Intensive care unit-acquired weakness: early diagnosis, symptomatology and prognosis
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CHAPTER

INTRA-EPIDERMAL NERVE FIBER DENSITY IS REDUCED IN ICU-ACQUIRED WEAKNESS: AN OBSERVATIONAL PILOT STUDY

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Submitted
ABSTRACT

Introduction
Intensive care unit-acquired weakness (ICU-AW) is a frequent and important complication of critical illness. The pathophysiological spectrum of ICU-AW encompasses dysfunction and structural damage to muscle and/or large nerve fibers. It is unknown if small nerve fibers are also involved in ICU-AW. We hypothesized that small nerve fibers are also affected in ICU-AW and therefore investigated intra-epidermal nerve fiber density (IENF) in skin biopsies of patients diagnosed with ICU-AW.

Methods
Patients diagnosed with ICU-AW that were still in the ICU or hospital at least 20 days after ICU admission were included in this prospective observational pilot study. Skin biopsies were taken near the ankle in patients alive (n:5) or post-mortem (n:5). In patients alive, we evaluated the presence of sensory symptoms and performed the skin wrinkle test (SWT) at the moment of biopsy. IENF density was compared to reference values, matched for age and gender.

Results
For all 10 investigated patients, IENF density was below the 5th percentile of reference values. In the four patients evaluated with the SWT, abnormal results were found in two. Sensory symptoms were present in two patients. Only one patient had both abnormal SWT results and sensory symptoms.

Conclusions
IENF density is decreased in patients with ICU-AW, indicating the involvement of small nerve fibers.
INTRODUCTION

Intensive care unit-acquired weakness (ICU-AW) is a frequent and important complication of critical illness. It is a complex neuromuscular syndrome, involving muscles and/or large peripheral nerve fibers that can be affected functionally and structurally. Critical illness may also affect small nerve fibers, as was suggested in a cohort of critically ill neurosurgical patients. In patients with ICU-AW, loss of small nerve fibers has not been investigated. Indications of small fiber dysfunction in ICU-AW were described in a pilot study, using sympathetic skin responses. Loss of small nerve fibers is investigated by assessing intra-epidermal nerve fiber (IENF) density in skin biopsies. In the skin, small nerve fibers are comprised of Aδ and C fibers, which are responsible for sensory functions, like pain and temperature perception, and autonomic functions. The aim of this pilot study was to investigate if IENF density is decreased in patients with ICU-AW.

METHODS

Design and ethical approval

We conducted a prospective observational pilot study in the mixed surgical/medical intensive care unit (ICU) of the Academic Medical Center, Amsterdam, the Netherlands. The Institutional Review Board approved the study (NL38545.018.11; 2011_325#B2011284). All patients gave informed consent prior to inclusion in the study, or their relatives approved the scientific use of post-mortem tissue.

In- and exclusion criteria

Patients diagnosed with ICU-AW that were still in the ICU or hospital at least 20 days after ICU admission were eligible for inclusion. We excluded patients admitted because of neurological disorders, patients unable to give informed consent because of (temporary) mental incompetence, patients with coagulation disorders, impaired wound healing or leg infections. If patients with ICU-AW died while in the ICU and their relatives gave approval, post-mortem skin biopsies were taken within 24 hours.

Diagnostic criteria for ICU-AW

ICU-AW was diagnosed by physical therapists using muscle strength assessment when patients were awake (Richmond agitation and Sedation Scale between -1 (“drowsy”) and 1 (“restless”)) and attentive (able to follow verbal commands using arms or eye-lids). Strength was scored using the Medical Research Council (MRC) score of six muscle groups bilaterally. Individual muscle scores were summated to calculate the MRC-sum score (MRC-SS). ICU-AW was defined as a MRC-SS <48 (maximum score 60).

Intra-epidermal nerve fiber density

IENF density was analyzed in 3 millimeter punch skin biopsies taken from the distal leg, 10 cm above the lateral malleolus. Skin biopsy preparation and IENF density counts were performed according to guideline recommendations by one experienced investigator (AJvdK) blinded...
for age and gender. IENF densities were compared to reference values, matched for age and gender, and were defined as decreased when below the 5th percentile of reference values.\(^5\)

**Additional tests on small fiber function**

In patients alive at the moment of biopsy, we investigated small fiber function by clinical evaluation of sensory symptoms and signs and the skin wrinkle test (SWT). The SWT is a test for peripheral sympathetic nerve fiber function.\(^7\) We used the simulated SWT by applying EMLA cream (2.5% lidocaine and 2.5% prilocaine, AstraZeneca, The Netherlands) on the tip of the fourth finger and covering it with a plaster for 30 min.\(^7\) After that, wrinkling was scored on a scale ranging from 0 (no wrinkling) to 4 (complete distortion of the finger pulp by wrinkling). A wrinkling score <3 was defined as abnormal.\(^7\)

**Clinical data**

Possible risk factors in the medical history for development of a small fiber neuropathy were registered. Admission diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score and the maximal Sequential Organ Failure Assessment (SOFA) score during admission were additionally registered.

**RESULTS**

We included 10 patients with ICU-AW. Table 1 describes patient characteristics and results of the skin biopsies. IENF densities were below the 5th percentile in all skin biopsies (example shown in figure 1). There was no difference between biopsies obtained in alive patients and post-mortem (table 1). The SWT was abnormal in two patients; one with no sensory signs and symptoms and one with tingling and allodynia (table 1).

**DISCUSSION**

In this first pilot study, all 10 patients with ICU-AW had decreased IENF densities. Based on these results, our understanding of neuromuscular involvement in ICU-AW may need to be re-examined. Currently, it is thought that large fibers and/or muscles can be affected in ICU-AW and three underlying disorders are discerned: i.e. critical illness neuromyopathy (CINM), critical illness polyneuropathy (CIP) or critical illness myopathy (CIM).\(^1\) Our results suggest that small fibers may also be affected, when measured 20 days or more after admission to the ICU.

The loss of small fibers may be the results of either a mixed large- and small-fiber neuropathy or a pure small fiber neuropathy (SFN). In critically ill neurosurgical patients, abnormal IENF density was found both in patients with and without abnormalities on nerve conduction studies and myography, suggesting that small fiber loss in critical illness may be the result of both.\(^3\) However, without concurrent motor and sensory examinations, which could not be performed because all patients had altered consciousness, the clinical interpretation of these findings remains unclear. Future studies will need to use detailed electrophysiological studies, motor and sensory examinations together with skin and muscle biopsies in critically ill patients with and without ICU-AW, so to understand neuromuscular involvement fully. A protocol of such a study has been published recently.\(^8\)
Skin biopsies may also have other applications. If small fibers loss is the result of a mixed large- and small-fiber neuropathy, skin biopsies may be used as a tool to differentiate between CIP or CINM and CIM. Differentiation is important because nerve involvement is associated with a worse prognosis.\textsuperscript{9} It is often difficult because electromyography is hampered by technical problems or poor patient cooperation.\textsuperscript{1} Also, nerve biopsies are usually considered too invasive. As it is unknown when in the course of the disease these small fiber abnormalities occur, this is a first thing that should be investigated.

Skin biopsies may also be used to better understand sequelae of ICU-AW. ICU-AW patients frequently have autonomic dysfunction, when assessed using heart rate variability.\textsuperscript{10} Several causes have been proposed and small fiber dysfunction might be one of them.\textsuperscript{11} Also, survivors of critical illness sometimes exhibit chronic pain, which may be related to small fiber dysfunction.\textsuperscript{12}

Our study has some limitations. First, because of the limited sample size, our findings need confirmation in larger cohort of patients. Second, we included critically ill ICU-AW patients with a protracted course in the ICU. These patients may represent a subgroup, limiting
Table 1. Study results. Patient and admission characteristics and details of the neurological examination, including the skin wrinkle test (SWT) and the intra-epidermal nerve fiber density (IENF).

<table>
<thead>
<tr>
<th>age</th>
<th>gender</th>
<th>relevant co-morbidities</th>
<th>admission diagnosis</th>
<th>APACHEII score</th>
<th>maximal SOFA score (max 60)</th>
<th>MRC-SS score</th>
<th>sensory signs and symptoms</th>
<th>SWT score</th>
<th>day of biopsy*</th>
<th>IENF density</th>
<th>IENF lower limit of normal†</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>male</td>
<td>none</td>
<td>pneumosepsis</td>
<td>25</td>
<td>15</td>
<td>28</td>
<td>none</td>
<td>3</td>
<td>62</td>
<td>alive</td>
<td>0.60</td>
</tr>
<tr>
<td>43</td>
<td>female</td>
<td>none</td>
<td>abdominal sepsis</td>
<td>24</td>
<td>16</td>
<td>46</td>
<td>pain, alldynia</td>
<td>3</td>
<td>67</td>
<td>alive</td>
<td>0.60</td>
</tr>
<tr>
<td>71</td>
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<td>diabetes</td>
<td>abdominal sepsis</td>
<td>34</td>
<td>15</td>
<td>30</td>
<td>unreliable</td>
<td>missing</td>
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</tr>
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<td>43</td>
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<td>alcohol abuse</td>
<td>pancreatitis</td>
<td>16</td>
<td>missing</td>
<td>8</td>
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<td>74</td>
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<td>37</td>
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<td>chemotherapy</td>
<td>abdominal sepsis</td>
<td>20</td>
<td>13</td>
<td>31</td>
<td>allodynia, tingling</td>
<td>0</td>
<td>26</td>
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</tr>
<tr>
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<td>pneumosepsis</td>
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<td>13</td>
<td>45</td>
<td>n.a.</td>
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<td>post-mortem</td>
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<td>none</td>
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<td>29</td>
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<td>22</td>
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</tr>
<tr>
<td>66</td>
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<td>none</td>
<td>abdominal sepsis</td>
<td>17</td>
<td>20</td>
<td>24</td>
<td>n.a.</td>
<td>n.a.</td>
<td>68</td>
<td>post-mortem</td>
<td>0.60</td>
</tr>
<tr>
<td>78</td>
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<td>Sjögren's disease</td>
<td>endocarditis</td>
<td>29</td>
<td>14</td>
<td>12</td>
<td>n.a.</td>
<td>n.a.</td>
<td>32</td>
<td>post-mortem</td>
<td>1.70</td>
</tr>
<tr>
<td>49</td>
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<td>10</td>
<td>17</td>
<td>16</td>
<td>n.a.</td>
<td>n.a.</td>
<td>24</td>
<td>post-mortem</td>
<td>1.60</td>
</tr>
</tbody>
</table>

*: day after ICU admission; †: lower limit of normal is 5th percentile of age and gender matched reference values (as reported by)

APACHEII: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; MRC-SS: medical research council – sum score; SWT: skin wrinkle test; IENF: intra-epidermal nerve fiber density, n.a.: not applicable
generalizability of our results. We chose this late time-point to maximize the chance of finding nerve damage, which, in large fibers, has been found only several weeks after onset of critical illness. Third, we cannot exclude that in some patients IENF density may have been decreased because of co-morbid conditions that are associated with development of SFN. However, we found the same results in patients without these co-morbid conditions.

CONCLUSION
IENF density is decreased in patients with ICU-AW, when measured 20 days or more after onset of critical illness. Possible diagnostic usefulness of skin biopsies and the relation with autonomic dysfunction and pain in these patients needs to be investigated.

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CONFLICTS OF INTEREST
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