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Teaching Course 17

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

The role of Clinical neurophysiology in diagnosing CMS and Myotonic disorders

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The role of Clinical neurophysiology in diagnosing CMS and Myotonic disorders

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Conflict of Interest

In relation to this presentation and manuscript:

❑ the Author has no conflict of interest in relation to this manuscript.

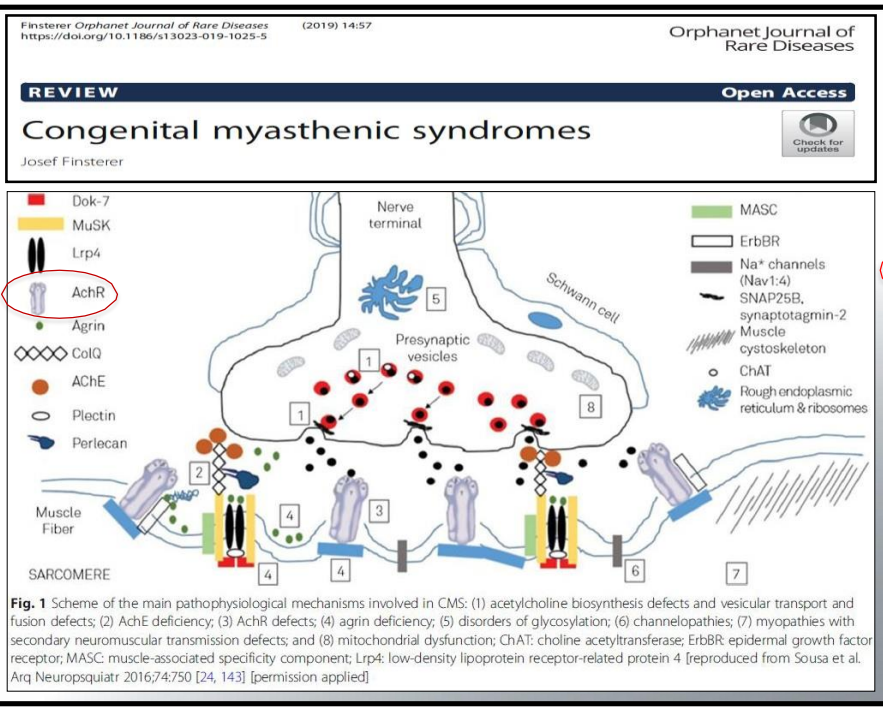
ean congress Oslo 2019 5 years ean

The role of Clinical neurophysiology

- In the evaluation of patients with an unknown NM diagnosis
  -myopathy, neuropathy, NMJ disorders - subgroups
- Help in confirming a specific diagnosis/syndrome
  -e.g. NMJ disorders, myotonia
- (Follow-up)

Normal findings do not always exclude a neuromuscular disease

Congenital myasthenic syndromes



32 subtypes of CMS
-15 postsynaptic
-8 presynaptic
-4 synaptic
-5 glycosylation protein

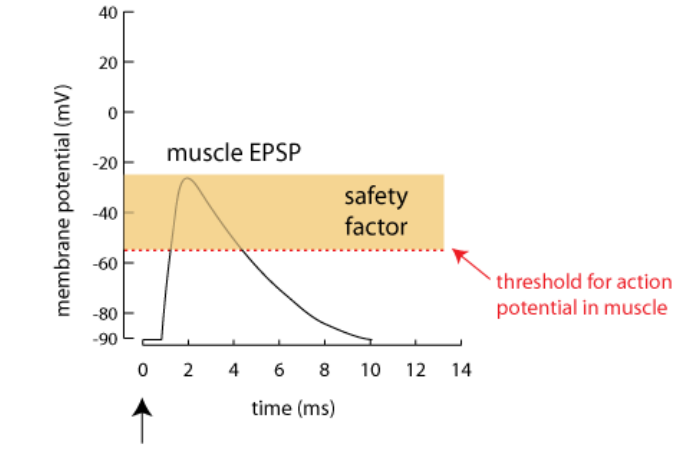
Electrophysiological evaluation

1. Nerve conduction studies and EMG
   - Differential diagnosis
   - Some CMS may show myopathy
   - M-response –amplitude, double discharges (slow channel)

2. Repetitive nerve stimulation
   - The most important method
   - Different patterns in presynaptic and postsynaptic (not always in CMS)
   - Tests do not differ hereditary from autoimmune NMJ diseases

3. Single fiber EMG – if RNS is normal

«Safety factor»



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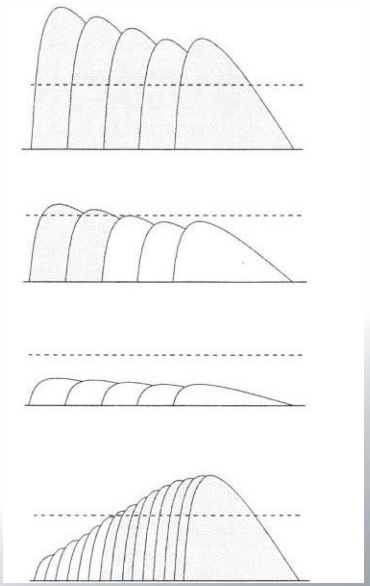
- Under normal circumstances the end plate potential always rises above threshold, resulting in a muscle fiber action potential

End plate potentials

Threshold →



Normal NMJ (3 Hz stimulation)

No decrement due to safety factor

Postsynaptic NMJ disorder (3 Hz)

Decrement

the last potentials fall below threshold – no muscle fiber action potential

Presynaptic NMJ disorder (3 Hz)

Low motor amplitude and some decrement

all potentials are below threshold

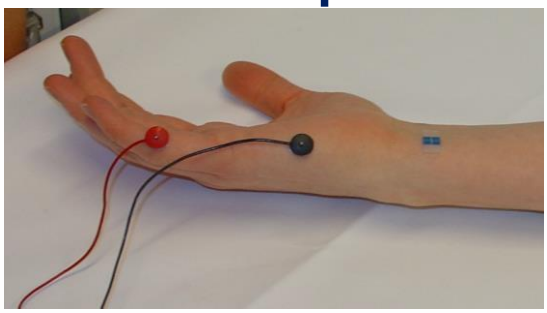
Presynaptic NMJ disorder (50 Hz)

Increment

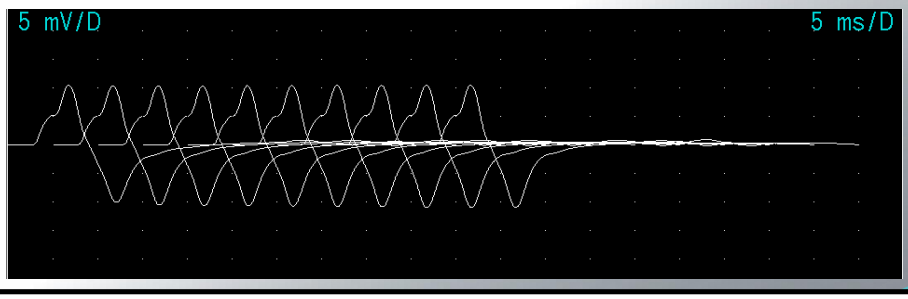
increased Ach release

Preston, Shapiro

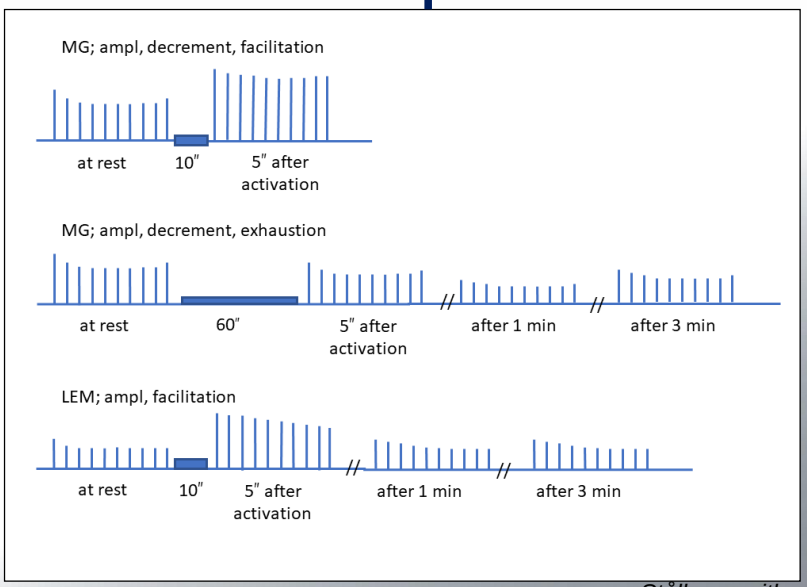
Repetitive nerve stimulation



- Stimulation of the ulnar nerve at the wrist
- Compound muscle action potentials (CMAP) recorded over ADM
- 10 stimuli, 3 Hz (protocol)
- Consider additional nerves and frequencies



RNS 3 Hz protocol



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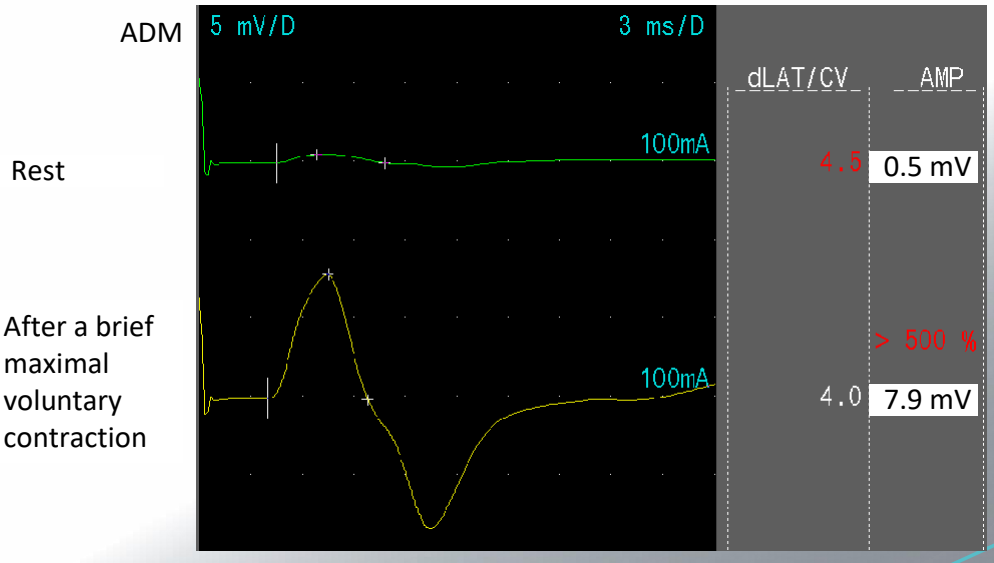
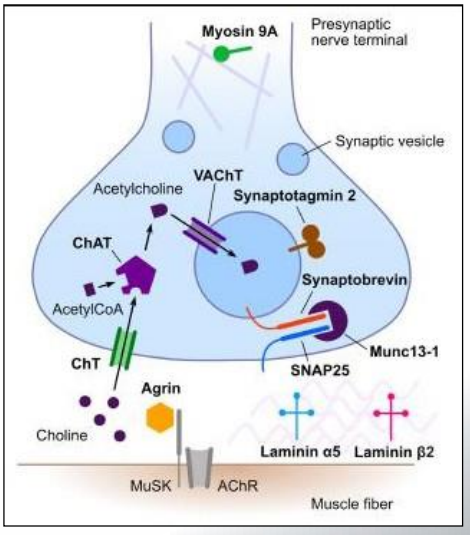
RNS in CMS

- Test weak muscles
  - Arms (distal, proximal), legs, face
- Start with low frequency stimulation
  - Decremental response in most postsynaptic and presynaptic CMS
- High frequency stimulation
  - Incremental response (> 60%) in presynaptic CMS if the increased calcium concentration in the nerve terminal can overcome a defect in synaptic vesicle release
  - Instead of high frequency stimulation (painful), a brief maximal muscle contraction can be used in cooperative patients
- Normal tests do not exclude CMS

> 500% facilitation (LEMS patient)



Presynaptic CMS

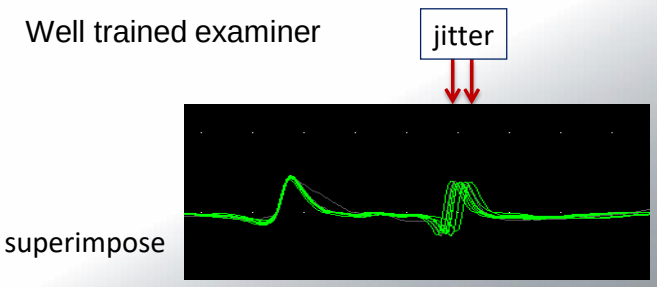


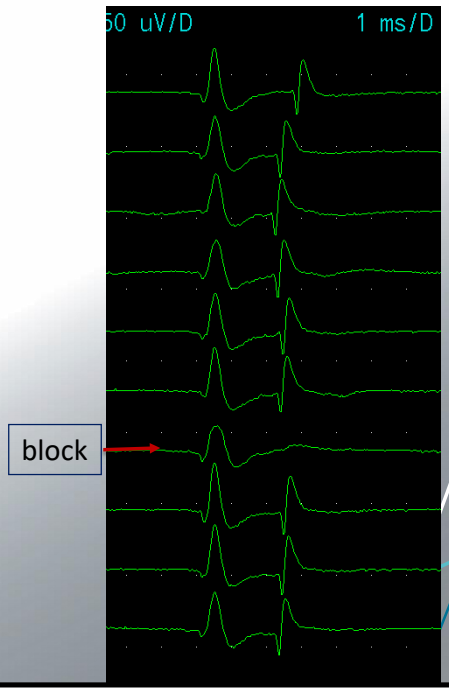
- **Facilitation/increment reported in:**
  - Synaptobrevin-1-CMS
  - Munc13-1-CMS
  - Synaptotagmin 2-CMS
  - Agrin-CMS (±)
  - Laminin α5-CMS
- **No facilitation in many presynaptic CMS**
  - Including ChAT

Nicolau and Milone. Frontiers in Neurology (2019)10:Article 257

Single fiber EMG

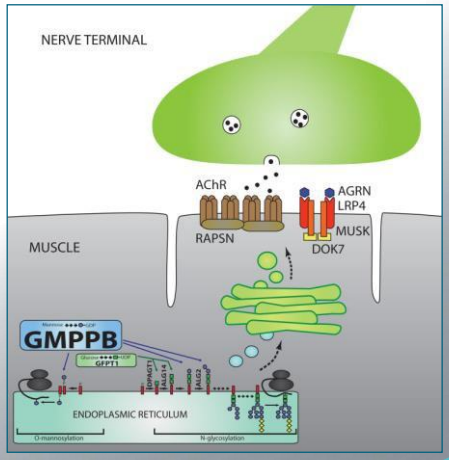
- If no decremental response
- More sensitive than RNS, often abnormal even in strong muscles
- "Jitter": variation in time interval between the firing of two adjacent muscle fibers from the same motor unit
- Well trained examiner





Some CMS cases – neurophysiology

Case 1. Slow channel (AchR)
Case 2. *CHRND* (AchR)
Case 3. Rapsyn
Case 4. Agrin
Case 5. *GMPPB*



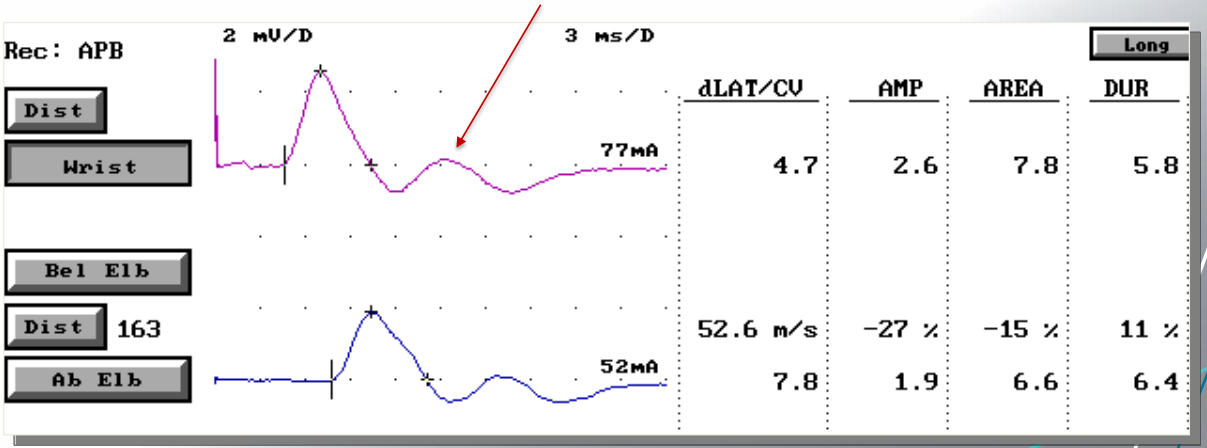
Belaya et al; Brain (2015) 138:2493-2504

Case 1

CMS - slow channel

Female, 19 y

Abnormal CMAP (repetitive discharge)



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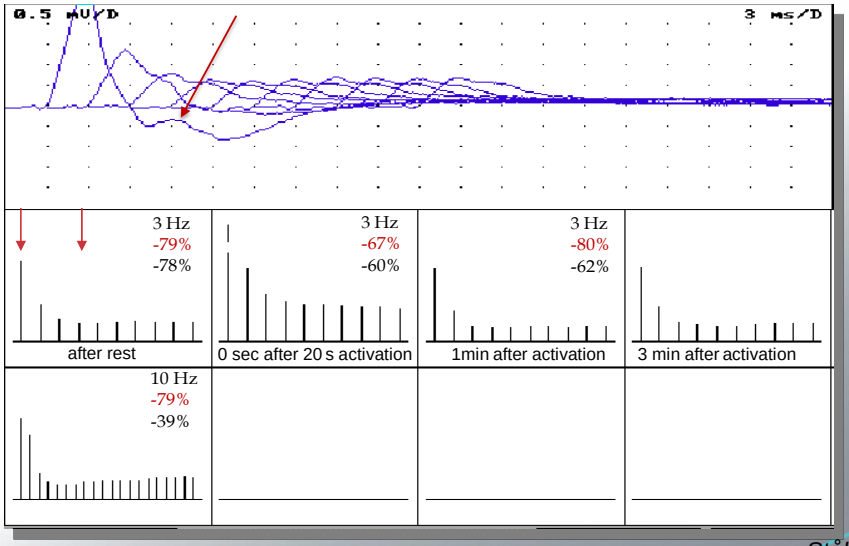
Slow channel - cont´d

RNS 3 Hz and 10 Hz (decrement)



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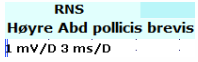
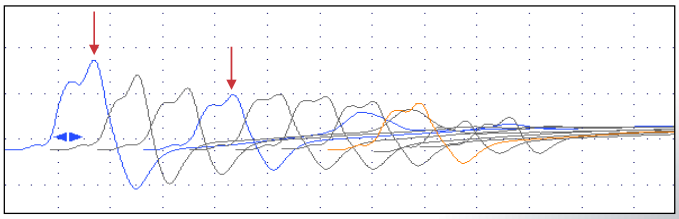
Case 2

Baby 8 weeks old; from birth hypotonic, respiratory problems, episodic dyspnea, ptosis



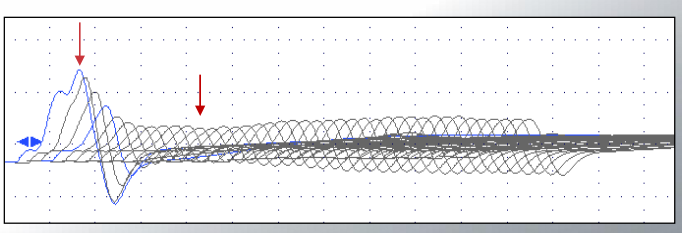
Mutation in the *CHRND* gene
(compound heterozygote)

3 Hz



-40%

20 Hz



-72%

Pyridostigmine some effect

Case 3

5-year old girl with rapsyn deficiency
Normal RNS - anconeus muscle

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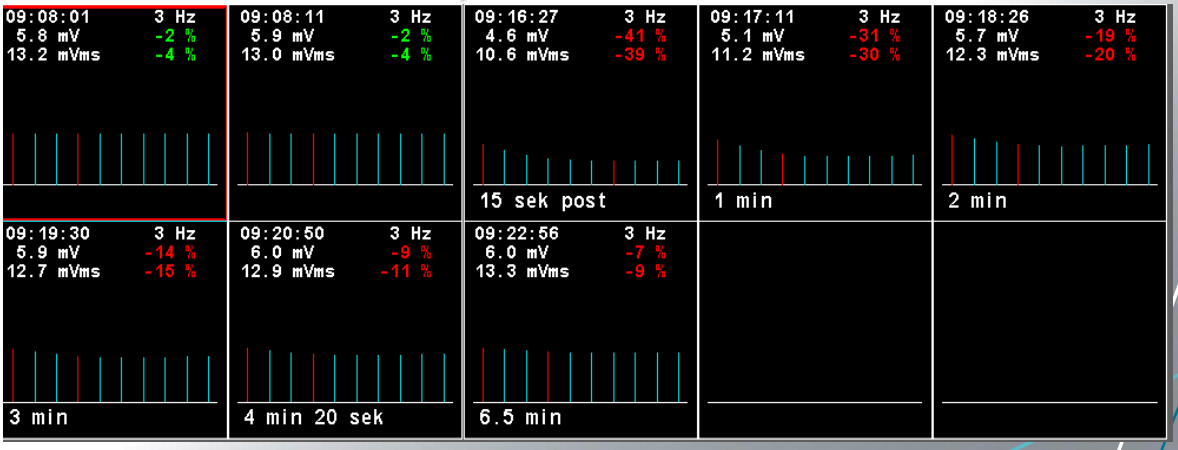
Rapsyn cont'd

RNS APB with 3 Hz stim following prolonged activation (15 Hz 5 min)

Rest: No decrement ↓ **Post 5 min 15 Hz**: Decrement



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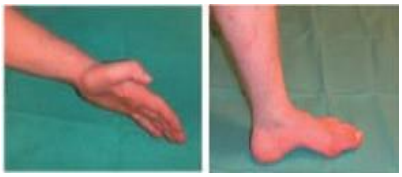
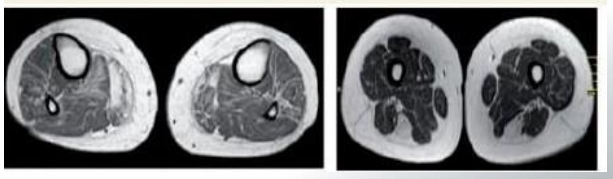
Case 4

Brain 2014: 137; 2429–2443

Agrin mutations lead to a congenital myasthenic syndrome with distal muscle weakness and atrophy

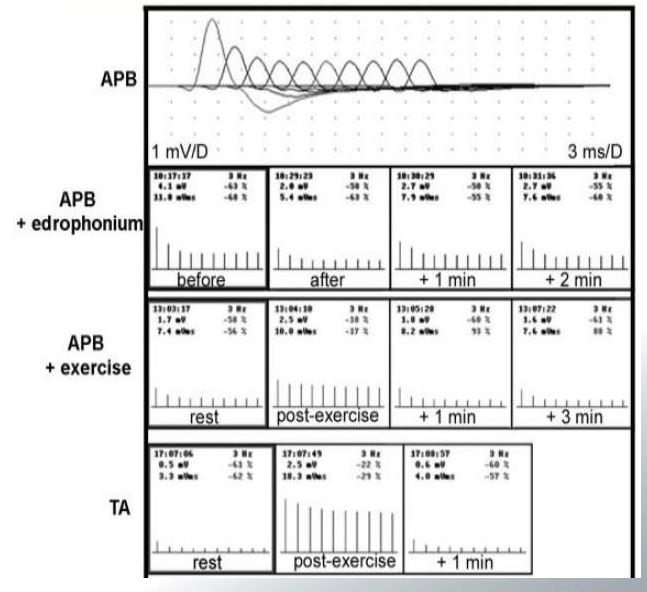
Sophie Nicole,[1,2,3,4,*] Amina Chaouch,[5,*] Torberg Torbergsen,[6,*] Stéphanie Bauché,[1,2,3,4] et al





-Five patients, 3 families
-Siblings (woman 45 y, man 43 y)
-Symptoms from 1.-2 decade
-Distal muscular weakness and atrophy
-Mild proximal weakness
-No ptosis/no facial or axial weakness
-CK normal
-Muscle biopsy: nonspecific myopathic changes

EMG: myopathy + increased jitter



Brain 2014: 137; 2429–2443

Rest APB: decrement (-63%)
(no decrement in ADM)

Edrophonium – no improvement

APB: post exercise facilitation (68%)

TA: post exercise facilitation (500%)

Presynaptic

Agrin cont'd

- In all 5 patients
  - distal muscle weakness and atrophy (uncommon in CMS)
  - RNS: decrement and post-exercise facilitation
- Agrin is a synaptic proteoglycan with critical function at the neuromuscular junction
- Facilitation indicates also a presynaptic effect of agrin

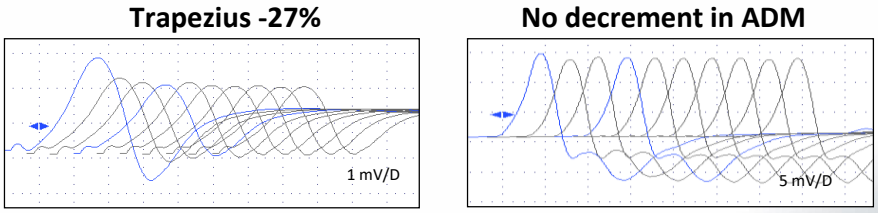
- Distal myopathy – remember agrin!

Case 5

Female in mid- thirties with *GMPPB* mutation

- Healthy family, unrelated parents
- Juvenile RA. No physical activity in school. Could not run, but bicycling was ok
- Over years increasing difficulties in climbing stairs, getting up from a chair and from a supine position. Proximal weakness in arms
- Findings
  - Positive Gowers sign
  - Proximal weakness (2-3), normal strength distally
  - 6 MWT 330 m (normal 658)
  - CK 800 U/L (35-210)
  - EMG: myopathic pattern
- Compound heterozygote for 2 mutations in *GMPPB* gene (known to give rise to both LGMD and a variant of CMS)

3 Hz RNS



- Decrement in trapezius indicates a myasthenic component
- No facilitation
- Treated with Pyridostigmine and after some time added Salbutamol (Ørstavik conferred dr Beeson, UK)
- Effect?
  - Some subjective improvement proximally, especially when rising from a squatting position
  - Difficult to find improvement on 6MWT and TUG-variation
  - RNS in trapezius– unchanged

Myotonic disorders

Myotonia

- Myotonia is due to increased excitability of the muscle membrane caused by dysfunction of muscle ion channels
- When myotonia is present in a EMG investigation, it is often an important clue to the diagnosis

Table 1. Myotonic disorders and their mimics.

Clinical and electrical myotonia*	Electrical (without clinical) myotonia	Myotonia-like symptoms without electrical myotonia
Myotonic dystrophy type 1	Myotubular myopathy	Schwartz-Jampel syndrome
Myotonic dystrophy type 2	Polymyositis	Stiff-person syndrome
Thomsen disease	Malignant hyperpyrexia	Neurogenic muscle cramps
Fluctuating myotonia congenita	Acid maltase deficiency	Hereditary familial episodic ataxia type 1
Myotonia levoir	Hypothyroidism	Brody disease
Becker disease	Severe denervation	
Paramyotonia congenita	Caveolinopathy	
Hyperkalemic periodic paralysis with paramyotonia		
Myotonia fluctuans	*Medications/agents:*	
Myotonia permanens	HMG-CoA reductase inhibitors	
Acetazolamide-responsive myotonia	Colchicine	
Hyperkalemic periodic paralysis with	Clofibrate	
	Propranolol	
	Fenoterol	
	Terbutaline	
	Penicillamine	
	Diazocholesterol	
	Monocarboxylic acids	
	Cyclosporine	
	Anthracene-9-carboxylic acid	
	2,4-dichlororophenoxyacetic	

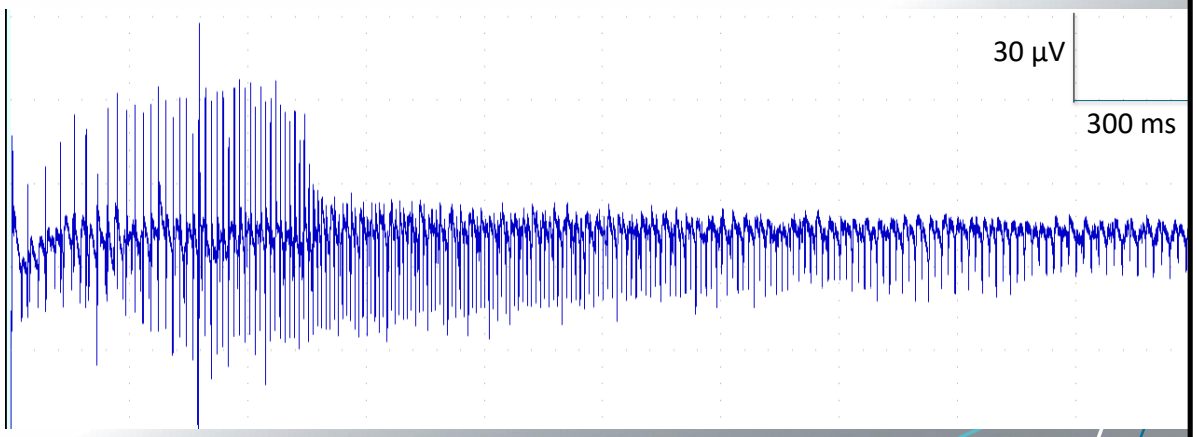
*Clinical myotonia may be absent or difficult to observe in some patients.

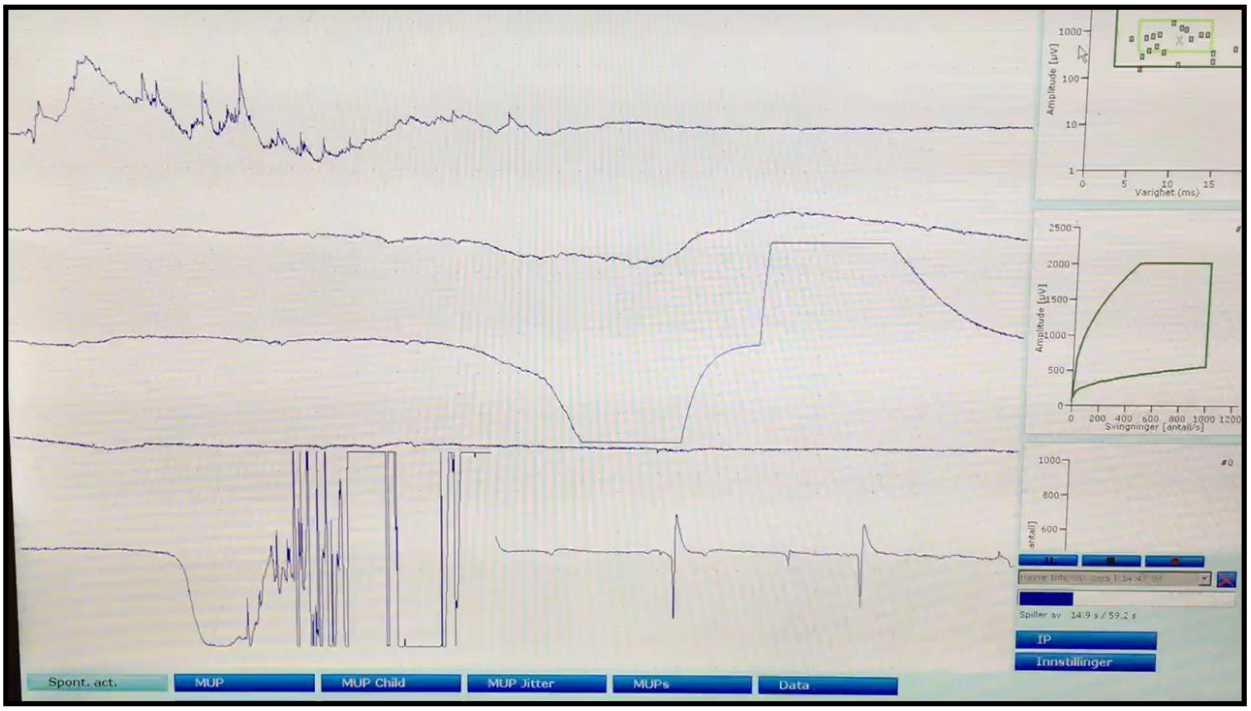
Heatwole et al; Muscle Nerve (2013) 47:632-648

Myotonic discharges on EMG - definition

- Spontaneous repetitive discharges with a waxing – waning of both amplitude (10-1000 µV) and frequency (20-80 Hz), giving a characteristic sound
  - “Dive bomber” or “accelerating and decelerating motorcycle engine”
- Potentials resemble fibrillation potentials and positive sharp waves
- Provoked by needle insertion and movement, muscle contraction or tapping the muscle

Myotonic discharge





Non dystrophic myotonias

- EMG in general
  - Myotonic discharges and normal motor unit potentials
  - Pattern and location of EMG myotonia do not distinguish between the different types
- Myotonia congenita (MC)
  - Myotonia could be substantial
  - Repetitive nerve stimulation (high frequency) may show decremental response due to transient inexcitability of the muscle membrane. Non specific. No effect of cooling
- Paramyotonia congenita (PC)
  - Cooling – EMG myotonia could disappear and motor amplitude decrease > 75%

Short- (and long) exercise test

Evaluates the functional consequences of ion channel mutations.

Pre- and postexercise recordings of serial CMAPs (ADM)

Short exercise test

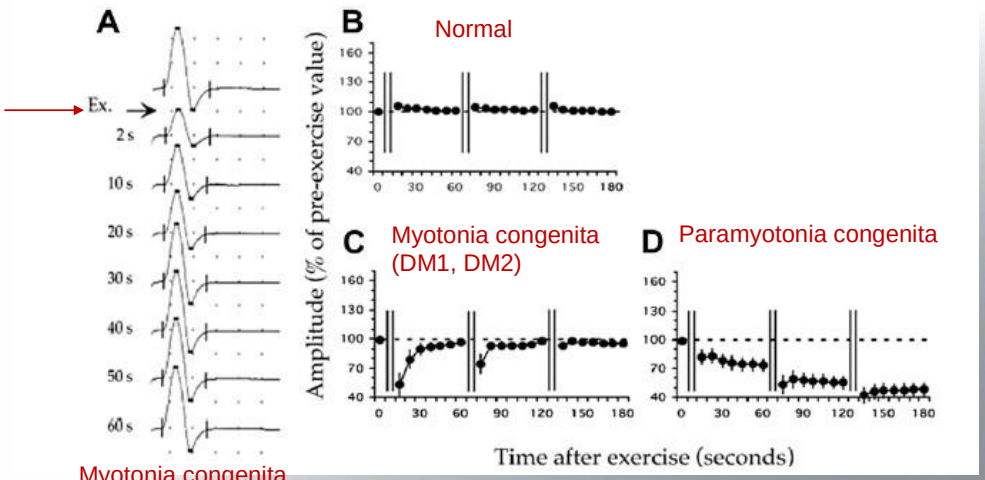
- The patient exercises 10 sec
- Serial CMAPs are recorded (60 sec) and compared with prior to the exercise
- Repeat (with limb cooling) improves sensitivity
- Especially high sensitivity in PC (up to 100%)

Long exercise test

- Sustained exercise in 5 min
- CMAP is tested over a period of 30-45 minutes
- CMAP decreases over time in periodic paralyses (genetic and metabolic)
- Different patterns in PC than in hyper- and hypokalemic PP

Fournier et al; Ann Neurol (2004) 56:650-661
Fournier et al; Ann Neurol (2006) 60:356-365

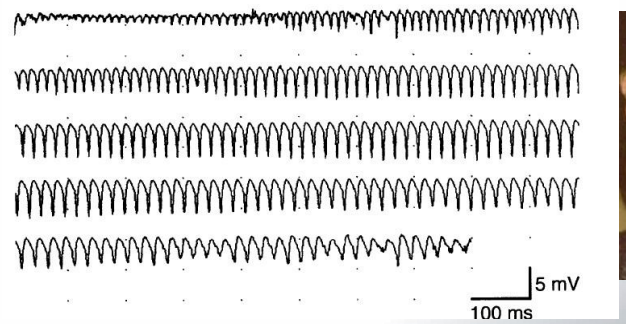
Short exercise test

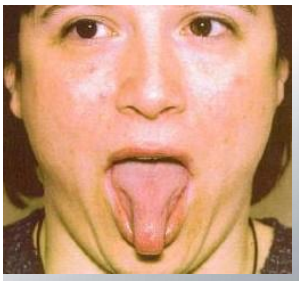


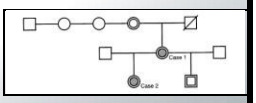
Myotonia congenita

Hehir and Logigan; Phys Med Rehabil Clin N Am (2013) 24:209-213
(modified from Fournier)

«Giant myotonic discharges» in a family with painful nondystrophic myotonia (NAV1.4-G1306A mutation)







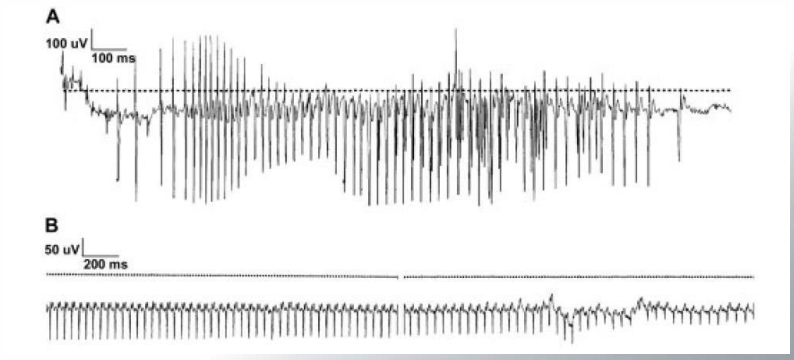
- Myotonic discharges up to 15-16 mV in addition to ordinary myotonia (1 mV)
- Ephaptic transmission between many and closely related muscle fibers
- Not described in other patients with the same sodium channel mutation (myotonia fluctuans)
- More severe phenotype

Torbergsen et al; Clin Neurophys (2003) 114:2347-2354
Torbergsen et al; Muscle Nerve (2015) 52:680-683

Myotonic dystrophies

- EMG:
  - Widespread myotonic discharges is the hallmark (DM1)
  - Pattern and location of myotonic discharges could differ in DM1 and DM2
  - Myopathic motor unit potentials, early recruitment (late if neuropathy), fibrillation potentials and positive sharp waves
- Nerve conduction studies
  - Low motor amplitudes (distal myopathy or/and peripheral neuropathy)
  - Sensorimotor neuropathy (diabetes)

Myotonic discharges in DM1 and DM2



A: DM1: waxing and waining frequency and amplitude
B: DM2: gradually declining of frequency and amplitude

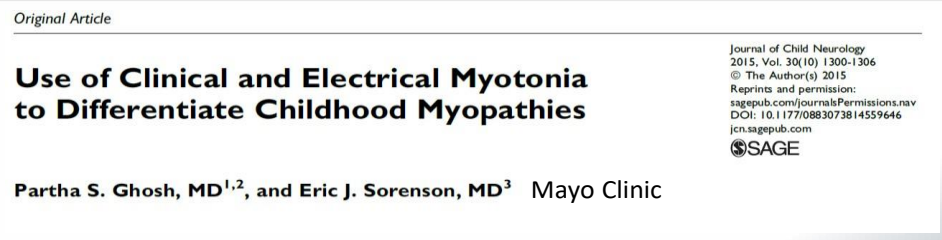
Logogian et al; Muscle Nerve (2007) 35:479-485

DM1	DM2
Long runs of myotonic discharges (< 2 sec – up to 30 sec)	Shorter runs of myotonic discharges, more subtle
Waxing and waning Distal > proximal	Only waning in some (easily misclassified) Distal and proximal No myotonia in 20%
Myopathic EMG: Distal > proximal, face	Myopathic EMG: Distal and proximal, more in proximal leg than DM1
Neurography: neuropathy in some	Neurography: neuropathy in some
No myotonia in congenital DM1	

Congenital myotonic dystrophy

- Myotonic discharges are not present early in congenital DM
- Myotonic discharges are frequently absent before 10 years, then its incidence increases with age
- If congenital DM is suspected – investigate mother

- Myotonic dystrophy type 2 has no congenital form, not encountered in small children



Original Article

Use of Clinical and Electrical Myotonia to Differentiate Childhood Myopathies

Journal of Child Neurology
2015, Vol. 30(10) 1300-1306

DOI: 10.1177/0883073814559646
jcn.sagepub.com
SAGE

Partha S. Ghosh, MD[1,2], and Eric J. Sorenson, MD[3] Mayo Clinic

- Retrospective review of EMG performed in patients < 18 years old
- 2030 patients investigated from 2004 - 2014
- 20 (1%) had myotonic discharges, age 3-17 years
  - 9/20 had clinical myotonia – 8 MC and 1 PC
  - 11/20 no clinical myotonia
    - Electrical myotonia more brief and scattered. EMG myopathic
    - Muscle biopsy confirmed myopathy
      - Congenital myopathy, muscular dystrophy, inflammatory myopathy
      - Genetic testing for DM in 4 patient - negative

Conclusions

- Electrodiagnostic testing plays an important role in distinguishing CMS from other similar NM disorders and may reveal features pointing to a specific molecular diagnosis

- Myotonia on EMG examination is caused by a small group of muscular disorders including nondystrophic and dystrophic myotonias, but may also be seen in a variety of NM disorders without clinical myotonia
- Electrodiagnostic testing can help distinguish among the various myotonic disorders

Thank you for your attention