Critical Illness Neuropathy

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INTRODUCTION

The clinical entity critical illness polyneuropathy occurs almost exclusively in patients in critical care units and has been characterized as a complication of sepsis and multiple organ failure.

Critical illness polyneuropathy is an acute neuromuscular disorder of severely ill patients characterized by distal axonal degeneration of motor fibers causing flaccid tetraparesis, decreased or absent deep tendon reflexes, and muscle wasting of the limbs in absence of neurological disorder that commonly accompanies pts with SIRS & MOF.

Sensory fibers and cranial nerves are generally preserved. It is a diffuse axonal polyneuropathy seen in severely ill patients, in the intensive care unit; most patients have been on multiple drugs and cannot be weaned from ventilatory support; electrophysiological studies show evidence of an axon loss polyneuropathy, predominantly motor; of unknown etiology.

CIP/CIM are characterized by clinical or electrophysiological evidence of neuromuscular weakness with no primary neurological disorder.

It may be a common cause of the difficulty in weaning patients from the ventilator, particularly those who show intractable ventilator dependence.

It is usually associated with or accompanied with a coma producing septic encephalopathy. The neuropathy is usually not apparent and may be noted only when the brain dysfunction is resolving.

Patients usually have a protracted hospital course complicated by multi-organ failure and the systemic inflammatory response syndrome. Elevated serum glucose levels and reduced albumin is risk factors for nerve dysfunction, as is prolonged intensive care unit stay.

Acute myopathy, critical illness myopathy (CIM), frequently develops in a similar setting, often in association with the use of corticosteroids and/or neuromuscular blocking agents.

During the critical phase of a major illness, such as severe sepsis, pneumonia, adult respiratory distress syndrome (ARDS) or major surgery, the aims of treatment include addressing the primary disease and avoiding known complications such as multiple organ failure (MOF) CIP/CIM.

EPIDEMIOLOGY

The prevalence and impact of acquired neuromuscular weakness is likely larger than generally recognized. Greater than 50% of patients mechanically ventilated for more than 7 days will develop electrophysiological abnormalities with 25-33% developing clinically overt weakness. Acquired neuromuscular dysfunction is associated with difficulty in separating from mechanical ventilation, increased hospital costs, and increased mortality. The potential economic impact of this problem is large, with one estimate of an average of $66,000.00 per patient in excess hospital charges attributable to acquired neuromuscular weakness in the ICU. (Fig. 1)
PATHOGENESIS
The pathogenesis of CIP is still poorly understood, the actual etiology, however, has yet to be determined. The pathogenesis needs to be clarified to treat patients more effectively. The causes of CIP are unknown, though they are thought to be a possible neurological manifestation of systemic inflammatory response syndrome.

Polyneuropathy may develop after one week of the systemic inflammatory response syndrome, but the frequency tends to correlate with the duration of the severe illness. Sepsis and multiorgan dysfunction increase the risk of CIP, as shown in both retrospective and prospective series in one small series; electrophysiological evidence of acute neuropathy was present as early as 2 days after the diagnosis of sepsis.

Critical illness polyneuropathy may be part of the final common pathway of the systemic inflammatory response syndrome, sepsis, and multiple organ failure, with cytokines such as the tumor necrosis factor- playing a pivotal role on the activation of the body defense system. Thus, CIP/CIM are likely represent an organ failure of sepsis and SIRS, presumably as a result of the same basic mechanisms that lead to multiple organ dysfunction, such as inflammation, apoptosis, thrombosis, and oxidant injury. (Fig. 2 & Fig. 3).

Micro vascular changes in peripheral nerves & increased endothelial expression of P-selectin and ATP depletion leads to bioenergetics failure & Activation of specific proteolytic stems leads to Myofilament loss & Apoptosis.

Number of other conditions, such as the underlying disease,
diabetes, malnutrition, immobility, dialysis, and the use of neuromuscular blocking agents, corticosteroids, or amino glycosides, has been also postulated. Corticosteroids and neuromuscular blocking agents, which are widely used in intensive care, may contribute to the development of CIP and CIM, as may elevations in blood sugar, which frequently occur in critically ill patients.

Critical illness polyneuropathy is associated with varying degrees of weakness & axonal degeneration on EMG & denervation atrophy on muscle biopsy. Causative role of CIP in resp failure is controversial because it has been associated with other condition that affects global muscle function such as sepsis & MOF.

CIM is usually associated with CIP and is reported in case of asthma & may be related to glucose corticoid & NMB agents. Mechanical Ventilation has direct harmful effect on diaphragmatic structure & function. Disuse atrophy, tonic effect of PEEP cofounding effect of anaesthesia & NMB agents.

**CLINICAL FEATURES**
- Often presents with difficulty in weaning. (Note that time to successful discontinuation of ventilation is not reduced by respiratory muscle "training" and that it is determined by time to resolution of neuropathy).
- It is mixed motor and sensory neuropathy but motor signs tend to predominate.
- Tends to cause distal muscle weakness (as do inflammatory, diabetic, porphyries neuropathy), particularly affecting lower limbs.
- Cranial nerves are unaffected - in common with other axonal neuropathies. Discrepancy between facial grimacing and decreased limb movement on painful stimulus is often striking.
- Reflexes usually disappear during the course of the illness but absent reflexes are not a prerequisite for diagnosis subclinical in 50%.
- NB features may be modified by presence of co-existing septic encephalopathy.
- Neuromuscular weakness typically becomes apparent when an attempt is made to wean the patient from the ventilator, although there are earlier clues, which include relative lack of movement after regaining consciousness, and (not inevitably) loss of deep tendon reflexes that had been present earlier.

**Diagnosis & Differential Diagnosis**
Monitoring patients for signs of flaccid limbs, reduced deep-tendon reflexes, and respiratory weakness may be the first step to detecting CIP. However, overt clinical signs are not always present.

Physical assessment includes a neurologic exam when possible, monitoring unexplained respiratory failure or difficult weaning from the mechanical ventilator, performing reflex stimulation, and observing patterns in deep-tendon stimulation.

The diagnosis of CIP relies on electrophysiological testing and biopsies. Assessing nerve conduction and needle EMG of the peripheral nervous system will identify polyneuropathies in most cases

**ELECTROPHYSIOLOGICAL STUDIES**
Nerve conduction studies reveal compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes to be considerably reduced with minor changes in velocities and latencies consistent with axonal degeneration of peripheral nerve motor and sensory fibers. Fibrillation potentials and positive sharp waves detected by needle EMG indicate the presence of spontaneous muscle activity and denervation as CIP progresses. Electrophysiological tests will yield the same results in the phrenic nerve if CIP is the cause of weaning difficulties. (Fig. 4 & Fig. 5)

The differential diagnosis of CIP is challenging. Guillain-Barré syndrome is one of the most difficult Neuromuscular disorders to differentiate from CIP. Characteristics that
distinguish Guillain-Barré syndrome from CIP are facial weakness, ophthalmoplegias, Dysautonomia, profuse sweating, sustained tachycardia, and labile blood pressure. Patients with either Guillain-Barré syndrome or CIP show a reduction in CMAP with EMG testing, but this is more pronounced with Guillain-Barré syndrome, and minimal spontaneous activity is observed for Guillain-Barré syndrome compared with CIP.

Electrophysiological distinction between the axonal form of Guillain-Barré syndrome and CIP may not be reliable. Mean CSF protein level in Guillain-Barré syndrome is significantly higher than in CIP. A systematic approach is suggested in Fig. 6. The algorithm illustrates the early ruling out of spinal cord disease (e.g., in cases of trauma, coagulation disturbance, infection, acute disseminated encephalomyelitis, and then moving on to a clinical-biochemical-electromyography assessment.
A neuromuscular transmission defect. Slow inactivation of neuromuscular blocking agents, unrecognized myasthenia gravis or myasthenia [Lambert-Eaton] syndrome is easily detected with repetitive nerve stimulation, revealing either a detrimental or incremental response. Neuropathies other than CIP that may manifest after ICU admission include Guillain-Barré syndrome.

Acute immune-mediated demyelinising polyneuropathy (and its various subtypes), porphyria and recurrent chronic inflammatory demyelinising polyneuropathy. These are easily ruled out.

Demyelinating inflammatory neuropathies usually cause slowing of conduction velocity and conduction block on electromyography studies and produce increased protein in the cerebrospinal fluid. Biochemical screening for porphyria during acute attacks should be positive.

TREATMENT REMAINS ELUSIVE

There is no direct treatment for CIP and CIM; Possible prevention:
- Treatment of underlying sepsis /SIRS
- Glycemic control with insulin (?40~48%)
- Minimize steroid and depolarizing NMBA
Possible treatment
- intensive psychological care and reassurance
- intensive physiotherapy and supportive care
- Intensive rehabilitation program

For the most part, management consists of resolving the conditions that resulted in the patient being transferred to the ICU.

Hyperglycemia and sepsis are associated with the underlying conditions, which should be aggressively managed and controlled in the acute care hospital. An intensive insulin protocol is encouraged,

Early identification and treatment of infection in high-risk patients can help to avoid sepsis. Other factors that may improve or prevent CIP and CIM include supportive care that limits end-organ dysfunction, Use of low-tidal-volume ventilation for patients with adult respiratory distress syndrome. The use of semi recumbent positioning to prevent VAP protocols that provide daily interruptions of sedative infusions. More judicious employment of neuromuscular blocking and corticosteroid drugs can also help.

Neuromuscular blocking drugs, used in surgery, can build up in the system in the event of liver or kidney failure, causing muscle weakness. This buildup can contribute to CIP and CIM. The path to better management of CIP and CIM lies in early diagnosis, intervention, and diagnostic testing should be considered for all patients with unexplained weakness after recovery from or during a critical illness.

Although the prognosis is favorable once the patient leaves the acute care hospital, these conditions result in substantial morbidity, mortality and costs And could likely be improved with earlier diagnosis and more timely intervention. To achieve this goal, however, more awareness on the part of the medical establishment is needed, as well as further research into the causes of and treatments for CIP and CIM.

PROGNOSIS AND OUTCOME

Short-term prognosis:
- high mortality rate with sepsis/ SIRS
- take weeks to months to recover
- Prolonged ventilator support?
- scoring system? APACHE III

Long-term prognosis:
- 50% chance of complete recovery
- Depending on the initial severity

TAKE HOME MESSAGE

CIP is an acute, predominantly motor axonal polyneuropathy occurring in critically ill patients. Onset in ~3d as 3 D’s (Difficulty weaning and distal weakness with DTR ↓). Electrophysiological studies are valuable and sensitive. Neither therapy nor prevention is available. Weeks to months are needed to recover (50%).

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