New aspects in management of neuromuscular emergencies and intensive care

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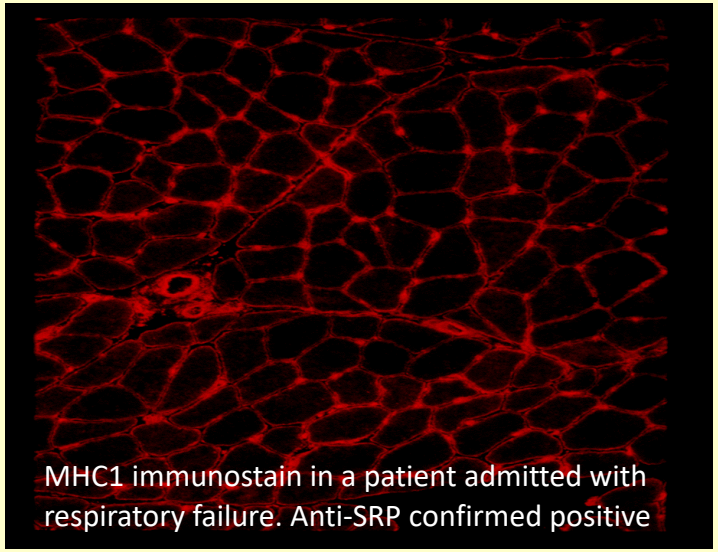
Topics of this presentation

1. The neuromuscular emergency and mechanics of failing respiration
2. Newly acquired neuromuscular disorders in the ICU
   - Guillain Barré Syndrome and AIDP
   - Myasthenic crisis in the ICU
   - Acute muscle disease presenting to the ICU
3. Neuromuscular disease arising in the ICU: “ICU-AW”
4. ICU presentations of pre-existing neuromuscular disease
   - Conditions that are newly diagnosed in the ICU
   - Critical care of advanced chronic muscle disease

1. The patient with a neuromuscular emergency

Neuromuscular emergencies may present with

- rapidly worsening weakness
- respiratory failure and infection
- oropharyngeal weakness and aspiration
- cardiac failure, or cardiac dysrhythmia
- dysautonomia
- acute rhabdomyolysis



MHC1 immunostain in a patient admitted with respiratory failure. Anti-SRP confirmed positive

Initial consideration: is the problem truly new, or is there an underlying chronic neuromuscular condition?

Toxins or neuromuscular depressant drugs must be excluded.

Areflexia, dysautonomia and flaccid tone may suggest a neurogenic disorder; preserved reflexes are more likely in acute myopathy or disorders of the neuromuscular junction.

The pattern of weakness and atrophy may suggest a specific genetic myopathy

The patient with a neuromuscular emergency

Fatiguing weakness with sustained innervation points to the neuromuscular junction and is often overlooked

Respiratory and oropharyngeal muscle assessment have priority for triage to ICU

Respiratory assistance mostly involves endotracheal intubation and positive pressure ventilation; some marginally affected patients could benefit from non-invasive measures

Non-Invasive Ventilation may be the main option when invasive ventilation is not desired

Monitoring on the ward is unreliable and dangerous - better to admit patients to an ICU, even for 24 h

Emergency intubation of a cyanotic patient with hypoxemia or significant hypercapnia generally indicates inadequate monitoring

Bedside Respiratory Monitoring – the "20-30-40 rule"

Parameter	Normal value	Critical values
Forced Vital Capacity	40-70 mL/kg	15-20 mL/kg
Peak Inspiratory Pressure	Male: > -100 cm H^2O Female: > -70 cm H^2O	-30 to - 40 cm H^2O
Peak Expiratory Pressure	Male: >200 cm H^2O Female: >140 cm H^2O	40 cm H^2O
Cough	Male: > 330 L/min Female: > 280L/min	Peak cough flow >160L/min or mouth or PEF >60L/min at tube for extubation
Assisted by Transcutaneous Capnography and overnight oximetry		

Damian & Wijdicks Neuromuscular Dis 2019

2. Newly acquired neuromuscular disorders in the ICU

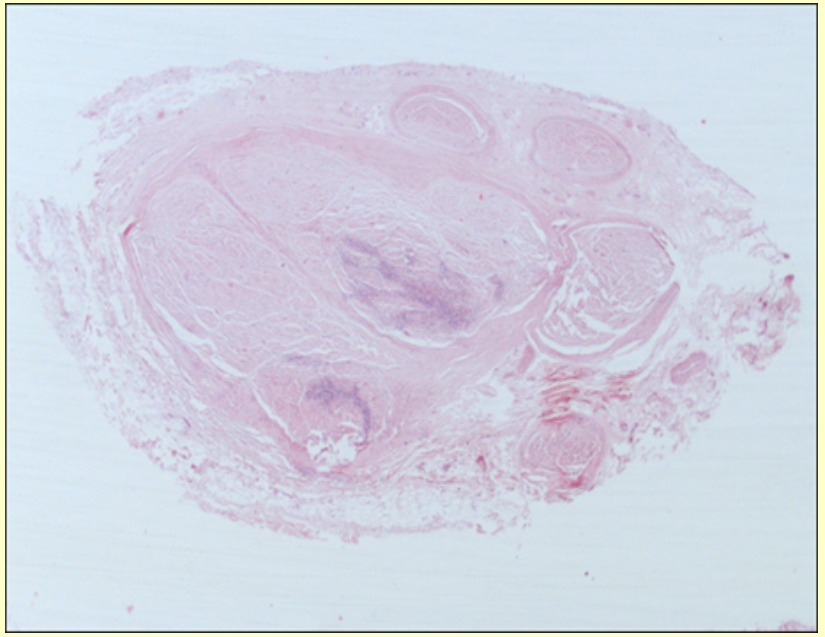
Newly acquired neuromuscular disorders may be admitted to the ICU at presentation or during the early course and include:

- Guillain Barré syndrome, other severe neuropathies and the “acute flaccid paralysis syndrome”
- Myasthenic crisis and other disorders of neuromuscular transmission
- Acute inflammatory or toxic muscle disease

Undiagnosed chronic, often genetic, muscle disease may present to ICU as a seemingly new acquired disorder due to acute decompensation

Guillain Barré syndrome in the ICU

30% of patients require respiratory support. Mortality in the ICU is <10%, but 20% in the acute hospital [Damian et al. 2013]



Dysautonomia occurs in up to 70% of patients in the ICU

Reasons for admission to the ICU are respiratory compromise, oropharyngeal weakness, or severe dysautonomia.

Confounders include:

- Vasculitic, paraneoplastic, infectious and toxic neuropathy
- Neoplastic infiltration or intravascular lymphoma
- Acute flaccid paralysis syndromes with acute anterior horn cell disease (West Nile Virus, Polio)
- Viral acute myelitis “plus”syndromes predominantly caused by Enterovirus D68/E71, Zika, Hepatitis E, are increasing in some geographical regions.

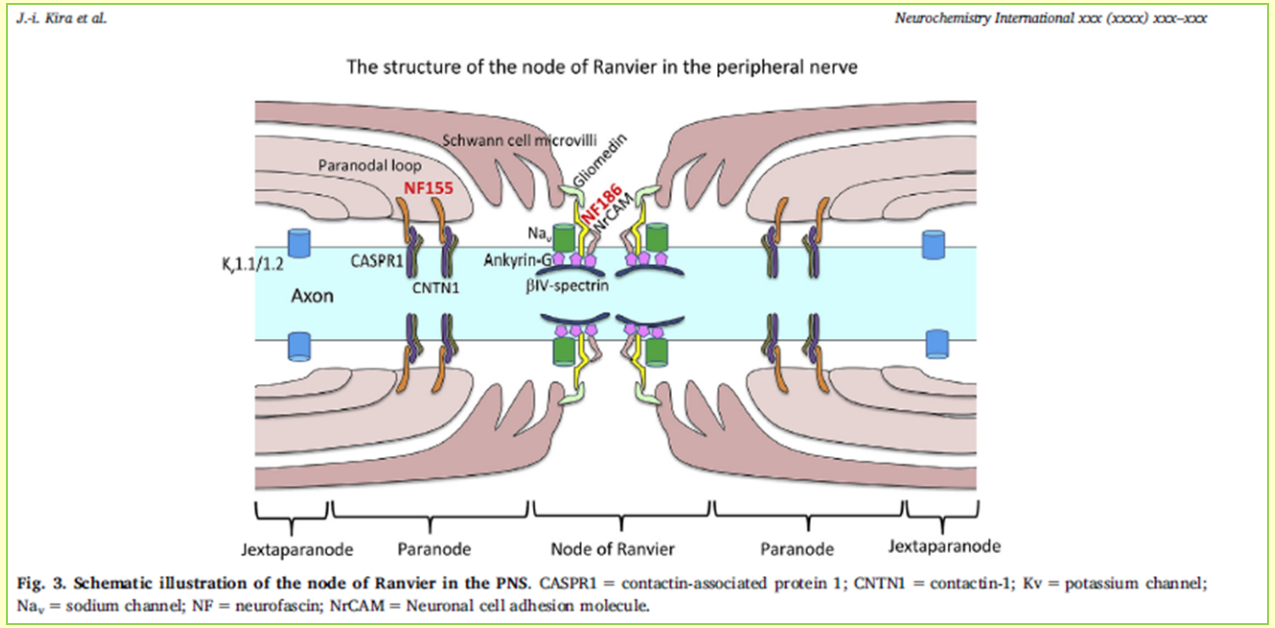
Guillain Barré syndrome in the ICU

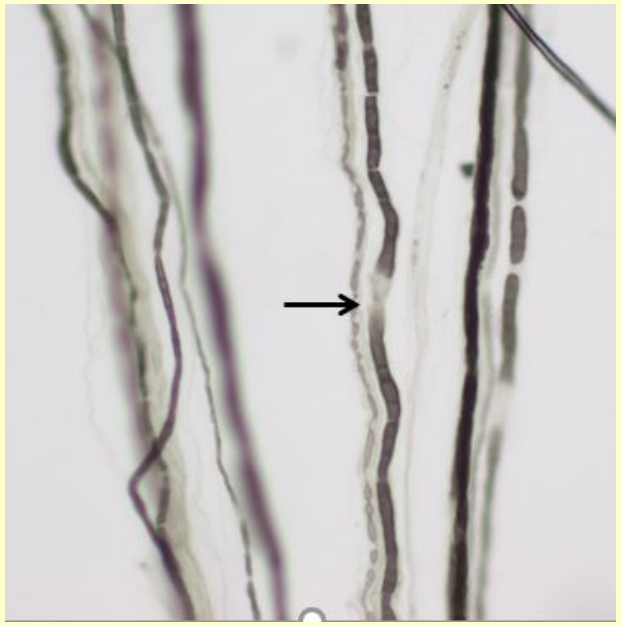
Once mechanically ventilated, there is no benefit from deferring tracheotomy more than a week

Patients whose IgG fails to rise after the initial course of IVIg might benefit from repeat IVIg treatment

The most severely affected patients ina locked in state are mostly seen in an axonal variant. Recovery is very protracted: more than 6 months of ventilatory support, and often incomplete.

Antibody tests may reveal a subtype of GBS or an overlap between GBS and CIDP





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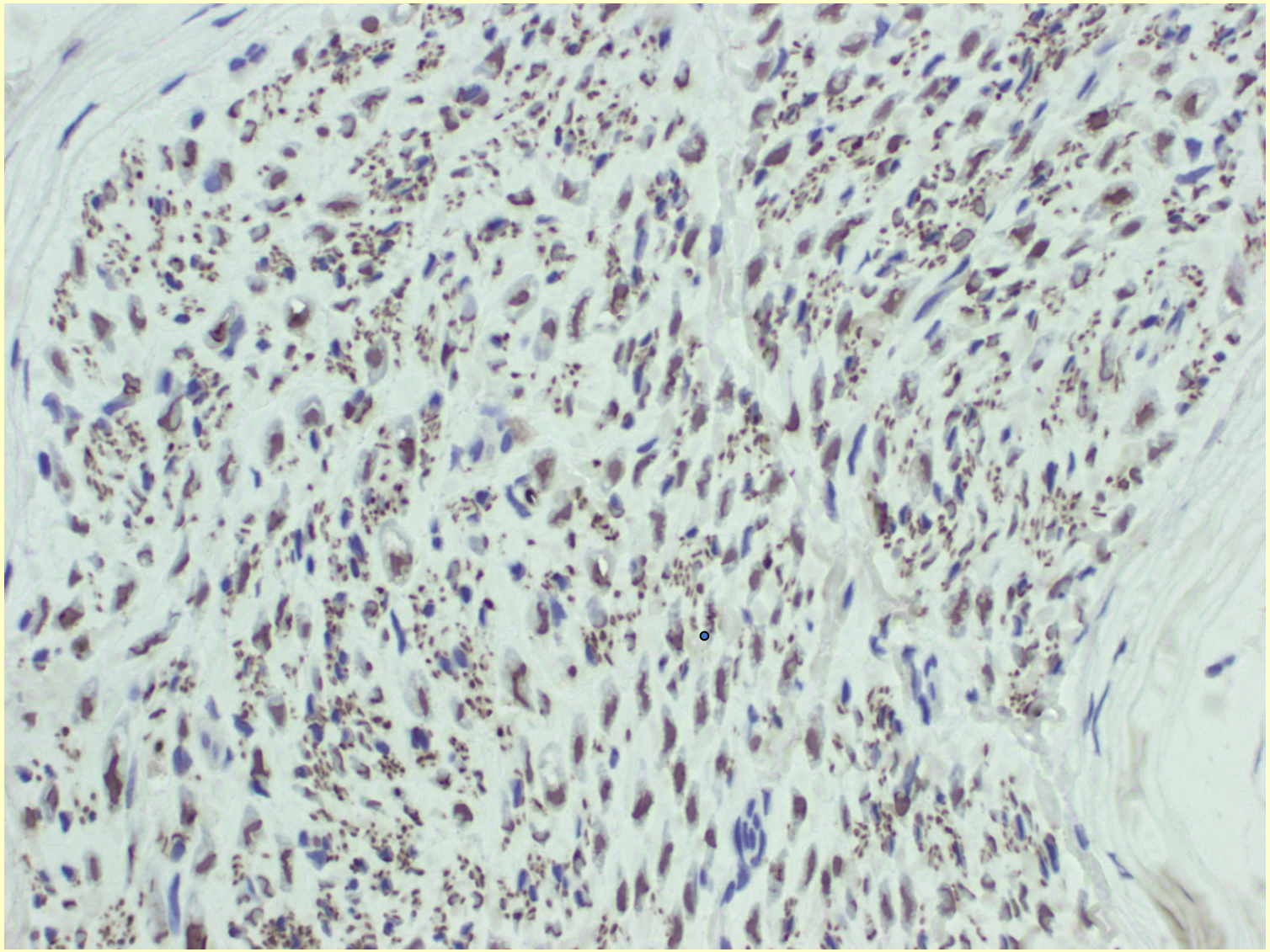

NFP x40

Rt sural nerve, fascicle #2: patchy loss of small axons?

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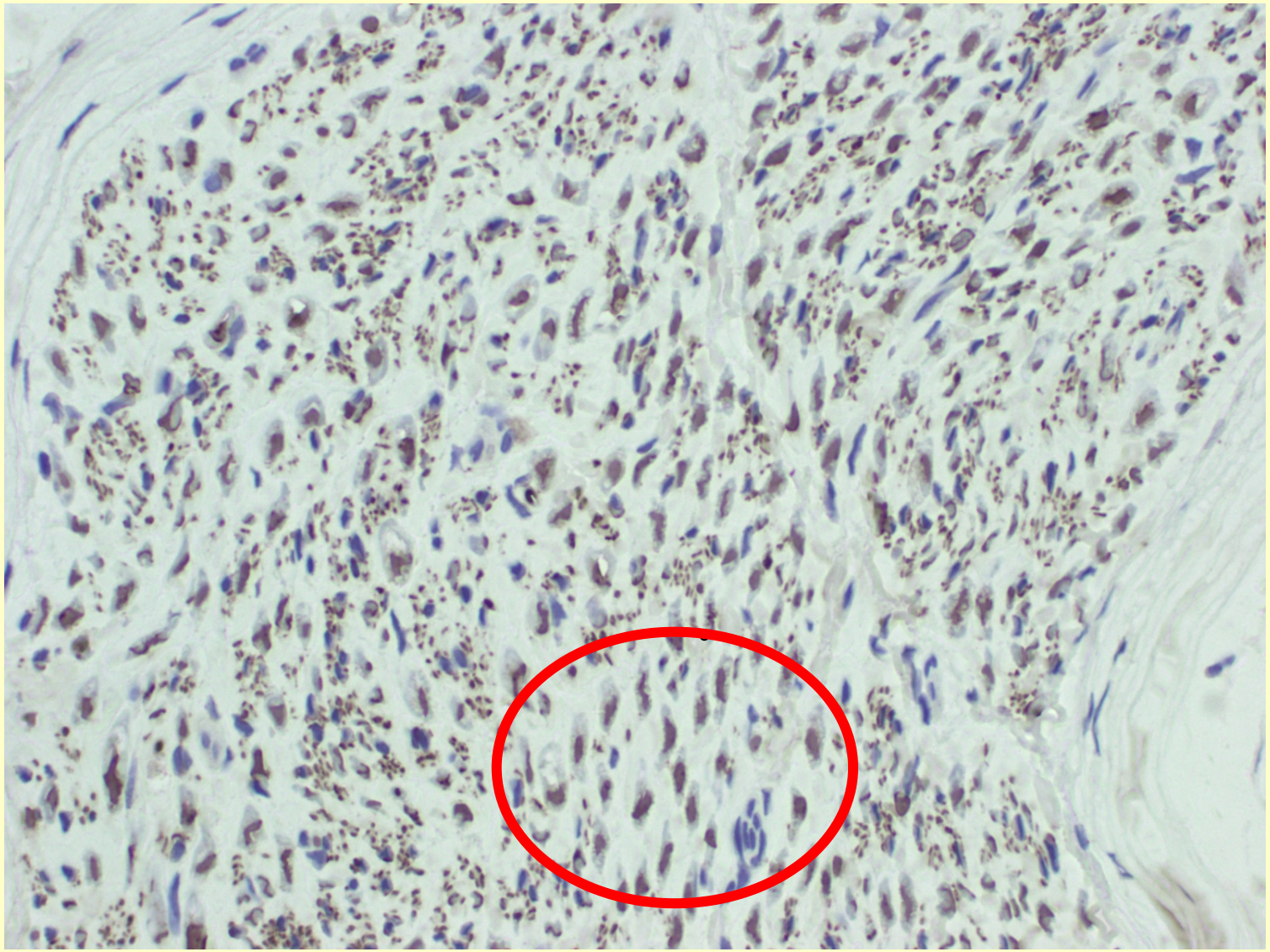


NFP x40

Rt sural nerve, fascicle #2: patchy loss of small axons?

Guillain Barré syndrome in the ICU

Autonomic dysfunction includes orthostatic hypotension, diabetes insipidus, sensitivity to drugs, and cardiac dysrhythmia.

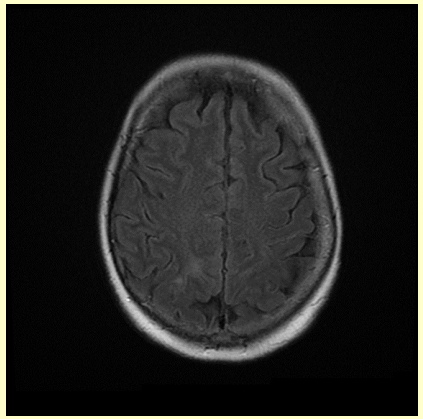
Hypertension and persistent tachycardia affect over 50% of ventilated patients; life-threatening complications may occur in up to 20%.

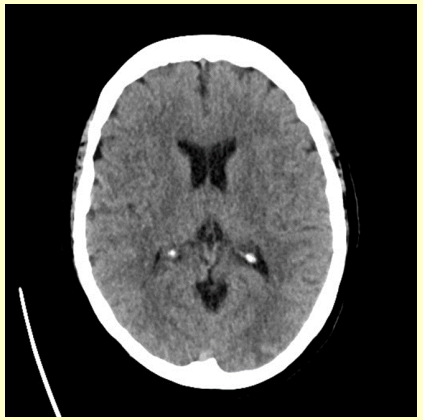
Vagal spells with bronchorrhea, bradycardia and hypotension may be triggered by invasive procedures and cholinergic drugs

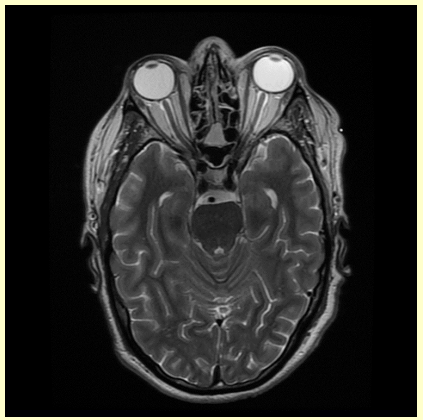
SIADH may cause hyponatremia; diabetes insipidus can also occur

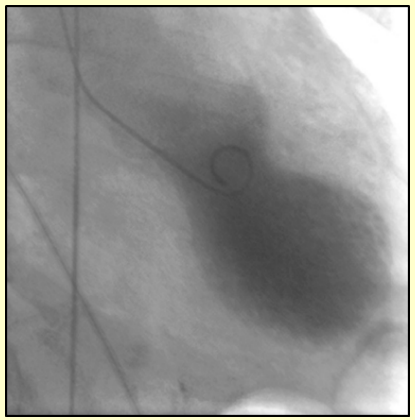
Posterior reversible encephalopathy syndrome (PRES) may occur as a central autonomic disturbance.

Neurogenic (Takotsubo) cardiomyopathy may be related to autonomic dysfunction.









Myasthenia gravis (MG) in the ICU

Immune attack against nicotinic acetylycholine receptors (AchR) and related proteins (Muscle- Specific Kinase = MuSK; Low density lipoprotein receptor- related protein = LRP4). Occasionally, inflammatory myopathy may be associated

Defective neuromuscular junction causes fatigable focal weakness

Overall incidence of 0.5–5 cases per 100,000

Myasthenic crisis occurs in 10–60% of MG patients:

- *Respiratory failure or oropharyngeal or vocal cord weakness requiring intubation and/or mechanical ventilation for more than 24 h*
- *1/3 of the patients may have recurrent myasthenic crisis, pointing towards some individual predisposition*
- *Cholinergic crisis rarely causes respiratory failure*

Myasthenic crisis

Precipitating causes include:

- Viral or bacterial infection in 48% (respiratory infection, or sepsis, aspiration in 10%),
- Pyridostigmine dosing errors
- Incautious initiation of high dose IV corticosteroids (adversely affects neuromuscular transmission and diminishes the effect of pyridostigmine)
- Surgical procedures (particularly extensive thoracic or abdominal surgeries)
- Pregnancy
- Emotional stress
- Exposure to drugs with neuromuscular blocking action (especially aminoglycosides, ketolides, anti-PD1 Abs = ICIs; occasionally, botulinum toxin)

Early recognition may allow timely rescue treatment with IVIg or PLEX, but:

Respiratory failure may be difficult to recognise early

MG crisis management principles

BiPAP-NIV may avoid intubation, but patients should be intubated if in doubt

Medications that impair neuromuscular transmission should be avoided (incl. betablockers)

Pyridostigmine is discontinued at the start of mechanical ventilation to reduce bronchial secretions, and reintroduced for weaning

Start steroids in high doses, as an initial adverse effect on the neuromuscular junction is irrelevant

Thymectomy benefits only after months, but think of thymoma in recurrent/refractory crises

Mortality rate of <5% from specialised centres may not reflect wider practice:

Mortality in UK ICUs overall was found to be 8.7%, varying up to 50%, and acute hospital mortality from myasthenic crisis reached 22%

Management of myasthenic crisis in the ICU

The prognosis of myasthenia gravis may depend on timely therapy (higher mortality where PLEX are delayed)

Deaths can be attributed to belated admission to the ICU, inappropriate transfer from ITU to the general ward, and recurrent crises being refused re-admission

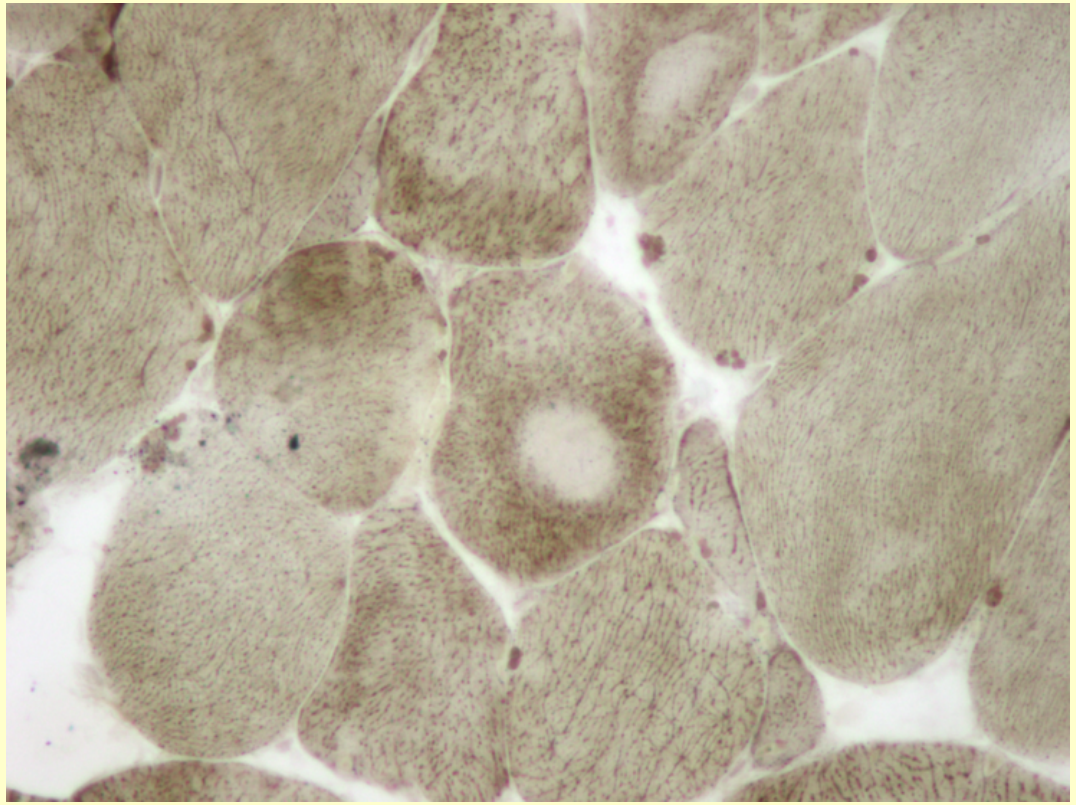
Cardiac failure with neurogenic stunned myocardium can be observed

Early tracheotomy is unnecessary

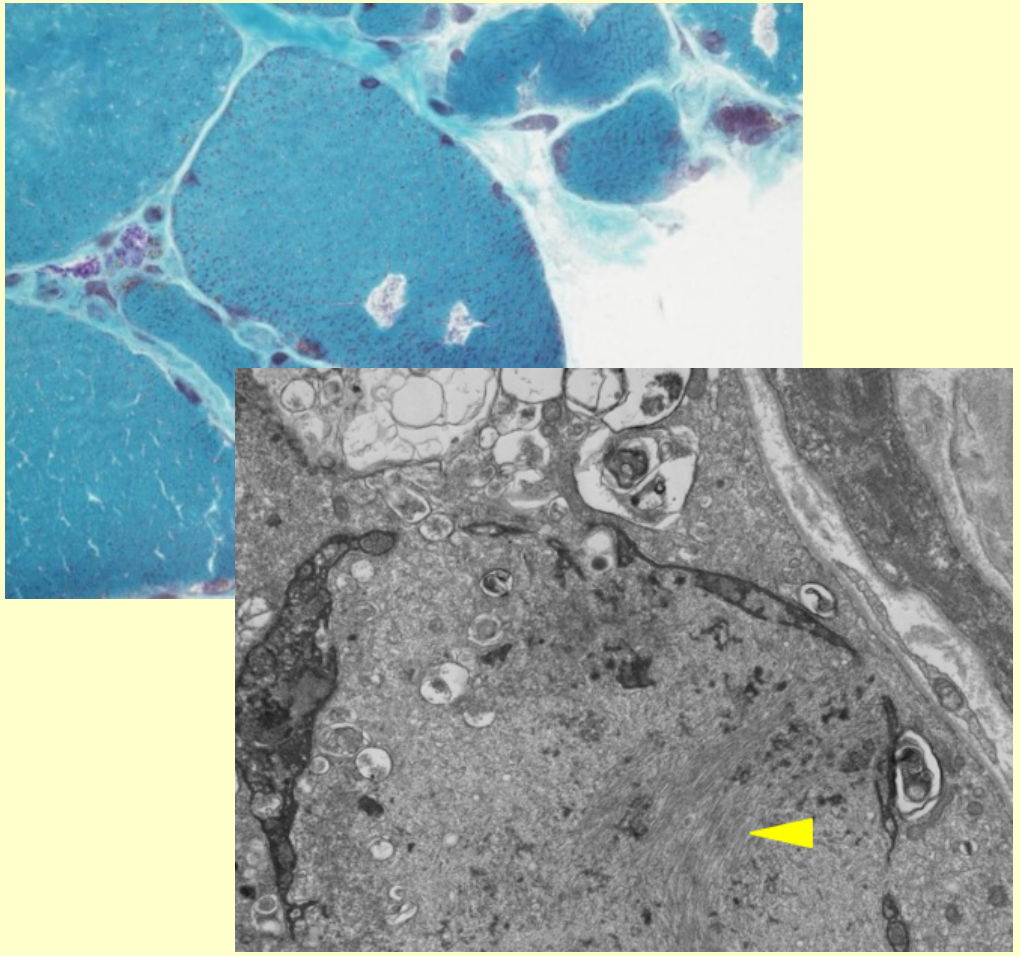
Successful intubation predicted by low secretion volume; T-piece trials, normal chest x-ray, MIP exceeding –50 cm H_2O, VC improvement by 4 mL/kg from pre-intubation to pre-extubation, but predictions are generally far from reliable

Failure does not mean “futility”

Differentials - Cases initially diagnosed as MG in the ICU



A 78 y/o woman admitted after a fall.
6 months decline mobility. Bilateral ptosis, ophthalmoplegia, bulbar weakness.
Core myopathy



A 69 year old woman with 6 years ptosis, fluctuating ophthalmoplegia and swallowing probs. PABPN1 +ve

Acute inflammatory myopathies in the ICU

May require ICU admission through severe weakness, lung involvement (severe interstitial lung disease associated with antisynthetase syndromes) or cardiac complications (pulmonary hypertension, inflammation of the heart muscle or coronary vessels)

Most often inflammatory myopathies in the *dermatomyositis* and in the *necrotizing spectrum* ("necrotizing autoimmune myopathy", NAM with anti-SRP and anti-HMGCR antibodies) are most often seen in the ICU

NAM most often require second-line immunosuppressants (Rituximab, Tacrolimus)

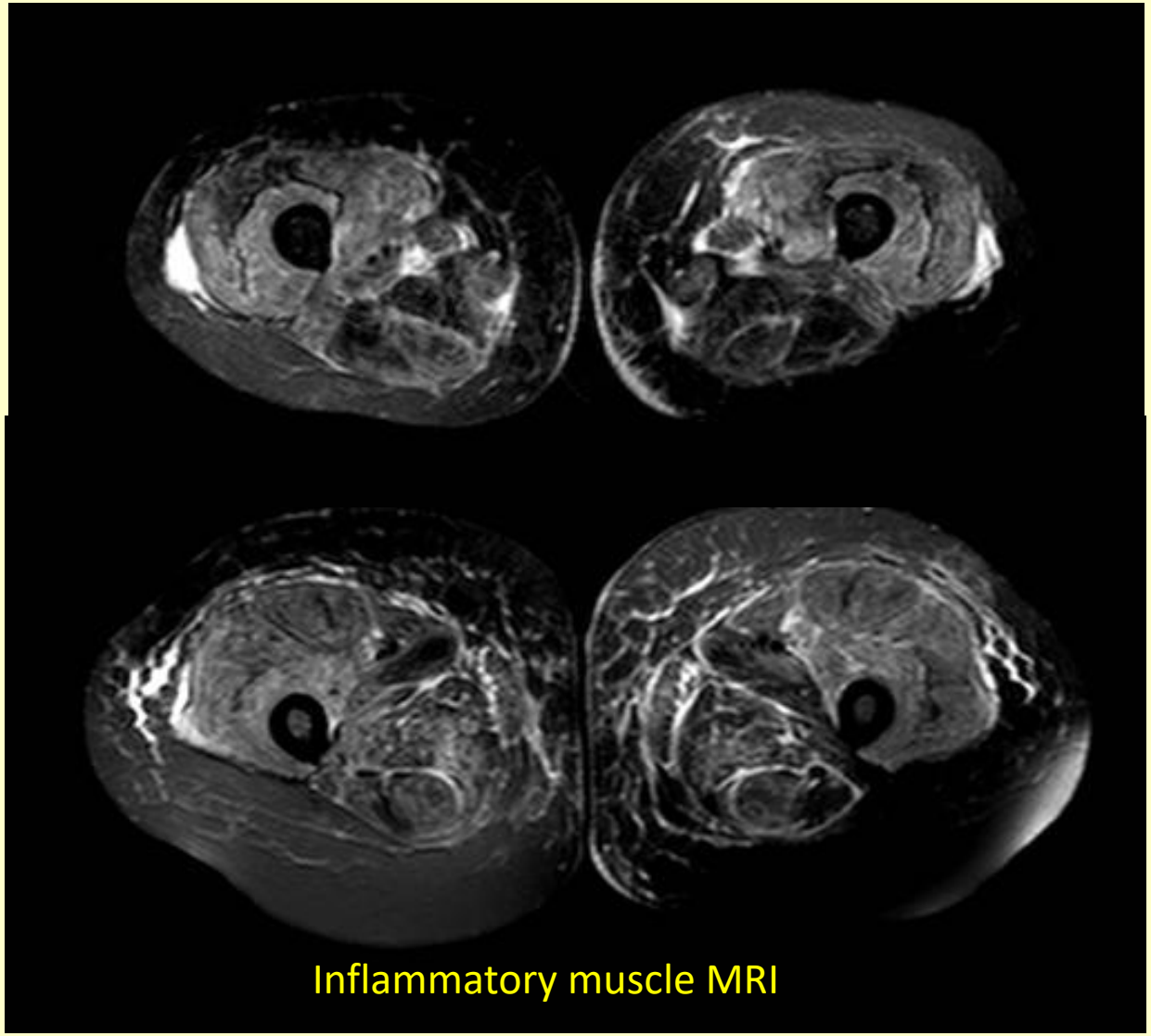
Major cardiac pathology significantly worsens prognosis. Antimitochondrial antibodies may be particularly associated with severe cardiac disease

ECG changes in $\leq$1/3 of cases, and prompt a thorough cardiac workup

Muscle biopsy is mandatory, but treatment should not be delayed while awaiting biopsy

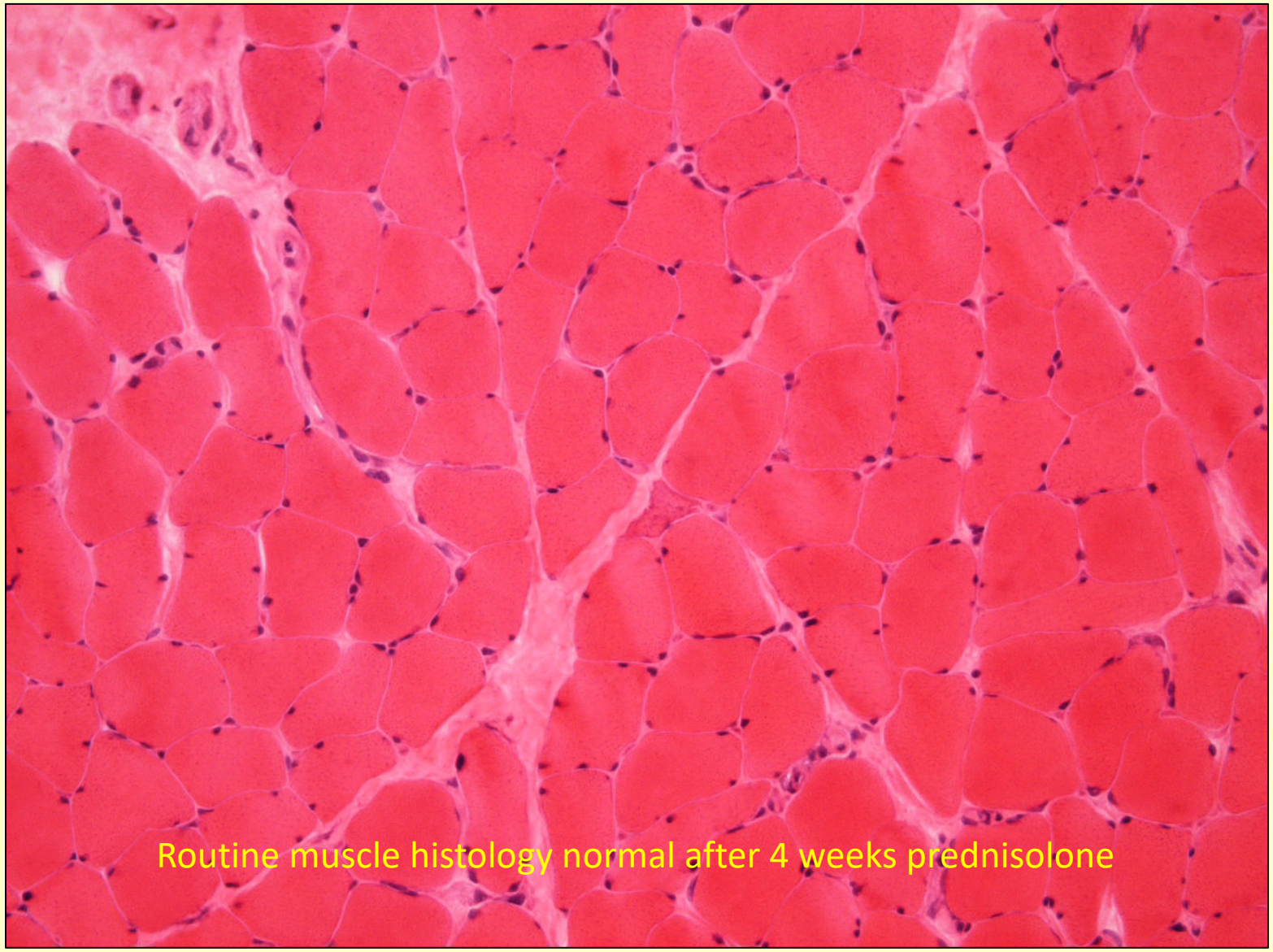
Intermittent pulse steroid regimens are combined with high dose daily steroids

20 year old student, 6 weeks rash, dysphagia. 2 weeks limb weakness. 0.5g/kg prednisolone/d. Admitted to ITU with respiratory failure, on NIV



Inflammatory muscle MRI

20 year old student, 6 weeks rash, dysphagia. 2 weeks limb weakness. 0.5g/kg prednisolone/d. Admitted to ITU with respiratory failure, on NIV



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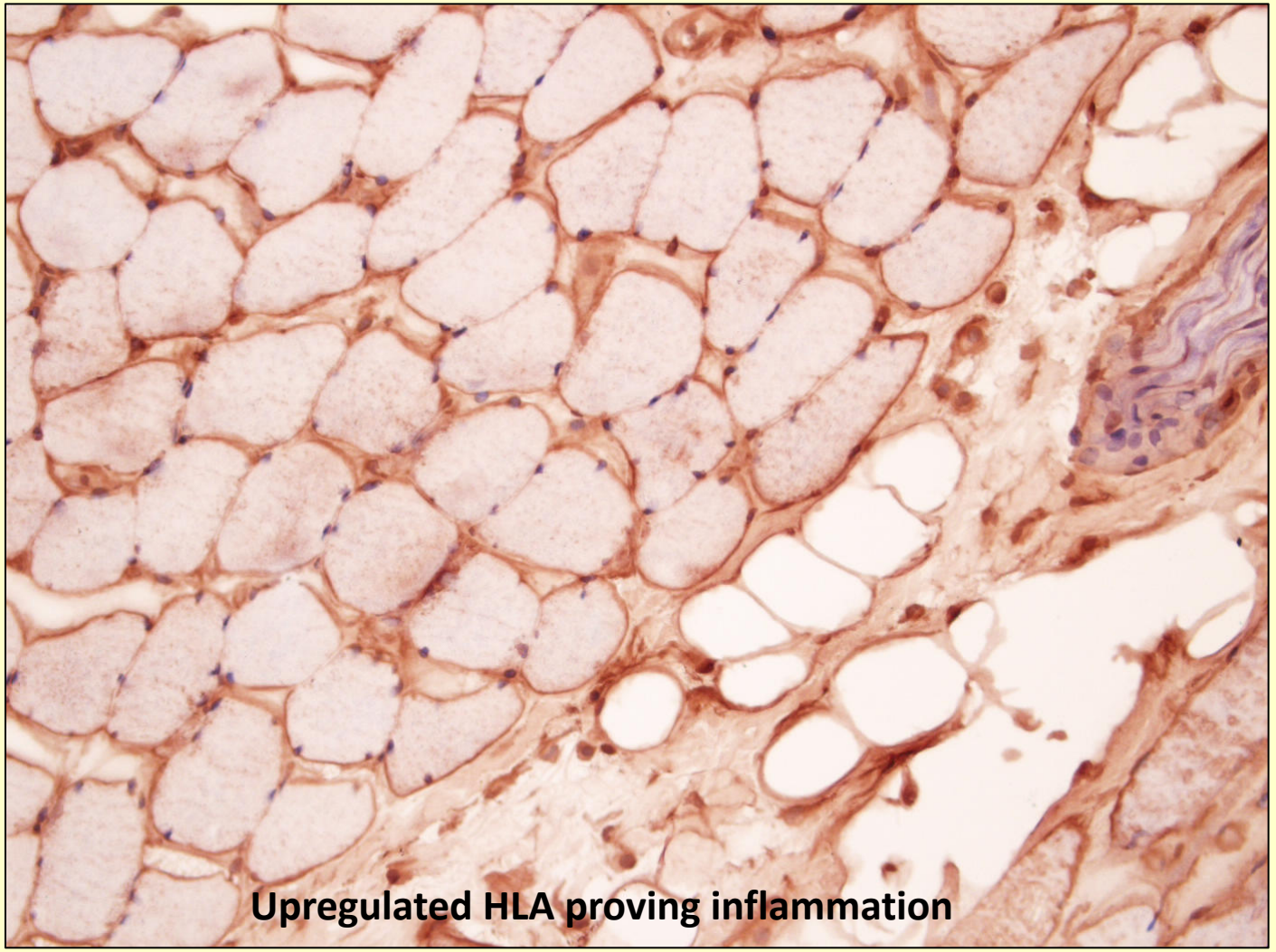
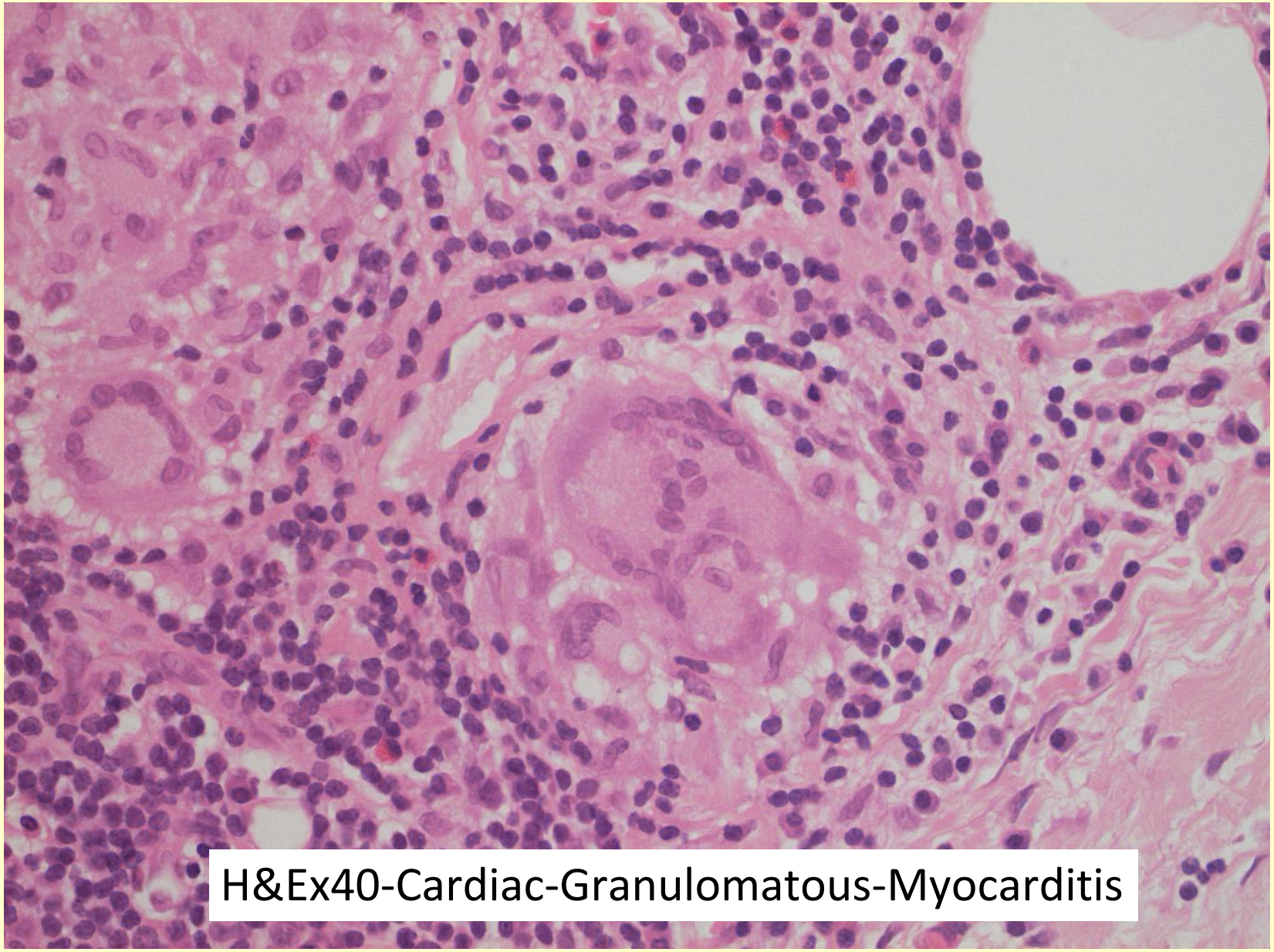
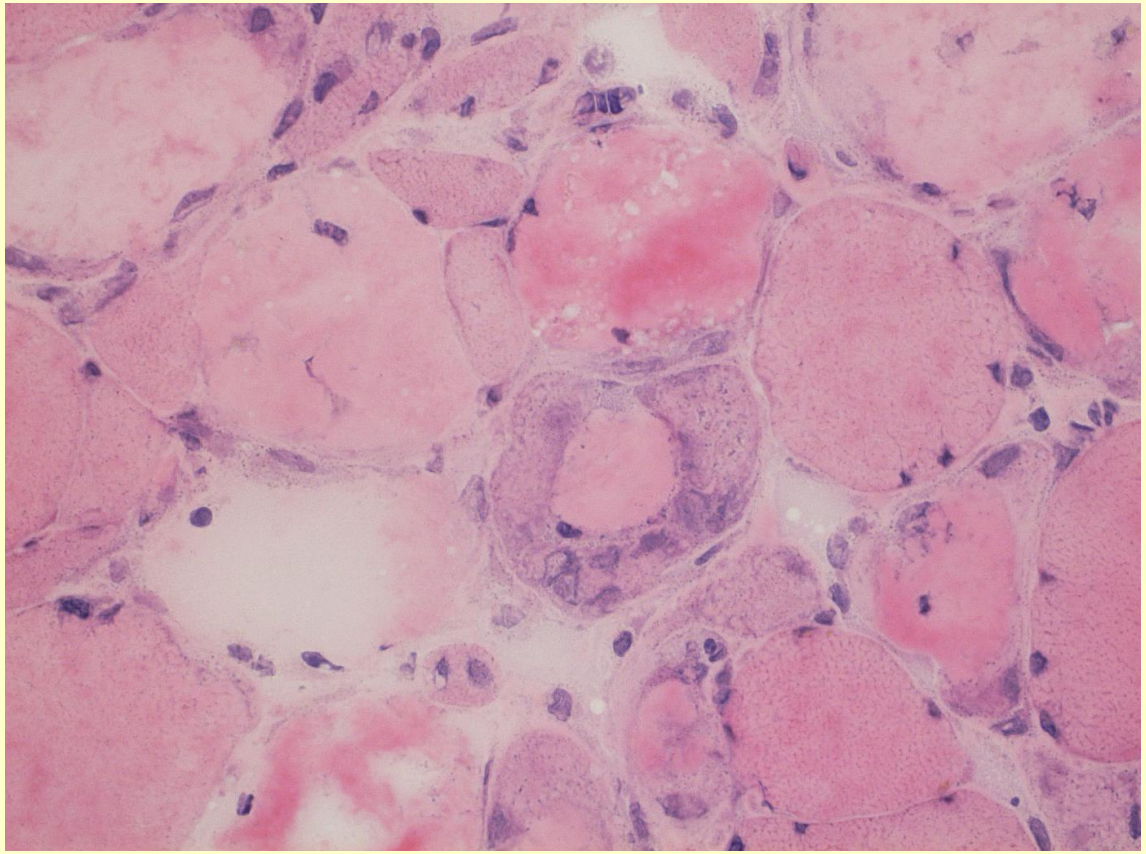
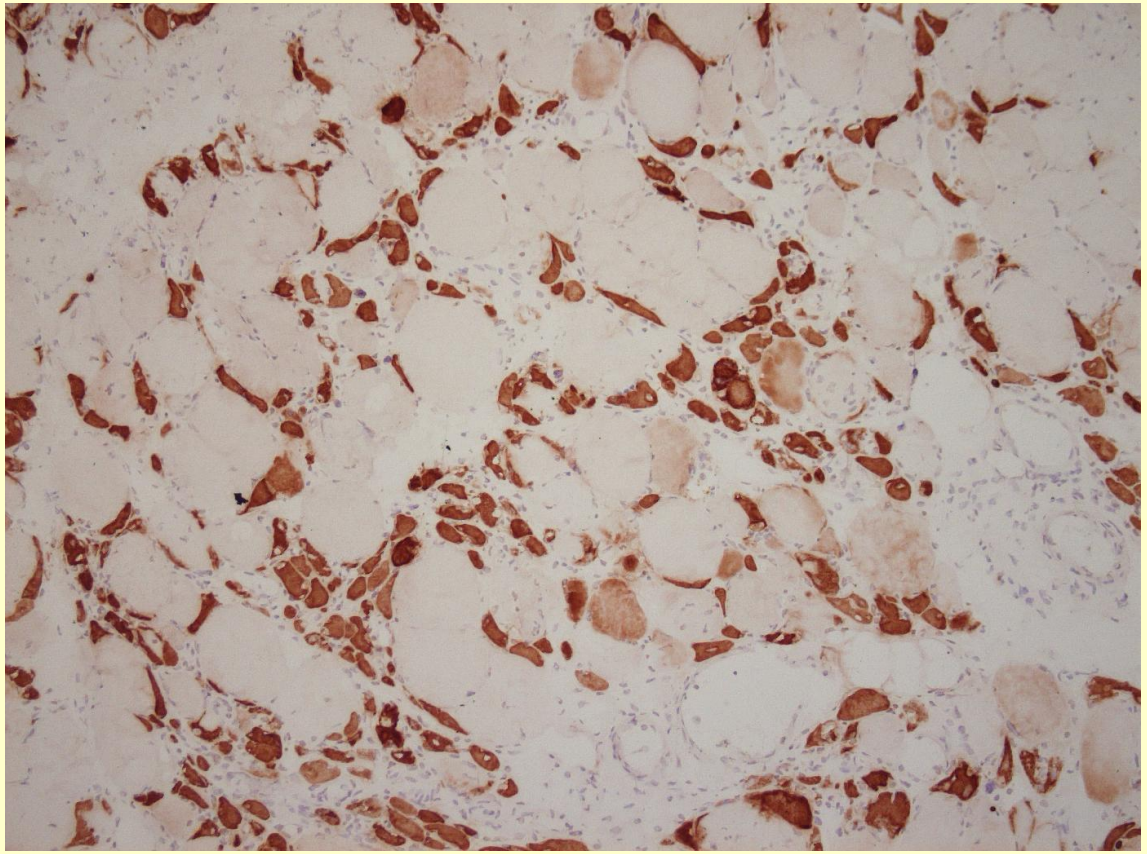


26 y/o designer admitted for ECMO after catastrophic heart failure



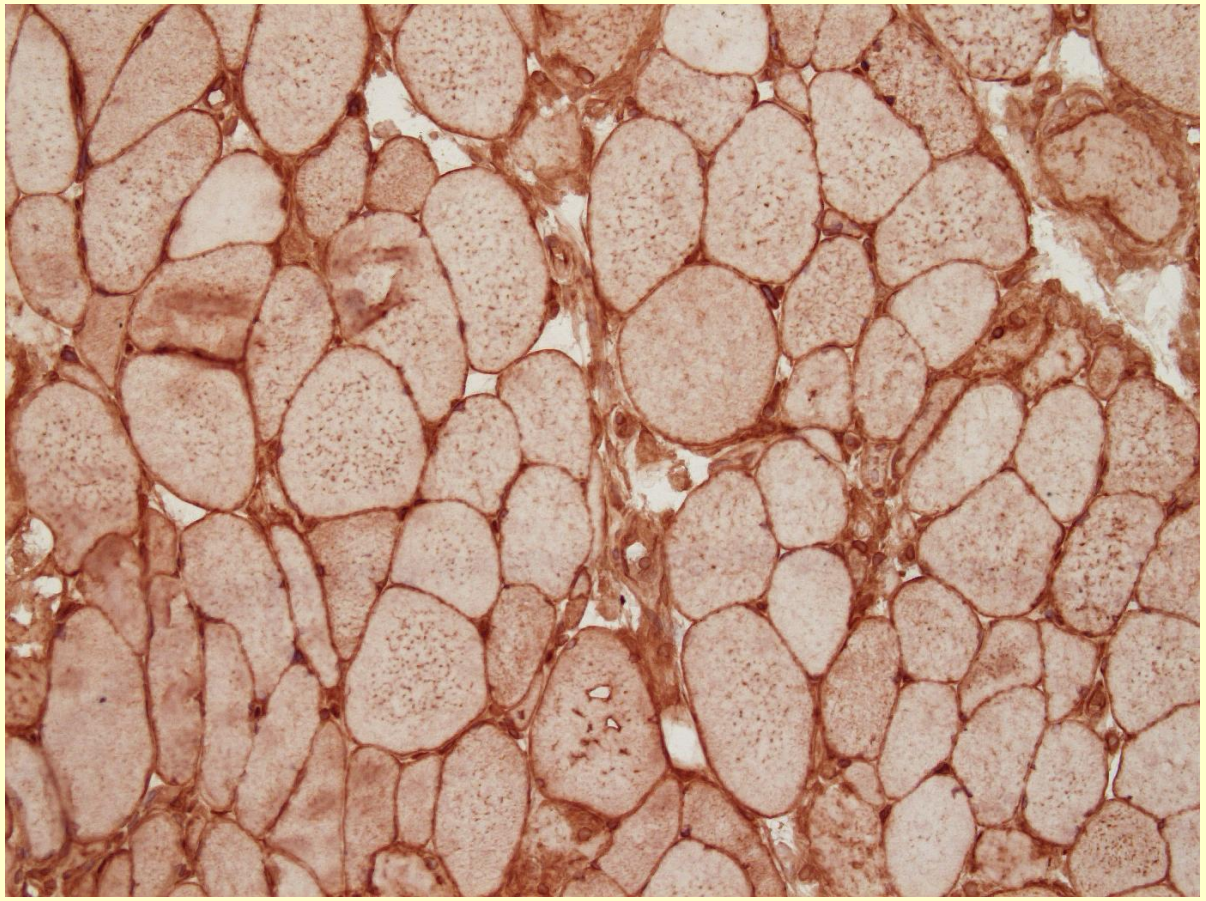
79 y/o lady with 2 months weakness with progression to respiratory failure and tetraplegia: Necrotising Autoimmune Myopathy (NAM)

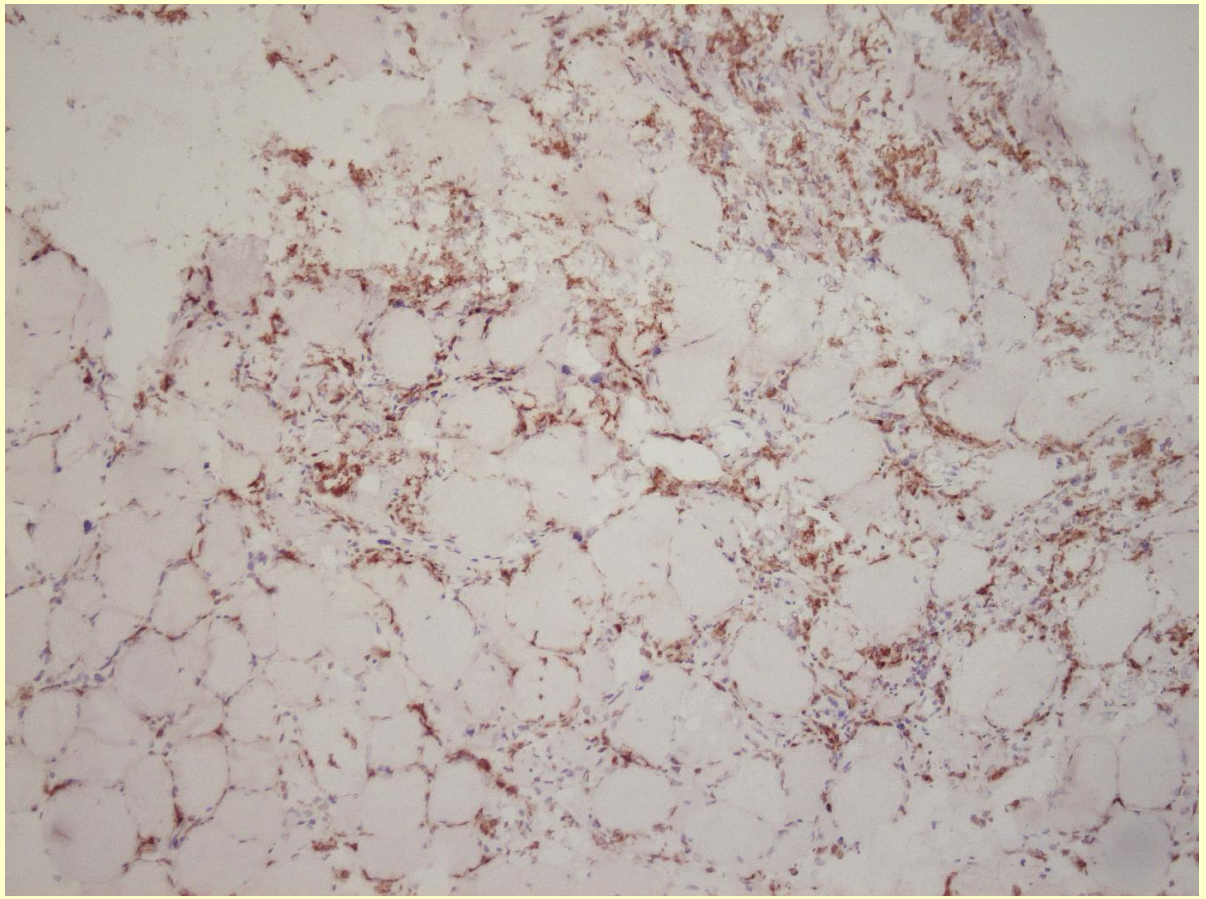




Necrotic cells (left – H&E x40) and regeneration (right – neonatal myosin x10) with little evidence of inflammation. Biopsy in the ICU

Anti-SRP antibody positive NAM





MHC1 upregulation (left – MHC class 1 immunostain x40) and lymphocyte infiltration (right – CD68 x10) prove inflammatory nature

MSS: Anti-aminoacyl tRNA synthetases (Anti-ARS) (cytoplasmic antigens, Antisynthetase syndrome is IM with ILD, Mechanics hands, Raynauds, Arthritis, Fever)	
Anti-Jo1 (anti-histidyl)	15%-25% of PM; HLA: DRw52; DRB1*0301
Anti-PL7 (threonyl)	3%-5% of PM/DM, ILD > 90%, milder than Jo-1, pericarditis, gastric symptoms
Anti-PL-12 (alanyl)	3% of PM/DM, ILD in > 90%, skin lesions, NAM, gastric symptoms
Anti-EJ (glycyl)	2% of PM, ILD in > 90%; DM in 10% to 80%
Anti-OJ (isoleucyl)	2% of PM/DM; ILD > 90%, Skin lesions
Anti-KS (asparaginyl)	<2% of PM; ILD > 90%; Myositis in 25%; Skin lesions Japanese
Anti-Ha/YRS (tyrosyl)	Japanese, antisynthetase syndrome
Anti-ZO (phenylalanyl)	Japanese, antisynthetase syndrome

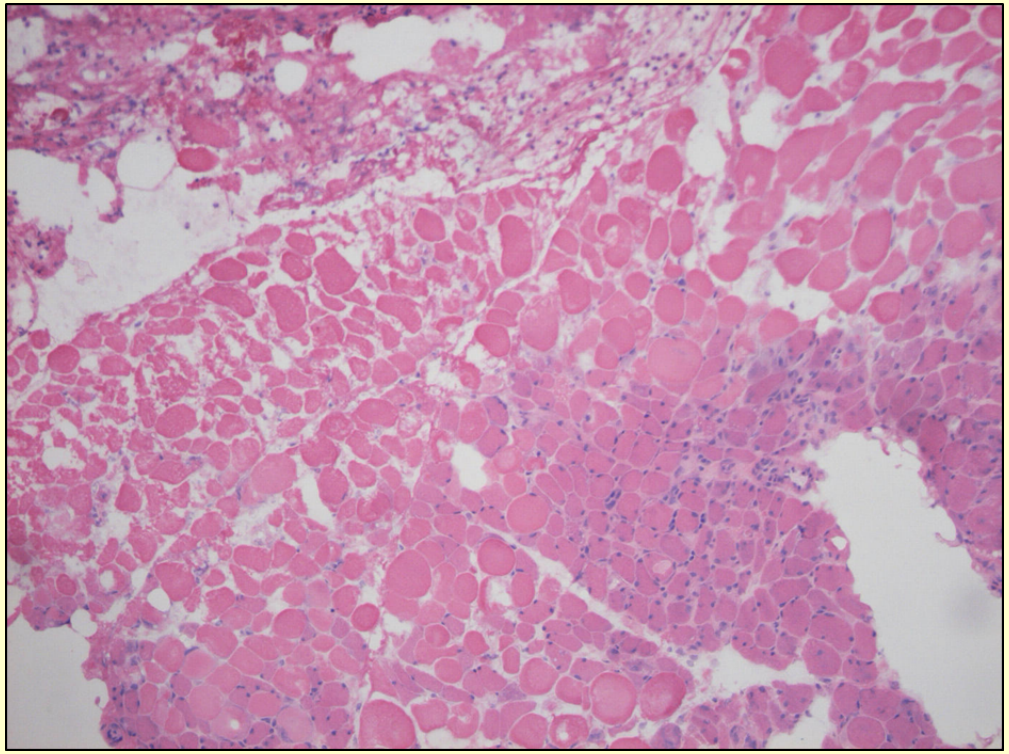
Other Myositis -specific antibodies	
Anti-NXP2 (nuclear transcription)	DM; 37% have calcinosis; adults: lung disease and cancer (CLL, Ovary, prostate, pancreas, gall bladder, lung)
Anti-MDA5 (immune factor)	DM (often amyopathic), ILD with rapid progression; ulcers, palmar papules
Anti-Mi2 (nuclear transcription)	DM in 5% -35%; PM 5%-9%, HLA DRw53; V- & shawl-sign, cuticular overgrowth
Anti-TIF1γ 155/140 (nuclear transcription)	DM/JDM, in adults 75% malignancy
Anti-SAE (post translational)	DM, in adults < 5%, amyopathic early on
Anti-KU (DNA regulation)	Systemic sclerosis, PM/Scleroderma, Japanese
Anti-KJ (translation factor)	PM < 1%; Raynaud's; ILD
Anti-SRP (protein translocation, cytoplasmic)	5% of PM, 18% of IMNM, HLA DRw52); 20% ILD; myalgia, <3% have neoplasm
Anti-HMGCR 200/100	IMNM, statins association
Anti-NT5C1A (nucleotidase)	IM-VAMP; sIBM in >70; DM/PM 10%

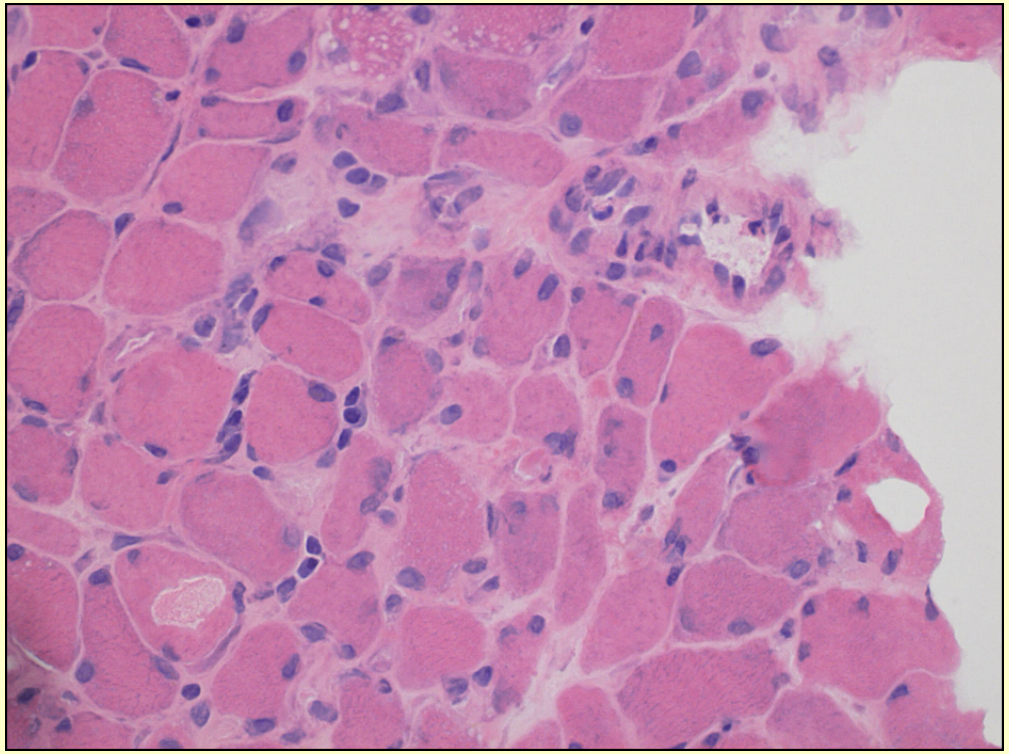
Acute Rhabdomyolysis

Rhabdomyolysis: very high creatine kinase (CK) potentially causing renal failure

Self-limiting and ICU treatment focuses on renal protection

Muscle biopsy is unrewarding in the initial 4 weeks after acute rhabdomyolysis





43 y/o female - acute paraneoplastic necrotizing myopathy

Rhabdomyolysis

Causes of rhabdomyolysis:

- Muscle ischemia
- Excessive physical exertion
- Infection
- Toxicity including malignant hyperthermia and serotonin syndrome
- Metabolic or endocrine disorders
- Paraneoplastic myopathy (paraneoplastic immune panel and CT/PET imaging)
- Inflammatory myopathy (anti- MAS or anti-SRP antibodies in MSA panel)

Recurrent exertion-triggered rhabdomyolysis may have genetic causes (Channelopathies; metabolic myopathies, ANO5, CPN3, RYR1 variants)

Next Generation Sequencing using a “rhabdomyolysis panel” is rapid and cost-effective once toxic causes are excluded

3. Neuromuscular disease arising during treatment in the ICU

Toxicity of drugs used in the ICU, and immunological derangements (Graft-versus-Host disease; side effects of immune checkpoint inhibitors)

Patients with symmetric weakness, often sparing facial and ocular muscles, often have a combination of critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) now termed “ICU-acquired weakness (ICU-AW)”

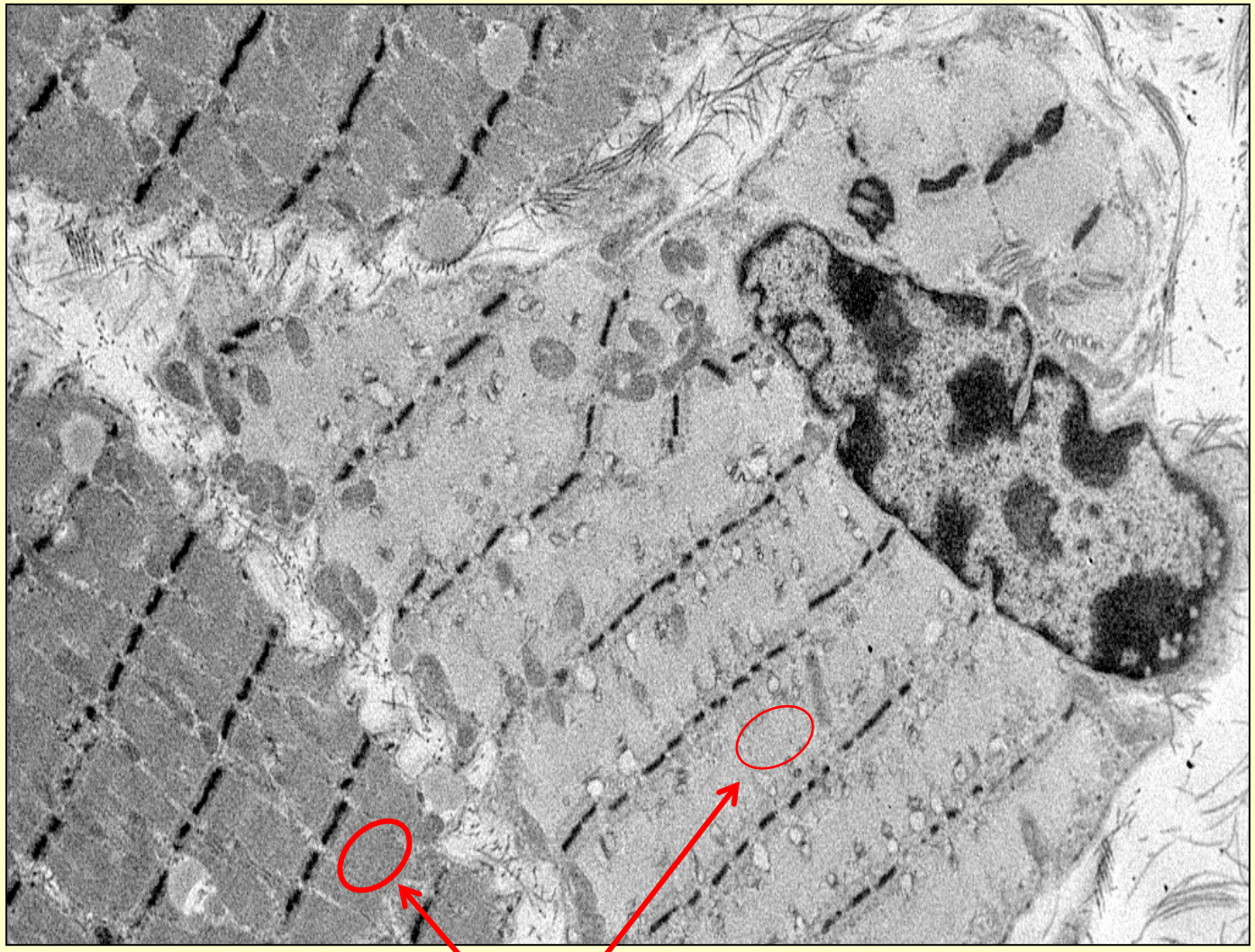
ICU-AW affects up to one third of patients who are ventilated for over 7 days, particularly those treated for sepsis and multiple organ failure.

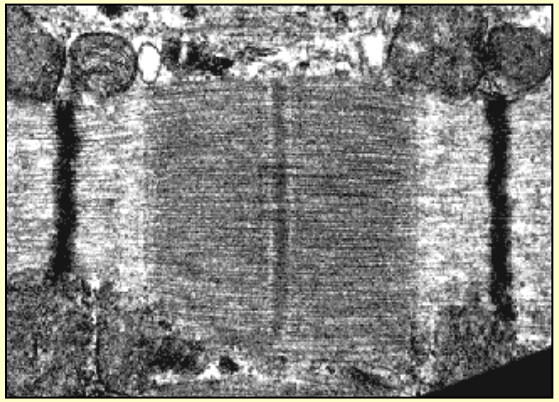
Electromyography does not separate CIP from CIM

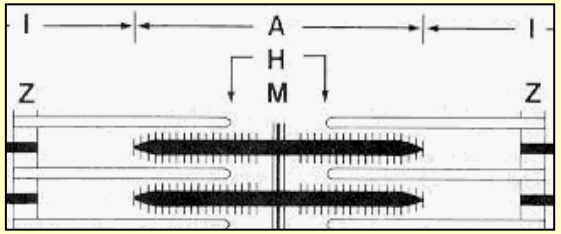
Muscle biopsies can show variably acute myosin-loss myopathy, necrotizing myopathy, or diffuse Type 2 fibre atrophy.

Critical Illness Neuromyopathy (ICU – Acquired Weakness):

1. Acute myosin loss myopathy

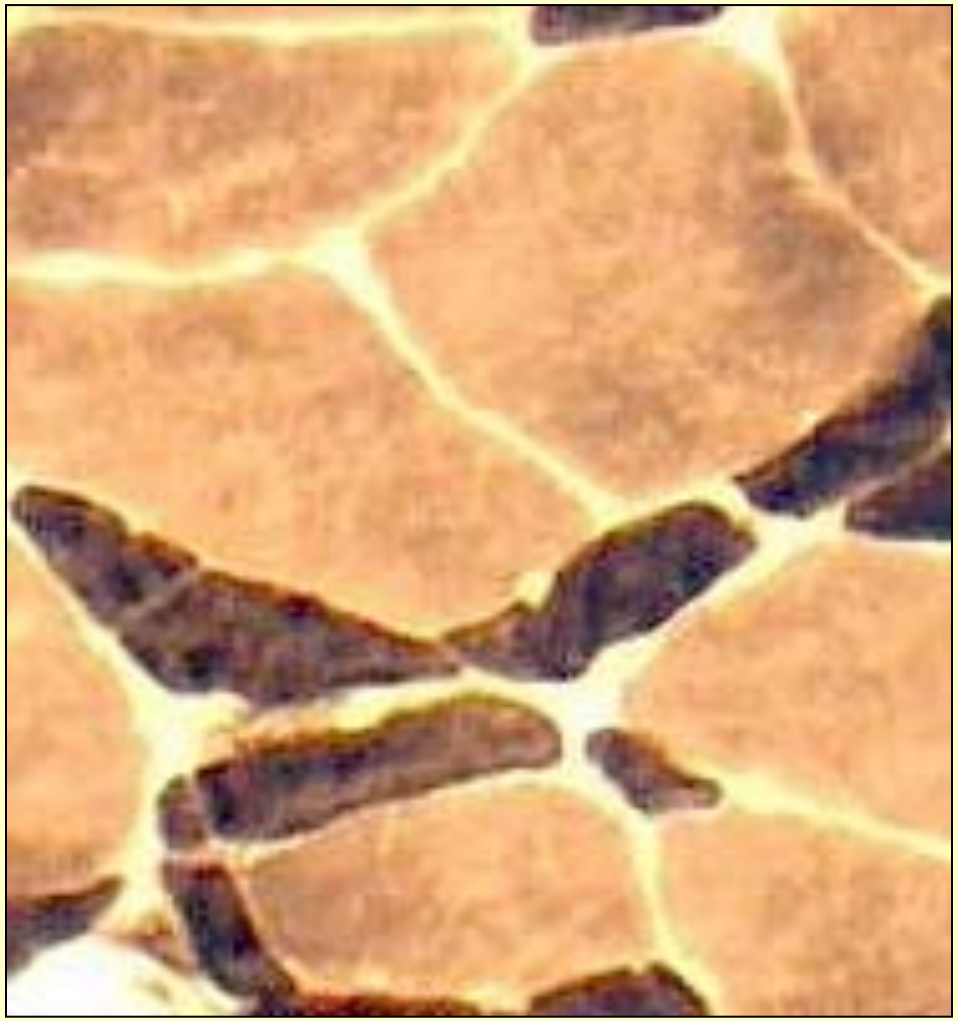




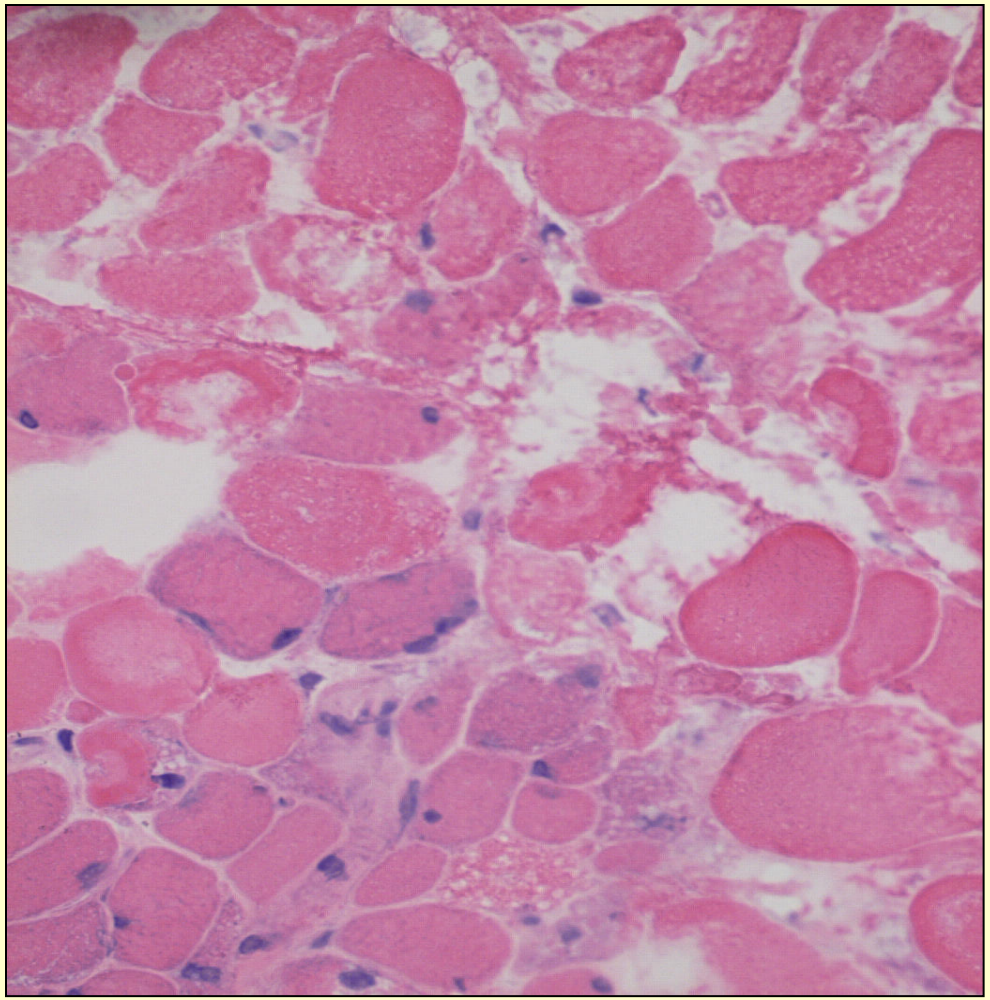


Critical illness neuromyopathy (ICU – Acquired Weakness)

2. Acute type 2 fibre atrophy



3. Acute necrotizing myopathy



4. The ICU presentation of pre-existing chronic neuromuscular disease

Chronic neuropathies and anterior horn cell disease

Amyotrophic lateral sclerosis

Chronic myopathies but newly diagnosed in the ICU

Acute complications of chronic myopathies

4. ICU presentation of chronic neuromuscular disease - Genetic neurogenic disorders

Chronic neuropathies rarely cause admission to the ICU, but respiratory failure may be prominent in some variants of CMT

CMT2A (MFN2 mutations) and CMT2C (TRPV4) feature stridor and diaphragmatic failure

CMT4A (GDAP1); CMT4B1 (MTMR2); and HMN6-SMARD1 (IGHMBP2) commonly cause respiratory problems

Occasionally, acute intermittent porphyria may present as an acute neuromuscular disorder

X-linked SBMA Kennedy: Respiratory failure, laryngospasm, dysphagia, or aspiration pneumonia cause admission to the ICU

ALS in the ICU

10% of Amyotrophic Lateral Sclerosis (ALS) may present with respiratory symptoms

Admission to an ICU is often not part of the intended pathway, but this happens quite frequently due to acute decompensation over an infection precipitating respiratory distress earlier than anticipated

Such patients may not have made an advanced directive

The level of function at the end of ICU care is almost always worse than on admission

Non-invasive home ventilation prolongs survival and improves quality of life; invasive ventilation is controversial, and international practice varies

It is often complicated by fronto-temporal syndrome

Neurogenic cardiomyopathy in ALS also may cause dyspnoea and chest discomfort in the absence of coronary obstruction

Chronic myopathies presenting to the ICU

A 58 year old male goes on a honeymoon to the Rocky Mountains

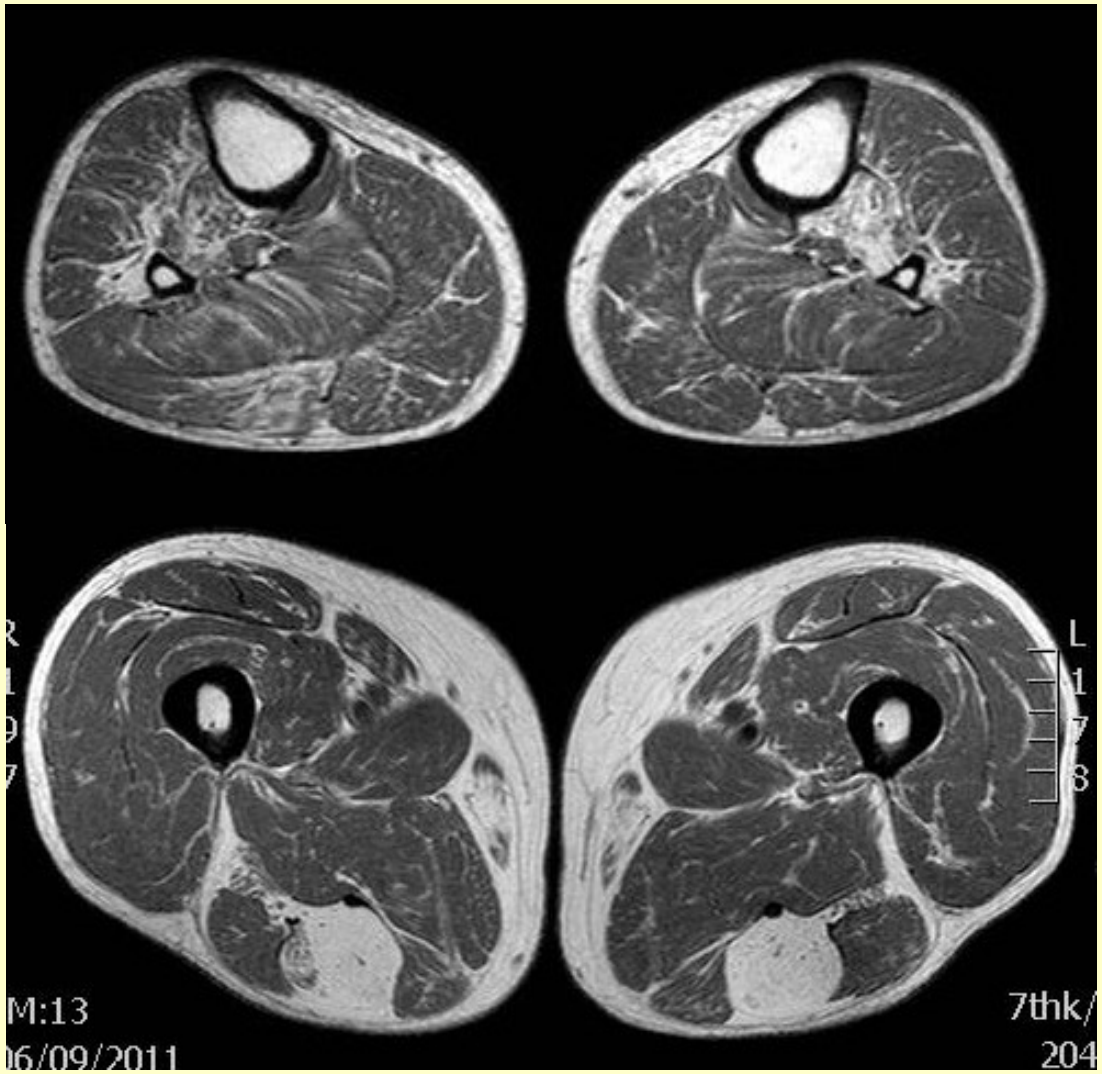
Hiking in high altitude developed acute respiratory failure

Intubated, taken to San Francisco and diagnosed with GBS

Treated with IVIg but did not improve

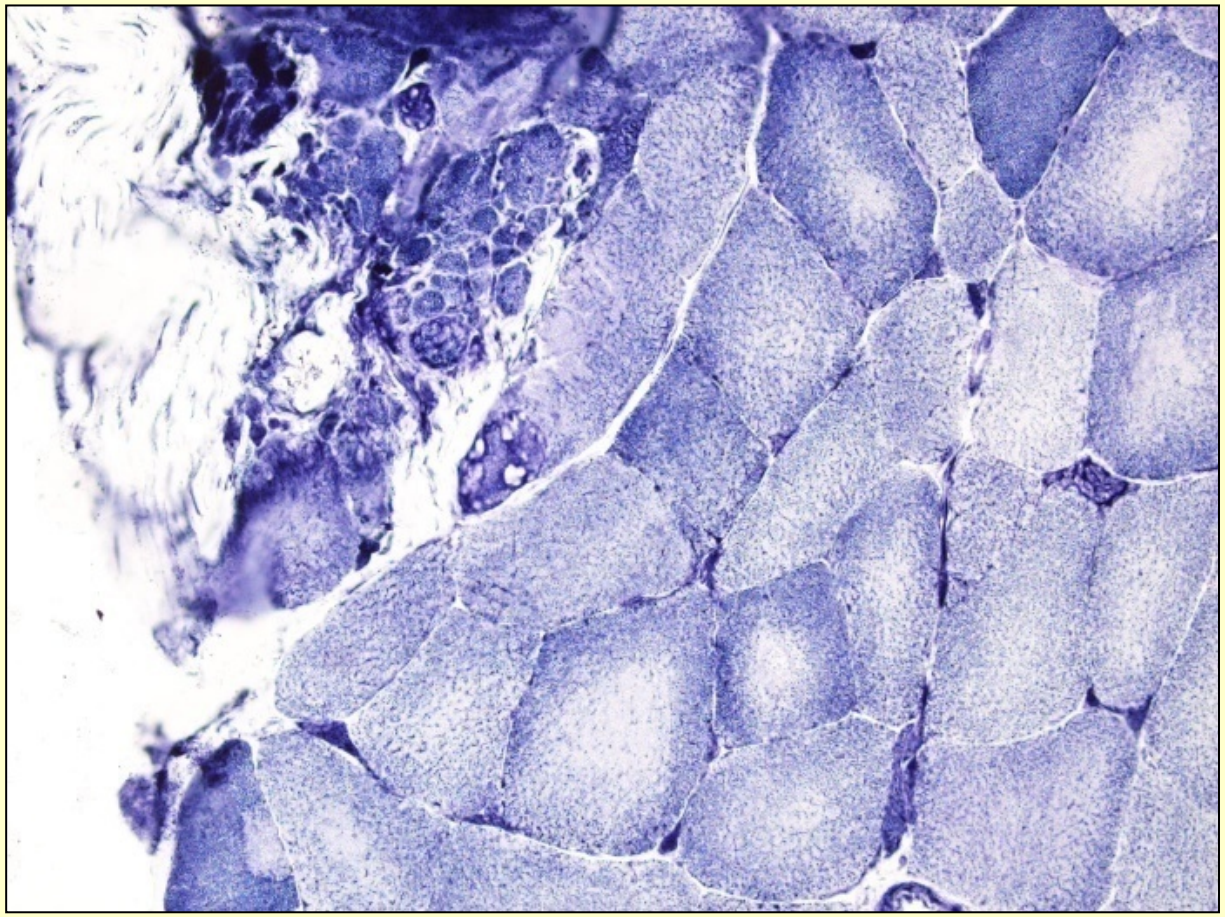
Repatriated on the ventilator

He has wasted calves and Achilles tendon toe contractures

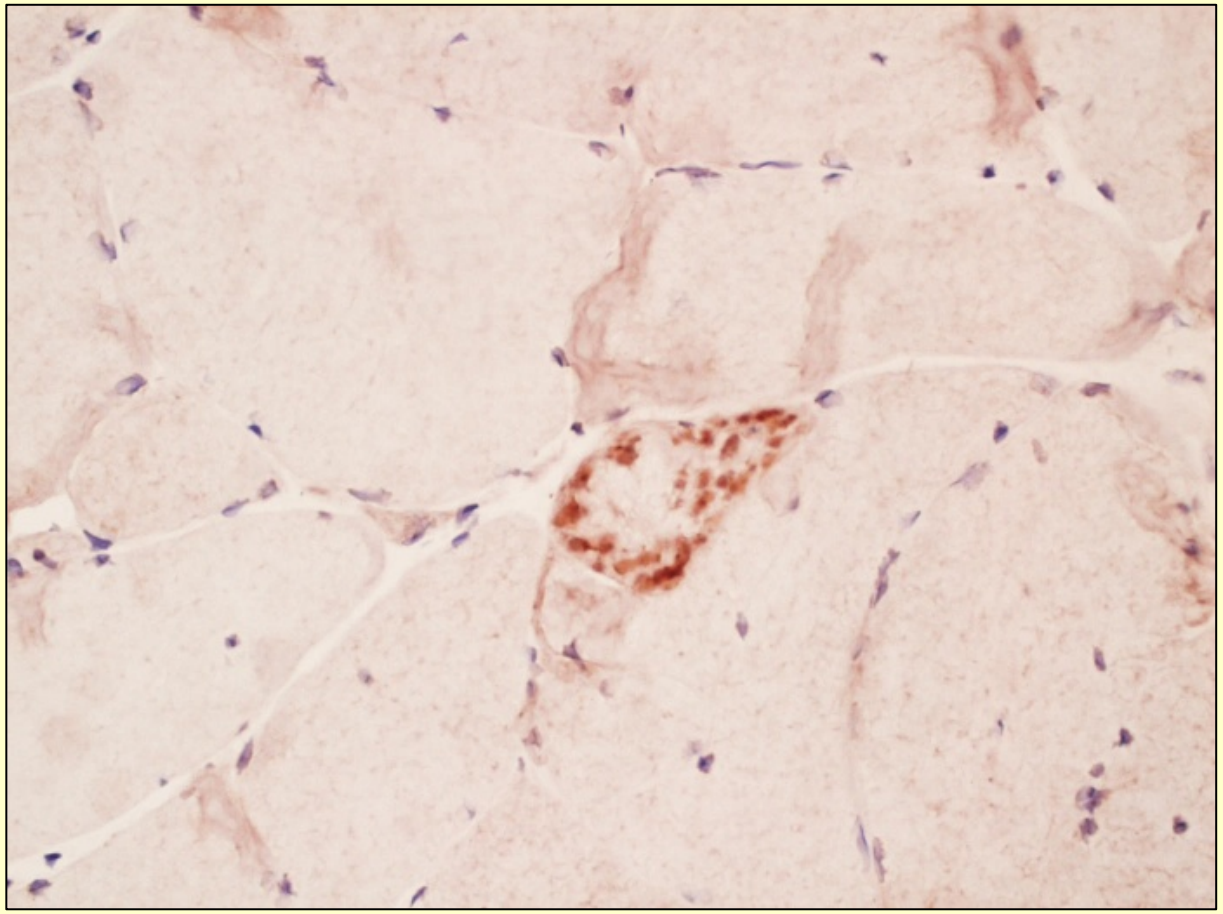


EMG was myopathic and muscle biopsy was performed

NADH-TR

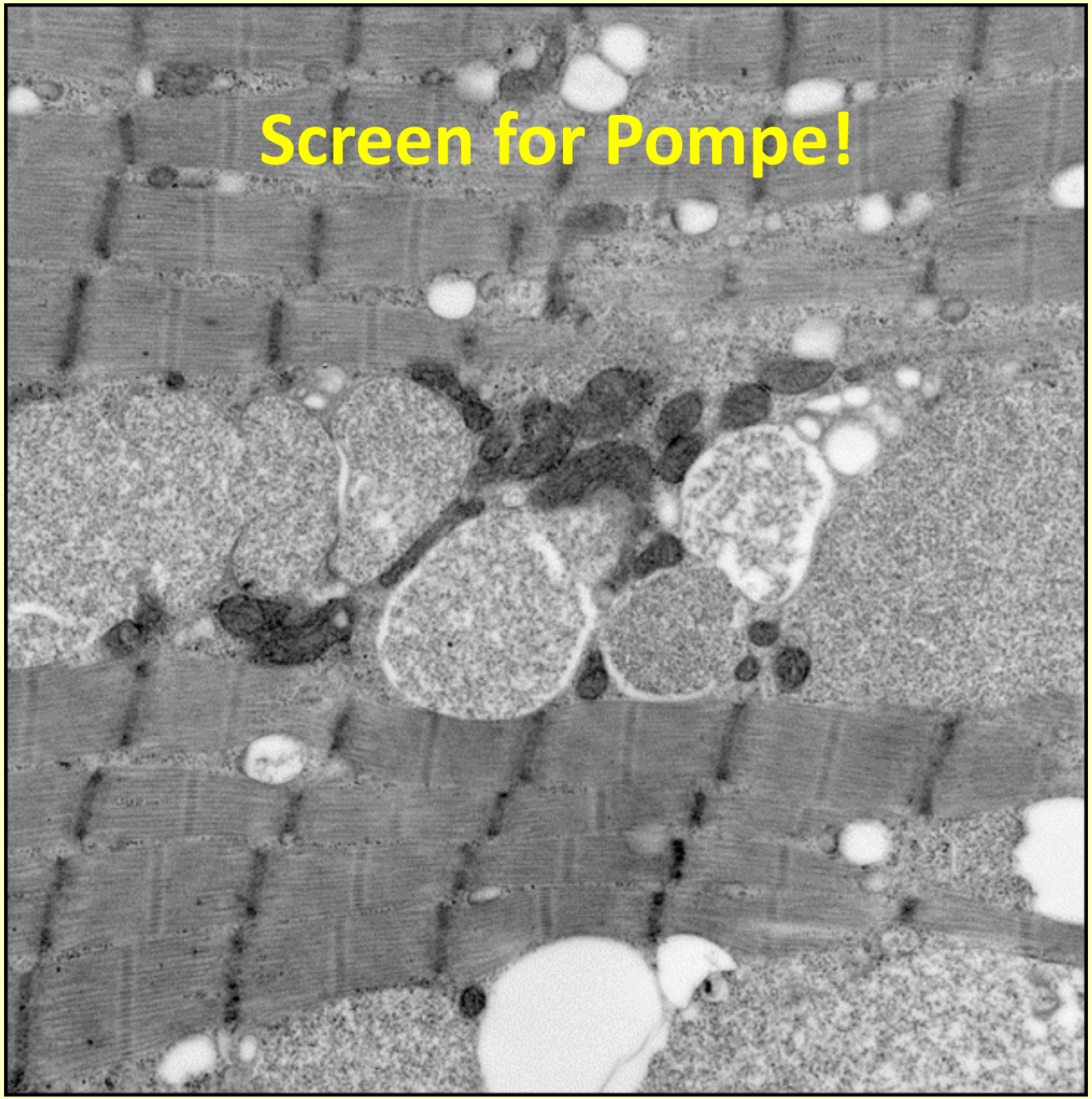


Myotilin



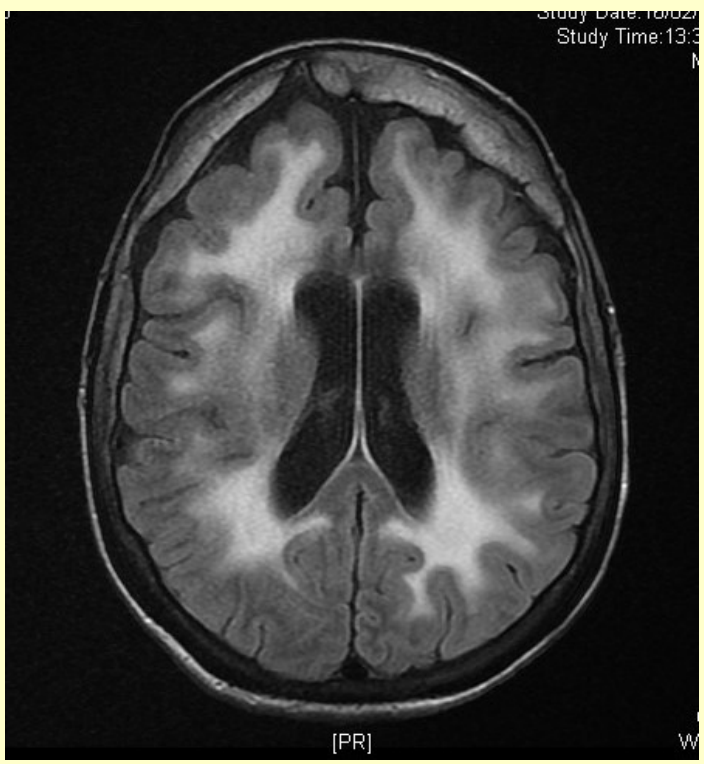
Hereditary myopathies causing *adult* onset early respiratory failure

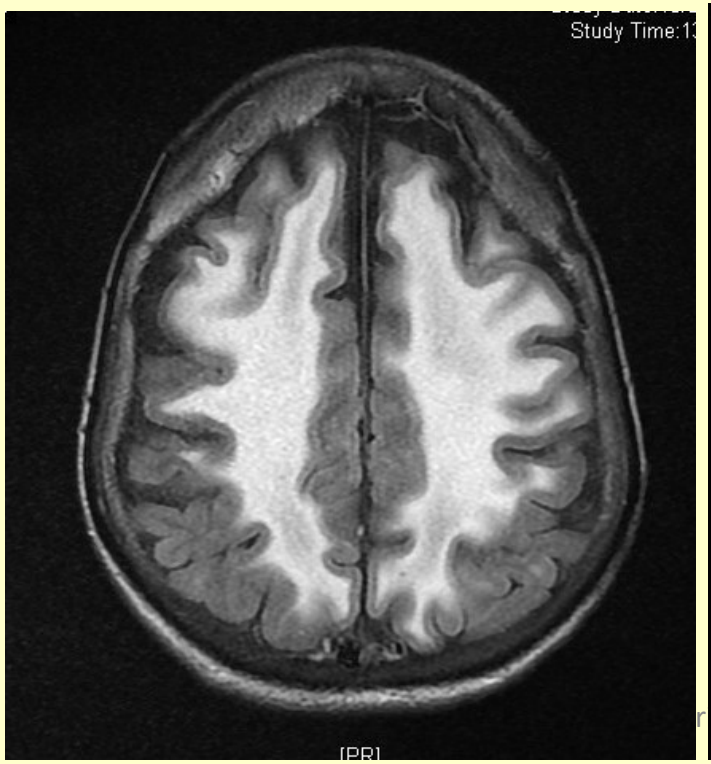
- Titinopathy “HMERF” Hereditary Myopathy with Early Respiratory Failure (TTN: AD OMIM 603689 incorporates 607359): Type 1 (2q24-31 Swedish Titin R279W mutation) FN3 119 domain of exon 343, ; Type 2 (2q21 French)
- Glycogen storage disorders: GSD 2 (Alpha-glucosidase = Pompe) and 3 (Debrancher): most often with exercise intolerance
- Mitochondrial myopathy: often with multisystemic features, PEO, and CNS involvement
- Myofibrillar myopathies: Desmin (cardiac), αB-crystallin (cataracts), Myotilinopathy (Spheroid body variant of myotilinopathy [Foroud 2005 S39F mutation in TTID gene])
- Limb-girdle MDs: Calpainopathy (LGMDR1/D4); Fukutin-related (LGMDR9); COL6 (LGMDD5/Bethlem): more often mild or late respiratory involvement; other leading features
- Oculopharyngodistal MD (AD/AR OMIM 164310)
- Variants of “congenital” myopathies: Nemaline rod OMIM 102610 (ACTA1 mutations 1q42 variable inheritance Asn115Ser; Gly268Cys; Ile136Met, MYPN); TPM3/SEPN1 centronuclear and cap myopathies; myotubular myopathies (MTM1 mutations)

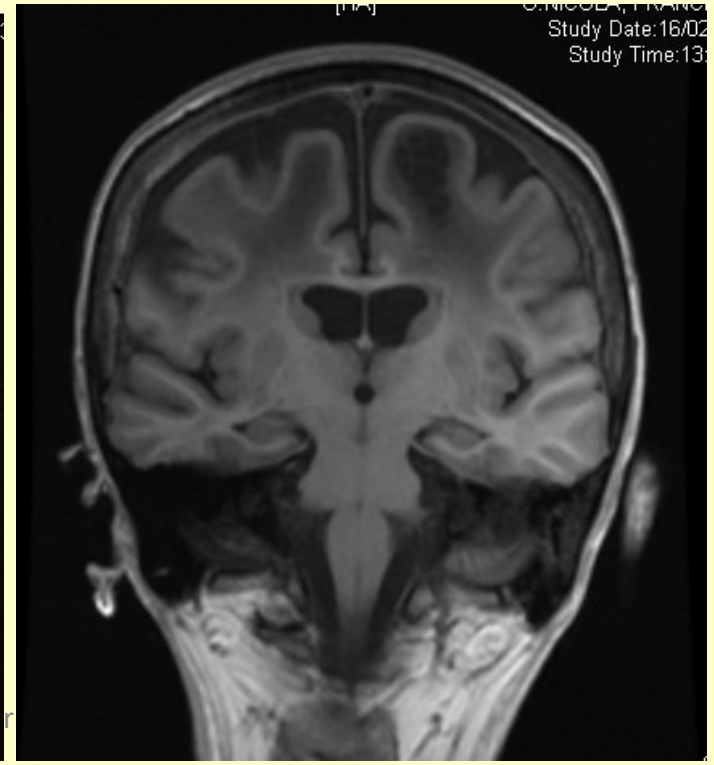

Screen for Pompe!

Chronic myopathies presenting to the ICU

- A 43 year old female is admitted with respiratory failure. She required emergency intubation and tracheotomy for a difficult airway
- “Muscular dystrophy” was diagnosed 30 years ago. Teenage scoliosis surgery. Epilepsy, normal intelligence, independent, though wheelchair bound with distal arm movements only. Molecular diagnosis was unknown.
- The intensive care team wish to withdraw treatment: “This is muscular dystrophy”

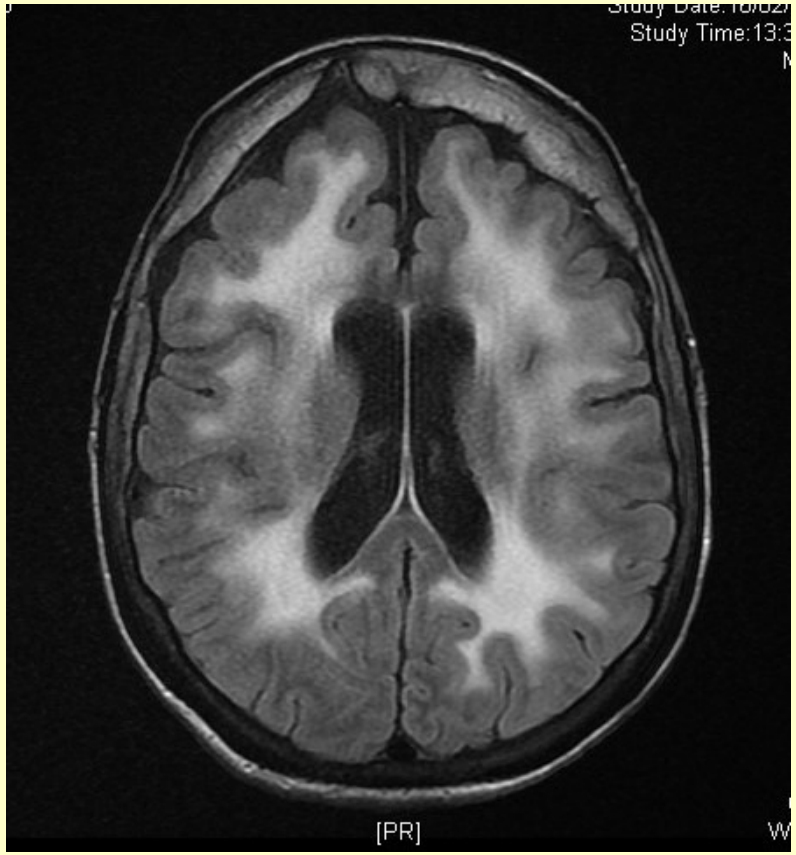


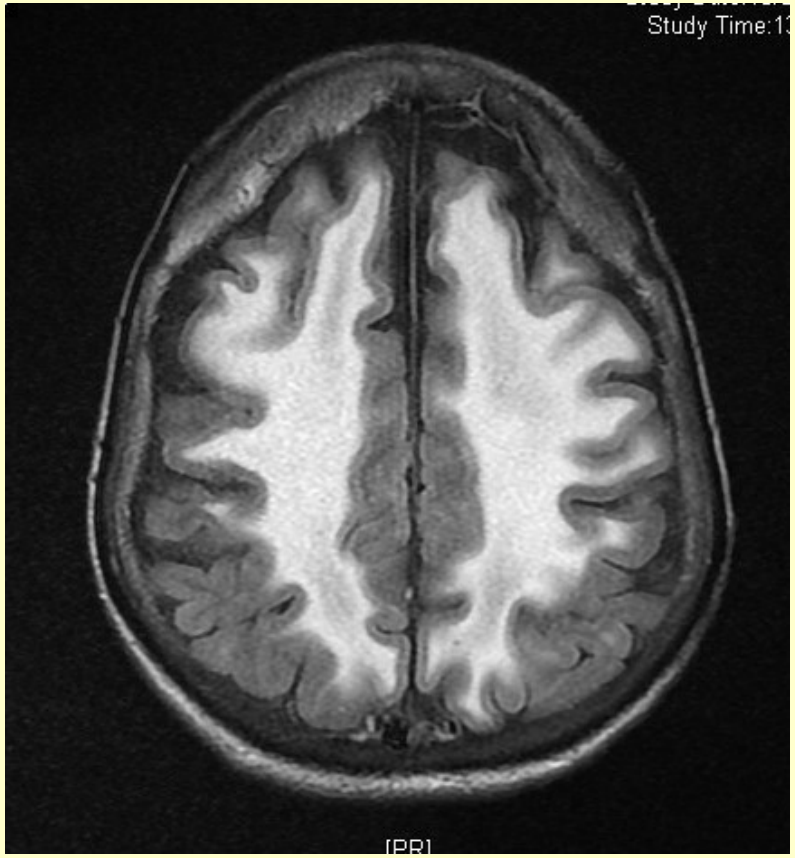


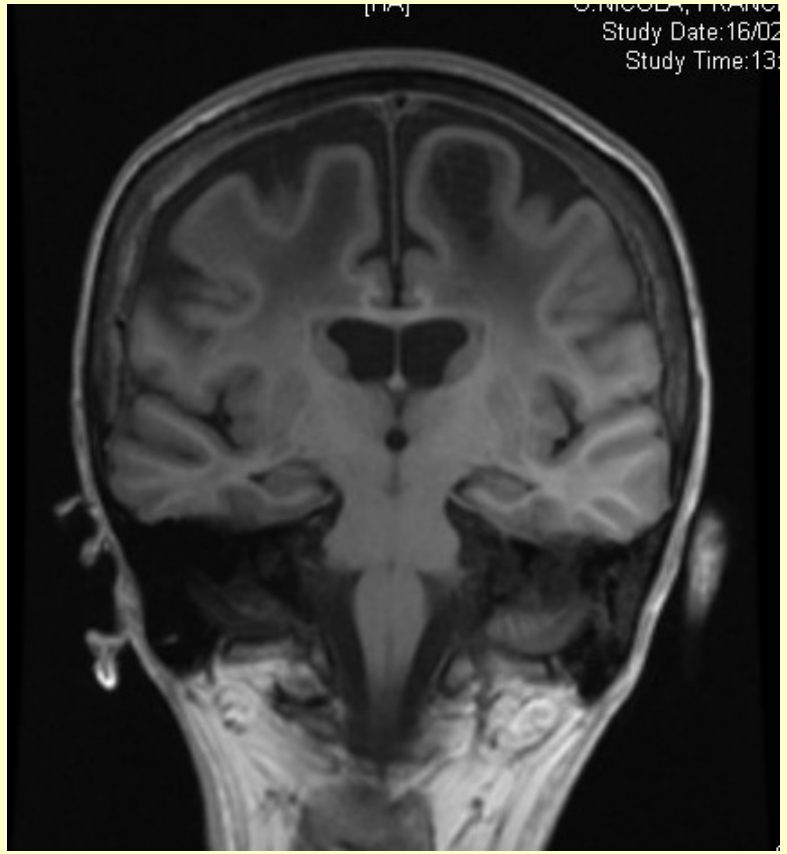


Genetic myopathies can have characteristic multisystemic features

- The molecular diagnosis is a **Laminin2 (Merosin)** mutation
- She spent 2 months in the ICU; 6 weeks in a respiratory ward; now decannulated, on NIV 6h at night and back to normal function. This was 3 years ago. There has been no progression







Neuromuscular disorders in which sudden cardiac death has been reported [Finsterer J, Int J Cardiol 2016]

- Myotonic dystrophy: n=169
- Mitochondrial disorders: n=59
  - MELAS, MERFF, KSS, other: n=11
  - Beta-oxidation defects: n=42
  - Other (Carnitine deficiency, CPT2, CACT, MCAD, MCADD, Barth): n=6
- Laminopathy: n=31
- Desminopathy: n=31
- Becker muscular dystrophy: n=16
- Duchenne muscular dystrophy: n=11
- Danon X-linked vacuolar myopathy (Lamp2): n=10
- Amytrophic lateral sclerosis: n=10

Cardiac disease in chronic muscle disorders

- Cardiac involvement may be a prominent early symptom in muscle disease
- Potential life expectancy for patients with DMD has doubled from 19 to 38 years, so active treatment provides longer potential benefit
- Some myopathies (e.g. Becker muscular dystrophy; myofibrillar myopathies) typically develop cardiomyopathy and may require transplantation
- Patients with Becker-type dystrophinopathy constitute 50% muscular dystrophy patients who undergo cardiac transplantation
- The prognosis of muscular dystrophy undergoing transplantation is similar to that of other patients (1 year survival: 89% vs 91%; 5 year survival 83% vs 78%: Wu RS et al. *J Heart Lung Transplant. 2010;29:432-8)*
- Others feature dysrhythmia and may acutely require pacemakers or ICDs (e.g. laminopathy or myotonic dystrophy)
- Detailed genetic information is needed to choose the right device (PPM for Emery-Dreifuss EMD Type 1; ICD for EMD type 2/3)

Critical care in advanced chronic muscle disease

Multidisciplinary care and timely interventions have doubled life expectancy for patients with Duchenne Muscular Dystrophy (DMD): the potential benefit for DMD patients from critical care treatment is today relatively greater

Patients can make informed decisions on their treatment preferences, including ceilings of care, if there has been a timely discussion

Weaning from the ventilator is prolonged, but there is a high chance that patients will be liberated from the ventilator, and even that tracheotomy can be reversed

Patients do **not** remain “stranded” in the ICU with nowhere to go since home ventilation has become available

Slow trajectory means that a level of function near the pre-ICU baseline can be achieved at the end of weaning

Early competent rehabilitation is essential

Conclusions

Neuromuscular specialists should provide guidance to intensivists

Their role includes optimizing pre-ICU care and monitoring, understanding respiratory and cardiac complications, and identifying risks for the patient in the ICU and after step down

They should guide diagnostic procedures with a minimum of delay and as little invasive procedures as possible to start specific treatment and inform prognostication

The critical care team should understand current life expectancy and quality of life potential

It is also necessary to act as the patients' advocate

Acknowledgements:
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