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Congenital Myasthenic Syndrome

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What is myasthenia?

- Myasthenia = muscle weakness
- Defect of the neuromuscular junction, affecting neurotransmission
- Easily fatigued muscles
- Fluctuating – hour, day, week, hormones

- Typically see muscle weakness in…
  - Oropharyngeal & Facial – e.g. ptosis, swallow
  - Limb girdle & trunk

- **Myasthenia is treatable**

mus “muscle” & thenos “weakness”

Myasthenia Gravis

- Autoimmune disorder
- Acute onset
- Typically diagnosed between 20-40 years old.
- Managed with steroids, Azothioprine, +/- Thymectomy

Congenital Myasthenic Syndromes

- Genetic fault
- Generally autosomal recessive inheritance
- Weakness seen in childhood
- Can be very severe in childhood – respiratory compromise
- Targeted medication; e.g. Pyridostigmine, 3.4 DAP, Salbutamol

LEMS – Lambert-Eaton Myasthenic Syndrome

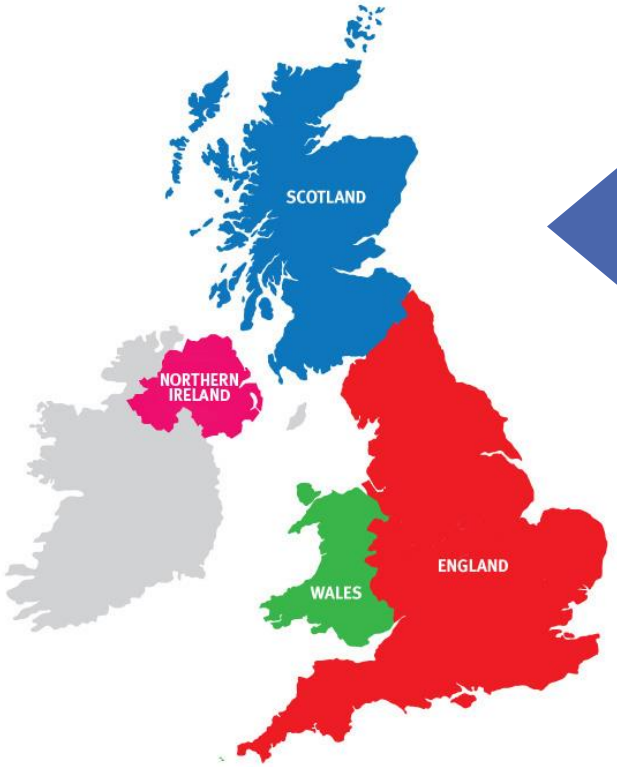
Similar to MG – antibody response, but effects ACh release (pre-synaptic)

Tends to affect limbs and gut, but less commonly oropharangeal

Small cell tumours – often benign

Prevalence of CMS

CMS is classified as a rare disease (<1 in 2,000 of the general population)



600 patients

1:100,000

Myasthenia Gravis more common ~ 15:100, 000

Key Features of CMS

Weakness of muscles that is brought on by activity and which improves with rest.

Fatigable muscle weakness

Areas effected

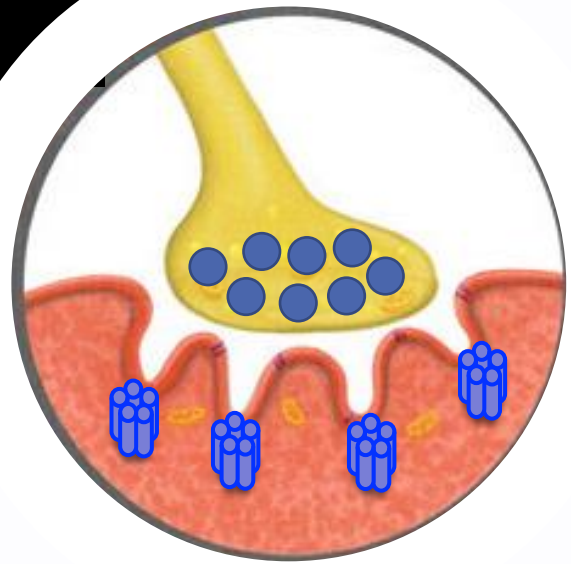
- Eyes and Face
- Bulbar – swallow
- Respiratory
- Skeletal muscle

- Ptosis and/or diplopia
- Delayed or altered swallow, chew
- Apnoeic episode or chest infections
- Delayed motor skills, limited functional independence
- Asymmetry and pain

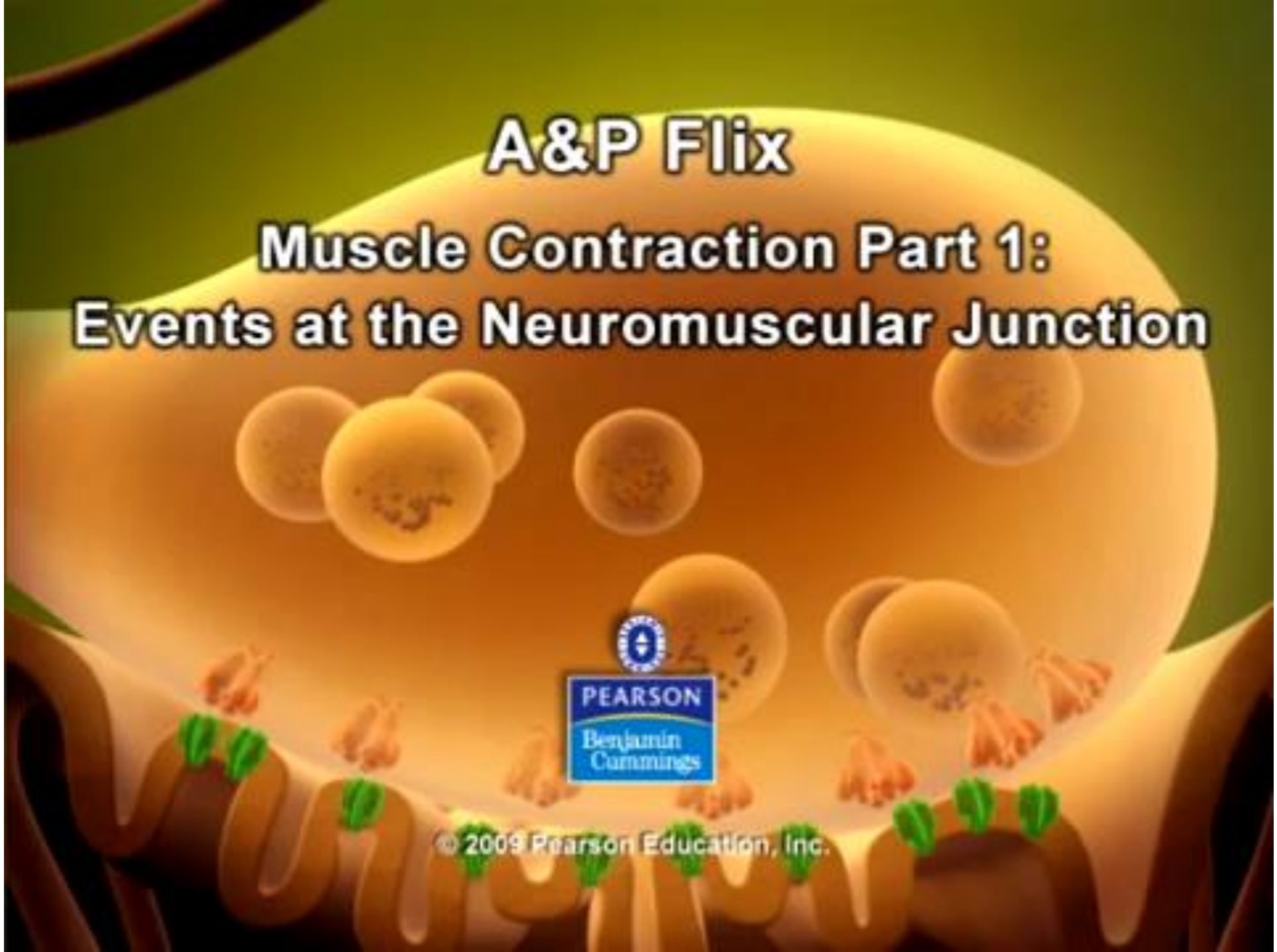
Symptoms

CMS causes dysfunction of the NMJ

2



The neuromuscular junction


A&P Flix
Muscle Contraction Part 1:
Events at the Neuromuscular Junction
PEARSON
Benjamin
Cummings
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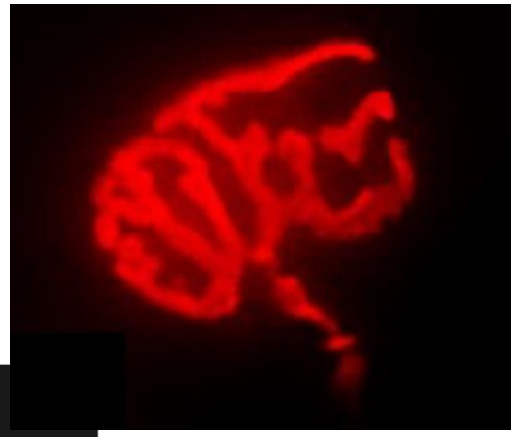
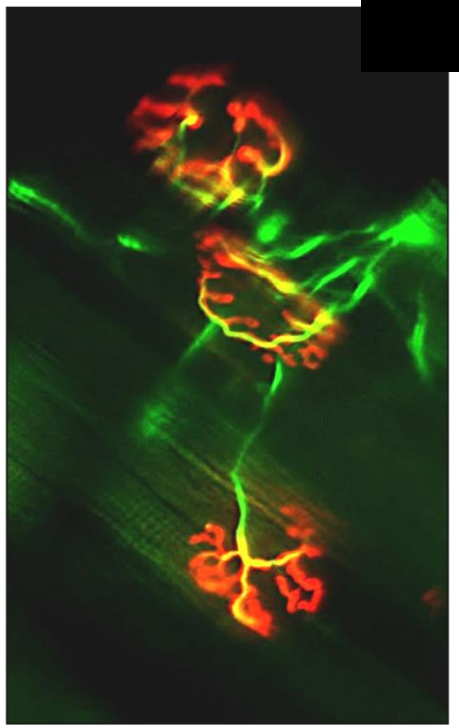
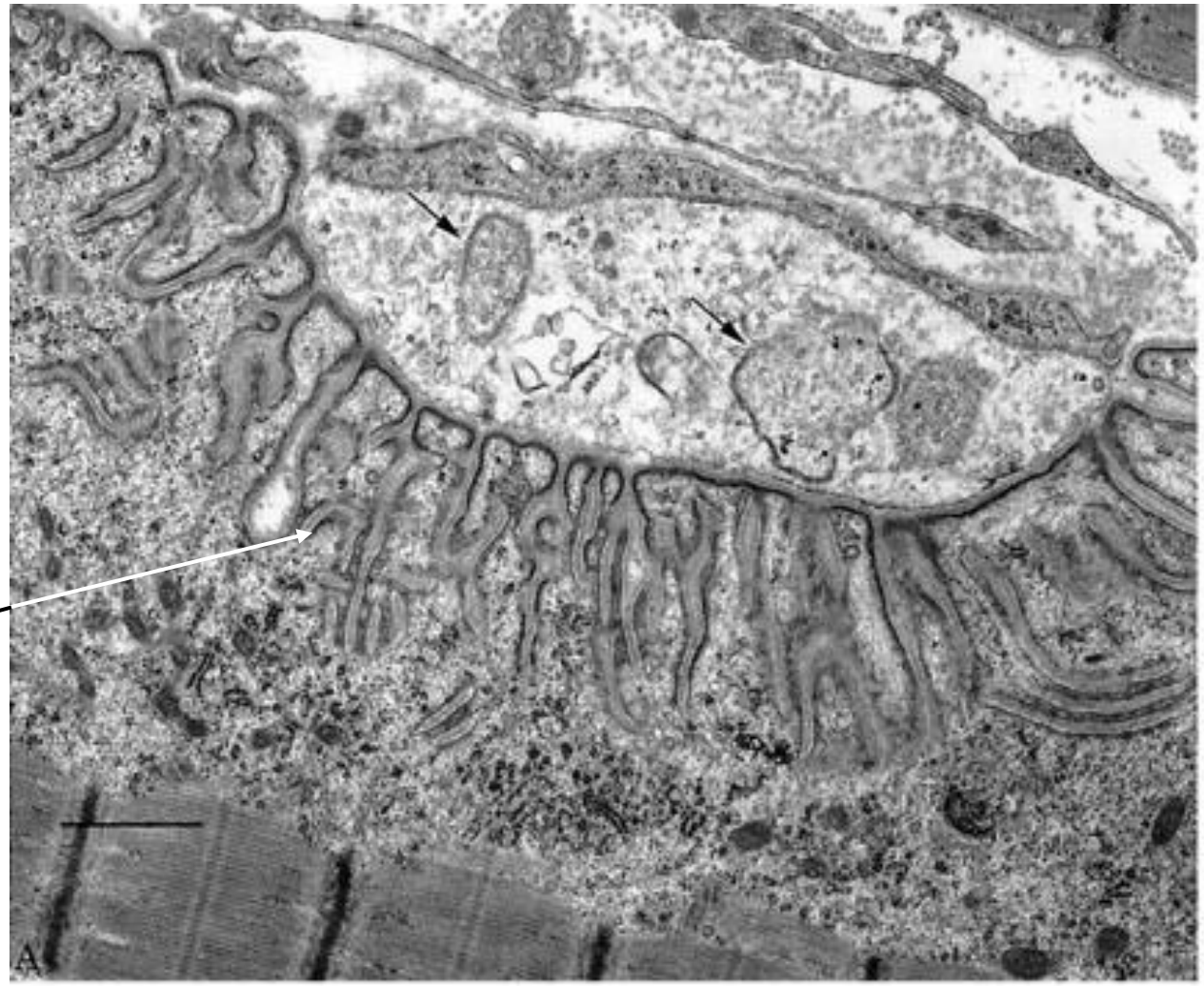
What does the neuromuscular junction look like in reality?





Post-synaptic folds

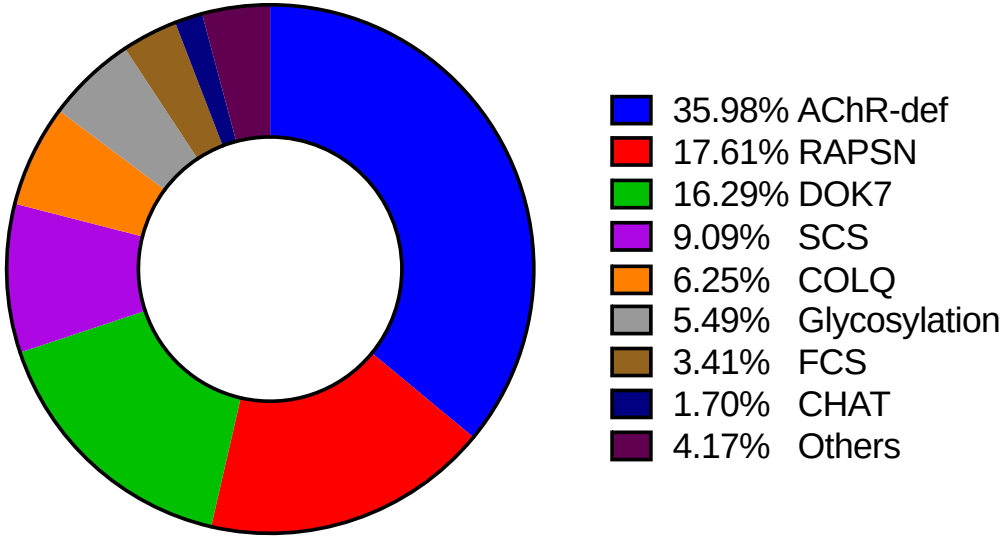


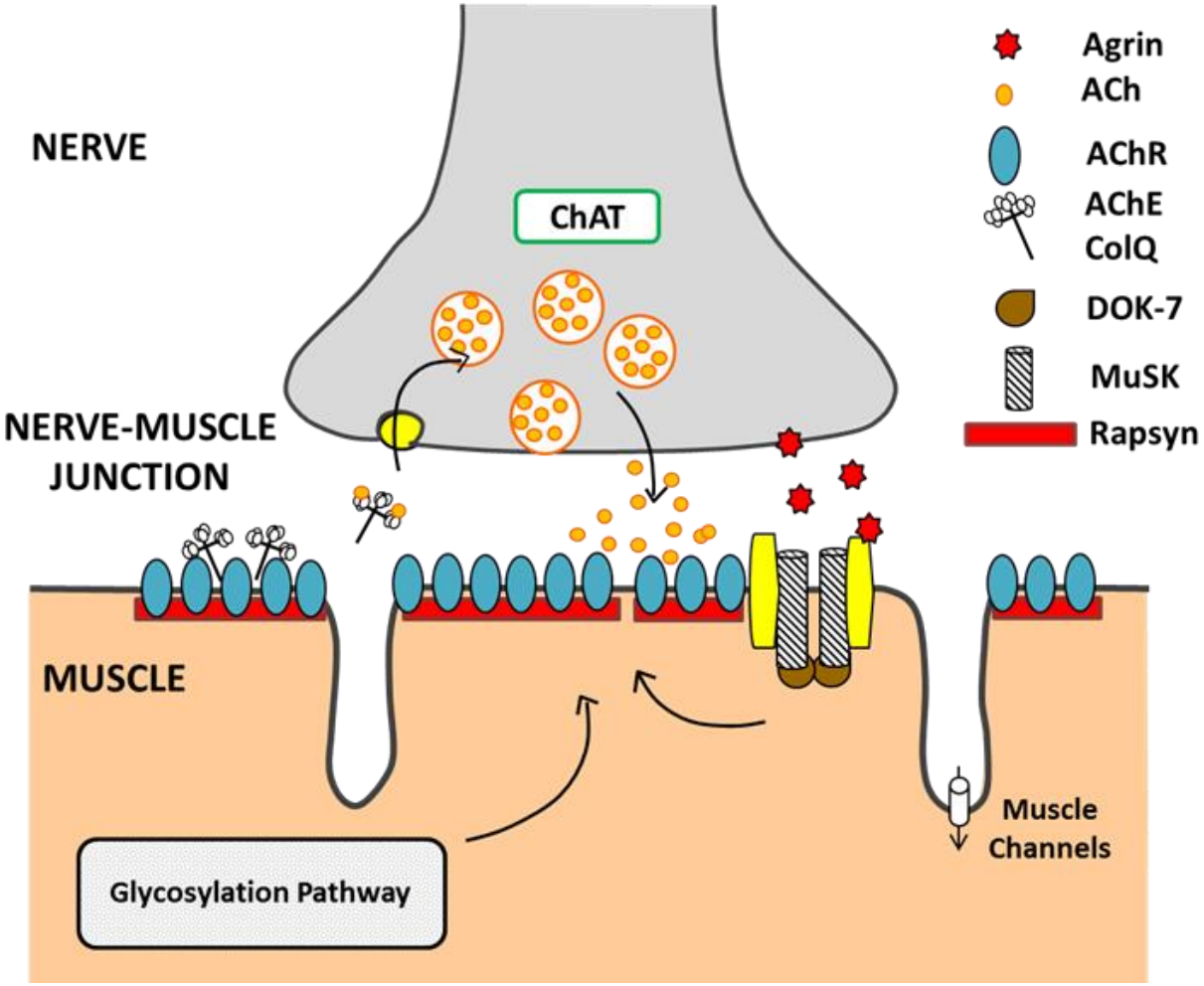
Nerve

Muscle

Types of CMS

- 30+ different phenotypes
- Different presentations between types
- Managed with different medication





With thanks to Dr P. Rodriguez-Cruz

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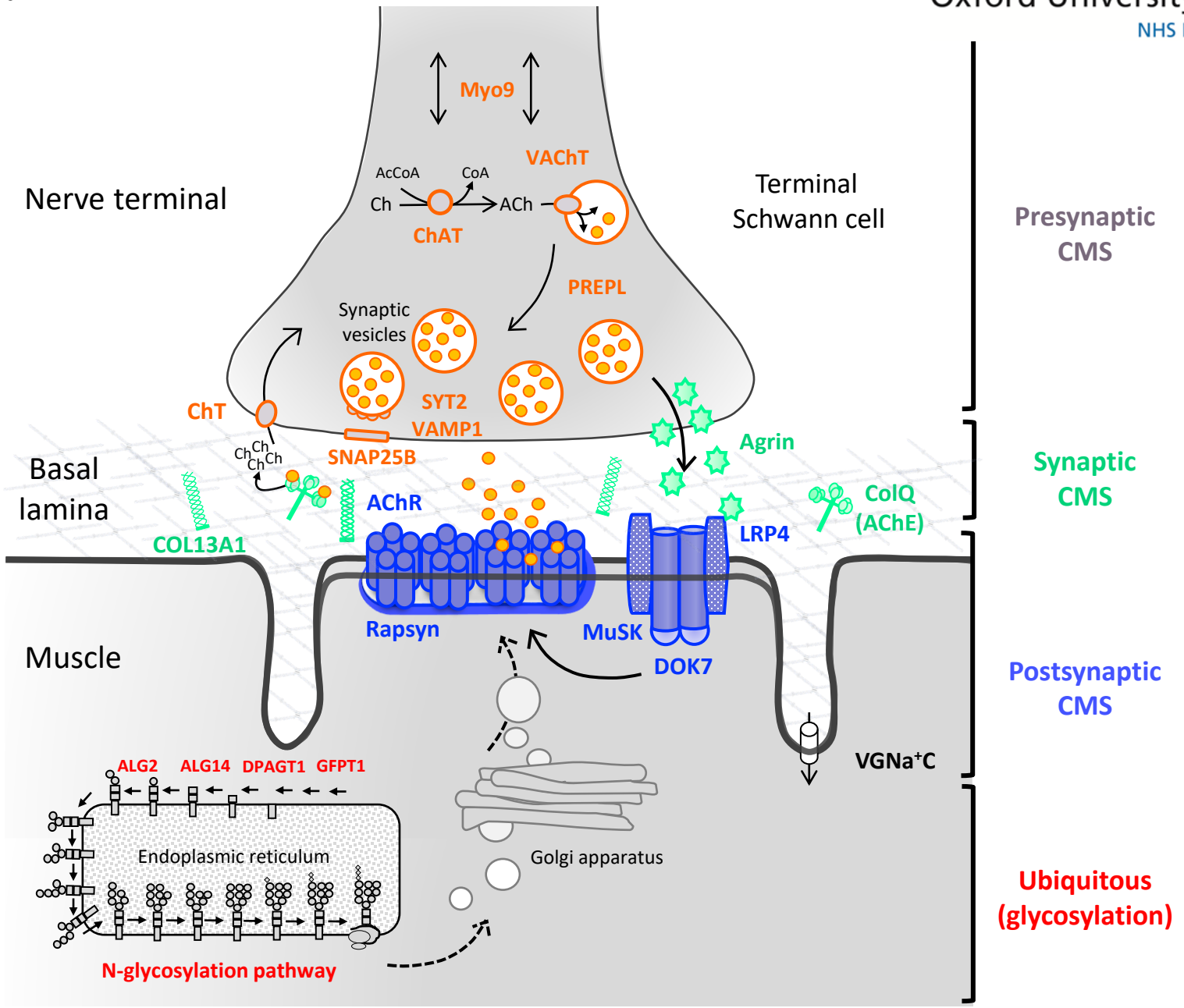

CMS Clinic

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- Multi-professional team – Neurologist, Geneticist, Clinical Fellow, Physiotherapist, Myasthenia Nurse
- Assessments:
  - Subjective history – any change, illness impact
  - Clinical examination
  - Standardised assessments
- Medication changes – timings, dosage, additional / stop
- Physical advice – activity, skill acquisition, pacing, MSk
- Links with professionals beyond OUH:
  - Local Consultants
  - Community AHPs
  - Schools / Work / Gyms

Assessing Fatigue & Fatigability

Myasthenia specific outcome measures – there are NO validated OCM for CMS (at present).

- Functional:
  - Quantitative Myasthenia Gravis Scale (QMG)
  - Myasthenia Gravis Composite (MGC)
  - Timed assessments – RTS / STS in 1 min / 6MWT / Grip Strength – repeated & sustained

- QoL Questionnaires:
  - MG-QOL 15
  - MG-ADL
  - MFIS
  - PedsQL

- Objective assessment: muscle grading and gait

Natural History Study – Oxford 2021

Background:

- Congenital Myasthenia features and symptoms are highly variable
- Limited published evidence on the different CMS phenotypes
- Emerging therapies for the management of CMS
- Need to have suitable and sensitive outcome measures to monitor effectiveness of therapies
- Better understanding of CMS

Methods and Timelines:

- Assessments timed with routine clinic appointments
- 2 year study
- Recruitment in first 6 months
- Initiating in Spring/Summer 2021

CMS is a treatable condition

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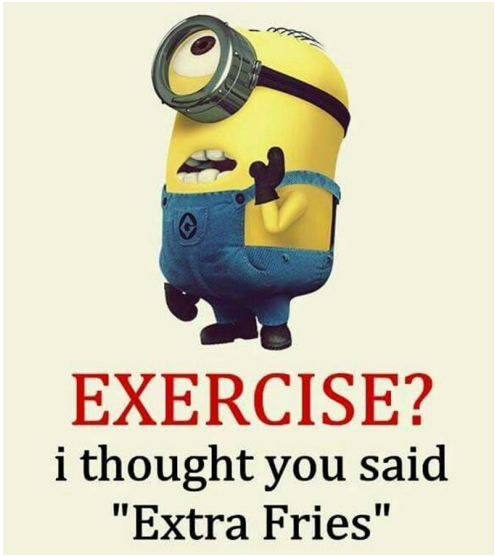
Drug Therapy:

Fast acting: stimulate Ach production – e.g. Pyridostigmine

Slow acting: Clustering AChR – e.g. Salbutamol

FUTURE: Gene Therapy



Medical Care:

Respiratory Management

Dietetics

Spinal & Orthopaedic Teams

Psychology – fatigue / mm fatigue

Activity:

Exercise & Pacing advice

Adaptations to environment / task – Home/ Work/ Education

Physiotherapy MSK Ax – disuse injuries

Postural management – seating and orthotics

Types of Congenital myasthenic syndrome

Table1

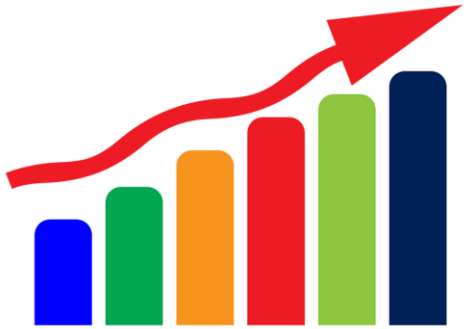
CMS Type	Inheritance	Treatment (Not all registered for use in CMS)
Acetylcholine receptor deficiency ***CHRNE, CHRNA, CHRND and CHRNB genes***	AR	Pyridostigmine, 3,4-DAP, Salbutamol/Ephedrine*
Rapsyn deficiency ***RAPSN gene***	AR	Pyridostigmine, 3,4 DAP
DOK7 CMS ***DOK7 gene***	AR	Salbutamol/Ephedrine, 3,4 DAP
ChAT deficiency CMS with episodic apnoea' ***CHAT gene***	AR	Pyridostigmine, Salbutamol*
Acetyl-cholinesterase deficiency ***COLQ gene***	AR	Salbutamol/Ephedrine
Slow channel syndrome ***CHRNA, CHRNB, CHRND and CHRNE***	AD	Quinidine, Fluoxetine
Fast channel syndrome ***CHRNA, CHRNB, CHRND and CHRNE***	AR	Pyridostigmine, 3,4 DAP, Salbutamol/Ephedrine*
Disorders of glycosylation **GFPT1, DPAGT1, ALG2/14, GMPPB**	AR	Pyridostigmine, 3,4 DAP, Salbutamol/Ephedrine

Treatment of Congenital myasthenic syndrome

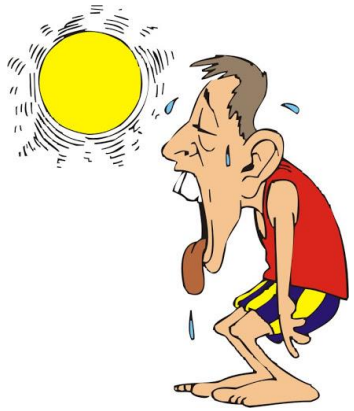
Table2

Drug	Type of CMS	Possible side effects
Pyridostigmine (Mestinon®)	ChAT, Fast channel, RAPSN, ACh Receptor Deficiency, Glycosylation	Diarrhoea, abdominal cramps, breathing difficulty, sweating, slow heart rate, increased weakness (uncommon)
Ephedrine or Salbutamol	DOK7, Acetylcholinesterase (ACHE) deficiency, ACh Receptor Deficiency, Fast channel, ChAT	Anxiety, high blood pressure, fast heart rate, chest pain, (uncommon) difficulty passing urine, tremor, breathing difficulty, confusion
3,4-DAP	DOK7, ACh Receptor deficiency Fast Channel Glycosylation	Tingling in hands and around mouth (common)
Fluoxetine	Slow channel syndrome	Low blood pressure, sleep disturbance, urinary frequency, suicidal thoughts or self-harm (uncommon)
Quinidine	Slow channel syndrome	Heart rhythm disturbances, blood disorders, behaviour changes (uncommon)

Physiotherapy in Myasthenia



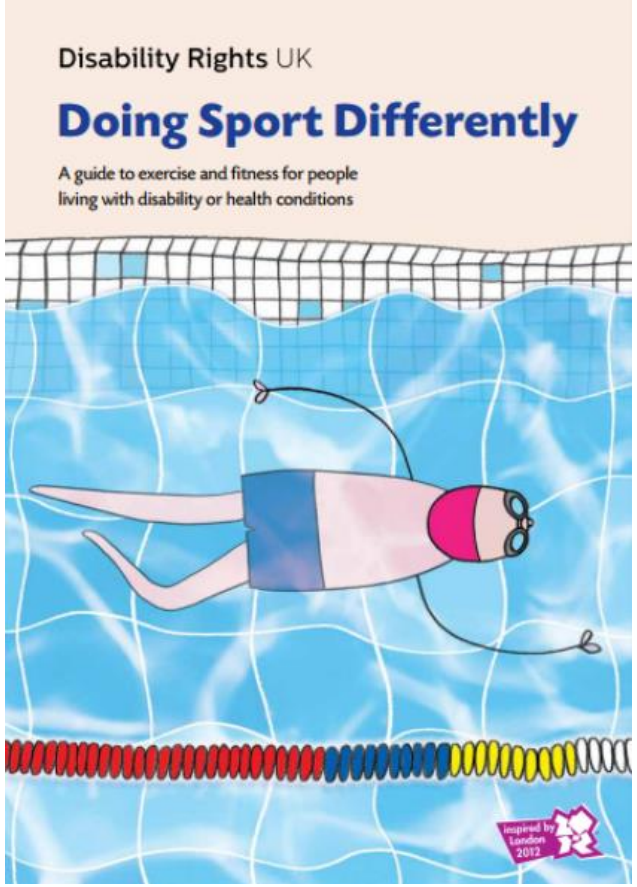
- Graded, targeted exercise is beneficial and safe!
- Pacing advice is key
- Medication
  - Established?
  - Timing
  - Side effects
- Environmental factors – weather & stress



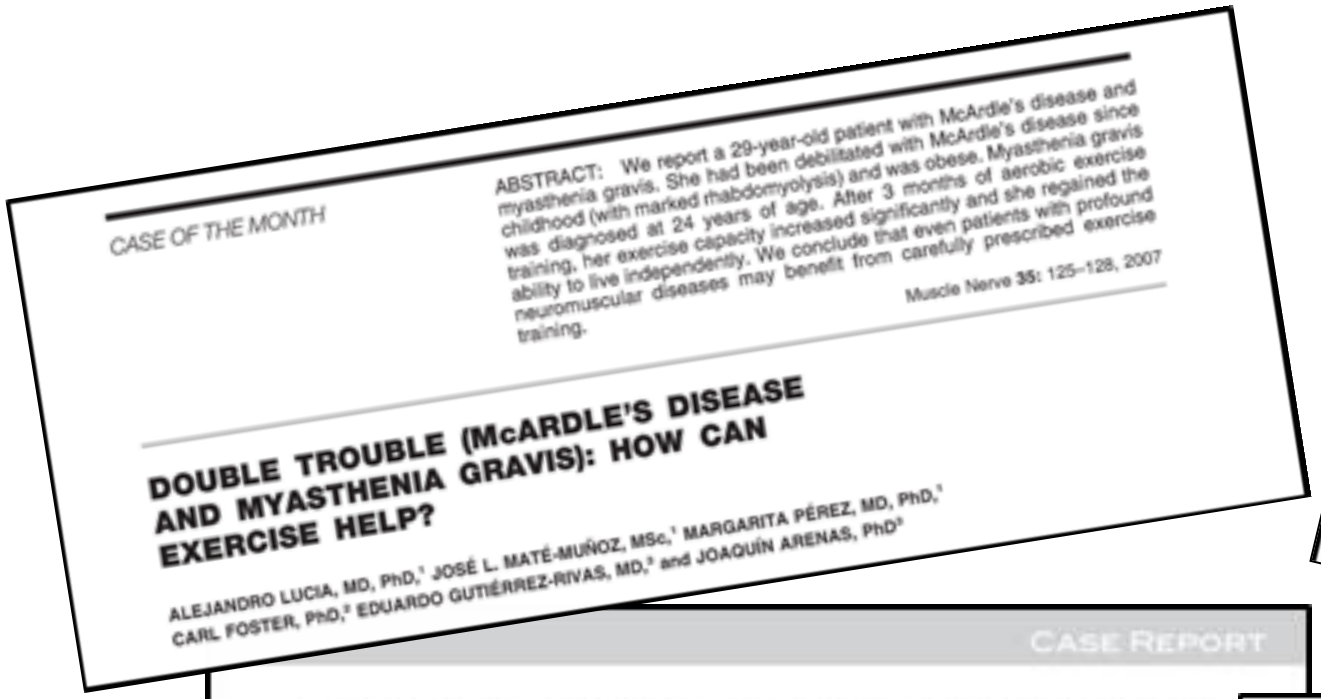
- Remember your fatigability indicators – education to the child / parent / school of when to rest / slow down

The impact of exercise in CMS

Negatives	Positives
• Muscle fatigability with repetitive movements • Post exercise fatigue • Impact on ADLs • Exercise induced myalgia • Ocular and speech difficulties	• Improves cardiovascular fitness and endurance • Maintain joint flexibility, muscular strength, and balance • Reduces the risk of diabetes and CVD • Set up good habits for life • Improved balance • Easier ADLs • Weight loss • Self confidence / peer support



The impact of exercise in Myasthenia



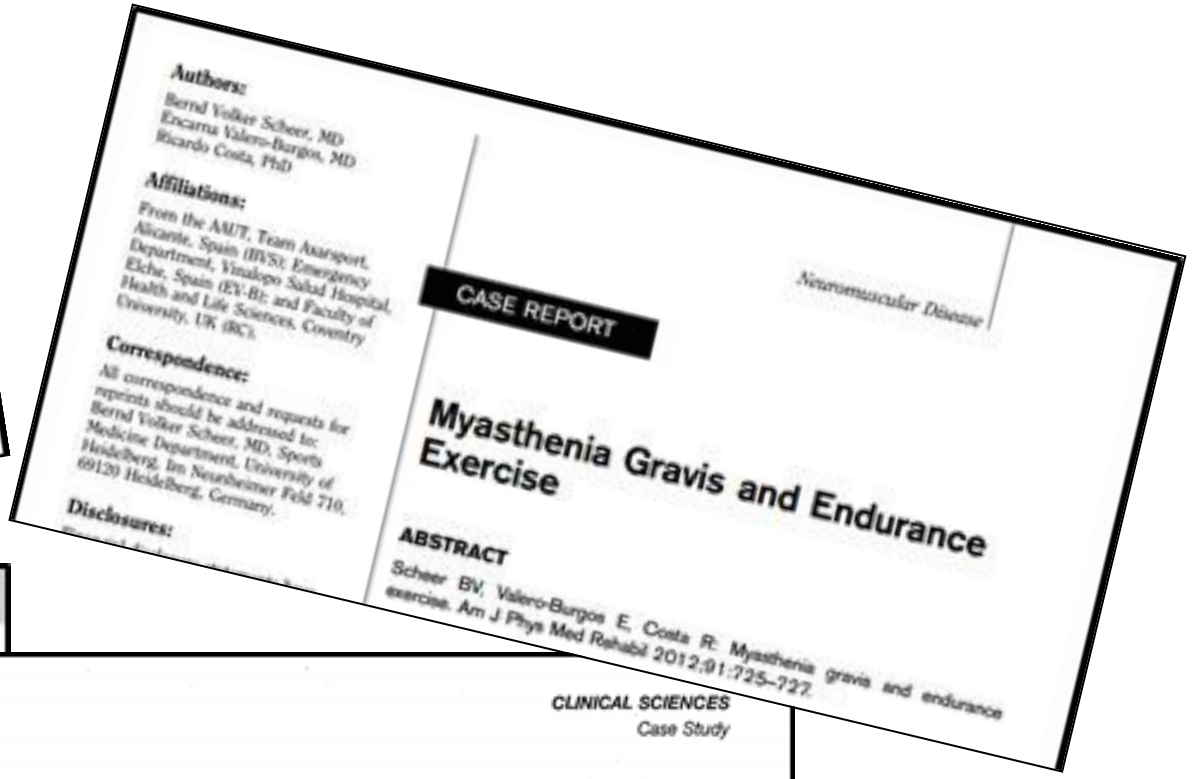
CASE OF THE MONTH

ABSTRACT: We report a 29-year-old patient with McArdle's disease and myasthenia gravis. She had been debilitated with McArdle's disease since childhood (with marked rhabdomyolysis) and was obese. Myasthenia gravis was diagnosed at 24 years of age. After 3 months of aerobic exercise training, her exercise capacity increased significantly and she regained the ability to live independently. We conclude that even patients with profound neuromuscular diseases may benefit from carefully prescribed exercise training.

Muscle Nerve 35: 125–128, 2007

DOUBLE TROUBLE (McARDLE'S DISEASE AND MYASTHENIA GRAVIS): HOW CAN EXERCISE HELP?

ALEJANDRO LUCIA, MD, PhD,[1] JOSÉ L. MATÉ-MUÑOZ, MSc,[1] MARGARITA PÉREZ, MD, PhD,[1] CARL FOSTER, PhD,[2] EDUARDO GUTIÉRREZ-RIVAS, MD,[3] and JOAQUÍN ARENAS, PhD[3]



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Disclosures:

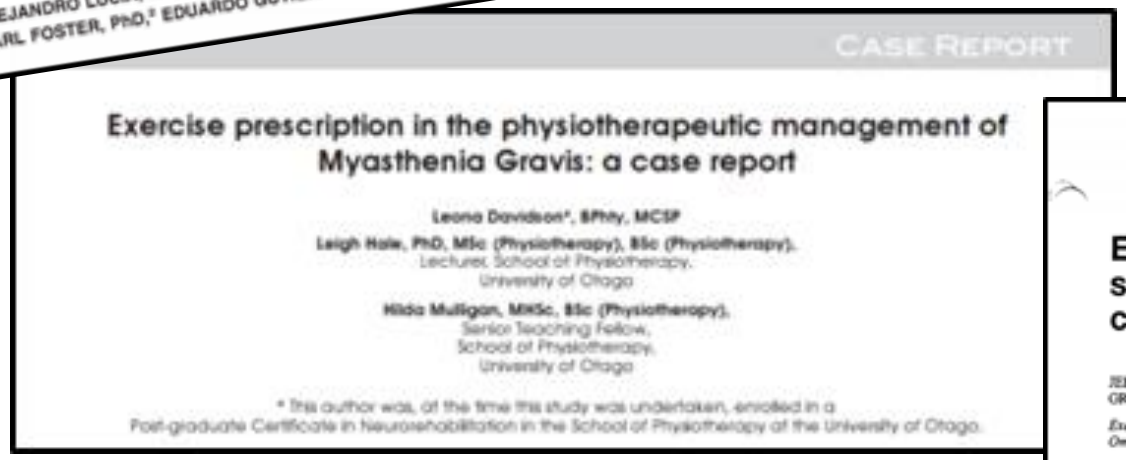
Neuromuscular Disease

CASE REPORT

Myasthenia Gravis and Endurance Exercise

ABSTRACT

Scheer BV, Valero-Burgos E, Costa R. Myasthenia gravis and endurance exercise. Am J Phys Med Rehabil 2012;91:725–727.

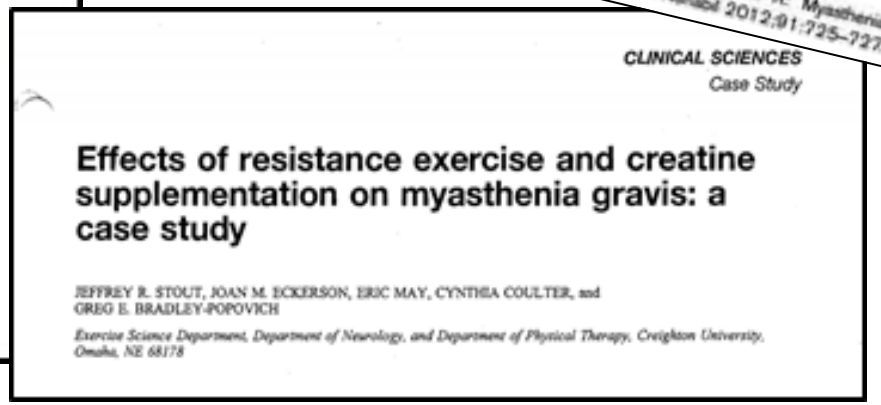


CASE REPORT

Exercise prescription in the physiotherapeutic management of Myasthenia Gravis: a case report

Leona Davidson*, BPhty, MCSP
Leigh Hale, PhD, MSc (Physiotherapy), BSc (Physiotherapy),
Lecturer, School of Physiotherapy,
University of Otago
Hilda Mulligan, MHSc, BSc (Physiotherapy),
Senior Teaching Fellow,
School of Physiotherapy,
University of Otago

* This author was, at the time this study was undertaken, enrolled in a Post-graduate Certificate in Neurorehabilitation in the School of Physiotherapy of the University of Otago.



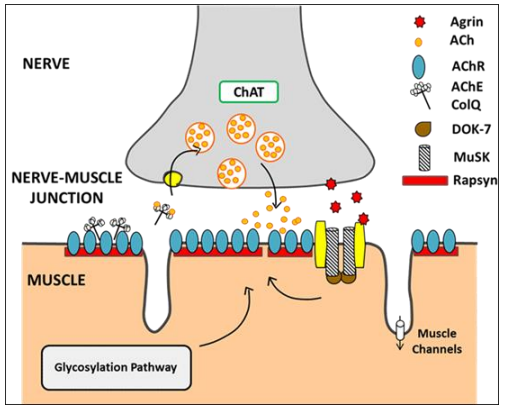
CLINICAL SCIENCES
Case Study

Effects of resistance exercise and creatine supplementation on myasthenia gravis: a case study

JEFFREY R. STOUT, JOAN M. ECKERSON, ERIC MAY, CYNTHIA COULTER, and GREG E. BRADLEY-POPOVICH

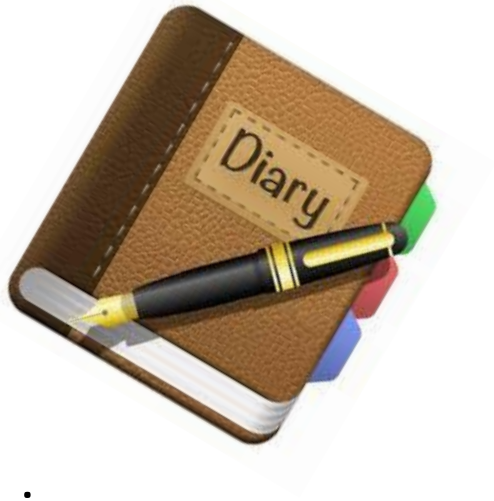
Exercise Science Department, Department of Neurology, and Department of Physical Therapy, Creighton University, Omaha, NE 68178

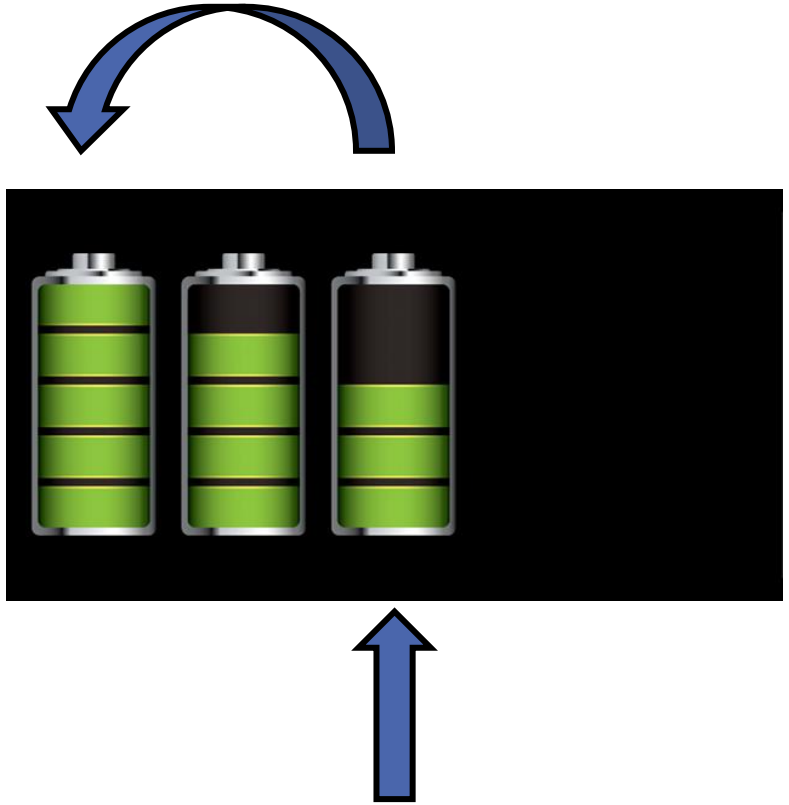

What activities are important to you?
Core Stability
Neck strength
Legs
Arms
Stairs
Independence
Posture
Work



Remember: weakness with repetition

- Pacing is key – battery charge
- Watch for signs of fatigue
- Diary
- Managing exercise induced myalgia
- Specialist support / guidance – Physio / P.Trainer





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Key things to remember…

- MG and CMS are different
- CMS is treatable
- Listen to your patient
- Specific graded exercise is safe and should be encouraged with guidance
- Pacing and education on triggers and signs of fatigue is key

Thank you for listening