Chapter 14
ICU-Related Neuromuscular Weakness and Neuromuscular Differential Diagnoses in the ICU

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Introduction

Patients admitted to the Intensive Care Unit (ICU) are critically ill. The survival rate of patients admitted to the ICU has increased, revealing the long-term consequences of surviving a critical illness. Survival often comes with the cost of injuries to multiple organ systems, including the central and peripheral nervous system. The combination of physical, cognitive and mental sequelae seen in patients with a prolonged ICU stay is called the post intensive care syndrome (PICS) [1]. Generalized muscle weakness is one of the main issues in PICS. This weakness, nowadays called ICU-acquired weakness (ICUAW), is caused by a variety of pathologies, including critical illness myopathy (CIM), critical illness polyneuropathy (CIP), or a combination of critical illness neuromyopathy (CIPNM) [2]. The many different terminologies used in the past hampered studies on ICUAW. Therefore, in 2009, criteria for ICUAW were established in a consensus meeting [3]. ICUAW is a very serious condition, it leads to prolonged mechanical ventilation [4], increased hospital stay and increased morbidity and mortality [5–7].

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Epidemiology

In 1984, Bolton et al. described five relatively young patients developing severe weakness during ICU admission [8]. The patients were admitted to the ICU for different reasons but all developed profound limb weakness and decreased tendon reflexes. Electrophysiological studies showed a sensory-motor axonal polyneuropathy, which was defined as CIP. Later studies showed that an acute primary myopathy, the CIM, was as common as CIP and was frequently associated with CIP [9]. Over the years, the syndrome of weakness in the ICU was recognized and described by many groups. The incidence reported varies, but overall 40% of ICU patients develop ICUAW [5, 10–14]. The incidence rates depend on the group of ICU patients studied and the criteria used for the diagnoses. For example, in ICU patients with sepsis, the incidence of ICUAW is much higher, up to 64%, compared to patients with other diseases [15, 16]. Appleton et al. reported a substantially lower incidence when using clinical examination for diagnosis (32%) compared to the use of electrophysiological techniques (47%) [17].

Pathophysiology and Risk Factors of ICUAW

ICUAW occurs most often in severely ill ICU patients with multi-organ failure. Therefore, ICUAW has been considered as a part of the multi-organ failure syndrome, involving the nerves and muscles [18–21]. The pathophysiological mechanisms leading to ICUAW are multifactorial and partly unknown [21]. For thorough research on this topic, nerve and muscle tissue should be investigated at different time points during the disease. This is problematic in ICU patients who often have coagulation disorders, and the test results do not lead to changes in therapy [9]. If nerve biopsies are performed, pure sensory nerves such as the sural nerve or superficial peroneal nerve are sampled [9]. This is suboptimal, as ICUAW primarily affects strength. Motor nerves have rarely been investigated and post-mortem tests lead to a selection bias of the more severely ill patients [22, 23]. Biopsy of the motor nerve to the gracilis muscle, a superficial muscle that is located on the medial surface of the thigh whose action overlaps that of stronger muscles, may be considered for research purposes or complex differential diagnoses [24].

One of the factors leading to muscle weakness is bed rest. In healthy elderly patients, a period of 10 days of bed rest was found to lead to a significant decrease in muscle mass, muscle strength and physical condition [25, 26]. A study following 222 ICU survivors reported a 3–11% relative decrease in muscle strength for every additional day of bed rest in the ICU, after adjusting for other potential risk factors contributing to long-term weakness [27]. In ICU patients, bed rest is combined with a strong inflammatory response, severe metabolic derangements, microvascular changes leading to increased permeability, altered energy delivery, mitochondrial dysfunction and possibly channelopathies [2]. Reduced excitability of motor nerves as a consequence of inactivation of sodium channels is a major event causing muscle weakness during critical illness. This acquired channelopathy involves

voltage-gated Na^+-channels (VGSC) and is one of the earliest consequences of critical illness [28]. Dysfunction of alpha motor neurons during repetitive firing can be an even earlier event preceding the electrical failure of peripheral axons and causing inadequate muscle force generation in the early phases of sepsis at a time when nerve conduction is still normal. Furthermore, in CIM, muscle atrophy results from increased protein degradation not compensated by protein synthesis [29].

Diaphragm weakness has been considered an integral part of ICUAW since its initial description. Historically, difficulty in weaning from the ventilator and limb muscle weakness with decreased or absent deep tendon reflexes were described as the typical presentation of the syndrome [8]. A recent study showed that diaphragm weakness can be twice as common as limb weakness, suggesting that weakness of the diaphragm and limbs might represent two distinct entities [30]. However, differences in the diagnostic method used to document diaphragm and limb weakness may have played a role. The pathophysiological mechanisms leading to diaphragm weakness are similar to ICUAW, but mechanical ventilation-induced diaphragm inactivity in itself is another contributing factor [31, 32].

Given these pathophysiological mechanisms leading to ICUAW, the most important risk factors are bed rest, sepsis, hyperinflammatory states and multiple organ failure [18–20, 33–37]. Furthermore, hyperglycemia, a condition frequently found in ICU patients, is also an independent risk factor for ICUAW. Controlling hyperglycemia to a normal range with intensive insulin therapy possibly reduces the incidence of ICUAW, but the risk of hypoglycemia with slightly but significantly increased mortality outweighs the potential benefits [33, 38–40] (Fig. 14.1).

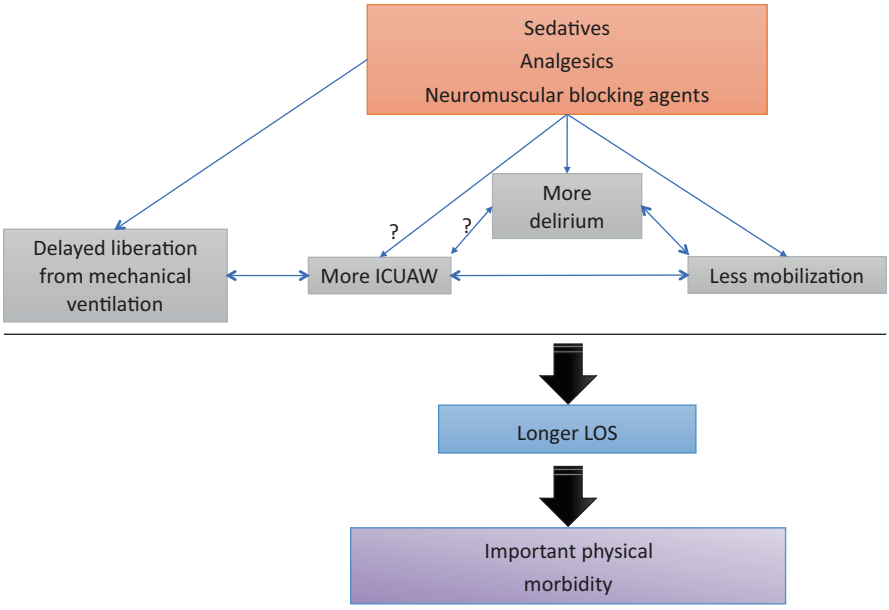

Fig. 14.1 Potential impact of sedatives, analgesics, and neuromuscular blocking agents on ICU-acquired weakness (ICUAW), delirium, and mobilization [41]

Several case reports suggested a link between ICUAW and administration of corticosteroids and prolonged administration of neuromuscular blocking agents [12, 20, 36, 39]. However, other prospective studies could not confirm these relations [19, 27, 33, 35, 38, 39, 42–44]. Finally, age was described as a factor independently related with ICUAW [20, 38].

Clinical Features and Diagnosis

ICUAW is a syndrome of generalized limb weakness that develops during the ICU stay for which there is no alternative explanation other than the critical illness itself (Case Vignette 1) [3, 16].

Case Vignette 1

A 62-year-old man with a medical history of diabetes mellitus type 2 and hypertension is admitted to the intensive care unit (ICU) with a severe pneumonia. Pneumococci turn out to be the cause, and the condition of patient deteriorates rapidly into a full blown sepsis. Besides treatment with adequate antibiotics, hemodynamic support with noradrenaline is needed, and hydrocortisone is administered. The lungs are severely affected, so mechanical ventilation in prone position is needed for several days. To enable this, sedative drugs are administered in quite high doses. Neuromuscular blockage is only needed for several hours.

After 5 days the situation gradually improves, proning is no longer needed and with decreasing intensity of mechanical ventilation the sedation can be tapered. Due to a temporarily deteriorated kidney function, it takes a while before he starts to wake up. When he is able to follow commands, it turns out that he has ICU acquired weakness (ICUAW), with severe, diffuse, symmetric muscle weakness involving all four limbs and sparing of facial muscles.

As this is thought to be caused by the severe inflammatory response that occurred during the sepsis and no special treatment options are currently available, no diagnostic tests are done. Physical therapy including bed cycling and mobilization in a chair is initiated and intensified over the days. A tracheostomy is placed and weaning off the ventilator is also started. After a week, the ICU nurse and physical therapists report that there is only minimal improvement. Are we sure that ICU-AW is the cause?

Electroneurography and electromyography are performed. A combined axonal neuropathy and myopathy are found with involvement of both proximal and distal muscles and nerves in all four limbs. At the level of the neuromuscular junction, no abnormalities are found. As this is supportive for a severe critical illness neuromyopathy, the treatment as initiated is continued. Gradually, over weeks, the patient improves and is discharged from the hospital to a rehabilitation unit.

Learning Points

1. **Severe generalized limb muscle weakness developing in a patient admitted to the ICU because of severe pneumonia necessitating mechanical ventilation is most likely ICU-acquired weakness (ICUAW).**
2. **Recovery of muscle strength may take weeks.**
3. **Specific treatment strategy to prevent or cure ICUAW is currently not available. Physical therapy, weaning off the ventilator and appropriate feeding are key.**

Limb muscle involvement is symmetric and is more pronounced in the lower extremities [45]. Facial muscles are usually spared. The recent ATS clinical practice guidelines emphasize the importance of clinical examination using the "Medical Council Research" (MRC)-scale. The consensus is that for a diagnosis of ICUAW the MRC-scores for six different bilaterally tested muscle-groups should be summed (the so-called "MRC-sum score" or MRCSS) [3, 16, 46].

An MRC-SS <48 indicates significant ICUAW, whereas a score below 36 is considered severe ICUAW [47]. However, already a mild reduction in muscle strength, with MRC-SS ≤55, is associated with decreased survival [48]. Importantly, ICUAW is not limited to ICU patients as it may represent a spectrum of weakness which can occur in any serious illness irrespective of the care location [41].

Both proximal and distal muscle groups should be tested whenever possible, including deltoids, biceps, wrist extensors, iliopsoas, quadriceps and ankle dorsiflexor muscles. In patients in whom it is impossible to bilaterally test all six muscle groups, an average MRC score <4 can be used. Testing strength using handgrip dynamometry has been described, but reliability and optimal cut-off values of this method need to be validated [11, 49, 50].

For optimal testing of muscle strength, the patient should be awake and alert. Many ICU patients have a decreased level of consciousness or delirium. Electrophysiological testing might be a preferable method in these patients. In daily clinical practice, the use of electromyography (EMG) and nerve conduction studies (NCS) were found to be variable [16]. Furthermore, variations in the timing (early or late after ICU admission), the number of nerves and muscles tested and diagnostic thresholds were described [51, 52].

More recently, ultrasound of nerves and muscles has been described as a possible method to diagnose ICUAW [53]. This easy-to-use bedside available diagnostic tool could enable easily repeated investigations of limb muscles, even in patients unable to cooperate in strength assessment. However, only limited studies combining ultrasound and strength assessment are available [54]. Therefore, the clinical relevance of ultrasound in ICUAW needs to be determined.

For evaluation of diaphragm function, the standard test is measurement of transdiaphragmatic twitch pressure (PdiTw) generated in response to bilateral anterior magnetic phrenic nerve stimulation [31]. Furthermore, ultrasound of the diaphragm can be used [55].

In the patient with the classical clinical picture of ICUAW a "wait and see" diagnostic policy is appropriate, but if any abnormalities outside the usual spectrum are found, other diagnoses should be excluded. Additional testing should be performed, especially if other clinical conditions with possible therapeutic options are considered (see Table 14.1 for an overview of conditions to consider). A useful diagnostic algorithm was described by Latronico et al., and the acronym "MUSCLES" as

Table 14.1 Differential diagnosis of ICU-acquired weakness (ICUAW)

Brain disorders
Brainstem infarcts
Brainstem encephalitis
Central pontine myelinolysis
Spinal cord and anterior horn disorders
Anterior spinal artery thrombosis
Acute transverse myelitis (immune-mediated)
Infective myelitis (West Nile, polio, cytomegalovirus, HIV)
Postinfective myelitis (zoster, West Nile)
Acute spinal cord compression (epidural abscess, metastasis)
Hopkins syndrome
Neuropathies
Critical illness polyneuropathy
Guillain–Barré syndrome and postinfective and paraneoplastic radiculitis
Toxic neuropathy
Vasculitic neuropathy
Neuromuscular junction diseases
Myasthenia gravis and myasthenic syndromes
Prolonged neuromuscular blockade
Hypermagnesemia
Myopathies
Critical illness myopathy
Drug-induced rhabdomyolysis
Myositis and pyomyositis
Toxic myopathies
Metabolic myopathies, unmasked (CPT, mitochondrial)
Compartment syndrome
Propofol syndrome
Unmasking of subclinical myopathy
Cachexia and disuse
Phrenic neuropathy (idiopathic)
Infective radiculitis (cytomegalovirus)
Lymphomatous and carcinomatous infiltration
General medical conditions
Electrolyte disturbances (hyponatremia, hypokalemia, hypophosphatemia)
Porphyria
Paraneoplastic disorders

suggested by Marramattom et al. can be helpful to remember the most common causes of generalized weakness in the ICU [2, 56].

Furthermore, undiagnosed neuromuscular disorders already existing before ICU admission can be a diagnostic pitfall (Case Vignette 2) [57]. As some of these diseases can present with respiratory insufficiency as first symptom and could have therapeutic options, it is crucial to quickly establish the correct diagnosis.

Case Vignette 2

A 46-year-old man is admitted to the ICU for observation after a fall from the stairs, leading to several broken ribs and a pneumothorax on the right side. He used to work as a truck driver but due to problems with his back, he stopped a year ago. Despite drain placement for the pneumothorax, the respiratory situation deteriorates after 2 days and a chest X-ray shows a massive atelectasis of the right lung. Also, the patient develops fever and laboratory abnormalities indicative of an infection are found, so antibiotic treatment for a possible pneumonia is started. Intubation is needed to enable bronchoscopy in order to solve the atelectasis. After a successful bronchoscopy, the patient is extubated. However, after several hours he fails, and reintubation is needed. This is quite unexpected. It is considered too soon after admission, and no severe sepsis has occurred so there are no real risk factors for ICU-AW. Is anything else wrong with this patient? The nurse taking care of the patient that day mentions that she had noticed that the patient had difficulty swallowing before intubation.

Further history is obtained from the patient's partner. She explains that apart from the back problems, the patient also had slowly increasing weakness in the limbs and difficulty walking. To illustrate this, she shows some holiday videos of the patient walking in a park. A typical walking pattern suggestive of proximal muscle weakness is seen. This information raises the suspicion of a pre-existing neuromuscular disease. Further diagnostics, including electroneurography and electromyography are performed. Nerve conduction studies do not show abnormalities, but needle electromyography indicates a generalized myopathy with fibrillation potentials and positive sharp waves. Furthermore, laboratory testing reveals increased serum creatine kinase activity and a deficiency of GAA enzyme activity leading to a diagnosis of late Pompe disease. Knowing this, a prolonged weaning from mechanical ventilation is expected, and a tracheostomy is performed. Despite several efforts, ventilatory support remains needed and the patient is transferred to a long-term ventilation facility.

Learning Points

1. **If a patient is not able to breathe independently after extubation, an as-yet undiagnosed disorder involving the diaphragm should be suspected.**
2. **Thorough history taking from the patient and family is paramount.**
3. **Late onset Pompe disease manifests with slowly progressive muscle weakness, which often goes unnoticed.**

Muscle biopsy may be required in case of diagnostic uncertainty or if muscle weakness persists despite rehabilitation and may be useful to improve prognostication. Thick filament myopathy with selective loss of myosin filaments is the hallmark of CIM in the early stage of the ICU stay [58]. It is due to increased catabolic and reduced anabolic muscle activity, and portends a good prognosis [59]. Prognosis is worse in case of myofiber necrosis, which is usually scattered. Rarely, a diffuse necrotizing myopathy is documented in patients with severe conditions and is associated with marked elevated serum CK levels and poor prognosis [60, 61]. Disuse atrophy, mainly affecting type 2 fibers, or denervation atrophy (due to concomitant CIP) is also common and may coexist with myosin loss or muscle necrosis. Sustained muscle atrophy in survivors of critical illness with persistent weakness is associated with decreased satellite cell content and impaired muscle regrowth, suggesting diminished regenerative capacity [62].

General Principles of Management

A specific treatment strategy to prevent or cure ICUAW is currently not available [47, 63]. Rapid and adequate treatment of the critical illness leading to the ICU admission and optimal supportive care are the most important first steps. Furthermore, additional injury should be prevented by protective ICU treatment strategies wherever possible. For example, by using lung protective ventilation further damage to the lungs, diaphragm and other respiratory muscles can possibly be minimized [31, 32]. There is ongoing debate about the optimal feeding strategy and the effects of enteral and parenteral feeding on ICUAW [64]. As bed rest is such an important risk factor for muscle weakness, early mobilization strategies have been investigated extensively. So far, results have been conflicting and the quality of evidence is low due to methodological limitations of the studies performed [47]. For optimal early mobilization, minimization of sedation is necessary [41, 65].

Theoretically, electrical muscle stimulation could preserve muscle strength in patients incapable of physical exercise. The studies performed in this field were recently reviewed [66]. No benefit in global muscle strength, ICU mortality, or ICU length of stay in comparison with usual care alone was found.

Short- and Long-Term Consequences

ICUAW was found to be associated with an increased risk for extubation failure, necessitating reintubation [47, 67]. Therefore, patients with ICUAW should be observed carefully for respiratory insufficiency for a prolonged period after extubation. Several factors seem to play a role in the extubation failure in patients with ICUAW: insufficient cough strength, increased risk for pulmonary atelectasis, swallowing disorders and (aspiration) pneumonia [68]. Furthermore, ICUAW leads to a

prolonged need for mechanical ventilation, ICU and hospital admission and increased mortality [47]. This increased risk for mortality is not limited to the ICU admission period, but extends to the period after ICU discharge and even long after hospital discharge [6, 48].

Conclusive Remarks

ICUAW is a common complication of critical illness and has a major impact on clinical course, survival, and long-term sequelae of the ICU stay. Diagnosis is clinical, though electrophysiological and ultrasound investigations of peripheral nerves and muscles are increasingly considered in these patients to better define etiology. As such, it is vital that neurologists and intensive care physicians fully appreciate the diagnostic approach to the weak ICU patient. Pathophysiological mechanisms are increasingly emerging, particularly nerve-muscle membrane sodium channelopathy, severe metabolic derangements, microvascular changes, altered energy delivery and use, and possibly central motor neuron dysfunction. Pharmacological treatments are lacking, but early rehabilitation with minimization of sedation may reduce muscle wasting and weakness, thus facilitating the patients weaning from the ventilation and recovery of physical function. Future research is needed to fully elucidate the pathophysiology of ICU-associated neuromuscular disorders and to make specific treatments available in this important field of medicine.

Self Assessment Questions

1. Which of the following factors is—as far as we know—most important in the development of ICU-acquired weakness?

   (a) Breakdown of actin-myosin interaction.
   (b) Damage of the neuromuscular junction.
   (c) Disorder of sodium channels in motor nerves. (*)
   (d) Disturbance of the muscular T-tubuli system.

2. Which of the following is—as far as we know—most probably the earliest event in ICU-acquired weakness?

   (a) Breakdown of signal propagation in nerves.
   (b) Dysfunction of alpha motor neurons. (*)
   (c) Protein degradation in muscles.

3. Long-lasting mechanical ventilation leads to intrinsic diaphragm weakness.

   (a) True. (*)
   (b) False.

4. Which of the following factors is most contributing to ICU-acquired weakness?

   (a) Hyperglycemia. (*)
   (b) Hypokalemia.
   (c) Hypoxemia.
   (d) Hypernatremia.

5. Sepsis is a major risk factor for ICUAW in patients who are mechanically ventilated in the ICU.

   (a) True. (*)
   (b) False.

6. Which of the following agents is most *probably* involved in the development of ICU-acquired weakness?

   (a) Antipsychotic agents.
   (b) Calcium-entry-blocker.
   (c) Neuromuscular blocking agents. (*)
   (d) Tranquilizers.

7. Which of the following agents is most *probably* involved in the development of ICU-acquired weakness?

   (a) Antibiotics.
   (b) Antiviral drugs.
   (c) Corticosteroids. (*)
   (d) Non-steroid anti-inflammatory agents.

8. Which muscle group is generally most affected in ICU-acquired weakness?

   (a) Facial muscles.
   (b) Lower limb muscles. (*)
   (c) Upper limb muscles.

9. Which component of the muscle fibre is characteristically most severely involved in ICU-myopathy?

   (a) Myosin. (*)
   (b) The nucleus.
   (c) The sarcolemma.
   (d) The sarcoplasmatic reticulum.

10. Electrical muscle stimulation was shown to be useful for preserving muscle strength in patients incapable of physical exercise.

    (a) True.
    (b) False. (*)

11. ICU acquired weakness leads to a prolonged need for mechanical ventilation.

    (a) True.
    (b) False. (*)

12. ICU acquired weakness leads to an increased risk for mortality. When?

    (a) During stay in the ICU.
    (b) During stay in the hospital after ICU.
    (c) Even long after hospital discharge.
    (d) A-C are all true. (*)

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