Chapter 121

Intensive Care Unit-Acquired Paresis: Spectrum of Neuromyopathies

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HISTORY

Muscle weakness and atrophy occurring during the course of sepsis was described in 1892 by Sir William Osler. The first description on this entity came almost a century later when Charles Bolton described an axonal polyneuropathy in four patients who had sepsis and coined the term CIP. This has been found to be increasingly associated with a severe systemic response to infection, resultant multiorgan failure with resultant motor weakness with mortality as high as 30–50%. This is now recognized to be a very important etiology for difficulty in weaning patients in the intensive care unit (ICU) setting with prolonged ICU/hospital stay.

EPIDEMIOLOGY

The prevalence of this disorder varies from 20% to 90%, and now with increased awareness, improved sedation protocols, judicious use of neuromuscular blocking agents (NMBAs), good glycemic control, the incidence of this disorder is coming down. Systemic inflammatory response syndrome (SIRS) occurs in response to severe infection or trauma of mechanical, thermal or chemical nature. SIRS is associated with the release of several mediators, such as cytokines and free radicals, with resultant effect on the microcirculation throughout the body including the central nervous system and peripheral nervous system. In patients who have been in the ICU for a week or longer, a good number of them would have SIRS, either as a primary event or as a complication of invasive procedures such as endotracheal intubation or insertion of central lines. SIRS, when associated with documented infection, the term sepsis could be applied. Severe sepsis and septic shock is reserved for those patients with organ dysfunction and hypoperfusion/hypotension, despite adequate fluid replacement. Although critical illness weakness (CIW) was thought to be an axonal neuropathy, there has been an increasing incidence of reports of a concomitant myopathy, which could be mainly related to high doses of steroids and NMBAs. This is of great relevance in the developing world setting, where there are limited resources; the development of CIW would prolong the ICU stay with increased morbidity and mortality. There is a paucity of studies looking at the patterns of electrophysiological abnormalities and putative predictors for the development of weakness.

Pathogenesis and Microcirculatory Changes

When there is SIRS with multiorgan dysfunction syndrome, there is a disturbed humoral and cellular response, with increased capillary permeability and endothelial damage. There is microcirculatory dysfunction with tissue hypoxia. In this setting, when corticosteroids and NMBAs are added, there is oxidative stress. The blood vessels supplying peripheral nerves lack autoregulation and the cytokines are responsible for increased capillary permeability, there is endoneurial damage and hypoxia. The glutathione level, both total and reduced form, is reduced in the muscle. There is mitochondrial dysfunction and oxidative stress, glutamine depletion to 15%, impaired reutilization of oxidized glutathione due to reduced nicotinamide adenine dinucleotide phosphate (NADPH), with increased muscle catabolism.

Critical illness polyneuropathy (CIP) was described about 30 years ago to be a rare complication of sepsis and multiorgan failure. The initial reports of cases had only a few cases of associated myopathy, mainly occurring in conjunction with prolonged use of NMBAs and steroids in the required settings. There is recent literature on myopathies occurring in patients who have had no exposure to the implicated agents. Such findings, plus the increased use of extended electrophysiological technique including direct muscle stimulation (DMS), along with the profuse use of punch biopsies have revealed that the incidence of CIM maybe on par, or if not more than the classical critical illness myopathy (CIM) form of weakness in the ICU. There are some investigators who use of the term “CIW” as the apt term for this condition, pending the fact that the site of lesion in this disorder is speculative. It therefore only seems reasonable to use the term CIP or critical illness myopathy (CIM) to describe the electrophysiological findings in a subset of patients with CIW.

Recent studies have revealed that some patients experience prolonged (from 6 hours to > 7 days) neuromuscular (NM) blockade after termination of vecuronium therapy. The prolonged blockade has been associated with metabolic acidosis, elevated magnesium levels, females, renal failure and high plasma concentrations of 3-desacetyl vecuronium. There could be dysfunction of voltage and ligand-gated sodium, potassium, calcium and other ion channels in nerve and muscle membranes, microtubule integrity and functional integrity of fast axonal transport mechanisms, neurotransmitter release and reuptake mechanisms, synaptic cleft integrity, transmitter receptor turnover at the neuromuscular junction (NMJ), T-tubule function, the mechnochemical mechanisms of myofibrillar excitation: contraction coupling and cross-bridge formation. The integrity of these structural and molecular mechanisms is vital to maintain normal muscle strength. If abnormalities develop in any of these mechanisms, in various combinations, this could manifest as weakness.

Taking into account the various probable sites of involvement, the term “polyneuromyopathy” has been used in recognition of the multifactorial nature of this problem. Hence, it might be prudent to use the term “CIW.”
Section 16  Chapter 121  Intensive Care Unit-Acquired Paresis: Spectrum of Neuromyopathies

There could be different components encompassing the spectrum of CIW:
- Myopathic component
- Neuropathic component
- Neuromuscular junction component
- Metabolic component
- Encephalopathic component.

The recognition of these components helps in the understanding that “CIW” is a continuum and should not be seen in isolation.

SPECTRUM OF CRITICAL ILLNESS WEAKNESS

Critical Illness Neuropathy

Charles Bolton had first described this entity in 1984. CIN is an acute sensorimotor polyneuropathy and this occurs in about 50-70% of patients who develop SIRS. SIRS occurs in about 20-50% of patients admitted to ICU’s which makes CIN one of the important causes of acute polyneuropathy. This is not identified clinically in most patients, as this is usually preceded by an encephalopathy. On clinical examination, they exhibit features of flaccid weakness of the extremities which is often severe with loss of tendon reflexes. The neuropathy is a distal axonopathy, of both motor and sensory axons, with no inflammation. Electrodiagnostic studies will demonstrate reduction or absence of both compound muscle and sensory nerve action potential (SNAP) and electromyography (EMG) shows features of denervation.

Nerve Conduction Studies would demonstrate the involvement of the phrenic nerves along with the peripheral neuropathy which would account for the difficulty in weaning. This would cause significant burden on the duration of ventilation, morbidity and ICU mortality. It is important to recognize this entity early and differentiate from more commonly occurring conditions like Guillain-Barré syndrome (GBS), porphyria, botulism, myasthenic crisis, prolonged blockade due to NMBAs and CIM.

DIAGNOSTIC CRITERIA FOR CRITICAL ILLNESS POLYNEUROPATHY

The proposed diagnostic criteria for CIP include:
- The patient is critically ill (sepsis and multiple organ failure, SIRS)
- Limb weakness or difficulty weaning patient from ventilator after non-neuromuscular causes such as heart and lung disease have been excluded
- Electrophysiological evidence of axonal motor and sensory polyneuropathy
- Absence of decremental response on repetitive nerve stimulation. Other acute axonal polyneuropathies, such as those due to thiamine deficiency, porphyria, etc. should be excluded:
  - Definite diagnosis of CIP in criteria 1–4 are fulfilled
  - Probable diagnosis of CIP if criteria 1, 3 and 4 are fulfilled
  - Diagnosis of ICU Acquired weakness is established if only criteria 1 and 2 are fulfilled.

Critical Illness Myopathy

This is an acute myopathy that often affects critically ill patients. While acute quadruplex myopathy has been the commonest designation, it has been given a number of descriptive titles that identify its major features, including CIM, acute quadruplex myopathy, acute (necrotizing) myopathy of intensive care, thick filament myopathy, acute corticosteroid myopathy, acute hydrocortisone myopathy, acute myopathy in severe asthma, acute corticosteroid and pancuronium-associated myopathy and critical care myopathy. All of these designations refer to a common syndrome, and a single description for this disorder therefore seems appropriate.

By definition, patients are critically ill and weakness may occur independently of, or in association with, CIP. CIM develops in at least one-third of ICU patients treated for status asthmaticus, in 7% of patients after orthotopic liver transplantation and in patients after heart transplant. In one prospective study, all 22 critically ill patients showed clinical, electrophysiological and muscle biopsy evidence of a primary myopathy.

The clinical features overlap with those of CIP and prolonged NMJ blockade and include flaccid weakness which tends to be diffuse, involving all limb muscles and the neck flexors, and often the facial muscles and diaphragm. Thus, most patients are difficult to wean from mechanical ventilation. The tendon reflexes are often depressed, but normal reflexes do not exclude CIM. Electrodagnostic testing is important in separating these disorders. Stimulation of muscle directly and indirectly (by stimulating the nerves to the muscle) is a very sensitive aid in this aspect. The myopathy may also be part of a generalized reduction in membrane excitability in the setting of sepsis, resulting in weakness, encephalopathy and transiently low SNAP amplitudes (which quickly normalize as the myopathy recovers). During the initial descriptions of the condition, most cases were associated with prolonged use of corticosteroids or NMBAs, either as single agents or in combination. Such reports had prompted these agents to be implicated as major etiological factors in this condition. But of late there have been reports of several cases that have occurred in isolation or absence of clinical use of either steroids or NMBAs. In patients who are exposed to vecuronium, repetitive nerve stimulation studies have shown transient features of prolonged NMJ blockade, especially during the week after discontinuation of the paralytic agent, and this could mimic or aggravate the weakness in CIM.

DIAGNOSTIC CRITERIA FOR CRITICAL ILLNESS MYOPATHY

Given the controversy in differentiating CIM from a putative motor variant of CIP, diagnostic criteria for CIM are necessary for research studies. Moreover, a diagnosis of a “motor” variant of CIP should not be made without excluding myopathy with myosin loss histopathologically. The proposed major diagnostic features for CIM are:
- Sensory nerve action potential amplitudes more than 80% of the lower limit of normal (LLN) in two or more nerves
- Needle EMG with short duration, low amplitude motor unit potentials (MUPs) with early or normal full recruitment, with or without fibrillation potentials
- Absence of a decremental response on repetitive nerve stimulation
- Muscle histopathologic findings of myopathy with myosin loss.

Supportive features are:
- Compound muscle action potentials (CMAP) amplitudes less than 80% LLN in two or more nerves without conduction block
- Elevated serum creatine kinase (CK) (best assessed in the first week of illness)
- Demonstration of muscle excitability.

By definition, patients should be critically ill and weakness should have started after the onset of critical illness. For a definite diagnosis of CIM, patients should have all four major features. For probable CIM, patients should have any three major features and one or more supportive feature. For possible CIM, patients should have either—major features 1 and 3 or 2 and 3 and one or more supportive feature.

The typical features of CIM on nerve conduction studies are low amplitude, sometimes broadened or absent CMAPs with relatively preserved SNAPs.

CRITICAL ILLNESS NEUROMYOPATHY

Combined CIP and CIM which could be usually mild but severe in some cases and this is the most common cause of weakness in...
Neurology

the critically ill patient. Electrophysiological studies could show mild drop in CMAP and SNAP to severe drop in CMAP and SNAP, depending on the severity of affection. Needle EMG could show mild changes in milder cases and histopathology could range from mild changes to a necrotic pattern. In the severe form, mortality could be high or could have a protracted recovery.

Diagnosis

The diagnosis needs to be considered when there is difficulty in weaning some patients who are critically ill from mechanical ventilation (see Diagnostic Criteria for Critical Illness Neuropathy and Critical Illness Myopathy) and this cannot be explained by increased respiratory or cardiac load, metabolic disturbances, nutritional disorders, anemia or delirium. The setting is that while withdrawing sedation, the ICU staff identifies patients who are weak and flaccid. There will be paucity of limb movements in patients whose sensorium is low but would have facial grimacing. The deep tendon reflexes are usually absent, but could be preserved and a reliable sensory examination is not possible. In this setting, CIP/CIM should be considered and appropriate electrophysiological studies including nerve conduction studies, phrenic nerve conduction and EMG should be done and muscle biopsy, if feasible. There would be a need to do follow-up studies and then discern if the patient has CIN, CIM or critical illness neuromyopathy (CINM).

Differential Diagnosis

It is important to exclude pre-existent causes and exclude central nervous system causes of weakness, in order to avoid unnecessary diagnosis and giving a pessimistic prognosis. Metabolic disturbances like hypokalemia and hypophosphatemia can cause acute myopathic process and hypermagnesemia can impair NM transmission. Sepsis alone does not impair NM transmission, but NMBAs, cytotoxic drugs, statins and antiretroviral drugs can affect NM transmission.

It is important to rule out an axonal variant of GBS which is amenable to treatment with intravenous immunoglobulin/plasma exchange. They usually have an antecedent diarrheal illness due to Campylobacter jejuni. The presence of bifacial weakness, a high cerebrospinal fluid (CSF) protein, dysautonomia, if present, testing for antibodies to gangliosides and serial conduction studies would help in differentiating the disorders.

Predictors for Outcome

Critical illness polyneuropathy and myopathy can cause severe disability after critical illness. The patients with CIW cause limb and diaphragmatic weakness that could persist for months or years after resolution. Leitjen had studied 50 patients undergoing mechanical ventilation for more than 7 days, 29/50 had developed peripheral neuropathy, and they spent more days on the ventilator and had an ICU mortality of 48 versus 19% (without CIP) and this was found to be statistically significant.

De Jonghe et al. have found ICU-acquired CIW and 90% had electrophysiological evidence of dysfunction: axonal motor-sensory polyneuropathy-CIN (33.3%), critical illness motor syndromes (CIMS) (pure motor) (13.3%) and axonal polynuropathy with concomitant myopathy-CINM (48.1%). CIM group had classical axonal.

Motor sensory neuropathy with markedly low phrenic nerve amplitudes; CIMS (pure motor) had markedly reduced motor amplitudes with phrenic nerve abnormalities and elevated CK levels and CINM had combination of myopathy with axonal motor sensory neuropathy. Patients with CIMS had higher exposure to steroids and NMBAs while those with CINM had higher exposure to steroids only. The overall mortality was 43.4%, but subgroups with CIM (75%) and CINM (69.2%) had higher mortality.

It is important to identify CIW in the ICU, as this would help in predicting increased morbidity, prolonged ICU and hospital stay and higher mortality. This is important in a resource crunch situation, as along with prolonged hospital stay, the cost of treatment would be higher. Hence, it is important to implement measures to reduce the incidence of CIW and resultant morbidity and mortality.

The most crucial advances in ICU care is the concept of introducing early rehabilitation, early passive mobilization, electrical muscle stimulation, daily cycle sessions with a bedside ergometer, these would improve quadriceps muscle force and functional outcome in patients who leave the ICU. There is scope for further research on this very important entity.

REFERENCES

Chapter 121  Intensive Care Unit-Acquired Paresis: Spectrum of Neuromyopathies