Managing Acute Neuromuscular Weakness
Neuromuscular Emergencies

Approach to an acute, rapidly progressing, generalized lower motor neuron weakness

aka

Approach to an acutely floppy person
Today’s Agenda

Practical approach to weakness

Focus on specific neuromuscular disorders:
  Guillain Barre Syndrome
  Myasthenia Gravis

  Focusing on crises
Weakness is not always neurological

Causes of generalized weakness

- Neurological
  - Upper Motor Neuron
  - Lower Motor Neuron
  - Both UMN and LMN
- Non-neurological
Weakness is not always neurological

Causes of generalized weakness

- Neurological
  - Upper Motor Neuron
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  - Both UMN and LMN
- Non-neurological
Non-neurological

Hypoglycemia

Electrolyte abnormalities: $K^+$, Ca, Mg, PO$_4$

Sepsis

Acute coronary syndrome

Cardiopulmonary disease

Adrenal insufficiency

Anemia

Dehydration/hypovolemia

Drugs

Fibromyalgia/Arthritis

Malignancy

Depression/conversion disorder
Most important Neurological Investigation
When the weakness is neurological

Causes of generalized weakness

- Neurological
  - Upper Motor Neuron
  - Lower Motor Neuron
  - Both UMN and LMN
- Non-neurological
<table>
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<th><strong>Lower motor neuron</strong></th>
<th><strong>Upper motor neuron</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flaccid</td>
<td>Spasticity</td>
</tr>
<tr>
<td>Decreased tone</td>
<td>Increased tone</td>
</tr>
<tr>
<td>Decreased muscle stretch reflexes</td>
<td>Increased muscle stretch reflexes</td>
</tr>
<tr>
<td>Profound muscle atrophy</td>
<td>Minimal muscle atrophy</td>
</tr>
<tr>
<td>Fasiculations present</td>
<td>Fasiculations absent</td>
</tr>
<tr>
<td>May have sensory disturbances</td>
<td>May have sensory disturbances</td>
</tr>
</tbody>
</table>
Bilateral UMN weakness

Cerebrum
- Bilateral strokes
- Parasagittal tumors
- Diplegic CP

Brainstem
- Midbrain/pons/medulla

Spinal cord disease
- Trauma
- Infection/Abscess
- Neoplasm – primary or metastatic
- Haemorrhage
- Inflammation (myelitis)
- Degenerative disorders
- Demyelination
4 anatomic stations underlying LMN weakness

1. The anterior (ventral) horn cell
2. The peripheral nerve, (ventral and dorsal nerve roots i.e., radiculopathy, plexus i.e. plexopathy, or nerve i.e., neuropathy)
3. The neuromuscular junction
4. The muscle (i.e. myopathy)
Rapidly progressive bilateral LMN weakness

**Anterior horn**
- ALS
- Poliomyelitis
- SMA

**Root**
- Radiculopathies from compression

**Plexopathies**
- Lumbosacral - ischemic

**Polyneuropathies**
- Guillain-Barre syndrome
- Critical illness polyneuropathy
- Thiamine deficiency
- Diabetes

**NMJ disorders**
- Myasthenia Gravis
- Botulism
- Neuro-muscular blocking agents
- Lambert-Eaton myasthenic syndrome

**Myopathies**
- Inflammatory (polymyositis)
- Electrolytes
- Periodic paralyses
- Drugs (steroids, alcohol)
- Muscular dystrophy
- Endocrine (Cushing’s, Thyroid disease)
- Critical illness myopathy
- Mitochondrial myopathies
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Spinal shock
### Duration of spinal shock

Table 2  Recovery of reflexes: four phases of spinal shock

<table>
<thead>
<tr>
<th></th>
<th>0–1 day</th>
<th>1–3 days</th>
<th>1–4 weeks</th>
<th>1–12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPR</td>
<td>++ ++</td>
<td>++ ++</td>
<td>+/0</td>
<td>+/0</td>
</tr>
<tr>
<td>BC reflex</td>
<td>+/-0</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>AW reflex</td>
<td>+/-0</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>CM reflex</td>
<td>+/-0</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Babinski sign</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>
| Flexor withdrawal reflex | 0 | +/-0 | ++ | ++++
| DTRs             | 0       | +/-0     | ++        | +++         |
| Tibial H-reflex  | 0       | ++       | +         | +++         |
| Extensor spasm   | 0       | 0        | 0         | +           |
| Interlimb reflexes | 0   | 0        | 0         | +           |
| Reflex neurogenic bladder | 0 | 0 | 0 | +
| Autonomic hyper-reflexia | 0 | 0 | 0 | +

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www.nature.com/sci
How to localize LMN lesion?
Localization clues

• Are there **sensory/autonomic** disturbances?

• Is the **face** involved? (involvement of cranial nerves/facial or bulbar muscles)

• What are the **reflexes** like?

• Is the weakness more **proximal or distal**?
## Localization of ‘LMN’ Disorders

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<thead>
<tr>
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Suggested approach

1. Stabilizing Management – **ABCs**
   
   *Watch for signs of impending respiratory failure resulting from neuromuscular weakness*

2. Lesion **localization** with good clinical history and examination

3. Think of **causes** of weakness
   
   – Adjunctive diagnostic tests
   – Treat appropriately
Is **mental status** impaired?
   CNS lesion above spinal cord

Is there **sensory** involvement?
   GBS can present with pain

Is there **bladder** involvement?
   Myelopathy results in sensory level and bladder dysfunction
   Autonomic dysfunction in GBS can affect bladder

What is the **pattern** of weakness?
   Unilateral, bilateral, generalized; Proximal or distal weakness

Are there **bulbar** signs?
Is there **facial** weakness?

Is there diplopia or blurred **vision**?
   Botulism can also cause blurred vision
History

Over what **duration** did the symptoms develop?

* **Sudden**: vascular cause
  * **Acute/subacute**: Inflammatory, infectious/parainfectious, toxic/metabolic (polyneuropathies, myelopathies), myopathies, NMJ disorders
  * **Insidious**: Tumor-related, Degenerative (Myopathies, muscular dystrophies, ALS)
  * **Episodic**: Hypokalemic/hyperkalemic periodic paralysis, NMJ disorders (end of the day?)

Is there **fluctuating pattern to weakness**?

* NMJ disorders – fatiguability of vision, bulbar signs
* Periodic paralysis from potassium – attacks of weakness
History

**Drug history**
- Statins, Traditional medications, Steroids, chemotherapy, antibiotics, colchicine, HAART, magnesium-containing antacids
- Exposure to insecticides: organophosphate poisoning

**Pre-existing neuromuscular disorder**
- MG, ALS

**Infectious symptoms/recent illness**
- 70% of AIDP has antecedent viral illness or Campylobacter jejuni
- 40% of myasthenic crisis triggered by infection
- Decompensation of other NM disorders as a result of sepsis

**Diet**
- Canned goods – botulinum toxin
Targeted Examination

Pupils

Pupillary reactivity may be lost with botulism and in Miller-Fisher variant of AIDP (triad of ophthalmoplegia, ataxia and areflexia)

Extraocular muscles

Ptosis and ocular muscle weakness is characteristic of myasthenia gravis

Ophthalmoplegia in GBS and MG

Face, palate, tongue and neck strength
Pattern of Weakness

Objectives muscle weakness

- Yes
  - Generalized
    - Cachexia
    - Myasthenia gravis (worse with exertion)
    - Periodic paralysis
  - Localized

- No
  - Cardiopulmonary disease
  - Anemia
  - Chronic infection
  - Malignancy
  - Depression
  - Deconditioning
  - Arthritis
  - Fibromyalgia

Asymmetric
- Regional neurologic disorders
- Cerebrovascular or spinal cord disease
- Demyelinating disorders
- Compression neuropathy
- Mononeuropathy/mononeuritis multiplex
- Disuse atrophy
- Myasthenia gravis

Symmetric

Specific pattern
- Muscular dystrophy
- Hereditary neuropathy
- Myasthenia gravis

Proximal
- Myopathy
- Duchenne muscular dystrophy
- Myasthenia gravis

Distal
- Peripheral neuropathy
- Motor neuron disease
- Myasthenia gravis
Targeted Examination

**Fasiculations**
Organophosphate poisoning, ALS

**Fatiguability**

**Reflexes**
Areflexia associated with GBS

**Coordination**
Ataxia occurs with Miller-Fisher variant of AIDP

**Sensation**
Cervical or upper thoracic sensory level associated with quadripareisis suggests a cervical cord lesion
Failure to recognize a crisis can lead to death

Do I need to intubate and ventilate?
Signs of impending respiratory failure

Vital signs

Hemodynamic instability
Signs of Dysautonomia in GBS
Bradycardia may require pacing
Don’t miss pulmonary embolism
Signs of impending NM respiratory failure

Tachypnea, tachycardia, agitated

Unable to speak in full sentences, count to 20

Profound weakness of neck flexion

Use of accessory muscles
Paradoxical breathing pattern
Orthopnea

Signs of bulbar dysfunction (nasal voice, accumulation of saliva, weak cough and gag)
   → consider aspiration!
Impending respiratory failure

SpO2 usually is normal

ABG will not show hypercapnia till very late due to intact ventilatory drive and compensatory increased rate of breathing → not a good guide for deciding when to intubate

Look at NIF

-20 cm H₂O
-40 cm H₂O
Intelligent use of drugs for intubation

Use **non-depolarizing paralytic agent** eg. atracurium instead of depolarizing agent eg. succinylcholine

- Especially in pre-existing neuromuscular disorders eg skeletal muscle myopathies

- Prevents severe **hyperkalemia** associated with succinylcholine and neurologic injury

- Risk of hyperkalemia usually several days after event
  - Acute spinal cord injury: severe hyperkalemia occurs at 21d
  - GBS: at 7d
  - Complete denervation of muscles: 3d
  - Partial denervation: 7d
Adjunctive diagnostic tests

Hb, Electrolytes, CK levels, AST/ALT levels, thyroid screen, cortisol, ESR, autoimmune screen

CXR (pneumonia, atelectasis), ECG (arrhythmias from autonomic dysfunction)

CSF analysis
  GBS: albumino-cytologic dissociation
  Myelitis: pleocytosis

Neuro-radiologic testing
  CT/MRI brain
  CT myelography/MRI spine

Electrophysiological studies: NCS, EMG, SSEP, MEP, VEP
Take home points

Is the patient **stable**?
- Impending respiratory failure
- Hemodynamic compromise

Do I need to **intubate**?
- Intelligent use of drugs

Is the weakness **neurological**?

How to **localize** the lesion and determine etiology
Case scenario 1

50 year old woman with URTI symptoms 2 weeks ago
History of tingling in feet and hands for 3 days with back pain, and gait instability.
Now weakness starting from the legs, currently unable to stand on her own or hold utensils reliably.

On examination, there is flaccid tone of her lower limbs, with areflexia in all limbs with down going planters. Power is MRC 3/5 of her upper and lower limbs.
What are your differential diagnoses?
LMN Weakness

4 anatomic stations underlying LMN weakness

1. The anterior (ventral) horn cell
2. The peripheral nerve, (ventral and dorsal nerve roots i.e., radiculopathy or nerve i.e., neuropathy)
3. The neuromuscular junction
4. The muscle (i.e. myopathy)
Bilateral LMN weakness

**Anterior horn**
- ALS
- Poliomyelitis

**Root**
- Radiculopathies from disc herniation

**Plexopathies**
- Lumbar

**Polyneuropathies**
- Guillain-Barre syndrome
- Diabetic

**NMJ disorders**
- Myasthenia Gravis

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**Spinal shock**
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Clinical features of classic GBS

Motor > sensory polyradiculoneuropathy
1. Weakness – usually begins distally, symmetrical
2. Positive neuropathic sensory symptoms
   – tingling, pain ~ 50%
3. Areflexia/hyporeflexia (or hyper-reflexia in 10%)
4. Diaphragmatic and cranial nerve weakness ~ 50%
5. Autonomic involvement > 50%

Acute-to-subacute onset
Nadir within 4 weeks
Monophasic illness

Seminars Neurol
2008;28:152-167

NEJM
2012;366:2294-304
<table>
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<th>Differential diagnosis of GBS†</th>
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<tr>
<td><strong>Peripheral neuropathy</strong></td>
</tr>
<tr>
<td>• Vasculitic neuropathy</td>
</tr>
<tr>
<td>• Diphtheric neuropathy</td>
</tr>
<tr>
<td>• Acute intermittent porphyria</td>
</tr>
<tr>
<td>• Critical illness neuropathy</td>
</tr>
<tr>
<td>• Diabetic-uraemic neuropathy with acute peritoneal dialysis</td>
</tr>
<tr>
<td><strong>Disorders of neuromuscular junction</strong></td>
</tr>
<tr>
<td>• Myasthenia gravis</td>
</tr>
<tr>
<td>• Eaton-Lambert syndrome</td>
</tr>
<tr>
<td><strong>Disorders of muscle</strong></td>
</tr>
<tr>
<td>• Inflammatory myopathy</td>
</tr>
<tr>
<td>• Toxic myopathy/acute rhabdomyolysis</td>
</tr>
<tr>
<td>• Periodic paralysis</td>
</tr>
<tr>
<td><strong>Disorders of CNS</strong></td>
</tr>
<tr>
<td>• Brainstem stroke</td>
</tr>
<tr>
<td>• Brainstem encephalitis</td>
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</tbody>
</table>

† Differential diagnosis of acute onset flaccid paralysis. Disorders of the central nervous system (CNS) may present with acute generalized flaccid paralysis.

May be **normal** in early phase of GBS

Supportive findings at initial CSF analysis \(\sim 50\%, \, 90\%\) by clinical nadir
- Elevated CSF protein concentration
- Normal cell count or < 10 WBCs

Should still make the diagnosis based on history and examination for prompt treatment; not essential to repeat CSF

If CSF **pleocytosis** is seen
- Infectious (HIV, CMV, Lyme)
- Carcinomatous
Other tests:

Other tests: Electrodiagnostic testing - NCS

Exclude other diagnoses

- MRI brain
- MRI spine
  - Myelopathy, infiltrative or compressive causes of polyradiculopathy
  - May show enhanced nerve roots or cranial nerves as part of spectrum of GBS

Anti-ganglioside antibodies
### Spectrum of disorders of in the Guillain-Barre syndrome and associated Ig G autoantibodies

<table>
<thead>
<tr>
<th>Subtypes and variants</th>
<th>IgG autoantibodies to</th>
</tr>
</thead>
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<tr>
<td><strong>Guillain–Barré syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyneuropathy</td>
<td>None</td>
</tr>
<tr>
<td>Facial variant: Facial diplegia and paresthesia</td>
<td>None</td>
</tr>
<tr>
<td>Acute motor axonal neuropathy</td>
<td>GM1, GD1a</td>
</tr>
<tr>
<td>More and less extensive forms</td>
<td></td>
</tr>
<tr>
<td>Acute motor–sensory axonal neuropathy</td>
<td>GM1, GD1a</td>
</tr>
<tr>
<td>Acute motor-conduction-block neuropathy</td>
<td>GM1, GD1a</td>
</tr>
<tr>
<td>Pharyngeal–cervical–brachial weakness</td>
<td>GT1a &gt; GQ1b &gt;&gt; GD1a</td>
</tr>
<tr>
<td><strong>Miller Fisher syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Incomplete forms</td>
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<tr>
<td>Acute ophthalmoparesis (without ataxia)</td>
<td>GQ1b, GT1a</td>
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<td>CNS variant: Bickerstaff’s brain-stem encephalitis</td>
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<td></td>
<td>AIDP</td>
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<td>NCS findings</td>
<td>Demyelinating neuropathy</td>
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<tr>
<td></td>
<td>features</td>
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<tr>
<td>Progression and nadir</td>
<td>Longer, later (18.0 d)</td>
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<tr>
<td>Facial involvement</td>
<td>71%</td>
</tr>
<tr>
<td>Require Mechanical</td>
<td>27%</td>
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<tr>
<td>ventilation</td>
<td></td>
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<tr>
<td>Autonomic dysfunction</td>
<td>More</td>
</tr>
<tr>
<td>Recovery</td>
<td>Faster</td>
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Would you treat this patient?

What with?
Typical monophasic clinical course of the disease
Immunotherapy for Guillain-Barre Syndrome

1. Plasma exchange
   - Beneficial when given in 1st 4 weeks
   - Best effect when started within 1st 2 weeks
   - Exchanging one plasma volume, 5 separate occasions over 1 – 2 weeks

2. Intravenous immunoglobulin
   - 0.4 g/kg/day for 2 – 5 days
   - Best effect when started within 1st 2 weeks
Plasma exchange is better than just supportive treatment

- Reduced proportion of patients needing ventilation
- Reduced time taken to recover walking with an aid

IVIG is equivalent to PE for treatment

Change in disability

Time to walk unaided

Proportion of patients unable to walk at 1 year
When and who to treat?

Patients who are unable to walk

Unknown whether IVIG is effective in mildly affected patients

Start treatment preferably within the 1\textsuperscript{st} 2 weeks from onset
General supportive care

1. Monitor pulmonary function (NIF, VC) every 2-12 hours
2. Check for autonomic dysfunction (BP, HR, pupils, ileus, bladder/bowel dysfunction)
   • Caution with vasoactive medication and morphine derivatives
   • May require pacing
   • Caution with stimulation of patient eg. suctioning
3. Check for swallowing dysfunction, allow feeding with NGT
4. Treat pain eg amitriptyline, gabapentin
5. Prevent and treat infections
6. Prophylaxis against DVT – watch for PE!
7. Prevent corneal ulceration from facial weakness
8. Prevent decubitus ulcers and contractures
9. Rehabilitation ASAP
When do you need to admit to ICU?

1. Rapidly progressive severe weakness
2. Severe autonomic dysfunction
3. Insufficient swallowing with high chance of pulmonary infection
4. Impaired respiration (NIF ≤ 20)
5. Need for artificial ventilation
20/30/40 Rule

VC < 20 ml/kg

MIP < -30 cm H$_2$O

MEP < 40 cm H$_2$O

OR

Reduction of 30% in VC/MIP/MEP

Lawn et al. Arch Neurol 2001
Proposed flowchart for the use of clinical and respiratory factors in the management of Guillain-Barré syndrome. Hughes disability scale score of less than 3 indicates that the patient is able to walk unassisted more than 5 m. Hughes disability scale score of 3 or more indicates that the patient is unable to walk more than 5 m or less (ie, bedridden or receiving mechanical ventilation). VC indicates vital capacity; PImax, maximal inspiratory pressure (expressed as positive values for simplicity); PEmax, maximal expiratory pressure; and ICU, intensive care unit.
Guillain-Barre Dangers

Failure to recognize may cause death

- Aspiration
- Respiratory failure
- Autonomic instability
  - Major cause of death
  - Severe sudden hypotension
  - Cardiac arrhythmia
Take home points

• Recognizing GBS early
• Bulbar symptoms/signs are bad
• Do regular NIF monitoring
• Watch out for autonomic dysfunction
• Protect the corneas!
Case scenario 2

A 26-year-old woman presents with symptoms of progressive fatigue and intermittent double vision for 1 month.

Examination:
- Vital signs and mental status are normal.
- The patient is unable to fully abduct either eye.
- Motor examination demonstrates mild weakness of hip and shoulder muscles without atrophy or fasciculations.
- DTR’s are 2+ throughout.
- Sensory examination is normal.
- Serum CK is 150 (0-175 U/L).
Diagnosis?
Myasthenia Gravis

Immune attack directed against post-synaptic elements of NMJ (esp. Nicotinic ACh receptor)

Fluctuating weakness and fatiguability of ocular (in > 80%), bulbar, and limb muscles

Diagnosis:

- Clinical picture
- Edrophonium (Tensilon) test
- Repetitive stimulation test/SFEMG
- ACh receptor antibodies (present in 80% generalized, 50-70% ocular)
- Acquired anti-MuSK Abs (present in 40-50% of seronegative patients)
Myasthenia Gravis

Epidemiology:
- Women > Men (3:2)
- Bimodal incidence
  - Females: 20-30s
  - Males: 50-60s
- MuSK-MG: younger women, with predominantly facial, bulbar and respiratory weakness, mild limb weakness

5-10% co-association with other autoimmune disorders

Association with thymic abnormalities
- 10-15% thymoma
- 50-70% thymic lymphoid hyperplasia
While speaking to the patient, you note that her voice is soft and gurgly, and she can barely hold her head up. She looks sweaty as well.

What do you do?
Recognizing Myasthenic crisis

Defined as sudden worsening of respiratory, bulbar function, and/or profound muscle weakness

*Triggers:*

Concurrent infection
Medications
  - Aminoglycosides, macrolides, quinolones, antimalarials, phenytoin, carbamazepine, beta-blockers, calcium channel blockers, baclofen, NM-blocking agents, steroids
Drug withdrawal
Pregnancy
Surgery
Bulbar signs are BAD

May result in difficulty swallowing, chewing, and speaking

Unable to keep the jaw closed after chewing

Speech may be nasal (from weakness of the soft palate) and slurred (from weakness of the tongue, lips, and face)
Myasthenic crisis

DDx from cholinergic crisis
  – Abdominal pain, diarrhea, hypersecretion, pinpoint pupils

Hold ChE-Is

Atropine 2 mg/hr
Management of Myasthenic crisis

Intubation to protect airway

Respiratory support required if
- Negative inspiratory force of less than -20 cm H2O
- Clinical criteria (bulbar/respiratory/profound muscle weakness)

Treat precipitating factors

IVIG or plasmapheresis

PLEX may have faster more extensive effect?
Take home points

- Bulbar symptoms/signs are BAD
- d/dx cholinergic crisis
- Regular NIF monitoring
- Think of and avoid triggering factors
Questions?