Neuromuscular Disorders in the Intensive Care Unit - when and how

M. S. Damian, Addenbrookes Hospital, Cambridge
Background to this talk?

- Neuromuscular admissions to the ICU are increasing
- The incidence of individual conditions is not clear
- The true outcomes of these patients are unclear
- Mortality rates in patients treated with Myasthenia and Guillain Barre Syndrome have not significantly improved in the last 20 years, neither have treatments [Damian MS, Howard R, Int Care Med 2013]
- Bad medicine is expensive
  (Example: An MG case with recurrent crises.
  1 year pre-Rituximab: £39,810 costs incl. 14d ICU stay
  1 year on Rituximab: ca. £8,000 total costs, no ICU stay

M. S. Damian, Addenbrookes Hospital, Cambridge
Which neuromuscular symptoms may require treatment in the ICU?

- Severe respiratory weakness
- Bulbar weakness and aspiration
- Cardiomyopathy and heart failure
- Arrhythmia
- Dysautonomia
- Acute rhabdomyolysis and renal failure
3 main groups of patients with neuromuscular disease may require treatment in the ICU

I. Patients with severe new onset of neuromuscular disease

II. Patients with pre-existing chronic neuromuscular conditions who develop acute complications

III. Patients whose neuromuscular disorder arises in the ICU
Severe new onset neuromuscular disease in the ICU

- Guillain Barre Syndrome
- Severe acute neuropathy
- Acute flaccid paralysis syndrome (WNV, enterovirus 71- mostly with encephalitis)
- Myasthenic crisis and other disorders of the neuromuscular junction
- Acute myopathies
- New manifestations of chronic conditions

M. S. Damian, Addenbrookes Hospital, Cambridge
Guillain-Barre Syndrome

- Incidence 10-20 per million per year
- 50% prodromal infection: respiratory, gastrointestinal
- 90% have under 4 weeks progression
- 60% become bedbound, 30% tetraplegia
- Patients who are elderly, became bedbound within a week, and have facial and bulbar weakness are most likely to develop respiratory failure and need intubation
- 25% of ventilated cases still unable to walk after 6 months
- 40% retain residual deficits

M. S. Damian, Addenbrookes Hospital, Cambridge
Guillain-Barre Syndrome and Intensive care

• 78% of patients needing ventilation require it more than 3 weeks [Lawn, Wijdicks 1999]
• Autonomic dysfunction occurs in 60%
• Mortality in >60% from respiratory failure, secondary infection and pulmonary embolism
• Cardiac arrhythmia accounts for 20-30% of deaths
• Arrhythmia may occur unpredictably during both de- or remyelinating phases and may be triggered by medications
• 2/3 of deaths are after ICU discharge: there must be a persistent risk of death during recovery [Damian and Howard 2013]

M. S. Damian, Addenbrookes Hospital, Cambridge
Respiratory Issues in GBS

- Higher mortality in patients who are elderly, have pulmonary disease, autonomic involvement, bulbar dysfunction, rapid progression (Hughes 3 on admission).
- Bedside respiratory monitoring with the “20/30/40 rule”: critical values to consider intubation are FVC less than 15-20ml/kg body weight; maximum inspiratory pressure < -30 H₂O; maximum expiratory pressure < 40cm H₂O
- Cough can be measured in PECF L/min, where a value < ca.160 may indicate potential delayed failure of extubation through inadequate clearing of excretions (PECF 60L/min at ET tube) [Winck JC 2015; Bach JR 1996, Pitts T Lung 2014]
- 42% of attempted extubations failed [Nguyen TN 2006]
## Bedside Respiratory Monitoring

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal value</th>
<th>Critical value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced Vital Capacity</td>
<td>40-70 mL/kg</td>
<td>15-20 mL/kg</td>
</tr>
<tr>
<td>Peak Inspiratory Pressure</td>
<td>Male: &gt; -100 cm H²O</td>
<td>-30 to - 40 cm H²O</td>
</tr>
<tr>
<td></td>
<td>Female: &gt; -70 cm H²O</td>
<td></td>
</tr>
<tr>
<td>Peak Expiratory Pressure</td>
<td>Male: &gt;200 cm H²O</td>
<td>40 cm H²O</td>
</tr>
<tr>
<td></td>
<td>Female: &gt;140 cm H²O</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>Male: &gt; 330 L/min</td>
<td>Peak cough flow</td>
</tr>
<tr>
<td></td>
<td>Female: &gt; 280L/min</td>
<td>&gt;160L/min or mouth or PEF &gt;60L/min at tube for extubation</td>
</tr>
</tbody>
</table>

M. S. Damian, Addenbrookes Hospital, Cambridge
Respiratory Issues in GBS II

• Inadequate protection of airways through bulbar weakness, or a cough too weak to clear airways in borderline respiratory failure requires intubation

• Non-invasive ventilation (NIV) as a temporizing measure in GBS is unhelpful [Lawn and Wijdicks]

• Emergency intubation of a patient in extremis, or in a patient who has already developed significant abnormalities of blood gases indicates inadequate monitoring

• Clear admission criteria to the ICU for monitoring, as well as criteria for intubation and start of mechanical ventilation are needed

• Effective critical care outreach after discharge from the ICU avoids readmissions

• Almost every patient can be weaned
Protocol to decide on ITU admission

M. S. Damian, Addenbrookes Hospital, Cambridge

Wijdicks, 2001
Dysautonomia in GBS patients

- Orthostatic hypotension, diabetes insipidus, cardiac arrhythmia (brady/tachycardia, asystole), drug sensitivity, and ileus are common [Zochodne 1994]
- Life-threatening autonomic symptoms in ca. 20%
- No single autonomic test will accurately predict severe risk
- Vagal spells are bronchorrhea, bradycardia and hypotension and may be triggered by invasive procedures and cholinergic drugs
- Hypertension and persistent tachycardia affect over 50% of ventilated GBS patients [Pfeiffer 1999]
- PRES has been reported as a central autonomic disturbance in GBS, affecting mainly women over 55y [Chen 2015; Rigamonti 2012]
- Takotsubo cardiomyopathy in GBS may be related to autonomic dysfunction [Martins RP 2010]
- SIADH may cause hyponatremia in GBS

M. S. Damian, Addenbrookes Hospital, Cambridge
GBS Differential diagnosis - acute neuropathy

- **Vasculitic Neuropathy** (especially mononeuritis multiplex course with multiple nerve infarcts, acute disorder with systemic features, skin features)

- **Paraneoplastic neuropathy**: often combined with encephalopathy; axonal and demyelinating nerve conduction abnormalities; poorly responsive to treatment

- **Porphyria** (disorders of heme synthesis, especially acute intermittent and variegate with abdominal pain, may be asymmetric, severe motor/sensory/autonomic, CNS symptoms: psychosis or excessive depression, axonal nerve damage)

- **Infectious neuropathies/neuronopathies** (HIV: like GBS with elevated CSF cells, West Nile virus, Brucellosis, Leptospirosis, Polio) → always test for HIV

- **Toxic neuropathies**: many causes, from tick paralysis to botulism. Voriconazole is a newly recognised cause of severe neuropathy in severely ill patients

- **Neoplastic** infiltration / intravascular lymphoma
Vasculitis with Peripheral Neuropathy - Classification

[KG Gwathmey, Lancet Neurol 2014]

1. Primary systemic vasculitides
   a. Small vessel (microscopic polyangiitis; eosinophilic granulomatosis with polyangiitis; granulomatosis with polyangiitis; essential mixed cryoglobulinemia; Henloch-Schoenlein purpura)
   b. Medium vessel vasculitis (polyarteritis nodosa)
   c. Large vessel vasculitis (giant cell arteritis)

2. Secondary systemic vasculitis associated with connective tissue disease (RA, SLE, Sjogren, systemic sclerosis, dermatomyositis, MCTD), sarcoidosis, Behcet’s disease, infection, drugs, malignancy, urticarial vasculitis

Less commonly presenting in Intensive Care:

3. Non-systemic/localised vasculitides (Non-systemic vasculitic neuropathy, diabetic radiculoplexus neuropathy, localised cutaneous neuropathy)
Differential diagnosis to vasculitis: A 61yr old male with 1 month rapid progression to tetraplegia and respiratory failure

L superficial radial N. biopsy: 'myelin ovoids' = acute axonal degeneration

-patchy axonal loss;
-regeneration clusters

PM Left median N.: - malignant lympho-reticular infiltrate
Disorders of the Neuromuscular Junction

M. S. Damian, Addenbrookes Hospital, Cambridge
Mutations affecting NMJ: Rapsyn (deficient clustering of AchRs); Reduced quantal release; ChAT (defect in Ach resynthesis); Endplate Ach deficiency; SCN4A (postsynaptic failure to stimulate AP); Perlecan (defect in Ach location)
When do myasthenic patients require ICU treatment?

1. **Myasthenic crisis:**
   - Weakness and respiratory failure acutely triggered by infection, general illness, or medication mistakes in an MG patient
   - Respiratory distress, pupillary dilatation, sweating, tachycardia

2. **Cholinergic crisis:**
   - Induced by excessive cholinesterase inhibitor treatment
   - Weakness accompanied by cholinergic symptoms (bradycardia, dry skin, bronchial secretions, abdominal pain, twitching and cramping, miosis)

3. **Combination of 1 and 2:** Patients in a crisis situation ineffectively treated with or unresponsive to cholinesterase inhibitors
Management of Myasthenic Crisis

• Recognise crisis early: test fatiguability, not just initial strength, check respiratory function, cough and swallowing, O²-saturation and counting in 1 breath 3-hourly.
• **Caution:** Myasthenia has a more erratic course than GBS.
• Investigate for causes of crisis: infection, drug errors
• Secure airway. Intubate if in doubt (VC near 15ml/kg, inspiratory pressure below 20mmHg)
• Treat infection, rehydrate, remove inappropriate medication
• Defer tracheostomy, as a rapid recovery is possible
• Discontinue pyridostigmine initially during ventilation, reintroduce gradually observing i.v. dose requirements (iv. = 30x oral dose, iv. Neostigmine = 60x oral dose of pyridostigmine)
• Perform PLEX (?more reliable than IVIG?).
• Start high-dose steroids (if ventilated) 2x1g i.v. then 100mg oral
ICU specific aspects of MG crisis

- Intensive respiratory therapy and initial non-invasive BiPAP may reduce ventilator days
- Often only a short period of ventilation is needed - avoid early tracheostomy
- Relatively high risk of reintubation as standard predictors of extubation success unreliable. PECF may be additional useful parameter
- Death in myasthenic crisis is not expected: <5% in literature
- 8.7% mortality in UK ICUs, 22 acute hospital mortality
- Causes of mortality are late admission (impending crisis unrecognised by ward; ICU admission refused due to fluctuation), inappropriate ward transfer, and failure to treat recurrent crises (prognostic misinterpretation)
  - 2/3 of deaths occur after discharge to ward - aftercare is a major problem
  - Avoid failed ward transfers by providing clear handover protocols with defined monitoring plan, and no transfers at night

M. S. Damian, Addenbrookes Hospital, Cambridge
Clinical Features of MuSK +ve MG

- Female predominant (80%) Onset neonatal to 68 years, Peak 4th decade
- ≤50% of European anti-AChR antibody negative MG patients.
- More common in: Afro-Americans and in warmer latitudes. Female 80% to 90%; HLA association: DR14-DQ5
- Bulbar onset associated with rapidly progressive course
- Facial weakness (100%), dysarthria 100%, ocular 90%, respiratory crises common; limb weakness 30%
- Response to Pyridostigmine is unsatisfactory: early PLEX and escalation of immunosuppression advised (Rituximab)
It's not always MG or GBS

- Muscle diseases 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 positive, done after biopsy

M. S. Damian, Addenbrookes Hospital, Cambridge
20 year old student, 6 weeks rash, dysphagia. 2 weeks limb weakness.
0.5g/kg prednisolone/d. Admitted to ITU with respiratory failure
Cardiac Involvement in Inflammatory Myopathy

• In 2/3 of cases, unfavourable prognosis once symptomatic
• Cardiac changes frequently secondary to chronic steroid use and refractory interstitial lung disease
• More frequent with widespread connective tissue disease (Anti-Jo1 disease)
• Myocarditis in Polymyositis
• Small vessel vasculitis and abnormal vasoconstriction in Dermatomyositis
• Granulomatous myocarditis in sarcoid myopathy

M. S. Damian, Addenbrookes Hospital, Cambridge
Acute rhabdomyolysis and toxic-metabolic muscle disease

- Multiple toxic causes
- Inflammatory myopathy: anti-MAS or anti-SRP
- Paraneoplastic myopathy.
- Genetic disorders:
  - McArdle and other glycogen storage diseases
  - Carnitine palmitoyltransferase 2 deficiency
  - Defects of oxidative phosphorylation and beta-oxidation
  - Disorders of intracellular calcium handling (MH/RYR1)
  - Investigate with next generation sequencing panel
- Muscle hyperactivity syndromes (MNS, inhalational anaesthetics + myotonia)

M. S. Damian, Addenbrookes Hospital, Cambridge
II. Preexisting neuromuscular disease presenting acutely to the ICU

- New respiratory failure
- New cardiac failure and arrhythmia
- Complications of previously diagnosed neuromuscular disease
  - Respiratory failure in muscular dystrophy
  - Cardiac failure and transplantation
  - Dysrhythmia
  - Perioperative considerations

M. S. Damian, Addenbrookes Hospital, Cambridge
Myopathies presenting with respiratory failure

- Myofibrillar myopathies
- Myosin-loss myopathy
- Acid Maltase deficiency
- Amyloid myopathy
- Inflammatory myopathies (esp. Jo-1)
- Congenital Myopathies (Rod; Centronuclear; Multiminicore)
- Toxic myopathy: Hydroxychloroquine
58 year old male, hiking in high altitude developed increasing shortness of breath, acute respiratory failure, intubated, diagnosed with GBS and treated with IVlg
Weaning after 2 months, continued NIV; CK normal; EMG myopathic.

M. S. Damian, Addenbrookes Hospital, Cambridge
Hereditary myopathies causing adult onset isolated respiratory failure

- Titinopathy “HMERF” Hereditary Myopathy with Early Respiratory Failure (AD OMIM 603689) Type 1 (2q24-31 Swedish Titin R279W mutation); Type 2 (2q21 French)
- Glycogen storage disorders: GSD 2 (Acid maltase) and 3 (Debrancher): most often with exercise intolerance
- Mitochondrial myopathy: with multisystemic features, PEO, CNS
- Myofibrillar myopathies: Desmin (cardio), αB-crystallin (cataracts), Myotilinopathy (Spheroid body variant of myotilinopathy [Foroud 2005 S39F mutation in TTID gene])
- Limb-girdle MDs: Calpainopathy (2A); Fukutin-related (2I): mild respiratory involvement; other leading features
- Oculopharyngodistal MD (AD/AR OMIM 164310)
- Distal myopathy with early respiratory failure (AD OMIM 607569) (HIBM-ERF)
- Variants of congenital myopathies: Nemaline rod OMIM 102610 (ACTA1 mutations 1q42 variable inheritance Asn115Ser; Gly268Cys; Ile136Met); ? TPM3/SEPN1 centronuclear and cap myopathies
Genetic myopathies and cardiomyopathy

- Dystrophinopathies (esp. exon 48-53)
  - Duchenne Muscular Dystrophy
  - Becker Muscular Dystrophy
  - Manifesting female carriers rarely

- Limb-Girdle Muscular Dystrophies
  - 1A Myotilin,
  - 1B Laminopathies
  - 1E
  - 2C-F Sarcoglycanopathies

- FKRP (LGMD 2I and MDC1C)
- Fukuyama CMD
- Barth Myopathy (Xq28 Taffazin)
- Danon Disease (Xq22 Lamp-2)
- Myofibrillar Myopathies
Cardiac disease and transplantation in chronic muscle disease

- Cardiac failure may be an initial symptom and myopathy may be diagnosed in the ICU or after transplantation.
- Some myopathies (e.g. Becker muscular dystrophy; myofibrillar myopathies) typically develop cardiomyopathy and may require transplantation.
- 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).
- Patients with Becker-type dystrophinopathy constitute 50% of 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).
Critical Care issues in Duchenne muscular dystrophy

- Potential life expectancy for patients with DMD has doubled 38 years (Reason: MDT care with planned protocols and interventions such as NIV).
- MDT management allows discussion of issues such as ventilation and tracheotomy with the patient before the situation arises.
- It is essential that the critical care team understand current life expectancy and quality of life potential.
- Recovery after ICU treatment is determined by the quality of long-term care and whether non-invasive ventilation and cough-enhancement techniques have been instituted in a timely fashion.
- Long-term home ventilation makes weaning less concern before starting ICU treatment.
- The risk of dysrhythmia and of cardiac failure is increased.
- Anaesthetic complications in DMD include intraoperative heart failure, inhaled anesthetic-related rhabdomyolysis and malignant-hyperthermia-like syndrome, and succinylcholine-induced rhabdomyolysis and hyperkalemia (use non-depolarizing muscle relaxants).
ICU management of chronic neuromuscular disease

- What are the patient’s wishes?
- What is long-term survival and quality of life?
- Does treatment benefit patient’s quality of life?
- Decisions on ICU admission need to be adequately informed:
  Life expectancy is much better through protocolised care and timely interventions (eg. NIV)

M. S. Damian, Addenbrookes Hospital, Cambridge
Initial clinical assessment:
• Is the neurology characteristic (true fatiguing for MG; areflexia, dysautonomia and flaccid tone for GBS) ?
• Are there historical or clinical features suggesting pre-existing chronic neuromuscular disease (disability, respiratory or cardiac problems; muscle atrophy, contractures etc.) ?
• Is there a family history suggesting genetic neuromuscular disease ?
• Are there suspect toxic medications?

Standard diagnostic workup:
• Exclude brain and spinal cord disease
• Electrophysiological testing: conclusive or equivocal?
• Is creatine kinase elevated?
• Is the initial treatment response satisfactory ?

Specialised investigations:
• Muscle MRI or CT: are there signs of degenerative muscle disease
• Inflammatory myopathy blood panel
• Muscle biopsy: Obtain high quality histology from a carefully selected muscle including immunohistochemistry and electron microscopy. Conserve frozen tissue sample
• Genetic analyses: agree plan for genetic testing. Sequencing panels.
• Involve specialist laboratory services/neuromuscular centre
Acknowledgements:
Histology courtesy Hadi Manji, Queen Square, Andrew Dean and Dominic O’Donovan, Neuropathology, Cambridge University Hospitals