Critical Illness Myopathy

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Acute myopathy is a common problem in intensive care units. Those at highest risk for developing critical illness myopathy are exposed to intravenous corticosteroids and paralytic agents during treatment of various illnesses. Diffuse weakness and failure to wean from mechanical ventilation are the most common clinical manifestations. Serum creatine kinase levels are variable. Electrodiagnostic studies reveal findings of a myopathic process, often with evidence of muscle membrane inexcitability. Based on animal model studies, the loss of muscle membrane excitability may be related to inactivation of sodium channels at the resting potential. In addition, human and animal pathologic studies reveal characteristic loss of myosin with relative preservation of other structural proteins. In some patients, there is also upregulation of proteolytic pathways, involving calpain and ubiquitin, in conjunction with increased apoptosis. Fortunately, the disorder is reversible, but there may be considerable morbidity.

Introduction

Critical illness myopathy, also called acute quadriplegic myopathy and other names (Table 1), is a common problem in hospitalized patients. It was first recognized in 1977 [1], and most early reports involved critically ill asthmatics [2–5]. Subsequently, patients with other illnesses that require intensive care unit (ICU) management, were found to develop this disorder [6–9]. Any patient treated in the ICU is at risk for developing critical illness myopathy. Those at highest risk are exposed to intravenous corticosteroids and paralytic agents, especially at high doses. Some affected patients are exposed to intravenous corticosteroids only. Rarely, others with sepsis or the systemic inflammatory response syndrome [10] develop critical illness myopathy without exposure to either intravenous corticosteroids or paralytic agents [11,12].

This disorder is also of interest to rheumatologists, because critically ill patients with connective tissue diseases can develop this myopathy. For example, patients treated in the author's hospital for severe complications of systemic lupus erythematosus have developed critical illness myopathy.

Epidemiology

The incidence of critical illness myopathy in status asthmaticus was 36% in one prospective study [2], and up to 45% in some retrospective studies [3]. Up to 76% of patients treated for status asthmaticus may develop elevations in creatine kinase (CK), suggesting the incidence of subclinical myopathy is even higher [2]. The prospective incidence of significant critical illness myopathy after liver transplantation is 7% [8]. Retrospectively, an incidence of 1.4% was reported [9].

In addition to intravenous corticosteroids and paralytic agents, higher illness severity, renal failure, and hyperglycemia may also be risk factors [8,9]. Some patients with critical illness myopathy also have the axonal sensorimotor polyneuropathy terminal critical illness polyneuropathy [13,14]. It is conceivable that this associated polyneuropathy is also a risk factor for myopathy, but this notion is yet to be proven. Many patients with myopathy also have the systemic inflammatory response syndrome or multi-organ dysfunction, but others do not [5].

Clinical Features and Differential Diagnosis

The clinical features of critical illness myopathy have been well-described. Children and adults may be affected. The onset is acute, but it is difficult to pinpoint. Weakness is usually noted only after days or weeks of ICU treatment, because encephalopathy, sedation, or paralytics may initially mask it. Patients typically present with generalized weakness, failure to wean from the ventilator as a result of diaphragm involvement, or both. The weakness tends to be diffuse, but proximal predominant weakness may occur [7]. Facial muscles may be weak, but extraocular muscle involvement is rare. Tone is reduced, and tendon reflexes are normal or depressed. Occasionally, reflexes are increased when a central nervous system disorder is also present. If sensation can be adequately assessed, then it is normal.

The differential diagnosis of neuromuscular weakness occurring in the ICU is broad (Table 2). The approach to evaluating these patients has been reviewed by Campellone [15]. Regarding localization, any part of the motor unit may be affected. Recall that the motor unit includes an anterior horn cell, its motor axons and neuromuscular junctions, and the innervated myofibers.

Table 1. Critical illness myopathy aliases

Acute quadriplegic myopathy
Acute myopathy of intensive care
Acute necrotizing myopathy of intensive care
Thick filament myopathy
Critical care myopathy
Acute myopathy of status asthmaticus
Acute corticosteroid and pancuronium-associated myopathy

The "traditional" neuromuscular disorders that tend to cause diaphragm or bulbar weakness and can lead to ICU admission include Guillian-Barré syndrome, myasthenia gravis, amyotrophic lateral sclerosis and some myopathies, including inflammatory myopathies, and muscular dystrophies [6]. It is unusual for most of these disorders to arise in the ICU, although myasthenia gravis may be precipitated by severe illness and drugs, such as aminoglycosides. Guillian-Barré syndrome can also rarely arise in the ICU. The axonal form may be particularly difficult to differentiate from critical illness myopathy without a muscle biopsy. Of these disorders, a rheumatologist may consider the diagnosis of inflammatory myopathy in patients with connective tissue diseases and newly acquired ICU weakness. However, it would be extraordinarily unusual for inflammatory myopathies to present in the ICU. Inflammatory myopathies tend to be less acute and more "proximal" than critical illness myopathy. Although inclusion body myositis commonly affects distal and proximal muscles, it should not be confused with critical illness myopathy because of the slow time course in inclusion body myositis. In rare instances, a fulminant diffuse case of polymyositis might be confused with critical illness myopathy. In such patients, a muscle biopsy specimen would be required to differentiate these processes.

On the other hand, neuromuscular weakness is more often acquired in the ICU and is usually caused by critical illness myopathy or critical illness polyneuropathy [6]. Prolonged neuromuscular junction blockade from high doses of paralytic agents in conjunction with renal insufficiency [16] is a rare cause. These patients have abnormal decremental responses on repetitive nerve stimulation. The clinical features of these three disorders overlap. Although critical illness polyneuropathy usually affects sensory and motor fibers, sensory examination may be limited in ICU patients. The CK level should not be elevated with critical illness polyneuropathy or prolonged neuromuscular junction blockade, but only half or fewer patients with critical illness myopathy have an elevated CK, as will be discussed later in this report. Because of the overlap in clinical and laboratory features, electrodiagnostic and sometimes pathologic studies are necessary for differentiating critical illness polyneuropathy, myopathy, and prolonged neuromuscular junction blockade.

Table 2. Causes of generalized neuromuscular weakness in the intensive care unit

Central nervous system
Septic or toxic-metabolic encephalopathy
Brain stem stroke
Central pontine myelinolysis
Cervical myelopathy
Anterior horn cell disorders (*eg*, amyotrophic lateral sclerosis)
Peripheral neuropathies
Critical illness polyneuropathy
Guillain-Barré syndromes
Porphyria
Paraneoplastic
Vasculitis
Nutritional and toxic
Neuromuscular junction disorders
Myasthenia gravis
Lambert-Eaton myasthenic syndrome
Botulism
Prolonged neuromuscular junction blockade
Myopathies
Critical illness myopathy
Cachectic myopathy
Rhabdomyolysis
Inflammatory and infectious myopathies
Muscular dystrophies
Toxic
Acid maltase deficiency
Mitochondrial
Hypokalemia
Hypermetabolic syndromes with rhabdomyolysis (*eg*, neuroleptic malignant syndrome)

In addition to critical illness myopathy, rhabdomyolysis is also a relatively common cause of myopathy in the ICU. The cause is usually drugs or infection. Cachectic myopathy (as is discussed later in this report) can also occur in chronically ill patients, and some of the features of this disorder also overlap with critical illness myopathy.

Laboratory and Electrodiagnostic Findings

In critical illness myopathy, the CK may be elevated or normal. In the prospective series on patients with status asthmaticus, all with myopathy had an elevated CK [2]. In retrospective series of critical illness myopathy, about half had elevated CKs. Elevated CKs are less common in patients with transplants. In some patients, a rise in CK may be missed if the myopathy is not recognized until weeks after development, because the levels tend to peak by 5 days and normalize by 16 days [2].

Electrodiagnostic studies typically reveal normal sensory responses, with some exceptions [7,17–19]. Motor amplitudes are often reduced, but they are sometimes normal. In many cases, the low motor responses can be explained by a lack of muscle membrane excitability. Membrane inexcitability can be confirmed by direct needle

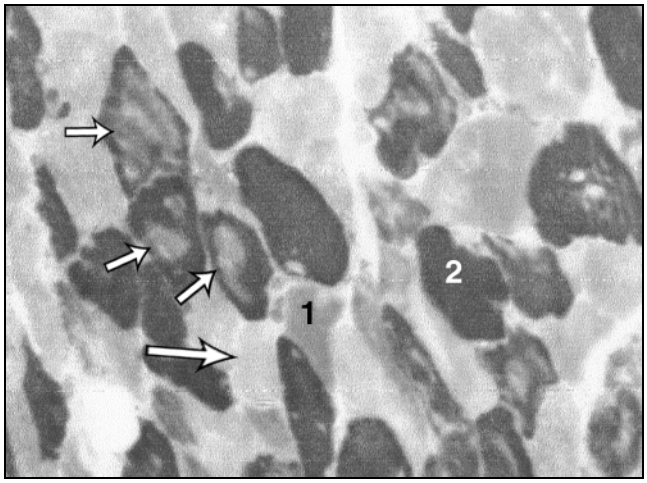

Figure 1. A myosin-adenosine triphosphatase (pH 9.4) reacted cryostat section from a patient with critical illness myopathy reveals a moderate number of atrophic fibers and fibers with reduced, patchy reactivity (*see short arrows* for examples) caused by myosin loss. Some fibers are uniformly pale as a result of diffuse myosin loss (*see arrow* for example). A normal Type 1 fiber (1) and a normal Type 2 fiber (2) are shown.

stimulation of muscle [20,21]. In neurogenic processes, the motor responses recorded as a compound muscle action potential after nerve stimulation may be low, but direct muscle stimulation with recording from the same muscle can bypass the dysfunctional axons and reveal a larger direct muscle response. Conversely, if the muscle membrane is not depolarizable, then the nerve-evoked compound muscle action potential and the directly stimulated muscle responses will be low. In addition, a decremental response following repetitive nerve stimulation may be noted in some patients with critical illness myopathy who typically have received paralytic agents. This finding is caused by a defect is neuromuscular junction transmission, and it is usually transient.

In critical illness myopathy, needle electrode examinations often, but not always, reveal fibrillation potentials indicating structural or physiologic disconnection of motor nerve terminals from muscle fibers. In some cases, this finding may be caused by muscle necrosis; in others, it could be caused by muscle membrane inexcitability. In addition, early or normal recruitment of low amplitude, short-duration, polyphasic motor unit potentials, consistent with myopathy, is identified if patients have enough power to activate motor units.

It has been controversial as to whether patients with critical illness polyneuropathy can also have low motor with normal sensory responses. Given these findings, it is difficult to differentiate motor neuropathy from myopathy. However, direct muscle stimulation should be helpful in differentiating the disorders, and muscle biopsy may be diagnostic. In critical illness myopathy, the characteristic pathologic features, including myosin loss (discussed later in this report), should be present. To avoid diagnostic confusion between critical illness myopathy and a "motor" form of critical illness neuropathy, diagnostic criteria for critical illness myopathy have been proposed [22]. For a definite diagnosis of critical illness myopathy, patients should have relatively preserved sensory amplitudes, needle electromyographic features typical of myopathy, absence of a decremental response on repetitive nerve stimulation, and muscle histopathologic features of myopathy with myosin loss. It may be reasonable to substitute evidence of myopathy from direct muscle stimulation for the typical histopathologic findings.

The group at the University of Pennsylvania first reported muscle membrane inexcitability in critical illness myopathy [20,21]. Recently, these findings were confirmed by Trojaborg *et al.* [23••]. These authors studied 22 patients with weakness and critical illness. Compound muscle action potential amplitudes tended to be reduced. The most common nerve conduction pattern was normal or mildly reduced sensory amplitudes in conjunction with disproportionately reduced motor amplitudes. However, some patients had absent sensory responses, raising the possibility that weakness was caused by sensorimotor polyneuropathy. Direct muscle stimulation was performed in 20 patients. The ratio of the nerve-evoked compound muscle action potential to the direct muscle stimulation-induced compound muscle action potential was determined in 13 patients. The ratio was greater than 0.5 in all, suggesting impaired muscle membrane excitability. Conventional electromyography revealed fibrillation potentials in 82% of the muscles tested. In addition, quantitative electromyography was performed in nine patients; five exhibited a myopathic pattern, while four had no firing motor unit potentials. Some of the patients with myopathic patterns had abnormal sensory responses. Muscle biopsies were performed in all of the patients who underwent quantitative electromyography, and the findings were typical of critical illness myopathy in eight of nine patients. The other exhibited only Type 2 fiber atrophy. Thus, the authors were able to identify that a myopathy was the primary cause of electrophysiologic dysfunction in these patients despite the presence of low-sensory responses.

Pathology and Pathogenesis

The pathologic features of critical illness myopathy are characterized by focal, diffuse, or multi-focal loss of myosin thick filaments. This abnormality may be suspected when unusual basophilic mottling is seen on hematoxylin- and eosin-stained cryostat sections. Necrosis occurs in some fibers (0% to 65%), but inflammation does not occur [7]. Disruption of the intermyofibrillar network may also be evident with oxidative histochemical stains. Myosin-adenosine triphosphatase identifies regions of myofibers that do not react (stain) when myosin loss is present (Fig. 1). Myosin loss can be confirmed ultrastructurally or immunohistochemically. Other structural proteins (such as actin, titin, and nebulin) can be

reduced to modest degrees, but myosin loss overshadows the loss of other structural proteins [11]. Occasional patients with acute weakness have substantial muscle necrosis histologically. Such acute necrotizing myopathy has been considered to be a separate entity by some [24], but it is unclear if it is really separate or part of the spectrum of critical illness myopathy.

As suspected, Matsumoto *et al.* [25•] recently noted that the Type 2 (fast twitch) fibers were more commonly atrophic and had greater loss of myosin than the slow Type 1 fibers. Actin reactivity was present in these atrophic Type 2 fibers. Reports also confirm earlier observations from humans [25•] and animals [26] that thick filament loss lags weakness. In weak patients, thick filament loss is more likely to be identified when muscle biopsy specimens are obtained after 10 to 14 days of exposure to intravenous corticosteroids [7,25•].

Insight into the pathogenesis of critical illness myopathy comes from an animal model utilizing intraperitoneal corticosteroids in conjunction with sciatic nerve transsection [26,27]. Botulinum toxin administration can be used instead of sciatic nerve transsection in this model [28]. The animals develop myosin loss in calf muscles and muscle membrane inexcitability. Of note, these animals are not critically ill.

Rich *et al.* [29,30,31••] performed a series of elegant animal experiments to determine the cause of the muscle membrane failure noted in humans. Intracellular recordings of affected muscle fibers revealed that a substantial number were unable to generate action potentials. An alteration in muscle sodium current density was the most likely cause of membrane dysfunction. A decreased density of the adult sodium channel isoform was found, but there were high levels of messenger ribonucleic acid for the embryonic sodium channel isoform. These investigators then compared the sodium channel activities between excitable and inexcitable muscle fibers, using intracellular recording and loose patch voltage clamp techniques, and they concluded that the inexcitability of denervated-steroid-treated muscle fibers is caused by increased inactivation of sodium channels at the resting potential.

It has not been determined whether these ion changes occur in humans with critical illness myopathy. It is also uncertain as to whether corticosteroids, denervation, or both are prerequisites. The exact cause of the alteration in sodium current is also unknown. Rich and Pinter [31••] proposed that this voltage-dependence of inactivation could be altered in excitable fibers in one of two ways. First, there could be an alteration in sodium channel gene expression. Second, there could be post-translational modification of sodium channels.

Therefore, from the animal model and from the human experience, it seems that the exposure to systemically-administered corticosteroids is the primary risk factor for the induced alteration in myosin and muscle membrane proteins. Denervation, as a result of structural or pharmacologic causes (including paralytic exposure), seems to increase the likelihood of development of the syndrome.

In humans, critical illness is required, but its role is unknown. Currently, there is no convincing evidence that critical illness myopathy is an autoimmune or inflammatory condition. However, because it often occurs in the setting of systemic inflammatory response syndrome, there has been some interest in determining whether or not immune factors can precipitate the process. Bazzi *et al.* [32] found human leukocyte antigen (HLA)-I and membrane attack complex expression in muscles from two patients with critical illness myopathy. In a prospective study of 30 patients with ICU-acquired weakness [33•], many with critical illness myopathy have had increased expression of HLA-DR, HLA-I, interleukin-10, membrane attack complex, and tumor necrosis factor-alpha-R75, but most of the patients in the study also had critical illness polyneuropathy. Small collections of macrophages and T-helper cells were also present. Only two disease controls were studied. Further work is needed to determine whether or not there is an inflammatory component in this process.

It is of greater interest as to whether or not disruptions in myosin and membrane proteins are caused by increased proteolysis or perhaps caused by transcriptional dysregulation. Calpain, a calcium-activated protease, is a major proteolytic enzyme in skeletal muscle. There is evidence in humans that increased calpain expression occurs in critical illness myopathy, suggesting that changes in cellular calcium homeostasis may play a role [11,34]. Calpain may degrade myosin [11]. It has also been suggested that the non-lysosomal, ubiquitin proteosome pathway is also upregulated in patients with critical illness myopathy. This finding is somewhat controversial. Interestingly, this pathway is upregulated by corticosteroids.

Apoptotic pathways, which are associated with some proteolytic enzymes, may also undergo increased activity. Di Giovanni *et al.* [35••] studied three patients with critical illness myopathy. They found that all had biopsy specimens that revealed thick filament loss and overexpressed caspases and the proteolytic proteins calpain and cathepsin B, and there was also increased expression of ubiquitin. In addition to elevated cathepsin B, acid maltase activity was also increased, consistent with lysosomal activation. Furthermore, more than 70% of the muscle fibers had apoptotic nuclei. This pattern was not seen in controls. The authors felt that these findings suggested that these proteases led to apoptosis and may play a role in the pathogenesis of critical illness myopathy. Exogenous factors, such as glucocorticoids and oxidative stress, could help trigger apoptosis and proteolysis in the patients.

Finally, because there is some overlap, clues to the pathogenesis of critical illness myopathy may come from understanding cachectic myopathy. Cachectic myopathy occurs after prolonged disuse in ill patients. Patients with cachectic myopathy typically have normal CK levels, essentially normal electromyograms, and histopathologic

findings limited to only Type 2 fiber atrophy. There is no myosin loss. In cachexia, there is activation of the nuclear factor kappaB that may be activated by tumor necrosis factor. Subsequent down-regulation of MyoD, a regulator of skeletal muscle differentiation, has been noted in cachectic myopathy [36]. It is unknown whether such a change is present in critical illness myopathy.

Conclusions

There is no specific treatment for critical illness myopathy. It is prudent to avoid paralytic agents as much as possible and to utilize the lowest possible doses of intravenous corticosteroids in ICU patients. In high-risk patients, such as those with status asthmaticus, frequent assessment of the serum CK may be helpful in uncovering patients who are developing myopathy. Once critical illness myopathy is identified, the dose of corticosteroids should be tapered to as low of a level as is possible, and future intravenous corticosteroid use should be avoided, because this disorder can recur. Patients should be treated with physical therapy and appropriate bracing. Most patients recover fully, and many are able to ambulate within 2 months. On the negative side, there is considerable morbidity and cost as a result of mechanical ventilation and prolonged ICU stays.

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