Intensive care unit-acquired weakness: early diagnosis, symptomatology and prognosis
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CHAPTER 1
GENERAL INTRODUCTION
During admission to an Intensive Care Unit (ICU), many critically ill patients develop generalized muscle weakness, a condition called Intensive Care Unit – acquired weakness (ICU-AW). ICU-AW can be caused by muscle problems, peripheral nerve problems or a combination of both. As the name of the condition implies, the hallmark symptom is muscle weakness, but also non-motor signs and symptoms, such as sensory and autonomic deficits, may be part of ICU-AW. The aims of the research described in this thesis are to investigate whether ICU-AW can be identified early after ICU admission, to investigate the non-motor signs and symptoms of ICU-AW and to investigate the long-term impact of ICU-AW on survival and physical functioning. In this chapter, the rationale underlying the aims of this thesis described.

**INCIDENCE OF ICU-ACQUIRED WEAKNESS**

The first patients with ICU-AW were described in the 1980’s. At first it was thought that ICU-AW was a rare complication of critical illness. However, in a recent systematic review, an incidence of 46% (95% confidence interval: 43-49) was reported in ICU patients with sepsis, multiple organ dysfunction syndrome (MODS) or prolonged mechanical ventilation. This increase in incidence of ICU-AW seems to parallel improvements in critical care leading to survival of severely ill patients that previously would have died. Based on the expectation that critical care will continue to improve, the incidence of ICU-AW is likely to rise in the coming years.

No specific data on the current incidence of ICU-AW are available for the Netherlands. In the period 2010-2013, around 14000 patients were treated annually for more than 4 days on ICUs in the Netherlands (neurological admissions excluded; data from “National Intensive Care Evaluation”). Estimating an incidence of ICU-AW of 50% in these patients, around 7000 patients developed ICU-AW each year. Or, on a population level, it can be estimated that 40 per 100,000 inhabitants develop ICU-AW in the Netherlands annually.

**AN EARLY ICU-AW DIAGNOSIS**

The first aim of this thesis is to investigate whether ICU-AW can be diagnosed early after ICU admission. The current diagnostic method, according to expert consensus, is a clinical examination using manual muscle strength assessment. To reliably perform this assessment an awake and attentive patient is needed. However, early after ICU admission many patients are sedated or suffer from delirium and this makes muscle strength assessment impossible or unreliable, thereby causing a diagnostic delay. This delay may be harmful because important prognostic information is withheld from families and physicians. Also, early initiation of future treatments may be more effective as abnormalities in the early stages of ICU-AW can still be reversible. Direct muscle stimulation, a specialized electrophysiological test, has been identified as possible method to diagnose ICU-AW early, but this test is not widely available.

**NON-MOTOR SIGNS AND SYMPTOMS OF ICU-AW**

The second aim of this thesis is to investigate non-motor signs and symptoms of ICU-AW. The polyneuropathy underlying ICU-AW in some patients is probably not limited to motor fibers. For example, sensory symptoms, such as pain and decreased sensation, are reported in patients...
with ICU-AW. These symptoms may arise because of large sensory fiber dysfunction but also because of small nerve fiber dysfunction. Studies specifically investigating small nerve fiber involvement in ICU-AW have not been performed.

Small nerve fibers also mediate autonomic functions. In the general ICU population, autonomic dysfunction is frequently found and associated with increased mortality. As small nerve fibers may be involved in ICU-AW, autonomic dysfunction may be more frequent in this population. A pilot study provided preliminary evidence that autonomic dysfunction occurs in patients with ICU-AW.

LONG-TERM IMPACT OF ICU-AW

The final aim of this thesis is to investigate the long-term impact of ICU-AW on survival and physical functioning. ICU-AW is independently associated with an increase in ICU- and hospital mortality. Survivors with ICU-AW may suffer from long-term physical impairments. However, ICU-AW is not the only factor that influences physical impairments in critical illness survivors. The magnitude of the attributable effect of ICU-AW on long-term physical impairments is unknown because most studies lacked a properly selected control group or did not adjust for confounders.

HYPOTHESES UNDERLYING THIS THESIS

For the investigations whether ICU-AW can be diagnosed early after ICU admission, we hypothesized (I) that ICU-AW could be diagnosed early and accurately using a prediction model based on a small and specific set of clinical and laboratory parameters; (II) that plasma neurofilament levels could serve as an early biomarker for ICU-AW; and (III) that a small subset of conventional electrophysiological recordings done early after ICU admission was feasible and could establish a diagnosis of ICU-AW.

For the studies investigating the non-motor signs and symptoms of ICU-AW, we hypothesized (I) that patients with ICU-AW have autonomic dysfunction and are more prone to develop autonomic dysfunction compared to patients without ICU-AW; and (II) that small nerve fibers are damaged in ICU-AW as evidenced by decreased intra-epidermal nerve fiber density in skin biopsies.

With regard to the long-term impact of ICU-AW on survival and physical functioning we hypothesized that ICU-AW is independently associated with an increase in post-ICU mortality and that survivors with ICU-AW have decreased physical functioning at 6 months after ICU discharge.

OUTLINE OF THE THESIS

Studies investigating possibilities for an early diagnosis of ICU-AW are bundled in part I. After an overview of the current diagnostic methods for ICU-AW in chapter 2, the next chapters contain studies that investigate diagnostic methods for early diagnosis of ICU-AW. In chapter 3, an early prediction model using easily available clinical and laboratory parameters is investigated. In chapter 4 the use of neurofilaments in plasma as an early diagnostic biomarker is described. In chapter 5 early conventional electrophysiological recordings are investigated.
Studies investigating non-motor signs and symptoms of ICU-AW are bundled in **part II**. In **chapter 6**, a pilot study on the feasibility of three different methods for measuring autonomic dysfunction in critically ill patients is performed. Next, the presence of autonomic dysfunction is assessed in patients with and without ICU-AW in **chapter 7**, using heart rate variability, the most feasible measure of autonomic dysfunction. In **chapter 8**, it is investigated if ICU-AW also affects small nerve fibers, by measuring intra-epidermal nerve fiber density in skin biopsies.

Finally, **part III** describes the long-term impact of ICU-AW. In **chapter 9** the impact of ICU-AW on survival and physical functioning after ICU discharge is investigated.

The thesis is concluded with a general discussion in **chapter 10**, a summary and summary in Dutch.

**REFERENCES**