INTRODUCTION

Thirty to fifty percent of critically ill patients admitted to the intensive care unit suffer from generalized neuromuscular weakness due to critical illness polyneuropathy, critical illness myopathy, or a combination of them, thus prolonging mechanical ventilation and their intensive care unit stay. A distinction between these syndromes and other neuromuscular abnormalities beginning either before or after ICU admission is necessary. These intensive care unit-related diseases are associated with both elevated mortality rates and increased morbidity rates. Generally, over 50 % of patients will completely recover. Most of them recover after 4-12 weeks, but some patients have been reported to keep on suffering from muscle weakness for at least 4 months ***(Apostolakis et al., 2015)***.

Critical illness is any disease process which causes physiological instability leading to disability or death within minutes or hours. Perturbation of the neurological and cardiorespiratory systems generally has the most immediate life-threatening effects. Fortunately such instability can be reliably detected by deviations from the normal range in simple clinical observations such as level of consciousness, respiratory rate, heart rate, blood pressure and urinary output ***(Lim et al., 2007)***.

Critical illness polyneuropathy and myopathy are inflammatory conditions involving peripheral nerves and skeletal muscle that typically appear in patients with severe sepsis and

multiorgan failure, and are recognized only when patients fail to wean from mechanical ventilation ***(Hudson and Lee, 2003)***.

Critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) are secondary disorders, and typically accompany severe sepsis and other conditions associated with progressive systemic inflammation ***(Hund, 2001)***.

CIP is a diffuse sensory and motor axonal neuropathy that is discovered in at least 50% of patients with severe sepsis and septic shock. The onset is variable, occurring from 2 days to a few weeks after the onset of the septic episode. CIP is considered the most common peripheral neuropathy in critically ill patients ***(Maramatton and Wijdicks, 2006)***.

CIM is a diffuse inflammatory myopathy that involves both limb and truncal muscles. Predisposing conditions include severe sepsis and septic shock, and prolonged periods of drug-induced neuromuscular paralysis, particularly when combined with high-dose corticosteroid therapy. CIM has also been reported in one-third of patients with status asthmaticus who are treated with high-dose corticosteroids ***(Lacomis, 2002)***.

The diagnosis of CIP can be confirmed by nerve conduction studies (which show slowed conduction in sensory and motor fibers) ***(Van Mook and Hulsewe-Evers, 2002)***.

The diagnosis of CIM can be confirmed by electromyography (which shows myopathic changes) and by

muscle biopsy (which shows atrophy, loss of myosin filaments, and inflammatory infiltration ***(Lacomis, 2002)***.

Prognoses of patients differ depending on electrophysiological findings during early critical illness: early electrophysiological differentiation of ICU acquired neuromuscular disorder enhances the evaluation of clinical prognosis during critical illness ***(Koch et al., 2011)***.

Changes in nerve conduction studies occur in the majority of patients early in the course of severe sepsis and predict the development of acquired neuromuscular dysfunction and mortality in intensive care unit patients. Most patients with acquired neuromuscular dysfunction after sepsis have both critical illness myopathy and critical illness neuropathy ***(Khan et al., 2006)***.

Most cases of respiratory muscle weakness in the ICU are the result of an idiopathic polyneuropathy and myopathy that is specific to ICU patients, particularly those with sepsis, prolonged mechanical ventilation, and prolonged neuromuscular paralysis ***(Rich et al., 1995)***.

An acute myopathy has been reported in ventilator-dependent asthmatic patients treated with high-dose steroids and neuromuscular blocking agents ***(Griffin et al., 1995)***.

Acquired weakness syndrome in critically ill patients have been shown to be a major cause of mortality and long-term

morbidity ***(Herridge et al., 2008; Khan et al., 2008).*** A key component of these syndromes is the development of respiratory muscle weakness, which leads to prolonged duration of mechanical ventilation, difficulty weaning patients from the ventilator, and recurrence of respiratory failure after extubation. Clinical studies have identified sepsis and hyperglycemia as the two major risk factors for development of intensive care unit acquired weakness, including respiratory muscle weakness. In addition to these factors, an extensive literature has recently emerged revealing that mechanical ventilation per se also produces deleterious effects on the diaphragm. A number of studies using animal models showing that relatively short durations of controlled mechanical ventilation rapidly produce diaphragm weakness and atrophy ***(Callahan et al., 2009)***.

Aim of the Work

The aim of the work is to study the causes and pathogenesis of neuromuscular weakness related to critical illness patients and updates in diagnosis and management.

Chapter 1

CLINICAL FEATURES OF CRITICAL ILLNESS MYOPATHY AND CRITICAL ILLNESS POLYNEUROPATHY

Introduction and Definition

Neuromuscular weakness is a common occurrence in patients who are critically ill, developing in ≥25 percent of patients who are in the intensive care unit (ICU) and ventilated for at least seven days ***(De Jonghe et al., 2002).***

Neuromuscular weakness related to critical illness is partly a consequence of improved survival in patients with multiorgan failure and sepsis, but is also a consequence of treatments administered in the ICU, including intravenous glucocorticoids and sometimes paralytic agents. Neuromuscular weakness in the ICU is most often due to critical illness myopathy or to critical illness polyneuropathy ***(Zhou et al., 2014).***

In a critically ill patient who develops flaccid generalized weakness, the major considerations in the differential diagnosis are critical illness myopathy and critical illness polyneuropathy, or a combination of the two. Prolonged neuromuscular junction blockade is rare ***(Zhou et al., 2014).***

Intensive care unit acquired weakness (ICUAW) is a syndrome of generalized limb weakness that develops while the patient is critically ill and for which there is no alternative explanation other than the critical illness itself ***(Stevens et al., 2009)***.

Patients with ICUAW are then classified into those with critical illness polyneuropathy (CIP), critical illness myopathy (CIM), or critical illness neuromyopathy (CINM). Those with CIM are further subclassified (histologically) into cachectic myopathy, thick filament myopathy, and necrotizing myopathy ***(Appleton and Kinsella, 2012).***

Generalized muscle weakness, which develops during the course of an ICU admission and for which no other cause can be identified besides the acute illness or its treatment, is labeled "intensive care unit acquired weakness" (ICUAW) ***(Hermans and Van den Berghe, 2015).***

ICUAW may affect peripheral as well as respiratory muscles. The "loss of flesh and strength" in patients with life-threatening infections was described in the nineteenth century. However, it took another century before it was understood that ICUAW can be evoked either by critical illness polyneuropathy (CIP), by critical illness myopathy (CIM) or by both during the course of critical illness ***(Hermans and Van den Berghe, 2015)***.

ICUAW is a frequent complication of critical illness and is associated with a high morbidity and mortality of acute critical illnesses. In addition, recent data revealed that ICUAW may also have longer-term consequences, beyond the hospitalization phase. For example, ICUAW may be an important contributor to the post intensive care syndrome (PICS) This term includes the physical, mental, and cognitive

dysfunctions that are part of the persisting disabilities, which extend beyond the acute hospitalization and have major impact on the quality of life of the growing population of ICU survivors ***(Needham et al., 2012).***

Because weakness in critically ill patients has been described in a variety of clinical situations and ascribed to more than one etiology, several descriptive terms have been coined to attempt to define and differentiate weakness syndromes. ***(Deem, 2006).***

These include critical-illness polyneuropathy, critical-illness myopathy, and acute quadriplegic myopathy. Unfortunately, these terms may be too restrictive in that they imply a single and distinct cause of weakness for each patient or group of patients, when in fact the pathology appears to be more complex, with considerable overlap between the "syndromes." For example, myopathy appears to be present in the majority of cases that might once have been classified as polyneuropathy ***(Latronico et al., 2005).***

In addition, these terms are not necessarily applied to patients with clinical evidence of weakness; for example, critical-illness polyneuropathy has been defined solely by abnormalities on electrophysiologic testing (nerve-conduction studies and electromyography [EMG]) in several studies. These factors create considerable confusion when trying to read the literature on ICU-acquired weakness. Thus, additional terms have been coined that reflect the complexity and uncertainty of

the cause of ICU-acquired weakness, including "critical-illness neuromuscular abnormalities**.** "Critical illness myopathy and neuropathy**,** "critical illness polyneuropathy and myopathy," and "critical illness polyneuromyopathy ***(Garnacho et al., 2005).***

Critical illness polyneuropathy (CIP), first described by Bolton and colleagues in 1986 ***(Bolton et al., 1986)***, is a frequent complication of critical illness, acutely and primarily affecting the motor and sensory axons. This disorder can cause severe limb weakness and prolonged weaning ***(Hermans et al., 2008).***

Improvement of diagnostics later on revealed that muscle may be primarily involved, which is called myopathy in critical illness or critical illness myopathy (CIM). The condition has also been described in children ***(Williams et al., 2007).***

Classification:

In ICU Patients Causes of generalized weakness in the ICU setting may be considered in the context of (1) pre-existing versus new-onset weakness, and (2) localization of the disease process within the nervous system. Various pre-existing neurological disorders, such as Guillain-Barre´ syndrome, myasthenia gravis, Amyotrophic lateral sclerosis (ALS), spinal cord injury, and myopathies that lead to ICU admission are well known ***(Dhand, 2006).***

New onset generalized extremity and/or respiratory muscle weakness may be further divided into previously undiagnosed/

newly acquired neurological disorders, and critical illness related disorders. Some examples of neurological disorders that may occur after admission to ICU are Guillain-Barre´ syndrome following infective illness or surgery, spinal cord infarct after aortic surgery, and muscle weakness due to severe electrolyte disorder. In addition, certain disorders may be unmasked (eg, myasthenia gravis) or precipitated (eg, rhabdomyolysis) by infection or medications used in the ICU ***(Gorson, 2005).***

Finally, patients with rapidly progressive weakness and respiratory compromise (Guillain-Barre´ syndrome, acute transverse myelitis) may get admitted to ICU before there is enough time to establish the diagnosis, or patients with unusual presentation of isolated/ predominant respiratory muscle weakness (ALS, myotonic muscular dystrophy) may remain unrecognized for a considerable time after admission to the ICU ***(Dhand, 2006).***

However, neuromuscular disorders as a consequence of critical illness are now recognized as the most important cause of newly acquired weakness in the ICU. Occurrence of CIP, CIM, or a combination of the two is reported in 30–50% of patients with critical illness. A study of 92 patients with neuromuscular weakness in an ICU reported CIM in 42%, CIP in 12%, demyelinating neuropathy in 13%, motor neuron disease in 7%, neuromuscular junction disorders in 3%, and other neuropathies in 13% of those patients ***(Dhand, 2006).***

Another approach, which is very relevant to clinical assessment, is to classify the causes of weakness in an ICU patient according to central (intracranial) nervous system, spinal cord, and peripheral (neuromuscular) lesions. Neuromuscular disorders are, in turn, best understood as affecting different parts of the motor unit. By definition, the motor unit consists of the anterior horn cell body, its axon, terminal nerve endings, and the number of muscle fibers that it innervates. It is helpful to divide neuromuscular disorders based on involvement of components of the motor unit: the anterior horn cell, peripheral nerve, neuromuscular junction, and muscle Table (1). Summarizes the pre-existing and new onset causes of weakness in relation to site of involvement. The neuromuscular complications of critical illness, as noted, also affect all the components of the motor unit ***(Dhand, 2006).***

Table (1): Classification of Neurological Causes of Motor Weakness in Intensive Care Unit Patients: ***(Dhand, 2006).***

Localization	Pre-existing	Previously Undiagnosed/New-Onset	Critical Illness Related
Spinal cord	Trauma Infarction Transverse myelitis	Acute ischemia Epidural abscess Acute transverse myelitis	Not described
Anterior horn cell	Amyotrophic lateral sclerosis Poliomyelitis (West Nile virus)	Amyotrophic lateral sclerosis (predominant diaphragm weakness) West Nile virus poliomyelitis	Hopkins syndrome
Peripheral nerve	Guillain-Barre´ syndrome Chronic inflammatory demyelinating polyneuropathy	Incidential Guillain-Barre´ syndrome Porphyria, vasculitis, toxic, compressive	Critical illness polyneuropathy
Neuromuscular junction	Myasthenia gravis Lambert-Eaton syndrome Botulism	Unmasked myasthenia gravis Atypical myasthenia gravis (predominant respiratory weakness, muscle-specific tyrosine kinase antibody) Toxic	Prolonged neuromuscular blockade
Muscle	Muscular dystrophy Polymyositis Periodic paralysis Metabolic/congenital Mitochondrial	Rhabdomyolysis Toxic myopathies Polymyositis Myotonic dystrophy Adult-onset acid maltase deficiency Pyomyositis Hypokalemic Hypophosphatemic	Critical illness myopathy

Incidence

CIP and CIM is common problem among patients in intensive care units, and incidence in studies varies greatly among patients in intensive care units. This variation in incidence in the rate due to many factors, including the timing of the diagnosis during the period of critical illness as well as

the different diagnostic criteria used and risk factors that the patient suffered ***(Hermans and Van den Berghe, 2015).***It is estimated that about 20 million people need intensive care unit (ICU) admission for life support worldwide. In the United States, about 750,000 people require mechanical ventilation, with almost 300,000 requiring prolonged life support (more than 5 days) every year. Physical impairment is common in these patients and may persist for years and may manifest as profound muscle weakness ***(Herridge et al., 2011).***

The incidence of CIP and/or CIM appears to be about 33-50% of patients who are critically ill in the intensive care unit (ICU) and on a mechanical ventilator. This has been demonstrated in small, but well-performed, single-site prospective studies, as well as larger multi-center ones (Table 2) ***(Bird et al., 2013).***

Table (2): Major prospective studies: reporting the combined incidence of critical illness polyneuropathy and/or critical illness myopathy ***(Bird et al., 2013).***

Study	Design	Definition of CIP/CIM	Incidence
Stevens and colleagues	Systematic review of 24 studies (19 prospective)	Clinical and electrodiagnostic, or elecrodiagnostic, evidence of either	46%
Khan and colleagues	Cohort study of 20 surviving patients with severe sepsis Baselne and weeky neurologic examinations and NCS/ needle EMG	Clinical and electrodiagnostic evidence of either	50%
Del Letter colleagues	98 ICU patients on a mechanical ventilator for > 4 days Biweekly neurologic examinations and NCS/needle EMG on days 4,11, and 25	Clinical and electrodiagnostic evidence of either	33%
De Jonghe and colleagues	95 ICU patients on mechanical ventilation > 7 days Baseline neurologic examination and NCS/needle EMG, then weekly neurologic examinations	Clinical evidence of either	25%
Bednarik and colleagues	60 ICU patients; SOFA score 3 or 4; did not require mechanical ventilation Daily neurologic examination for 28 days and NCS/needle EMG in week 1 and in week 5	Clinical or electrodiagnostic evidence of either	Clinical and electrodiagnostic evidence in 28% Electrophysiologic evidence in 57%

CIM: Critical illness myopathy, CIP: Critical illness polyneuropathy, EMG: Electromyography, ICU: Intensive care unit, NCS: Nerve conduction study, SOFA: Sequential organ failure assessment.

Two excellent studies address this issue from this very different perspective, but they reach the same conclusion. Khan

and colleagues conducted a prospective cohort study of patients with severe sepsis in the ICU. Twenty patients survived the analysis period and half (50%) of those developed CIP, CIM, or features of both, most by day 14 of illness. They also found that, of those affected, 10% had CIP, 10% had CIM, but 80% had evidence of both disorders. Stevens and colleagues performed a systematic review of 24 studies (19 prospective) of critically-ill patients who developed CIP and/or CIM. Most of these studies avoided the problem of distinguishing between CIP and CIM by combining them in some fashion as an endpoint. Of the total 1,421 patients in these studies, 46% (655 patients) developed one or both of these disorders ***(Bird et al., 2013).***

The 46% incidence of CIP and/or CIM in the large, systematic review by Stevens and colleagues is remarkably similar to the 50% incidence found by Khan and colleagues. In this systematic review, studies with more than 10 patients were included in the analysis if they met two criteria. The first was that the study enrolled patients in the ICU and they had electrodiagnostic (EDX) findings or a combination of clinical and EDX findings, with the EDX tests obtained in at least all of the patients who had positive clinical findings. The second was that they compared the patients with CIP and/or CIM with patients in the ICU who had negative clinical and/or EDX findings ***(Bird et al., 2013).***

Khan and colleagues conducted a prospective cohort study of patients with severe sepsis in the ICU. Commonly-used