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
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
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

Nerve terminal

Muscle

Endoplasmic reticulum

N-glycosylation pathway

Vesicles

PREPL

H+

AcCoA

Ch

AcCh

AChR+Rapsyn-GFP

serum

HEK

Anti-Hu IgG

Alexa Fluor

Merged picture

AChR-MG

Anti-human antibody

(now pos)

HC
AChR deficiency mutations ‘all’ in the ε sub-unit
Glycosylation, ubiquitous

? rapid turnover of AChR → low threshold when attenuated

Limb girdle muscular dystrophies
O-glycosylation
N-glycosylation
ENDOPLASMIC RETICULUM

5 glycosylation genes associated w CMS

Kinetic abnormalities of AChR: slow and fast channel syndromes

PROLONGED ACTIVATION
Shortened ACTIVATION
Wild type
Slow
Wild type
Fast

Single channel recordings of mutant AChR

Claire Newland
Richard Webster
Classification

- AChR Deficiency
  - AChR ε subunit
  - RAPSYN
  - Glycosylation defects

Classification

- ChAT
- COLQ
**Classification**

- PRE
  - CHAT
- SYNAPTIC
  - COLQ
- POST
  - AChR
    - Deficiency
      - AChR ε subunit
      - RAPSN
      - 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)
    - (AGRIN)
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

postsynaptic muscle membrane
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

Ophthalmoplegia

YES

AChR

NO

DOK7

RAPSN

77% diagnosed

Early life crises

PRE

SYNAPTIC

POST

CHAT

AChR

Deficiency
AChR ε subunit
RAPSN
Glycosylation defects

Kinetic Abn
Slow channel
Fast channel

Instability NMJ
DOK7
(MUSK)
(AGRN)
(LRP4)

COLQ

SYNAPTIC

PRE

CHAT

COLQ
Rapsyn CMS
Sudden life-threatening crises infancy & early childhood

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

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

pp.te by minor infections between attacks well significant morbidity/mortality

Acknowledgements
Dr Zuberi Glasgow
Rapsyn-N88K clusters unstable

? cause of febrile-i

N88K

AGrin

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

later onset
mild progressive weakness
myopathic features

PRE SYNAPTIC POST

CHAT COLQ

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

Neurotransmission → disassembly of AChR clusters

→ structural damage and endplate myopathy in absence of DOK7
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**

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

Pre SYNAPATIC POST
CHAT COLQ

AChR Deficiency
AChR ε subunit
RAPSYN
Glycosylation defects

Kinetic Abn
Slow channel
Fast channel

Instability NMJ
DOK7
(MUSK)
(AGRIN)
(LRP4)

3,4-DAP
blocks K+ channels
prolongs AP

MUSCLE
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**

- **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)

**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

- **AChR Deficiency**
  - AChR ε subunit
  - RAPSN
  - Glycosylation defects

- **Kinetic Abn**
  - Slow channel
  - Fast channel

**Instability NMJ**
- DOK7
- (MUSK)
- (AGRN)
- (LRP4)

**Ephedrine: progressive improvement in DOK7**

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

10 patients

**oral ephedrine**

**NEUROLOGY** 2010;74:1517-1523, D. Lashley,
EPHEDRINE 4mths  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

- Pre SYNAPTIC
  - CHAT
  - COLQ

- AChR
  - Deficiency
    - AChR ε subunit
    - RAPSYN
    - Glycosylation defects
  - Kinetic Abn
    - Slow channel
  - Fast channel

- Instability NMJ
  - DOK7 (MUSK)
  - (AGRIN)
  - (LRP4)
Ephedrine and Salbutamol in COLQ

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.

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,

3 albuterol improved

COLQ CMS: reduced breakdown of ACh

Salbutamol ephedrine
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

Change in performance for subscales of the QMG score

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

AChR deficiency syndrome

Example: Before After

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

- Destabilising effects of enhanced neurotransmission through anticholinesterase medication
  - Mestinon

- Stabilisation through clustering pathway
  - β2 ADR agonists

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

Suspected CMS

Features of DOK7, COLQ, or SCS

- **Yes**
  - avoid pyridostigmine
  - await genetic diagnosis (if urgent try salbutamol)

- **No**
  - **start pyridostigmine**

**Features**

- fast channel
- RAPSYN
- AChR defn
- glycosylation
- CHAT
- slow channel

**Drugs**

- salbutamol
- fluoxetine
- ephedrine
- quinidine
- 3,4-DAP

**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