CRITICAL ILLNESS ASSOCIATED NEUROMUSCULAR DISORDERS – KEEP THEM IN MIND

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Neuromuscular disorders complicating sepsis and critical illness are not new and scarce phenomena yet they receive little attention in daily clinical practice. Critical illness polyneuropathy and myopathy affect nearly half of the patients with sepsis. The difficult weaning from the ventilator, the prolonged intensive care unit and hospital stay, the larger complication and mortality rate these disorders predispose to, put a large burden on the patient and the health care system.
The aim of this review is to give an insight into the pathophysiological background, diagnostic possibilities and potential preventive and therapeutic measures in connection with these disorders to draw attention to their significance and underline the importance of preventive approach.

Keywords: *critical illness polyneuropathy, critical illness myopathy, sepsis, pathophysiology, physiotherapy*

KRITIKUS ÁLLAPOTOKKAL ÖSSZEFÜGGŐ NEUROMUSCULARIS ZAVAROK – FIGYELJÜNK RÁ!

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A szepszishez és egyéb súlyos, kritikus állapotokhoz társuló neuromuscularis tünetek nem ritka és újonnan felismert jelenségek, ennek ellenére a mindennapos klinikai gyakorlatban kevés jelentőséget tulajdonítanak nekik. A kritikus állapothoz társuló polyneuropathia (CIP) és myopathia (CIM) a szeptikus betegek közel felét érinti. Ezeket a betegeket nehezebb leszoktatni a lélegeztetőgépről, ezáltal megnyúlik az intenzív osztályos és a kórházi tartózkodásuk ideje, ami mind a beteg, mind az egészségügyi ellátórendszer szempontjából kedvezőtlen.
A közlemény célja, hogy összefoglaljuk a CIP/CIM patofiziológiai hátterét, a diagnosztikai lehetőségeket, áttekintést nyújtsunk a preventív és terápiás lehetőségekről és felhívjuk a figyelmet ezekre a kórképekre, valamint a korán megkezdett kezelés fontosságára.

Kulcsszavak: *kritikus állapothoz társuló polyneuropathia, kritikus állapothoz társuló myopathia, szepszis, patofiziológia, fizikoterápia*

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Even first described in the 1980s[1–3], critical illness polyneuropathy (CIP) and myopathy (CIM) were thought to be scarce complications of critical illness but in line with the development of intensive care and decreasing in-hospital mortality, thirty years' research has proven that they affect nearly half of the critically ill patients. The generalized muscle weakness affecting primarily the limb and respiratory muscles presents in difficult weaning from the ventilator and prolonged immobilization with consecutive complications. Beside short term complications, critical illness neuromuscular disorders predispose to protracted physical disability, increase hospital costs and set a severe social burden. With extensive research we are starting to find out more about the pathophysiological background and the more we know the more complicated it seems. Probably the complexity of pathophysiology explains why no specific treatment could be developed so far and this underlines the significance of certain preventive measures, such as tight glucose control and early rehabilitation which have

been shown to be effective in decreasing the incidence and severity of CIP and CIM. The aim of the present work is to summarize the present knowledge on the pathophysiology and possible diagnostic and therapeutic options and to draw attention to the clinical importance of this clinical syndrome.

Historical background

Muscle wasting in connection with critical illness had already been recognised by *Hippocrates* and several great physicians of the last centuries such as *William Osler* who wrote about the "rapid loss of flesh and strength" in life threatening infections in 1892[4–6]. Hence until the middle of the 20th century the early mortality rate of infectious diseases and critical conditions was so high that there was no time for neuromuscular complications to develop. With the evolution of modern intensive care the (early) mortality of sepsis has decreased significantly but parallel to this, ICU-acquired complications and comorbidities have become apparent.

In 1977 *MacFarlane* and *Rosenthal* reported on electrophysiologically verified severe myopathy presenting in the form of quadriplegia in a patient with status asthmaticus[7]. In the '80s *Bolton* et al. were the pioneers to report patients with weaning difficulty, acute onset paresis and primary distal, axonal degeneration of motor and sensory nerve fibres[1]. The 1990s was the decade of etiological debates. It took time to differentiate the newly discovered neuromuscular disorder from Guillain-Barré syndrome (GBS)[3], and to clarify the role of neuromuscular blocking agents (NMBAs) as well as steroids in its pathogenesis. The millennium brought the spread of portable electrophysiological devices which made early electrophysiological examinations possible without imposing the risk of intrahospital transport. However, extensive research has been set back by the lack of commonly applied nomenclature. Authors used different terms and criteria to describe nearly the same conditions. Finally in 2009, a round table conference was held in Brussels where the term intensive care unit-acquired weakness (ICUAW) was introduced and within this critical illness polyneuropathy, critical illness myopathy and in case of coexistence critical illness neuromyopathy (CINM) were defined[6].

ABBREVIATIONS

AKT: v-akt murine thymoma oncogene homologue 1 protein kinase B
AMPK: 5' adenosine monophosphate-activated protein kinase
ARDS: adult respiratory distress syndrome
ATP: adenosine-triphosphate
CIM: critical illness myopathy
CINM: critical illness neuromyopathy
CIP: critical illness polyneuropathy
CMAP: compound muscle action potential
DMS: direct muscle stimulation
GBS: Guillain-Barré snydrome
GLUT-4: glucose transporter 4
ENG: electroneurography
EMG: electromyography
EMS: electrical muscle stimulation
FOX-O: forkhead transcriptional factor
ICU: intensive care unit
ICUAW: intensive care unit-acquired weakness
IGF-1: insulin-like growth factor 1
IgM: immunoglobulin M
IL: interleukin
IVIG: intravenous immunoglobulin
LAS: lysosomal-autophagy system
MAFbx: atrogin-1, muscle atrophy F-box protein
MOF: multi organ failure
MRC: medical research council
mRNA: messenger ribonucleic acid
mTOR: mammalian target of rapamycine
MUP: motor unit potential
MURF-1: muscle ring finger ubiquitin ligase
NMBA: neuromuscular blocking agent
PDK-4: pyruvate-dehydrogenase kinase 4
PI3-k: phosphatidylinositide 3-kinase
SIRS: systemic inflammatory response syndrome
SNAP: sensory nerve action potential
TNF-α: tumor necrosis factor alpha
TOF: train-of-four stimulation
UPS: ubiquitine-proteasome system
US: ultrasound
4E-BP1: eukaryotic translation initiation factor 4E-binding protein 1

Incidence

Due to the numerous terms used and the differences in diagnostic criteria the incidence of CIP and CIM is still unknown. In the beginning, mainly polyneuropathy was in the focus of research but recent studies suggest that pure CIM might be more frequent than pure CIP[8, 9] and their coexistence is seen in many cases[8–10]. Overall estimates have ranged between 13-89%. In the 2011 review by *Latronico* and *Bolton*[11] the incidence was estimated in different patient populations as follows: in patients with mechanical ventilation of 4-7 days duration or with increased risk of developing multi-organ failure (MOF) it was 25-33% based on clinical assess-

ment[12–14] and 30-85% based on electrophysiological examination[8, 15, 16]. Incidence was reported between 34-60% in patients with adult respiratory distress syndrome (ARDS)[17, 18], 24-77% in those with longer (>1week) ICU stay[19–22], 56-80% in those with MOF with or without sepsis or systemic inflammatory response syndrome (SIRS)[16, 23–25], and 100% in those with septic shock[26], severe sepsis and coma[27]. The 2009 Brussels criteria might help to have a clear picture on the incidence[6] which is important in the scope of the worse prognostic and outcome characteristics of polyneuropathy[8, 9].

Diagnostic methods

CLINICAL ASSESSMENT

Both CIP and CIM are primary direct consequences of SIRS and sepsis, hence it is crucial to exclude other pre-existing neuromuscular disorders before the final diagnosis. For this reason, a thorough review of medical records, time course of symptoms and confounders is inevitable.

Both CIP and CIM present in the form of general weakness predominantly affecting the limbs and respiratory muscles and the diaphragm. Facial muscles innervated by the cranial nerves are usually spared, if affected those are rather signs of myopathy not neuropathy[28]. The weakness is symmetrical and generally more pronounced in the lower extremities (length-dependent pattern in CIP[29, 30]) but CIM might present proximal as well[28]. Deep tendon reflexes are usually decreased or absent but can be preserved. In pure CIP hypaesthesia may be present but paraesthesia or allodynia are not typical like in other sensory-motor axonal type polyneuropathies. Typically the patient reacts on exerted pain stimulus administered on the nail with facial grimacing but no movement in the limbs is seen. In CIM sensation is usually spared.

For quantification of muscle strength the Medical Research Council (MRC) scoring system is used widely due to its simplicity and its fair inter-observer reliability[31]. It grades the strength of 3 predefined muscle groups in each extremity from 0 to 5 that gives a total of 60 points. A sum of <48 or an average score of <4 in each muscle group indicates ICUAW.

For objective assessment of maximum voluntary muscle contraction force two devices are used[6, 32]. The *standard hand dynamometer* evaluates hand grip strength on a calibrated continuous scale while the *genioglossus myometer* measures the maximum tongue protrusion force. The limitation of all clinical tests is that they require an alert and cooperative patient which is hard to achieve even with the latest sedation protocols favouring light sedation with daily interruption of sedatives[33]. MRC scoring is applicable for a crude assessment of muscle strength, the used scale is nonlinear. It does not measure distal muscle function like hand grip strength, which is usually affected first in the course of critical illness. Dynamometers and myometers are far more precise. Dynamometer measures distal muscles which show a good correlation with the MRC scores[34], but they are less suitable for assessing the function of very weak muscles (MRC 1-3) and require costly equipment.

Objective techniques to assess muscle force through evoking contractions via electrical or magnetic stimulation[32] are not widely applied at present due to their limited regular availability at the ICUs.

ELECTROPHYSIOLOGICAL TESTING

Electrophysiology is the gold standard method to diagnose critical illness neuromuscular disorders. Beside electroneurography (ENG), needle electromyography (EMG) and neuromuscular junction testing, direct muscle stimulation (DMS) is a recently developed method that enables the electrophysiologist to examine an unconscious, uncooperative patient, unable to perform voluntary muscle contraction. Beside the need for cooperation, there are several other limiting factors of electrophysiological testing. One is the extensive interstitial oedema, typically present in critically ill patients. It develops as a result of the hyperkatabolic state, hypoalbuminemia, transcapillary leak and acts as an electric seal[35], which should make the examiner more cautious when interpreting low sensory nerve action potentials (SNAP). Attention should also be paid to keep proper skin temperature, electrical artefacts and electrophysiological alterations in the medical history.

The clinical and electrophysiological onset time of the disorders is still a matter of debate, but there is growing evidence that clinical signs and weakness are well preceded by electrophysiological alterations. The latter may appear within days after the onset of SIRS and sepsis[8–10, 36]. They indicate temporary functional lesions and turn to definite morphological lesions in the later phase. These early alterations are good indicators of the impact of SIRS and sepsis and good predictors of higher mortality and to the development of CIP and CIM[10, 37].

ELECTRONEUROGRAPHY

As CIP is an axonal type sensory-motor neuropathy it is characterized by amplitude reduction and normal or near-normal conduction velocity. The distal latency is within the normal range. The same applies to CIM that is the reduction of amplitude – a result of the muscle fibre atrophy – with intact conduction velocity and distal latency. The characteristic feature of CIM is a longer duration of the elicited potentials, explained by the varying conduction properties of the degenerated muscle fibres and reduced excitability[38, 39]. The other difference between the two disorders is that while in CIP both motor and sensory parameters are pathological, in CIM sensory fibres are usually spared.

ELECTROMYOGRAPHY

EMG is performed with a concentric needle electrode in three stages of muscle contraction: at rest, at mild and at full voluntary contraction. It is important to underline, that critically ill patients under mechanical ventilation and sedation or with septic encephalopathy usually cannot perform proper contraction only in a later stage of the disease when they regain their consciousness. Therefore recruitment cannot be evaluated in the acute / subacute phase of the disease. At rest positive sharp waves and fibrillation potentials characterise both CIP and CIM, representing muscle denervation and necrosis. The degree of alterations can vary in different muscles. If the patient is capable of muscle contraction, motor unit action potentials (MUAP) can be recorded which show a myopathic character in CIM with short duration and low amplitude MUAPs sometimes firing in short bursts. In CIP MUAP characteristics vary with time. Acutely normal morphology turns to short duration, low amplitude, polyphasic MUAPs in the next weeks[30, 40]. Classical long duration, high amplitude reinnervating MUAPs can be found no sooner than the third week after the onset of the disease[15, 40]. In neuropathy the interference pattern shows a reduction while in myopathy early recruitment of MUAPs appears and the "envelope" amplitude of the maximal contraction is reduced[28, 29].

Phrenic nerve conduction study and diaphragm myography

On phrenic nerve ENG bilaterally reduced CMAP amplitudes with normal conduction velocity can be found[2]. The inconvenience caused by forced diaphragm contraction and local irritation by the stimulating electrode on the neck limits the use of this technique in the daily clinical routine. Diaphragm EMG can be performed from three approaches: a) using *transcutaneous surface electrodes*. This is a non invasive technique but positioning of the electrodes is not easy and other electrical devices of the ICU may cause artefacts. b) The *classical needle electrode testing of the diaphragm* bears the risk of several complications, like pneumothorax, liver puncture, etc. and it is difficult to interpret but this is the most precise technique. Short duration, low amplitude MUPs can be expected here as well. c) Diaphragm MUPs can be also collected with a set of *ring electrodes placed on a special nasogastric or oesophageal tube*. The key point of this non-invasive inner surface electrode testing is also positioning[41].

Examination of neuromuscular transmission

Repetitive nerve stimulation, single fibre EMG and TOF (train-of-four) testing play a role in the exclusion of other diseases (myasthenia gravis) or drug effects (eg. neuromuscular blocking agents) causing weakness through the blocking of neuromuscular transmission.

Direct muscle stimulation

The technique of direct muscle stimulation was developed by *Rich* et al. to overcome the problem of eliciting voluntary muscle contraction in a non-cooperative patient[42, 43]. It compares the CMAP amplitudes elicited through stimulating the nerve (nCMAP) and the muscle (mCMAP) itself.

Neuropathy is suspect when the CMAPs elicited by stimulating the nerve are decreased though they are preserved when stimulating the muscle. In this case the ratio of nerve and muscle elicited CMAPs is <0.5. In myopathy CMAPs are reduced or absent (<3mV) both by stimulating the nerve or the muscle signing the decreased excitability of muscle membrane. The nerve/muscle ratio is >0.5 **(Table 1.)**.

NERVE AND MUSCLE BIOPSY

Histology helps to decide in questionable cases but it is no longer obligatory for diagnosis, or rather the

Table 1. *Differential diagnostic tool to CIP and CIM based on direct muscle stimulation*

	Neuropathy	Myopathy
nCMAP	↓	↓
mCMAP	n	↓
nCMAP / mCMAP	<0.5	>0.5

indication and prognostic value is not clarified yet. While electrophysiological alterations appear early in the course of critical illness, histological alterations turn up in the later phase. In case of CIP nerve histology shows primarily distal axonal degeneration involving both motor and sensory fibres without sign of demyelination or inflammation[1]. Central nervous system histology revealed the chromatolysis of anterior horn cells that is the disintegration of the chromophil substance, indicating the exhaustion of the cell or the damage to the axon[30]. Muscle histology shows denervation damage of type I and II muscle fibres and also myopathic characteristics[27, 30]. Later in the course of CIP, while recovery is ongoing, muscle biopsy will show grouped atrophy of the muscle fibres.

In CIM a mixed histological picture of acute necrosis with regeneration, selective loss of thick filaments (myosin) and atrophy of type II (fast twitch) muscle fibres can be seen[27, 44]. The selective loss of myosin signed by the loss of myofibrillar adenosine triphosphate on immunohistology is so characteristic that it led to the term "thick filament myopathy"[45].

ULTRASONOGRAPHY

In recent years attention has turned to assessing muscle mass loss in ICU patients[46]. Presently B-mode ultrasonography (US) of rectus femoris (RF) muscle seems to be the most suitable technique. RF is the largest muscle of the body and was shown to have good correlation with lean body mass[47]. US was proven to be as accurate as magnetic resonance imaging beside being portable, non-invasive, easy to use and cost effective[48]. However it is yet to be determined if cross sectional area[46, 49] or muscle layer thickness[47, 50] of rectus femoris muscle is the more reliable parameter for monitoring, which is less affected by interstitial oedema.

LABORATORY TESTING

Elevated serum creatine kinase levels are reported especially in the necrotizing type of CIM[51, 52] but the kinetics of serum level and the sensitivity is poorly studied.

Differential diagnosis

As mentioned before, the exclusion of other diseases resulting in acute onset tetraparesis is crucial to achieve diagnosis. Impairment of neuromuscular transmission can be excluded with simple electrophysiological testing (eg. TOF stimulation or repetitive nerve stimulation) and the review of patient history concerning NMBAs, chemotherapy, antiretroviral drug administration. Apart from critical illness, several central nervous system disorders may also result in generalized muscle weakness. Myopathy may be caused – among others – by electrolyte disturbances (hypokalemia, hypophosphatemia), drugs (statins and fibrates). The so called propofol infusion syndrome presents with severe metabolic acidosis, cardiac failure, hypertriglyceridaemia and rhabdomyolysis along with a consequent renal failure. It develops in patients receiving high doses of propofol (5 ml/kg/h) for more than two days[53].

The classical differential diagnostic entity was the Guillain-Barré syndrome which presents also with acute onset tetraparesis, but certain clinical, laboratory and electrophysiological features help differentiation. These are the ascending characteristic, involvement of cranial and autonomic nerves, delayed onset time, elevated cerebrospinal fluid protein content and demyelinating characteristics on ENG (except for the axonal subtypes of GBS)[54].

The common diabetic and alcoholic polyneuropathies may mimic the electrophysiological characteristics of CIP and give false positive diagnosis especially when there is no documentation in the previous history.

Pathophysiology

The pathophysiology of critical illness associated neuromuscular disorders is complex. They are no longer handled as isolated events, rather they are an integral part of the process leading to multiorgan dysfunction and failure and this way, the mutual and additive role of microcirculatory, cellular and metabolic pathophysiological mechanisms is presumable[11].

It was previously described in 1996 that electrophysiological alterations precede morphological deterioration[27] and emerging evidence suggests that definitive morphological lesions are established by functional failure. Yet, it is still undiscovered how the peripheral nerve and muscle exhibit a rapid onset of breaking down and this functional problem can turn out to be reversible[55].

One explanation is the concept of sepsis-induced bioenergetic failure introduced by *Bolton* et al. in the 1990s which is still relevant today and grossly describes the pathophysiological process. The key point is that excitable tissues such as the nerves and muscles spend much of their energy on sustaining

excitability and function hence they are prone to develop dysfunction early in case of reduced energy supply and use[29].

Microcirculatory dysfunction is known to be a major pathophysiological factor in the development of sepsis-associated multiorgan failure[56–58]. The decrease in the number of perfused capillaries and the heterogeneity of microvascular circulation lead to alterations in oxygen extraction and tissue hypoxia in sepsis[59, 60]. These microcirculatory changes can resolve rapidly in response to adequate therapy but if they persist they predispose to higher mortality[11, 57, 61, 62].

Mitochondrial dysfunction provoked by stress hormones, inflammatory cytokines, insulin resistance, reactive oxygen species or nitrous oxide also plays a pivotal role in the pathogenesis of cellular and organ failure through reduced adenosine-triphosphate (ATP) biosynthesis, energy generation and use[63, 64]. *Brealey* et al. found a correlation between muscle ATP concentration, mitochondrial dysfunction and the severity of septic shock, suggesting that bioenergetic failure is an important pathophysiological mechanism for muscle and multi organ dysfunction[65]. Furthermore, restoration of mitochondrial biogenesis, which maintains normal mitochondrial number, structure and function was found to be an important factor favouring survival[66, 67].

Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) are known to suppress the insulin effect through the direct inhibition of the Akt signalling process culminating in peripheral insulin resistance and cellular energy depletion. *Constatin* et al. found a significant upregulation of muscle pyruvate dehydrogenase kinase 4 (PDK4) mRNA and protein expression in critically ill patients, pointing to the inhibition of muscle carbohydrate oxidation in these patients[68, 69]. *Weber-Carstens* et al. described faulty glucose transporter-4 (GLUT 4) disposition and diminished glucose utilization in the muscle of critically ill patients[70]. They explained the impaired transposition of the GLUT 4 transporter from perinuclear space to sarcolemma with the impairment of the insulin signalling pathway and the dysfunction of an AMPK energy sensor as a result of the lack of metabolic stimulation caused by the absence of muscle contraction.

Epi- and endoneurial vessel and concomitant leukocyte activation shown by increased E-selectin expression on the endothelial surface lead to the cessation of vascular autoregulation, endoneurial oedema and the accumulation of further cytopathic factors in the perineurial spaces[71]. Hyperglycemia and hypoalbuminaemia can further enhance these processes which finally lead to ischemic hypoxia of the peripheral nerves even if oxygen supply is adequate[8, 11, 23, 29]. Beside the onkotic effects of the high serum glucose level, advanced glycation end-products induce basement membrane hypertrophy in endoneurial microvessels and disrupt the blood-nerve-barrier by stimulating the release of transforming growth factor beta and vascular endothelial growth factor by pericytes[72].

The next step in the pathophysiological cascade to be blamed for early electrophysiological disturbances is "channelopathy". Energy depletion leads to the insufficiency of membrane voltage-dependent sodium channels, that results in a shift of the voltage dependence of sodium channel fast inactivation towards more negative potentials[73–75]. The depolarization of resting membrane potential due to endoneurial hyperkalaemia or hypoxia can also be accounted for the hypo-, inexcitability of peripheral nerves and muscles[43, 76]. This similar appearance of channel dysfunction further supports the unifying hypothesis of CIP and CIM as different manifestations of one disorder[11] but in vivo findings are yet to be verified in humans.

The prominent muscle wasting in septic patients is the result of the alterations in the balance of muscle protein synthesis and muscle protein breakdown.

In healthy volunteers bed rest immobilization itself caused rapid muscle loss within a week, most prominently in the lower limbs[77]. In septic patients immobilization due to bed rest is aggravated by sedation and accompanied by insulin resistance and release of septic cytokines which are also inhibitory factors of muscle protein synthesis. Consequently the loss of lean body mass in critically ill patients was 1-1.6% per day, 7% per week in three weeks observational studies[78, 79] and 16-20% on ultrasound measurement in the first week in patients with septic shock[80].

Muscle protein synthesis is promoted via the PI3-K/AKT/mTOR pathway which is activated by local IGF-1 and nutrients and act through the initiation of several translational factors. Amino acids, especially branched-chain leucin, are known to stimulate muscle protein synthesis via both insulin-dependent (through PI3-K receptor) and insulin-independent mechanisms[81]. Yet in sepsis a leucin-resistance through the defect in leucin induced translation initiation has been observed[82]. Septic cytokine production, namely IL-1, IL-6, TNF-α directly inhibit the PI3-K/AKT/mTOR pathway with the deactivation of AKT protein kinase B resulting in decreased muscle protein synthesis[69]. Decreased mTOR kinase activity was evidenced by

reduced phosphorylation of both eukaryotic initiation factor (eIF)4E-binding protein (BP)-1 and ribosomal S6 kinase (S6K)1[83].

The physiological role of the shift toward marked degradation of muscle fibres in the septic patient is to liberate energy and substrates for gluconeogenesis and synthesis of acute phase proteins.

There are three main proteolytic ways acting in the process of critical illness associated muscle wasting (calpain-caspase system - CCS, ubiquitin-proteasome system - UPS, lysosomal autophagy system - LAS). The CCS is responsible for the initiation of breakdown of muscle fibres through releasing actin and myosin fibres from myofilaments thus exposing them to further cleavage by the proteasome system. Calpains are cystein proteases which are activated by the elevation of cytosolic Ca^{2+} level, in this case promoted by inflammatory cytokines[84]. The ATP-dependent UPS is responsible for the large-scale degradation of damaged myofibrilla. Proteins ligated with the polypeptide ubiquitin are destined to breakdown by the 20S core of the 26S proteasome system. The key elements of the ligation process are the muscle specific MAFbx and MURF-1 E3 ubiquitin ligases which are induced by the FOX-O transcription factor just like the cathepsin B, D, and L enzymes in the LAS[69, 85]. The role of the LAS system in the critically ill has not been clarified yet: autophagy either protects against the collection of toxic myofibrillar aggregates, which initiate muscle dysfunction, or it exacerbates the loss of the myofibrillar apparatus to induce atrophy[86].

At the moment, these molecular pathways seem to be responsible for septic muscle protein synthesis and breakdown but to what extent and in what temporal dispersion that is yet to be elucidated. After the standardized environment and results of animal research, human research produces divergent and sometimes contradictory results[69, 70, 85, 87] concerning gene expressions, protein activities and the clinical relevance of the different biochemical mechanisms. In a comprehensive molecular study *Constantin* et al. showed the simultaneous downregulation of signalling proteins thought to increase muscle protein synthesis (Akt1, mTOR, 4E-BP1, p70s6k) and a parallel activation of molecular pathways driving muscle protein breakdown (MAFbx, MuRF1, 20S proteasome, cathepsin-L). Yet, the catabolic changes were paralleled by initiation of a cellular program of anabolic restoration at the transcriptional level, as suggested by a significant increase in mRNA of anabolic factors[69]. Compared to this *Jespersen* et al. found decreased MuRF1/MAFbx levels and a higher Akt/mTOR/S6k/4E-BP1 anabolic signalling expression and in septic patients what they explained with the exogenous administration of insulin which is an activator of this anabolic pathway through receptor PI3-K[87].

Beside the loss of contractile elements (overwhelmingly myosin loss), mitochondrial dysfunction and muscle membrane inexcitability, oxidative stress, impaired excitation-contraction coupling also contribute to the impaired force-generating capacity of muscle in critically ill patients[88].

Risk factors

Over the years several factors have been suspected to be responsible for the development of CIP and CIM, the role of some factors has still remained debatable. The severity and duration of SIRS and sepsis[12, 14, 22, 25, 89–91], number of organ failures[25, 89, 90], duration of vasopressor and catecholamine support[20], duration of ICU stay[20, 23], renal failure[14], hyperglycaemia[17, 20–23, 89, 90], low serum albumin[23, 89, 92], hyperosmolality[93], parenteral nutrition[88, 93], neurological failure[94], immobility[89, 95], female sex[12, 89] presently seem to be evident risk factors.

Three prospective observational studies concluded that corticosteroids had a negative effect concerning the development of CINM[12, 96, 97], yet several others reported that they had no effect[14, 20, 93, 98–100] especially if tight glucose control was kept. One study showed that they were protective probably though decreasing the cathecholamin and vasopressr need[21].

Aminoglycoside antibiotics were also identified as risk factors in some studies[15, 22, 37] but not in others[11, 12, 17, 20, 21, 23, 93, 101].

In the 1980s and 1990s prolonged application of neuromuscular blocking agents was considered as a causative factor in the development of ICUAW[93, 102–105]. In line with the introduction of intermittent administration NMBA rptpcols, and Hoffman-eliminating short acting agents the direct causative connection has become questionable although immobility caused by NMBAs cannot be disregarded.

Renal replacement therapy was also found to be a protective[93] and causative factor[106–108] at the same time, but it is still a question whether renal replacement therapy or renal insufficiency itself is to be blamed.

Therapy

Up to the present day no specific, evidence-based effective therapy has been developed for the man-

agement of critical illness-associated neuromuscular disorders. No hormonal therapies, nutritional or antioxidant supplements could prove to be decisive, yet several supportive and preventive measures have been found to be effective.

Since the large-scale prospective, randomized, controlled trial of *Van den Berghe* et al, where intensive insulin therapy reduced the risk of CIP and the duration on mechanical ventilation beside many other ICU complications[20] and knowing the pathological effects of hyperglycaemia there is no need to emphasize the significance of strict glucose control in the critically ill. Only the original Van den Berghe target range (4.4-6.1 mmol/l) has been modified to <10 mmol/l[108] since the former protocol had turned out to increase the number of hypoglycaemic episodes and ICU mortality[109].

One of the major advances in rehabilitation of these patients is the shift toward preventive approach. Rehabilitation started early in the ICU after reaching hemodynamic stability with repeated daily passive mobilization, early physical and occupational therapy up to the patient's physical and mental status is associated with better outcomes[110, 111]. In connection with this we have to emphasize the role of daily interruption of sedation and the spontaneous breathing trials. These measures help to preserve muscle mass, improve functional independence, shorten ventilator dependency, delirium, ICU and hospital stay[33, 112, 113].

A promising advancement of the last two years was the introduction of electric muscle stimulation (EMS) in the ICU[114]. EMS was proved to improve muscle strength and muscle mass in chronic obstructive pulmonary disease and chronic heart failure patients[115–119]. In the critically ill its use is not circumscribed yet[69, 120–123]. So far it seems to stimulate biochemical mechanisms which are responsible for muscle protein synthesis and to stimulate muscle glucose uptake through the facilitation of GLUT-4 transposition to the sarcolemma[70], this way it can improve insulin resistance. *Gerovasili* et al. found that EMS might affect beneficially local and systemic microcirculation based on near-infrared spectroscopy measurement[124] and might help to preserve muscle mass according to ultrasound measurement[121]. *Routsi* et al. found that daily EMS sessions prevented critical illness neuromyopathy[120]. Several trials are ongoing to clarify its affectivity and feasibility in preventing muscle wasting, to elucidate its biochemical effect and to determine the optimal treatment parameters[125, 126]. Presently EMS seems more potent in preserving muscle strength compared to muscle mass[113].

The role of immunoglobulins (IVIG) in the prevention of CIP and CIM is quite contradictory. In a retrospective chart analysis by *Mohr* et al. the administration of high dose immunoglobulin M (IgM) enriched IVIG was found to be protective[101]. *Brunner* et al. could find no beneficial effect of IgM enriched IVIG in their prospective randomised controlled double blind trial, however they administered IVIG only after the evolution of electrophysiological alterations and in smaller dose than in the Mohr study[127].

Other therapeutic or preventive measures, like the administration of nutritional (leucin or glutamine supplementation), hormonal (growth hormone, testosterone or oxandrolone administration), antioxidant supplements have not proved to be effective so far.

Conclusions

The aim of this review was to give an insight into these long known but during daily clinical work often neglected disorders. Breathing insufficiency and movement inability as consequences of ICUAW are major contributors to ICU and hospital mortality. Along with the development of medical care more lives can be saved but the number of physically disabled survivors is rising also setting severe social, health care and economical problems.

The author cannot stress the importance of preventive approach and early intervention. Early mobilization and physiotherapy, the application of liberal sedation protocol and strict glucose control are proven to be beneficial not only from the aspect of neuromuscular complications. They favourably influence the course of critical illness interfering with septic cascade at multiple sites and thus help to preserve and/or restore organ function. Rehabilitation should start already in the ICU.

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