ICU Related Neuromuscular Complications

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ABSTRACT

The spectrum of neuromuscular diseases encountered in the ICUs today has rapidly evolved over the last decades. Multiple predisposing factors are involved in the development of neuromuscular complications in intensive care patients. Those complications broadly classified into weakness from the preexisting neuromuscular disease exacerbated by critical illness or the complication of the critical illness itself. Patients, when unresponsive, confused, or sedated precludes careful clinical examination. A careful schematic approach that involves acquiring extensive history, any underlying infections, use of any offending medications, and the course of presenting illness will help in delineating the underlying etiology. Here in this review, we describe many causes and the pathophysiology that contribute to the development of neuromuscular weakness in the ICU. A comprehensive investigation protocol must strictly be adhered to all the cases in the ICU settings to reduce the mortality and morbidity.

Keywords: *Critical illness polyneuropathy, critical illness myopathy, ICU related neuromuscular weakness, myopathy, complications of sepsis.*

Introduction

Critically ill patients in the ICU get exposed to multiple risk factors that increase the likelihood of damage to the peripheral nervous system. Fluid and electrolyte disturbances, catabolic stressors, nutritional deficiency, and medications collectively increase the risk for neuromuscular damage, thus prolonging hospital stay, delaying recovery and increasing morbidity and mortality.[1, 2] The most common causes of neuromuscular weakness in ICU patients are critical illness neuropathy and critical illness myopathy, which usually presents as failure to wean off from ventilator and decreased limb movements.[1,2,4,5] The incidence rate for acquiring weakness from critical illness neuropathy (CIN) and critical illness myopathy (CIM) has drastically increased and is twice as common as primary neuromuscular causes such as GBS and motor neuron diseases.[3,4] Recently, CIM is more commonly encountered than CIP. 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 a patient in ICU motor weakness can be broadly classified due to:

1. NEUROMUSCULAR COMPLICATIONS OF CRITICAL ILLNESS
2. PRE-EXISTING NEUROMUSCULAR DISORDERS

Motor weakness can further lateralized to the anatomical site of involvement of a disease process. Table 1 provides common causes of ICU associated weakness in neuromuscular patients.

1. Neuromuscular Complications of Critical Illness

ICU acquired neuromuscular weakness is a major cause of morbidity in critically ill patients.[3-4] It significantly affects the overall prognosis and increases the length of hospitalization.[3-4] The three most common causes of acquired neuromuscular weakness in ICU patients are critical illness polyneuropathy, critical illness myopathy, and prolonged neuromuscular blockade.

CIP affects between one third and half of the most severely critically ill patient in the intensive care units (ICU).[2,5] A systematic review reported a median prevalence of CIP as 43% (interquartile range 25–75%) in over 31 studies.[3] Critical illness polyneuropathy and myopathy is seen in approximately 25–45% of critically ill patients who are admitted to intensive care units.[5]

Both CIP and CIM present as symmetrical, diffuse flaccid muscle weakness affecting extremities and respiratory muscles with relative sparing of cranial nerves.[2-3,5] 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.[2,5] See Figure 1.

Critical Illness Polyneropathy

CIP usually presents as sensorimotor axon loss polyneuropathy, affecting distal muscles more than proximal muscles in the early course, later progressing to generalized muscle weakness with absent reflexes.[2-3,5] It was initially described as a rare complication secondary to sepsis and multi-organ failure.[2,4,6] The majority of the patients have

Table 1: Causes of generalized weakness in ICU and their anatomical localization

Localization	Preexisting Neuromuscular Disorder	Complication of Critical illness
Spinal cord	Trauma Infarction Transverse myelitis	Unknown
Anterior horn cell	ALS Poliomyelitis	Hopkins syndrome
Peripheral nerve	GBS Chronic inflammatory demyelinating polyneuropathy	Critical illness polyneuropathy
Neuromuscular junction	Myasthenia gravis Lambert-Eaton syndrome Botulism	Prolonged neuromuscular blockade
Muscle	Muscular dystrophy Polymyositis Metabolic/congenital Mitochondrial	Critical illness myopathy

concomitant encephalopathy due to underlying sepsis or organ failure.[2,7] Hyperglycemia, hypoalbuminemia, and parenteral nutrition are also known to exacerbate the development of CIP.[5,7] Impaired microcirculation due to inflammatory responses leads to decreased nerve perfusion resulting in nerve hypoxia.[6-7]

The earliest clinical suspicion arises when it is difficult to wean the patient from a ventilator, and other common presentations include tetraplegia and absent deep tendon reflexes.[4,7] Severity is proportional to the length of ICU stay.[5,7]

The most important diagnostic test is the Electro diagnostic study (nerve conduction+ electromyography). Nerve conduction velocities may be normal or reduced, but the amplitude of sensory responses and motor responses is significantly decreased or even absent.[3,7] Features of acute denervation such as fibrillation, positive sharp waves, and reduced recruitment are evident in needle electrode studies. Motor unit potential has a long duration, high amplitude and polyphasic morphology.[3] Nerve biopsy shows severe axonal degeneration of motor and sensory fibers affecting distal segments primarily.[3]

Treatment usually comprises aggressive management of SIRS and supportive measures such as fluid resuscitation, antibiotic therapy, and physical therapy.[5] Recovery usually occurs over weeks to months.[2,5] Long term progno-

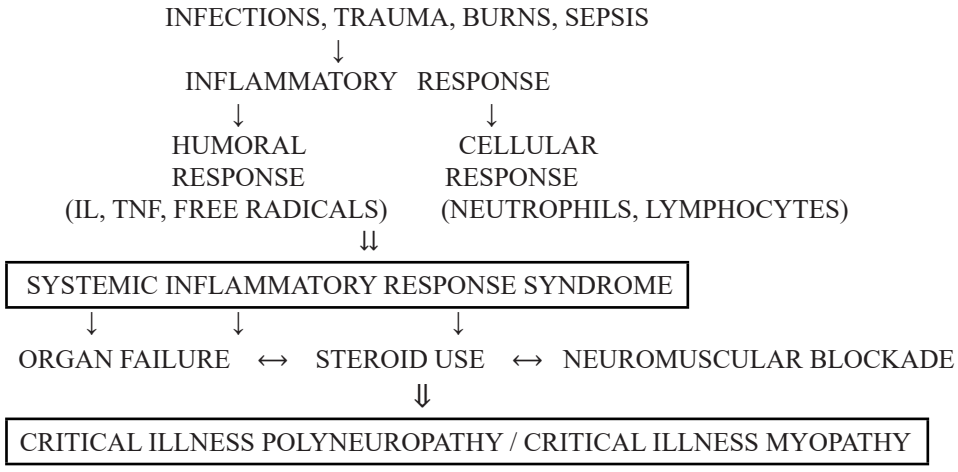


Figure 1: Pathogenesis of development of critical illness polyneuropathy/myopathy in ICU

sis depends upon the severity of the underlying disease process and patients with only CIM having a better prognosis than those with CIN only or even those with CIN+CIM.[5]

Critical Illness Myopathy

CIM is the major contributor of ICU related neuromuscular weakness.[2-3,5] CIM usually develops in patients taking prolonged high dose steroids or on neuromuscular blocking agents.[6,8] It characteristically presents as diffuse weakness affecting both limbs, affecting distal muscles and proximal muscle groups. Facial muscle and sometimes ocular muscle involvement can be seen.[8]

Myosin loss is the hallmark finding of CIM.[8] Corticosteroid use causes myosin loss, which is further triggered by the use of neuromuscular blockade agents used commonly in ICU settings. CIM can be further sub-classified as thick filament myopathy, catabolic myopathy, and acute necrotizing myopathy of intensive care.[9] See table 2 for more details.

Elevated muscle enzyme (CK) is observed in necrotizing sub types and in other two subtypes it is either normal or only occasionally elevated.[9] Electro diagnostic studies play an essential role in the diagnosis of CIM with nerve conduction studies exhibiting 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. EMG at rest is positive for fibrillation potentials/ Positive sharp waves.[3]

Muscle Biopsy shows muscle fiber necrosis, atrophy, and regeneration, mostly affecting type II fibers, in the absence of any inflammatory marker. Selective loss of thick filament (myosin) in the absence of thin filament (actin) is the hallmark.[2,5,9]

Management is usually conservative. Discontinuation of steroids and neuromuscular blockade agents is recommended. There is growing evidence in support of using intensive insulin therapy for reducing the incidence of both CIM and CIP.[3] Although target blood glucose is to reach normal fasting levels with insulin infusion, an optimal dose remains controversial as intermediate blood glucose levels are safer as shown in a multi-center randomized trial.[3]

Prognosis usually depends upon the severity of illness.[3,5]

Table 2: Subtypes of critical illness myopathy encountered in the intensive care unit

SUBTYPES	THICK FILAMENT MYOPATHY	CATABOLIC MYOPATHY	NECROTIZING MYOPATHY OF INTENSIVE CARE
UNDERLYING CAUSES	Corticosteroid use, NM blockade agents, severe asthma exacerbation	Interleukin-1 and TNF induced damage seen in respiratory failure, shock, sepsis	Overwhelming infections, toxic shock

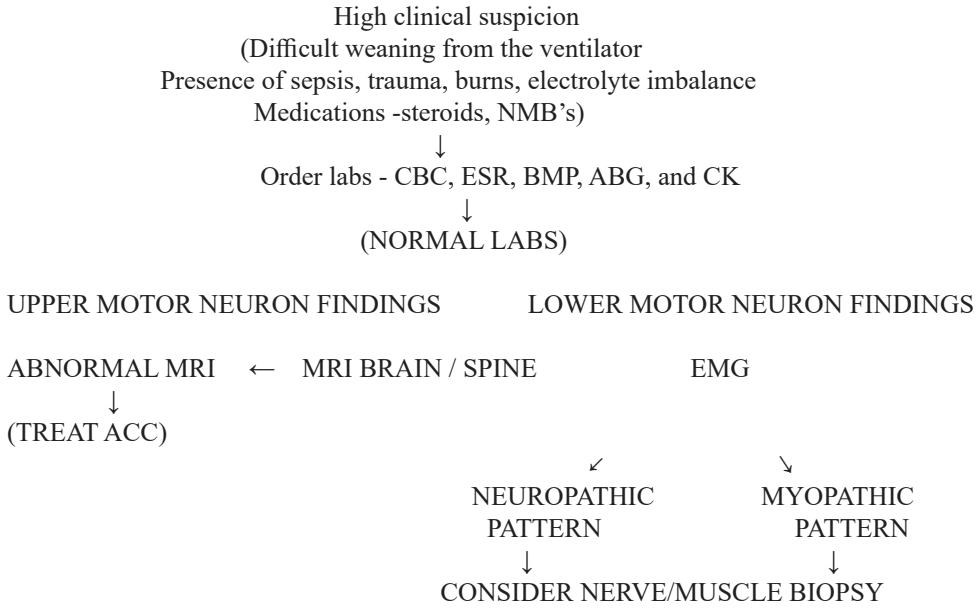
Neuromuscular Blockade

The disturbance in the neuromuscular transmission secondary to the use of neuromuscular blocking agents has been increased in recent years.[1] Competitive non-depolarizing neuromuscular blocking agents (NMB's) such as pancuronium, vecuronium, and newer benzylisoquinoline NMB's such as atracurium, cisatracurium are used extensively in ICU settings to aid in mechanical ventilation.[1,10] Concomitant antibiotic (aminoglycoside) and polypeptide antibiotics increases this block. Prolonged neuromuscular blockade by drugs, electrolyte disturbances, and metabolic acidosis acts synergistically with sepsis and SIRS in the pathogenesis of CIM and CIP.[1,5,10-11] Slow repetitive stimulation demonstrates an abnormal decrease in the compound muscle action potential. Careful evaluation of the concomitant drugs must be checked in case of any unexplained weakness.[1]

Established treatment of ICU related weakness is not available. The one successful intervention studied so far is intense insulin therapy that targets blood glucose of 80-110 mg/dL. This intervention reduced electro physiologically diagnosed polyneuropathy by 49% in patients in the intensive care for 7 days. In some series of patients IVIG is reported to be beneficial although further studies are needed. Also, preventing the factors that could trigger weakness from certain antibiotics like aminoglycosides must be employed.[11,19]

Hopkins syndrome (Post-asthmatic amyotrophy)

Although rare, Hopkins syndrome (post-asthmatic amyotrophy) is poliomyelitis like illness, which presents acutely following an asthmatic attack, mostly in the pediatric age group.[12-14] It is an anterior horn cell disorder that presents as an acute flaccid paralysis of the limbs post



(CBC: complete blood count, ESR: erythrocyte sedimentation rate, BMP: basic metabolic panel, ABG: arterial blood gas analysis, CK: creatine kinase, ACC: accordingly, MRI: magnetic resonance imaging, EMG: electromyography)

Figure 2: Approach to weakness in an ICU setting

asthma attack classically.[12-13] The sensation of touch and pain, bowel, and bladder sphincter functions preserved.[13] It could pose a diagnostic challenge to the neurologists if asthma were not diagnosed previously in the patient.[12] The pathogenesis of the disease, elucidated by the combination of viral infection and immunocompromise in the patient, which aids the viral invasion into the anterior horn cell.[13-14] Immunoglobulin (IVIG) and pulse therapy with corticosteroids are the mainstays of therapy.[13-14] Approach to muscular weakness in the ICU is depicted in figure 2.

2. Weakness Due to Preexisting Euromuscular Disorders

Spinal cord disorders. Motor weakness due to spinal cord disorders can be further classified into compressive and non-compressive myelopathy. Compressive myelopathy causing quadriparesis can be due to degenerative changes, trauma, tumor infiltration, abscess formation secondary to an infection, and syringomyelia.[15]

The most common cause of non-compressive myelopathy is transverse myelitis. Transverse myelitis is mostly idiopathic or post-infectious secondary to infection with viruses (CMV, Herpes, and Coxsackie) or bacteria (Mycoplasma, Legionella). Other causes include multiple sclerosis, Devic's disease, and collagen vascular disease.[16-18]

Transverse myelitis can be diagnosed with high clinical suspicion as it presents characteristically with bilateral signs and symptoms, a demarcated sensory level with progression period ranging from hours to weeks. CSF shows characteristic pleocytosis/ or high immunoglobulin levels, and MRI shows increased segmental contrast enhancement.[18]

The standard care of treatment for transverse myelitis includes IV corticosteroids such as methyl prednisone or dexamethasone, which helps in reducing spinal cord swelling and inflammation. Plasma exchange can be tried in refractory cases.[16]

Anterior Horn Cell Disorders

Amongst anterior horn cell disorders, Amyotrophic lateral sclerosis (ALS) is the well-known culprit causing respiratory weakness, and in 10% as presenting compliant[19-20] due to primary phrenic motor neuron involvement. The most common cause of ICU admission in these patients is acute decompensation secondary to respiratory distress precipitated by an infection.[20]

ALS presents with characteristic simultaneous upper and lower motor neuron involvement. The most common presenting symptoms include weakness, atrophy, fascicula-

tion, difficulty swallowing, slurred speech.[21-22] The disease is usually relentlessly progressive, with death occurring in 50% in 3 years and 80% in 5 years.[22] The most common complication encountered in ALS patients in ICU is aspiration pneumonia, secondary to respiratory failure, which almost always requires tracheostomy and percutaneous endoscopic gastrostomy(PEG) tube placement.[20,23] The electrophysiological study is the choice of investigation, which shows widespread denervation on EMG.

Other disease processes involving the anterior horn cell include poliomyelitis, which has been successfully eradicated.[21] West Nile fever is also known to cause meningoencephalitis with acute flaccid paralysis, which usually presents with GBS like symptoms.[21,24-25] CSF fluid shows a lymphocytic predominant pleocytosis.[21,24-25] ELISA for IgM and IgG is highly sensitive and is the initial choice of investigation in cases with high clinical suspicion.

Peripheral Nerve Disorders

Amongst the peripheral nerve disorders, GBS is well known to cause weakness in the ICU.[20] GBS usually occurs weeks after flu-like or diarrheal illness caused by infectious agents such as CMV, EBV, HSV, Mycoplasma, Chlamydia, and Campylobacter.[26-27] Weakness follows a characteristic fashion as rapidly progressive ascending motor and sensory paralysis, which later progresses to respiratory weakness and bulbar involvement.[26] Autonomic involvement is also commonly seen, presenting as postural hypotension, fluctuation in blood pressure, and cardiac dysrhythmias.[20,26-28] Respiratory paralysis is the most common indication for ICU admission.[20] About 30% of patients require ventilator support at some time during the illness.[20,26,29]

The most characteristic lab finding in GBS is CSF albuminocytological dissociation, which usually occurs 48 hours after the illness.[27] Electro diagnostic studies show the slowing of nerve conduction velocity in addition to conduction block and temporal dispersion.[27]

Table 3: Provides a comparison between West Nile poliomyelitis and GBS.

Features	West Nile poliomyelitis (16)	GBS
Onset	infectious	post-infectious
Weakness	asymmetric	symmetric ascending
Sensory symptoms	uncommon	common
Bladder issues	common	uncommon
Encephalopathy	common	uncommon
CSF	pleocytosis	albuminocytological dissociation
NCS/EMG	Fibrillation/positive waves	Conduction blocks and temporal dispersion

Management of GBS in ICU settings is governed by two parameters, i.e., vital capacity, and ABG. Intubation is recommended if VC <12-15 ml/kg, falling VC, and in patients with retained secretions.[29] The recommended treatment options are IVIG or Plasma Exchange.[26,29]

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 the exchange of a total of 200ml of plasma/ kg body weight.[20,29] Albumin is the ideal replacement solution for exchange.[31] Blood pressure should be monitored every 30 minutes during the exchange period.

IVIG in the dose of 2g/kg divided over five consecutive days is the recommended treatment. IgA deficiency must be ruled out before starting the therapy.[32] The patient must be monitored for the development of side effects such as headache, malaise, nausea, and others. Combination therapies of IVIG and Plasma exchange are not recommended and have no added benefits over individual treatment.[20,30,36] Steroids are not helpful in the treatment of GBS in ICU patients.

Neuromuscular Junction Disorders

The most common myasthenic syndrome encountered in ICU includes myasthenia gravis (MG).[33] The underlying defect in Myasthenia gravis is the decreased number of available acetylcholine receptors (AChRs) at neuromuscular junction secondary to antibody-mediated immune destruction, thus compromising the neuromuscular conduction and presenting as the motor weakness.[34] The distribution of muscle weakness has a characteristic fashion involving extraocular muscles, facial, bulbar, and later respiratory

involvement, and it usually presents as diplopia, dysphagia, difficulty in swallowing, and dysarthric speech.[29,33-34] In almost 85% of patients, the weakness becomes generalized, affecting the limb muscles.[35]

Myasthenic crisis is the most common reason for ICU admission in patients with MG. Myasthenia crisis is associated with respiratory compromise, presenting as respiratory muscle insufficiency and inability to handle excessive oral and respiratory secretions that require intubation and mechanical ventilation.[34,36-37]

In the setting of clinical worsening of myasthenia prompts excessive dosage of cholinesterase inhibitors, which increases the risk of cholinergic crisis. It is rare to see cholinergic crisis without concomitant myasthenia crisis. Cholinergic crisis is characterized by excessive secretions, diaphoresis, bradycardia, urinary urgency, bronchospasm, cramps, and weakness secondary to the peak of nicotinic and muscarinic toxicity. It typically occurs 2 hours after the last dose, and treated with atropine, pralidoxime, and/or glycopyrrolate.[29]

The most common precipitants of the myasthenic crisis include intercurrent infections, aspiration, sepsis, surgical procedure, medications, and pregnancy.[38] About 30-70% of seronegative myasthenic patients may have antibody directed against Muscle-specific tyrosine kinase (MUSK), such patients tend to have severe disease and high frequency of respiratory crisis compared to AChR positive patients.[39-40]

A vital capacity 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 commonly used to define a myasthenic crisis.[29, 33-34]

Around two-third to 90% of the patients with a crisis require intubation and mechanical ventilation and ICU management of the complications. Sepsis is the most common complication encountered in patients with the crisis in ICU settings.[29]

IVIG and Plasma exchange is the mainstay of treatment in crisis patients.[36] A typical course of IVIG is 2g/kg body weight daily for five days[19]; Five rounds of plasma exchange every other day for ten days is standardized therapy. IVIG is generally administered to total dose off 1g/Kg. most common side effects secondary to infusion are headache, nausea and fever. Renal failure and myocardial infarction form the hypercoagulability and aseptic meningitis is also reported.[29]

The use of 5 days pulse therapy with high dose intravenous methylprednisolone reported to improve symptoms in the severe myasthenia with fewer side effects.[40]

Botulism and tick paralysis are amongst the other neuromuscular junction disorders encountered in ICU. More than 110 cases are reported per year in the United States.[41] Botulism presents with flaccid paralysis, areflexia, and autonomic disturbances. Early diagnosis is imperative as early antitoxin therapy is associated with a decreased hospital stay, morbidity, and mortality.[42] Mechanical ventilation is the mainstay of treatment. Tick paralysis is associated with areflexia, ascending motor paralysis, and preserved sensations.[43-44] A careful search for the ticks and their removal aids in the rapid resolution of symptoms.[43-44]

Muscle Disorders

Inflammatory myopathies commonly encountered in the ICU are dermatomyositis and polymyositis. Both present with proximal muscle weakness and pain.[45] Dermatomyositis has characteristic skin lesions such as purplish periorbital (heliotrope) rash, which spreads to back and neck as shawl sign and Gottron's sign presenting as a rash over knuckles.[45-46] Dermatomyositis is also more commonly associated with malignancies.[46]

The initial investigation for diagnosis involves CK levels, definitive diagnosis made by muscle biopsy, and H&E stain. Steroids are the mainstay of treatment for inflammatory myopathies.[45-46]

Electrolytes Disturbances

Hypokalemia is the main culprit associated with weakness due to electrolyte disturbances in ICU patients.[47] Low magnesium is associated with increased mortality by 2 to 3 fold in the ICU patients. IV Magnesium as slow infusions of magnesium sulfate is the preferred in the ICU in cases of hypomagnesemia.[47]

Hypokalemic periodic paralysis presents with a recurrent weakness that can later progress to respiratory failure.[48] Patients with hypokalemia <3.5 mEq/l respond well to oral or IV potassium replacement. In refractory cases, hypophosphatemia should be suspected.[49]

Conclusion

Multiple predisposing factors are involved in the development of neuromuscular weakness in a critically ill patient in ICU. It could be due to a preexisting neuromuscular disease, which got exacerbated in critical illness or the complication of the critical illness itself. A thorough history and physical examination are of paramount importance, and should not be omitted even though the majority of patients are unresponsive, confused, or sedated. Particular impor-

tance should be given to the clues, such as the use of offending medications, underlying infections, history, and course of presenting illness, which help significantly in delineating the underlying disease process. Nevertheless, extensive imaging studies, biopsies, electrodiagnostic studies are required to reach the diagnosis in the majority of critically ill patients. A comprehensive investigation protocol must strictly adhere to all cases of weakness in ICU settings.

The spectrum of neuromuscular disease encountered in ICUs today has rapidly evolved over the last decades. Nowadays, weakness due to CIM and CIP presents twice to thrice more commonly than due to primary neuromuscular disorders.

Early diagnosis and prompt treatment are necessary not only to reduce morbidity and mortality in critically ill patients but also to reduce skyrocketing health care expenses.

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