CRITICAL ILLNESS MYOPATHY

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The field of critical care medicine has flourished, but an unfortunate result of improved patient survival in the intensive care unit (ICU) is the occurrence of certain acquired neuromuscular disorders. The two most common disorders are an acute myopathy predominantly associated with the use of intravenous corticosteroids and neuromuscular junction (NMJ) blocking agents, and an axonal sensorimotor polyneuropathy termed critical illness polyneuropathy.¹,¹³ The myopathy has been given a number of descriptive titles that identify its major features, including critical illness myopathy, acute quadriplegic myopathy,¹¹ acute (necrotizing) myopathy of intensive care,⁵,¹⁴ thick filament myopathy, acute corticosteroid myopathy, acute hydrocortisone myopathy, acute myopathy in severe asthma,³ 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. To parallel the description of the peripheral nerve disorder, we suggest using only the term “critical illness myopathy” for this acute muscle disorder.

FEATURES OF CRITICAL ILLNESS MYOPATHY

Critical illness myopathy develops in at least one-third of ICU patients treated for status asthmaticus,³ in 7% of patients after liver transplantation,² and in an unknown percentage of adults and children with other critical illnesses. Major risk factors are the administration of intravenous corticosteroids and NMJ blocking agents.²,⁵ Critically ill patients who receive intravenous corticosteroids alone or neither intravenous corticosteroids nor NMJ blockers are occasionally affected.¹¹ An increased severity of the underlying illness, renal failure, and hyperglycemia are also risk factors.² Patients often have features of the systemic inflammatory response or multi-organ dysfunction syndromes.

Although the myopathy occurs acutely, the time of onset is usually difficult to determine because of commonly associated encephalopathy, pharmacologic paralysis, or sedation. The major feature is 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 also difficult to wean from mechanical ventilation. Tendon reflexes are often, but not always, depressed.

The clinical features overlap with those of critical illness polyneuropathy and prolonged NMJ blockade. Therefore, electrodiagnostic testing is important in separating these disorders. The typical features of critical illness myopathy on nerve conduction studies are low-amplitude, sometimes broadened or absent compound muscle action potentials (CMAPs) with relatively preserved sensory nerve action potentials (SNAPs).⁵,¹⁴ Low-amplitude diaphragmatic CMAPs may indicate that ventilator dependence is due to neuromuscular weakness. The CMAP and sometimes SNAP amplitudes increase during clinical recovery. It is uncertain whether this increase in SNAP amplitudes is due to improvement in an associated neuropathy or to other factors such as lessening limb edema. Critical illness 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).¹² Primarily in patients exposed to vecuronium, repetitive nerve stimulation studies may...
also show transient features of prolonged NMJ blockade, especially during the week after discontinuation of the paralytic agent.

Needle electromyography discloses fibrillation potentials and positive sharp waves in limb (and diaphragm) muscles in some, but not all patients. Spontaneous activity may be less prominent than that seen with denervation from critical illness polyneuropathy, but its presence cannot be used to distinguish critical illness polyneuropathy from critical illness myopathy. Unfortunately, analysis of motor unit potentials (MUPs) in the ICU patient may be difficult due to limited voluntary activity, for example, from encephalopathy, severe weakness, or medications. Identifying MUPs with a low amplitude and duration, and early rapid recruitment provides evidence for a myopathy. However, early reinnervation is also associated with low-amplitude polyphasic MUPs. In critical illness myopathy, automated decomposition serial quantitative MUP analysis may reveal low-amplitude, normal-duration MUPs that increase in amplitude during recovery.

Electrical inexcitability of muscle membrane can be demonstrated by direct needle muscle stimulation in patients with severe critical illness myopathy who have markedly reduced or absent CMAPs. In contrast, muscle is easily excitable in patients with nerve injuries. Serial studies have shown recovery of muscle membrane excitability as strength improves. Although direct muscle stimulation is impressively abnormal in some, its usefulness is limited in less severely affected patients, because the lack of normative data means that modest amplitude reductions cannot be identified.

Nonetheless, muscle membrane inexcitability likely plays a major role in reducing CMAP amplitudes and in causing weakness. In a rat model of critical illness myopathy produced by denervation and high-dose corticosteroids, similar membrane inexcitability has been demonstrated, and in vitro intracellular recording of individual muscle fibers demonstrated a loss of the ability of myofibers to produce an action potential when electrically stimulated. Although the exact mechanism has not been identified, this inexcitability is likely due to a reduction in sodium current.

An elevation in serum creatine kinase (CK) occurs in at least 50% of patients and supports a diagnosis of critical illness myopathy. In a prospective study of patients with status asthmaticus and critical illness myopathy, all had serum CK elevations which peaked 2–5 days after intravenous corticosteroid exposure and normalized by 16 days. Therefore, a normal serum CK obtained weeks after probable onset of weakness certainly does not exclude the diagnosis of critical illness myopathy.

Pathologic studies generally reveal myofiber atrophy (especially of type 2 fibers); a variable degree of myofiber necrosis and regeneration affecting between 0–65% of fibers; no lymphocytic inflammation; basophilic stippling of some myofibers with hematoxylin and eosin on cryostat sections; features of a disrupted intramyofibrillar network with oxidative reagents; and a patchy or complete reduction in myosin-ATPase reactivity in nonnecrotic fibers. This ATPase staining pattern is due to a loss of myosin which occurs in up to 78% of patients and can be confirmed either immunohistochemically or by electron microscopy. An absence of myosin mRNA has also been identified. Myosin loss and myofiber necrosis probably contribute substantially to persisting weakness, but it is likely that muscle membrane inexcitability also accounts for the weakness seen early, especially in patients with low-amplitude CMAPs.

Myosin loss is characteristic of critical illness myopathy. It sometimes occurs focally in other disorders such as dermatomyositis, but more widespread myosin loss is essentially pathognomonic of critical illness myopathy. Myosin loss can also be provoked in rodents treated with corticosteroids following denervation. In critical illness myopathy, milder losses of actin and other structural proteins may also occur. The precise cause of myosin loss is uncertain. There may be upregulation of calpain, a calcium-protease, and of ubiquitin. Both play roles in protein degradation, and they may play a role in myosin loss. However, their upregulation may be secondary phenomena.

CONTROVERSIES REGARDING CRITICAL ILLNESS MYOPATHY

There are controversies regarding the diagnosis of critical illness myopathy. The disorder may sometimes be difficult to differentiate from rhabdomyolysis due to drugs and sepsis. Vecuronium use, in particular, is sometimes associated with severe myofiber necrosis and laboratory features of rhabdomyolysis. It is uncertain whether this entity is distinct from critical illness myopathy or whether it is part of the spectrum, and the necrosis obscures thick filament loss.

When an ICU patient develops generalized flaccid weakness and has an elevated serum CK level and the electrophysiologic hallmarks of critical illness myopathy, differentiation from critical illness polyneuropathy is not difficult. However, some patients have only electrophysiologic features (fibrillation po-
tentials and low-amplitude CMAPs) common to both. SNAP amplitudes may also be low in myopathy patients due to the causes listed earlier as well as from coexisting critical illness polyneuropathy. In addition, as noted above, evaluation of voluntary MUPs may be limited. Muscle biopsy may help differentiate critical illness myopathy from a neurogenic disorder in many, but often a confident pathologic diagnosis cannot be made.

Critical illness polyneuropathy in the form of an axonal sensorimotor polyneuropathy is well-established. A more controversial issue is whether a pure motor form of critical illness polyneuropathy exists. It has been proposed as a diagnostic entity in quadriparetic ICU patients having the clinical and electrophysiologic features of critical illness myopathy. Unfortunately, the presence of reduced CMAP amplitudes, relatively preserved SNAPs, and fibrillation potentials alone is not useful in separating critical illness polyneuropathy from myopathy, especially when needle EMG evaluation is limited. Furthermore, in the acute setting of critical illness polyneuropathy, “neurogenic” MUP changes are not expected. Currently, a motor form of critical illness polyneuropathy has not been adequately proven by pathologic or electrophysiologic studies.

**SUGGESTED DIAGNOSTIC CRITERIA FOR CRITICAL ILLNESS MYOPATHY**

Given the controversy in differentiating critical illness myopathy from a putative motor variant of critical illness polyneuropathy, diagnostic criteria for critical illness myopathy are necessary for research studies. Moreover, a diagnosis of a “motor” variant of critical illness polyneuropathy should not be made without excluding myopathy with myosin loss histopathologically.

For critical illness myopathy, we propose diagnostic criteria emphasizing the electrodiagnostic features for a “probable” diagnosis and requiring histopathologic identification of myosin loss (as well as supportive nonpathologic features) for a “definite” diagnosis. Some patients may either be unable to recruit MUPs or have a preexisting or coexisting polyneuropathy and still have a myopathy. Therefore, we allow for diagnosis of “probable” or “possible” critical illness myopathy based upon a combination of major and supportive features even in the presence of low SNAP amplitudes or an equivocal needle electrode examination. When the results of Rich et al. are confirmed by others, direct needle stimulation of muscle may be added as a major diagnostic feature and method of differentiating critical illness polyneuropathy from myopathy, perhaps even in place of histopathologic proof.

The proposed **major diagnostic features** for critical illness myopathy are:

1. SNAP amplitudes >80% of the lower limit of normal (LLN) in two or more nerves; 2) needle EMG with short-duration, low-amplitude MUPs with early or normal full recruitment, with or without fibrillation potentials; 3) absence of a decremental response on repetitive nerve stimulation; and 4) muscle histopathologic findings of myopathy with myosin loss. **Supportive features** are:

   1. CMAP amplitudes <80% LLN in two or more nerves without conduction block; 2) elevated serum CK (best assessed in the first week of illness); and 3) demonstration of muscle inexcitability. By definition, patients are or were critically ill, and weakness should have started after the onset of critical illness.

For a **definite diagnosis** of critical illness myopathy, patients should have all four major features. For **probable critical illness myopathy**, patients should have any three major features and one or more supportive feature. For **possible critical illness myopathy**, patients should have either major features 1 and 3, or 2 and 3, and one or more supportive feature.

These criteria are for research protocols. Whether a clinician should routinely pursue a muscle biopsy in order to distinguish critical illness myopathy from other myopathies or from critical illness polyneuropathy is questionable. One should consider a muscle biopsy if another myopathic process such as an inflammatory myopathy is suspected or if the histologic findings may affect management. For example, a firm diagnosis of critical illness myopathy may lead to avoidance of intravenous corticosteroids in the future, if possible, to prevent recurrence.

**REFERENCES**

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