Critical illness polyneuromyopathy

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Critical illness polyneuropathy (CIP) and myopathy (CIM), more commonly known as critical illness polyneuromyopathy (CIPNM), has become a topic of interest over the past 25 years. Muscle biopsies, nerve biopsies, and specialized electrophysiologic conduction studies have revealed that CIM may be as common as CIP and that CIM and CIP may coexist in the same patient. While there is no standardized terminology to define or diagnose this neuromuscular disorder of the critically ill, the term CIPNM is widely utilized because it incorporates components of both neuropathic and myopathic diseases.1

Bolton and colleagues2 first described CIPNM in 1984 as a complication secondary to critical illness in which motor and sensory axons were affected, causing muscle weakness and difficulty in weaning patients from mechanical ventilation. CIPNM is an acute axonal sensory-motor polyneuropathy that appears as flaccid quadriparesis and is often complemented with a loss of tendon reflexes, primarily affecting the lower limbs of critically ill patients.3,4

Unlike other neuromuscular diseases, such as Guillain-Barré syndrome or myasthenia gravis, CIPNM tends to occur after the development of respiratory insufficiency in patients with systemic inflammatory response syndrome (SIRS), sepsis, or multiple-organ dysfunction syndrome. Numerous mechanisms have been proposed to explain the pathophysiology of CIPNM, most of which are complex and not fully understood or proven. While the rate of intensive care unit-acquired weakness varies greatly among patients, an estimated 25–85% of critically ill adult patients will develop neuromuscular weakness, most commonly CIPNM, during hospitalization. While no specific pharmacologic treatments exist for CIPNM, the outcome for most patients is related to the severity of the illness and neuromyopathy, as well as early intervention to treat the underlying condition. Electrophysiologic studies, such as electromyography, electroneurography, and muscle and nerve biopsies, are considered the gold standard for aiding in the diagnosis of CIPNM. Preventive measures such as the early provision of appropriate nutrition, glucose control, physical rehabilitation, and the cautious use of medications such as corticosteroids and neuromuscular blocking agents (NMBAs) can help reduce the occurrence of CIPNM.

Conclusion. CIPNM is an acute axonal sensory-motor polyneuropathy commonly seen in critically ill patients with sepsis and multigorgan failure. While no specific pharmacologic treatments exist, preventive measures such as the early provision of appropriate nutrition, glucose control, physical rehabilitation, and the cautious use of medications, including corticosteroids and NMBAs, can help reduce the incidence of CIPNM.

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rates within the intensive care unit (ICU) did not significantly differ between groups \( (p = 0.31) \), in-hospital mortality rates in patients with CIP were significantly higher than in patients without CIP \( (p = 0.03) \), as were the lengths of ICU and hospital stays \( (p < 0.0001 \text{ for both}) \).

While various risk factors have been linked to the development of CIPNM, the disease can be difficult to identify due to the severity of illness and patients’ unresponsiveness as a result of sedation. This article provides an overview of the clinical characteristics of CIPNM and focuses on the prevention and treatment of the disease.

**Clinical presentation**

Acquired, progressive muscle weakness tends to be the primary symptom demonstrated in patients with CIPNM.\(^6\) Although muscle weakness may not be easily identifiable due to difficulty or failure in weaning the patient from mechanical ventilation, it may be the most commonly observed symptom after sedation has subsided and the underlying medical condition has resolved. Difficulty in weaning the critically ill patient from a ventilator may be due to involvement of the phrenic nerve leading to diaphragmatic denervation.\(^7\) The phrenicus is a pair of nerves that originate in the cervical spine roots and travel down the thorax to innervate the diaphragm.

Physical examination of the patient in the early stages of CIPNM may yield inconclusive results in the presence of septic encephalopathy or sedation. Even in the absence of these conditions, a more complete neurologic examination may not be useful, as the presence of normal reflexes does not necessarily rule out CIPNM.\(^7\) In addition to a complete physical and neurologic examination, useful signs that may indicate neuromuscular respiratory failure and assist in the diagnosis once the patient has been successfully extubated include hoarse voice, periods of breathlessness, inability to clear bronchial secretions due to unsuccessful cough, and rapid shallow breathing.\(^1\)

Limb muscle weakness, muscle atrophy, reduced or absent deep tendon reflexes, or loss of peripheral sensation may also be observed. Limb muscle weakness, when present, tends to be more distal than proximal in CIP and more proximal than distal in CIM, with both commonly occurring symptomatically. Numerous patients have had both proximal and distal weakness without a clear distinction of CIP or CIM; therefore, thorough neurologic assessments are crucial before a diagnosis is determined.\(^1,4,8\) Muscle atrophy and decreased peripheral sensation may also be seen in CIPNM and are often present during sedation or mechanical ventilation. These symptoms are frequently more severe than expected secondary to immobilization. Patients may have diminished or missing deep tendon reflexes, though these reflexes may be normal in up to one third of patients later diagnosed with CIPNM.\(^9\)

Cranial nerves and facial muscles tend to be spared in CIPNM, but assessment of these nerves can be helpful in the diagnosis due to the lack of grimacing when painful stimuli are introduced to distal muscles.\(^10\) In other neuromuscular conditions, such as Guillain-Barré syndrome and myasthenia gravis, clinical involvement of cranial nerves is quite common and manifests as weakness of both facial and ophthalmologic musculature. Approximately 50% of patients with Guillain-Barré syndrome will experience symptoms involving the facial nerves.\(^11\) Ocular symptoms such as ptosis, diplopia, or both are often the initial symptoms of myasthenia gravis, occurring in 14–36% of patients.\(^12\)

**Epidemiology**

While the rate of ICU-acquired muscle weakness tends to be the primary symptom demonstrated in patients with CIPNM,\(^6\) the disease can be difficult to identify due to the severity of illness and patients’ unresponsiveness as a result of sedation. This article provides an overview of the clinical characteristics of CIPNM and focuses on the prevention and treatment of the disease.

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of E-selectin in the vascular endothelium. E-selectin, a cell adhesion molecule expressed on endothelial cells activated by proinflammatory cytokines, is important in the inflammatory process through its role in the accumulation of leukocytes at the site of injury. This recruitment of leukocytes can induce tissue injury, resulting in enhanced cytokine production. These cytokines, which are also present in sepsis, have histamine-like properties that can alter vasoregulation and increase microvascular permeability. Increased microvascular permeability can facilitate passage of neurotoxic factors and exacerbate endothelial edema, which can gradually lead to hypoxemia and energy depletion. These deficits in the energy supply lead to primary axonal degeneration.\(^8\,\!^{14-16}\)

Hyperglycemia and passive glucose uptake are commonly observed in patients with sepsis and severe illness and have been found to impair the microcirculation to peripheral nerves. Hyperglycemia has also been noted to contribute to energy depletion, leading to increased generation and reduced scavenging of reactive oxygen species, which results in mitochondrial dysfunction.\(^14\) Hyperkalemia and hypoalbuminemia may also promote endothelial edema and hypoxemia, resulting in tissue damage.

**Diagnosis**

Currently, no standardized diagnostic criteria for CIPNM exist. In addition, there are no definitive laboratory tests that can confirm the diagnosis. Creatine kinase levels, while easy to obtain, are typically only slightly elevated or normal in most patients with CIPNM.\(^7\) These factors make the diagnosis more challenging and increase the need for more invasive diagnostic techniques.

Electrophysiologic studies, such as electromyography, electroneurography, and muscle and nerve biopsies, are considered the gold standard for aiding in the diagnosis of CIPNM.\(^4\) It has been proposed that 72 hours after admission, approximately 50% of patients will have electrophysiologic signs of neuromuscular dysfunction that can be detected through these studies. Due to the invasiveness of these tests and the complexity in interpreting the results, adequate comprehension and cooperation from the patient are necessary.\(^6\) Electromyography is an invasive procedure in which a needle electrode is directly inserted into a specific muscle. Three independent steps are performed during electromyography to assess muscle movement. First, the neurologic specialist monitors the muscle’s activity at rest. During needle insertion, a normal muscle at rest will exhibit a short burst of activity but no obvious voluntary activity. The formation of fibrillation potentials and positive sharp waves indicates denervation or myonecrosis, both of which can cause muscle fibers to separate from their endplate.\(^6\) Second, motor unit potentials are assessed through voluntary, directed activation of the muscle from the patient. The duration, amplitude, and frequency of these potentials are measured. In myopathic syndromes, these are typically short and of low amplitude. Finally, the response to maximum voluntary muscle contractions is evaluated. Increasing the force of muscle contraction normally results in an increase in motor unit potentials. In patients with CIPNM, there is a loss of functional motor unit potentials with axonal nerve injury.\(^8\,\!^{10,17}\) While it has been suggested that electromyography studies may be helpful in distinguishing CIP from CIM, the interpretation of the results is limited if patients is not fully cooperative or if other conditions such as edema or existing neuropathy (i.e., diabetic neuropathy) are present.\(^18\)

Another procedure that can assist with a conclusive diagnosis of CIPNM is electroneurography, which induces a motor response through stimulation of a peripheral nerve. Easy to perform at the bedside, electroneurography measures distal motor and sensory delays, motor and sensory conduction velocity, amplitude of motor responses, and nerve action potentials.\(^8\) Characteristically, patients with CIPNM will demonstrate a reduction in the amplitude of the nerve action potentials but normal conduction velocity. These characteristic responses can be compared with those of patients with demyelinating neuropathies, such as Guillain-Barré syndrome, in which the nerve action potentials have normal amplitude and conduction velocity is reduced.\(^16\)

While muscle and nerve biopsies can detect structural abnormalities, these procedures are quite invasive and do not always promise a definitive diagnosis.\(^15\) Histopathologic changes in peripheral nerves have been noted in numerous postmortem examinations of critically ill patients with CIPNM.\(^19,20\) Common findings during these examinations included axonal degeneration with loss of myelin in peripheral nerves. Distal nerve segments tended to be affected most severely, and mild irregularities were seen in vagal, phrenic, and intercostal nerve segments.

Another tool that has been used for over half a century in assessing muscle function is the Medical Research Council of Great Britain (MRC) muscle-grading system score (Table 1).\(^21,22\) Originally developed in 1917 by Boston orthopedist R.W. Lovett, the MRC score was utilized to aid in the evaluation of paralytic injuries during World War II. Its use requires patient cooperation; therefore, it should be reserved for patients who are no longer sedated or who are being weaned from mechanical ventilation. The MRC scale assesses muscle force using a scale of 0 (paralysis) to 5 (normal power) in three muscle groups in each of the upper and lower limbs, with a maximum possible score of 60.\(^23\) A cumulative MRC score of less than 48 is sugges-
tive of an ICU-acquired weakness, such as CIPNM.15,23

Risk factors

SIRS, sepsis, and MODS are all strongly associated with the development of polyneuromyopathy. CIPNM has also been associated with numerous independent risk factors, such as female sex, renal or hepatic failure, electrolyte disturbances, hyperglycemia, and the use of parenteral nutrition and medications including neuromuscular blocking agents (NMBAs), corticosteroids, catecholamines, and sedatives.4,6,24

While medications such as NMBAs and corticosteroids have been associated with CIP, evidence is inconclusive regarding their role in the occurrence of CIPNM. It has been suggested that the presence of SIRS or sepsis leads to increased microvascular permeability and sepsis-induced muscle changes that allow NMBAs to penetrate nerves and muscles, causing direct toxic effects. Furthermore, NMBAs can increase the quantity of corticosteroid receptors on muscle cells, thereby sensitizing the cells to direct effects from exogenous corticosteroids.15,24

Prevention and treatment

While there are no specific pharmacologic agents for the treatment of CIPNM, several preventive and therapeutic approaches can reduce patients’ risk of developing this complication.

Glucose control. Hyperglycemia, commonly found in patients in the acute phase of critical illness, has been implicated as a strong independent risk factor in the development of CIPNM. Two large, randomized controlled trials conducted by van den Berghe and colleagues25,26 in 2001 and 2006 examined the effects of intensive versus conventional insulin therapy on the mortality rates of surgical and medical patients in the ICU.

Results of the prospective, randomized, controlled study conducted in surgical patients revealed a significant reduction in the mean mortality rates in patients receiving intensive insulin therapy versus the conventional regimen (4.6% and 8%, respectively) (p < 0.04). In addition, intensive insulin therapy decreased the prevalence of overall in-hospital mortality (p = 0.01), bloodstream infections (p = 0.003), and prolonged inflammation (p < 0.02). Hyperglycemia occurred in 39 patients in the intensive-treatment group versus 6 patients in the conventional-treatment group.25

Van den Berghe and colleagues26 later tested the same insulin treatment protocol from 2001 in medical ICU patients in a prospective, randomized, controlled study. For patients who had been in the ICU for fewer than three days, intensive insulin therapy reduced blood glucose levels but did not significantly lower in-hospital mortality (p = 0.33). In contrast, for patients whose ICU stay was three days long or longer, intensive insulin therapy led to a significant decrease in in-hospital mortality (p = 0.009). A prospective subanalysis of patients enrolled in both studies found a reduction in the occurrence of CIPNM in both surgical ICU patients (28.7% in the intensive-treatment group versus 51.9% in the control group, p < 0.001) and medical ICU patients (38.9% in the intensive-treatment group versus 50.5% in the control group, p = 0.02).27

More recently, Hermans et al.28 investigated the effects of intensive insulin therapy on the rate of CIPNM in patients receiving prolonged mechanical ventilation (longer than 14 days). The investigators retrospectively studied electrophysiologic data from critically ill patients suspected of having CIPNM before and after the implementation of an intensive insulin treatment protocol within an ICU setting. Intensive insulin therapy was associated with significantly lower blood glucose concentrations (from 144 to 107 mg/dL, p < 0.0001) and a significantly lower frequency of CIPNM (p < 0.0001).

Investigators of the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study evaluated the difference in mortality rates between patients undergoing intensive glucose control (target blood glucose concentration of 81–108 mg/dL) versus conventional glucose control (target blood glucose concentration of <180 mg/dL).29 The results revealed an increase in mortality rates among patients receiving intensive versus conventional insulin therapy (27.5% versus 24.9%, respectively; p = 0.02). In addition,
the rate of hypoglycemia was higher in patients who had undergone intensive glucose control (6.8% versus 0.5%, \( p < 0.001 \)). The investigators concluded that conventional glucose control, as defined above, resulted in lower mortality rates than intensive glucose control and further recommended against the use of the lower target blood glucose concentration in critically ill patients. The effects of this new recommendation on the prevalence of CIPNM have yet to be examined, and, until further research is published, clinicians should be aware of the potential increased risk of CIPNM development secondary to hyperglycemia.

Corticosteroids. Although the role of corticosteroids in the development of CIPNM has been highlighted in the literature over the past decade, the direct effects of their use on CIPNM are inconclusive.

De Jonghe et al. established a significant association between corticosteroid use and the occurrence of ICU-acquired paresis but were unable to establish a causal relationship. Of the patients evaluated \( (n = 95) \), significantly more patients with muscular weakness were taking corticosteroids \( (p = 0.001) \), but no association was found between muscular weakness and the cumulative corticosteroid dose or the total duration of treatment. The authors also performed a multivariate analysis of risk factors and identified corticosteroids as an independent risk factor of ICU-acquired paresis \( (p < 0.001) \).

Herridge et al. evaluated the physical abilities of 109 survivors of acute respiratory distress syndrome (ARDS) 3, 6, and 12 months after hospital discharge. The results of this longitudinal study demonstrated that at 3 months, the use of any systemic corticosteroid was a major determining factor of patients’ ability to exercise. The effects of systemic corticosteroids were lost at 6 months, and the burden of illness and rate of illness resolution became the determining factors for exercise ability. The study’s investigators did not identify the corticosteroid dosage or duration of treatment in this study. The authors concluded that of the extrapulmonary conditions exhibited by the survivors of ARDS, muscle wasting and muscle weakness were the most pronounced.

Hough et al. performed a secondary analysis of a completed randomized, placebo-controlled trial to identify the incidence and outcomes of ICU neuromyopathy and the role of methylprednisolone in ARDS survivors. Of the 128 patients randomized to receive placebo \( (n = 65) \) or methylprednisolone \( (n = 63) \), 34% showed evidence of neuromyopathy, but the investigators found no association between methylprednisolone use and the development of neuromyopathy. Patients with neuromyopathy had received mechanical ventilation for a significantly longer period of time \( (p = 0.02) \) and had a significantly longer length of hospital stay \( (p = 0.005) \) than those who did not develop neuromyopathy. There were no significant differences observed in the 180-day mortality rates of patients with neuromyopathy versus those without this condition. The authors concluded that neuromyopathy is common in patients with ARDS and is associated with poor clinical outcomes; however, no association was found between the development of neuromyopathy and corticosteroid use.

The results of two randomized controlled trials have been instrumental in shaping the current recommendations for the use of corticosteroids in the treatment of septic shock, but neither study identified CIPNM as a potential complication associated with the use of corticosteroids in the critically ill. The results of recent clinical trials suggesting a relationship between corticosteroid use and CIPNM should be interpreted with caution.

Neuromuscular blockade. Mechanically ventilated patients quite often receive both an analgesic and a sedative and, at times, an NMBA. The use of NMBA may delay patients’ recovery from CIPNM, thereby lengthening the duration of mechanical ventilation, increasing the length of stay in the ICU, and increasing mortality rates. Occasionally used to reduce oxygen consumption, eliminate spontaneous breathing, and facilitate mechanical ventilation (most commonly in patients with acute lung injury or ARDS), NMBA have been associated with muscle weakness in ICU patients.

Nondepolarizing NMBA are competitive inhibitors of nicotinic acetylcholine receptors at the neuromuscular junction and are classified as benzylisoquinolinium compounds (e.g., atracurium, cisatracurium) or aminosteroidal compounds (e.g., pancuronium, vecuronium, rocuronium). One of the major toxicities associated with the use of NMBA is muscle weakness. The aminosteroidal compounds may accumulate in patients with renal or hepatic insufficiency, leading to enhanced muscular weakness. However, benzylisoquinolinium compounds undergo ester hydrolysis and Hoffman degradation. The lack of metabolism in and elimination through the liver and kidneys prevents drug accumulation, thereby reducing the frequency of prolonged muscle weakness. NMBA may also increase creatine kinase levels, resulting in myopathies.

In a multicenter, double-blind trial of ICU patients with early acute ARDS, Papazian and colleagues evaluated clinical outcomes 2 days after NMBA therapy was initiated. Patients were randomly assigned to receive 48 hours of therapy with cisatracurium or placebo. The primary outcome evaluated was the percentage of patients who died either before hospital discharge or within 90 days after study enrollment. The hazard
ratio for death at 90 days in the cisatracurium group as compared with the placebo group was 0.68 (95% CI, 0.48–0.98; p = 0.04). In addition, the crude 90-day mortality rate was 31.6% in the cisatracurium group versus 40.7% in the placebo group (p = 0.08). Analysis of secondary outcomes revealed that in the 90 days after enrollment, patients in the cisatracurium group had significantly more ventilator-free days (p = 0.03), more days free of organ failure (other than lungs) (p = 0.01), and more days outside the ICU (p = 0.03) compared with the placebo group.

The rate of ICU-acquired paresis also was evaluated as a secondary outcome. Muscle strength was evaluated based on patients’ median MRC scores on day 28 and at the time of ICU discharge. ICU-acquired paresis was defined as an overall MRC score of less than 48. The median MRC score of both groups on day 28 and at ICU discharge was 55, suggesting a lack of muscular weakness. In addition, the percentage of patients without ICU-acquired paresis did not significantly differ between the two groups on day 28 or at ICU discharge. The authors indicated that the short duration of cisatracurium use could explain the lack of muscular weakness in the study population. Although this study demonstrated beneficial outcomes of utilizing cisatracurium in patients with early-onset ARDS, the beneficial effects of using NMBAs continue to be uncertain.

Rehabilitation strategies

Intense physical therapy is important for mechanically ventilated patients as it helps reduce the risk of delirium, stiffness, and ulcers and increases ventilator-free days. It is also the primary rehabilitation treatment for CIPNM. 37

Kress et al. 38 conducted a randomized controlled trial of 128 medical ICU patients receiving infusions of sedatives such as midazolam and propofol that were either interrupted on a daily basis (intervention group) or at the discretion of the physicians (control group). Results of the trial revealed a significant decrease in both the median duration of mechanical ventilation (p = 0.004) and the median length of stay in the ICU (p = 0.02) among patients enrolled in the intervention group. In addition, diagnostic testing to evaluate mental status changes was needed in only 6 patients in the intervention group versus 16 patients in the control group (p = 0.02). The authors concluded that through daily interruption of sedation in mechanically ventilated patients, durations of both mechanical ventilation and length of ICU stay were decreased.

Girard and colleagues 39 evaluated patient outcomes when spontaneous awakening trials (SATs, through discontinuation of sedation) were combined with spontaneous breathing trials (SBTs, through the assessment of weaning parameters). A total of 336 patients were randomized to undergo a daily SAT followed by an SBT (intervention group) or to receive sedation per standard care plus a daily SBT (control group). Patients in the intervention group had significantly shorter ICU stays and hospital stays (p = 0.01 and 0.04, respectively) and significantly more ventilator-free days (p = 0.02) compared with the control group.

Schweickert et al. 40 conducted a randomized controlled trial to assess the usefulness of combining daily sedation interruption trials with early physical and occupational therapy in mechanically ventilated ICU patients versus daily sedation interruption with physical therapy ordered at the discretion of the primary care team. The primary endpoint—the number of patients who returned to an independent functional state at hospital discharge—was significantly greater in the intervention group (p = 0.02).

While none of the studies reviewed here examined the direct effects of minimal sedation on the development and progression of CIPNM, mechanically ventilated patients with or without sepsis, MODS, or potentially interacting medications (e.g., NMBAs) have a higher risk of developing CIPNM. The sedation practices evaluated in conjunction with early mobilization can result in greatly improved outcomes in these patients. Based on the mechanisms that have been proposed to explain the pathophysiology of CIPNM, several additional therapeutic approaches, though limited, have been identified to assist in the prevention of or reduction in the occurrence of CIPNM. Due to an efflux of amino acids from the muscle in the critically ill patient, nutritional support should include supplementation of specific amino acids, such as glutamine and arginine, which may increase muscle protein synthesis. 6,14 Glutamine is thought to stimulate protein synthesis and play a role in the inhibition of protein breakdown. When Bolton and colleagues 2 first described CIPNM, they suggested that malnutrition may be a cause of the problem. The initiation of feeding, preferably enteral, as early as possible after admission to the hospital in conjunction with appropriate amino acid supplementation may lessen or halt the effects of CIPNM. 4

Further research on the potential role of antioxidants, antiinflammatory agents, immune-modulating therapies, and hormonal interventions has been recommended. 6 Although antioxidants have been investigated in the critically ill population, data regarding their effects on CIPNM are lacking. Interventions aimed at the inflammatory cascade initiated by sepsis have been explored. While studies have evaluated the effects of antiinflammatory and immune-modulating therapies, such as anti-tumor necrosis factor antibodies and human recombinant activated protein C, on critically ill patients, none focused on neuromuscular function outcomes. 6,14
Conclusion

CIPNM is an acute axonal sensory-motor polyneuropathy commonly seen in critically ill patients with sepsis and multiorgan failure. While no specific pharmacologic treatments exist, preventive measures such as the early provision of appropriate nutrition, glucose control, physical rehabilitation, and the cautious use of medications, including corticosteroids and NMBAs, can help reduce the occurrence of CIPNM.

References