The Pathophysiology of Neuromuscular Dysfunction in Critical Illness

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KEYWORDS

• Neuromuscular dysfunction • Critical illness • Polyneuropathy • Polymyopathy
• Intensive care unit outcome

KEY POINTS

- Disability after critical illness is heterogeneous and related to multiple morbidities.
- Neuromuscular dysfunction comprising critical illness polyneuropathy and myopathy (intensive care unit-acquired weakness) represents a prevalent and clinically important contributor to long-term functional dependency.
- These are an integral part of the multiorgan dysfunction syndrome and may share common microcirculatory, cellular, and metabolic pathophysiological mechanisms with other organ dysfunction syndromes.
- Emerging basic science is crucial to elucidate mechanisms of tissue injury and repair and to provide a foundation and rationale for future targeted clinical interventions.

INTRODUCTION

In 1984, Bolton and colleagues described the clinical course of 5 critically ill patients who developed a severe motor and sensory polyneuropathy. As the acute phase of their primary illness subsided and difficulties in weaning from the ventilator emerged, flaccid and areflexic limbs became evident. Electrophysiological studies demonstrated a primary axonal polyneuropathy with sparing of the central nervous system and how this polyneuropathy improved over time.[1] This seminal observation highlighted a new and prevalent entity among critically ill patients.[2,3]

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Intensive care unit-acquired weakness (ICUAW) is characterized by muscle wasting and weakness, and up to 30% of patients may experience long-term functional dependency.[4,5] This neuromuscular dysfunction is associated with prolonged mechanical ventilation and ICU stay, as well as increased ICU, hospital, and 1-year mortality.[2,6] It is an important sequela of an episode of critical illness and represents a burgeoning public health challenge as more patients survive to ICU discharge after an episode of critical illness.[7,8] Recent estimates report a staggering proportion of up to 1 million patients per year worldwide who may develop this condition.[9] Although several studies over the past 2 decades have improved understanding that functional disability is a robust and long-lasting observation in survivors of acute respiratory distress syndrome (ARDS) and sepsis,[10–13] there remain lacking definitive preventative and interventional strategies to mitigate this dysfunction and its attendant quality of life and economic ramifications. It is, therefore, fundamental that one achieves a better understanding of the underlying basic science of neuromuscular dysfunction to inform treatment.

This article aims to provide a concise review of the current knowledge of the pathophysiology of neuromuscular dysfunction with an emphasis on basic and translational science.

THE CONDITION

ICUAW refers to a syndrome of generalized limb weakness in critically ill patients in whom etiologies other than critical illness are excluded.[9] The neuromuscular dysfunction in patients with ICUAW may comprise polyneuropathy (critical illness polyneuropathy [CIP]), myopathy (critical illness myopathy [CIM]), or the coexistence of the 2 conditions (critical illness neuromyopathy [CINM]),[9,14] as described in **Box 1**. In addition, muscle disuse atrophy may overlap and further contribute to ICUAW.

RISK FACTORS

Risk factors have been explored in several studies. A recent systematic review and meta-analysis identified female sex, APACHE II score, multiple organ failure (MOF), systemic inflammatory response syndrome (SIRS), sepsis, use of neuromuscular-blocking agents (NMBAs), aminoglycosides, norepinephrine, duration of mechanical ventilation, parenteral nutrition, hyperglycemia, electrolyte disturbances, hyperosmolality, and lactate level as risk factors for ICUAW.[15]

Other risk factors have been described more inconsistently across studies. Age, pre-ICU functional status, comorbidities, frailty, and trajectory of health status may all affect the post-ICU functional status; however, the interaction among these factors and their effect on the acute episode of critical illness, persistence, and the long-term functional and cognitive outcomes remain incompletely understood. Future studies

Box 1
Neuromuscular dysfunction in patients with intensive care unit-acquired weakness

- CIP, in patients who have electrophysiological evidence of an axonal polyneuropathy
- CIM, in patients with ICUAW who have electrophysiologically and/or histologically defined myopathy
- CINM, in patients who have electrophysiological and/or histologic findings of coexisting CIP and CIM