CRITICAL ILLNESS POLYNEUROPATHY

A Useful Concept

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Critical illness polyneuropathy (CIP) has been described in the last 13 years.\(^4,12,18,19\) It is a predominantly motor, axonal polyneuropathy occurring as a complication of the systemic inflammatory response (septic) syndrome (SIRS). In two prospective studies, it has occurred in 50–70% of patients with SIRS.\(^13,18\) Since up to 50% of patients in major medical and surgical critical care units (CCUs) suffer from the syndrome,\(^18\) CIP must now be regarded as a particularly common neuromuscular disorder. It occurs worldwide, reports having come from Canada, the United States, Britain, France, The Netherlands, Austria, and Spain.\(^4,12\)

SIRS occurs in response to severe infection or trauma of any type.\(^4\) Thus, bacteria, fungi or viruses, and major trauma of a mechanical, thermal, or chemical nature will induce SIRS. SIRS is associated with the release of several mediators, such as cytokines and free radicals. The chief effect is on the microcirculation throughout the body, including the central and peripheral nervous systems. Most patients who have been in a CCU for longer than 1 week will have SIRS, either as a primary event or as a complication of invasive procedures such as endotracheal intubation or insertion of intravascular lines. The mortality rate may be 50%.

CIP is often occult and has been overlooked in most CCUs. The clinical examination of the peripheral nervous system is often unreliable because of the attendant septic encephalopathy,\(^4,19\) and the presence of an endotracheal tube and intravascular lines. For example, deep tendon reflexes may be preserved in even moderately severe CIP. Comprehensive electrophysiological studies are the only method of clearly establishing the diagnosis. Thus, in two studies utilizing only clinical methods, no instances of CIP were encountered.\(^3,8\) CIP may be missed at autopsy unless the spinal cord, peripheral nerve, and muscle are examined comprehensively.\(^19\)

The alert doctor or nurse in the CCU may observe weak limb movements or reduced deep tendon reflexes in a patient who has been in the CCU for 1 to several weeks, and has been suffering from SIRS. Often the first sign is difficulty weaning from the ventilator, after the exclusion of pulmonary and cardiac causes. If CIP is present, electrophysiological studies will show findings typical of a primary axonal degeneration of motor and sensory fibers in multiple nerves.\(^4\) Since reduced compound muscle action potentials, fibrillation potentials, and positive sharp waves may also be seen in primary myopathies, polyneuropathy can be diagnosed with certainty only if the sensory nerve action potentials (SNAPs) are reduced. Because of tissue edema, SNAPs may be spuriously low. Thus, near-nerve needle recordings may be necessary, or serial studies may reveal a significant fall in SNAP amplitudes. Phrenic nerve conduction and needle EMG of the chest wall and diaphragm should be performed to establish that the CIP is the cause of difficulty weaning from the ventilator. If SIRS can be treated successfully, a possibility in at least 50% of patients, recovery from CIP occurs in weeks in mild cases and months in more severe cases.

There are conditions other than CIP to be considered. A pure axonal motor neuropathy has been described as a regular complication of neuromuscular blocking agents.\(^8\) These agents may also cause

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**Abbreviations:** CCU, critical care unit; CIP, critical illness polyneuropathy; CIW, critical illness weakness; CMAP, compound motor action potential; CPK, creatine phosphokinase; EMG, electromyography; ICU, intensive care unit; SIR, systemic inflammatory response (septic) syndrome; SNAP, sensory nerve action potential

**Key words:** critical illness polyneuropathy; systemic inflammatory response syndrome; sensorimotor, axonal polyneuropathy; sepsis; critical illness weakness

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transient neuromuscular blockade which may be prolonged for days in the presence of renal or hepatic failure. Cachectic myopathy (due to prolonged recumbency in the CCU) frequently results in muscle wasting and weakness but may be difficult to define due to normal creating phosphokinase (CPK) and electrophysiological studies, and muscle biopsy which is normal or shows type 2 muscle atrophy. The acute necrotizing myopathy of intensive care is rare and likely precipitated by one of a number of infectious, chemical, or other insults in the ICU. This necrotizing myopathy has the features of myoglobinuria, marked necrosis on muscle biopsy, and occasionally poor recovery instead of the usual rapid recovery. However, myopathies of a similar nature may occur in which (despite initially severe muscle weakness, high CPK levels, and myoglobinuria) needle EMG of muscle shows only brief runs of positive sharp waves. A normal muscle biopsy may be found. Recovery is often rapid. Also, thick filament myopathy has been described, usually in asthmatic or organ transplant patients, when exposed to neuromuscular blocking agents and steroids. Muscle biopsy shows a loss of thick filaments centrally in the muscle fiber.9,10 There have been suggestions that patients originally thought to have CIP may, instead, have a myopathy or possibly a combination of both—a polyneuromyopathy.11,16 Systematic studies, including both nerve and muscle biopsy, supported the concept of polyneuromyopathy.11 However, when we have performed muscle biopsy on such patients, denervation atrophy with mild muscle necrosis was the usual result. Rarely a severe axonal polyneuropathy and muscle necrosis have occurred. The technique of direct muscle stimulation recently described by Rich and colleagues may help future investigations.

Neuromuscular blocking agents and steroids may singly or in combination have toxic effects on peripheral nerve and muscle. However, prospective studies by us and Berek and colleagues failed to show such an effect. It is my view that sepsis is often an important underlying factor, even in patients with acute asthma. Thus, in addition to sepsis-induced early changes in the microvasculature associated with impaired perfusion of peripheral nerve, there may be increased permeability of capillaries. Toxic substances or their metabolites, including neuromuscular blocking agents and steroids, could thereby gain entry to both peripheral nerve and muscle.4 Hund and colleagues have identified a toxic factor in the serum of patients with CIP. Nonetheless, CIP is the usual cause of difficulty in weaning from the ventilator and remains the commonest neuromuscular disorder encountered in our CCU.

Disorders of central drive, phrenic nerve trauma, neuromuscular transmission defects, and myopathy are less common.14 In a prospective study from the Netherlands, it was shown that CIP had a significant association with mortality and rehabilitation problems among survivors.

There should be a systematic approach to patients in the CCU who have limb and respiratory weakness (Fig. 1). The problem is classified in two main categories. The first category is those patients who develop paralysis rapidly before admission to the ICU. Because of the acuteness of the situation, there is not sufficient time for investigation of the underlying cause until stabilization has been achieved in the ICU. Conditions to be considered are high cervical spinal cord dysfunction due to trauma, neoplasm or infection, motor neuron disease in which the respiratory muscles are affected before the other muscles, Guillain–Barre syndrome, and other acute polyneuropathies (e.g., porphyria or acute axonal forms of Guillain–Barre syndrome, including the pure motor variety common in Northern China). Mild, chronic polyneuropathies (e.g., diabetic polyneuropathy) may affect the nerves of respiration predominantly or sepsis may worsen a pre-existing polyneuropathy after admission to the ICU. Occasionally, defects in neuromuscular transmission, myasthenia gravis, and Lambert–Eaton myasthenic syndrome present with primary respiratory failure. Finally, there are myopathies, ranging from mild to severe forms, associated with myoglobinuria and muscle necrosis, but usually with a good outcome.

The second category are patients who have been admitted to the CCU for severe, primary illnesses or trauma and later develop neuromuscular disease. “Anoxic” myopathy affects mainly anterior horn cells and may result from cardiac arrest, aortic atherosclerosis, surgery of the aorta, or severe pulmonary disease.1 A prime consideration is critical illness polyneuropathy, but also to be considered are axonal motor neuropathies induced by neuromuscular blocking agents, thick filament myopathy, transient neuromuscular transmission disorders complicating the use of neuromuscular blocking agents, cachectic myopathy, and muscle necrosis of varying severity. If difficulty in weaning from the ventilator occurs, we have found that phrenic nerve conduction and needle EMG of the diaphragm is the most specific method of identifying a neuromuscular cause.

The management of all of the above neuromuscular disorders involves the close collaboration of neurologists, neurophysiologists, and intensive care physicians. The results are important in specific
treatment, such as the use of plasmapheresis and hyperimmune globulin to treat Guillain–Barre syndrome. Results are also important in determining a long-term prognosis. For example, the identification of motor neuron disease has an invariably poor prognosis; critical illness polyneuropathy has a good prognosis if sepsis can be treated successfully. The information is valuable, not only in counseling the patient and family, but in studies of cost-effectiveness of CCU management.

Thus, knowledge of CIP and other neuromuscular conditions encountered in the CCU are not only "useful," but are essential for all who care for critically ill or injured patients. While many practical questions in CCU management can now be answered, there are still many unanswered questions. New approaches are still needed, such as the neurobiological method of Hund and colleagues,\(^7\) which identified a circulating toxin in CIP patients.

I am grateful to Dr. Bryan Young for reviewing the manuscript, and to Ms. Tina Dobson for secretarial work.

REFERENCES

patients. The principal finding is a syndrome of subacute onset (weeks) in critically ill patients, termed “critical illness polyneuropathy,” a term used to describe an electroclinical syndrome of subacute onset (weeks) in critically ill patients. 

It is seen in the setting of some patients with critical illness, multisystem organ failure, and sepsis. The diagnosis is made after no convincing evidence of other possible causes of neuropathy (e.g., diabetes, renal failure, alcoholism, porphyria, axonal Guillain–Barre syndrome, etc.) or other causes of weakness (e.g., clearcut electrophysiological evidence of neuromuscular junction or muscle disease) can be found. Muscle biopsy is not performed in most patients. The long-term outlook for complete recovery is approximately 50% among those who survive the critical illness.

The term “critical illness polyneuropathy” seems reasonable to describe the electrophysiological findings in a subset of patients with critical illness weakness (CIW). However, the implication that weakness is solely due to a polyneuropathy is distinctly misleading. Several considerations suggest that much of weakness and conduction velocities are affected minimally. Fibrillation potentials may be seen in distal and some proximal muscles. There is no evidence of conduction block. Myopathic potentials are absent. It is seen in the setting of some patients with critical illness, multisystem organ failure, and sepsis. The diagnosis is made after no convincing evidence of other possible causes of neuropathy (e.g., diabetes, renal failure, alcoholism, porphyria, axonal Guillain–Barre syndrome, etc.) or other causes of weakness (e.g., clearcut electrophysiological evidence of neuromuscular junction or muscle disease) can be found. Muscle biopsy is not performed in most patients. The long-term outlook for complete recovery is approximately 50% among those who survive the critical illness.

Part of the puzzle that has been pieced together is the concept of “critical illness polyneuropathy,” a term used to describe an electroclinical syndrome of subacute onset (weeks) in critically ill patients. The principal finding is weakness, usually distal greater than proximal and sparing facial muscles, often (but not always) with distal atrophy. Nerve conduction studies and needle electromyography demonstrate findings consistent with an acquired sensorimotor axonal polyneuropathy. Compound motor action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes are diminished. Distal motor and sensory peak laten-
the weakness may not be due to a polyneuropathy. First, there is the issue of correlation (or lack of correlation) of electrophysiological findings and clinical symptoms. For example, diminished SNAP and CMAP amplitudes, and prolonged peak and distal latencies coupled with diminished conduction velocities are also seen in asymptomatic patients with diabetes mellitus of less than 5 years duration.6 These patients are not weak. In demyelinating polyneuropathies, physiological evidence of demyelination can be found in motor nerves of patients who have only sensory symptoms2,12 and no weakness. Patients with unelicitable motor responses (not due to artifact or poor technique) in the legs can still be ambulatory. Electrophysiological abnormalities, even significant deviations from norms, may occur with few or no clinical symptoms or findings.7

Second, in the case of “critical illness polyneuropathy,” diminution of CMAP amplitudes is the most consistent finding with little effect on latencies and conduction velocities. The magnitude of these amplitude drops (over 50% in a number of motor nerves) is striking. While the amplitude drop could correlate with weakness due to axonal dysfunction (a neuropathy), it could also be due to primary dysfunction of distal muscles used for recording CMAPs, or from both muscle and axonal dysfunction.

A third consideration arises from the fact that the ICU setting is extremely complex and most clinical issues are multifactorial. A diagnostic tool now being used to explore the causes of weakness is muscle punch biopsy. Less invasive than conventional biopsy,9,18 this method of muscle assessment can also be used serially. Various types of muscle pathology have been described, including a necrotizing myopathy,1,10 but not all of these studies have an electrophysiological component.9 Other recent investigations have revealed that some patients experience prolonged (from 6 h to >7 days) neuromuscular 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 vercuronium.15 These findings give credence to concern about how many additional drugs will be found to have altered half-lives and even longer effects on nerve and muscle function (e.g., receptor expression).

The enormous complexity encountered in CIW would seem to dwarf the sophistication of the tools thus far applied to address it on molecular and clinical levels. On a molecular level, there are unquantified and lingering effects of multiple metabolic aberrations and medications (metabolized by different mechanisms and at different rates in individuals of different ages) on the mobilization of full muscle power to resistance testing on command. Only a few sites of action of these multiple factors are known. Potential sites of action include: (1) the multiplicity of voltage and ligand-gated sodium, potassium, calcium, and other ion channels in nerve and muscle membranes; (2) the molecular mechanisms of intracellular calcium ion sequestration and release in axoplasmic and sarcoplasmic reticulum; (3) neurotransmitter synthesis; (4) the molecular mechanism of neurotransmitter packaging at the Golgi apparatus; (5) vesicle loading onto microtubules in the axon hillock; (6) microtubule integrity and functional integrity of fast axonal transport mechanochemical motors kinesin and dyenin; (7) neurotransmitter release and reuptake mechanisms; (8) synaptic cleft integrity; (9) transmitter receptor turnover at the neuromuscular junction; (10) T-tubule function; and (11) the mechanochemical mechanisms of myofibrillar excitation-contraction coupling and cross-bridge formation. These are only a few of the myriad molecular mechanisms that must remain unaffected to maintain normal strength. Abnormalities of these mechanisms in various combinations might well produce weakness and leave no detectable footprints by “conventional” methods of assessment (no muscle enzyme elevations in serum, no abnormalities in the metabolic factors commonly measured, no abnormalities in conventional light and electron microscopic sections of nerve and muscle, no specific findings on conventional neuromuscular electrophysiological testing, etc.) as to the cause. In a recent review on axonal channelopathies, a number of acquired and inherited abnormalities of peripheral nerve Na+ and K+ channels are discussed in which no structural abnormalities of the axon or myelin sheath are to be found.8 Ion channel function may be prolonged, partially blocked, or completely blocked by drugs, toxins, or antibodies, as well as by defective channel protein gene expression; well-established examples in hereditary and acquired muscle and nerve diseases exist.8 None of these considerations has thus far been investigated in CIW.

On a more clinical level, little is known about weakness associated with recumbency for 1 or 2 (let alone 4 or more) weeks unassociated with illness. Aside from postural effects, there is much to be understood about the effects of prolonged muscle disuse on extremity and respiratory muscle function. It
is not understood why our species needs sleep periodically and why we cannot function (cannot carry out motor tasks, cannot stand, cannot talk, cannot think) without it. In the typical ICU, the critically ill do not experience anything resembling a circadian rhythm for wakefulness and sleep. To clarify the causes of CIW, it is likely that all these issues will need to be seriously considered and investigated, not simply dismissed.

The term “polyneuromyopathy” has been used in recognition of the multifactorial nature of this problem. A different term that succinctly describes what we see (no less, no more) in the critically ill would be CIW. CIW could be followed by a series of modifiers such as documented: (a) myopathic component, (b) neuropathic component, (c) neuromuscular junction component, (d) metabolic component, and (e) encephalopathic component. Such “no less, no more” terminology or a similar scheme would remind us that there is much unknown. Documentation of one factor does not necessarily explain the weakness and should not result in the termination of further reflection or investigation. Those who have already worked in this difficult area are to be congratulated for their efforts. Further investigation of weakness in the setting of severe illness may yield new insights into mechanisms of neuromuscular function, prevention of predictable problems, and treatment of specific mechanochemical or other molecular abnormalities.

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