Neuromuscular Weakness in Critically Ill

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Abstract
Neuromuscular weakness in critically ill has been increasingly reported in the recent years. Occasionally it may lead to difficulty in weaning the patients from mechanical ventilation, which is difficult to diagnose clinically. Though in well-planned studies the incidence has been reported to be high, the diagnosis is often missed due to the presence of various confounding factors in the form of drug effects, underlying disorder and coexisting abnormalities of the central nervous system. A high index of suspicion with detailed neurological and electrophysiological examination is required for an early and accurate diagnosis. A wide spectrum of disorders and drugs can be responsible for the critical illness neuromuscular abnormality. The most frequent and defined disorders include; critical illness polyneuropathy (CIP) which is characterized by a sensorimotor reversible polyneuropathy presenting as distal symmetrical weakness with loss of deep tendon reflexes. Acute myopathy is another important disorder in this group which usually presents with quadriplegia often related to steroid use. Persistent blockade of neuromuscular junction is also defined in critically ill patients. It is, therefore, important to understand these disorders and their implications in the management of these patients. Some of the conditions require prolonged neuro-rehabilitation. The various acquired disorders leading to neuromuscular abnormalities in critical care, and their diagnosis and management are discussed.

INTRODUCTION
Critical care is becoming part of medical care in all the disciplines of Medicine. With advances in field of mechanical ventilation, antimicrobial therapy and other supportive management, a large number of patients are surviving for long periods in intensive care units (ICU) and receive prolonged mechanical ventilation. Neurological examination in patients primarily suffering from non-neurological ailments and especially those receiving assisted ventilation is frequently omitted. At the same time detailed clinical neurological assessment is difficult in these patients. Physicians in ICU are more concerned in monitoring cardiorespiratory parameters, therefore, a neurological examination is often neglected. On the other hand, neuromuscular weakness leads to difficulty in weaning a patient from mechanical ventilation due to involvement of muscles of respiration. Due to lesser attention and difficulty in neurological examination, the neuromuscular weakness, though quite common in ICU, has been recognized quite late and has been reported only during last two decades. Electrophysiological studies are very important tool for accurate diagnosis of neuromuscular dysfunction in these patients. Early recognition is important for removing offending agent and continuation of supportive treatment, since most of the conditions are reversible and carry good prognosis provided there is improvement in underlying condition. A high index of suspicion is important to clinch the diagnosis. Therefore, though reportedly common, it is rarely diagnosed in routine practice. Understanding of prevalence, etiology, pre-disposing conditions, clinical and laboratory diagnosis would lead to early recognition, probable prevention and appropriate management.

Abnormalities of neuromuscular system complicating critical illness was first reported around 20 years back in a young woman with asthma who developed weakness following mechanical ventilation.1 She had also received hydrocortisone and pancuronium. This was followed by a report of five cases of polyneuropathy in critically ill patients reported by Bolton et al.2 With the improvement in medical facilities and advancement in management of acutely ill patients in tertiary hospitals, many neuromuscular complications of acute systemic illness involving both central and peripheral nervous system have come into light in the past couple of decades.

Critical Illness Neuromuscular Abnormalities (CINMA)
This is a group of disorders with clinical or laboratory evidence of neuromuscular weakness in critically ill patients in the absence of a primary neurological disorder responsible for that weakness. CINMA encompasses a wide spectrum of
disorders ranging from polyneuropathy to neuromuscular junction dysfunction and myopathy (Table 1). This entity can be diagnosed in critically ill patient who has weakness of any muscle group, presents with signs of sensory abnormality or decreased deep tendon reflexes. Electrophysiologically and histological examinations may reveal abnormalities. Among the various disorders that can cause CINMA, critical illness polyneuropathy (CIP) characterized by primary axonal degeneration of motor and sensory fibres, is the most common entity. The second most fully described syndromes are of pure motor deficits comprising of muscle atrophy of type II fibres, necrotizing myopathy and motor axonopathy. Other potential risk factors for the neuromuscular weakness in critically ill patients like previous neuromuscular disease, diabetes mellitus, alcoholism, HIV, malignancy and renal failure should be kept in mind during evaluation.

Sepsis, as we all know, is an infection with systemic manifestations and positive cultures for bacterial, viral or fungal infection. Sepsis syndrome describes a constellation of features that may occur with or without infection or positive cultures. It includes fever or hypothermia, tachycardia, tachypnoea, hyperdynamic circulation, hypercatabolic state, evidence of organ hypoperfusion and dysfunction. More recently the umbrella term - systemic inflammatory response syndrome (SIRS) is used for both the above conditions. At least 70% of patients with sepsis admitted to ICU develop neurological complications. If the septic condition persists for more than two weeks then an axonal peripheral neuropathy is a common finding known as critical illness polyneuropathy (CIP). A myopathy may also develop. Ventilatory problems, mainly in the form of difficulty in weaning from the ventilator may also be present.

Although reversible, ICU-acquired neuromuscular weakness often markedly prolongs the total duration of hospitalization and subsequent care. Even after recovery medical, economic and psychosocial costs of ICU acquired weakness present a major problem in critical care medicine.

### Table 1 : Critical illness neuromuscular abnormalities (CINMA) : Anatomic and functional classification

<table>
<thead>
<tr>
<th>Clinical context</th>
<th>Anatomic disorder</th>
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<tbody>
<tr>
<td>1. Sepsis</td>
<td>Sensory motor axonopathy(CIP)</td>
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<tr>
<td></td>
<td>Critical illness myopathy</td>
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<tr>
<td>2. Non-depolarizing NM blockers</td>
<td>Motor axonopathy, necrotizing myopathy, thick filament myopathy, NM junction abnormalities.</td>
</tr>
<tr>
<td>3. Corticosteroids</td>
<td>Motor axonopathy, necrotizing myopathy, thick filament myopathy, steroid myopathy and atrophy.</td>
</tr>
<tr>
<td>4. Asthma</td>
<td>Muscle necrosis</td>
</tr>
<tr>
<td>5. Immobilization</td>
<td>Diffused type II fibre atrophy</td>
</tr>
<tr>
<td>6. Malnutrition</td>
<td>Muscle atrophy</td>
</tr>
<tr>
<td>7. Dyselectrolytemia, hypophosphatemia, hyperkalemia, hypokalemia, hypercalcemia, hypermagnesemia</td>
<td>Muscle cell dysfunction.</td>
</tr>
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#### Critical illness polyneuropathy (CIP)

A diffuse axonal polyneuropathy has been described as a cause of weaning failure and muscle weakness. It has been found to occur in 70% of patients in sepsis and multiorgan failure (MOF). By definition CIP is an acute reversible neuropathy that develops during the treatment of critically ill patients. Primary neuropathies requiring ICU admission like GBS have to be ruled out. The course of CIP is monophasic and self-limiting and shows remarkable recovery if the patient survives the underlying critical illness. Pathophysiological mechanisms for this condition are still not clear and various explanations have been put forth. In critically ill patients with sepsis, hyperglycemia and hypoalbuminemia are associated with decrease in peripheral nerve function. Hyperglycemia increases endovascular resistance with decrease in blood flow to the nerves. Microcirculation of various organs is disturbed in sepsis and blood vessels supplying nerves are susceptible because they lack autoregulation. Cytokines like TNF and IL-1 secreted in sepsis increase microvascular permeability leading to endoneural edema, which causes hypoxia leading to axonal degeneration. All these mechanisms have been postulated but none is proved.

In a prospective study in patients with sepsis and MOF conducted by electrophysiological studies done on 10th and 25th day of illness in 73 patients, as many as 46 patients had electrophysiological evidence of CIP on day 10 and four more were added on second EPS. Duration of mechanical ventilation, length of ICU stay and in-hospital mortality were significantly greater in patients with CIP. After multivariate analysis hyperosmolality, parenteral nutrition and use of neuromuscular blocking agents (NMBAs) were independent risk factors for occurrence of CIP.

Many workers have reported CIP in critically ill patients (Table 2). Majority of reports of CIP have been in patients with sepsis and multiorgan failure. We have reported a case of CIP in patient with acute severe, asthma requiring mechanical ventilation without evidence of sepsis and another two cases of CIP with different outcomes. There is only one more case report of CIP from India in a patient with renal failure and sepsis. It is likely that this entity is not recognized very often considering its high incidence reported from the West.

CIP needs to be differentiated from other causes of acute onset flacid paralysis and areflexia in critically ill patients. Neuropathy in critically ill patients can be due to various causes like aminoglycosides, antibiotics, metronidazole, prolonged NMB use, Guillain Barre syndrome, pancreatic diseases, nutritional disturbances, thiamin and vitamin E deficiency, pyridoxine abuse, hypophosphatemia, porphyria and remote effects of cancer. These need to be kept in the differential diagnosis and looked for before keeping a diagnosis of CIP. Although sepsis is a frequent cause of CIP, similar changes have been reported in non-septic critical conditions like acute pancreatitis, major surgery, cardiovascular shock, severe trauma, burns or respiratory failure. Therefore CIP might indicate the failure of just
another organ system due to the stress of the underlying critical condition. Difficulty in weaning from the ventilator is a common manifestation which brings this condition to light. On neurological examination, a severe tetraparesis with relative sparing of cranial nerves is seen. By means of EPS studies denervation of facial muscles has been documented but never severe enough to impede eye closure. The tendon reflexes are decreased or absent but may be normal in one-third of the patients. The diagnosis is often missed because the patients are critically ill and often there is altered level of consciousness either due to disease or sedation. Use of muscle relaxants in patients on mechanical ventilation makes neurological examination meaningless. Attachment of supportive equipment also makes the examination difficult. A high index of suspicion, a detailed neurological examination supported by EPS is required to make a firm diagnosis.

Electrophysiological studies shows reduced compound motor and sensory nerve action potential amplitudes with normal conduction velocities. Needle EMG reveals fibrillation potentials and positive sharp waves indicating denervation. Morphological studies have shown axonal degeneration of both motor and sensory fibres without evidence of inflammation or microinfarcts resulting in denervation of proximal and distal muscles. Muscle biopsy shows scattered atrophic fibres in recent denervation and grouped muscle fibre atrophy in long standing cases. This condition should be differentiated from abnormalities of neuromuscular transmission and myopathies, though they can even coexist.

There is no specific treatment for CIP and management is mainly supportive. The extent to which CIP increases mortality and secondary morbidity in critically ill patients by prolonging time on mechanical ventilator is unknown. Patients in ICU with CINMA, have been reported to have higher mortality of 48% as compared to that of 19% in patients without CINMA. Recovery is remarkable and overall outcome is favourable if the underlying condition is effectively treated. In incomplete recovery a pressure palsy of peroneal nerve is common.

CIP can be easily differentiated from Gullian Barre syndrome (GBS) by the presence of demyelinating features on EPS and increased CSF proteins. Preservation of tendon reflexes at the peak of the disease is strongly against GBS. Facial diplegia with lack of eyelid closure is not seen in CIP, despite EPS changes in facial muscles. It is difficult to differentiate axonal variants of GBS though most patients of CIP have history of preceding severe sepsis or multiorgan failure (MOF). The basic difference lies in the pathology where GBS is an immune-mediated injury and CSF shows albuminocytological dissociation. As discussed before, weakness and weaning failure should be attributed to peripheral nerve disorders only when lesions of CNS have been ruled out on the basis of clinical findings and imaging studies. However, CIP may also develop in patients with primary CNS disease. Porphyria is another cause of acute muscle weakness which may be precipitated by multiple drug administration. However, it can be differentiated by bathing suit distribution of neuropathy, sensory involvement, abdominal pain and mental changes.

**Disorders of neuromuscular transmission**

In recent years there have been reports of prolonged neuromuscular blockade in patients being treated with non-depolarizing neuromuscular blocking agents (NMBA) including pancuronium, vecuronium and atracurium. Metabolism of these drugs might be reduced leading to increased plasma levels which may persist for up to two weeks after discontinuing the drug. An abnormal decrease in compound muscle action potential amplitudes with slow repetitive stimulation has been demonstrated (decremental response) in such cases. Concomitant use of aminoglycoside and polypeptide antibiotics increases the neuromuscular block. Latent myasthenia gravis may be unmasked. Neuromuscular transmission dysfunction generally coexists with neuropathy or muscle dysfunction and thus might be overshadowed by the features of neuropathy or myopathy. Botulism is a rare cause of muscle paralysis which causes anticholinergic features, including dry skin and mucous membranes, pupillary dilatation, external ophthalmoplegia along with paralysis of limb and muscles.

**Myopathy**

Myopathic changes occur frequently in ICU patients.

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**Table 2 : Critical illness polyneuropathy- Case reports**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient group</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>1. Tepper et al</td>
<td>Septicemia shock</td>
<td>19 of 25 patients (76%) in ICU patients.</td>
</tr>
<tr>
<td>2. Coakley et al</td>
<td>ICU patients</td>
<td>Of 44 patients in ICU, 19 combined motor and sensory, 4 predominantly sensory axonal neuropathy, 11 pure motor syndrome</td>
</tr>
<tr>
<td>3. Lacomis et al</td>
<td>Organ transplant</td>
<td>Of 92 patients in ICU : 13% CIP, 42% myopathy</td>
</tr>
<tr>
<td>4. Thiele RL et al</td>
<td>Post-cardiac surgery</td>
<td>7 out of 1511 patients</td>
</tr>
<tr>
<td>5. Garnedro- Montero et al</td>
<td>Sepsis</td>
<td>50 out of 73 ICU patients</td>
</tr>
<tr>
<td>6. Thiele RL et al</td>
<td>Post-cardiac surgery</td>
<td>12 out of 37 ICU patients</td>
</tr>
<tr>
<td>7. Mohrm et al</td>
<td>Survivors of MOF</td>
<td>7 out of 33 patients</td>
</tr>
<tr>
<td>8. Hund EF</td>
<td>Weaning failure</td>
<td>7 ICU patients with weaning difficulty</td>
</tr>
<tr>
<td>9. Leijten et al</td>
<td>ICU patients</td>
<td>29 out of 50 patients</td>
</tr>
<tr>
<td>10. Young GB</td>
<td>One case of severe septic illness with CIP</td>
<td></td>
</tr>
<tr>
<td>11. Witt NJ et al</td>
<td>ICU patients</td>
<td>30 out of 43 patients</td>
</tr>
<tr>
<td>12. Coronel B</td>
<td>Case report of 15 patients with CIP with difficult weaning</td>
<td></td>
</tr>
<tr>
<td>13. Lopez JB et al</td>
<td>Case report of 5 patients with CIP in ICU</td>
<td></td>
</tr>
<tr>
<td>14. Khilnani et al</td>
<td>2 cases of sepsis with CIP with different outcome</td>
<td></td>
</tr>
<tr>
<td>15. Garnacho- Montero</td>
<td>Sepsis with MOF</td>
<td>50 of 73 pts</td>
</tr>
</tbody>
</table>

ICU - Intensive care unit, CIP - critical illness polyneuropathy, MOF - multiple organ failure, SIRS - Systemic inflammatory response syndrome.
Three main types have been described - critical illness myopathy, myopathy with selective loss of myosin (thick) filaments, and acute necrotizing myopathy of intensive care.

1. **Critical illness myopathy**: Myopathic changes on EMG examination and biopsy have been described in ICU patients. Though, in some patients myopathy is more predominant but usually it is mild and associated with CIP. Myopathy have been reported in upto 78% of patients with denervation due to axonopathy. Histologically this myopathy is characterized by abnormal variation in muscle fibre size and fibre atrophy, internalized nuclei, rimmed vacuoles, fatty degeneration of muscle fibres and single fibre necrosis. No inflammatory changes are seen and CK levels are mostly normal. This myopathy affects both fibre types but may be limited to type II myofibres. Factors leading to the development of critical illness myopathy may be same as for CIP. Proinflammatory cytokines IL-1 and TNF are important mediators of sepsis-induced muscle proteolysis.

2. **Thick filament myopathy**: Another form of myopathy is observed in patients who have been on corticosteroids for acute severe asthma or organ transplantation, along with the use of neuromuscular blocking agents (NMBA). This myopathy is characterized by the selective loss of myosin filaments, and changes of neuropathy are usually absent. A similar myopathy has been observed in patients of myasthenia gravis who have been on large parenteral doses of corticosteroids. Increase in number of corticosteroid receptors over muscle after denervation could be a reason for the toxic effects of steroids. Corticosteroids and sepsis stimulate muscle proteolysis. Triggering factors like use of NMBA, denervation and membrane inexcitabilty could contribute to the production of such myopathy. CIP may potentiate such myopathy.

In another study it was found that critically ill patients on pancuronium and corticosteroids developed persistent tetraplegic syndrome with increase in creatine kinase (CK). None of these patients were septic or had MOF. A strong association between CK increase and pancuronium administration was found. Duration of deficit ranged from 4 to 52 weeks and could be correlated to the total dose of corticosteroids received. EPS showed neuropathy and myopathic changes. Muscle biopsy showed significant myopathic changes. CK enzyme levels seemed be a marker of the disorder. The blockng agent corticosteroid myopathy (BACM) has also been used for this myopathy.

Another way of monitoring the dose of NMBA is train of four (TOF) testing. This involves four electrical stimuli to a peripheral nerve and monitoring of the motor response. Level of neuromuscular blockade can be established from the motor response and the dosage of NMBA can be adjusted accordingly.

3. **Necrotizing myopathy**: A subgroup of critically ill patients with myopathy may develop prominent muscle necrosis with vacuolation and phagocytosis of muscle fibres. CK is frequently elevated in these patients. The disease can even progress to frank rhabdomyolysis in severe cases. This type of myopathy has also been found to occur in patients with acute severe asthma and has also been correlated with the use of both NMBA and steroids together or high doses of NMBA alone. This myopathy is not commonly seen in septic patients.

Diagnosis of myopathy in critically ill patients is difficult. EPS and serum investigations are not sensitive. CK has been reported normal in many patients showing myopathy on biopsy. Needle EMG may suggest a wrong diagnosis of neuropathy due to presence of spontaneous activity. This could occur due to separation of myofibres from the muscle end-plate. Direct muscle stimulation and calculation of the ratio of nerve and muscle evoked compound muscle action potential amplitudes is useful for detection of myopathies. Muscle biopsy is the diagnostic method of choice but is invasive and thus not recommended routinely. It should be performed in ICU patients with severe weakness not clearly attributable to CIP. As far as therapy is concerned, no specific treatment is available. It is recommended that long term NMBA infusion and high dose steroid therapy should be avoided especially when used together. Dosages of drugs should be adjusted for hepatic and renal dysfunction, if present. Daily interruption of sedative drug infusions decreases the duration of mechanical ventilation and the length of stay in intensive care unit. Serial CK measurements and repeated electrodiagnosis may help in early detection of myopathy.

**Failure to wean from ventilation due to neuromuscular weakness**

Patients who have CIP and have recovered from the underlying condition while on mechanical ventilation may not sustain trial of spontaneous breathing due to weakness of respiratory muscles. Lemaire in a review reported that peripheral neuromuscular disease was responsible in 17% of cases of difficult weaning. With clinical history, examination, CK levels and EPS studies it is possible to reach at a precise diagnosis of neuromuscular weakness. In critically ill patients detailed examination may not be possible due to encephalopathy, sedation and mechanical ventilation. Bedside EPS testing is the cornerstone to establish the presence of neuromuscular weakness. It should include sensory and motor conduction, compound muscle and sensory nerve action potential amplitudes, distal motor and F wave latencies, needle EMG and repetitive stimulation studies. Phrenic nerve conduction and compound diaphragm action potential amplitudes and EMG of intercostal muscles may be important in patients with intractable dependence on ventilator. When appropriate levels of NMBA and porphyrins may be required along with the regular measures of CK. History of use of steroids, other medications, history of other chronic illness or any prior neurological deficits should be inquired. Lumbar puncture is indicated if GBS is suspected. In occasional patient muscle biopsy may be useful in establishing a diagnoses of myopathy. Establishing a diagnosis of neuromuscular weakness in critically ill patients is important because weaning a patient with denervation is unlikely to be successful.
Similarly mobilization may not be possible. Positioning should be planned to avoid additional damage by pressure. NMBAs and steroids should be used in minimum required doses and regular monitoring of CK should be done. Renal and hepatic function, acidosis and electrolyte imbalance should be monitored. The diagnosis also gives us information on prognosis and may influence the morbidity and mortality associated with the illness as described earlier and might avoid unnecessary investigations. Neuropsychological and muscle histological abnormalities are extremely common in long term mechanically ventilated patients and any weakness should not be attributed to irreversible neurological damage, giving a pessimistic prognosis eventhough most of these disorders are reversible.

Another manifestation of neuromuscular weakness caused by ICU acquired acute myopathy and neuropathy is acute neuromuscular respiratory failure (NM-ARF). This may arise after resolution of the respiratory and cardiac dysfunction and successful weaning from the ventilator. Diagnosis of NM-ARF is difficult. Dyspnoea may be absent, chest radiograph is normal and arterial blood gases worsen only in the late stage.\textsuperscript{30} NM-ARF is responsible for unplanned ICU readmission or even unexpected death. Therefore a strict monitoring of respiratory muscle function is recommended after discharge to the general ward of patients with proven NM-ARF. Chest physiotherapy can resolve the condition.

Prospective studies of CINMA done so far have included a small number of patients with various EPS findings but have insufficiently reported clinical correlates and long term outcome in such patients. Therefore for evaluation of risk factors, pathophysiological mechanisms and the long term clinical outcome, further prospective studies are required. These ultimately may help in suggesting measures for prevention and treatment. The diverse spectrum of disorders under CINMA suggest that a single cause is unlikely. Subclinical neuromuscular abnormalities may occur as early as 2nd day and can be detected with the use of EPS.\textsuperscript{31}

**Prevention of neuromuscular weakness in ICU**

All efforts should be made to prevent occurrence of neuromuscular weakness in critically ill patients as this leads to prolonged requirement of mechanical ventilation and increased morbidity. Consequently increased duration of ICU stay leads to enhanced cost of care. Since most common cause of this complication is sepsis, an early and appropriate treatment of sepsis is very important. Use of neuromuscular blocking agents should be minimized. With currently available assist-controlled modes of mechanical ventilation, it is possible to avoid use of these agents to a large extent. A check on serum electrolytes, serum phosphate, magnesium and serum calcium and its correction, whenever deranged, is important. Physician should have knowledge of pharmacological agents causing neuromuscular weakness. Use of such agents should be discontinued at first sign of muscular weakness. Ideally use of electrophysiological studies would help in the early detection of such abnormality but such facilities are not widely available.

In conclusion, neuromuscular weakness in the critically ill is an important entity requiring recognition. The wide spectrum of disorders involved and the presence of underlying illness make the diagnosis difficult. With regular neurological examination and electrophysiological studies accurate diagnosis is possible quite early. Much is yet to be learnt about the pathogenesis and the treatment modalities for these conditions. However, most of these disorders are reversible. Efforts of weaning and neurorehabilitation should be guided by the results of EPS studies.

**References**


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**Announcement**

**3rd Mayo-IID International Symposium on Diabetes Organized by Indian Institute of Diabetes**

(in collaboration with World-India Diabetes Foundation and Division of Endocrinology, Mayo Clinic, Rochester, USA) **14th and 15th February 2004** at Le Meridien Kovalam Beach Resort, Trivandrum, Kerala, India.

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