Critical Illness Polyneuropathy and Critical Illness Myopathy

ICU consults for patients who are either diffusely weak or have difficulty being weaned from mechanical ventilation may be due to CIP, CIM, or a combination of these two.

By Amir S. Khoiny, M.D. and Réza Behrouz, D.O.

Neurologists frequently receive consultation requests from the intensive care unit (ICU) regarding patients who are either diffusely weak or have difficulty being weaned or liberated from mechanical ventilation (MV). In many cases, this is due to critical illness polyneuropathy (CIP), critical illness myopathy (CIM), or a combination of these two entities. Whether CIP and CIM are distinct entities or represent separate targets for a common pathophysiological mechanism is unclear. The two often co-exist and are subsequently not easily differentiated from one another. Hence, they are commonly referred to as critical illness myopathy and/or neuropathy (CRIMYNE) or critical illness neuromuscular abnormalities (CINMA).[1] This article is an overview of clinical and diagnostic features as well as therapeutic options in CIP/CIM.

Epidemiology and Pathophysiology

The differential for muscle weakness in the ICU is quite vast (Table 1). As an ICU-associated phenomenon, CRIMYNE is the most common form of acquired neuromuscular disorder in the ICU.[2] Patients in the ICU have about 47 percent to 90 percent risk of developing either CIP or CIM.[12] Recent studies suggest that CIM is perhaps more frequent than CIP.[2]

The pathophysiology of CIP and CIM is not completely understood. It is presumed to be a complicated interaction of metabolic, bioenergetic, and inflammatory phenomena.[3] There are many proposed pathophysiologic mechanisms that include microvascular alterations of the peripheral nerves, altered lipid serum profile which promotes neuronal impairment, and bio-energetic failure due to muscle ATP depletion from a dysfunctional complex I of the respiratory chain.[1]

Clinical Features

CIP and CIM share many of the same clinical features and frequently co-exist. For clinicians, it is often difficult to differentiate the two due to suboptimal patient cooperation during motor and sensory examination.[4] Typically, CIP/CIM is unmasked as a pathological entity when there are multiple failed attempts at weaning the patient from MV in the context of seemingly normal pulmonary, mental, and cardiovascular status. The cause for this is often phrenic nerve and/or diaphragmatic dysfunction. The clinician may notice flaccid, symmetrical weakness when sedation for MV is held. Distal muscles are more commonly affected in CIP, whereas CIM affects distal and proximal muscles. Both CIP and CIM also reduce deep tendon reflexes and can result in muscle atrophy. Bulbar muscle involvement is highly unusual and should prompt a broader differential diagnosis. CIP patients who are able to cooperate with sensory examination (and who do not have significant pedal edema) may also exhibit distal sensory loss to vibration, pain, and temperature.[5]

Many clinicians use the Medical Research Council (MRC) sum score to screen for CIP/CIM.[5]

An MRC score for individual muscle testing ranges from 0 to 5, indicating no movement to normal strength, respectively (Table 2). The MRC sum score evaluates 12 total muscles. In the upper extremity an MRC score for both right and left shoulder abduction, elbow flexion, and wrist extension is performed, while in the lower extremities an MRC score for right and left hip flexion, knee extension, and foot dorsiflexion is assessed. The MRC sum score can range from 0 to 60 with an arbitrary cutoff score below 48 suggesting ICU-acquired weakness. This screening test has inherent limitations because it requires full cooperation of the patient.[6] Furthermore, the score only demonstrates weakness without suggesting a particular cause.

Severe sepsis, systemic inflammatory response syndrome (SIRS), and multiple organ failure are very common risk factors for developing CIP/CIM.[6] Other risk factors include increased ICU stay duration, hyperglycemia, electrolyte abnormalities, hypoalbuminemia, renal failure, and parenteral nutrition.[3] While aminoglycosides have previously been thought to be a risk factor, more recent studies have not demonstrated a definitive causal relationship. In addition, based on recent studies, corticosteroids and neuromuscular blocking agents do not appear to be strong risk factors for developing CIP and CIM, as was previously assumed.[5]

Diagnostics

Laboratory

Serum creatine kinase (CK) is not particularly helpful in the diagnosis of CIP/CIM. This is because CK levels may be normal in people who have CIM but do not have muscle necrosis or have scattered muscle necrosis. Furthermore, in those with CIM and muscle necrosis, the CK elevation is typically transient and may be missed on a single laboratory analysis.[5]

Electrophysiology

CIP is an axonal sensori-motor polyneuropathy depicting a reduction in total number of nerve fibers. On nerve conduction studies (NCS), this is reflected as reduced amplitudes on compound motor action potentials (CMAP), sensory nerve

Table 1. Selected potential causes of weakness in the ICU.[10]

AIDP = acute inflammatory demyelinating polyneuropathy;
NMO = neuromyelitis optica;
ADEM = acute disseminated encephalomyelitis

Muscle Diseases
Critical illness myopathy
Inflammatory myopathy
Hypokalemic myopathy
Rhabdomyolysis
Muscular dystrophy
Myotonic dystrophy
Mitochondrial myopathy
Acid maltase deficiency

Neuromuscular Junction Disorders
Myasthenia gravis
Neuromuscular blocking agents
Antibiotic induced myasthenia
Organophosphate poisoning
Snake bite
Insect/marine toxins
Lambert-Eaton myasthenic syndrome
Congenital myasthenic syndromes
Hypomagnesemia
Botulism
Tick paralysis

Peripheral Neuropathies
Guillain-Barré syndrome (AIDP)
Chronic idiopathic demyelinating polyneuropathy (CIDP)
Critical illness polyneuropathy
Phrenic neuropathy
Toxic neuropathies
Vasculitic neuropathy
Porphyric neuropathy
Diphtheria
Lymphoma
Cytomegalovirus-related polyradiculo-neuropathy

Anterior Horn Cell Disorders
Amyotrophic lateral sclerosis
Paraneoplastic motor neuron disease
West Nile virus infection
Acute poliomyelitis
Spinal muscular atrophy

Spinal Cord Disorders
Trauma
Hematoma
Spinal cord infarction
Epidural abscess
Demyelinating disorders: multiple sclerosis, transverse myelitis, NMO, ADEM
Infective myelitis
Paralytic rabies

Table 2 – Medical Research Council (MRC) Scoring for CIP/CIM

Functions Assessed

Upper Extremity: Wrist Extension, Elbow Flexion, Shoulder Abduction

Lower Extremity: Ankle Dorsiflexion, Knee Extension, Hip Flexion

Score For Each Movement

0 No Visible Contraction
1 Visible Muscle Contraction, But No Limb Movement
2 Active Movement, But Not Against Gravity
3 Active Movement Against Gravity
4 Active Movement Against Gravity And Resistance
5 Active Movement Against Full Resistance

Scoring & Interpretation

Maximum Score: 60
(4 Limbs, Maximum of 15 Points Per Limb) = Normal

Minimum Score: 0 = Quadriplegia

action potentials (SNAP), or both. Because the myelin sheath is not affected in CIP, NCS show normal velocity and normal latency. This feature is an important factor in differentiating between CIP and Guillain-Barré syndrome, a largely demyelinating condition.[6] When encountering diagnostic dilemmas, electrodiagnostic procedures are commonly employed. Testing is usually performed at one to two weeks after the initial symptoms. However, decreased amplitude in nerve conduction findings have been found in affected individuals anywhere from two to five days from ICU admission.[3] A simplified screen for both CIP/CIM in ICU patients has recently been proposed that solely evaluates the CMAP amplitude of a peroneal nerve. A peroneal nerve amplitude reduction that is less than two standard deviations from the normal has a sensitivity of 100 percent and a specificity of 67 percent for CIP/CIM.[7] Needle electromyography (EMG) examination in ICU patients frequently shows positive sharp waves and fibrillation potentials in resting muscles two to three weeks after onset. This indicates non-specific acute pathological changes in the muscle arising either from a nerve or directly from the muscle.

Patients in the ICU are rarely cooperative enough to evaluate voluntary motor unit size and recruitment pattern, two pivotal factors in differentiating CIP from CIM. Suggested standard electrophysiological evaluation involves bilateral ulnar and sural sensory nerves as well as bilateral ulnar and peroneal motor nerves. Standard needle examination is typically of one upper region (e.g. biceps and abductor digiti minimi) and one lower region (e.g. tibialis anterior and quadriceps femoris). In cases of difficult weaning, phrenic nerve conduction along with needle examination of the diaphragm may be helpful.

Unfortunately, findings in CIM are very similar to CIP. CIM patients will have decreased amplitude CMAPs as do CIP patients. While CIM should have preserved sensory amplitude SNAPs, normal SNAPs do not rule out CIP because there have been pure motor forms of CIP. Further, fibrillation potentials and positive sharp waves on EMG can be seen in either CIM or CIP.[3] A routine needle EMG is able to differentiate CIP from CIM only if the patient is fully cooperative. CIM typically shows early (rapid) voluntary recruitment with motor units showing low amplitude and with short duration.[6]

Direct Muscle Stimulation

Direct muscle stimulation (DMS) in conjunction with standard testing (NCS/EMG) is a method to distinguish CIP from CIM in non-cooperative patients without performing a muscle biopsy. To perform this test, stimulating and recording electrodes are both placed into the muscle (Figure 1). In CIM, the action potential is reduced in both the standard study and in DMS. In CIP however, the standard study will show low amplitude action potential while DMS will be normal. This is due to the fact that stimulation does not go through a damaged motor nerve. This procedure is technically demanding and difficult to get reliable findings and therefore is not routinely performed.[3]

Muscle Biopsy

Muscle biopsy is the gold standard for the diagno-

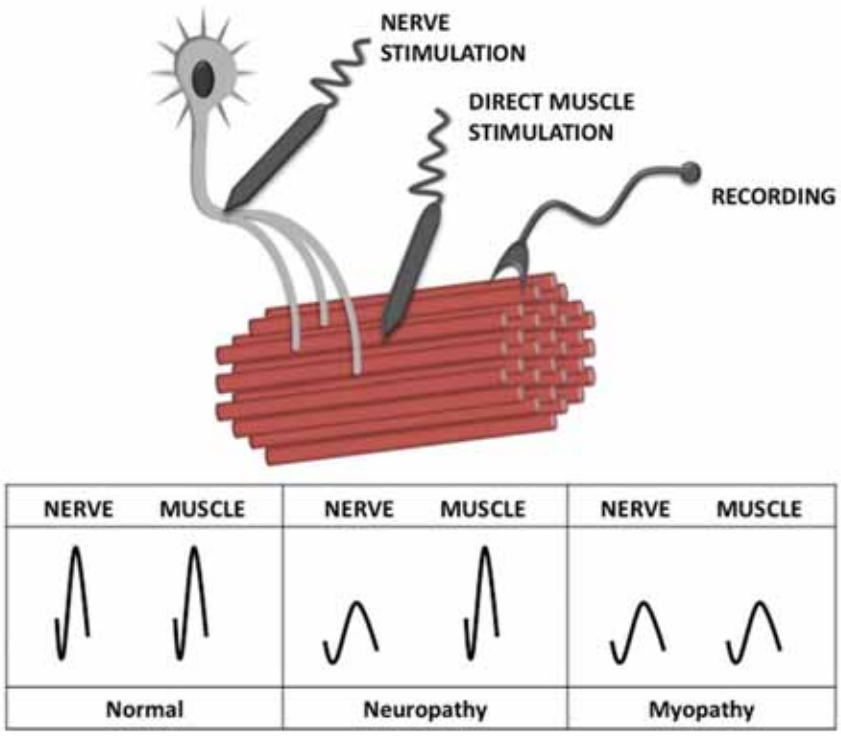

Figure 1. - Comparison of nerve stimulation (standard study) and direct muscle stimulation (DMS). In CIP, the standard study shows a low amplitude action potential while in DMS the action potential is normal. In CIM, the action potential is reduced in both the standard study and in DMS. (Artwork by Réza Behrouz, DO, adapted from [4])

sis of CIM. It must be understood that it is an invasive test with its own potential risks. Additionally, because there are no therapeutic differences between CIP and CIM, the test is not commonly performed. Recently, some have suggested that evaluating the myosin/actin ratio may allow for a faster biopsy diagnosis of CIM.[5] It is important to impress that while CIM is generally considered a solitary clinical entity, there are 3 different CIM types based on histopathology:

1.) acute necrotizing myopathy (myonecrosis),
2.) thick-filament myopathy (loss of thick myosin filaments), and
3.) non-necrotizing, cachectic, myopathy (type 2 fiber atrophy).[8]

Nerve Biopsy

Nerve biopsy to diagnose CIP is rarely performed. It may be normal early in the disease despite abnormal neurophysiological testing. When performed later in the course of CIP, nerve biopsy typically shows only axonal degeneration without inflammation.[8]

Management

Unfortunately, there is no specific medical therapy for CIP/CIM. Intravenous immunoglobulin (IVIg), anti-oxidant therapy, growth hormone and testosterone have not shown any benefit for CIP/CIM.[5] Supportive care, particularly early physical therapy, is the mainstay of therapy. Deep vein thrombosis prophylaxis and prevention of decubitus ulcers is important. Aggressive antibiotic therapy is recommended in cases of sepsis. Because the role of steroids and neuromuscular blocking agents is still unclear, using these medications sparingly may help prevent CIP/CIM.[8]

Lastly, there is mixed opinion about tight glucose control in preventing CIP/CIM. A 2009 Cochrane review evaluating very tight glucose control (80-110 mg/dl) in ICU patients determined that CIP/CIM incidence was decreased with intense insulin therapy. This review also reported decreased MV dependency as well as length of ICU stay and improved 180 day mortality.[9] However, a significant number of hypoglycemic episodes occurred in patients under intensive glycemic control. Later, a randomized controlled

study showed increased mortality when using a very narrow margin (81-108 mg/dl) management of serum glucose.[11] Some experts therefore suggest considering less stringent control of blood glucose, ranging between 108 mg/dL and 150 mg/dL.[3]

Proognosis and Recovery

CIP/CIM has been associated with delayed recovery in the ICU.[12] In fact, MV is up to five times longer in those afflicted with the disease than those who are not.[3] CIP/CIM is also associated with longer hospitalization stays and increased mortality.[5] About one-third of those discharged from the hospital with a diagnosis of CIM/CIP have severe disability (e.g. paraplegia or tetraparesis).[6] Frequent mild disabilities noted in these patients include muscle atrophy, foot drop, decreased reflexes, and distal sensory loss.[2]

In general, mild cases of CIP/CIM show improvement over weeks, while improvement in severe cases may take many months, if they develop at all.[5] While the treatment of CIP/CIM is the same, small studies have shown that patients with CIM tend to have better outcomes compared to those with CIP.[5]

Conclusion

Neurologists are frequently asked to evaluate weakness in ICU patients. There are many potential causes of ICU weakness but the most frequently encountered are CIP/CIM. CIM occurs slightly more often than CIP, but they commonly co-exist. To evaluate these patients, a comprehensive history including the patient's past neurological history and family history is imperative. Also, a complete neurological assessment is highly recommended, although a depressed mental status confers significant limitations on the examination.

While serum CK is generally not necessarily helpful in the diagnosis of CIP/CIM, electrophysiological studies are. Unfortunately however, they are typically incapable of distinguishing between the CIM and CIP. In some cases, direct muscle stimulation may be able to differentiate the two entities. Muscle biopsy is the gold standard for diagnosis, but because CIP and CIM are clinically quite similar, performance of this procedure would not drastically alter management. It is therefore not routinely performed unless another form of myopathy or a concomitant muscular dystrophy is suspected.

Unfortunately, there are no specific therapies for CIP/CIM; small studies have not found success with either IVIg or plasmapheresis.[2] Treatment of CIP/CIM is for the most part supportive and entails early and intensive physical therapy. As with almost all conditions, the more severe cases typically have prolonged and less complete recovery, while the milder forms of CIP/CIM usually recover fully over weeks to months. ■

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