Neuromuscular Weakness in the Intensive Care Unit

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Disclosure;

Speaker’s Bureau - Athena Diagnostic Inc.
- Pfizer Inc.

Objectives;

- Learn the clinical, diagnostic and pathological features of Critical Illness Polyneuropathy (CIP) and Critical Illness Myopathy (CIM)
- Understand CIP & CIM are commonly seen in critically ill patients
- Understand that high dose steroids and NMJB agents are the predominant factor in CIM, whereas SIRS and MODS in CIP
- Learn the preventive measurements, and management of neuromuscular weakness in the ICU
Causes of generalized weakness in the ICU

**Brain Disorders:**
- Septic or toxic encephalopathy
- Brain stem stroke
- Central pontine myelinolysis

**Spinal cord or anterior horn cell disorders:**
- Cervical myelopathy, or cord injury
- Amyotrophic lateral sclerosis

**Peripheral neuropathies:**
- Critical illness polyneuropathy (CIP)
- GBS “acute axonal variant”
- Porphyria, Paraneoplastic, Vasculitis, Nutritional
Causes of generalized weakness in the ICU

**Myopathies:**
- Critical illness myopathy (CIM)
- Rhabdomyolysis
- Cachectic myopathy
- Polymyositis, Dermatomyositis, Viral myositis
- Toxic myopathies
- Muscular dystrophies, Acid maltase deficiency
- Mitochondrial myopathies

**Neuromuscular junction disorders:**
- Prolonged neuromuscular junction blockade (PNMJB)
- Myasthenia gravis (with/without precipitating drugs)
- Lambert-Eaton myasthenic syndrome
- Botulism
Causes of generalized weakness in the ICU

Hypermetabolic syndromes with rhabdomyolysis:

- Neuroleptic malignant syndrome
- Malignant hyperthermia
- Serotonergic syndrome
- Central anticholinergic syndrome
- Heat stroke
Suspected Critical Illness Neuromuscular Disease in ICU patients

- Critically ill patients with sepsis, multi organ dysfunction, or systemic inflammatory syndrome (SIRs)
- Received high corticosteroids doses and NMJB agents
- Have been in the ICU on ventilator for > 1 week
- Symmetric limbs weakness, with or without facial weakness
- Respiratory weakness & difficulty weaning-off ventilator
- Other causes have been excluded (heart or lung disease)
Systemic Inflammatory Response Syndrome

“SIRS”

- Coined by the Society of Critical Care Medicine and the American College of Chest Physicians 1992

- A syndrome of sepsis and multiple organ dysfunction (MODS)

- Seen in 20-50% of ICU patients on ventilator for >1 week

- Life-threatening, with mortality rate of 30-50%

- Evoked by sepsis, trauma, burns, or surgery

- Cellular and humoral responses causing microcirculation changes

- Septic encephalopathy is a common early complication

- Commonly associated with CIP/CIM, singly or in combination

**SIRS**

- **Cellular response**: Lymphocytes, monocytes, and neutrophils
- **Humoral response**: IL's, TNF, FOF, arachidonic acid, coagulation factor, proteases

**Adhesion molecules**

- Endothelial cell damage, increased capillary permeability, arteriolar vasodilatation, fibrin platelet aggregates, sluggish capillary flow
Critical Illness Polyneuropathy (CIP)

Historical Note

- Coma-polyneuropathies (Mertens 1961)
- Acute polyneuropathy in patients with burns (Henderson et al. 1971)
- Primary distal, axonal motor sensory neuropathy (Bolton et al 1977-1984)
- Critical Illness Polyneuropathy “CIP” (Zochodne et al 1987)
Critical Illness Polyneuropathy (CIP)

- 50-70% of ICU patients with SIRS has EDX evidence of polyneuropathy. ± half of these have clinically significant polyneuropathy (Bolton 2003)

- SIRS/MODS for 1-2 weeks, and antecedent septic encephalopathy are invariably present

- Corticosteroids, NMJB, aminoglycosides, hypoalbuminemia & hyperglycemia are risk factors

- Distal, symmetric axonal motor sensory neuropathy
CIP

Clinical Presentation:

- Symmetric weakness and difficulty weaning from ventilator
- Facial weakness is rare, and EOM’s are spared
- Tendon reflexes are attenuated, lost or preserved
- Distal sensation is impaired, but difficult to assess
- Muscle atrophy in the distal extremities is common
- Neuropathic pain is not characteristic of CIP
- Autonomic dysfunction is uncommon in CIP
- CIP has been reported in children, but less commonly
CIP

Approach to Achieving a Diagnosis:

- Patients charts need to be meticulously surveyed
- Exclude conditions prior to ICU admission, or worsen rapidly in the ICU
- Laboratory Testing
- Electrodiagnostic Studies
- Normal CSF Studies
- Occasionally muscle biopsy is needed
- Nerve biopsy is rarely indicated
CIP

Electrodiagnostic Studies:

- NCS should preferably include the phrenic nerve
- Conduction velocity usually normal, or mildly slow
- CMAP amplitude decline *predates clinical symptoms*
- SNAP amplitude decline, or absent *occur later*
- NEMG; prominent distal denervation and reduced MUP’s.
- Chest muscles and diaphragm NEMG might be needed
- Few may have myopathic features
- Overall features of distal axonal motor sensory neuropathy
CIP

Nerve and Muscle Biopsy Features:

- **Nerve biopsy:**
  - Varied degrees of primary axonal degeneration
  - Notable lack of primary demyelination or inflammation
  - Central chromatolysis of anterior horn and DRG ganglion cells

- **Muscle biopsy:**
  - Acute and chronic denervation and occasional myopathic changes

- Others reported normal autopsy and nerve biopsy pathology, despite clinical and EDX features of CIP

CIP

Denervation of muscle fibers

Severe loss of axons in a nerve fascicle
CIP

Pathophysiology:

- **Strong association between CIP and sepsis, SIRS and MODS**
- **SIRS induced humoral and cellular factors implicated**
- **Microvascular changes in peripheral nerves induce energy deficit, hypoxia & primary axonal degeneration**
- **Endoneural edema secondary to cytokine’s, hyperglycemia and hypo-albuminemia induces nerve hypoxia**
- **PNMJB agents may cause terminal motor axonopathy ??**

(Fenzi et al. 2003, Low et al. 1999, Wernig et al. 1980)
**CIP**

**Differential Diagnosis:**

- Other axonal neuropathies, such as axonal GBS
- Transient weakness secondary to PNMJB agents
- Weakness secondary to CIM
- Coexisting mononeuropathies or plexopathies due to compression, direct trauma or ischemic
- CIP may occur independently or in association with CIM
Similar neuropathies related to sepsis or SIRS in settings other than the ICU

- Rapid decline of an axonal polyneuropathy in end stage RF
- CIM > CIP tendency in organ transplant patients, on immunosuppressant therapy and NMJB agents
- CIP like syndrome in severe COPD requiring ventilator
- CIP like syndrome in severe burns or chemical trauma (varied reported frequency 3-50%)

Management:

- Avoidance of, and early treatment of sepsis and SIRS
- Appropriate antibiotics, maintained circulation, oxygenation and vigorous treatment of septic shock
- Management of airways and ventilator weaning difficulty
- Attention to nutritional and metabolic status, positioning, pulmonary hygiene and DVT prophylaxis
- Physiotherapy, rehabilitation and assistive devices
CIP

Attempts at direct treatment;

- IVIG may have preventive benefit, but failed to show improvement of CIP (Wijdicks et al 1994, Mohr et al 1997)

- Oxygen radical scavenger (N-acetylcysteine), antibodies against bacterial endotoxin and TNF, IL receptor antagonists and plasma exchange have been unsuccessful (Lowry et al 1994, Opal et al 1998, Spies et al 1994)

- Intensive Insulin therapy reduced the morbidity and mortality in critical illness, and the incidence of CIP (44%) (Van Den Berghe et al 2001)

- Detoxification plasma filtration shown mild improvement (Levy et al 1998)
CIP

**Prognosis:**

- Mortality rate ± 50% due to underlying disease

- Survivors of CIP recover partially in severe cases, and fully in mild or moderate cases over months

- Clinical & EDX evidence of CIP may remain up to 5 years

- 22% may have severe residual deficit at 1 year

- Considerable morbidity and high medical cost.
A 46 Y/O/F with history of bronchial asthma and COPD was admitted to the ICU for status asthmaticus and respiratory failure, requiring intubations and mechanical ventilation. She received vecuronium, IV aminophyline and methylprednisone. A few days after admission her blood gases deteriorated, and she was encephalopathic. Chest x-ray showed left lung pneumonia, and she was treated with penicillin and tobramycin. 10 days after admission her medical and neurological condition improved. Vecuronium and methylprednisolone were discontinued, and she continued to receive oral prednisone. She was noted to have severe weakness in all limbs and could not be weaned off ventilator.

A neurological consultation was requested.
**Examination:** afebrile, normotensive, alert and appears to understand all verbal commands.

- Mild facial paresis, otherwise normal CN’s examination
- Severe weakness of neck flexors and all limbs muscles, more prominent proximally and decreased muscle tone.
- Tendon reflexes depressed throughout
- She appears to have normal sensory perception.

**Laboratory test:** CK 846 IU/L, normal blood count except for WBC 9,680, hematocrit 33.2%, mild hyponatremia, elevated liver enzymes, otherwise normal serum chemistry, ESR 62 mm/h, normal TSH.
Electrodiagnostic Evaluation

- Motor NCS; normal latencies, conduction velocities, F waves, and low-amplitude CMAPs
- Sensory NCS; normal latencies, conduction velocities, and SNAPs
- Needle EMG; diffuse fibrillations & positive waves, early recruitment, numerous polyphasic MUPs of low amplitude and short duration
- RMNS (median & musculocutaneous); no clinically significant CMAP decrement or increment.
### Motor Nerve Conduction:

<table>
<thead>
<tr>
<th>Nerve and Site</th>
<th>Latency</th>
<th>Amplitude</th>
<th>Segment</th>
<th>Latency Difference</th>
<th>Distance</th>
<th>Conduction Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median nerve (left)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wrist</td>
<td>3.9 ms</td>
<td>4.1 mV</td>
<td>APB - wrist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elbow</td>
<td>8.2 ms</td>
<td>4.0 mV</td>
<td>Wrist - elbow</td>
<td>4.3 ms</td>
<td>240 mm</td>
<td>56 m/s</td>
</tr>
<tr>
<td><strong>Ulnar nerve (left)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wrist</td>
<td>2.9 ms</td>
<td>3.5 mV</td>
<td>ADM - wrist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>below elbow</td>
<td>6.9 ms</td>
<td>3.4 mV</td>
<td>Wrist - below elbow</td>
<td>4 ms</td>
<td>230 mm</td>
<td>58 m/s</td>
</tr>
<tr>
<td>above elbow</td>
<td>8.8 ms</td>
<td>3.3 mV</td>
<td>below elbow- above elbow</td>
<td>1.9 ms</td>
<td>105 mm</td>
<td>56 m/s</td>
</tr>
<tr>
<td><strong>Peroneal nerve (left)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ankle</td>
<td>3.8 ms</td>
<td>1.8 mV</td>
<td>EDB - ankle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fibula</td>
<td>10.9 ms</td>
<td>1.6 mV</td>
<td>Ankle - fibula</td>
<td>7.1 ms</td>
<td>320 mm</td>
<td>45 m/s</td>
</tr>
<tr>
<td>knee</td>
<td>13.2 ms</td>
<td>1.6 mV</td>
<td>Fibula - knee</td>
<td>2.3 ms</td>
<td>110 mm</td>
<td>48 m/s</td>
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<tr>
<td><strong>Tibial nerve (left)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ankle</td>
<td>4.4 ms</td>
<td>3.8 mV</td>
<td>AH - ankle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>popliteal fossa</td>
<td>13.1 ms</td>
<td>3.3 mV</td>
<td>Ankle - popliteal fossa</td>
<td>8.7 ms</td>
<td>385 mm</td>
<td>44 m/s</td>
</tr>
</tbody>
</table>
# Sensory Nerve Conduction:

<table>
<thead>
<tr>
<th>Nerve and Site</th>
<th>Segment</th>
<th>Latency Onset</th>
<th>Latency Peak</th>
<th>Amplitude</th>
<th>Distance</th>
<th>Conduction Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Median nerve</td>
<td>wrist</td>
<td>II digit - wrist</td>
<td>2.5 ms</td>
<td>3.4 ms</td>
<td>43 uV</td>
<td>140 mm</td>
</tr>
<tr>
<td>Left Superficial radial</td>
<td>forearm</td>
<td>Hand - forearm</td>
<td>2.4 ms</td>
<td>3.2 ms</td>
<td>40 uV</td>
<td>140 mm</td>
</tr>
<tr>
<td>Left Sural</td>
<td>distal leg</td>
<td>Ankle-distal leg</td>
<td>2.8 ms</td>
<td>3.7 ms</td>
<td>18 uV</td>
<td>120 mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>F- wave</th>
<th>Nerve</th>
<th>M-Latency</th>
<th>F-Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left median at the wrist</td>
<td></td>
<td>4.0 ms</td>
<td>25.5 ms</td>
</tr>
</tbody>
</table>
## Needle EMG Data:

<table>
<thead>
<tr>
<th>Muscle and Side</th>
<th>Insertional activity</th>
<th>Spontaneous Activity</th>
<th>Voluntary MUP’s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fibs</td>
<td>+Waves</td>
</tr>
<tr>
<td>Abductor hallucis</td>
<td>L normal</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Tibialis anterior</td>
<td>L normal</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Gastrocnemius Medial Head</td>
<td>L normal</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Rectus femoris</td>
<td>L normal</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pectinius</td>
<td>L increased</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>First dorsal interossei</td>
<td>L normal</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>L normal</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Brachioradialis</td>
<td>L normal</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Deltoid</td>
<td>L increased</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>L increased</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Initial Differential diagnosis:

- Patient’s primary illness
- Unmasking of an underlying neuromuscular disorder
- Brain/spinal cord disorders; encephalopathy, brainstem stroke or acute spinal cord disorders
- Newly acquired acute peripheral neuropathy; GBS, CIP
- Neuromuscular junction disorders; prolonged use of neuromuscular junction blocked or exacerbation of MG
- Acutely evolving myopathy; toxic, infectious, rhabdomyolysis, CIM
Critical Illness Myopathy (CIM)

**Historical Note**

- Animal model of thick filament myopathy (Karpati et al. 1972)
- Acute Quadriplegic Myopathy (MacFarlan et al. 1977)
- Primary myopathic disease in critically ill patients, recognized during the 1990’s
- Various names have been used;
  "acute quadriplegic myopathy (Hirano 1992), thick filament myopathy (Bolton 1993), necrotizing myopathy of ICU (Ramasy 1993), acute myopathy of intensive care (Lacomis 1996), critical care myopathy (Faragher 1996), acute illness myopathy (Ruff 1996)"
- The term CIM is now widely used (Latronico et al. 1996)
CIM

- Rapidly evolving myopathy in critically ill patients
- Should have started after the onset of critical illness
- Preexisting primary myopathy has been excluded
- Occur independently or in association with CIP
CIM

May develop in patients:

- Have been in the ICU for > 1 week
- On high doses IVCS (≥ 1000mg), especially in status asthmaticus (20-44%) or organ transplant patients (7% of liver, lung or heart transplant)
- Received non-depolarizing neuromuscular-blocking agents (vecuronium, pancuronium)
- Have severe illness “sepsis, MG, dialysis…”
- Rarely in SIRS or MODS patients, who were not exposed to IVCS or NMJB agents
- Propofol more likely causes rhabdomyolysis
CIM

Clinical Features:

- Mean age 6th decade
- Rapidly evolving symmetric weakness of limbs (proximal > distal), and neck flexors
- Facial muscles weakness in severe cases.
- Respiratory failure is common (80%)
- Tendon reflexes are often depressed
- Normal or mild distal sensory loss
- Often associated with varied rhabdomyolysis
CIM

- **Laboratory Studies;**
  - Serum CK; elevated or normal
    - High in 1st 2 weeks
    - Normal in all after 2 weeks

- **Electrodiagnostic Studies;**
  - NCV
    - Low CMAP amplitude, and normal nerve conduction
    - Sensory potentials are usually normal, but can be reduced in amplitude
  - NEMG
    - Irritative changes (Fibs & PSWs) occur early
    - Myopathic MUP’s (in some occur late in the course)
    - Inexcitability of muscle membrane to direct stimulus
    - Often normal, or mild non-specific changes
CIM

**Muscle Pathology:**

- Atrophic muscle fibers (type II > type I)
- Thick filaments (Myosin) loss on ATPase stain
- Variation in muscle fibers size
- Varying degrees of necrosis and regeneration
- Other changes occur in subtypes of CIM
  (necrosis in acute necrotizing myopathy of ICU)

  (Showlateral & Engel 1997, Danon et al. 1991, Hirano et al. 1992)
ATPase pH 9.4 stain

ATPase pH 4.3 stain

Myosin loss fibers (arrows): No staining at both pH 9.4 and pH 4.3
Normal myofibrillar ultrastructure

Critical Illness Myopathy

Thick filament loss with relative preservation of thin filaments & Z-lines
Pathophysiology:

- Animal model of myosin-deficient myopathy
- IVCS in conjunction with NMBA induce myosin-loss myopathy
- Enhanced expression of ubiquitin and calpain (upregulation of the proteolytic and apoptotic system)
- Unexcitable muscle fiber membrane 2nd to increased inactivation of the voltage dependent Na+ channels
- Protracted immobility and high stress catabolic state
- The role of SIRS or MODS in CIM is unclear

Acute Necrotizing Myopathy of Intensive Care

- Severe acute myopathy and rhabdomyolysis induced by; sepsis, severe infections, compartment syndrome or chemical insult
- Muscle swelling and myalgias are common
- Serum CK markedly elevated
- Myoglobulinuria is often present
- EDX’s suggest severe myopathy
- Muscle biopsy; widespread necrosis of muscle fibers
- Recovery may not occur in severe cases
H & E stain

Necrotic muscle fiber, Early

Esterase stain

Necrotic muscle fiber, Late
Propofol Induced Rhabdomyolysis in the ICU

- Increased use in the neuro-ICU where sedation is required
- May cause rhabdomyolysis, especially in the setting of status epilepticus and/or renal failure
- The pathogenesis is uncertain
- Other adverse events: seizures, cardiac toxicity, metabolic acidosis, anaphylaxis, movement disorder, hypotension ...
Cachectic Myopathy

- Vague and poorly described entity
- Painless muscle weakness and wasting
- Usually seen in chronic conditions; cancer, severe CHF, severe COPD, advanced HIV, starvation and malnutrition
- May occur as a complication of critical illness
- Animal models suggest may be induced by cachectin or IL-1
- Muscle biopsy shows only type II muscle atrophy
- EDX’s and serum CK are normal
Type II muscle fibers atrophy
ATPase pH 9.4 stain

ATPase 4.3 stain
CIM

**Prognosis:**

- Full recovery in most once steroids tapered (weeks to months), mean time for ambulation is 8 weeks
- Relatively rapid recovery in those with normal muscle biopsy
- Severe necrotizing myopathy may have a poor prognosis
- Rhabdomyolysis and cachectic myopathy has better prognosis
- ICU mean time for liver transplant with CIM is 49 ± 36 days, versus 14 ± 14 days for those without CIM (Campellone et al 1998)
- High mortality from associated disorders (30% to 50%)
CIM

Management:

- Muscle biopsy is rarely needed
- There is no specific treatment for CIM, prevention is ideal
- Corticosteroids and NMJB agents or Propofol should be tapered off, discontinued or used in lowest possible dose
- Serial CK measurements during high-dose corticosteroids
- Aggressive treatment of underlying illness, metabolic disorders and an adequate nutritional intake
- Monitoring respiratory functions and early tracheotomy
- DVT prophylaxis (heparin, enoxaparin, pneumatic stockings)
- Physiotherapy, rehabilitation program and orthoses
- In rhabdomyolysis IV hydration with alkaline diuresis
Prolonged Neuromuscular Junction Blockade (PNMJB)

- Rare, and sepsis by itself does not cause PNMJB
- Usually in the setting of renal failure patients, who received non-depolarizing blocking agents (vecuronium, pancuronium)
- Concurrent corticosteroids & aminoglycosides may contribute
- Female gender, acidosis & hypermagnesemia are risk factors
- Flaccid generalized weakness, failure to wean and areflexia
- Cranial muscles usually affected
- EOM’s involvement is frequent, and suggests PNMJB
- Repetitive motor nerve trains is diagnostically helpful
- Some patients has superimposed CIM or CIP
Pathophysiologically:

- Prolonged circulating drug metabolites causing functional denervation
- Direct effects of NMBAs, steroids and sepsis on muscle
- Some patients have features of terminal motor axonopathy, myopathy, and myosin loss on EDX’s and muscle biopsy (Danon et al. 1991)
Management:

- Self-limited and recover over hours to days
- More prolonged weakness suggest an associated CIM, CIP or motor axonopathy.
- Avoidance of continuous infusions or frequent NMBAs boluses, and steroids should be avoided
- Neostigmine or edrophonium may transiently reverse the weakness
- Haemodialysis results in no significant improvement “only partially reduces the NMBAs metabolites serum level”
Thank you for your attention