Neuromuscular Hyperexcitability Disorders

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Learning Objectives

- Recognize the characteristic clinical features of neuromuscular peripheral nerve hyperexcitability disorders (NMH)
- Describe the characteristic neurophysiological/EMG features of these disorders
- Understand the varied pathophysiology of NMH
- Discuss the approach to diagnosis and management
Beware of the terminology

**Synonymous terms**
Isaacs syndrome = acquired neuromyotonia
Continuous muscle fiber activity = periph. nerve hyperexcitability
minipolymyoclonus = fasciculations (is not myoclonus)

**Non-synonymous terms**
Rippling muscle disease ≠ rippling muscle syndrome
Cramp-fasciculation syndrome ≠ Benign fasciculations and cramps

- Many terms are descriptive and not very accurate
- Clinical terms do not necessarily equate with EMG findings
Glossary – clinical vs EMG definitions

- **Myokymia** – “worm-like” writhing movements of muscle. Sometimes experienced as muscle vibration or tremor
- **Myokymic discharge** – Repetitive short bursts of 2-5 units at 0.1 to 2 Hz. Intraburst firing rate of 10-70 Hz

- **Neuromyotonia** – spontaneous movements of muscle with muscle stiffness (i.e. myokymia with stiffness)
- **Neuromyotonic discharge** – Irregular bursts of high frequency firing (100-300 Hz) lasting several seconds each

- **Myotonia** - Impaired relaxation of skeletal muscle following voluntary contraction
- **Myotonic discharge** – Repetitive muscle action potentials with waxing and waning frequency
Localization

- Muscle – myotonia, contracture

- Neural (NMJ, motor terminal, axon, AHC) – fasciculation, myokymia, neuromyotonia

- Nerve or muscle – CRDs, cramps, “ripples”

- Central motor pathways – spasticity, spasm, myoclonus
Complex repetitive discharges

- Regular “machinery” sound
- Begins and end abruptly
- Can result from chronic nerve or muscle pathology
- Ephaptic transmission between muscle fibers ??
Myotonia

- Muscle generator
- Myotoxic drugs: statins, chloroquine, colchicine
- Genetic myopathies
  - Na+ or Cl- channel mutations,
  - myotonic dystrophies
  - acid maltase deficiency
Contractures (silent cramps)

- Electrically silent muscle shortening
- Prolonged contracture $\rightarrow$ myoglobinuria
- Defect in muscle energy metabolism prevents relaxation
- Glycogen metabolism disorders
  - McArdle’s and others
- Brody’s syndrome (Ca++-ATPase mutation)
- Hypothyroidism
Central hyperactivity

- Spasticity, hypertonia, rigidity, dystonia
- EMG shows “poor relaxation”, normal MUP activity with normal recruitment frequency

- Exaggerated startle responses
- Stiff-man syndrome (GAD antibodies)
- Hyperekplexia (jumping Frenchman disease)
  - Glycine receptor mutation
- Tetanus
- Strychnine (glycine antagonist)
Origin of fasciculations & neuronal NMH

Intramuscular nerve & NMJ Kv channels

Muscle

paranodes
Kv channels
Paranode anatomy

Node of Ranvier $Na_v$ channels

paranodes $K_v$ channels

Also, contactin, neurofascin

Horresh et al. J. Neurosci., 2008
Nerve conduction studies in NMH

- Repetitive “afterdischarges” following the CMAP
- Indicates a neural origin (or NMJ)
Nerve conduction studies in NMH

Afterdischarges and Repetitive F waves (Neural origin)
Repetitive stimulation – cramp protocol

Figure. Repetitive nerve stimulation of left posterior tibial nerve at 0.5, 1, 2, and 5 Hz with surface electrodes over abductor hallucis. During baseline recording, there are a few spontaneous potentials. As the frequency of stimulation increases, the number of afterdischarges and the time during which afterdischarges occur increase.

Cramp discharges following repetitive stimulation in cramp-fasciculation syndrome

Tahmoush et al. Neurology 1991
Electromyographic findings in NMH

- An electrophysiological spectrum
- Fasciculations
- Myokymia
- Neuromyotonia
Myokymia

• Greek – “myo” (muscle) “kyma” (wave)
• Schultze, 1894
  – continuous undulating movements in leg muscles
• Clinical Myokymia
  – undulating rippling muscles like “snakes wriggling beneath the skin”
• Myokymic discharges
  – bursts of MUPs (multiplets). 10-70 Hz within a burst
  – bursts occur rhythmically at 0.1 to 3 Hz
Myokymia
Neuromyotonia (Needle EMG)

- MUP firing @ 150-300 Hz
  - abrupt onset & end
  - waning amplitude
  - “race car” sound
  - spontaneous or induced
<table>
<thead>
<tr>
<th>Neuromyotonia</th>
<th>Myokymia</th>
<th>Myotonia</th>
</tr>
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<tbody>
<tr>
<td>Nerve</td>
<td>Nerve</td>
<td>Muscle fiber</td>
</tr>
<tr>
<td>MUPs</td>
<td>MUPs</td>
<td>PSW/spike form</td>
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<tr>
<td>150-300 Hz</td>
<td>50-100 Hz waning</td>
<td>20-150 Hz waxing/waning</td>
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<tr>
<td>Fairly constant</td>
<td>waning</td>
<td>waxing/waning</td>
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<tr>
<td>Race Car</td>
<td>Marching</td>
<td>Dive-bomber</td>
</tr>
<tr>
<td>Longer bursts</td>
<td>Short bursts</td>
<td>Longer bursts</td>
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</tbody>
</table>
Myokymia/NMT
Clinical features and pathophysiology

A motor unit disorder
– Continues during general anesthesia or sleep
– Disappears with NMJ blockade
– Recurrent and spontaneous action potential firing

Mechanisms
– Demyelination (probably results in ion channel reorganization)
– Focal trauma (or nerve ischemia)
– Radiation
– Channelopathies (especially VGKC)
  • Genetic and autoimmune causes
– Toxins (Gold, Mercury, venoms)
**Focal Myokymia**

Focal clinical myokymia – usually fasciculations

<table>
<thead>
<tr>
<th>MS</th>
<th>Pontine tumor/mass</th>
<th>Radiation plexopathy</th>
<th>GBS, CIDP, ALS</th>
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</thead>
</table>

Facial myokymia (? ocular myokymia)

Benign myokymia (especially eyelids)
Precipitating factors include stress, fatigue, and excessive caffeine or alcohol intake. AChE inhibitors
Generalized Myokymia

Inherited VGKC disorders
Episodic ataxia with myokymia (EA1)
Myokymia with neonatal seizures

Venoms
Timber rattlesnake
Green mamba (alpha-dendrotoxin)

Autoimmune myokymia/NMT
Isaacs syndrome and related disorders
Acquired neuromyotonia
- 1948, first described by Denny-Brown
- 1961, Isaacs (2 cases) established peripheral generator
- 1965, Mertens & Zschocke, coined term “neuromyotonia”
- 1993, Newsom-Davis, identified VGKC antibodies

- Clinical fasciculations, myokymia, muscle rippling, muscle hypertrophy, hyperhidrosis, weight loss
- Associates with MG, thymoma, SCLC, encephalitis
- Voltage-gated K+ channel antibodies (50-60%)
- Improvement with plasma exchange
Morvan syndrome

- 1870, Augustin de Morvan - la chorée fibrillaire
- Peripheral nerve hyperexcitability (myokymia, NMT)
- Dysautonomia – especially hyperhidrosis, BP lability
- Encephalopathy – severe Insomnia, fluctuating delirium, hallucinations
- Normal brain MRI
- Thymoma in 50% or more
- VGKCC antibodies (CASPR2)
- Immunotherapy

Ligouri et al. Brain 2001
Josephs et al. J Clin Neurophys 2004
Cramp-fasciculation syndrome

- Muscle aching, cramps, exercise intolerance, fascics
- Frequent severe cramps (unusual muscles, abdomen)
- normal NCS; afterdischarges and cramps after RNS
- EMG: fasciculations
- mild CK (usually < 2x nl)
- muscle biopsy:
  non-specific neuropathic angular fibers, grouping

_Tahmoush et al. Neurology 1991_
_Vernino et al. Neurology 1999_
Other causes of cramps

- Benign cramps and fasciculations (both are common after prolonged exercise)
- Familial cramp syndromes
  - otherwise asymptomatic with mild elevated CK
- Metabolic disorders: dehydration, thyroid changes
- Drugs
- Secondary to other neuromuscular disorders
  - ALS, myopathies, neuropathies (CIDP)

- Both neuropathic cramps and NMH may worsen during REST following exercise
Rippling Muscle Disease

- Inherited, often benign, myopathy
- Usually autosomal dominant with phenotypic variability
- RMD-1 maps to chromosome 1q41
- RMD-2 is mutation in calveolin-3 (*CAV3*, allelic with LGMD 1C)
- AR form is rare and severe with very high CK

- Self-propagating electrically silent rippling
- Normal to mild myopathic units
- Prolonged muscle mounding on percussion (“myoedema”)
- Percussion-induced rapid contraction (PIRC)
- CK elevated
### Rippling Muscle Disease

Kubisch et al, 2003

<table>
<thead>
<tr>
<th>A</th>
<th>Control</th>
<th>Homozygous RMD Pat.1 (L86P)</th>
<th>Homozygous RMD Pat.2 (A92T)</th>
<th>Heterozygous RMD Pat.3 (A45T)</th>
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<tbody>
<tr>
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<td>Dysferlin</td>
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<thead>
<tr>
<th>B</th>
<th>Control</th>
<th>Pat.1</th>
<th>Pat.2</th>
<th>Pat.3</th>
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Rippling Muscle Disease

Differentiate from acquired *Rippling Muscle Syndrome*

- Sporadic forms (etiology unknown)
- Rippling muscle may be seen with abundant fasciculations
- Autoimmune RMS
  - associated with MG
  - may improve with immunosuppression or PLEX/IVIG
  - some cases with thymoma
  - probably two autoimmune forms
  - *electrically silent*, associated striational Ab, (? mechanosensitive Ca\(^{++}\) channels)
  - *electrically active*, brief NMH, associated with VGKCC Ab (? Forme fruste of Isaacs syndrome)
Rippling muscle syndrome

- Rare acquired disorder similar to inherited rippling muscles
- Association with MG and thymoma

- Muscle rippling following stretch or contraction
- Muscle mounding following percussion (myoedema)

Vernino et al, Muscle Nerve 2002
# Autoantibodies in Neuromuscular (antibody-mediated disorders)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Antibody target</th>
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<tbody>
<tr>
<td>Myasthenia Gravis</td>
<td>muscle AChR</td>
</tr>
<tr>
<td>Autoimmune Autonomic Ganglionopathy</td>
<td>ganglionic AChR</td>
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<tr>
<td>Lambert-Eaton syndrome</td>
<td>P/Q calcium channel</td>
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<tr>
<td>Neuromyotonia (NMH)</td>
<td>VGKCC</td>
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Voltage-gated potassium channel COMPLEX
VGKCc antibodies

- Various phenotypes
  - Neuromyotonia – peripheral nerve hyperexcitability
  - Morvan syndrome
  - Limbic encephalitis
  - Seizures

- Antibodies modulate excitability of neurons

- Ab assay measures precipitation of VGKC complex brain membranes complexed to dendrotoxin

- This complex includes Kv1.1, 1.2 and 1.6 channels as well as LGI1, CASPR2, contactin2 and other things

- False positive rate may be as high as 3% in controls
Most VGKCc-antibodies do not bind to potassium channels

- CASPR2 – Neuromyotonia
- LGI1 – Limbic Encephalitis

Specific assays for LGI1 & CASPR2 are now available

The significance of VGKC Ab, when LGI1 and CASPR2 are negative is QUESTIONABLE

*Lancet Neurol 2010; 9: 776–85 (Dalmau)*
*Brain 2010: 133; 2734–2748 (Vincent)*
Treatment of Neuromuscular Hyperexcitability

• Milder cases may be minimally symptomatic (rest, stretching)
• All pharmacological treatment is OFF LABEL
• Symptomatic Treatment
  – Carbamazepine is first line
  – Other AEDs; Phenytoin, Gabapentin
  – Benzodiazepines, muscle relaxants
  – Quinine
• Immunotherapy (for severe autoimmune cases)
  – immunosuppression
  – PLEX/IVIG
• Treatment of co-existing conditions
  – thymoma removal
Know the lingo (clinical vs. EMG terminology)

Localize peripheral vs. central hyperactivity

Nerve vs. muscle generators

Primary vs. secondary causes of NMH

Think about genetic, autoimmune and toxic causes

Treatment is empiric, based on patient symptoms & probable etiology