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Polyneuropathy and myopathy in the elderly

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ABSTRACT

Critical illness polyneuropathy and myopathy is associated with intensive care unit therapies; it is an independent predictor of mortality and will be increasingly affecting the practice of critical care.
Most patients with this illness are over 50 years of age, and as our population demographics shift in favor of an aging population, physicians must be aware that this malady will have a rising incidence in the perioperative period. Intensivists, anesthesiologists, surgeons, and geriatricians/internists must remain vigilant. Here we present a concise overview of critical illness polyneuropathy and myopathy, its diagnosis, associations, and possible interventions.

Keywords: *polyneuropathies, critical illness, intensive care, aging, aged, postoperative care.*

Critical illness polyneuropathy and myopathy (CIPNM, also referred to as CIP, CIM, or CIP/CIM) may be broadly defined as acquired neuro-muscular weakness associated with intensive care unit (ICU)-related therapies (1). Although CIPNM can occur in all age groups, most patients are >50 years old (2). Moreover, age has been one of the independent predictors of CIPNM-related mortality (3).
Other identified risk factors of CIPNM include sepsis, multiple organ dysfunction syndrome, number of invasive procedures, ICU length of stay, serum albumin, serum glucose, as well as drugs such as neuromuscular blockers, corticosteroids and aminoglycosides (4).
CIPNM develops in about 75% of ICU patients (5). It may reach 100% in complicated sepsis; it occurs in 67% of patients with acute respiratory distress syndrome and, in mechanically ventilated patients without acute respiratory distress syndrome, it may reach 25-33% clinically, with confirmation in nearly 60% of those who have electromyography (5). Additionally, over 50% of patients admitted to an ICU for over seven days will acquire this pathology (5).
As the overall age of our population increases, CIPNM is likely to become more prevalent.
There will be more surgeries performed

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on the elderly, merely because of their increasing numbers and as a result of their increasing ability as a group to maintain higher levels of activity than ever before. This encompasses an entire spectrum from elective arthroscopic procedures to emergent laparotomies and thoracic procedures (6).

Inherent to the increase in both surgical and non-surgical ICU admissions in the elderly, a new unique set of challenges is arising. For example, pathologies that were traditionally seen and described in younger individuals will now be more likely to affect the elderly. Such conditions include acute respiratory distress syndrome, which by itself increases the risk for CIPNM (7). This increase in age is apparent in reviewing the acute lung injury literature where Mercat et al. described patients with average ages of 60 in both experimental and control groups (8).

Also, as a group, the elderly tends to be malnourished and in the face of chronic illness will be more susceptible to CIPNM (9). Another contributor to this malady in regard to the elderly is immobility in the ICU, along with the possibility of prolonged ICU stays (10), increasing incidence of diabetes, let alone the need for drugs such as neuromuscular blocking agents (NMBAs) in their care. It is imperative to those specialists who care for the critically ill to understand CIPNM and its relation to our aging population.

CIPNM is a subset of a broader neuromuscular pathology spectrum that occurs almost exclusively in the ICU. Axonal neuropathy that is substantiated electrophysiologically has been designated critical illness polyneuropathy and documentation of a myopathy (usually by muscle biopsy) has been referred to as critical illness myopathy (11). It can be difficult to distinguish the two clinically and they may be part of a clinical spectrum, although this has not been definitively confirmed; the evidence that they may exist in tandem, however, is very convincing (5, 12). Zink et al. have reviewed the pathophysiology, clinical, electrophysiologic, and histopathological features concisely (5) and several other outstanding reviews of CIPNM are available (13).

This pathologic entity has clinical and electrophysiologic features. The patients commonly present as failure to wean from mechanical ventilation (with no pulmonary explanation) (11).

They are frequently found to have poor oxygenation and hypercarbia post extubation with high reintubation rates. Flaccid proximal and distal muscle groups, muscle atrophy and absence of deep tendon reflexes may be evident along with a decreased responsiveness to painful stimuli, temperature and vibration (11).

Electrophysiologic tests are used for diagnosis. Stimulation of peripheral nerves produces a motor response and compound muscle action potentials.

Distal motor and sensory latencies, conduction of the motor and sensory system velocities along with the compound muscle action potentials amplitude, nerve action potentials and their waveforms are measured.

What is demonstrated on examination is an axonal neuropathy with reduced amplitudes of nerve action potentials and reduced compound muscle action potentials. However, motor latencies of distal nerves, conduction velocities, and responses to the repetitive stimulation of distal nerve musculature are normal (11).

Zink et al. explain that muscle biopsies are the primary pathology standard (5). There are three myopathic entities, or acquired subtypes in the intensive care unit:

1) thick filament neuropathy;
2) minimal change myopathy;
3) necrotizing myopathy.

Also, from the neuropathic perspective there is axonal degeneration (motor and sensory) that becomes denervation atrophy affecting the respiratory muscles and limbs (11).

Primarily, CIPNM has been reported in 50-70% of patients with sepsis or systemic inflammatory response syndrome and may occur in up to 100% of patients with multiple organ failure (14). Stevens et al. found in their systematic review that two out of three reports looking into the systemic inflammatory response syndrome "reported a univariable relationship" between systemic inflammatory response syndrome and CIPNM, and in six of twelve studies regarding sepsis and CIPNM found a "significant, unadjusted association" with CIPNM (14). There are also over a dozen other risk factors associated with CIPNM, including female gender, renal failure, renal replacement therapy, critical illness (non-sepsis), hyperosmolar states, intravenous nutrition, decreased serum albumin levels, prolonged lengths of stay in the ICU, central nervous system dysfunction, use of vasopressor/inotropic support, hyperglycemia, ineffective control of sepsis, corticosteroid use, aminoglycoside use, and NMBAs administration (5). NMBAs and corticosteroid use are the most commonly identified risk factors associated CIPNM.

The association of NMBA with CIPNM is not well understood and the literature is still inconclusive. Two prospective trials (4, 15) identified NMBAs as an independent risk factor for CIPNM while several others did not (16, 17).

It must also be acknowledged that the effect of the use of corticosteroids on neuromuscular function also continues to be controversial as their implication in CIPNM has been difficult to parse out secondary to their frequent use in combination with NMBAs (16, 17).

The Cochrane Collaborative Study in 2009 stated, "Until recently, the only possible way to affect the incidence of critical illness polyneuropathy and critical illness myopathy was controlling risk factors. This approach includes aggressive treatment of sepsis and avoiding or limiting the use of corticosteroids, and keeping NMBAs to the lowest possible dose and the shortest time possible" (13). While multiple pathophysiologic mechanisms have been proposed to explain CIPNM by Hermans et al., generally (13), Zink et al. have summarized the specific data regarding the potential action/interaction of NMBAs and corticosteroids succinctly (5). In view of the above statement interventions to interdict CIPNM need to be addressed at this juncture.

In addition to effective control of systemic inflammatory response syndrome/sepsis, limiting corticosteroid use and minimizing the utilization of NMBAs, several other treatment strategies have been suggested (13). These include nutritional supplementation, use of antioxidants, use of immunoglobulins, derivatives of testosterone, growth hormones, intensive use of insulin to control hyperglycemia and aggressive physical therapy (18).

Evidence suggests that glutamine deficiency plays an important role in CIPNM (13). Additionally, arginine's importance to the body's protein metabolism in burns and sepsis has made it a favorite supplement in combination with glutamine to improve nitrogen balance.

Nonetheless, Heyland et al. found the outcomes to be variable in severely stressed patients who received "targeted" nutritional supplementation (19).

Antioxidants may be able to scavenge free radicals (13). Glutathione levels were found to be low in burn patients and in muscle biopsies of patients who were critically ill. In addition, preliminary animal studies of endotoxin-induced skeletal muscle weak-

ness have shown to be partially prevented by the administration of eicosapentanoic acid, an ingredient in commercially available enteral tube feeds with fish oil.

The utility of antioxidants in CIPNM has yet to be firmly confirmed. Also, there is no good evidence to encourage the use of immunoglobulins in CIPNM (13). Testosterone derivatives oxandralone and nandrolone can improve nitrogen balance in patients after surgery and in those with chronic obstructive pulmonary disease (13). Therefore, there may be a place for their use in ill patients. Direct evaluation of their efficacy on CIPNM has not been evaluated, and should only be considered if serum free testosterone levels warrant consideration of these agents in therapy.

There is some evidence that use of high dose Human Growth Hormone may result in a positive nitrogen balance and improved muscle strength (13), which may assist with liberation from ventilatory support. Critical illness is characterized by relative "resistance" to Human Growth Hormone, and this results in low levels of insulin-like growth factor I and II.

The increased protein turnover in critically ill patients occurs in some part to Human Growth Hormone resistance and low production of insulin-like growth factors.

Intensive insulin therapy has been shown to decrease the incidence of CIPNM in surgical and medical intensive care patients. It has also increased the rate of liberation from the ventilator.

However, concerns have been raised about the morbidity and mortality of hypoglycemia (13).

Finally, most authors agree that physical therapy and rehabilitation are very helpful in preventing the progression of CIPNM and during the post-critical illness recovery phase (13). Especially in view of their potential immobility and length of ICU stay for elderly patients (10). This intervention should be implemented as expeditiously as possible because such immobility leads to deconditioning, an important contributor to a clinical deterioration that directly and indirectly prolongs hospitalization, nosocomial infections, falls, and increased mortality in the aged.

CONCLUSIONS

It is of paramount importance, in view of our aging population, that those who care for the elderly surgical patients understand CIPNM, its potential problems and the interventions to ameliorate its effects. CIPNM is a disease entity that requires understanding and vigilance on the part of intensivists, surgeons, anesthesiologists, and internist/geriatricians.

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