocking agents.

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**Figure 1.** Pathogenesis of development of critical illness polyneuropathy/myopathy in ICU
Critical Illness Polyneuropathy
CIP usually presents as a sensorimotor axon loss polyneuropathy, which in an early course affects distal muscles more than proximal; later it progresses to generalized muscle weakness with absent reflexes. Most patients have concomitant encephalopathy due to an underlying sepsis and/or organ failure. Hyperglycemia, hypoalbuminemia, and parenteral nutrition are also known exacerbating factors for the development of CIP. An impaired microcirculation due to inflammatory responses leads to a decreased nerve perfusion resulting in nerve hypoxia. The earliest clinical suspicion arises when it is difficult to wean the patient off of the ventilator; other common presentations include tetraplegia and absent deep tendon reflexes. The severity is proportional to the length of an ICU stay.

The most important diagnostic test is the electrodiagnostic study. The nerve conduction velocities may be normal or reduced, but the amplitude of sensory and motor responses is significantly decreased or even absent. Features of acute denervation, such as fibrillation, positive sharp waves, and reduced recruitment are evident on needle electrode studies. Nerve biopsy shows severe axonal degeneration of motor and sensory fibers primarily affecting distal segments.

The treatment usually comprises of an aggressive management of SIRS and supportive measures, such as fluid resuscitation, antibiotic therapy, and early physical therapy. Recovery usually occurs over weeks to months. Long term prognosis depends upon severity of the underlying disease process.

Critical Illness Myopathy
CIM is the major contributor of an ICU related neuromuscular weakness. CIM usually develops in patients who are on prolonged high dose steroid treatment and/or neuromuscular blocking agents. It characteristically presents as diffuse weakness affecting both limbs, distal muscles more than proximal. Facial and sometimes ocular muscle involvement can be seen.

Myosin loss is the hallmark finding of CIM. Corticosteroid use causes myosin loss, which is further triggered by the common use of neuromuscular blockade agents in ICU settings.

CIM can be further sub-classified as thick filament myopathy, catabolic myopathy, and acute necrotizing myopathy of intensive care. An elevated creatine kinase (CK) is observed in all types of CIM and it is a hallmark feature of the illness. Electrodiagnostic studies play a significant role in the diagnosis of CIM. Nerve conduction studies exhibit low amplitude or even absent motor responses, whereas sensory responses are preserved. Needle EMG studies show short duration, polyphasic and low amplitude motor unit action potentials. Muscle biopsy shows muscle fiber necrosis, atrophy and regeneration mostly affecting type II fibers in absence of any inflammatory marker. The hallmark finding is a selective loss of the thick filament (myosin) in absence of the thin filament (actin).

Management is usually conservative. Discontinuation of steroids and neuromuscular blockade agent is recommended. There is growing evidence in support of using intensive insulin therapy for reducing the incidence of both, CIM and CIP. Prognosis usually depends upon the severity of the illness.

Neuromuscular Blockade
Competitive non-depolarizing neuromuscular blocking agents (NMBs), such as pancuronium and vecuronium, as well as newer benzylisoquinolinium NMBs like atracurium and cisatracurium are used extensively in ICU settings to aid in
CONCLUSION

Multiple predisposing factors are responsible for the development of neuromuscular weakness in a critically ill patient. Thorough history and physical examination is paramount and should not be omitted despite that the majority of patients are unresponsive, confused or sedated. A comprehensive investigation protocol should be followed in all cases of weakness in ICU settings. The spectrum of neuromuscular diseases encountered in ICUs nowadays has rapidly evolved over the last decades. Early diagnosis and prompt treatment is necessary to reduce morbidity and mortality in critically ill patients and reduce the skyrocketing health care expenses.

Notes

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