

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**

Jacqueline A. Palace
Oxford, United Kingdom

Email: jacqueline.palace@clneuro.ox.ac.uk

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. She has received support for scientific meetings and honorariums for advisory work from Merck Serono, Biogen Idec, Novartis, Teva, Chugai Pharma and Bayer Schering, Alexion, Roche, Genzyme, MedImmune, EuroImmune, MedDay, Abide and ARGENX, and grants from Merck Serono, Novartis, Biogen Idec, Teva, Alexion and Bayer Schering. She has received grants from the MS society, Guthrie Jackson Foundation, NIHR, Oxford Health Services Research Committee, EDEN, MRC, GMSI, and John Fell for research studies

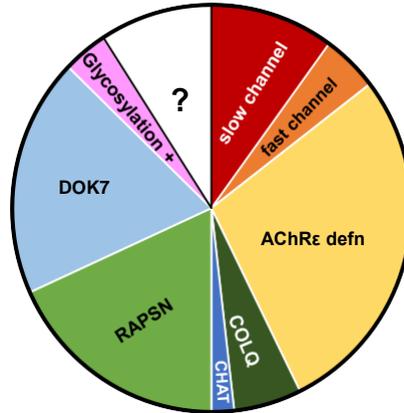
The Congenital Myasthenic Syndromes

- 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?



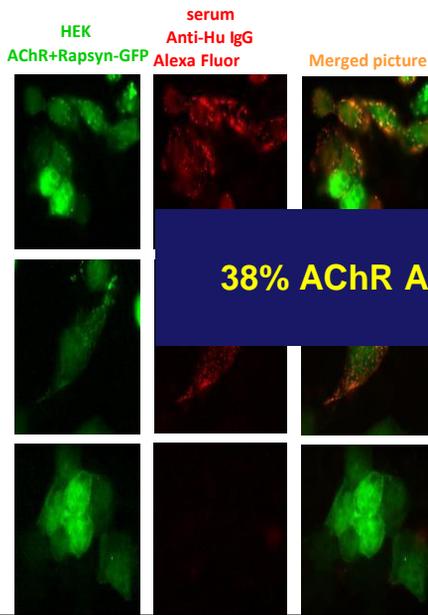
- EMG:
 - decrement on RNS specific
 - jitter/block on SFEMG more sensitive, less specific
 - non-stim vs stim SFEMG
- fatiguable ptosis & Cogan's lid twitch
- response to pyridostigmine / objective tensilon test / ice pack test
- fluctuation of weakness
(not feeling low in energy, tired & fatigued as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

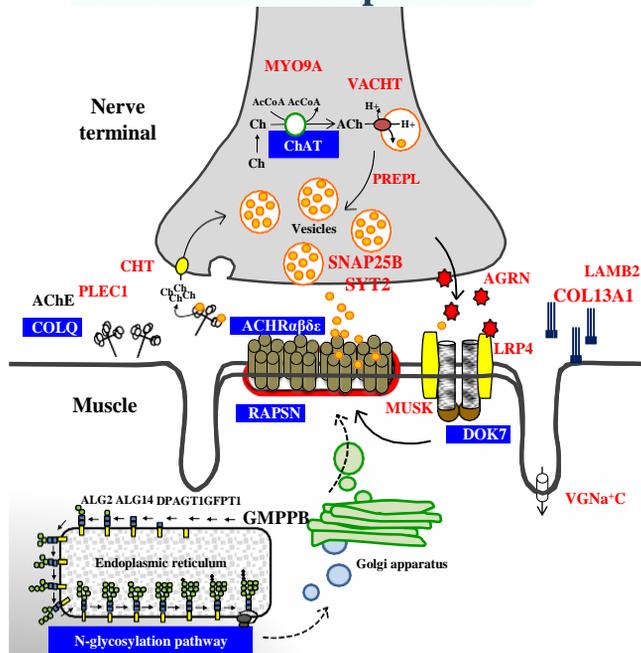
(now pos)

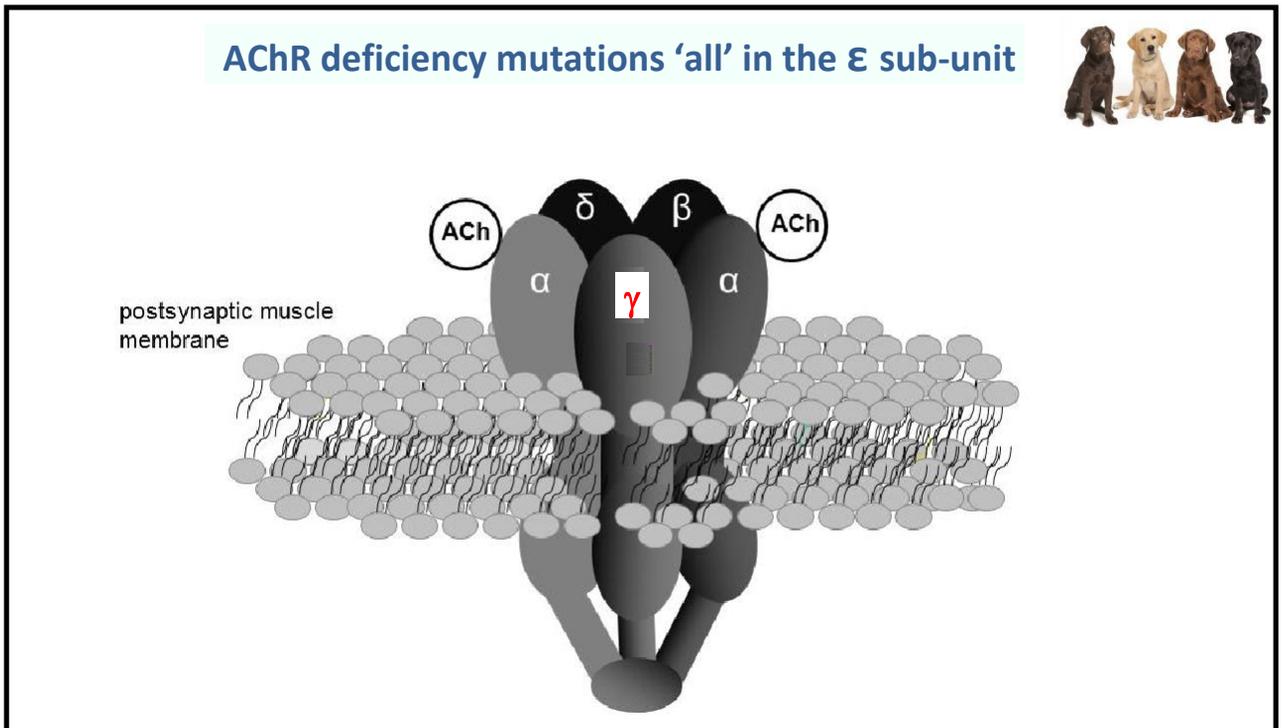
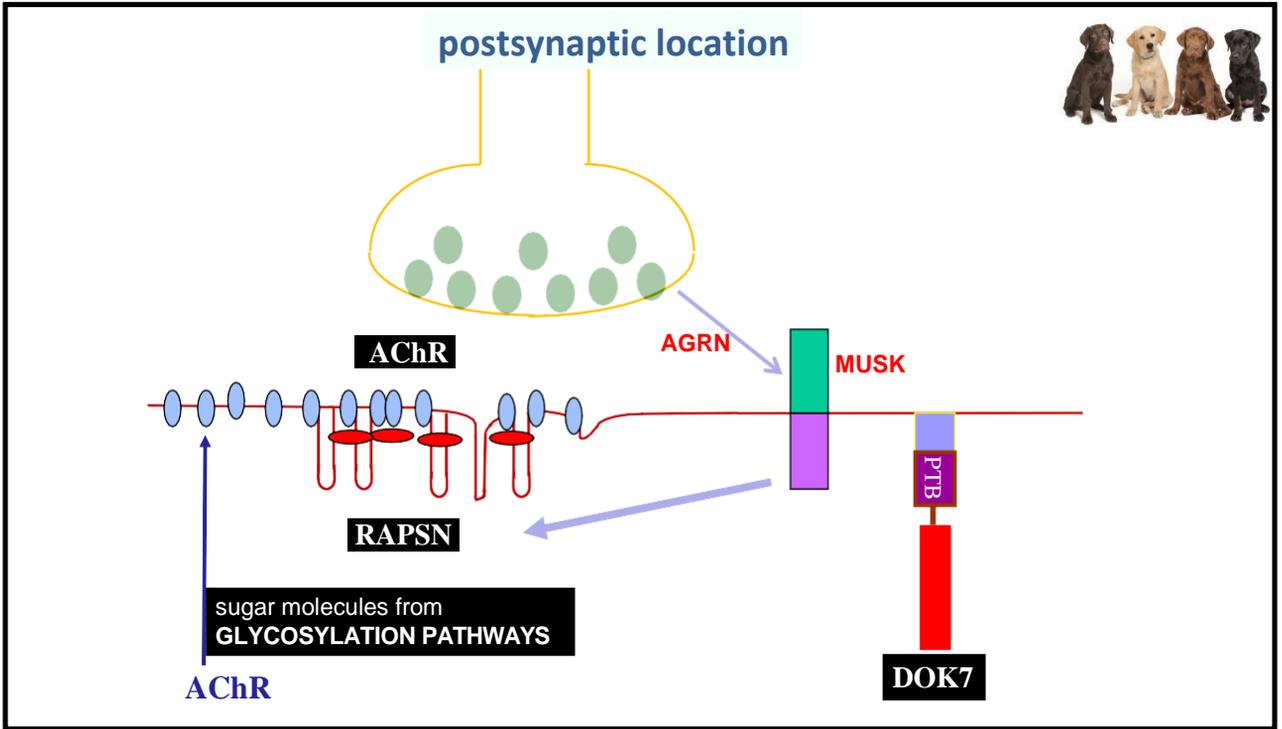
HC



Leite et al 2008

CMS-associated proteins

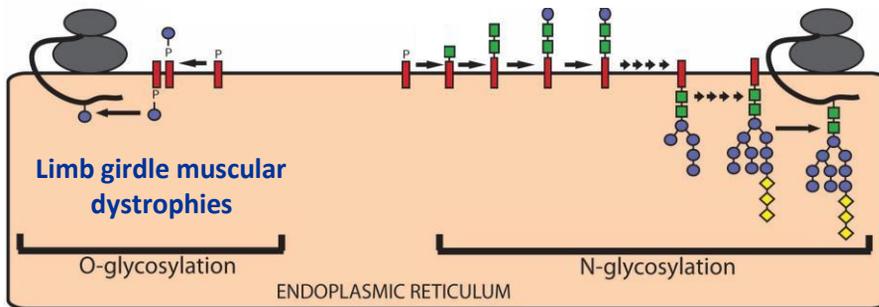




Glycosylation, ubiquitous

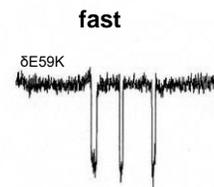
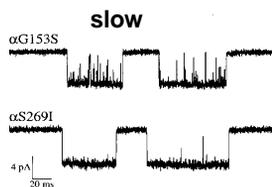
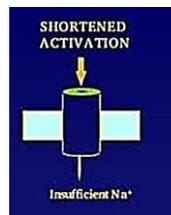


? rapid turnover of AChR → low threshold when attenuated



5 glycosylation genes associated w CMS

Kinetic abnormalities of AChR: slow and fast channel syndromes



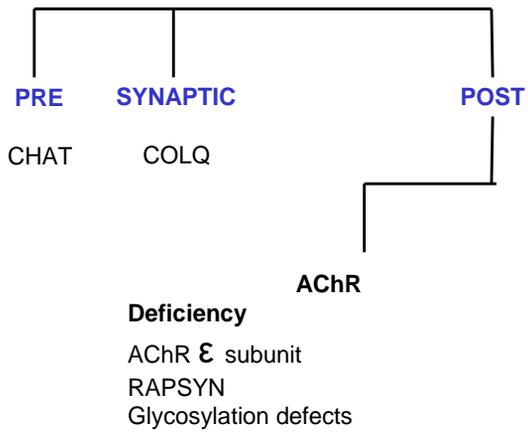
Single channel recordings of mutant AChR

Claire Newland
Richard Webster

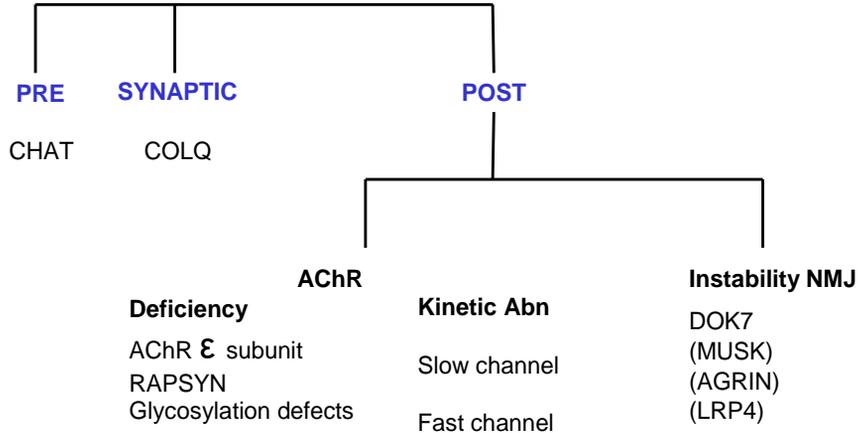
Classification



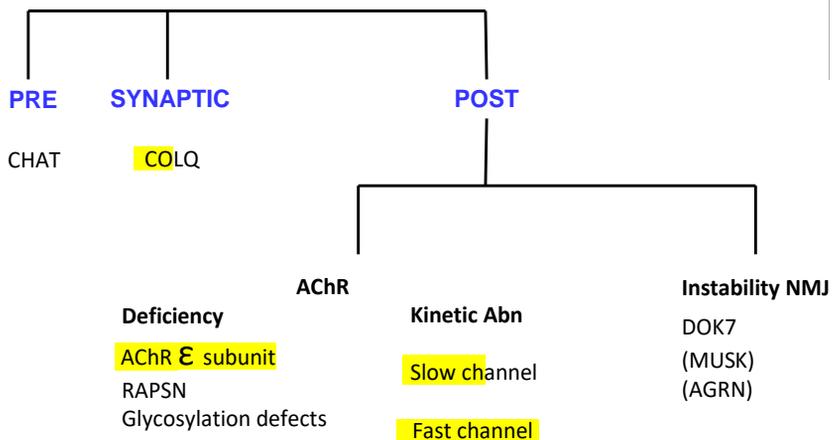
Classification



Classification



Restricted EOM range



AChR deficiency (ϵ mutation)

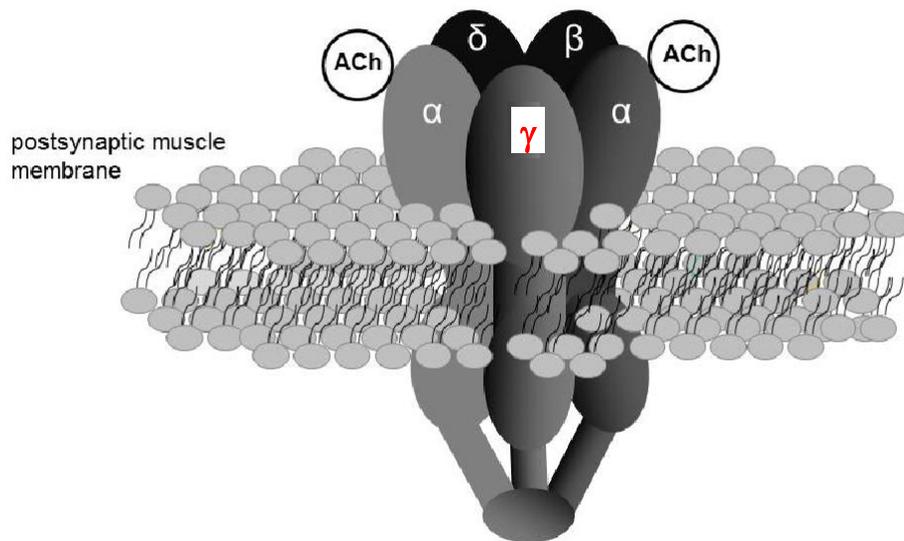


- 2yr old boy
- 3/52 feeding problems, nasal regurg, poor cough, slow palatal movements and pooling w excess airways secretions
- ptosis, poor facial expression
- 14 months complete ophthalmoparesis





- **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

AChR mutations affect EOM:

Deficiency 'all' severe ophthalmoplegia

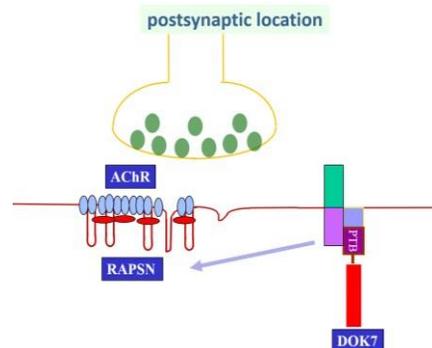
Fast channel 90% ophthalmoplegia (70% severe)

SCS 2/3 partial ophthalmoplegia

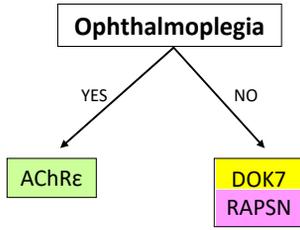
Reduced clustering of AChR

Rapsyn 'all' full EOM
majority squint

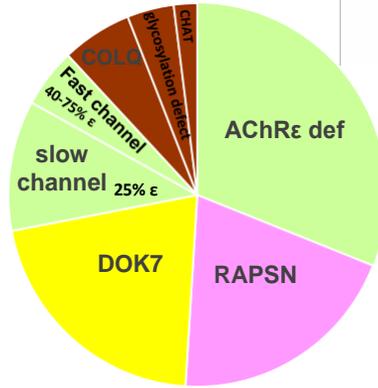
DOK7 93% full EOM



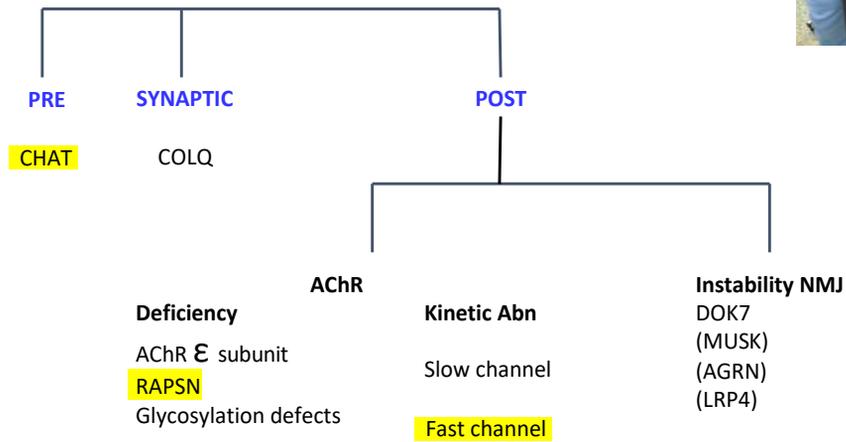
Gene screening algorithm



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

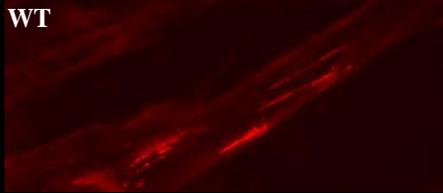
Excellent response to pyridostigmine
Crises cease after first few years life
Strength improves during childhood



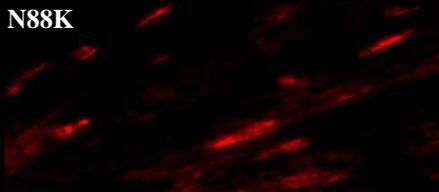
Acknowledgements
Dr Zuberi Glasgow



Rapsyn-N88K clusters unstable



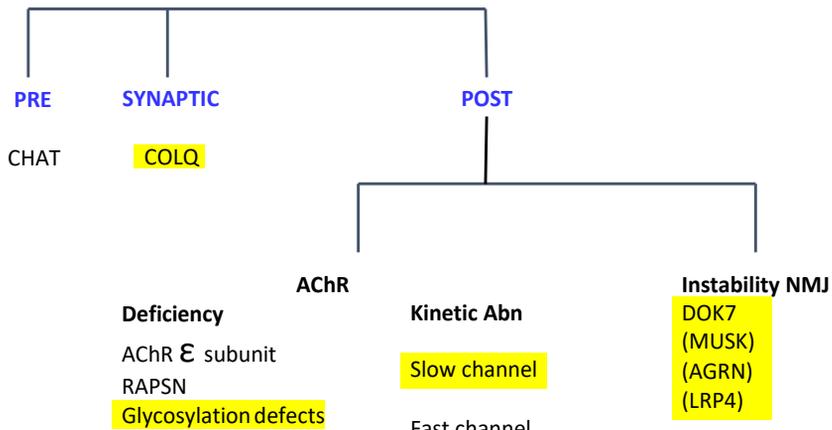
? cause of febrile-i



AGRIN

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

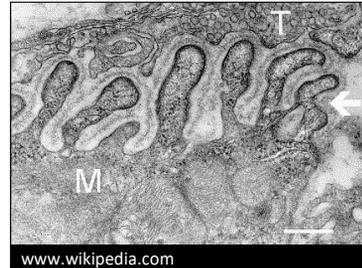
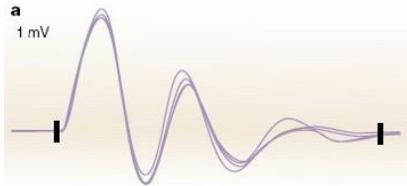
later onset
mild progressive weakness
myopathic features



Excitotoxic endplate myopathy



Prolongation of:
opening of AChR in Slow channel syndrome
endplate current COLQ (ACh esterase)



www.wikipedia.com

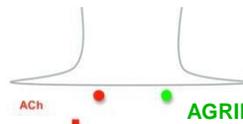
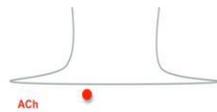
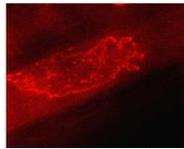
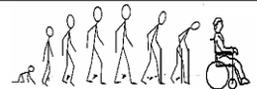
SCS NMJ



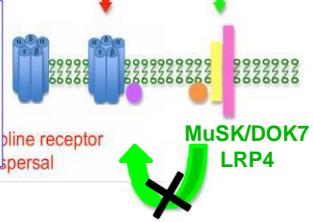
Engel AG, Lambert EH, Mulder DM, et al. Ann Neurol 1982;11:553-569.

Ca²⁺ accumulation → degeneration

Neurotransmission → disassembly of AChR clusters

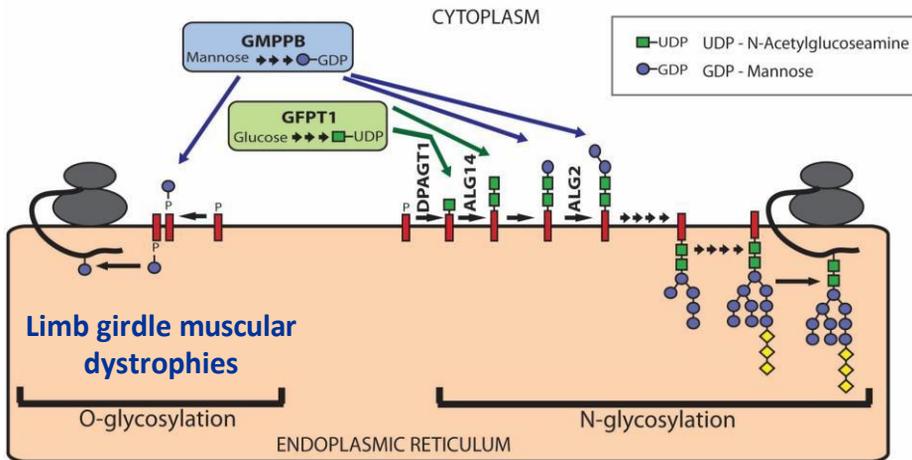
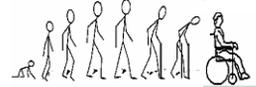


→ structural damage and endplate myopathy in absence of DOK7

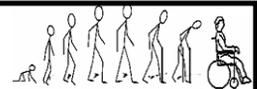


Slide from An Van Haesebroek

Glycosylation defects affect muscle as well as AChR



Glycosylation pathway mutations

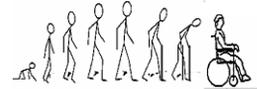


- Clinical features
 - limb-girdle muscle weakness
 - usually no ptosis
 - no ophthalmoplegia
 - no facial involvement
 - no bulbar involvement
 - myopathic feature biopsy



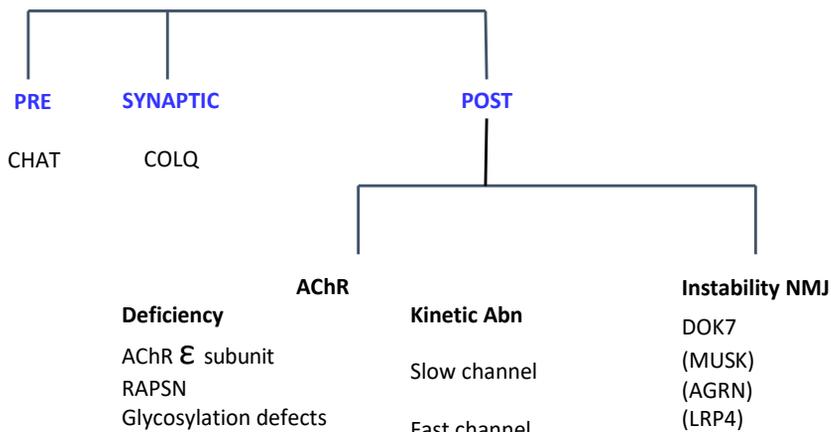
EASY MISS MYASTHENIC FEATURES

Glycosylation pathway CMS

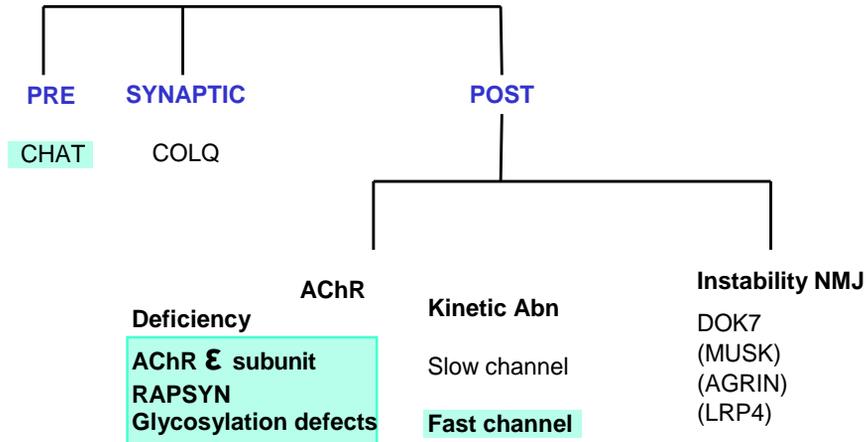


- Muscle biopsy
 - dystrophic features
 - ↓ labelling for alpha-dystroglycan
 - tubular aggregates
 - non specific / mild myopathic changes
- Muscle MRI
 - abnormal majority (T1)

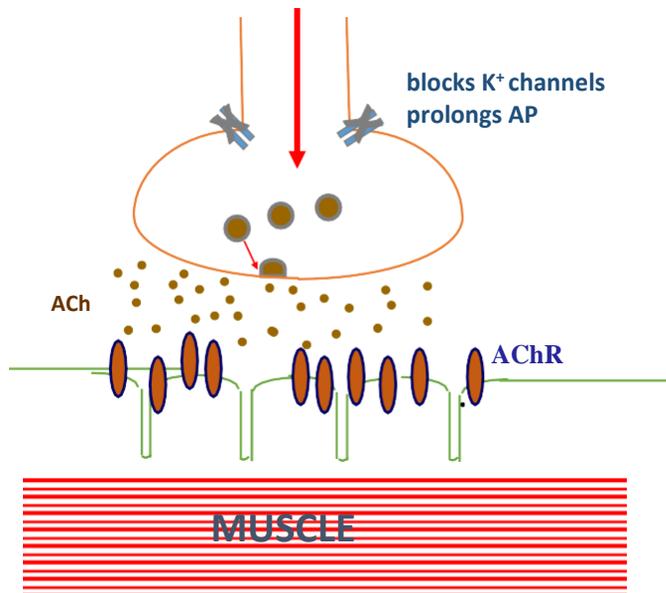
Treatment



Syndromes helped by increasing ACh levels AChE inhibitors and 3,4-DAP



3,4-DAP



Glycosylation CMS treatment response



- 24 GFPT1 'majority' pyridostigmine \pm 3,4-DAP
- 5 DPAGT1 all pyridostigmine, \pm 3,4-DAP
- 7 ALG2/ALG14 all pyridostigmine
- 8 GMPPB all pyridostigmine, \pm 3,4-DAP

Associated myopathy wont respond and may progress

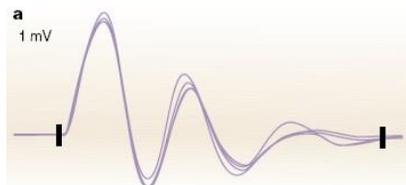
Cossins et al, Brain 2013
Belaya et al, Am J Hum Genetics 2012
Cruz et al, JNNP 2016
Guergueltcheva et al, J Neurol 2012

SCS and COLQ: 'to much message'



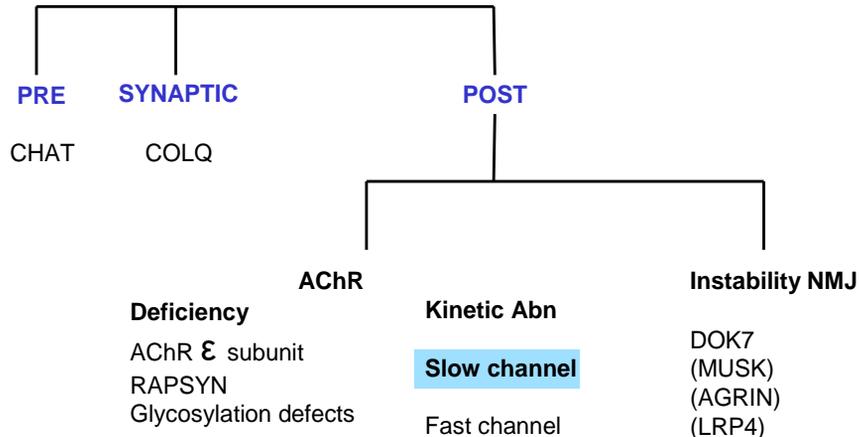
Slow channel syndrome:
prolonged opening of AChR

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



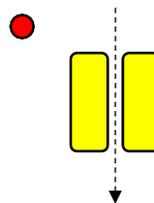
Slow channel syndrome



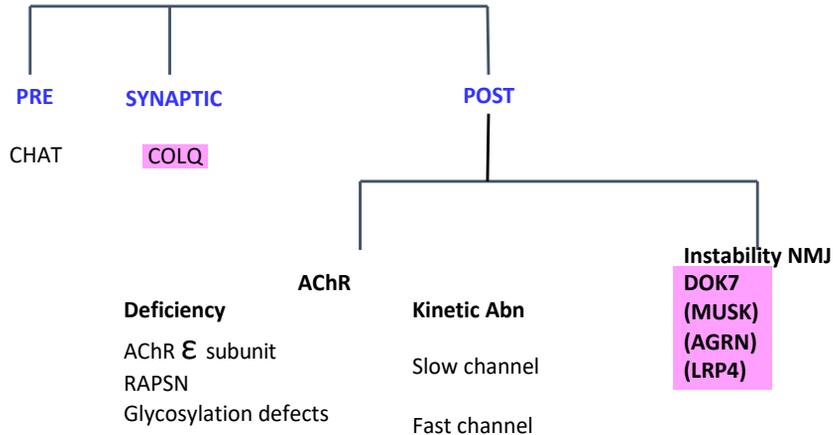
Worsened by increasing ACh levels

High dose Open Channel Blockers help:

- Fluoxetine
- Quinidine



Syndromes:
worsened by \uparrow ACh levels
helped by salbutamol or ephedrine



Ephedrine: progressive improvement in DOK7

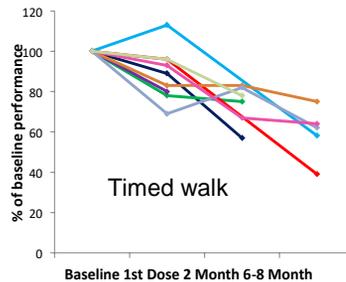
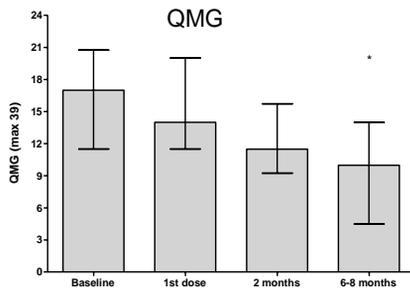
NEUROLOGY 2010;74:1517-1523, D. Lashley,



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

10 patients

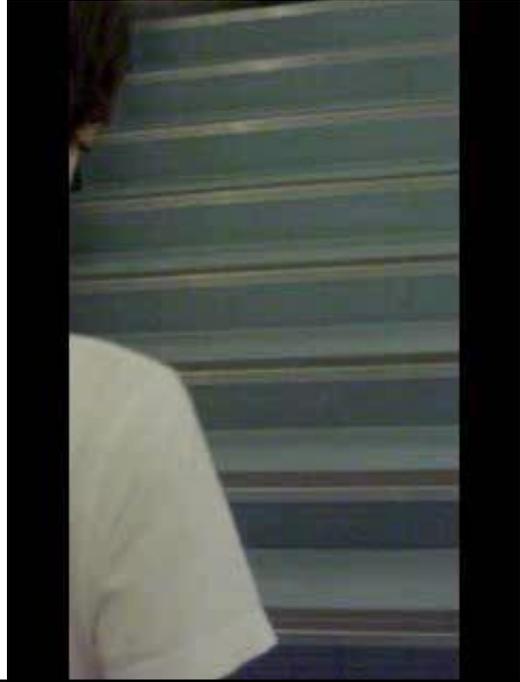
oral ephedrine



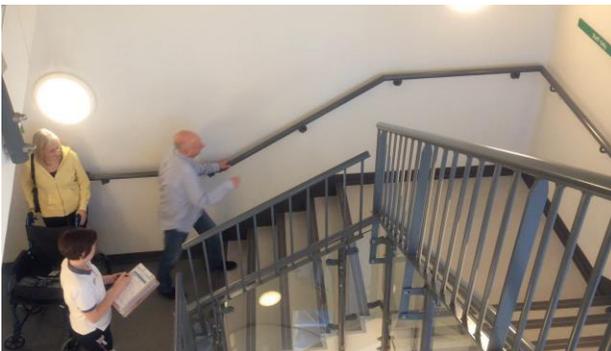
EPHEDRINE 4mnths 15mg



EPHEDRINE 2yrs 45mg

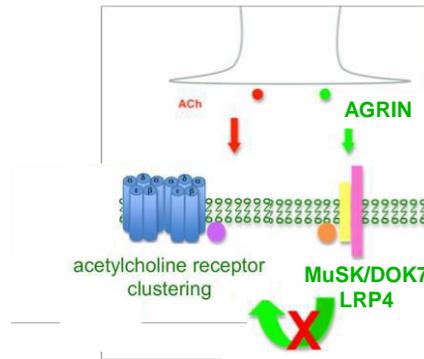


before salbutamol



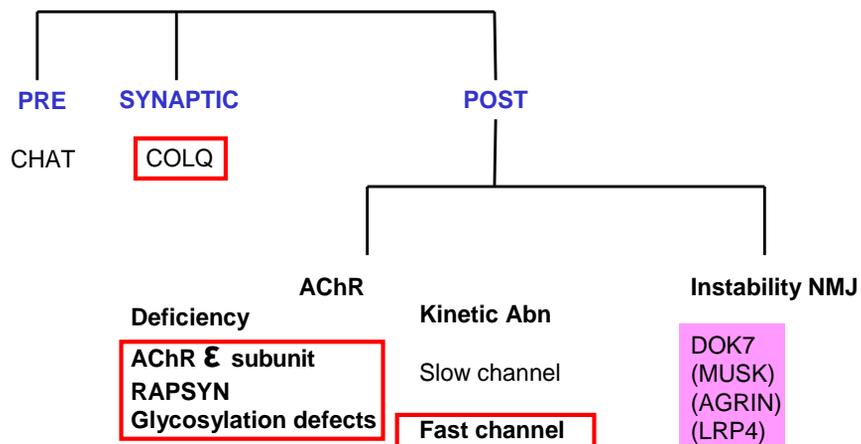
4 months later low dose salbutamol

Effect of salbutamol and ephedrine



slide adapted from An Van Haesebroek

Salbutamol/albuterol or ephedrine beyond clustering pathway mutations



Ephedrine and Salbutamol in COLQ



Congenital endplate acetylcholinesterase deficiency responsive to ephedrine

2 ephedrine +ve 150-200mg/day dramatic effect

Abstract—The authors describe two patients with congenital myasthenic syndrome (CMS) with end plate acetylcholinesterase (AChE) deficiency caused by mutations in the collagenic tail (ColQ) of AChE: a homozygous C-terminal Y2308 mutation in Patient 1, and a Prostagmia (serine/threonine bromide) test failed to distinguish between AChE deficiency and a slow-channel CMS. Both patients responded dramatically to ephedrine therapy.

albuterol dramatic improvement improved Neuromuscular Junction Acetylcholinesterase Deficiency Responsive to Albuterol

At age 5 years, he had persistent bilateral ptosis, complete ophthalmoplegia, mild facial weakness, and Medical Research Council grade 4/5 weakness and abnormal fatigability of the proximal limb muscles. When tired he refused to walk, Thirty months after the start of therapy, the dose of Albuterol was increased to 2.5 mg three times daily. On this regimen, the patient is now able to run around when playing and enjoys full participation with his peers in daily school activities. He has normal intelligence and

NMJJ-2.06
Ephedrine treatment of seven patients with Congenital Endplate (EP) Acetylcholinesterase (AChE) deficiency

7 ephedrine +ve 75-200mg/day mixed degrees of improvement

by manual muscle testing and endurance in walking and climbing steps and with disappearance or improvement of the decremental EMG response. In Pts 5-7 the following histories were obtained: Pt 5 was on 12 mg ephedrine/day during early childhood; as she grew older condition deteriorated but she improved at age 9 years when the dose increased to 80 mg/day. Pt 6 noted improved endurance on 75 mg e/day. Pt 7 improved at age 17 years when the dose was increased to 200 mg/day. Pt 60 became much weaker. Concomitant therapy with albuterol was cooperative. Concomitant therapy with ephedrine in EP AChE deficiency. The results point to a need to define the safety and

Therapy with ephedrine. There is no specific therapy for congenital EP AChE deficiency. However, at least two patients with EP AChE deficiency have derived marked subjective benefit from ephedrine (unpublished information to AGE). For this reason and because both Patients 1 and 2 were significantly disabled on ephedrine divided doses, but in Patient 2, it was effective only when the dose was increased from 150 to 200 mg. After the patient's symptoms improved, a normally active preschooler, Patient 1 became a normally active preschooler, Patient 2 participated in physical education without fatigue and plays soccer, and Patient 3 walks horizontally for longer than a minute. The results of this study improved in both patients, but more so in Patient 2 (table and figure 1) than Patient 1 (table and figure 2).

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

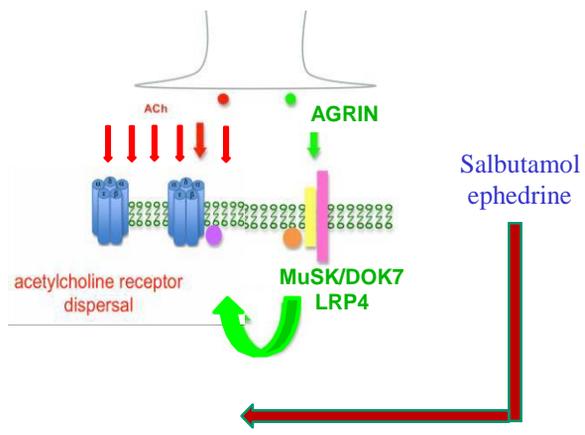
post 2wks salbutamol (4mg OD): walking all day school, climb up & down 2 flights stairs without rail, eating improved,

BENEFICIAL EFFECTS OF ALBUTEROL IN CONGENITAL ENDPLATE ACETYLCHOLINESTERASE DEFICIENCY AND DOK-7 MYASTHENIA

3 albuterol improved

Abstract
Background—Congenital myasthenic syndromes (CMS) are disabling heritable disorders. Anticholinesterase therapy is effective in most, but is contraindicated in ephedrine (EP) Acetylcholinesterase (AChE) deficiency, the slow-channel syndrome, Dok-7 myasthenia, EP Acetylcholinesterase (AChE) deficiency, and in not useful in CMS due to defects in MuSK, rapsin, and pleckstrin. EP Acetylcholinesterase (AChE) deficiency and Dok-7 myasthenia respond favorably to ephedrine (EP AChE) deficiency. Response to therapy was evaluated by 9-point manual muscle testing and endurance in walking and climbing steps. The adverse effects of therapy were like those

COLQ CMS: reduced breakdown of ACh



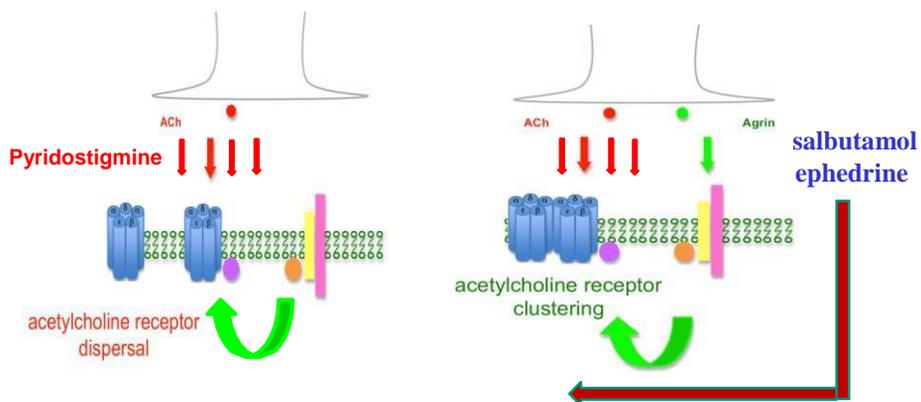


Observation: A group of severe patients with AChR deficiency

- Excellent initial response to pyridostigmine therapy
- Because severity and response: \uparrow 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



Change in performance for subcomponents of the QMG score

Pedro M. Rodríguez Cruz, MD
Jacqueline Palace, DM
Hayley Ramjattan, BSc
Sandeep Jayawant, MD
Stephanie A. Robb, MD
David Beeson, PhD

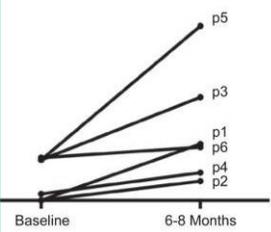
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The asthma drug that is being used to beat paralysis: How one patient went from using a wheelchair to walk unaided

- Jimmy Webster, 18, took salbutamol to treat congenital myasthenia
- Claimed he could stand and walk within three days of taking medication

By ALICE SMELLIE FOR THE MAIL ON SUNDAY
PUBLISHED: 22:23, 19 July 2014 | UPDATED: 08:29, 20 July 2014



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

β 2 ADR agonists



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