Neuromuscular Junction Disorders

HMS Child Neurology CME Course
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Objectives

- Update in juvenile myasthenia gravis including international guidance statements and recommendations regarding thymectomy
- Discuss approach to congenital myasthenic syndromes
Pediatric MG

Transient neonatal MG

- Self limited disorder in neonates due to transfer of maternal antibodies across the placenta

Juvenile MG

- Autoimmune MG in children

Congenital myasthenia syndrome (CMS)

- Disorders of impaired neuromuscular transmission due to genetic mutations
Myasthenia gravis is uncommon

- Improved diagnosis and treatment likely contribute to increased prevalence rates
  - Contemporary prevalence rates 20/100,000
  - Estimated to affect > 700,000 worldwide

- Young female and older male adults
- Children:
  - Age <10 F:M 1:1
  - Age >10 F:M 5:1
What causes myasthenia?

- Abnormalities at multiple levels
  - Thymus
  - Peripheral immunoregulatory system
  - NM junction

- Impaired NM transmission at multiple NMJs result in clinical weakness in the affected muscle
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Key Differentiating Features</th>
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<tbody>
<tr>
<td>Congenital Myasthenic Syndrome</td>
<td>Seronegative; onset in infancy or childhood; skeletal abnormalities (scoliosis); family history; no response to immunotherapies</td>
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<tr>
<td>Lambert-Eaton Myasthenic Syndrome</td>
<td>Hyporeflexia; relative sparing of extraocular muscles; proximal LE weakness; autonomic features (dry mouth, impotence, postural hypotension); low amp CMAPs with facilitation; VGCC Ab</td>
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<tr>
<td>Botulism</td>
<td>Pupillary and autonomic involvement; Rapid descending pattern of weakness; low amp CMAPs with facilitation</td>
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<tr>
<td>Motor Neuron Disease</td>
<td>Muscle atrophy/cramps/fasciculations; Corticobulbar features; upper motor neuron signs</td>
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<tr>
<td>Mitochondrial Disorders</td>
<td>Gradual onset without fluctuation; minimal or no diplopia w/ severe ophthalmoplegia; symmetric weakness</td>
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<tr>
<td>Oculopharyngeal Muscular Dystrophy (OPMD)</td>
<td>Gradual onset of ptosis without fluctuation; proximal weakness, dysphagia; family history</td>
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<tr>
<td>AIDP and Variants</td>
<td>Hyporeflexia/Areflexia; acute onset w/o fluctuation</td>
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<td>CN dysfunction due to CNS disorders</td>
<td>Affect consciousness, coordination, sensation; may have sudden onset; ocular weakness in distribution of individual nerves</td>
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<td>Thyroid ophthalmopathy</td>
<td>Proptosis</td>
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Patterns of Weakness in MG

Weakness fluctuates and is fatigable
- Variable (day to day, hour to hour)
- Generally worse at the end of the day

Weakness involves specific muscle groups
- Difficulty with task specific function
  - Pain and/or generalized fatigue in the presence of focal weakness
- Ocular weakness with asymmetric ptosis and binocular diplopia most common initial presentation
- Early or isolated oropharyngeal or limb weakness less common
MG Examination: Ocular Findings

- Normal pupillary function
- Ptosis
  - Generally asymmetric
  - Sustained upgaze may worsen or elicit ptosis
  - +/- ipsilateral frontalis muscle contraction
- Extraocular motility abnormality
  - Cover/uncover testing
  - Red lens testing
  - Asymmetric weakness of multiple extraocular muscles

MG Examination: Facial Weakness

- Orbicularis oculi:
  Weak forced eye closure

- Depressed or expressionless facial expressions

- “Myasthenic snarl” with attempted smiling — “Corners of my mouth don’t express themselves”

- Weak tongue protrusion on tongue to cheek
  - “Triple furrow” in MUSK

MG Examination cont.

- **Orbicularis oris:**
  - Transverse pucker (mild)
  - Air escapes with attempt to hold air in inflated cheeks (moderate)
  - Lips cannot be voluntarily opposed (severe)

- Decreased palate elevation

- Jaw closure weak, jaw opening usually spared

- Axial and limb weakness:
  - Neck flexion > extension
  - Deltoids, triceps, wrist and finger extensors more affected
  - May be asymmetric
MGFA Severity Class

- **0-Remission** (eyelid closure weakness on exam allowed)
- **1-Ocular**
- **2A** – Mild generalized w/predom limb weakness
- **2B** – Mild generalized w/predom bulbar weakness
- **3A** – Moderate generalized w/predom. limb weakness
- **3B** – Moderate generalized w/predom. bulbar weakness
- **4A** – Severe generalized w/predom limb weakness
- **4B** – Severe generalized w/predom bulbar weakness
- **5-crisis**
Diagnosis of MG

“Any diagnosis is easy once you think of it”

- Clinical history and exam suggestive of MG
- Antibody testing (AChR +/- MuSK)
  - If positive and clinical presentation consistent with MG, then sufficient for diagnosis

- Electrodiagnostic Studies
  - Routine EMG/NCS and repetitive nerve stimulation
  - Single fiber EMG
- Edrophonium Testing
- Ice Pack Testing
Electrodiagnostic studies

- Abnormal in 75% of generalized and < 50% of ocular MG (proximal and facial muscles included)
Electrodiagnostic Evaluation of MG

- SFEMG is highly sensitive 95-99% when clinically weak and/or facial muscles examined, not specific

Left sided images from Sfemg.org – Volitional – Frontalis and EDC
Ab Testing/Disease Heterogeneity

- **AChR Binding Ab**
  - Measures binding to purified AChR from human skeletal muscle labeled with radioiodinated alpha-bungarotoxin
  - Present in approx. 80% of generalized and 55% of ocular MG

- **AChR Modulating Ab**
  - Measures crosslinkage/rate of degradation of labeled AChR from cultured human muscle
  - Present in approx. 10% of patients with MG w/o binding Ab

- **AChR Blocking Ab**
  - Limited diagnostic value; present in 1% pts with MG w/o binding Ab

- **Anti-Striational Muscle Ab**
  - Not pathogenic: Clinical value is predicting thymoma in patients <50 yo
  - Found in 90% of pts w/thymoma and MG but also 30% of pts w/ thymoma w/o MG

- **MuSK Ab**
  - Present in 20-40% of patients with generalized MG w/o AChR Ab in the US

- **Anti-LRP4 (Lipoprotein Related Protein 4)**
  - Ab to Clustered AChR
  - Anti-Agrin?

Additional Antibody Studies

- Cell based Ab testing to clustered AChR
  - Serum AChR Ab not found by radioimmunoprecipitation assay (RIA) may be detectable
    - AChR ab with a low binding affinity and those present in the serum at lower concentration
  - Detected Ab in 38% (16/42) of AChR ab and MuSK ab neg patients
    - Particularly children with ocular/mild disease

Chest Imaging in MG

- Chest imaging to establish +/- thymoma
  - CT vs. MRI; Contrast vs without contrast
  - CT chest 10% false neg rate in thymoma

- Thymic hyperplasia is more common in children than in adults with MG
  - 75% in children versus about 60% in adults

- Pediatric thymoma is exceedingly rare:
  - <1% of all mediastinal tumors
  - Approximately 20% of thymoma in pediatric patients have paraneoplastic syndrome – 70% MG

Natural History of Pediatric MG

- **Children:**
  - Prepubertal patients more likely to have ocular disease and post-pubertal more likely to have generalized disease
  - Overall, a lower percentage of patients have generalized disease than in adult patients
  - Spontaneous remission in 15-35% of patients

- **Adults:**
  - ~80% w/ocular MG generalize within 1-3 year

Choosing therapy in MG

**Goal:**
- Tailored therapy to approximate normal clinical neuromuscular function (no symptoms or functional limitations from MG – some weakness on exam ok) while minimizing adverse events
  - Balance risks of therapy with morbidity and mortality related to uncontrolled disease – ongoing discussion
  - Asymptomatic or only mild symptoms from side effects of therapy – intervention not indicated

**Factors to consider:**
- Distribution, duration and severity of weakness
- Functional impairment
- Patient factors and medical comorbidities
Combination Therapy in MG

Normal Neuromuscular Transmission

Symptomatic Therapy

Pyridostigmine

PLEX/IVIG

Prednisone

(Rituximab)/MMF/AZA/Thymectomy (Tacrolimus, Cyclosporine, Methotrexate)

Immunomodulatory Therapy

Minutes to Hours  Days to Weeks  Weeks to Months  Months to Years
International consensus guidance for management of myasthenia gravis

Executive summary

ABSTRACT

Objective: To develop formal consensus-based guidance for the management of myasthenia gravis (MG).

Methods: In October 2013, the Myasthenia Gravis Foundation of America appointed a Task Force to develop treatment guidance for MG, and a panel of 15 international experts was convened. The RAND/UCLA appropriateness methodology was used to develop consensus guidance statements. Definitions were developed for goals of treatment, minimal manifestations, remission, ocular MG, impending crisis, crisis, and refractory MG. An in-person panel meeting then determined 7 treatment topics to be addressed. Initial guidance statements were developed from literature summaries. Three rounds of anonymous e-mail votes were used to attain consensus on guidance statements modified on the basis of panel input.

Results: Guidance statements were developed for symptomatic and immunosuppressive treatments, IV immunoglobulin and plasma exchange, management of impending and manifest myasthenic crisis, thymectomy, juvenile MG, MG associated with antibodies to muscle-specific tyrosine kinase, and MG in pregnancy.

Conclusion: This is an international formal consensus of MG experts intended to be a guide for clinicians caring for patients with MG worldwide. Neurology® 2016;87:1-7
“Children with acquired autoimmune ocular MG are more likely than adults to go into spontaneous remission

- Young children with only ocular symptoms of MG can be treated initially with pyridostigmine
- Immunotherapy can be initiated if goals of therapy are not met”
Juvenile MG Guidance Statements

- “Children are at particular risk of steroid side effects, including growth failure, poor bone mineralization, and susceptibility to infection, due in part to a delay in live vaccinations
  - Long-term treatment with corticosteroids should use the lowest effective dose to minimize side effects
  - Maintenance PLEX or IVIg are alternatives to IS drugs in JMG”
Thymectomy?

- Indicated for patients of all ages with thymoma.
- Benefit for patients with MG but without thymoma as treatment for their MG.
What is the thymus?

- Triangular, bi-lobed immune organ behind the upper portion of the sternum, near the heart
- Largest/most active in neonates and pre-adolescents
- With age, thymus shrinks - replaced by fatty tissue
- “Bootcamp” for the immune system
  - T lymphocytes mature, are selected, learn self-tolerance and then exit into circulation
  - Thymus helps prevent autoimmunity (Central tolerance, immunologic tolerance to self-antigens)
A bit of history...

1911 – 1941:
- Case reports of 6 patients with MG w/thymectomy

1941:
- "Operation was performed with the deliberate purpose of removing all the thymic tissue by complete exploration of the mediastinum"
- 5F and 1M (22-39 yo)
- >50% of patients improved

Landmark NEJM paper

Randomized Trial of Thymectomy in Myasthenia Gravis


Multi-center randomized clinical trial comparing thymectomy plus prednisone with prednisone alone in adults with AChR positive MG
Class I evidence that over 3 years thymectomy improved:

- Clinical outcomes
- Requirements for prednisone and AZA
- Symptoms and distress levels related to immunosuppressive therapy
- Need for hospitalizations to manage disease exacerbation

Consistent w/ recent Guidance Statements

- “Thymectomy is performed as an option to potentially avoid or minimize the dose or duration of immunotherapy”
Thymectomy in Children

- **Historical case series** - 19 reports of a total of 479 patients (included AChR ab neg patients)
  - Heterogenous patient group including AChR ab negative patients - ?
    MuSK or congenital myasthenic syndrome

  - Retrospective review of 20 children (13 months - 15.5 years) with thymectomy between 1996 and 2010 with AChR positive generalized JMG, some with prior immunomodulating therapy
  - 20/20 patients improved in disease severity
  - 1/3 w/complete stable remission at time of last follow-up

- **Perioperative morbidity low**
  - Routine pre-op PLEX or IVIG
  - 4 patients on steroids developed minor infections controlled with Abx
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Guidance Statements cont.

- “The value of thymectomy in the treatment of prepubertal patients with MG is unclear, but thymectomy should be considered in children with generalized AChR antibody–positive MG if the response to pyridostigmine and IS therapy is unsatisfactory or in order to avoid potential complications of IS therapy.”

- “For children diagnosed with seronegative generalized MG, the possibility of a congenital myasthenic syndrome or other neuromuscular condition should be entertained, and evaluation at a center specializing in neuromuscular diseases is of value prior to thymectomy.”
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Combination Therapy in MG

Normal Neuromuscular Transmission

Symptomatic Therapy

Pyridostigmine

PLEX/IVIG

Prednisone

(Rituximab)/MMF/AZA/Thymectomy (Tacrolimus, Cyclosporine, Methotrexate)

Minutes to Hours  Days to Weeks  Weeks to Months  Months to Years
MYASTHENIA GRAVIS IN CHILDREN: ITS FAMILIAL INCIDENCE

HAROLD B. ROTHBART, M.D.

Myasthenia gravis is not infrequently encountered in children, but its familial incidence has never been stressed. My purpose in this report is to present two cases of myasthenia occurring in brothers, in whom the onset was in early infancy, this also being an unusual feature. No attempt is made to review all the cases of myasthenia gravis arising in childhood. It soon becomes apparent to the reviewer that the literature is voluminous and that not a few cases reported in adults had their beginning in early life. There seems to be nothing strikingly different about the disease in children to warrant a detailed discussion of its clinical features.

REPORT OF CASES

CASE 1.—History.—Marvin W., aged 9, Jewish, admitted to the pediatric service Sept. 12, 1934, complained of generalized weakness, inability to move his eyes normally and drooping eyelids, noted since infancy but more marked during the past year.

Weakness of the eye muscles and abnormal drooping of the eyelids were first observed at 6 weeks of age. Although he developed normally, it was noticed that he could not run or skip a rope like other children and that he was unable to climb. His walk has always been awkward. When he arises in the morning his eyes are wide open but within half an hour the eyelids droop and the eyes become more fixed. He soon tires and this generalized weakness becomes more marked with the progress of the day. Rest periods restore his strength to a certain degree. His facial expression has always been masklike. He is unable to laugh or cry out loud. He has no difficulty in chewing or swallowing. "Asthmatic" attacks are described as having occurred during infancy with noisy breathing, particularly during the night. These were relieved by inhalation of steam. These attacks have not recurred within recent years, but occasionally rattling sounds in the throat are heard. The speech has always been nasal. The patient's general condition has been stationary until about one year ago, when weakness became more marked.
Congenital Myasthenic Syndromes

- Inherited disorders of neuromuscular transmission
- 3.8 per million prevalence in some populations (Britain)
  - 20 per 100,000 for autoimmune MG
- Classified by site and molecular mechanism of the underlying defect of neuromuscular transmission
- Pre-synaptic, synaptic and post-synaptic deficits
- > 20 genetic mutations associated with CMS
Figure 1: Neuromuscular endplate with locations of pre-synaptic, synaptic and postsynaptic proteins involved in congenital myasthenic syndromes

Green line represents synaptics basal lamina. Red line represents acetylcholine receptor on crests of the junctional folds. Blue line represents LRP4, MuSK, Dok-7, and rapsyn closely associated with the acetylcholine receptor.

SC = Schwann cell. NT = nerve terminal. MuSK = muscle-specific tyrosine kinase.
1. Post-synaptic Defects – most common
   - Reduced AChR expression
   - AChR kinetic abnormality
2. Synaptic Defect (Basal Lamina)
3. Presynaptic Defects
Clinical Manifestations of CMS in Infancy and Childhood

- Fluctuating fatiguable weakness
  - Worsening triggered by exertion or intercurrent illness
- Hypotonia and generalized weakness
  - Delayed motor development
  - Muscle hypotrophy
  - Reduced movement in utero
- Cranial muscle weakness
  - Ptosis/extraocular weakness
  - Pupillary abnormality in AChE deficiency
  - Facial weakness (mouth “tenting”)
  - Chewing/feeding difficulties
  - High-arched palate

- Respiratory Insufficiency
  - CNS signs can result from episodic hypoxic injury
- Skeletal deformities
  - Facial dysmorphism
  - High arched palate
  - Arthrogryposis multiplex
  - Scoliosis
- Family History
  - Affected siblings in AR disorders (most common)
  - AD in SCCMS
  - Hx of spontaneous abortions or SIDS
- Benefit from AChE Inhibitors
  - Exceptions: AChE deficiency and SCCMS

Differential Diagnosis

**Neonates, Infants and Children**
- Spinal muscular atrophy
- Congenital myopathies
- Congenital muscular dystrophies
- Infantile myotonic dystrophy
- Mitochondrial myopathy
- Brainstem abnormality
- Mobius syndrome
- Infantile botulism
- Seropositive and seronegative forms of autoimmune myasthenia gravis

**Adult Onset**
- Motor neuron disease
- Radial nerve palsy
- Peripheral neuropathy
- Limb girdle or facioscapulohumeral dystrophy
- Mitochondrial myopathy
- Seropositive and seronegative forms of autoimmune myasthenia gravis
- Systemic exertion intolerance disease
Diagnostic Approach

***Testing for AChR and MuSK antibodies (+/- VGCC Ab)

Repetitive CMAPs:
- One or more R-CMAPS with single or repeated stimulation
- May decrement (earlier) with RNS
- Seen in 50-60% of patients with slow channel syndrome and in cholinesterase deficiency

Repetitive Nerve Stimulation:
- +/- Rate dependant decrement in slow channel syndrome and in cholinesterase deficiency

Prolonged recovery:
- Muscle fatigued for 5 min using either exercise or 10 Hz stimulation
- Prolonged recovery (15–20 min) of compound muscle action potential amplitude to baseline in ChAT

29 yo F with cholinesterase deficiency
Diagnostic Approach

- Exclude myopathy, neuropathy or motor neuron disease
  - Myopathic findings of short duration low amplitude MUPs with early recruitment may be seen due to secondary endplate myopathy
  - Spontaneous activity rare
  - Motor unit potential instability

- Single fiber EMG
Any distinct clinical features?

| Distribution of weakness                      | Neck, wrist, digit extensors: SCCMS/AChE deficiency  
|                                               | Fatigable truncal weakness: SCCMS/AChE deficiency  
|                                               | Limb girdle: DOK7 (tongue wasting), AChE deficiency  
|                                               | Minimal or absent ocular findings: SCCMS, Rapsyn, DOK7, EP AChE deficiency  
| Pupillary involvement                         | AChE deficiency  
| Progressive myopathy                         | AChE deficiency  
|                                               | SCCMS  
| Episodic respiratory crises/Apneas            | ChAT deficiency, RAPSYN, ACHE def  
| Autosomal Dominant Pattern of Inheritance     | SCCMS  
| Lack of benefit from AChE inhibitors          | AChE deficiency, SCCMS, Rapsyn, DOK7  
| Reduced or absent DTRs                        | CMS syndromes resembling LEMS or EP AChE deficiency  
| Contractures                                  | Rapsyn  

Any distinct EDX features?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cause</th>
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| Repetitive CMAPs (R-CMAPs)                        | SCCMS (cholinesterase inhibitors increase the size and number of R-CMAPs)  
|                                                   | Cholinesterase deficiency                                            |
| Rate dependant decrement                         | SCCMS (cholinesterase inhibitors increase the size and number of R-CMAPs)  
|                                                   | Cholinesterase deficiency                                            |
| Exercise and prolonged recovery after RNS         | ChAT                                                                 |
| Association with seizures or intellectual disability | DPAGT1                                                              |
Most common types

- Primary AChR deficiency or kinetic abnormality/CHRNE (50%)
- Rapsyn deficiency (15-20%)
- AChE deficiency/COLQ (10-15%)
- DOK-7 (10-15%)
- ChAT (4-5%)

- All tests commercially available
Treatment algorithm. 3, 4-DAP, 3, 4-diaminopyridine; AChR, acetylcholine receptor; ChAT, choline acetyltransferase; DOK7, downstream of kinase-7.

Finlayson S et al. Pract Neurol 2013;13:80-91
Treatment for CMS

- All treatment is off label
- Pyridostigmine
  - Weight dose in peds (high dose is 7mg/kg/day)
- 3,4 DAP
  - Starting dose in children 0.25mg/kg/day
- Ephedrine and Oral salbutamol/albuterol
  - B2 adrenergic agonists
  - Improve NM transmission by stabilizing post-synaptic architecture
- Fluoxetine and quinididine in SCCMS
  - Mechanism of SCCMS is prolonged opening of the central ion channel pore of the AChR
  - Both meds bind the channel in open state and decrease channel opening time
CMS are rare but underdiagnosed

No immune abnormality so patients do not respond to immunotherapy

Although typically presenting in infancy, they can present later in adulthood

May patients carry a longstanding incorrect diagnosis such as undefined (on muscle biopsy) congenital myopathy

Worth pursuing a genetic diagnosis to guide prognosis, genetic counseling and treatment

Certain subtypes (AChE def, SCCMS and DOK-7) may worsen on pyridostigmine – diagnostic clarity is helpful initially
Thank you