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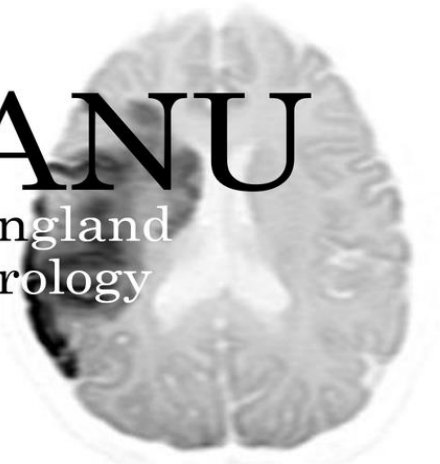

5 Things About: Neuromuscular Disease

Dr Katy Dodd

MANCHESTER 1824
The University of Manchester

Manchester Centre for Clinical Neurosciences

Salford Royal NHS
NHS Foundation Trust

Disclosures

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Katy Dodd

- Research funding from NorthCare Charity, Myaware and the Neuromuscular Study Group.

1. It’s not as hard as you think…

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Start with the background

New

Flare

Progression

1. It’s not as hard as you think…

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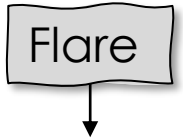
Start with the background



- Decompensation related to systemic illness?
  - Infection / metabolic screen
- Compliance?
  - Steroids / DMARDS / IVIG / Rituximab
- Missed treatments?
  - Holidays etc.
- Recent changes in treatment?
  - Attempts to wean down IVIG…
- Is the diagnosis correct? → Liaise with neurology

1. It’s not as hard as you think…

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Start with the background → Progression

- Decompensation related to systemic illness?
  - Infection / metabolic screen
- Is this expected?
- Is the diagnosis correct? → Liaise with neurology
- Have previous ceilings of care been discussed?

1. It’s not as hard as you think…

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New

- Localise the lesion

Wasting / Fasciculations | Tone | Reflexes | Motor Pattern | Fatiguability | Sensory Pattern

- Consider the speed of onset

Seconds	→	vascular / trauma
Hours-days	→	inflammation / infection
Weeks+	→	degenerative / genetic / metabolic / toxic / malignant

- Look for other clues

1. It’s not as hard as you think…

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Motor patterns

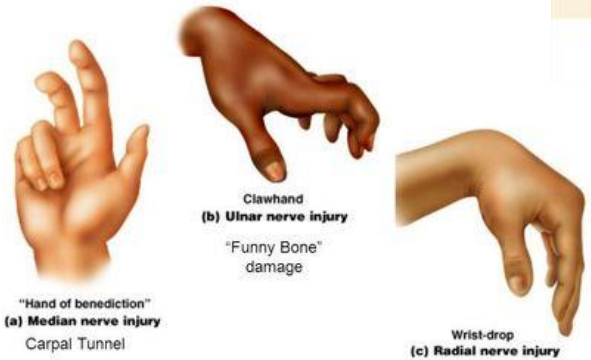
Symmetrical vs asymmetrical?

Proximal or distal?

CIDP
MG

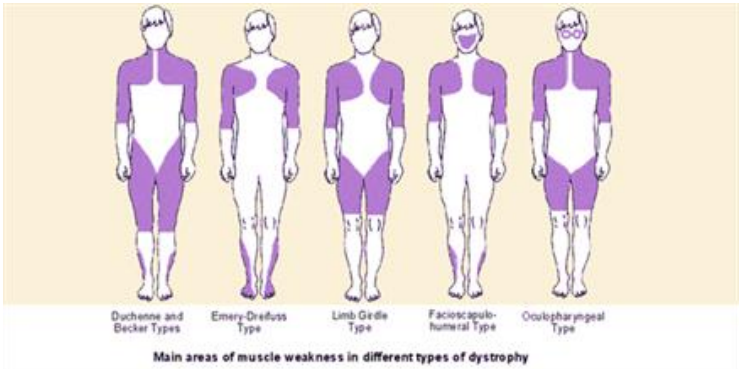
CIDP (DADS)
Axonal neuropathy

Individual nerve(s)?

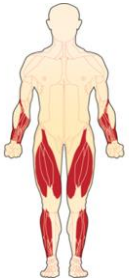


https://alliance-hw.com/hand-nerve-injuries

Specific pattern?



https://byjus.com/biology/muscular-dystrophy/



https://www.mda.org/disease/inclusion-body-myositis

Synthesise the information

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	LMN	UMN	LMN + UMN	NJM	Muscle
Acute - seconds	Mononeuritis Multiplex Compressive neuropathy	Stroke			
Sub-acute - Hours - days	GBS B12 (including NO)	CNS demyelination Cord compression B12 (NO)	B12 (NO) Cord + root compression	MG LEMS	Myositis
Chronic - weeks - months	Inflammatory – CIDP, MMN Genetic - CMT Nutritional - B12 (NO) Toxic – Alcohol, chemo Infiltrative – amyloid, lymphoma	B12 (NO) Tumour	MND B12 (NO)		Myopathy / muscular Dystrophy

Peripheral Nerve Clues

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Vascular	**Mononeuritis multiplex**	Asymmetrical, multiple individual nerves, painful, renal involvement
Compressive	**Compressive neuropathies / HNPP**	Asymmetrical, individual nerves, history of unusual positioning
Inflammation	**CIDP**	Progression of symptoms over 3 months
	Multifocal motor neuropathy	Asymmetrical, motor only, typically finger drop
Metabolic	**Critical care neuropathy / myopathy**	After ICU stay
	Nutritional / toxic neuropathy	Alcohol excess / poor nutrition or medications / chemo
	Subacute combined degeneration of the cord	B12 deficiency, Nitrous oxide use (functional B12 deficiency)
Infiltrative	**Amyloid**	Enlarged tongue, diarrhoea, heart failure, autonomic dysfunction
	Lymphoma	Weight loss, night sweats, lymphadenopathy
Genetic	**Charcot Marie Tooth**	Family history, high arches, hammer toes

Muscle Disorder Clues

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Inflammatory	**Dermatomyositis**	proximal weakness, heliotrope rash, gottron's papules, cancer
	Anti-synthetase syndrome	Jo-1 Abs,mechanic hands, ILD, arthritis
	Necrotising myopathy	severe weakness, v. high CK, SRP Abs (cancer) / HMGCR Abs (statins)
	Inclusion Body Myositis	long finger flexors and quadriceps, chronic
Metabolic / endocrine		Hypokalaemia / magnesaemia
		Hypothyroid
Genetic	**Muscular Dystrophies**	Myotonic dystrophy 1+2 (cataracts, heart block, frontal balding), Duchenne/ Becker (Big calfs), Limb girdle, FSH, Oculopharyngeal
	Glycogen Storage	McArdles (second wind), Pompe
	Fatty Acid Oxidation defects	CPTII
	Channelopathies	Periodic paralysis, Myotonia / paramyotonia congenita
	Mitochondrial	MELAS (deafness, diabetes, short, ptosis)
Toxic		Steroids Statins

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Neuromuscular Junction Disorder Clues

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Myasthenia Gravis	Females in 20s / Males in 60s / Thymoma (10%). AChR / MuSK Abs. Ocular then generalised. Fatigable weakness. Bulbar dysfunction (bulbar dysarthria, nasal regurg)
Lambert Eaton Myasthenic Syndrome	Autonomic symptoms (dry mouth, erectile dysfunction) VGCaCh Abs SCLC (50%)
Botulism	Acute descending paralysis starting in the face. Dry mouth, dilated pupils, postural hypotension, ileus. Not fatigable. Canned food / wounds.

Alternative diagnosis to MND clues: Don't miss something treatable

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Genetic	**Spinal muscular atrophy**	Young onset, LMN
	Kennedy's disease	Male, LMN, Gynaecomastia, perioral fasiculations
	Hereditary spastic paraparesis	Legs>arms, UMN only
Cord disease	**Compressive cervical myelopathy + lumbar radiculopathies**	Sensory involvement
Myopathy	**Inclusion body myositis**	Thighs / forearm flexor weakness
	Immune mediated necrotising myopathy	CK, statins, HMGCR Abs
Nerve	**Multifocal motor neuropathy**	No UMN signs

Cases

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Case 1.
55 M. Fit and well. Weakness 4 limbs over 1 week. Numbness to hands and feet.
O/E Proximal limb weakness and patchy sensory loss. Areflexic.

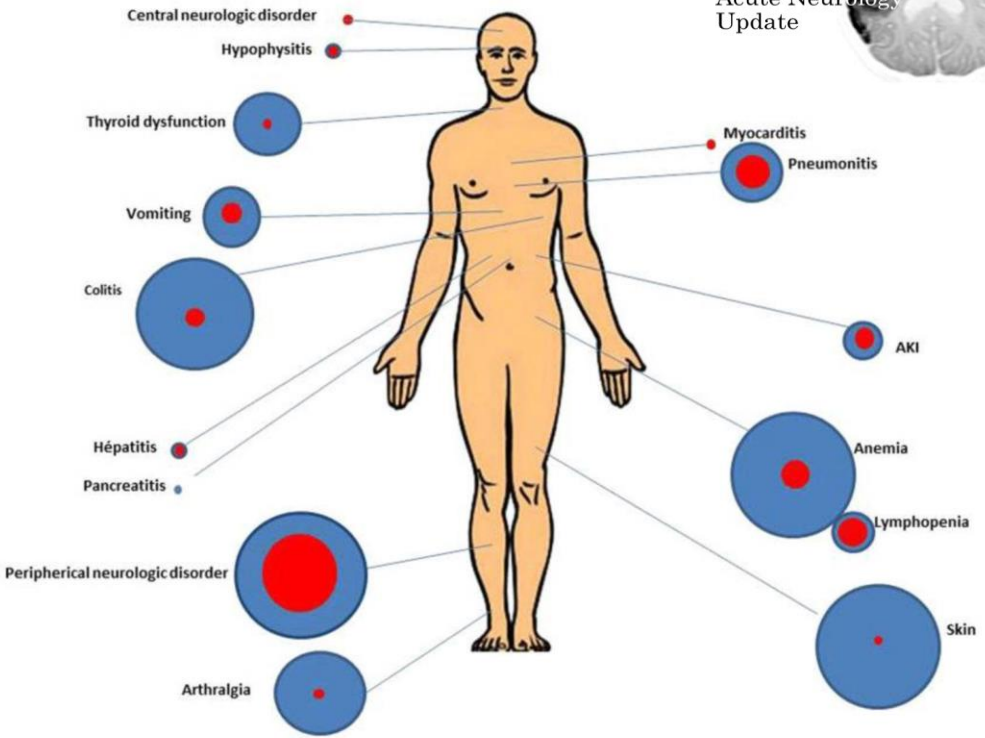
Case 2.
69 F. Fit and Well. Progressive weakness 4 limbs over 6 months. No sensory symptoms. O/E: wasting/fasciculations, asymmetrical limb weakness, brisk reflexes.

Case 3.
79 F. Fit and Well. Weakness of right hand, sudden onset, with pain.
O/E: right wrist drop with sensory loss over dorsum on hand. Rash and haematuria.

Case 4.
79 F. BG: melanoma. Weakness of 4 limbs over 2 weeks. Dysarthria and dysphagia.
No sensory symptoms. O/E: fatigable proximal limb weakness.

Checkpoint Inhibitor Toxicity

- Block immune checkpoints (CTLA-4, PD-1, PD-L1)
- Encourages T cell attack
- Revolutionised treatment of many cancers
- Autoimmune side effects common
- Neurological complications have high mortality (irMG = 30%)
- Need aggressive treatment



Ann Intensive Care. Feb. 2019. doi: 10.1186/s13613-019-0487-x.

2. (Relevant) investigations can be helpful

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- Check the basics:
  - B12, TFTs, CK, Igs +SEP, HIV
- Then consider fancier tests:
  - LP, glycolipids, nodal/paranodal, paraneoplastic abs, myositis abs
- Neurophysiology (if timed right)
- Maybe even imaging
- + potentially biopsy (nerve / muscle)
- Then genetics / mitochondrial screening

GBS phenotypes

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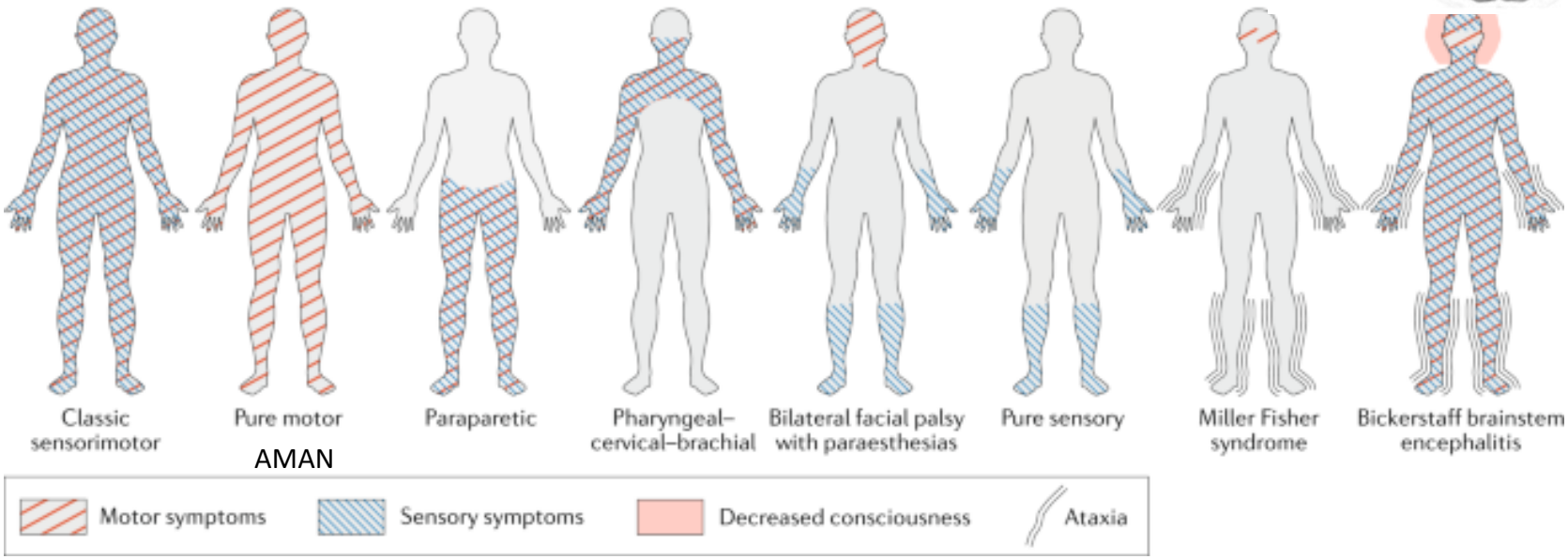

Ganglioside Antibodies:	GM1 GD1a	GT1a	GD1b	GQ1b GT1a	GQ1b GT1a

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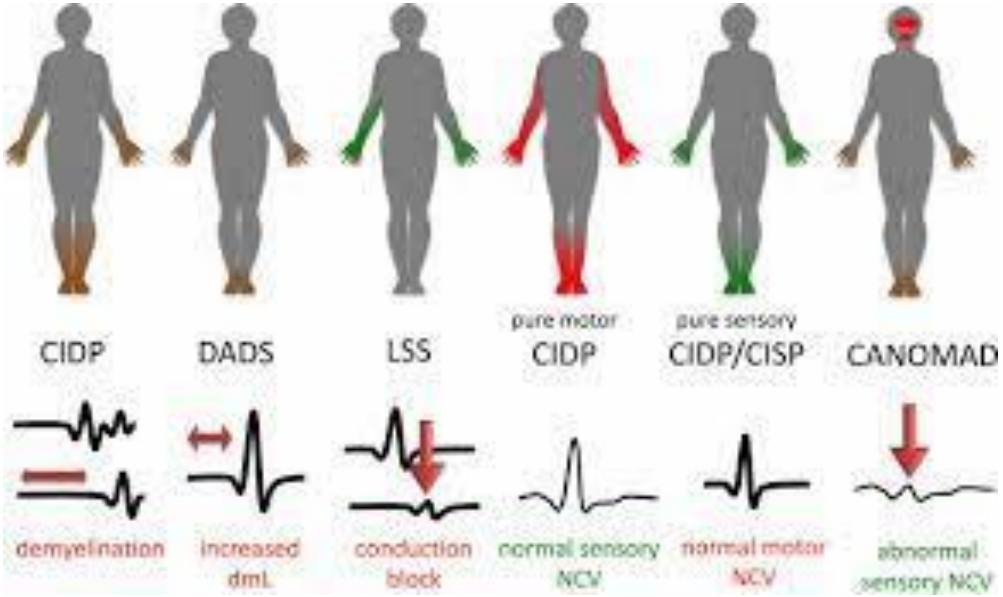
Chronic inflammatory demyelinating neuropathy

- “Chronic version of GBS”
- Sensory - motor syndrome
- Proximal and distal weakness
- Raised CSF protein and demyelinating NCS
- Often requires intensive immunosuppression / immunomodulation



Nodal / paranodal neuropathies

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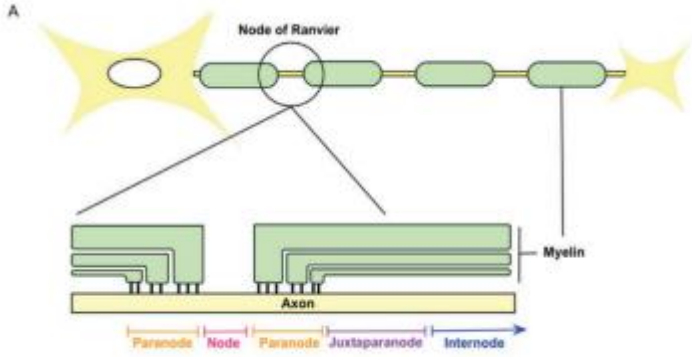

Table 2 Typical characteristics in patients with individual nodal/paranodal antibodies

Characteristics	Nodal/paranodal antibody: NF155	Pan-NF	CNTN1	Caspr1 or CNTN1:Caspr1 complex
Clinical features				
Neuropathy	Severe non-length-dependent sensorimotor neuropathy			
Age (median; years)	51.5	57.4	60	57.5
Male:female	1.6:1	3.5:1	3.3:1	2.3:1
Initial diagnosis GBS				
Ataxia				
Tremor				
Pain				
Cranial nerve palsies				
Respiratory failure				
Autonomic dysfunction				
Nerve root abnormalities				‡
Associated disorders				
Nephrotic syndrome (MGN–CNTN1, FSGS–pan-NF)		§	†	
IgG lymphoproliferative disorder				
CCPD	*			

Key

	Absent
+	<25%
++	25%–50%
+++	50%–75%
++++	75%–100%

Coloured boxes indicate frequency (as per key) of characteristic from our cohort.

*[18 40]

†[7–10 12]

‡[17]

§[1]

Caspr1, contactin-associated protein-1; CCPD, combined central and peripheral demyelination; CN, cranial nerve; CNTN1, contactin-1; FSGS, focal segmental glomerulosclerosis; GBS, Guillain-Barré syndrome; IgG, immunoglobulin G; MGN, membranous glomerulonephritis; NF155, neurofascin 155.

Neurophysiology in GBS

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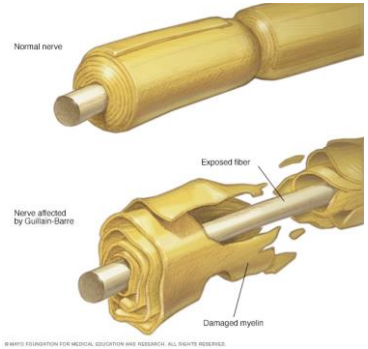
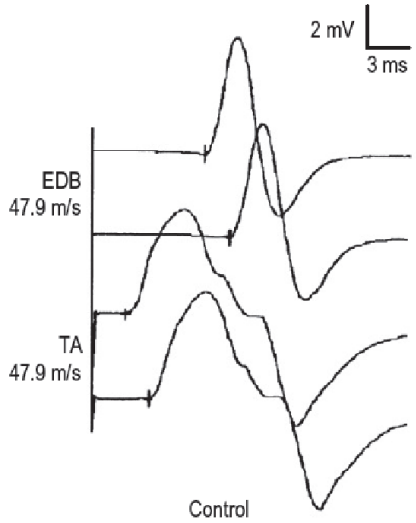
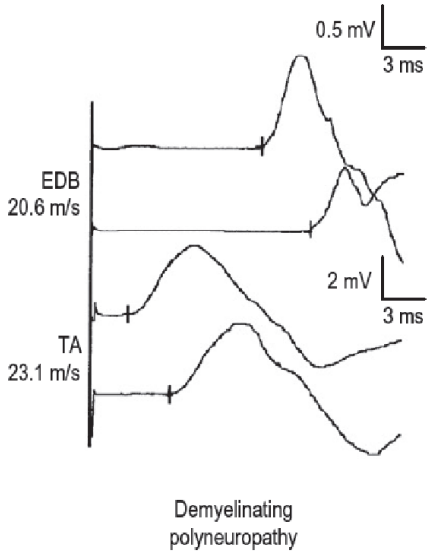
- Delayed F-waves
- Prolonged distal latency
- Reduced velocities
- To be done >2weeks after onset



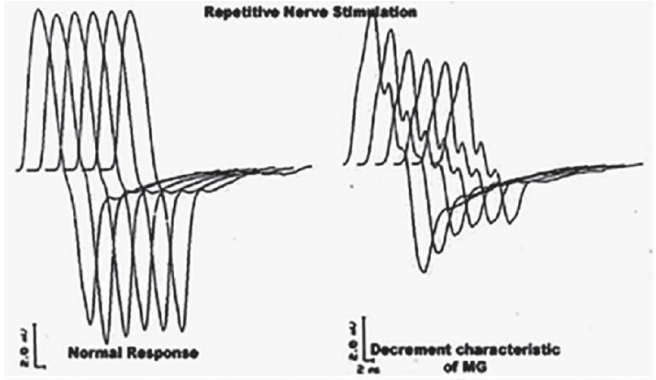


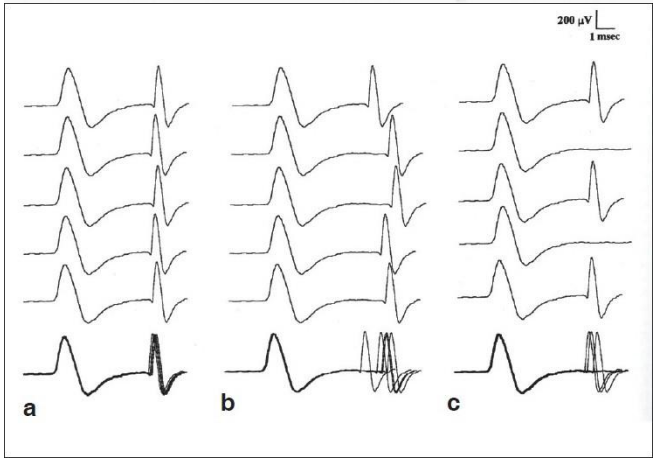


Neurophysiology in MG

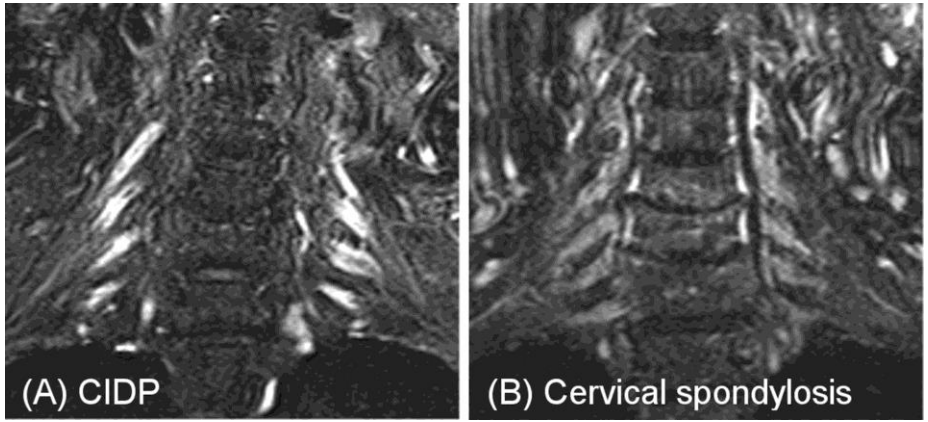
- Decrement on RNS
- Jitter on single fibre EMG

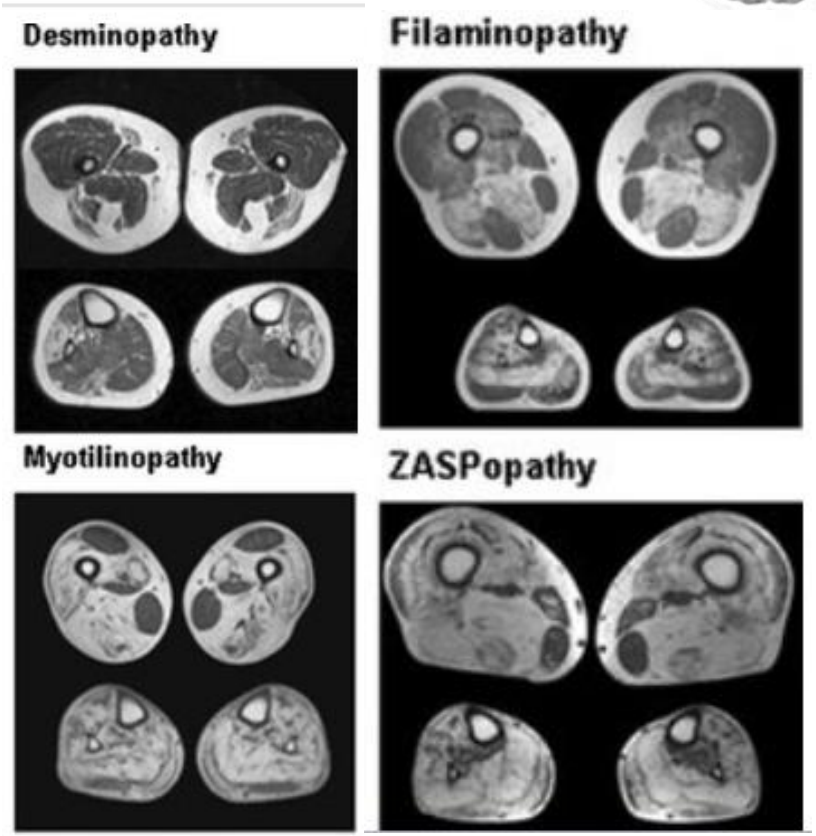
- Need to stop pyridostigmine 48 hours before (ideally – don't do this is acutely unwell)





Imaging


(A) CIDP
(B) Cervical spondylosis


Desminopathy
Filaminopathy
Myotilinopathy
ZASPopathy

Biopsy

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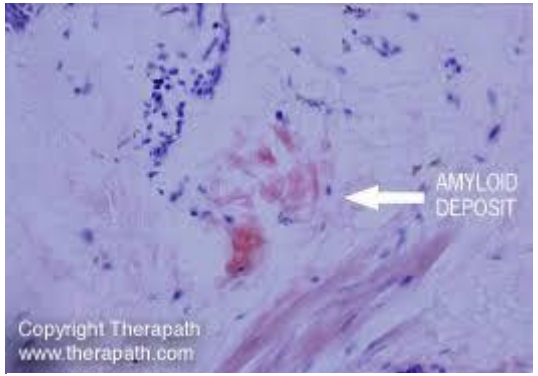

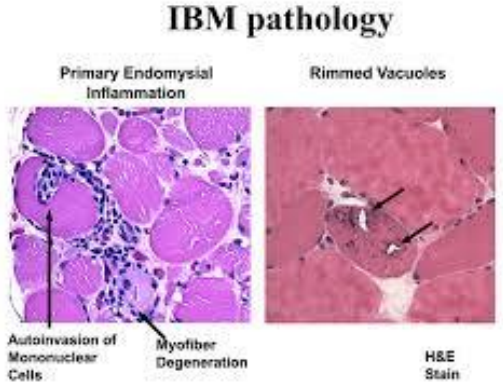

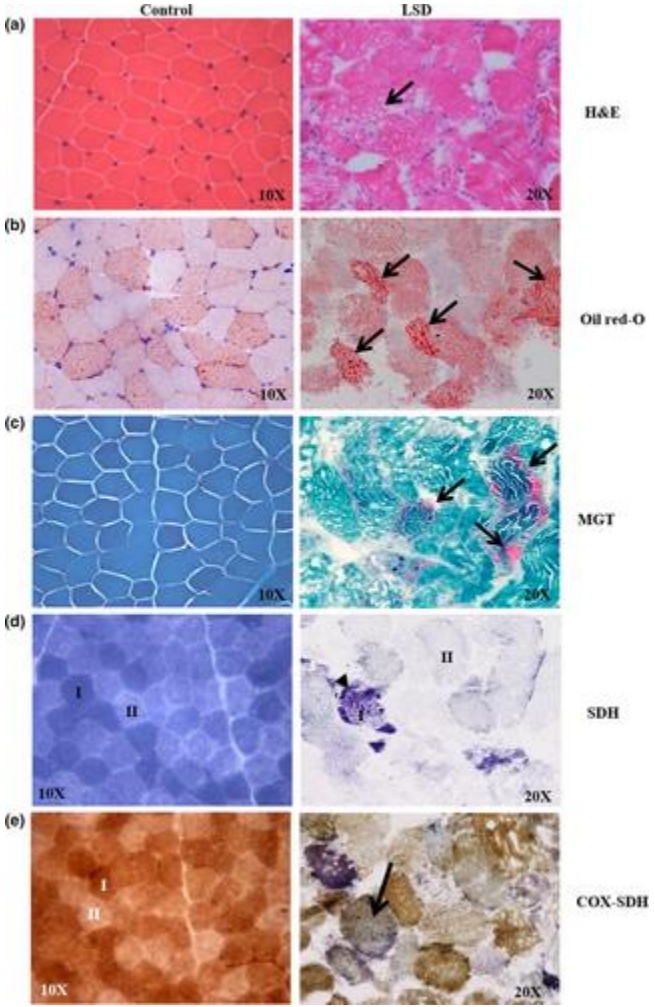

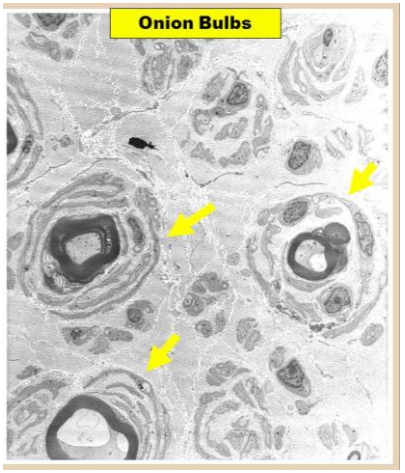

Genetics

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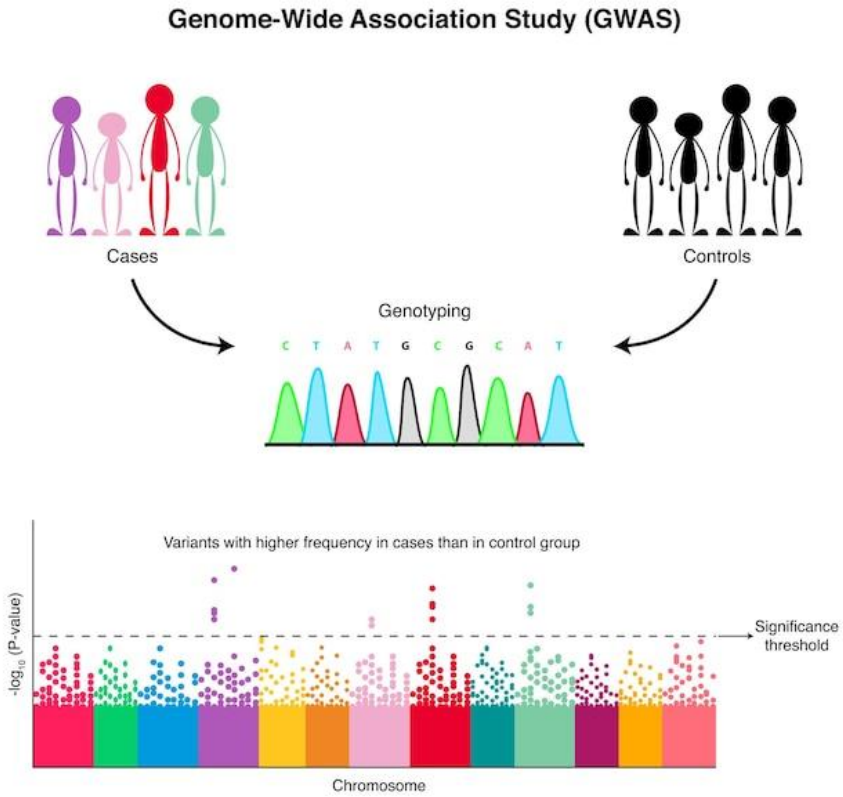

Repeat expansions causing neurologic disease

- CAG – at least 10 diseases (Huntington disease, spinal and bulbar muscular atrophy, dentatorubral-pallidoluysian atrophy and seven SCAs)
- CGG – fragile X, fragile X tremor ataxia syndrome, other fragile sites (GCC, CCG)
- CTG – myotonic dystrophy type 1, Huntington disease-like 2, spinocerebellar ataxia type 8, Fuchs corneal dystrophy
- GAA – Friedreich ataxia
- GCC – *FRAXE* mental retardation
- GCG – oculopharyngeal muscular dystrophy
- CCTG – myotonic dystrophy type 1
- ATTCT – spinocerebellar ataxia type 10
- TGGAA – spinocerebellar ataxia type 31
- GGCCTG – spinocerebellar ataxia type 36
- GGGGCC – *C9ORF72* frontotemporal dementia/amyotrophic lateral sclerosis
- CCCCGCCCCGCG – EPM1 (myoclonic epilepsy)

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3. Treatment options are similar between conditions (but with some important caveats)

- Inflammatory conditions (e.g. GBS, MG, Myositis)
  - IVIG / PLEX
  - ? Steroids
- Metabolic – correct abnormality
- Cancer related – treat the cancer
- Toxic – remove toxin
- Neurodegenerative / genetic – mainly supportive (at the moment)

IVIG / Plasma Exchange on a medical ward

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IV Immunoglobulins

- Serum immunoglobulins - low IgA - anaphylactoid reaction
- Thrombosis risk - review vascular risk factors
- Allergic risk - careful up titration of rate of infusion
- Approval required
- 0.4mg/kg / day for 5 days
- Consent

Plasma Exchange

- Requires central line (usually)
- Need to prescribe / order albumin
- 200-250ml/kg for 5 sessions

General Principles

Blood products (HIV, Hep B+C)

Not required in mild illness

Takes weeks to work

Equal efficacy, different risks

No evidence for repeat treatment in GBS

Supportive care

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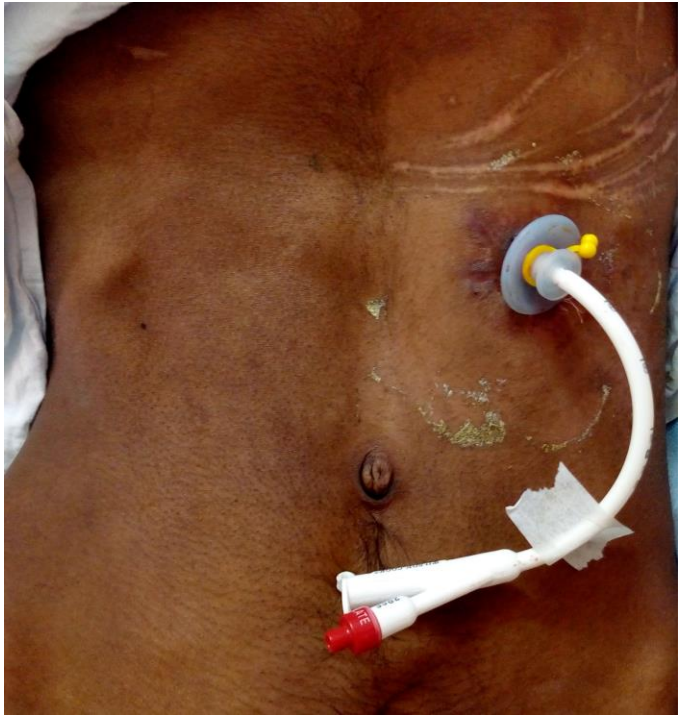
- **Supportive care** has a big impact on life expectancy
- Needs to be **personalised**
- **Nutrition important**
- Predict bulbar failure
- PEG / RIG insertion
- Can be risky, esp if respiratory failure
- **Respiratory** function needs to be monitored
- NIV prolongs life
- Secretion management and aspiration risk
- When to stop?



4. The most important thing is to avoid harm

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- Respiratory Monitoring
  - FVC
  - Early escalation of care
- Cardiac / autonomic monitoring
- VTE prophylaxis
- Good nursing care (pressure sores, dental care, etc.)

AIDP - Acute Inflammatory Demyelinating Poly(radiculo)neuropathy (Guillain-Barre Syndrome)

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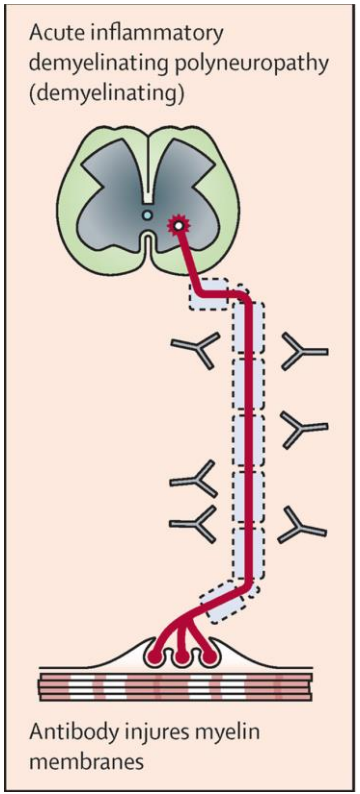
- ~25% require artificial ventilation
- Mortality ~5% in high income countries: respiratory failure, VTE, hospital acquired infections
- ~20% unable to walk unaided at 6 months
- But some cases mild and self-limiting
- Predictors of poor outcome: advanced age, need for ventilation, preceding campylobacter, axonal sub-type



Acute neuromuscular disease: preventing harm

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- Monitor respiratory function:
  - 4 hrly FVC or breath count (2 counts / sec)
  - Ceiling of care
- Screen for autonomic disturbance
  - History, L/S BP, ECG
- DVT prophylaxis
- Assess swallow
  - SALT + dietician
  - NG
- Physio/OT
- Check not on contraindicated medications
  https://www.myaware.org/drugs-to-avoid

Acute Neuromuscular Respiratory Failure: Escalation to ITU

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- Watch carefully if bulbar symptoms +/- rapidly worsening weakness?
- Call ITU if:
  - **FVC <20ml/kg body weight**

    (e.g. <1.4L in a 70kg man : SBC<14)
  - **or if falling (>30% from baseline within 24 hours)**
  - **Or if tiring / not managing secretions**
- DO NOT WAIT for a rise in CO2 or acidosis

5. New therapies are coming…

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- For auto immune conditions
- And for genetic conditions
- And maybe for neurodegenerative conditions

Emerging Therapies: (Neurological) Autoimmune Diseases

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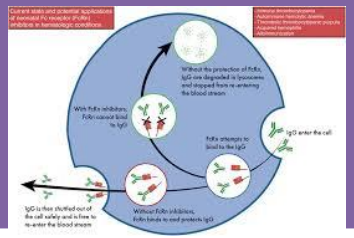
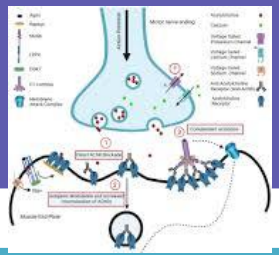
Efgartigimod
Razanolixizumab
Nipocalimab
Batoclimab

FcRn inhibitors



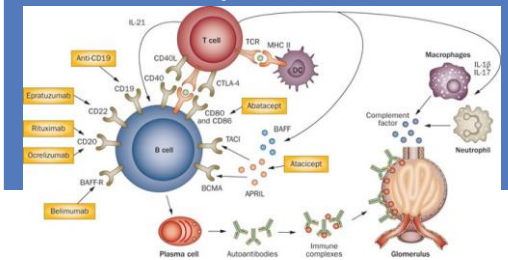
Complement Inhibitors



Eculizumab
Ravulizumab
Zilucoplan
Vemircopan
Pozelimab + Cemdisiran
Gefurlimab

Rituximab (CD20)
Inebilizumab (CD19)
Telitacicept (BAFF/APRIL)
Isacalimab (CD40)
Daratumumab (CD38)
CART

B / plasma cell depletion



Others

Tocilizumab (IL-6)
Stralizumab (IL-6)
Antigen-specific CAART

Emerging Therapies: (Neurological) Genetic Diseases

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Methods

- Short synthetic nucleotide (ASOs and RNAi)
- Virus-mediated gene therapy
- Genomic DNA editing/engineering (CRISPR/Cas9)

Conditions

- SMA: Zolgensma, Nusinersen, Risdiplam
- Duchenne Muscular Dystrophy
- Refractory Epilepsies
- Familial amyloid polyneuropathy

Therapeutic gene	Delivery vector	References
Adk (antisense)	AAV8	(Theofilas et al., 2011)
Fgf-2 and *Bdnf*	HSV	(Bovolenta et al., 2010, Paradiso et al., 2011)
Gabra1	AAV2	(Raol et al., 2006)
Gdnf	AAV2	(Kanter-Schlifke et al., 2007)
Kcc2	Lentivirus	(Magloire et al., 2019)
Kcna1	Lentivirus, AAV	(Wykes et al., 2012, Snowball et al., 2019)
Npy	AAV1/2, AAV1, AAV2	(Richichi et al., 2004, Sørensen et al., 2009, Noe et al., 2010)

Summary

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1. It's not as hard as you think…
    - Localise the lesion, consider speed of onset, look for clues
2. (Relevant) investigations can be helpful
3. Treatment options are similar between conditions (but with some important caveats)
4. The most important thing to do is avoid harm
    - Respiratory failure and aspiration
    - Cardiac arrhythmia and cardiomyopathy
    - DVT / PE
5. New treatments are coming