Acute Myopathy of Intensive Care: Clinical, Electromyographic, and Pathological Aspects

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An acute myopathy of intensive care occurs in critically ill patients treated with intravenous corticosteroids and neuromuscular junction-blocking agents. The full clinicopathological spectrum is uncertain. We evaluated the clinical, electrodiagnostic, and histopathological features of 14 patients who developed acute myopathy of intensive care after organ transplantation or during treatment of severe pulmonary disorders and sepsis. Patients received high-dose intravenous corticosteroids, usually in conjunction with relatively low to moderate doses of neuromuscular junction-blocking agents. After discontinuation of the latter drugs, most had diffuse, flaccid weakness with failure to wean from mechanical ventilation. Electrodiagnostic findings were consistent with a necrotizing myopathy. Muscle histopathology revealed myopathy with loss of thick filaments in 79%, mild myopathic changes in 14%, and atrophy of type 1 and type 2 fibers in 7%. Loss of thick filaments was identified in muscle biopsy specimens obtained 30 ± 11 days (mean ± standard deviation) after intravenous corticosteroid treatment but not in those obtained earlier (12 ± 2 days). Critically ill patients, including those receiving organ transplants, may develop acute myopathy of intensive care after exposure to intravenous corticosteroids and neuromuscular junction-blocking agents, although the exposure to the latter drugs may be minimal. Selective loss of thick filaments is common in acute myopathy of intensive care, especially if the muscle biopsy specimen is obtained 2 weeks or more after intravenous corticosteroid exposure.


During the last two decades, neuromuscular disorders were recognized as common causes of weakness occurring in critically ill patients. Bolton, Zochodne, and their colleagues [1-4] provided extensive evidence that an axonal sensorimotor polyneuropathy, termed critical illness polyneuropathy (PN), frequently affects patients who receive a week or more of treatment for sepsis or multiorgan failure. Prolonged neuromuscular junction (NMJ) blockade was identified in occasional intensive care unit (ICU) patients who had persistent weakness after prolonged use of neuromuscular junction-blocking agents (NMBAs) [5-7]. Although a myopathic process was identified in some of the earlier reports of weak ICU patients [5, 8, 9], an acute myopathic syndrome of critical illness was not identified as a common entity for another 5 to 10 years [10-36].

This acute myopathy of intensive care (AMIC) is associated with the use of intravenous (IV) corticosteroids (CSs), nondepolarizing NMBAs, or both. The myopathy was first systematically documented in patients treated intensively for status asthmaticus [8-23, 25-28], but patients treated for other severe pulmonary disorders and critical illnesses including sepsis and burns were also affected [24, 29-32, 34, 35]. Afflicted patients develop acute, diffuse, flaccid weakness often associated with failure to wean from mechanical ventilation. Elevations in serum creatine kinase (CK) concentration are noted in many. Following discontinuation of the CSs and with resolution of the underlying critical illnesses, the myopathy improves over weeks to months.

Despite thorough descriptions of the clinical features of AMIC, the exact pathophysiological mechanisms of this presumed toxic process remain uncertain. Electrodiagnostic studies are consistent with a necrotizing myopathy, although a component of terminal motor axonopathy is difficult to exclude [27, 30, 31]. Concurrent evidence of prolonged NMJ blockade is occasionally identified, especially early in the course of the illness [25, 32]. Perhaps the most important data regarding pathogenesis come from the pathology studies. In some patients with AMIC, histopathology reveals a myopathy with a selective patchy loss of thick (myosin) filaments [18, 20, 25, 29, 32, 36]. This histopathology...
is reproduced in an animal model utilizing denervation and CS administration. In this model, only the combination of nerve trauma and CSs causes reversible loss of thick filaments [37, 38]. In biopsy specimens from other patients with AMIC, reported histopathological findings are less distinctive and range from type 2 fiber atrophy to necrosis [9, 11–13, 17, 19, 21–23, 26, 29– 31, 34].

Many reports of AMIC emphasized the clinical and electrodiagnostic abnormalities but were limited by a lack of pathological correlation. Thus, the full range of clinicopathological features is uncertain. In this article, we describe 14 patients with AMIC who underwent detailed clinical, electrophysiological, and pathological evaluations.

Materials and Methods

Patients

During an 11-month period, there were approximately 8,000 ICU admissions and transfers into our ICUs. Sixteen ICU patients were diagnosed with AMIC. Critical care staff usually referred patients because of moderate to severe muscle weakness or failure to wean from mechanical ventilation. Two patients refused muscle biopsy and were excluded from this report. The other 14 were included retrospectively. In comparison, 5 ICU patients with acute weakness were diagnosed with critical illness PN during the study period. No patient with persistent weakness from prolonged NMJ blockade was identified.

The AMIC patients’ medical records were reviewed. Drugs that were administered, including doses for CSs and NMBAs, were recorded. Laboratory results from the time of ICU admission until the time of muscle biopsy were noted and included complete blood cell count (CBC); values for electrolytes, glucose, calcium, magnesium, phosphorus, albumin, CK, creatinine, and liver enzymes; and microbiological assay findings. In general, chemistries and CBC were assessed nearly daily, while albumin and liver enzymes were measured less frequently. With rare exceptions, CK was first assessed after neurological evaluation and prior to electromyography (EMG).

Manual muscle strength testing was performed on 16 to 20 muscle groups, 1 or 2 days before or coincident with EMG, by a neurologist and strength was graded on a 10-point modified Medical Research Council (MRC) scale. A mean MRC score (range, 0–10) (Table 1) represents the average score of all muscles examined [39].

Diagnostic Studies

Nerve conduction studies were performed at the bedside with a Nicolet Viking II unit using routine percutaneous stimulation. Limbs were warmed with heat packs if the hand temperature was less than 33°C or if the foot temperature was less than 32°C. The nerves studied are listed in Table 2. Baseline 3-Hz repetitive nerve stimulation was performed on either the ulnar or the median nerve. If the patient was able to exercise for 10 seconds, postexercise stimulation (single shock) was performed on a motor nerve that was not examined by repetitive stimulation. In most cases, if the patient could not exercise, repetitive stimulation at 20 to 30 Hz was performed. Concentric needle EMG was performed on distal and proximal upper- and lower-extremity muscles.

Muscle biopsies were performed at the bedside via percutaneous needle biopsy using the 14-gauge Biopsy system and the method of Coté and colleagues [40]. Biopsy of the vastus lateralis was performed in Patient 14 and of the deltoid in all others. Percutaneous biopsies were performed because many patients, their families, and ICU physicians are often reluctant to allow us to obtain muscle tissue by open biopsy in the critical illness setting. By obtaining multiple samples, we were able to examine at least 450 myofibers (usually > 1,000).

Cryostat sections (8 μm), embedded in gum tragacanth, were stained with hematoxylin and eosin (H&E), Gomori trichrome, NADH-TR, ATPase at pHs 4.3, 4.6, and 9.4, oil red O, and periodic acid–Schiff (PAS). Sections from 6 patients were reacted for actin (Sigma) at a dilution of 1:150 and pan-myosin (monoclonal antibody against fast and slow heavy-chain isoenzymes, Amersham Life Science) at a dilution of 1:5 via peroxidase immunohistochemistry. At least nine fascicles (range, 9–49) containing 50 or more muscle fibers were available for review for each patient. Paraffin sections, processed from specimens from 11 patients, were stained with H&E. Tissue was fixed in glutaraldehyde at the time of biopsy and processed routinely for electron microscopy (EM).

Muscle fiber diameters from 200 fibers were measured using an eyepiece graticule on ATPase-reacted cross sections. If the section was slightly oblique instead of transverse, the minimum diameter was measured. The approximate percentage of fibers undergoing degeneration or regeneration or exhibiting irregular or absent ATPase staining was judged subjectively on examination of at least 500 myofibers (Table 3).

Statistics

The Wilcoxon rank test (two tailed) was used to determine whether there was a difference in the rank totals regarding the times when the muscle biopsies were performed between the two groups of patients with muscle histopathological findings that did and did not include loss of thick filaments.

Results

Clinical and Laboratory Features

The sex, age, cumulative IV CS and N MBA doses, CK levels, and major diagnoses for each patient are listed in Table 1. Two of the patients with chronic obstructive pulmonary disease were admitted for lung volume resection surgery for end-stage emphysema. Four of the liver transplantation patients had fulminant hepatic failure at the time of transplantation; the other 3 had chronic liver disease. All 7 developed weakness soon after receiving an orthotopic liver transplant.

The transplant patients were not septic when myopathy was detected. The nontransplant patients frequently had multiple medical problems leading to ICU admission including sepsis. All patients received multiple drugs including antibiotics. The nontransplant patients who did not have bacteremia had a focus of
**Table 1. Summary of Clinical and Laboratory Features**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)/Sex</th>
<th>Disorders</th>
<th>Days from IV MP until Muscle Biopsy</th>
<th>IV MP mg (No. of Rx Days)</th>
<th>Vent Dep</th>
<th>CK (&lt;200 IU/liter)</th>
<th>MRC Score (0–10)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62/M</td>
<td>Severe COPD; s/p bullectomy; ischemic colitis; sepsis</td>
<td>47</td>
<td>3,180 (27)</td>
<td>262/0 (8)</td>
<td>X</td>
<td>236</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>58/M</td>
<td>Liver transplantation; alcoholic cirrhosis</td>
<td>39</td>
<td>3,615 (19)</td>
<td>26/10* (1)</td>
<td>X</td>
<td>&lt;20</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>44/M</td>
<td>Pneumonia; ARDS; history of alcoholism; renal insufficiency</td>
<td>24</td>
<td>1,760 (9)</td>
<td>145/85 (10)</td>
<td>X</td>
<td>219</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>66/M</td>
<td>Severe COPD; s/p bullectomy</td>
<td>42</td>
<td>1,590 (17)</td>
<td>21/0</td>
<td>X</td>
<td>&lt;20</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>62/M</td>
<td>s/p 2 Liver transplantations; sclerosing cholangitis</td>
<td>18</td>
<td>3,240 (16)</td>
<td>90/24 (3)</td>
<td>X</td>
<td>331</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>65/M</td>
<td>s/p 2 Liver transplantations; hepatitis C; diabetes</td>
<td>32</td>
<td>3,930 (10)</td>
<td>90/24 (5)</td>
<td>X</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>61/F</td>
<td>Liver transplantation; autoimmune hepatitis</td>
<td>20</td>
<td>1,760 (11)</td>
<td>7/13* (1)</td>
<td>X</td>
<td>&lt;20</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>79/F</td>
<td>Small-bowel obstruction; s/p lysis of adhesions; COPD; pulmonary edema; Staph. aureus sepsis</td>
<td>31</td>
<td>432 (10)</td>
<td>20/0</td>
<td>0</td>
<td>&lt;20</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>57/M</td>
<td>Severe COPD; pulmonary aspergillosis; s/p thoracotomy; gastrointestinal bleeding</td>
<td>14</td>
<td>2,320 (8)</td>
<td>144/0 (4)</td>
<td>X</td>
<td>136</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>65/F</td>
<td>COPD; pneumonia; respiratory failure</td>
<td>35</td>
<td>1,520 (9)</td>
<td>0/0</td>
<td>X</td>
<td>125</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>46/F</td>
<td>s/p Lung transplantation; bronchoalveolar cancer</td>
<td>31</td>
<td>1,635 (13)</td>
<td>30/30* (2)</td>
<td>X</td>
<td>92</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>49/M</td>
<td>Liver transplantation; hepatitis C; alcoholism</td>
<td>10</td>
<td>1,620 (10)</td>
<td>16/22</td>
<td>X</td>
<td>&lt;20</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>65/F</td>
<td>Liver transplantation; hepatitis C</td>
<td>10</td>
<td>2,480 (10)</td>
<td>10/39* (1)</td>
<td>X</td>
<td>103</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>46/M</td>
<td>Liver transplantation; graft rejection; ascending cholangitis; history of sclerosing cholangitis</td>
<td>12</td>
<td>3,220 (5)</td>
<td>0/18*</td>
<td>0</td>
<td>&lt;20</td>
<td>5</td>
</tr>
</tbody>
</table>

*aAdministered in operating room only.
*bDoxocurium rather than pancuronium.

IV MP = intravenous methylprednisolone; Rx = treatment; NMBA = neuromuscular junction–blocking agent; Vec = vecuronium; Pan = pancuronium; Vent Dep = ventilator dependent; CK = creatine kinase; MRC = Medical Research Council; X = present; 0 = absent; AFO = ankle foot orthoses; UE = upper extremity; LE = lower extremity; COPD = chronic obstructive pulmonary disease; s/p = status post; ARDS = adult respiratory distress syndrome.
infection (most often pulmonary), leukocytosis, and usually hypotension or multiorgan failure.

All patients had hyperglycemia that required intermittent insulin administration. The serum glucose level was periodically higher than 300 mg/dl (normal, 70–110 mg/dl) in 13 of the 14 patients. Three patients had renal insufficiency (creatinine >2.0 mg/dl) that reduced more than 50%. Two patients (Patients 3, 6, 12, and 13) received hemodialysis for overt renal failure. The nontransplant patients had normal liver function, except for Patient 2 who had increased liver enzyme levels. Serum magnesium concentrations were generally normal. Transient hypophosphatemia was usually not possible to determine. Weakness was generalized and always affected neck flexors. Distal and proximal muscles were affected approximately equally in 9 patients, and proximal muscles were weaker in 5 (Patients 2, 7, 8, 10, and 11). Facial muscles were weak in 8 patients (57%); only Patient 11 (7%) had extraocular muscle weakness. Eleven patients were severely weak (MRC score <5 of 10); the others had more moderate weakness but they were unable to ambulate. Twelve patients (86%) were slow to wean from mechanical ventilation. Two patients (Patients 1, 3, and 6) were areflexic, 4 had hyporeflexia (Patients 5, 8, 10, and 11), 5 had normal tendon reflexes except for absent ankle jerks (Patients 2, 4, 7, 12, and 14), and 2 had normal reflexes including ankle jerks (Patients 9 and 13). All patients at least grimaced to pain, but sensory testing was initially unreliable in most. No patient reported dysesthesias during the recovery period. Four patients (Patients 2, 4, 9, and 12) were transiently encephalopathic.

Because of severe multisystem disease, 2 patients were allowed to die. Postmortem evaluations were not allowed. In most of the others in whom follow-up was available, strength improved such that unassisted ambulation occurred within 3 months.

**Electrodiagnostic Testing**

Motor and sensory amplitudes are listed in Table 2. Conduction velocities were normal except for mild slowing in Patient 12. Excluding Patient 12, distal latencies were normal except for isolated median prolongation due to carpal tunnel syndrome (3 patients). Repetitive stimulation revealed no significant decremental (>10%) or incremental responses.

Needle examination revealed a variable degree of

### Table 2. Electrodiagnostic Studies

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Nerve Conduction Studies: Amplitudes (µV for Sensory; mV for Motor)</th>
<th>Needle Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sural S Med S Rad S Ulnar S Per M Tib M Ulnar M Med M</td>
<td>Fibrb LE Prox/D</td>
</tr>
<tr>
<td>1</td>
<td>10 11 12 5 0.8 2b NR 4b</td>
<td>+ + NF</td>
</tr>
<tr>
<td>2</td>
<td>5 27 14 0.3 4 NR 4</td>
<td>+ + +/+/+</td>
</tr>
<tr>
<td>3</td>
<td>6 18 5 11 0.2 3.6 1 1</td>
<td>0/0 +/+/+</td>
</tr>
<tr>
<td>4</td>
<td>7 13 0.5 1 1 6</td>
<td>+ + +/+/+</td>
</tr>
<tr>
<td>5</td>
<td>NR 9 1 1 1</td>
<td>+ 0/0 +/+/+</td>
</tr>
<tr>
<td>6</td>
<td>5 8 5 2 2</td>
<td>+ 0/0 +/+/+</td>
</tr>
<tr>
<td>7</td>
<td>3 41 1.6 3</td>
<td>0/0 0/0 +/+/+</td>
</tr>
<tr>
<td>8</td>
<td>10 14 9 1</td>
<td>0/0 0/0 +/+/+</td>
</tr>
<tr>
<td>9</td>
<td>2b 15 1.3 3</td>
<td>+/+- +/+/+</td>
</tr>
<tr>
<td>10</td>
<td>7 36 9 15 NR 3b 4b 2</td>
<td>+/+- +/+/+</td>
</tr>
<tr>
<td>11</td>
<td>6 26 27 1b 5b 2b</td>
<td>+/++ +/+/+</td>
</tr>
<tr>
<td>12</td>
<td>3b 13b 6b 8b 0.7b 4b 3b 2</td>
<td>+/NA +/NA NF</td>
</tr>
<tr>
<td>13</td>
<td>6 18 14 14 2.6 5 6b 4</td>
<td>0/0 0/0 +/+/+</td>
</tr>
<tr>
<td>14</td>
<td>NR (E) 12b 8b 0.3b 8 10</td>
<td>0/0 0/0 +/+/+</td>
</tr>
</tbody>
</table>

1Reduced more than 50%.
2Reduced 21–50%.
3Reduced 1–20% for age.

M = motor; S = sensory; Med = median; Rad = radial; Per = peroneal; Tib = tibial; Fibs = fibrillation potentials; UE = upper extremity; LE = lower extremity; Prox = proximal muscles; D = distal muscles; SD = short duration; LA = low amplitude; P = polyphasic; MUPs = motor unit potentials; NR = no response; E = edema; NF = no firing motor unit potentials; NA = not available; + = present; 0 = absent.
Table 3. Histopathological Features

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Mean Type 1 Fiber Diameter (μm)</th>
<th>Mean Type 2 Fiber Diameter (μm)</th>
<th>Necrosis</th>
<th>Regeneration</th>
<th>Irregular ATPase Staining</th>
<th>EM: Thick Filament Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Normal, 53–61)</td>
<td>(Normal, 42–62)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17*</td>
<td>17*</td>
<td>++</td>
<td>++</td>
<td>++++</td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>17</td>
<td>0</td>
<td>+</td>
<td>+++</td>
<td>X</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>33</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>X</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>32</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>25</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>30</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>9</td>
<td>51</td>
<td>38</td>
<td>+</td>
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<td>0</td>
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<tr>
<td>10</td>
<td>24</td>
<td>18</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>28</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>X</td>
</tr>
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<td>14</td>
<td>52</td>
<td>36</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Cannot differentiate fiber types due to very irregular ATPase staining and necrosis.

EM = electron microscopy; 0 = not present; + = in 1–33% of myofibers; ++ = in 34–65%; +++ = in 66–99%; ++++ = in 100%; X = present.

often diffuse fibrillation potential activity in 11 (79%) of the 14 patients. Patient 1 also had fibrillation potentials in facial muscles. Early or sometimes normal recruitment of motor unit potentials (MUPs) was noted. Some patients could not activate any MUPs in individual muscles that were severely weak. Short-duration, polyphasic, and often low-amplitude MUPs were noted in 13 patients. Patient 1 had no firing MUPs in limb muscles but had very polyphasic MUPs in facial muscles. Patient 12 had a limited study of only two muscles due to severe thrombocytopenia and an inability to activate any muscles; a follow-up study was refused. Serial studies were not performed.

Muscle Pathology

Moderate to severe type 2 fiber atrophy as well as a mild to moderate reduction in mean type 1 fiber diameters was evident in all biopsy specimens (see Table 3). The atrophic fibers were generally angulated and sometimes occurred in small groups. However, fiber-type grouping was only evident in the specimens from Patients 1 and 12. Myofiber degeneration, regeneration, or both were noted in 13 of the 14 patients. Rimmed vacuoles were noted in one specimen (Patient 7). Abnormal myosin-ATPase staining (at all pHs) occurred in some nonnecrotic fibers in 11 specimens (78%) (Fig 1).

The pattern of decreased ATPase staining was (a) patchy within atrophic and nonatrophic fibers of both fiber types (seven specimens), (b) diffuse but only within scattered atrophic type 1 and type 2 fibers (one specimen), and (c) patchy and predominantly within atrophic fibers (three specimens). Pan-myosin reactivity, assessed in 6 patients, correlated with the degree of reactivity on myosin-ATPase staining in serial sections (Fig 2). Myofibers with reduced ATPase activity had reduced myosin activity in a similar pattern; however, in Patient 13 the loss of myosin was more obvious with myosin immunohistochemistry. Actin staining was preserved within the areas of decreased myosin staining. In many atrophic and some larger fibers with and sometimes without irregular ATPase staining, basophilic stippling was noted on H&E-stained sec-

Fig 1. This representative cryostat section from Patient 3 reveals patchy, irregular reactivity for myosin-ATPase (pH 4.6) in many myofibers. Bar = 30 μm.
Fig 2. Serial cryostat sections from Patient 8. (A) Atrophic angulated myofibers are present including two that did not stain with ATPase at acid or alkaline pHs (arrows) (ATPase, pH 9.4 is shown). (B) The atrophic myofibers stained hypointensely for myosin. (C) Actin reactivity is preserved, and two fibers have relatively intense reactivity (arrows). Bar = 25 µ.

Fig 3. Electron micrograph from Patient 3 reveals loss of A bands (A) and thick filaments with relative preservation of I bands (framed by arrows) and thin filaments. Bar = 1.7 µ.

Discussion

The incidence of AMIC is uncertain. We believe that this retrospective study underestimates the incidence of AMIC, especially milder forms, in our ICUs in which there is an institutional referral bias toward organ transplantation. At least in the status asthmaticus population, AMIC is probably very common when IV CSs (of various types) and NMBAs are utilized. A prospective study of 25 patients treated for status asthmaticus revealed that 9 (36%) developed myopathy—all received both vecuronium and CSs—and 19 (76%) had elevated CK levels [22]. In that study, there was a positive correlation between the dose and duration of NMA therapy and the likelihood of developing myopathy. A positive correlation was not found regarding CS doses and myopathy. However, most patients who develop AMIC received at least the cumulative equivalent dose of 1,000 mg of methylprednisolone. For example, Shee [16] retrospectively noted that only the 4 of 9 patients with status asthmaticus who received more than 5 gm of hydrocortisone (equivalent to 1,000 mg of methylprednisolone) developed myopathy. In our patients, the cumulative doses of methylprednisolone (2,326 ± 1,036 mg, mean ± standard deviation [SD]) and the durations of treatment (12 days ± 6) were within the ranges of those reported in most patients with AMIC. At our institution, most organ transplant patients receive intraoperative NMBAs and high-dose methylprednisolone (usually 1 gm followed by a rapid taper to prevent graft rejection), placing them at risk for AMIC. Only Patient 8 received less than 1 gm of methylprednisolone (in addition to a low dose of vecuronium), and she had mild weakness.

In our patients, the doses of NMBAs used were low and the durations of administration short compared to those for other reported patients with AMIC [16, 29–31]. Nevertheless, we did note that our patients who received more than 80 mg of vecuronium in addition to CSs were all quadriplegic (MRC 0) at the time of diagnosis of AMIC, while most who received lower doses of NMBAs were not as weak (MRC scores of 1–8). Due to the lack of a control group of patients exposed to NMBAs and CSs who did not develop myopathy, we cannot determine whether the doses of NMBAs were related to the development of myopathy. Our ICU physicians generally now use “train of four” monitoring and intermittent (rather than continuous) NMA administration to limit the total exposure to NMBAs. Patient 10 was our only patient who did not receive a NMA. She had typical clinical, EMG, and pathological features of AMIC, but she had only mild weakness. Patient 14 received NMBAs during liver transplantation, but he was not weak postoperatively. Myopathy developed a week later only after he received high-dose IV Cs (without NMBAs) for acute graft rejection. He improved relatively quickly.
As in other studies, vecuronium was the NMBA used most commonly in our patients; 7 also received pancuronium; 1 received doxacurium in addition to vecuronium. Pancuronium and vecuronium are amino-steroid compounds structurally related to CSs; however, others observed AMIC in association with non-aminosteroids such as atracurium [28, 32, 33]. It is unknown whether the likelihood of developing AMIC depends on the type of nondepolarizing NMBA utilized.

In other reports, but not in our patient population, a small percentage of critically ill patients who received NMBAs (in very high doses) without CSs developed clinical and EMG features of AMIC [30, 32]. The pathological findings included myofiber necrosis, but loss of thick filaments was not observed. However, muscle necrosis may be common in an ICU population [41] for a number of reasons including sepsis and drug exposures. In addition, there is neither an experimental model of NMBA myopathy nor unique histopathology in the reported patients. Therefore, it remains unproved whether prolonged NMBA treatment alone (without CS exposure) causes the myopathy noted in these rare patients.

Clinical and Laboratory Features
The neurological findings that we describe are typical of AMIC. The precise onset of acute weakness is often difficult to pinpoint due to NMBA and sedative administration. Four of our patients were also initially encephalopathic on a toxic-metabolic basis, further masking their myopathic weakness. As we noted, there is usually diffuse weakness often including respiratory muscles. Our patients had uniform neck flexor weakness, and we noted facial weakness more frequently than in previous observations [16, 26, 29, 31]; facial weakness seemed to occur in the most severely affected patients. On the other hand, extracocular muscle involvement is rare [16, 17, 29, 31], and we observed it in only 1 patient. The weakness was reversible over weeks to months if the underlying diseases were successfully treated and the CSs and NMBAs were discontinued.

Only a minority of our patients had an elevated CK level despite the presence of pathological evidence of muscle necrosis in the majority. In a review of AMIC patients reported retrospectively, the CK level was elevated in about half [21]. We suspect that CK was usually measured too late (range, 9–41 days after exposure to CSs) to detect an increase. In the prospective series [22], the CK peak noted in patients with myopathy occurred 3.6 ± 1.5 days after treatment, and the CK was elevated for 9.8 ± 5.9 days. These data suggest that serial CK monitoring in patients at risk for AMIC should be performed early after exposure to IV CSs and NMBAs. A rising CK concentration could alert the clinician to an evolving myopathy. If feasible, the CS or NMBA, or both could be discontinued or given at a lower dose.

In addition to CSs and NMBAs, metabolic factors may play a role in potentiating AMIC. Infections, electrolyte abnormalities, and hyperglycemia (presumably due to CSs, sepsis, or preexisting diabetes mellitus) were common in our patients. Hyperglycemia is also common in patients who develop critical illness PN [2, 3]. The majority of our patients also had disturbances of renal or hepatic function. Patients with renal failure [42] and perhaps liver failure [32] are more likely to have prolongation of NMBA activity due to the persistence of metabolites; thus, the likelihood of developing NMBA-related neuromuscular toxicity may be increased in these settings. Our liver transplant patients who received vecuronium and pancuronium, which are acetylated in the liver and partially excreted in bile (especially vecuronium) [43], may have been at particular risk for NMBA toxicity during transplantation when they temporarily lacked a functioning liver. The roles of these metabolic factors as well as sepsis in potentiating AMIC are unknown and are difficult to study in humans because these variables cannot be controlled.

Electrodiagnostic Findings
Electrodiagnostic studies are very useful in determining the cause of flaccid weakness in ICU patients, especially when tendon reflexes are attenuated and the sensory examination is unreliable. Given these signs, which were present in most of our patients, the disease process could be localized to any component of the motor unit. In particular, we noted that AMIC was very difficult to differentiate from critical illness PN by clinical examination alone.

Our patients had rather typical electrodiagnostic findings of AMIC (see Table 2). The presence of generally diffuse fibrillation potentials and short-duration MUPs—sometimes with early recruitment—was compatible with a diffuse necrotizing myopathy. The low motor amplitudes were presumably due to loss of myofibers from necrosis. Purely on electrophysiological grounds, a coexisting terminal motor axonopathy is difficult to exclude, but we and others [28, 29] were unable to histopathologically identify degeneration of motor axons in several patients. In addition, the reported finding of electrical inexicatability of paralyzed muscles in several patients with AMIC raises the possibility that loss of sarcolemmal integrity alone or in addition to necrosis accounts for the low motor amplitudes [44].

Occasionally, sensory amplitudes were mildly reduced (generally 1–20% below the lower limit of normal in one or two nerves), but the motor amplitude reductions were substantially greater (generally <50% of the lower limit of normal). Others believe that the relatively minor reductions in sensory potentials in
some patients with AMIC may be due to technical factors such as edema at the recording site, as serial studies show rather rapid amplitude improvement [31]. However, a coexisting mild neuropathic process could still be present in some of these rare patients [21, 36] because the amplitude changes can also occur in non-edematous regions. Given this rapidity of improvement in amplitudes, the proposed neuropathic disturbance, if present, is unlikely to stem from significant axonal degeneration as is noted in critical illness PN [1–4].

Certainly, some of our patients who were exposed to NMBAs and CSs were also septic and had multiorgan failure, thus placing them at risk for critical illness PN [1–4] as well as AMIC, but the relative sparing of sensory amplitudes in the setting of low motor responses and the early recruitment of short-duration MUPs were the electrodiagnostic hallmarks that distinguished AMIC from critical illness PN.

In contrast, 2 of our patients did have sensory amplitude reductions that were as severe as the motor abnormalities. Patient 14 had reduced upper-extremity sensory responses and no sural response, but at the time of initial evaluation (consistent with reinnervation) in his muscle biopsy specimen, obtained only 10 days after liver transplantation, suggestive of an underlying chronic alcoholic polyneuropathy. In both patients, the neurological examination revealed greater proximal than distal weakness with normal sensation. Myopathic changes were also present in the biopsy specimen from Patient 14. Although an element of critical illness PN cannot be excluded in these patients, the distribution of weakness, rate of recovery, lack of both sepsis and multiorgan failure initially, and the EMG and histopathological findings (Patient 14) are most consistent with AMIC being the cause of acute weakness.

We did not identify prolonged NMJ blockade as a cause of weakness in the patients who were exposed to NMBAs despite the presence of renal [42] or hepatic failure [32]. Barohn and colleagues [32] showed that AMIC is preceded by NMJ blockade in some patients. It is possible that prolonged NMJ blockade occurred earlier in some of our patients prior to performance of the EMG, or that it was too subtle to be detected by repetitive stimulation alone. Nevertheless, their persistent weakness was due to myopathy.

**Muscle Histopathology**

In this relatively large series of AMIC patients whose evaluations included muscle biopsy, we found myopathic changes with selective thick (myosin) filament loss in the majority. In addition, myofiber necrosis was noted in other regions of these specimens. Patchy reductions in enzyme activity or absent staining of myofibers on serial ATPase-reacted sections at acid and alkaline pHs were predictive of thick filament loss that was confirmed by EM. We found that myosin heavy-chain and myosin-ATPase reactivity correlated. Actin was present in regions of decreased myosin staining. Because patchy loss of ATPase reactivity could occur due to early myofiber necrosis, which should affect all myofilaments, it is important to determine that there is preservation of actin (thin filaments), either immunohistochemically or by ultrastructural evaluation.

The loss of thick filaments was generally widespread but patchy within affected fibers of varying sizes and of both fiber types. Atrophic fibers were often most affected. Type 2 fibers, those most vulnerable to CS and disuse atrophy, were particularly involved. Others noted even more selective involvement of type 2 fibers in 2 patients with critical illness and myopathic features [45]. In Patient 8, myosin loss occurred only within the atrophic fibers in a diffuse rather than patchy pattern, which we consider to be part of the spectrum of AMIC [46] rather than a unique finding [47]. Atrophic fibers may be affected earlier in the course of AMIC, but serial muscle biopsies in a dose-escalation model would be required to determine whether the patterns of myosin loss change with dosing and with time. In the animal model, the degree of thick filament loss does increase during the weeks after CS exposure [37]. Loss of A-band density is evident by 7 days but only in a few fibers. At 13 days, many fibers are affected, and almost all are affected at 28 days; however, there is variability in thick filament loss among different regions of the same muscle as shown by EM [37].

In 3 patients, muscle biopsy specimens did not reveal thick filament loss. These biopsies were performed earlier (12 ± 2 days, mean ± SD) than those that did reveal thick filament loss (30 ± 11, p < 0.02). In Patient 13, the biopsy was also performed relatively early, and the myosin loss was subtle. It is likely that the appearance of thick filament loss lags behind the development of clinical weakness, as suggested by the animal model. It is less likely that the more subtle loss of thick filaments that might occur “early” was missed due to sampling error, given the relatively diffuse distribution of weakness and EMG abnormalities. Alternatively, the acute myopathy without thick filament loss could have a different pathogenesis. We were reluctant to evaluate these possibilities further by performing multiple or serial muscle biopsies on our patients.

**Pathogenesis of Loss of Thick Filaments**

Loss of thick filaments is not specific. It also occurs sporadically in the setting of dermatomyositis, thrombotic thrombocytopenia purpura, human immunodeficiency virus infection, and congenital myopathy [48,
49]. Sher and colleagues [50] first reported an acute myopathy with "selective lysis of myosin filaments" in the ICU setting in 1979 in a woman with allergic vasculitis, renal failure, and pneumonia. She received IV CSs; NMBA use was not noted. She recovered in 6 weeks. Danon and Carpenter [18] first described loss of thick filaments in AMIC associated with NMBAs and IV CSs and other reports followed [20, 25, 29, 32]. Despite the lack of specificity, we agree with Danon and Carpenter that a loss of thick filaments noted in acute myopathy associated with IV CS and NMBAs denotes a distinctive syndrome.

The precise cause of the loss of thick filaments in AMIC is uncertain. In the animal model, disassembly of myosin monomers—presumably due to an effect at the level of cellular protein regulation—is thought to lead to the loss of thick filaments [37, 38]. The experimental animal model, our study, and the work of others support the notion that IV CSs cause the loss of thick filaments, but that other factors may "trigger" the process [29] (Fig 4). An abnormal NMJ from pharmacological blockade in ICU patients and an abnormal end-plate following traumatic denervation in the animal model are likely triggers. Our study showed that the NMBA exposure may be minimal. Also in support of the view that an abnormal motor end-plate can incite this process is the fact that a patient with a dysfunctional end-plate from myasthenia gravis developed loss of thick filaments after receiving high-dose CSs [51]. Disuse (or immobilization) that leads to an increase in CS receptors [52] may also lower the threshold for this toxic myopathy. Interestingly, Achilles tenotomy in rats, which leads to soleus shortening and immobilization, causes corelike lesions with some preferential loss of thick filaments [53]. Other factors that may coexist in AMIC patients and alter the nerve and motor end-plate milieu, including critical illness PN, sepsis, cytokines, and hyperglycemia, may also play a role in potentiating AMIC [54] (see Fig 4). These variables require further study; however, they are difficult to control in humans but could be examined in animal models.

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