Practical Approach to ICU acquired weakness

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Case 1: The clinical dilemma

- M70Y, acute intestinal ischemia- resection
- Repeated infections, transient renal failure and clouded consciousness
- ICU and respirator support for about 4 weeks
- Infection cleared and consciousness regained
- Unable to be weaned off
- Quadriplegic & areflexic

What is it? Definition & causes

ICUAW: Definition of topic

- Generalized (usually severe) weakness (w/o respiratory insufficiency) that develops in the ICU and is not the cause of hospitalization
- Neuromuscular disorders predominant the list of causes, but CNS disorders should not be forgotten
- The term ICU acquired weakness (ICUAW) is now used to include all causes

What are the clinical features of ICUAW?

ICUAW: Clinical presentations

- Severe weakness despite return of sensorium (w/o confusion), apaert fro CNS conditions
- Inability to wean from mechanical ventilation
- Flaccid paralysis with loss of reflexes
- Peripheral sensory loss (hard to detect)
  - Edema
  - Cooperation
- Usually no cranial nerve involvement
- Focal weakness can also be found

How common is ICUAW?

ICUAW epidemiology: a common problem

- Overall incidence of weakness: 25-33%
- Patients in ICU > 7 days: 49-77%
- ICU patients with ARDS: about 60%
- Status asthmaticus in ICU: about 1/3
- Post liver transplant: 7%
- MOF + SIRS: almost all

What is the general DD for ICUAW?

DD for ICUAW

- **Brain disorders**
- **Spinal cord & anterior horn disorders**
- **Neuropathies**
- **NMJ disorders**
- **Myopathies**
- **General ‘weakening’ medical conditions (e.g. electrolyte disturbance)**

Patient 1: more data

- 70Y, acute intestinal ischemia- resection
- Repeated infections, transient renal failure- ICU and respirator
- About 1 month later infection cleared and consciousness regained (but still confused)
- Unable to be weaned off- diaphragmatic paralysis
- Quadriplegic & areflexic
- No NCV slowing, small CAMP & SNAP
- Abundant fibrillation with loss of units

What is your diagnosis?

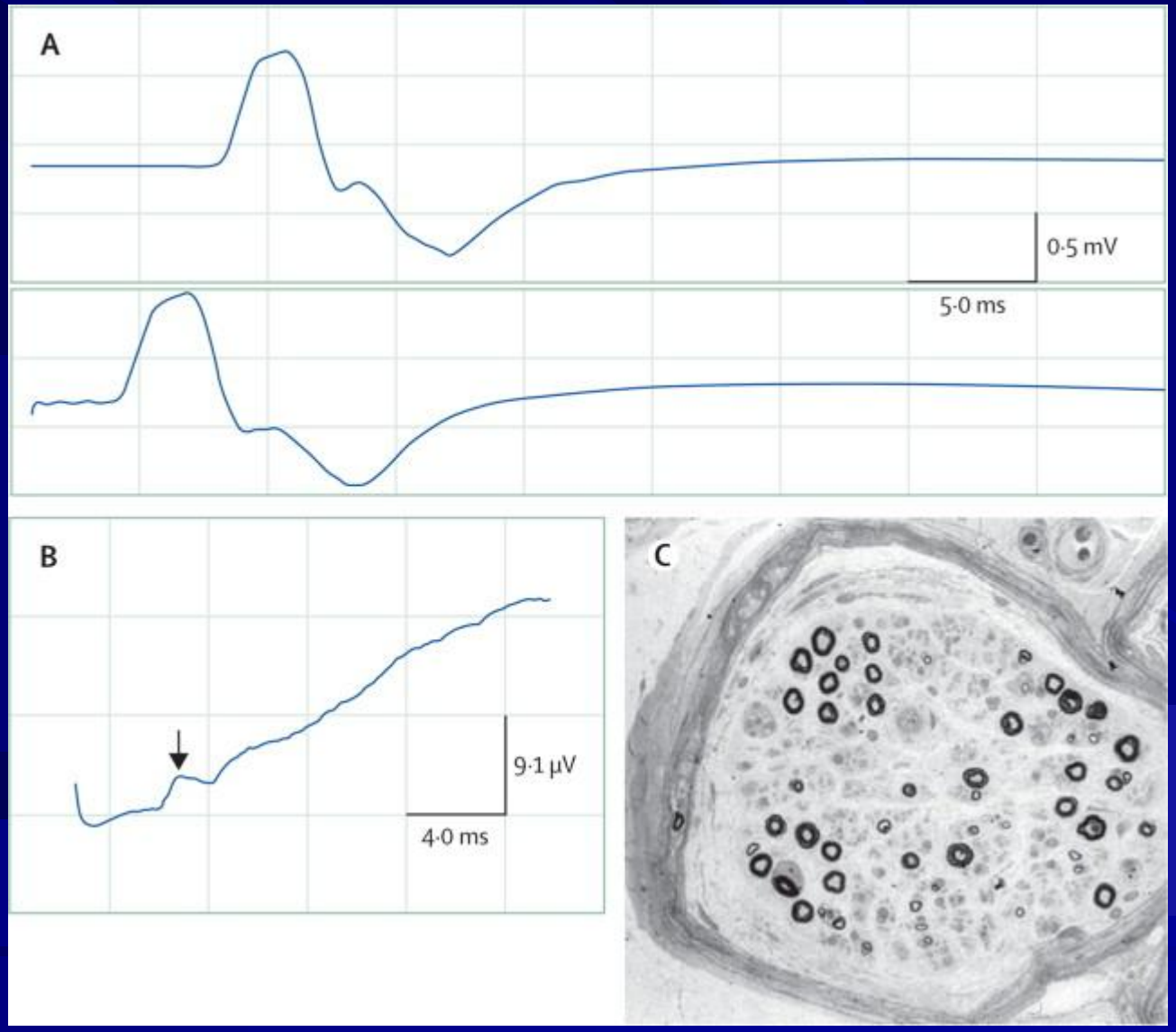
Critical Illness Neuropathy (CIP): all 4 diagnostic criteria needed (Latronico & Bolton Lancet Neurol 2011)

- Multiorgan dysfunction
- Limb weakness and/or difficult weaning from respirator (other causes excluded)
- Axonal motor and sensory neuropathy on NCV
- No decrement on RNS

CIP- Features

- Flaccid severe weakness
- Complete loss of tendon reflexes
- Reduced spino thalamic sensory modalities (can you be sure?)
- NCV- distal axonopathy (DL prolonged, low CMAP in 2 nerves, loss of SNAPs, near normal motor CV)
- EMG- active denervation (fibrillations mainly)

This is what patient 1 showed


A
0·5 mV
5·0 ms
B
9·1 µV
4·0 ms
C

Patient 2 (very rare)

FEMALE, 54 yrs
In ICU for Pulmonary embolism
Streptokinase $140x10^3$ IA
Steady recovery, but 11 days later rapid quadriparesis
Reflexes disappeared, no sensory impairment

Can you think of a diagnosis?

Patient 2- case report

Dg: **Streptokinase-induced GBS**

Mechanism: Immune response triggered by streptokinase (Med J Aus, 1995)

Thanks to F. Mastaglia for case description

Is GBS developing in ICU a common disorder?

GBS appearing in ICU

- Rare!
- Immune response to medication (streptokinase, interferon α)
- Post mycoplasma infection
- Post epidural?

Case 3

- It is April in Jerusalem
- A M75Y comes to ER with fever & confusion and clouded consciousness
- LP: 70 lymphocytes, mild protein elevation
- Very abnormal (“encephalopathic”) EEG
- 2 weeks later recovering in intermediate care unit, but quadriplegia is found

What is it?

West Nile fever and “GBS”- or polio-like disease

- Usual presentation: meningo-enecephalitis
- When recovering or during disease, quadriparesis may be found (“GBS”-AMAN)
- Segmental, isolated weakness is common
- NCV- axonal neuropathy (generalized)
- EMG- polio-like disease (focal active denervation)
- PNS disease- estimated 20% of hospitalized, severe West Nile viral infections

ICUAW- Neuropathic causes

- Critical illness polyneuropathy (CIP)
- GBS & paraneoplastic radiculitis
- Toxic
- Porphyria
- Infective radiculities (e.g CMV)
- Malignant infiltration (lymphoma)
- vasculitis

Case 4

- Asthmatic F45Y went into respiratory crisis
- After 2 weeks in ICU on respirator & anesthetized, given high dose steroids and NMBA- weaning fails
- The patient is also very weak, which started after one week and continued

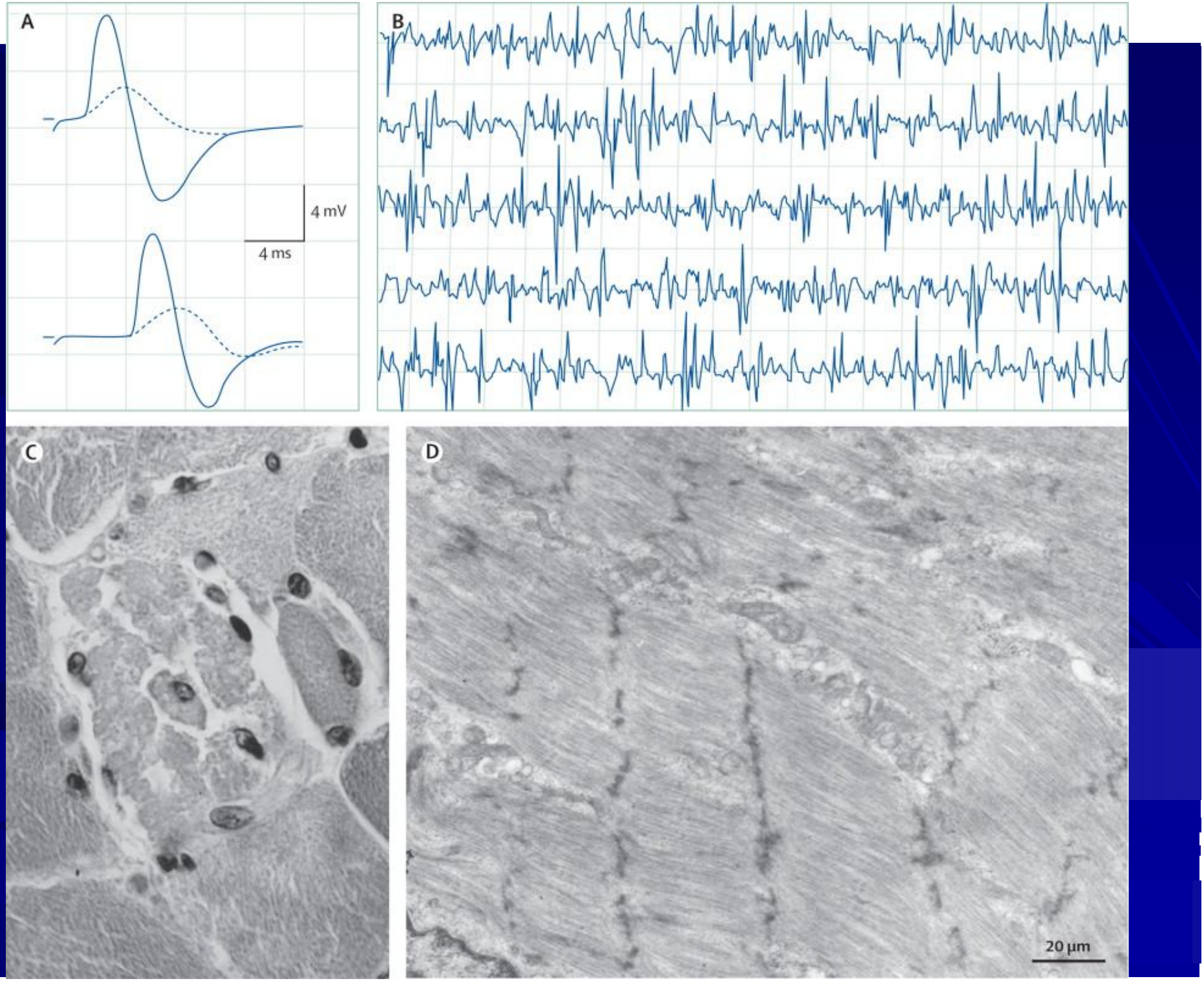
Is this “Acute Steroid Myopathy”?

Critical Illness Myopathy (all 7 diagnostic criteria needed?)

- Multiorgan dysfunction (ARDS enough?)
- Limb weakness and/or difficult weaning from respirator (other causes excluded)
- CMAP<80% of low normal in 2 nerves
- SNAP>80% of low normal
- Myopathic EMG in cooperative patient or reduced muscle excitability in non collaborative
- No decremental response on RNS
- Myosin loss or necrosis on biopsy

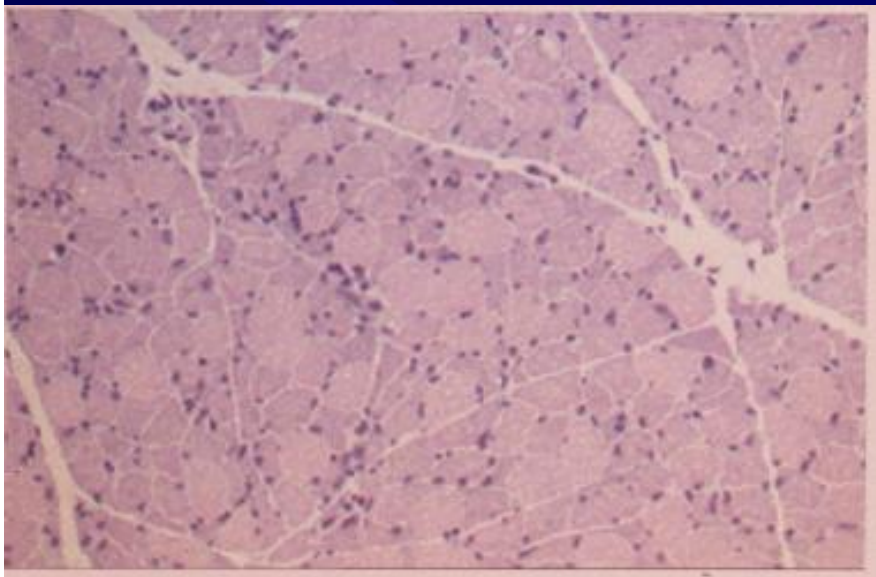
CIM- Features

- Flaccid quadriplegia, more proximal?
- Combined MRC < 48/60 (problematic)
- Neck flexors are involved
- Reduced/lost reflexes, no sensory deficit
- CPK- elevated in 76%
  - Median peak 1575 iu/L
- Normal sensory CV (technical difficulties)
- Myopathic EMG (difficult)
- Unexcitable muscle on direct stimulation!

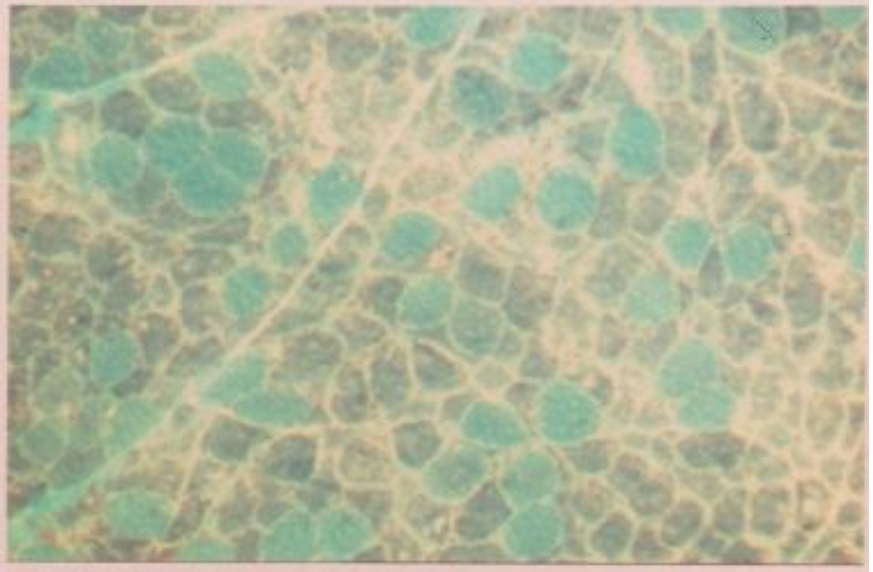

A
4 mV
4 ms
B
C
D
20 µm

Biopsy findings in ICU myopathy

- CIM: fiber atrophy (>type II), nonspecific changes, isolated necrotic fibers (cachectic)
- Necrotizing type- pan fascicular necrosis
- Thick filament myopathy
  - Focal loss of ATP'ase stain
  - Selective loss of heavy myosin filaments: A-band loss with preservation of I-bands and Z-disc

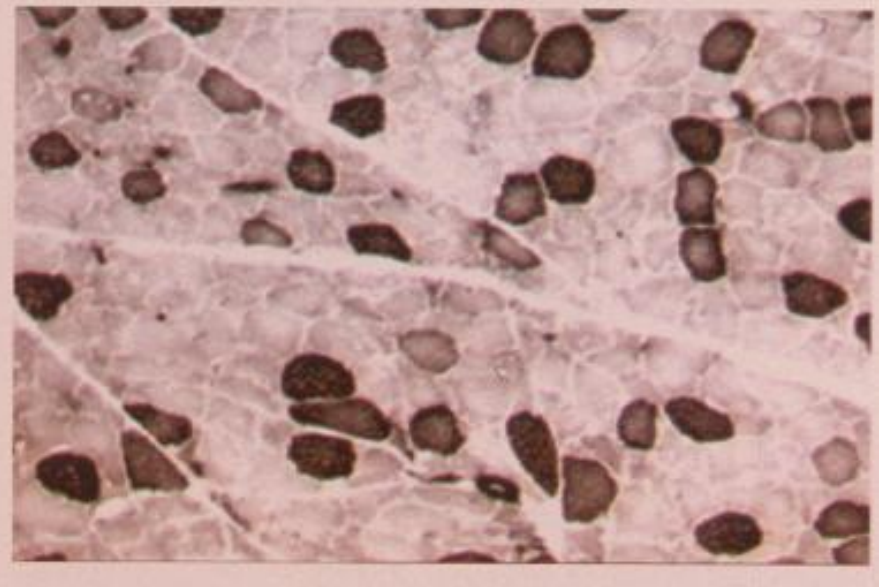


H&E

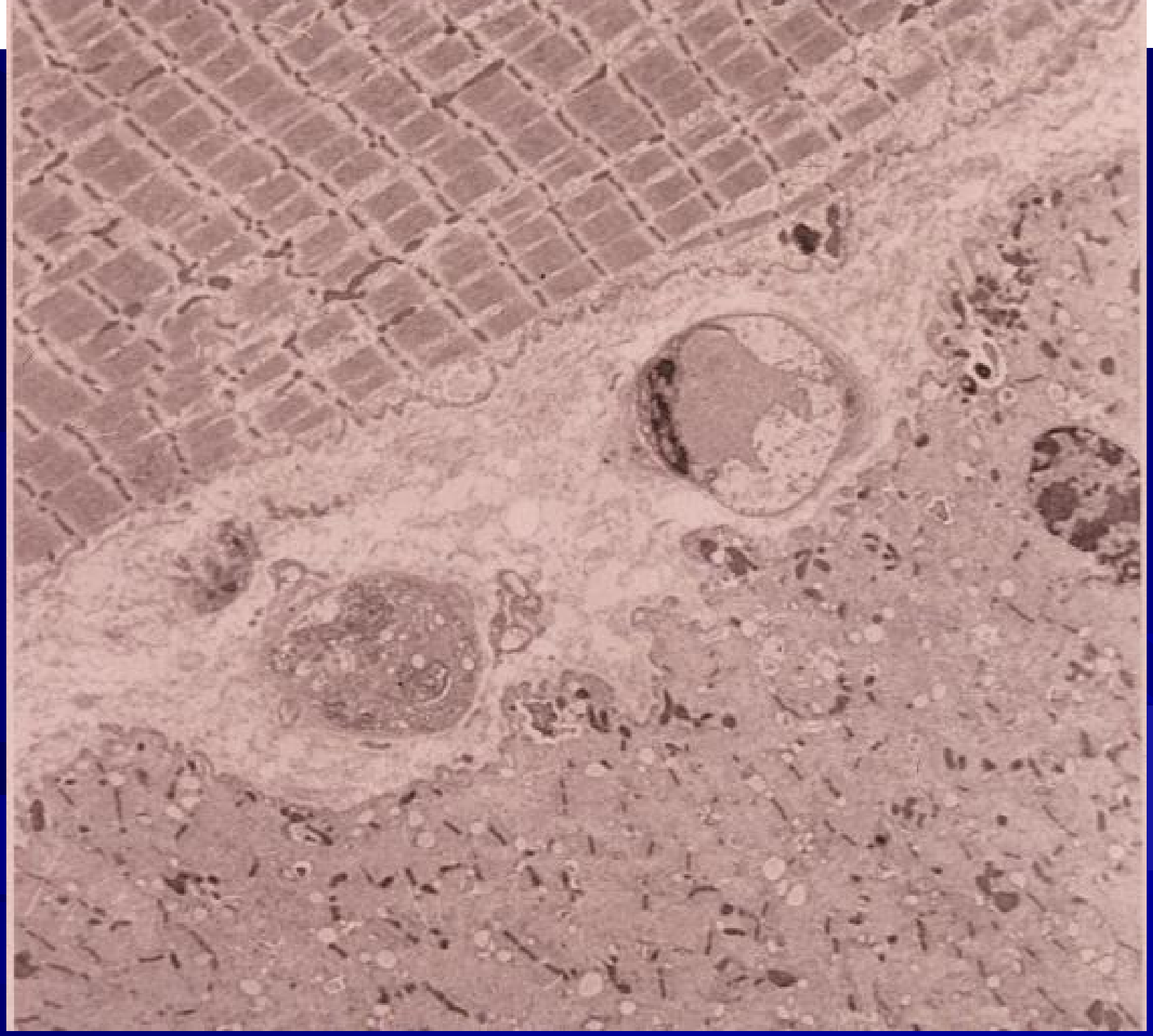


Trichrome

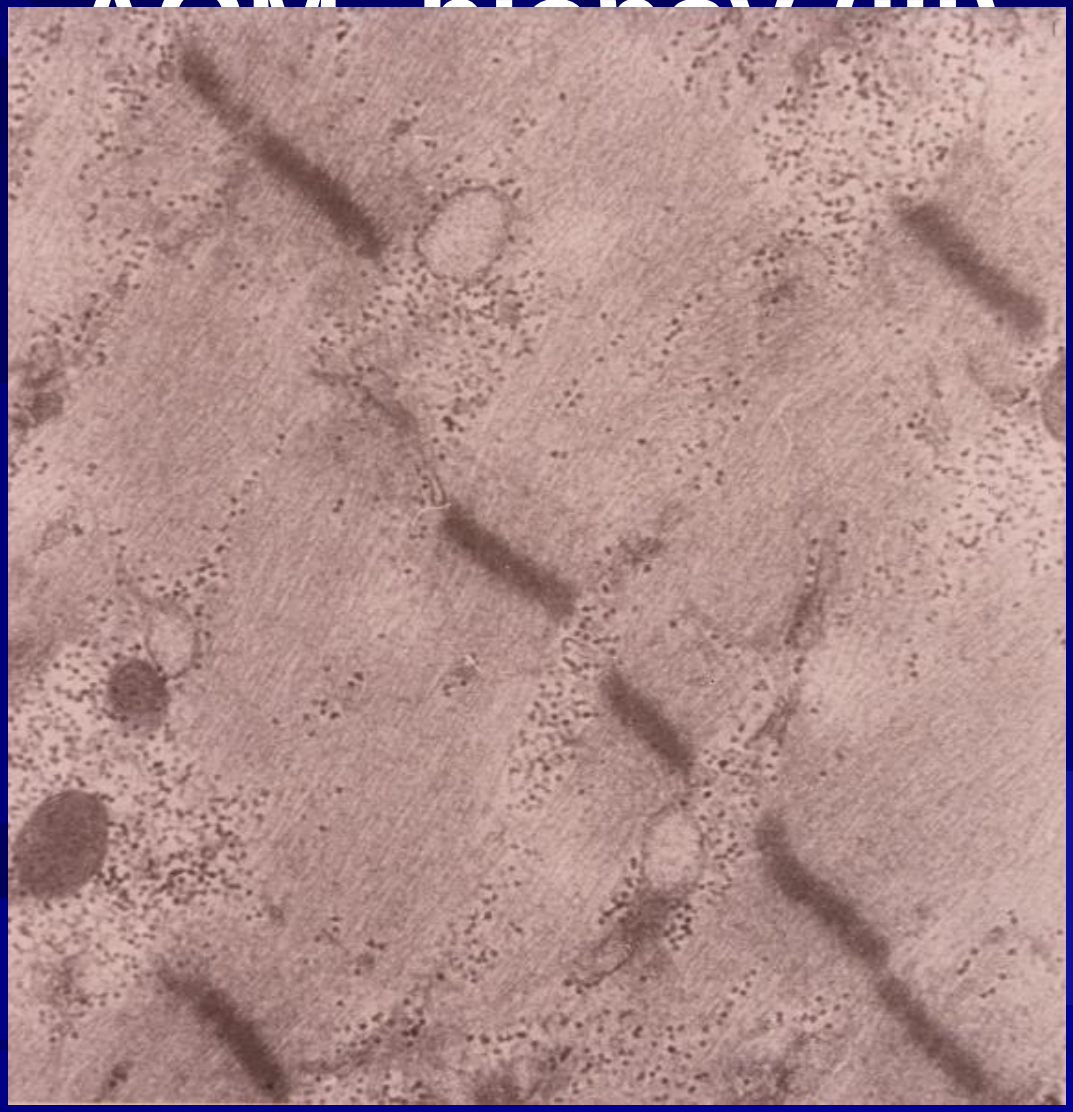
Patient 2



ATPase 9.4



AOM - biopsy (iii)



Case 5 (rare)

- 80Y physician
- Self reported as “always healthy” and active but not very ‘sportive’
- Viral pneumonia and high fever leading to respiratory difficulties (ARDS)
- Third day CK=60,000 and marked weakness

Dg: ?

Rhabdomyolysis in ICU

- Prolonged lying down (should not occur)
- Medications
- Metabolic predilection
  - Muscle: CPT deficiency + fever (More history of patient 5: life long exercise intolerance)
  - Muscle: Raynodine receptor defect or malignant hyperthermia (MH)

ICUAW- Myopathic causes

- Critical illness myopathy (CIM)
- Drug induced rhabdomyolysis
- Myositis (pyomyositis)
- Unmasking of metabolic myopathies
- Propofol syndrome
- Severe cachexia

Case 6

- M47Y marked over weight
- Bariatric surgery complicated by pulmonary embolism
- ICU for 1 week with preventive measures for venous thrombosis
- After 1 week right sided drop foot

What is the cause of this focal ICUAW?

ICU acquired focal weakness

- Post West Nile infection (polio-like)
- Hopkins syndrome (post asthmatic crisis)
- Pressure palsy (case 6)
- Compartment syndrome-device induced
- Phrenic neuropathy (idiopathic)
- Needle damage

Basic information about CIP/CIM

- CIM and CIP frequently occur together
- Risk factors
- Possible mechanisms
- Prevention
- Prognosis

ICUAW (CIP and CIM) Independent risk factors

- Females
- Duration of ICU stay and severity of illness
- Length of MOF
- CNS failure (encephalopathy)
- Duration of vasopressor support
- Renal failure
- Hyperosmolarity
- Hyperglycemia
- Low serum albumin
- Steroids? (> 1gr) but not NMBA

Mechanism of ICUAW

- Acquired channelopathy:
  - Increased inactivation of sodium channels- do they have special mutations?
- Over expression of proteases
- Steroid induced apoptosis
- Bioenergetic failure: mitochondrial toxicity by oxygen reactive species
- Sepsis reduces force generation- muscle protein degradation
- Impaired tissue microcirculation

Prevention of ICU weakness

- Reduce use of neuromuscular blockers & mechanical ventilation
- Daily wakening if possible + physiotherapy
- Mobility
- Strict glycemic control (iv insulin)- 35-50% risk reduction
- Unproven:
  - Increase protein administration (glutamine?)
  - Antioxidants (glutathione, acetylcysteine)?
  - Androgenic steroids (oxandrolone)??
  - Chronic electrical stimulation

Acute ICU weakness- Prognosis of CIP/CIM

- In 25% of patients ICUAW contributes to death
- 68% of survivors without residuae (or mild only)
- Some of survivors with severe seuelae (up to 28%)
- Better outcome of CIM compared to CIP
- Typical residual findings (mild):
  - Muscle wasting with weakness
  - Areflexia
  - Sensory loss
  - Painful sensory neuropathy
  - Foot drop

What about other causes of ICUAW?

Case 7 (rare)

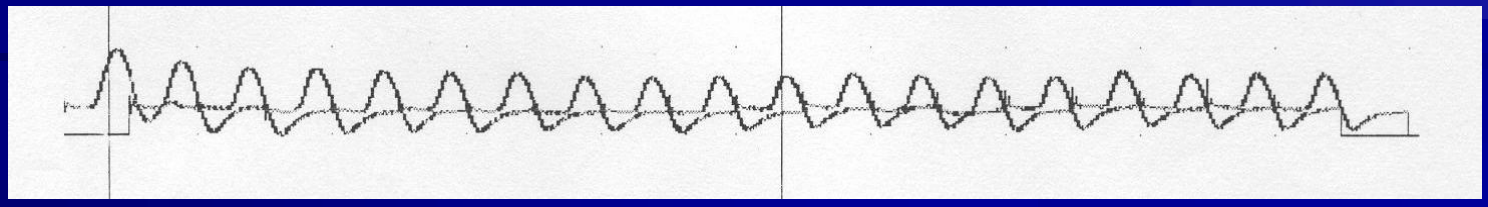
- 24Y, first pregnancy
- Very high blood pressure when delivery started-eclampsia
- Cesarean section followed by hemorrhage and re-operation
- After stabilization in ICU: no muscle movement even with painful stimuli & complete ophthalmoplegia, areflexia

Is it brain damage? Other possibilities?

ICUAW- NMJ causes

- Unmasking of myasthenia
- Prolonged neuromuscular blockade
- Hypermagnesemia (iatrogenic)

Repetitive nerve stimulation in patient 2 (after load of Ca):



Patient 8 (very rare)

- Female 82 years
- Bulbar myasthenia; AChR antibody 2.2 U/L; pyridostigmine responsive
- Conclusion: late onset myasthenia gravis

- **Hip replacement revision-slow recovery, placed in ICU for observation**
- **1 week later myasthenic crisis and respiratory arrest**

Any guess about the cause?

Drug-induced NMJ block (predilection)

- In known MG and LEMS patients
- Unmasking of unknown myasthenia
- In metabolically impaired NMJ transmission (e.g. hypocalcemia)
- Pseudocholine esterase deficiency
- Prolonged neuromuscular blockade
  - >10 days of NMBA
  - 14 days of recovery

Drug-induced NMJ block (drugs in ICU)

- Antibiotics (aminoglycosides!)-infection
  - Patient 8 had gentamycin coated artificial hip
- Antiarrhytmics (local anesthetic features)
- Beta blockers
- Curariform agents- prolonged action

Longer list in Curr Opin Neurol 2009

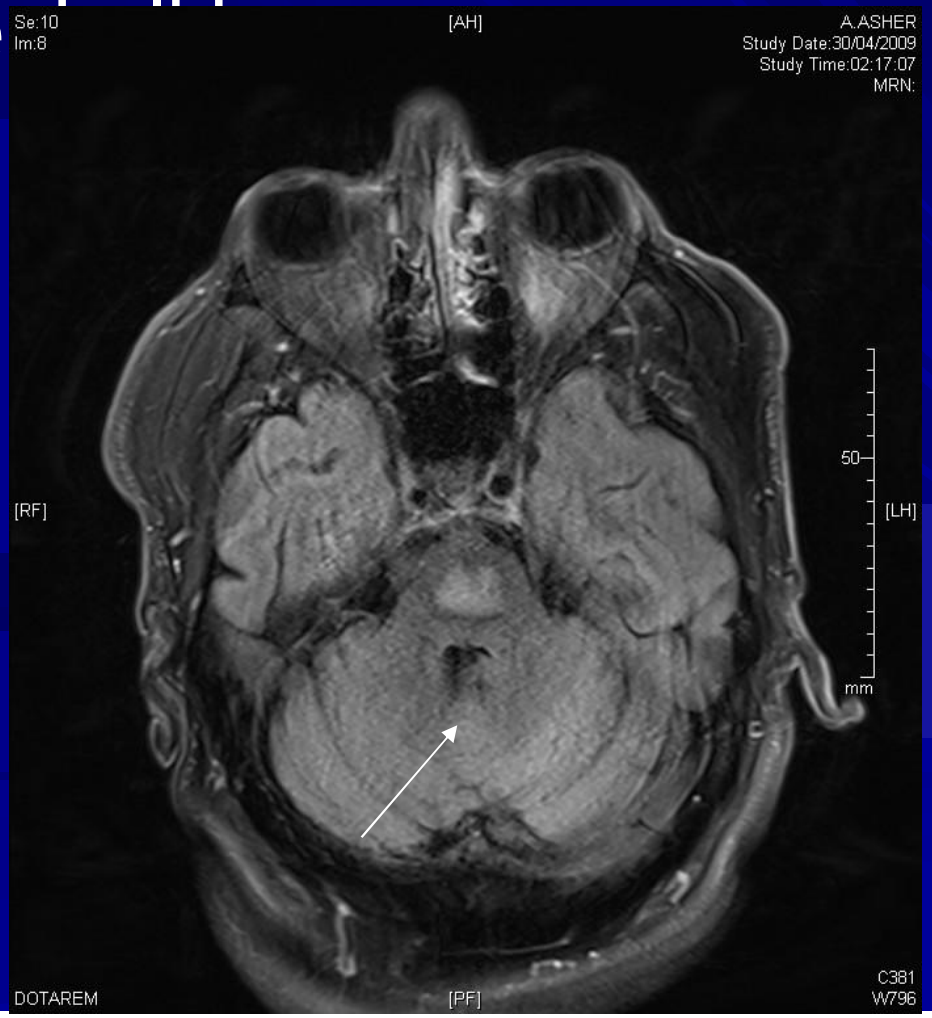
Case 9 (not so rare)

- 55 Y male
- Liver transplant after long time liver failure
- Post surgical recovery slow with many metabolic complication
- Inability to return to consciousness with flaccid quadriplegia (no pyramidal signs)
- No apparent eye movements

Dg: ? (Important to recognize)

ICUAW- Brain causes

- Brainstem infarct
- Brainstem ence
- Central pontine transplant)



Case 10

- M19Y drowned in a pool & resuscitated
- At admission to ICU: stupor and agitation with mild weakness. Medicated.
- Day 3: flaccid quadriplegia, coma, high fever (41.5 degrees!), tachycardia (exterme), low BP, normal CK
- Emergency treatment improved in hours

What was it? (think drugs)

Case 10: another unusual CNS cause of ICUAW

- Patient given haloperidol for agitation (single injection IM)
- Rapidly improved with Bromocriptine (20 mg PZ)

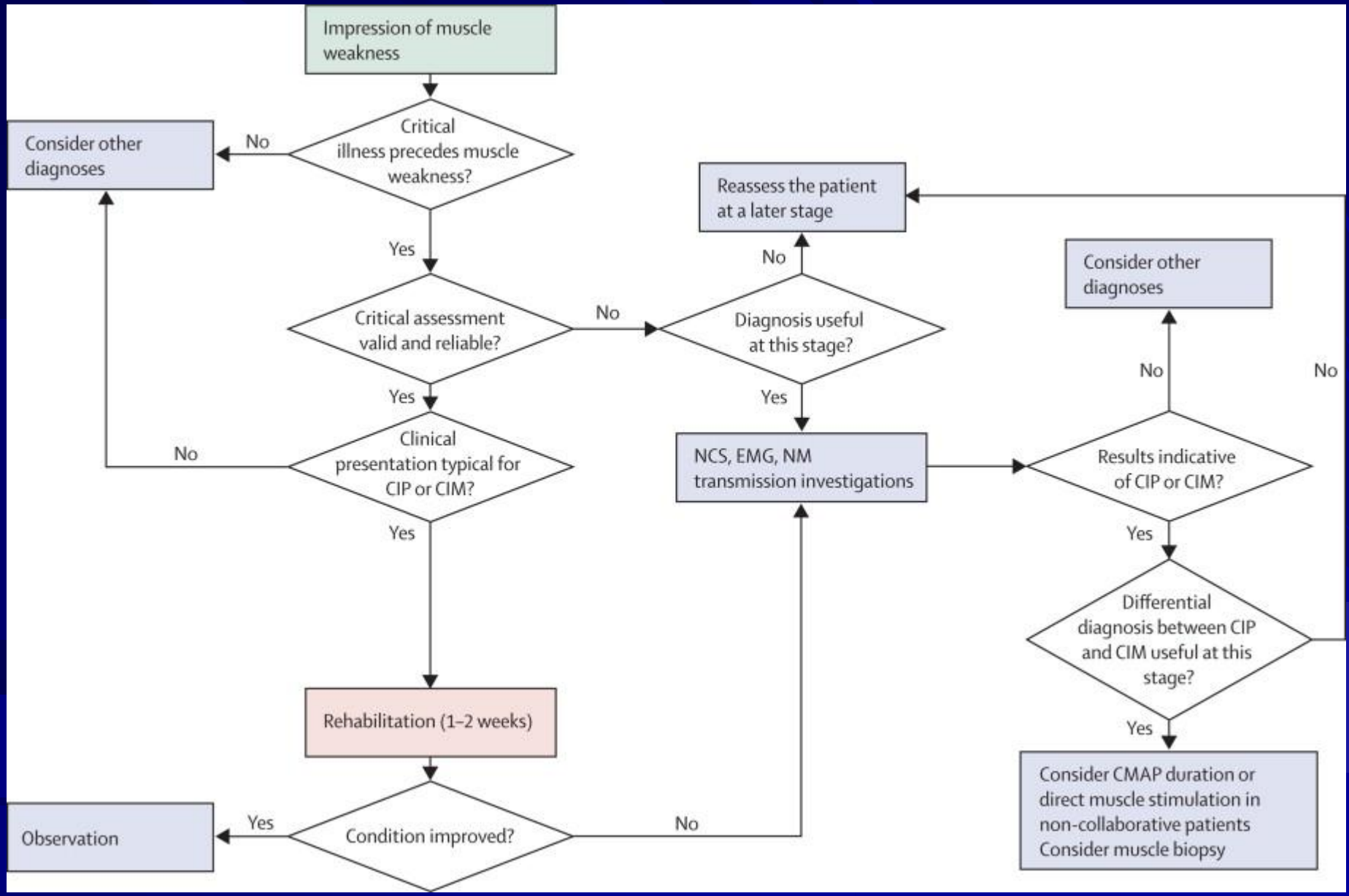
Neuroleptic Malignant Syndrome

ICUAW- spinal cord causes

- Ant spinal art occlusion hypercoaguble state)
- Immune mediated transverse myelitis
- Infective myelitis (West Nile, Polio, CMV)
- Postinfective myelitis (Zoster, West Nile)
- Spinal cord compression (abscess, tumor)

Quadriplegia of ICU (conclusions)

- Many causes- mostly neuromuscular
- ICUAW induced by several combined mechanisms
- Myopathy and neuropathy often co-exist and are similar
- Unpredictable appearance
- Complicate patient outcome
- Research into definitions, prevention and potentials therapies is needed


Impression of muscle weakness
Critical illness precedes muscle weakness?
No
Consider other diagnoses
Yes
Critical assessment valid and reliable?
No
Diagnosis useful at this stage?
No
Reassess the patient at a later stage
Yes
Clinical presentation typical for CIP or CIM?
No
Yes
NCS, EMG, NM transmission investigations
Results indicative of CIP or CIM?
No
Consider other diagnoses
Yes
Differential diagnosis between CIP and CIM useful at this stage?
No
Yes
Consider CMAP duration or direct muscle stimulation in non-collaborative patients
Consider muscle biopsy
Rehabilitation (1–2 weeks)
Condition improved?
Yes
Observation
No

Thank you