5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 17

Congenital myasthenic syndromes and the myotonic dystrophies - diagnostics and possible treatment (Level 3)

Congenital myasthenic syndromes (CMS)- clinical and genetic variety and possible treatment

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Highly Specialised Commissioning

NHS
Oxford University Hospitals
NHS Foundation Trust

UNIVERSITY OF OXFOR

Congenital Myasthenic Syndromes: diagnosis and treatment

Jackie Palace

Caution: no treatments are licensed for CMS

Disclosures: Jacqueline Palace is partly funded by highly specialised services to run a national congenital myasthenia service and a neuromyelitis service. S has received support for scientific meetings and honorariums for advisory work from Merck Serono, Biogen Idec, Novartis, Teva, Chugai Pharma and Baye Schering, Alexion, Roche, Genzyme, MedImmune, EuroImmun, MedDay, Abide and ARGENX, and grants from Merck Serono, Novartis, Biogen Idec, Teva, Al and Bayer Schering. She has received grants from the MS society, Guthie Jackson Foundation, NIHR, Oxford Health Services Research Committee, EDEN, M GMSI, and John Fell for research studies

The Congenital Myasthenic Syndromes

- Genetically determined myasthenias
- Rare in UK ~15-20 per million (similar to childhood MG)

- Muscle weakness:
  - ptosis, EOM, face, limbs, trunk, bulbar, respiratory
  - fatiguable
- EMG: decrement, jitter, blocking

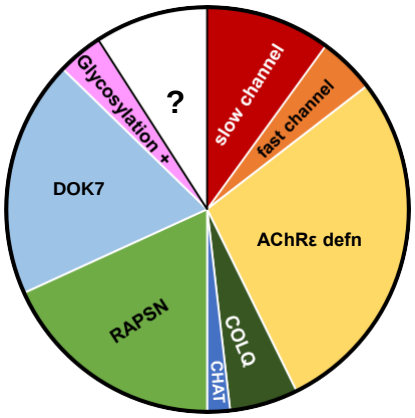
- Onset birth/infancy typical
- 'Stable' throughout life
- ↑ Consanguinity / Family history (most recessive)
- No antibodies, no response to immunotherapies
- Response + or - to anti-cholinesterases & 3,4-DAP

CMS gene discovery through decades

1980s → 1990s → 2000s → 2010-

30+ Genes: 450 Mutations in > 500 UK patients

Estimate <10 % no known mutation



Main mimics of CMS?

- sero-negative MG
- congenital myopathies (RYR, TPM3)
- muscular dystrophy (limb girdle)
- SMA
- hypermobility syndromes
- developmental coordination disorder (dyspraxia)
- chronic fatigue syndrome

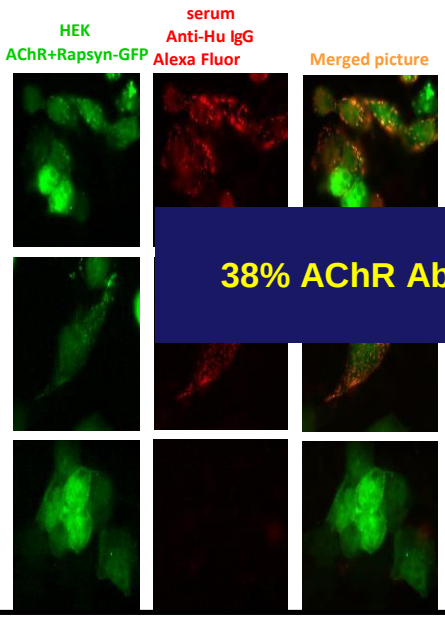
Do they have myasthenia?

- EMG:
  - decrement on RNS specific
  - jitter/block on SFEMG more sensitive, less specific
    - non-stim vs stim SFEMG
- fatiguable ptosis & Cogan's lid twitch
- response to pyridostigmine / objective tensilon test / ice pack test
- fluctuation of weakness
  (not feeling low in energy, tired & fatigued as day goes on)

They have myasthenia, is it CMS?

- no antibodies (but common in childhood MG)
- early onset (< 3yrs)
- FH or consanguinity (most autosomal recessive)
- gradual onset (can be → sub-acute)
- isolated ocular involvement very rare in CMS
- 'symmetrical' ptosis
- ophthalmoplegia static, no diplopia,
- ankle dorsi-flexion weakness
- stridor / arthrogryposis / 2ry myopathy
- worse with pyridostigmine

a sensitive (cell based) assay detects antibodies to clustered AChR

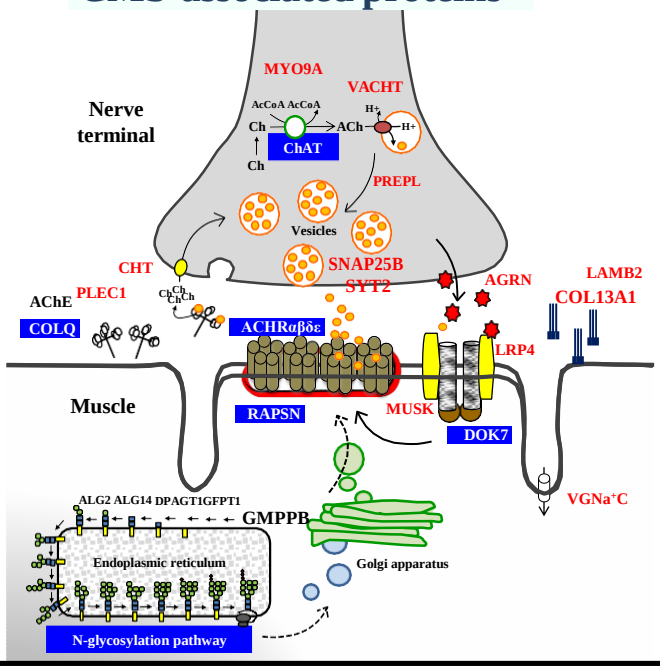


38% AChR Ab neg MG become positive

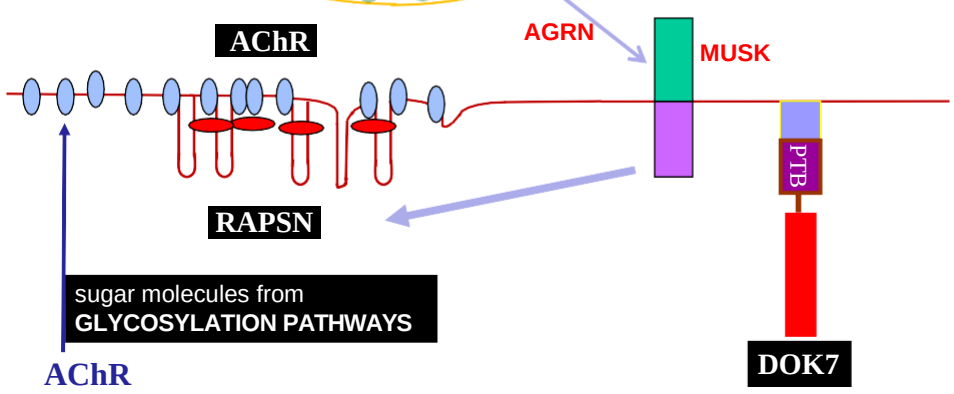
JAMA Neurol. 2015;72(6):642-649

Leite et al 2008

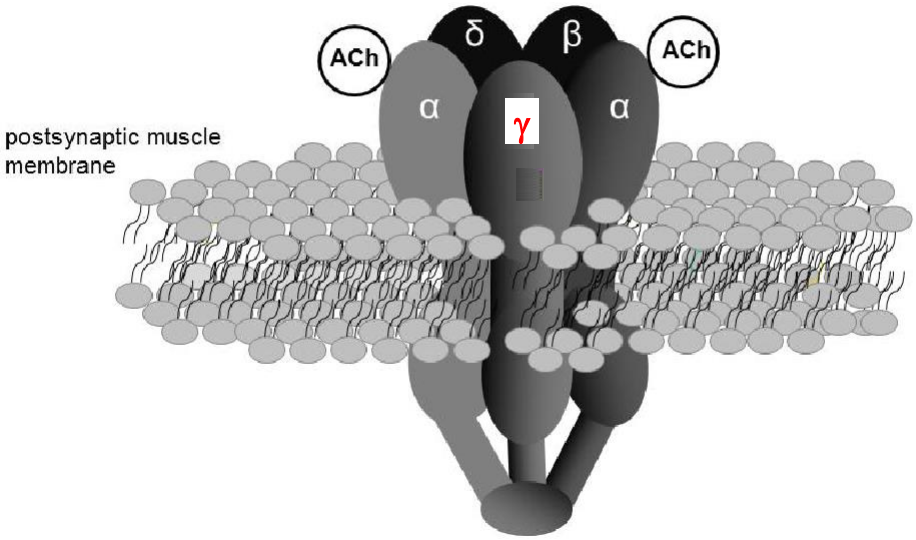
CMS-associated proteins



postsynaptic location

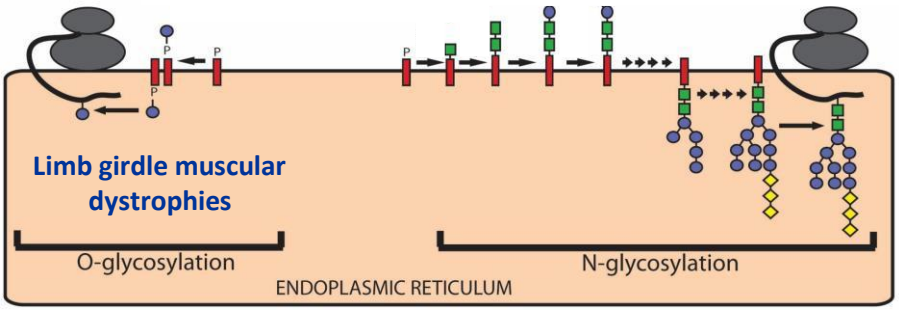


AChR deficiency mutations 'all' in the ε sub-unit



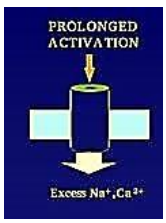
Glycosylation, ubiquitous

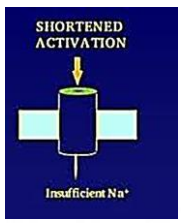
? rapid turnover of AChR → low threshold when attenuated



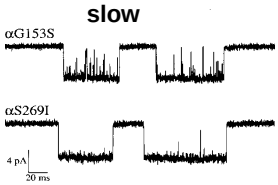
5 glycosylation genes associated w CMS

Kinetic abnormalities of AChR: slow and fast channel syndromes

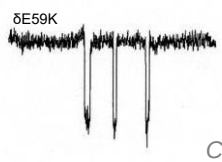




slow



fast



Single channel recordings of mutant AChR

Claire Newland
Richard Webster

Classification

PRE **SYNAPTIC** **POST**

CHAT COLQ

Classification

PRE **SYNAPTIC** **POST**

CHAT COLQ

AChR

Deficiency

AChR ε subunit
RAPSYN
Glycosylation defects

Classification

PRE

CHAT

SYNAPTIC

COLQ

POST

AChR

Deficiency

AChR ε subunit
RAPSYN
Glycosylation defects

Kinetic Abn

Slow channel

Fast channel

Instability NMJ

DOK7
(MUSK)
(AGRIN)
(LRP4)

Restricted EOM range

PRE

CHAT

SYNAPTIC

COLQ

POST

AChR

Deficiency

AChR ε subunit
RAPSN
Glycosylation defects

Kinetic Abn

Slow channel

Fast channel

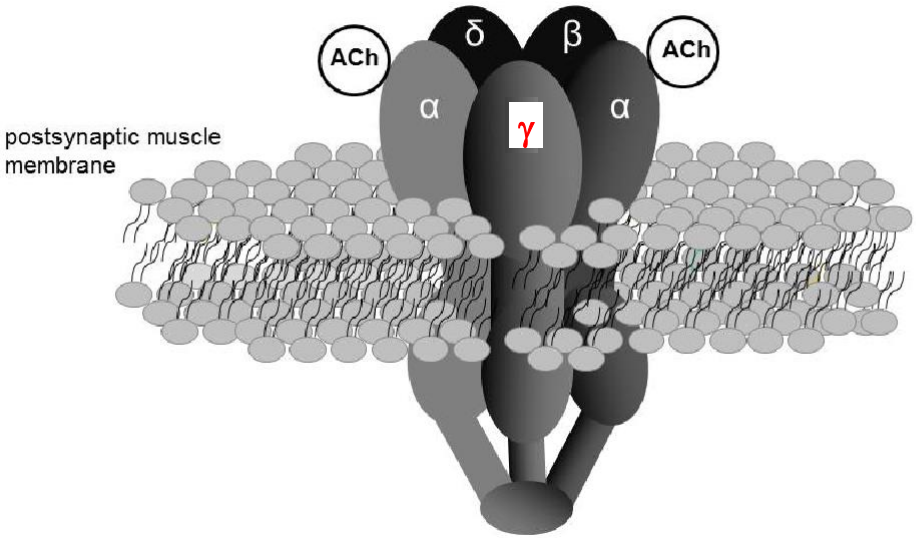
Instability NMJ

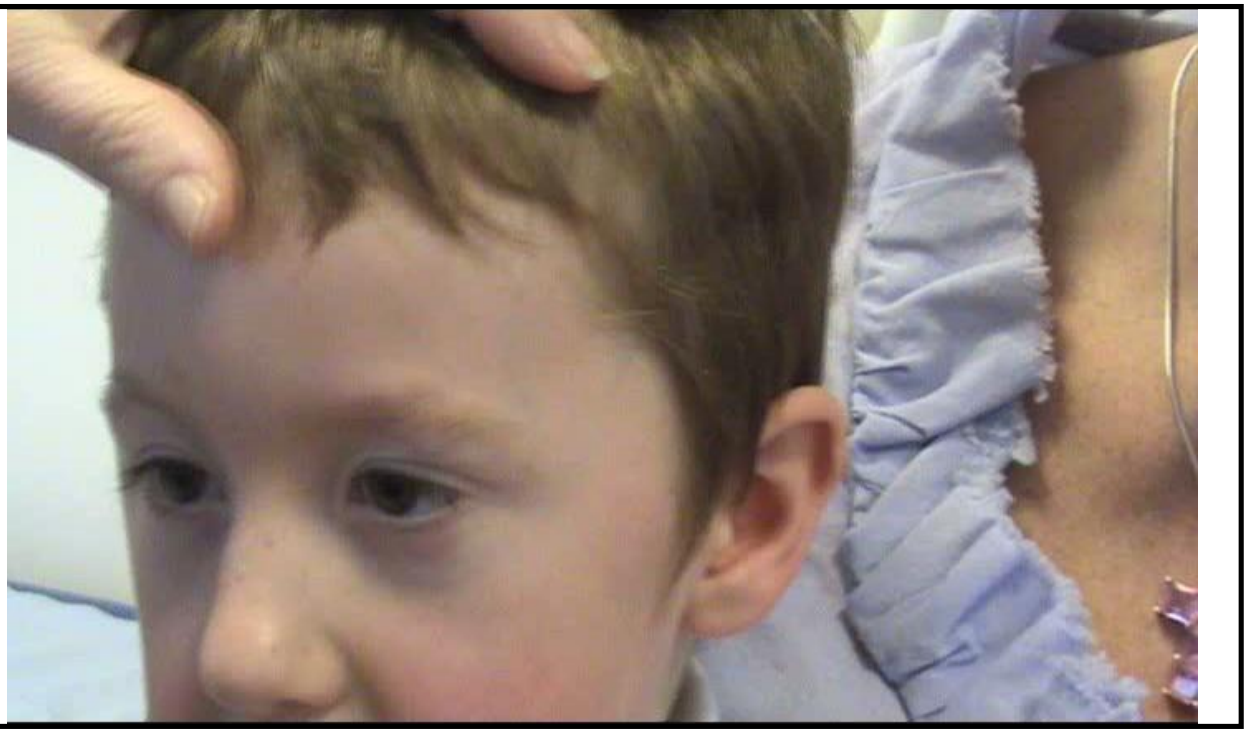
DOK7
(MUSK)
(AGRN)

AChR deficiency (ε mutation)

- **2yr old boy**
- **3/52 feeding problems, nasal regurg, poor cough, slow palatal movements and pooling w excess airways secretions**
- **ptosis, poor facial expression**
- **14 months complete ophthalmoparesis**

- **sister born 4 years later**
- **slow feeder**
- **at 1 month full EOM**
- **3 months later some restriction**
- **6 months feb 2011 eye movements worse**
- **10 months complete ophthalmoplegia**





Rapsyn mutation

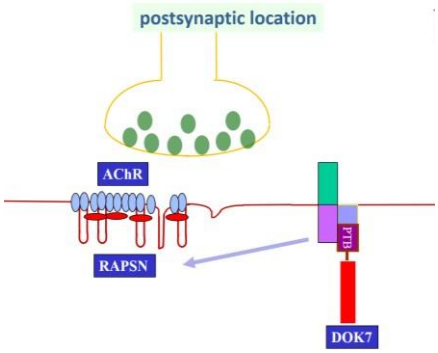
0/14 restricted EOM

11/14 strabismus

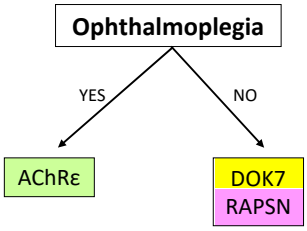
Variability in eye movements in CMS

<u>AChR mutations affect EOM</u>:
Deficiency ‘all’ severe opthalmoplegia
Fast channel 90% opthalmoplegia (70% severe)
SCS 2/3 partial opthalmoplegia

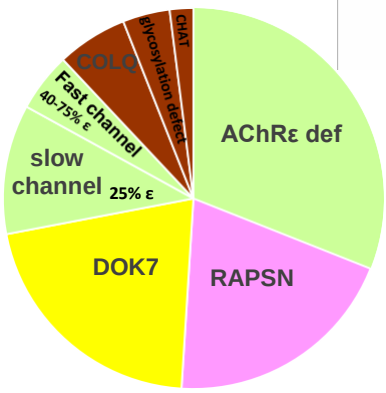
<u>Reduced clustering of AChR</u>
Rapsyn ‘all’ full EOM
majority squint
DOK7 93% full EOM



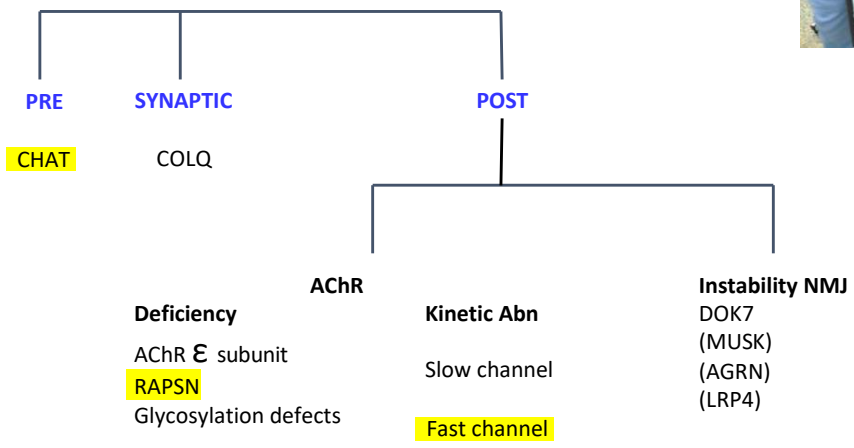
Gene screening algorithm



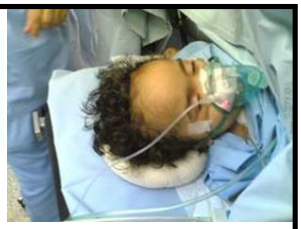
77% diagnosed



Early life crises



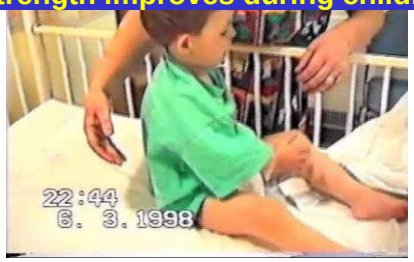
Rapsyn CMS
Sudden life-threatening crises infancy & early childhood



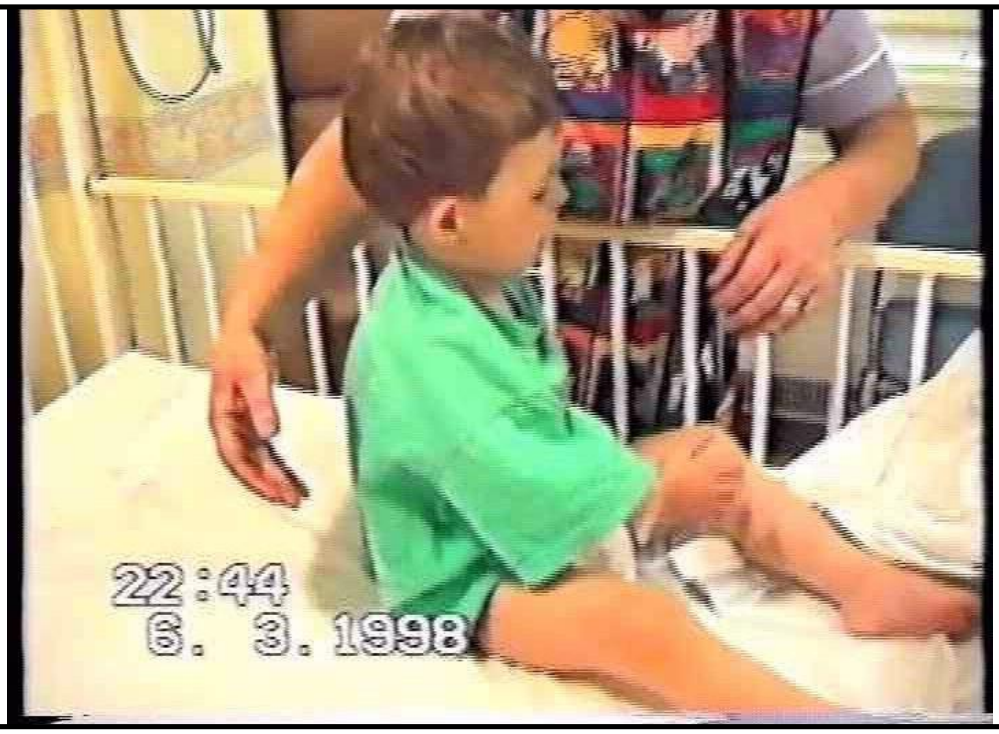
Hospitalisation:12/14
Ventilation:10/14
Sibling deaths:3/14

ppte by minor infections
between attacks well
significant morbidity/ mortality

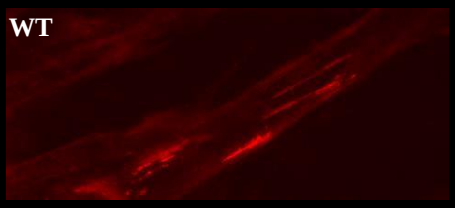
Excellent response to pyridostigmine
Crises cease after first few years life
Strength improves during childhood



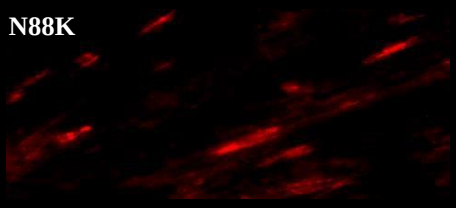
Acknowledgements
Dr Zuberi Glasgow



Rapsyn-N88K clusters unstable



? cause of febrile-i



AGRIN

Coussins J et al, Brain 2006;129:2773-2783

later onset
mild progressive weakness
myopathic features

PRE

CHAT

SYNAPTIC

COLQ

POST

AChR

Deficiency

AChR ε subunit

RAPSN

Glycosylation defects

Kinetic Abn

Slow channel

Fast channel

Instability NMJ

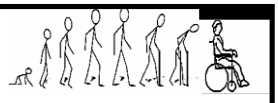
DOK7

(MUSK)

(AGRN)

(LRP4)

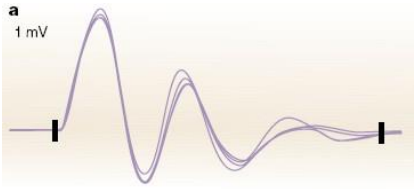
Excitotoxic endplate myopathy



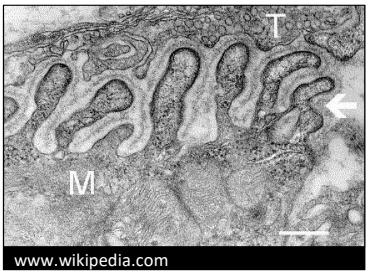
Prolongation of:

opening of AChR in Slow channel syndrome

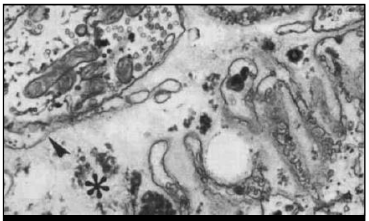
endplate current COLQ (ACh esterase)



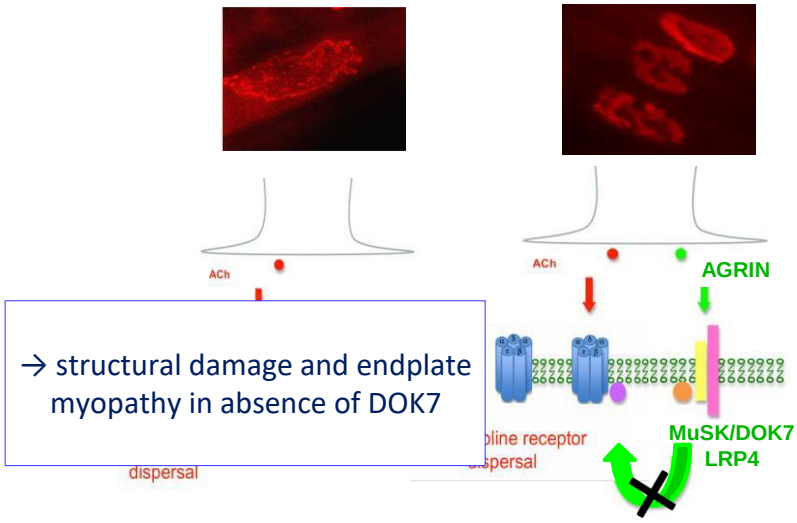
Ca^{2+} accumulation → degeneration



SCS NMJ



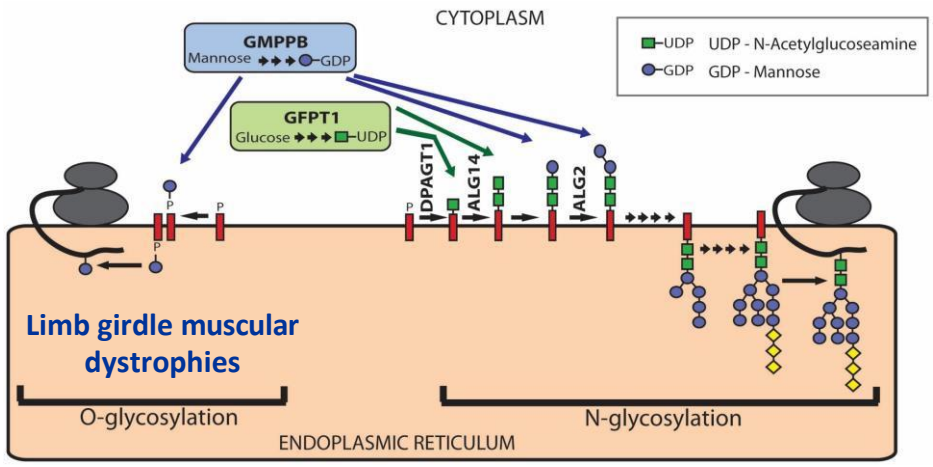
Neurotransmission → disassembly of AChR clusters



→ structural damage and endplate myopathy in absence of DOK7

Slide from An Van Haesebrook

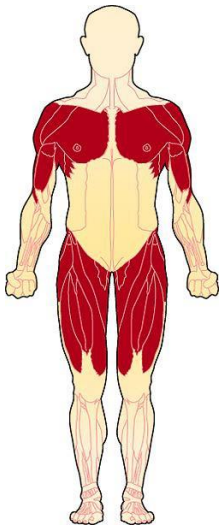
Glycosylation defects affect muscle as well as AChR



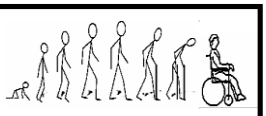
Glycosylation pathway mutations

- Clinical features
  - limb-girdle muscle weakness
  - usually no ptosis
  - no ophthalmoplegia
  - no facial involvement
  - no bulbar involvement
  - myopathic feature biopsy

EASY MISS MYASTHENIC FEATURES

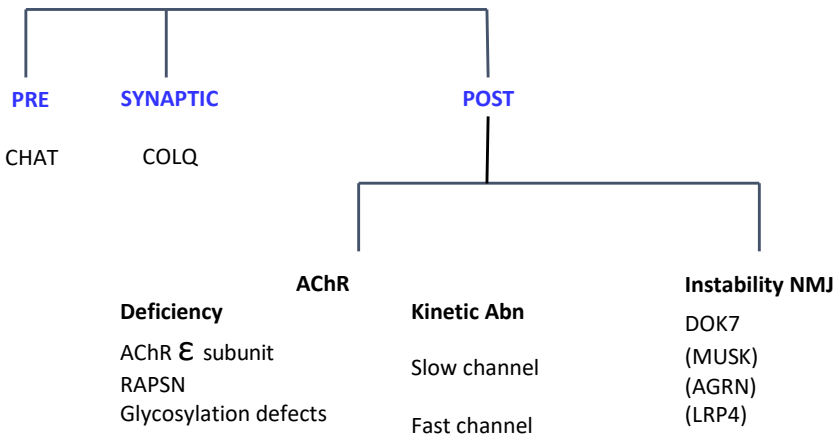


Glycosylation pathway CMS



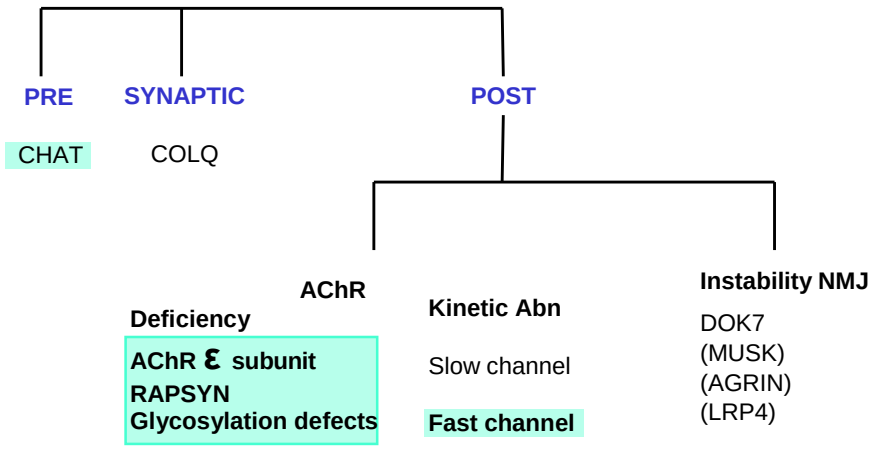
- Muscle biopsy
  - dystrophic features
  - ↓ labelling for alpha-dystroglycan
  - tubular aggregates
  - non specific / mild myopathic changes
- Muscle MRI
  - abnormal majority (T1)

Treatment

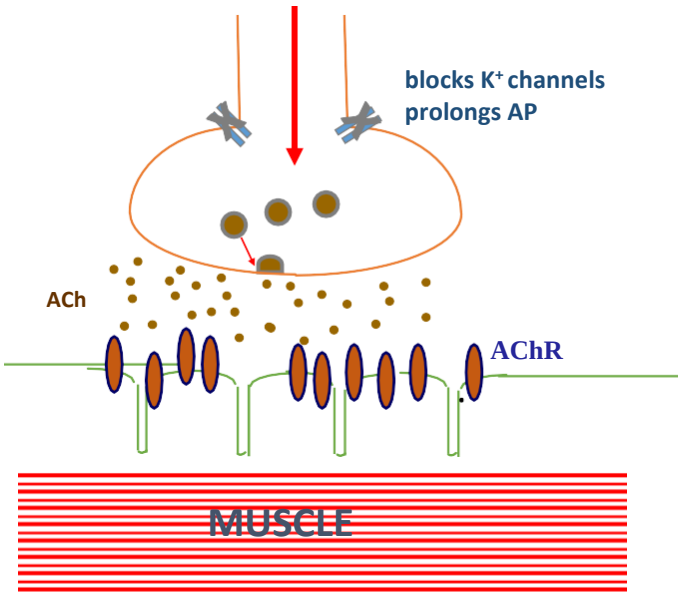


Syndromes helped by increasing ACh levels

AChE inhibitors and 3,4-DAP



3,4-DAP



Glycosylation CMS treatment response

- 24 GFPT1 ‘majority’ pyridostigmine ± 3,4-DAP
- 5 DPAGT1 all pyridostigmine, ± 3,4-DAP
- 7 ALG2/ALG14 all pyridostigmine
- 8 GMPPB all pyridostigmine, ± 3,4-DAP

Associated myopathy wont respond and may progress

Cossins et al, Brain 2013
Belaya et al, Am J Hum Genetics 2012
Cruz et al, JNNP 2016
Guergueltcheva et al, J Neurol 2012

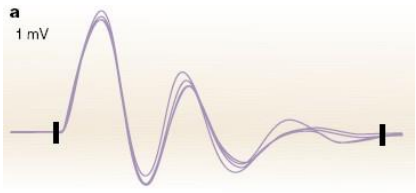
SCS and COLQ: ‘to much message’

Slow channel syndrome:

prolonged opening of AChR

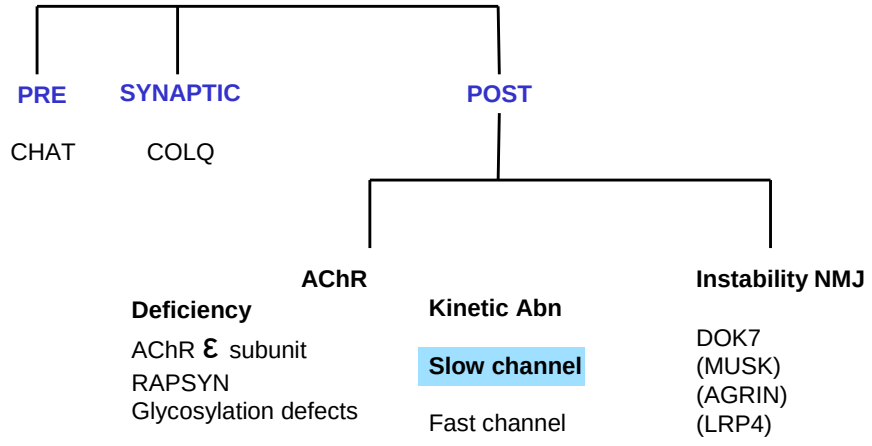
COLQ (ACh esterase):

reduced breakdown of ACh prolongs endplate current endplate current



Both worse with drugs that increase ACh

Open channel blockers for slow channel syndrome

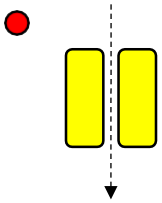


Slow channel syndrome

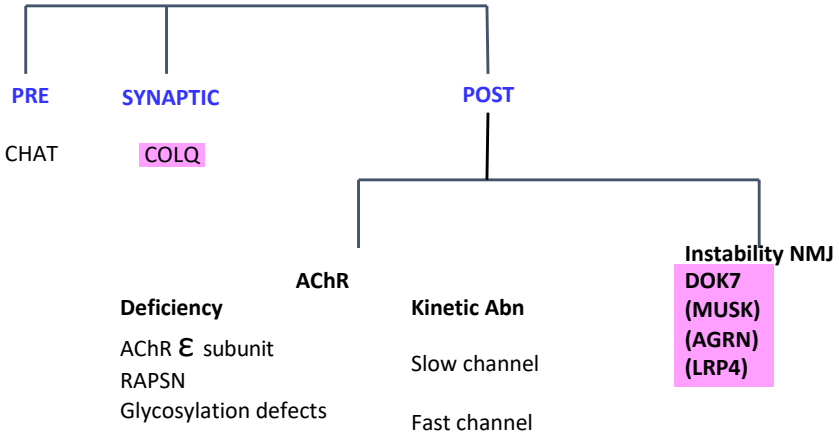
Worsened by increasing ACh levels

High dose Open Channel Blockers help:

- Fluoxetine
- Quinidine



Syndromes:
worsened by ↑ ACh levels
helped by salbutamol or ephedrine



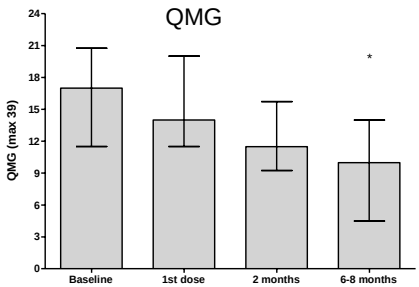
Ephedrine: progressive improvement in DOK7

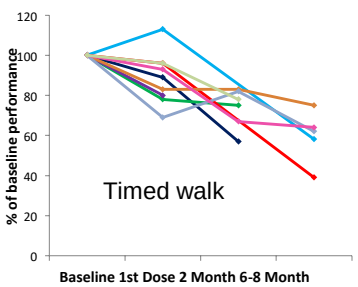
NEUROLOGY 2010;74:1517-1523, D. Lashley,

Pyridostigmine: no effect or worse
3,4-DAP: 2/3 no effect or worse

10 patients

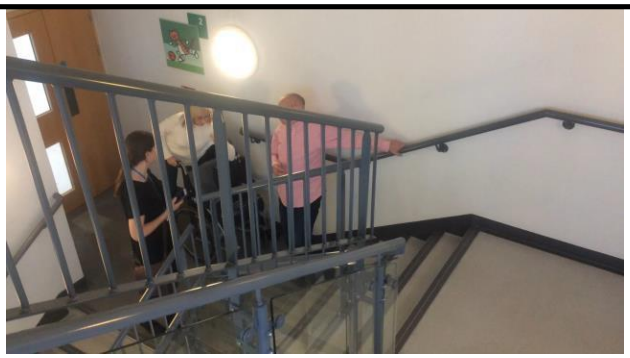
oral ephedrine



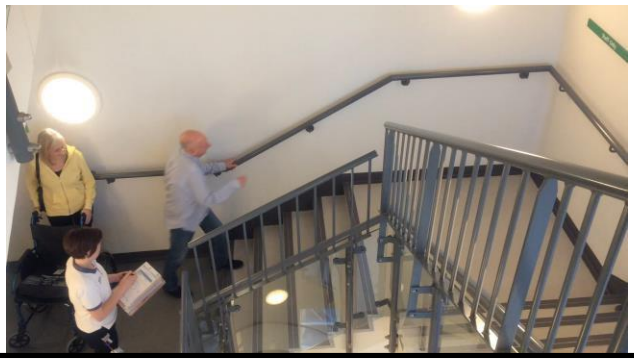


EPHEDRINE 4mnths 15mg

EPHEDRINE 2yrs 45mg

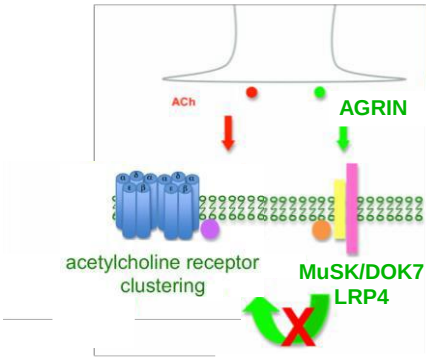


before salbutamol



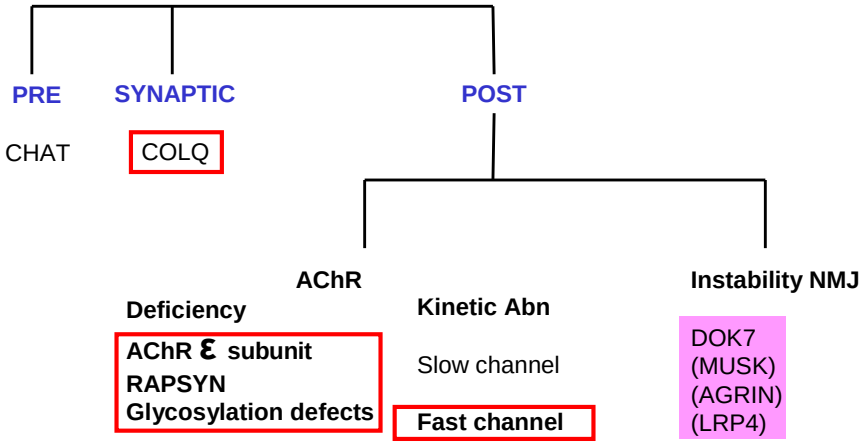
4 months later low dose salbutamol

Effect of salbutamol and ephedrine

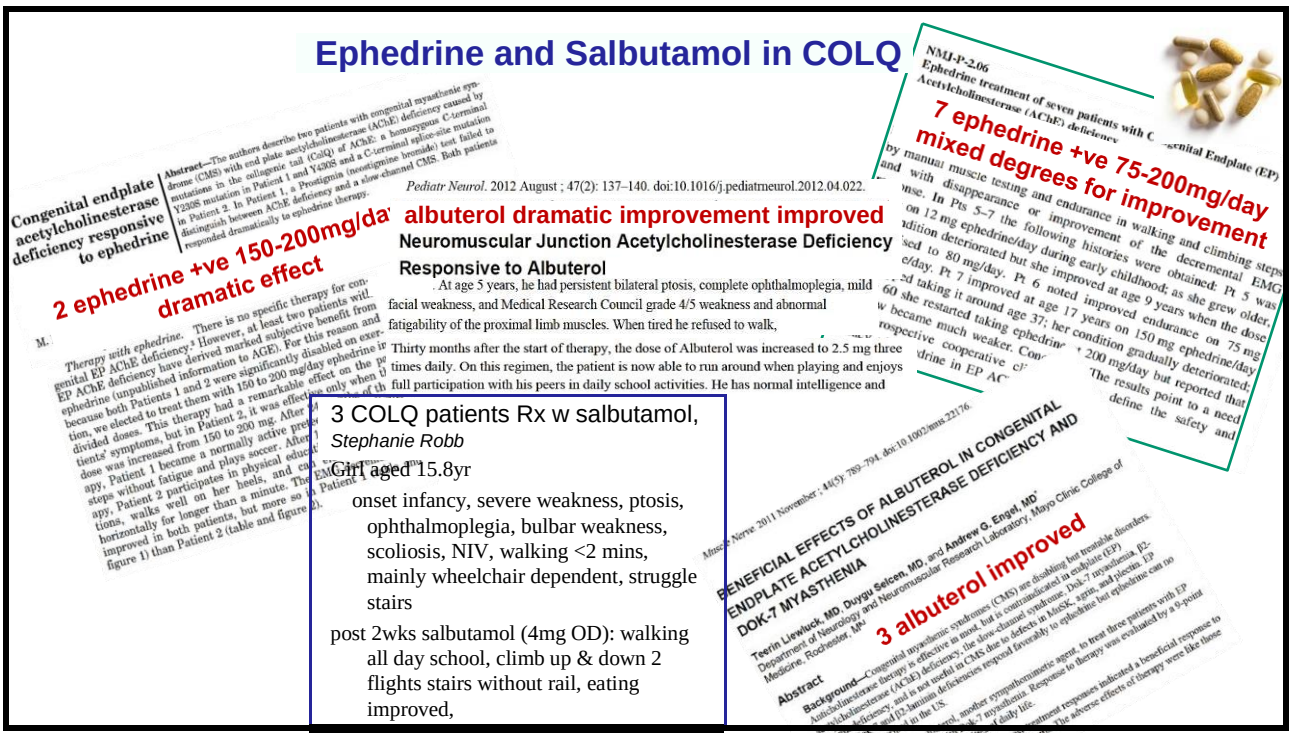


slide adapted from An Van Haesebrook

Salbutamol/albuterol or ephedrine beyond clustering pathway mutations



Ephedrine and Salbutamol in COLQ



3 COLQ patients Rx w salbutamol,

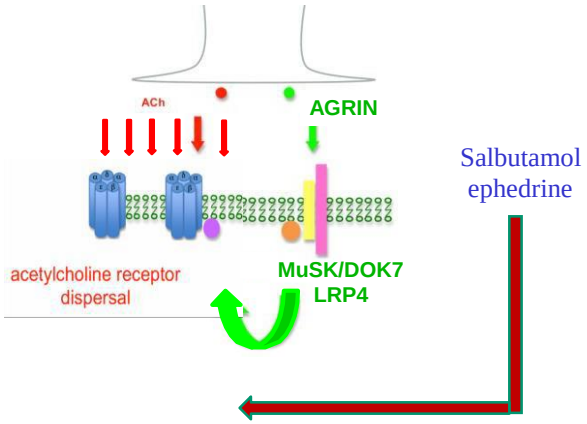
Stephanie Robb

Girl, aged 15.8yr

- onset infancy, severe weakness, ptosis, ophthalmoplegia, bulbar weakness, scoliosis, NIV, walking <2 mins, mainly wheelchair dependent, struggle stairs

post 2wks salbutamol (4mg OD): walking all day school, climb up & down 2 flights stairs without rail, eating improved,

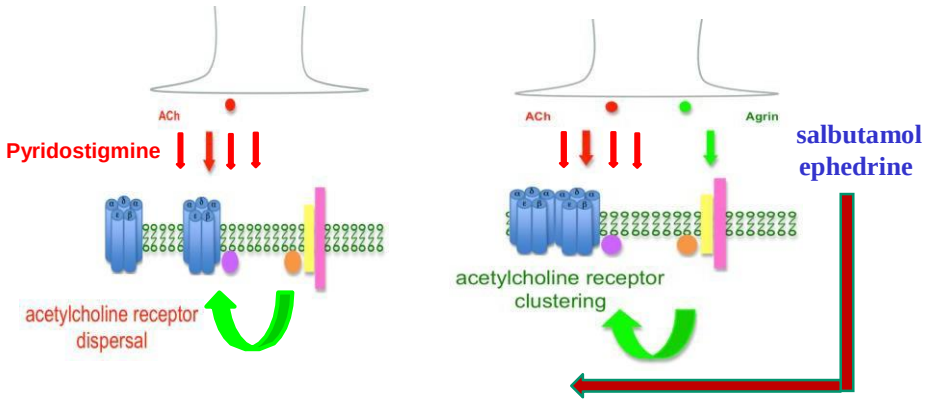
COLQ CMS: reduced breakdown of ACh



Observation: A group of severe patients with AChR deficiency

- Excellent initial response to pyridostigmine therapy
- Because severity and response: ↑ dosage over time
- End up on high doses which work for short period then wanes

Excess doses of pyridostigmine leads to AChR dispersion over time



Salbutamol and ephedrine in the treatment of severe AChR deficiency syndromes

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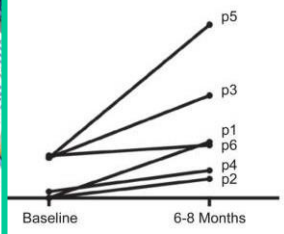


AChR deficiency syndrome

Example: Before After

Patient spent 12 years unable to weight-bear, with appropriate treatment ambulation achieved

ephedrine vs salbutamol

- similar efficacy, similar side effects
- more cramps w salbutamol
- ? speedier response to salbutamol
- salbutamol easier to obtain and greater familiarity

Balancing treatment

Destabilising effects of enhanced neurotransmission through anticholinesterase medication

Mestinon

Stabilisation through clustering pathway

β2 ADR agonists

Treatment Algorithm

Suspected CMS

↓

Features of DOK7, COLQ, or SCS

Yes → avoid pyridostigmine, await genetic diagnosis (if urgent try salbutamol)

No → **start pyridostigmine**

DOK7 | **COLQ** | **slow channel**

salbutamol **fluoxetine**

or ephedrine | **or quinidine**

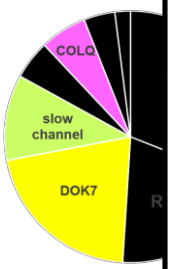
RAPSYN | **AChR defn fast channel** | **glycosylation** | **CHAT**

+ 3,4-DAP

+ salbutamol

Messages

- **Lots of clinical diagnostic clues for type of CMS, eg:**
  EOM involvement
  limb girdle weakness & myopathy
  worsening with pyridostigmine



- **respond well to specific & different treatments, tailored individualised therapy**
- **pyridostigmine and 3,4-DAP can worsen some CMS:**
  important to obtain specific genetic diagnosis 1st as will predict Rx response
- **early appropriate treatment reduces mortality from early life crises,**
  ? prevent permanent progressive endplate damage
- **salbutamol / ephedrine:** **months to work**
  broadening use
- **barriers to prescribing:** **all drugs unlicensed**
  lack of familiarity and high doses
  costs (eg *Firdapse*)


THANKS TO OUR PATIENTS
Those who refer them
And to Highly Specialised Commissioning