Critical illness myopathy unrelated to corticosteroids or neuromuscular blocking agents

N. Deconinck a, b, V. Van Parijs b, G. Beckers-Bleukx a, P. Van den Bergh b, c, *

a Laboratoire de Physiologie Générale des Muscles, Département de Physiologie, Université Catholique de Louvain, 1200 Brussels, Belgium
b Service de Neurologie, Clinique Universitaire Saint-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium
c Laboratoire de Neuropathologie, Clinique Universitaire Saint-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium

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Abstract

Acute myopathy occurs in critically ill patients, receiving neuromuscular blocking agents or corticosteroids during intensive care hospitalisation. We report three patients with acute quadriplegic myopathy, two of whom were not exposed to corticosteroids or neuromuscular blocking agents. The first of these latter two patients had a history of generalised anoxia with coma related to surgery, complicated by multiple organ failure and sepsis. The second patient, suffering from acute leukaemia, developed sepsis and acute respiratory distress syndrome with the need for mechanical ventilation in the intensive care unit. Electrophysiological studies and muscle biopsy findings were consistent with the diagnosis of critical illness myopathy with loss of myosin filaments. Selective loss of myosin was confirmed by biochemical analysis of muscle. These findings demonstrate that acute myopathy with loss of myosin filaments may occur in patients with severe systemic illness without exposure to corticosteroids or neuromuscular blocking agents.

Keywords: Myopathy; Myosin; Critical illness

1. Introduction

A variety of neuromuscular disorders may contribute to weakness during critical illness. They include critical illness polyneuropathy, drug-related neuromuscular junction defects, and myopathies. Many authors have provided extensive evidence that an axonal sensorimotor polyneuropathy, which has been named critical illness polyneuropathy, frequently occurs in patients affected by sepsis and multiple organ failure [1–4]. Prolonged neuromuscular junction blockade has been identified in occasional intensive care unit patients, who had persistent weakness after prolonged use of neuromuscular junction blocking agents [5–7]. Acute myopathy occurs in association with exposure to corticosteroids and/or neuromuscular blocking agents, and is often characterised by loss of myosin filaments [8–14]. Afflicted patients develop acute, diffuse, flaccid weakness, often associated with failure to wean from mechanical ventilation. Following discontinuation of corticosteroids and/or neuromuscular blocking agents and with resolution of the underlying critical illness, the myopathy improves over weeks to months. The exact pathophysiological mechanisms of this disorder remain unclear. We describe three patients with the typical features of acute myopathy with myosin loss, two of whom were not exposed to corticosteroids or neuromuscular blocking agents.

2. Case reports

2.1. Patient 1

A 65-year-old woman was admitted for emergency surgery of aortic dissection. The surgery was complicated by generalised anoxia with coma and the patient needed artificial ventilation in the intensive care unit. She remained comatose for more than a week. A persistent pneumothorax required thoracic drainage. During the first week of her intensive care unit stay, the patient developed transient renal failure, which was rapidly controlled by haemodialy-
caused by care unit, the patient rapidly developed bronchopneumonia, signs were observed. After admission to the intensive were normal, the patient responded to painful stimuli, and deep tendon reflexes were diminished. No upper motor neuron signs were observed. After admission to the intensive care unit, the patient rapidly developed bronchopneumonia, caused by Pseudomonas aeruginosa. Blood analysis revealed an inflammatory syndrome with an elevated white cell count 5 days after admission and persisting for more than 1 month. Creatine kinase levels (CK) peaked at 1300 IU/l (normal values, <170 IU/l) 7 days after admission. Anaemia and subnormal plasma protein levels were found. Thanks to correct nutritive intake, nitrogen balance was only slightly negative. Medical treatment consisted of norepinephrine (2 days) and dopamine (7 days). For sepsis, imipenem-cilastatin, 1 g/day, and amikacin, 1 g/day, were administered (14 days). The patient was discharged from the intensive care unit with significant limb weakness after 3 months.

2.2. Patient 2

A 52-year-old woman with acute monoblastic leukaemia was admitted to the haematology service for consolidation chemotherapy (cytarabine 1500 mg/day for 5 days, amantadine 180 mg/day for 3 days). During treatment, she developed dyspnoea, hyperthermia and confusion. She developed acute respiratory distress syndrome and needed mechanical ventilation in the intensive care unit until her demise. Endotracheal aspiration cultures showed the presence of herpes type 1 virus. On entry to intensive care unit, cerebrospinal fluid analysis showed an increased protein level with positive enterovirus cultures. Haemocultures were positive for Streptococcus viridans. Three weeks after admission, the patient developed transient renal failure, treated by hemodialysis. When sedative drugs (propofol and fentanyl) were discontinued after 3 weeks, the patient was quadriplegic and could not be weaned from the ventilator. On neurological examination, the patient was conscious, but could only respond to painful stimuli with facial movements. Cranial nerves examination was normal. Decreased deep tendon reflexes and muscle atrophy of the four limbs were noted. Cranial nerve action potentials (SNAPs) were recorded antidromically. Electromyography was performed with standard concentric needle electrodes.

3. Methods

3.1. Electrodiagnosis

Motor nerve conduction and repetitive stimulation studies were performed with percutaneous supramaximal nerve stimulation, while recording the compound muscle action potential (CMAP) with 11-mm plate-shaped electrodes. Using surface ring or plate-shaped electrodes, sensory nerve action potentials (SNAPs) were recorded antidromically. Electromyography was performed with standard concentric needle electrodes.

3.2. Muscle biopsy analysis

3.2.1. Histological techniques

Transverse 10-μm cryostat sections were processed for haematoxylin-eosin, modified Gomori trichrome, PAS, oil red O, NADH-TR, SDH and myosin ATPase after preincubation at pH 9.85, 4.50 and 4.25. Serial sections were immuno-reacted by standard immunoperoxidase and immunofluorescence methods with slow and fast myosin heavy chain antibodies (Novocastra). Glutaraldehyde-fixed, resin-embedded tissue was prepared for electron microscopy by standard methods. Thin sections were stained with lead citrate and uranyl acetate and examined with a Zeiss electron microscope EM109.

3.3. Biochemical techniques

Muscle biopsy specimens from the three patients and from seven control subjects were studied. For one-dimen-
4. Results

4.1. Electrodiagnostic findings (Tables 1 and 2)

Electrodiagnostic studies were performed 4, 6 and 5 weeks after admission for patients 1, 2 and 3, respectively. Nerve conduction studies were performed in patients 1 and 2. Motor distal latencies and conduction velocities were normal. Low-amplitude CMAPs were found and F-waves were frequently absent. Repetitive stimulation studies were normal. Sensory nerve conduction studies were basically normal. Sensory distal latencies and conduction velocities were normal. In patient 1, a slight reduction in median and ulnar SNAP amplitude was noted. Electromyography showed abundant fibrillation potentials and positive sharp waves in many muscles in patients 2 and 3, but not in patient 1. Brief, small, polyphasic motor unit action potentials with early recruitment were noted in all three patients. Often, motor unit action potentials could not be analysed, due to absence of recruitment.

Table 1
Electrodiagnostic findings – nerve conduction studies

<table>
<thead>
<tr>
<th>Nerve</th>
<th>CMAP amplitude (mV)</th>
<th>SNAP amplitude (µV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peroneus</td>
<td>Ulnaris</td>
</tr>
<tr>
<td>Patient 1</td>
<td>Absent (22)</td>
<td>2.5 (26.6)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>1.2 (22)</td>
<td>2 (36.6)</td>
</tr>
<tr>
<td>Patient 3</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Motor and sensory nerve conduction velocities and distal latencies are normal. CMAP, compound muscle action potential; SNAP, sensory nerve action potential; ND, not done; Normal values are given in parentheses.

4.2. Muscle biopsy analysis

Muscle biopsy was performed 4, 6 and 5 weeks after admission on patients 1, 2 and 3, respectively.

4.2.1. Histological findings (Fig. 1)

Large numbers of atrophic muscle fibres, scattered or in small groups, were observed in the biopsies of all three patients. Several atrophic fibres were dark on NADH staining. Oxidative enzyme stains were otherwise unremarkable. More type 2 than type 1 fibres were atrophic. Fibre type grouping was not observed. In the biopsy of patient 3, type 1 fibres were deficient (less than 10% of all fibres). On haematoxylin-eosin staining, pale fibres were occasionally observed in the three biopsies, but necrotic fibres were a rare finding. In other fibres, lack of ATPase staining and myosin immunoreactivity was observed, usually in the fibre centre. Electron microscopy showed relatively selective loss of myosin filaments in many muscle fibres of the three biopsies. However, some loss of actin filaments, especially in the biopsy of patient 1, was also noted.

4.2.2. Biochemical findings (Fig. 2 and Table 3)

One-dimensional SDS-PAGE showed a relatively constant actin-myosin ratio (5.1 ± 0.25) in the control muscles studied. Absolute concentrations of myosin and actin could be estimated with the help of standards of actin and myosin. The concentrations in control muscles (actin, 475 ± 31 pmol/mg and myosin, 94.9 ± 5 pmol/mg) were comparable with those described in other mammalian species [16]. A severe depletion of myosin levels was observed in the muscle samples of the three patients. Actin levels were also moderately diminished, especially in patient 1, but to a
Fig. 1. Haematoxylin-eosin (A,C,E) and lead citrate-uranyl acetate thin (B,D,F) muscle biopsy sections of patients 1 (A,B; deltoid), 2 (C,D; vastus lateralis) and 3 (E,F; deltoid). Atrophic fibres are abundant in A,C and E (Bar, 60 μm). Z-disks (Z) and actin filaments (A) are relatively well preserved with marked loss of myosin filaments ($P < 0.05$) (Bar, 0.4 μm).
5. Discussion

A syndrome of acute, severe muscle weakness with prolonged ventilator dependency occurs in intensive care unit patients with critical illness. Until recently, this syndrome was attributed mainly to an acute sensorimotor axonal polyneuropathy (critical illness polyneuropathy) [1,2]. Critical illness polyneuropathy generally occurs in patients with sepsis, who develop multiple organ failure [1–4]. The syndrome has occasionally been observed after prolonged use of neuromuscular blocking agents, especially vecuronium, where weakness is due to prolonged neuromuscular junction blockade [5–7]. Although usually subsiding within hours or days, it may persist for more than a week after discontinuation of neuromuscular blocking agents. Often, affected patients have renal failure with high plasma concentrations of the vecuronium metabolite, 3-desacetyl-vecuronium.

Acute quadriplegic myopathy with ventilator dependency was first described in 1977 [8] and is now being increasingly recognised as a major cause of muscle weakness in intensive care unit patients, following treatment with corticosteroids or neuromuscular blocking agents [9–14,17]. Patients with critical illness myopathy have acute onset, moderate to severe limb and respiratory muscle weakness with preserved cranial nerve function. Weakness typically develops over a period of several days. Deep tendon reflexes may be reduced or absent and muscle atrophy is usually observed. Electrodagnostic studies show reduction of CMAP amplitudes, proportional to the degree of weakness. Nerve conductions are normal and SNAP amplitudes are generally well preserved. Serum CK levels are mildly to moderately elevated in about 50% of the patients [18]. Sometimes, the levels are markedly elevated and extensive muscle fibre necrosis is noted on muscle biopsy [9,10]. Usually, however, muscle fibre degeneration is rare, and the muscle biopsy is characterised by muscle fibre atrophy, affecting type 2 more than type 1 fibres [11–14]. Selective, patchy loss of myosin has been repeatedly demonstrated immunohistochemically and ultrastructurally [11–14,19]. Although myopathy with loss of myosin filaments has been observed in the setting of dermatomyositis, thrombotic thrombocytopenia, AIDS, congenital myopathy and vasopressin therapy [20–22], critical illness myopathy with loss of myosin filaments following treatment with corticosteroids or neuromuscular blocking agents is considered a distinct entity [14]. Although the pathogenesis of this myopathy in these patients remains to be elucidated, it has been reproduced in rats by muscle denervation and simultaneous administration of high-dose corticosteroids [15,23] and is thought to be due to a potentiating effect of these two factors on myosin catabolism. It is hypothesised that a similar mechanism is responsible for myosin loss myopathy in intensive care unit patients, who are treated with high-dose corticosteroids and neuromuscular blocking agents, which results in pharmacologic muscle denervation.

Here, we report three patients with acute myopathy with myosin loss. We used SDS-PAGE to confirm the ultrastructural diagnosis and to measure actin and myosin levels and to determine their ratios. Although two out of the three patients were not exposed to either corticosteroids or neuromuscular blocking agents, similar preferential depletion of myosin was observed in muscle homogenates of all three patients. One-dimensional SDS-PAGE showed moderate reduction of actin levels in our three patients. Mild actin depletion in a myosin loss myopathy model in experimental rats has been reported [15,23]. Mildly to moderately reduced actin levels could be considered secondary to severe myosin depletion, which disturbs sarcromere organisation. These findings indicate that this type of myopathy can occur independently of corticosteroids or neuromuscular blocking agents treatment and, therefore, that other

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Biochemical studies</th>
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<tbody>
<tr>
<td>Muscle</td>
<td>Actin (pmol/mg)</td>
</tr>
<tr>
<td>Control</td>
<td>475 ± 31</td>
</tr>
<tr>
<td>Patient 1 Deltoid</td>
<td>357</td>
</tr>
<tr>
<td>Patient 2 Quadriceps</td>
<td>439</td>
</tr>
<tr>
<td>Patient 3 Deltoid</td>
<td>299</td>
</tr>
</tbody>
</table>

Each value is the result of four experiments on each muscle sample. Variation between experiments on the same muscle sample did not exceed 10 to 15%. The control mean is the result of biochemical studies on seven control biopsies and is given with the standard error of the mean. The IP_{0.05} for control actin/myosin ratio is 3.48–6.72; the ratio of the three patients is outside this interval.
pathogenetic factors may be responsible. Disuse and malnutrition, which are known to cause muscle fibre atrophy, may play a role, but are generally not associated with severe quadriplegic weakness and significant electrophysiological abnormalities [4,24,25]. The almost neutral nitrogen balance in our patients suggests that malnutrition is unlikely to be a significant factor explaining their myopathy. A common characteristic of our patients is that acute myopathy with myosin loss occurred during critical illness in a context of sepsis and multiple organ failure. Showalter and Engel reported five patients with acute myopathy with myosin loss, at least one of whom did not receive neuromuscular blocking agents or corticosteroids during critical illness [19]. They showed evidence of enhanced calpain expression and suggested that calpain degrades myosin in this myopathy. Although they did not study myosin, Latronico et al. found that critical illness myopathy was the predominant cause of acute weakness in 23/24 patients [17]. Most of their patients had not been treated with neuromuscular blocking agents and corticosteroids, but all had suffered from repeated infections and prolonged sepsis with or without multiple organ failure. It appears, therefore, that critical illness myopathy may be due to severe systemic illness itself.

Critical illness is defined as a syndrome of sepsis and multiple organ failure, with sepsis representing the systemic response to infection [2–4]. The inflammatory response to infection induces cytokine release, which activates a cascade of metabolic changes that constitute the septic syndrome. A catabolic state arises with activation of muscle proteases, gluconeogenesis and lipid breakdown. Eicosanoids result in vasoconstriction and increased vascular permeability. Decreased peripheral blood flow and impaired oxygen extraction finally lead to organ failure. It has been suggested that critical illness neuropathy is an integral part of the syndrome of multiple organ failure in the context of sepsis [2–4]. It is conceivable that the same mechanisms are in play in muscle. Thus, myopathy could be considered an integral part of the syndrome of multiple organ failure during sepsis [3,4]. Systemic infection with Streptococcus pneumoniae causes muscle atrophy, decreased twitch and tetanic tension, activation of intracellular proteases and protein degradation, and altered sarcoplasmic electrolyte composition in rats [26]. Mechanisms may include endotoxin-induced interleukin-1 release and release of tumour necrosis factor from macrophages, both of which activate muscle catabolism [27–29]. Muscle proteolysis in response to sepsis has also been documented in humans [30,31]. In the context of multiple organ failure, renal failure could also play a role in the genesis of myopathy, since acute uraemia is known to lead to muscle wasting by activation of muscle proteases [27]. Transient renal failure occurred in two of our patients before development of acute muscle weakness.

In conclusion, acute myopathy with loss of myosin may occur in critically ill patients not exposed to neuromuscular blocking agents or corticosteroids. Sepsis with or without multiple organ failure seems to be the main trigger in these patients. The characteristics of critical illness myopathy with myosin loss, with or without exposure to neuromuscular blocking agents and corticosteroids, are very similar. The frequency and severity of this myopathy may increase in the presence of confounding toxic and metabolic factors, such as uraemia, corticosteroids or neuromuscular blocking agents. Biochemical analysis by SDS-PAGE is a relatively simple, fast, quantitative and cost-effective method to demonstrate selective loss of myosin in critical illness myopathy.

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References