Ocular Myasthenia Gravis: Past, Present, and Future

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Ocular Myasthenia Gravis

1. Definition and Natural History
2. Epidemiology
3. Anatomy & Pathophysiology
4. Clinical features & Differential Dx
5. Diagnostic tests
6. Treatment
7. Future Options
Definition

• Weakness and fatigability of cranial, limb, respiratory muscles
  – “generalized”

• Levator palpebrae superioris, EOMs, and orbicularis oculi
  – “ocular”

• 15% purely “ocular”
Natural History

Ocular symptoms in Myasthenia Gravis:

• 50% present *solely* with

• 75-80% have on presentation

• 90% eventually develop
Natural History (Grob et al. ’81)

• ~2/3 will generalize
• Who?
• When?
  – first 7 months
  – OMG @ 1 year: 84% will NOT
  – OMG @ 2 years: 88%
  – OMG @ 3 years: 92%
Historical Perspective

- Thomas Wills 1672
- Samuel Wilks 1877
- Ernst Sauerbruch 1912
- Mary Walker 1934
- C.E. Chang 1962
- 1970s

Thomas Wills
Epidemiology: Incidence

• Incidence MG:
  4-14/100,000
  age and gender related
  • generalized: early peak ♀ late peak ♂
  • ocular: late peak
Generalized Myasthenia  (Grob et al. ‘81)

n=868
Ocular Myasthenia  (Grob et al. ‘81)

n=168
<table>
<thead>
<tr>
<th>Period</th>
<th>Mortality Rate</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1915-34</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>1935-39</td>
<td>40%</td>
<td>1934: anticholinesterase</td>
</tr>
<tr>
<td>1940-57</td>
<td>33%</td>
<td>1939: assisted ventilation</td>
</tr>
<tr>
<td>1958-65</td>
<td>14%</td>
<td>1960: pressure or volume</td>
</tr>
<tr>
<td>1966-85</td>
<td>7%</td>
<td>1966: steroid use</td>
</tr>
</tbody>
</table>
Epidemiology: Associated Conditions

- Thyroid dysfunction
- Rheumatoid Arthritis
- Ankylosing spondylitis
Anatomy & Pathophysiology

• Anatomy
  – Neuromuscular junction

• Pathophysiology
  – Causes
  – Autoimmune
Anatomy

- Central nervous system
- Peripheral nerve
- Neuromuscular junction
- Muscle
- Combination
Neuromuscular Junction

Electrical impulse

Chemical impulse

Electrical impulse
Neuromuscular Junction Disorders

• Myasthenia Gravis
• Lambert Eaton-Myasthenic Syndrome (LEMS)
• Toxic or Metabolic
  – Botulism
  – Hypermagnesemia
  – Drugs (D-Penicillamine)
  – Organophosphate toxicity
  – Snake, spider, scorpion bites
Pathophysiology: Causes

- Autoimmune
- Neonatal
- Congenital
- Drug-induced
Neonatal Myasthenia Gravis

- Passive transfer of IgG
- 10 – 30% mothers with MG
- 0 – 3 d after birth
- Transient: 1-6 weeks
- Weak cry, poor suck, hypotonia
Congenital Myasthenia Gravis

- Genetic defects
- Birth or infancy
- Ocular +/- generalized
- Fluctuate, stable
<table>
<thead>
<tr>
<th>Maternal MG</th>
<th>Neonatal MG</th>
<th>Congenital MG</th>
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<tbody>
<tr>
<td>Onset</td>
<td>0-3 days postnatal</td>
<td>birth - infancy</td>
</tr>
<tr>
<td>Weakness</td>
<td>generalized</td>
<td>ocular +/- generalized</td>
</tr>
<tr>
<td>Time Course</td>
<td>remission 1-6 wks</td>
<td>fixed</td>
</tr>
<tr>
<td>Antibodies</td>
<td>usually (+)</td>
<td>no</td>
</tr>
</tbody>
</table>
Drug-induced Myasthenia Gravis

- D-Penicillamine
Autoimmune Myasthenia Gravis

1. Postsynaptic disorder

2. Decreased acetylcholine receptors
   - Immune-mediated
Clinical Features: OMG

- Ptosis
- Diplopia
- Orbicularis oculi weakness
Ptosis

• Isolation or with ophthalmoplegia
• Fluctuates and shifts
• Usually asymmetric
• Examination:
  – Fatigability
  – “Cogan’s lid twitch”
  – Curtaining
  – Eyelid retraction
Ocular Motility Deficits

• Any pattern
  – pseudo INO
  – pseudo 3rd, 4th, 6th
  – pseudo cavernous sinus syndrome
  – Exam changes

• Medial rectus
Orbicularis Oculi Weakness

• Common

• Most commonly affected muscles:
  1. *levator palpebrae superioris*
  2. *EOMs*
  3. *orbicularis oculi*
  4. proximal limb
  5. facial expression, mastication, speech
  6. neck extensors
Differential Diagnosis

• **Ocular Myasthenia**
  – PEO
  – Oculopharyngeal dystrophy
  – Thyroid eye disease
  – Intracranial mass lesion
  – “Senile” ptosis

• **Bulbar Dysfunction**
  – Motor neuron syndromes
  – Oculopharyngeal dystrophy
  – Polymyositis

• **Generalized Myasthenia**
  – Lambert-Eaton syndrome
  – Botulism
  – Myopathy
Diagnostic Tests

• Anti-Acetylcholine Receptor Antibodies
• Tensilon Test
• Electromyography
• Response to mestinon
• Ice test
Anti-Acetylcholine Receptor Antibodies

- Present in 80-90% of generalized
- Present in 50% of ocular
- No difference in severity, response, or prognosis
Tensilon Test

• OMG: + 75%
• False positive
• Onset in 30s, lasts 1-5 minutes
• Heart disease and elderly
• Atropine available
Electromyography

• Repetitive nerve stimulation
  – 60-90% generalized
  – 20-30% OMG

• Single fiber EMG
  – 90-100% generalized
  – 80-90% OMG
Mestinon Response

- Poor in OMG
- Ptosis
- Motility
Ice Test

- Ice pack on more ptotic lid x 2 minutes

- Ptosis
  - 92% in MG
  - 0 non MG

- Substitute for tensilon

Borenstien et al. ‘75
Ice Test: Case of 75 year old woman

- Negative antiacetylcholine receptor antibodies
- Negative RNS and SFEMG
- Negative Tensilon test x 2
- No response to mestinon
- Ice pack at home when “eye” closed shut
• **Cholinesterase inhibitors** (Mestinon)
• **Immunosuppression:**
  – prednisone
  – cyclosporine
  – azathioprine (Imuran)
• **Thymectomy**
• **Acute therapies**
  – IVIg
  – Plasmapheresis
Cholinesterase Inhibitors (Mestinon)

• Response often incomplete
  – ptosis
  – diplopia

• Onset 30’, half life of 3-4 hours
• SE: diarrhea
• Caution: cardiac conduction defects
Prednisone

- OMG: good response
- Maintain high dose ~ 3 months or stable
- Lowest effective dose
  - once determined → alternate day therapy
  - majority need indefinitely
- Caution: steroid-induced exacerbation
Cyclosporine and Azathioprine

• Occasionally used in OMG

• Toxicity

• Indications:
  – resistant to steroids
  – need to reduce steroid dose
    • >50 mg qod
    • significant SE
Thymectomy

- **Definite indications:**
  1. Generalized: puberty – 60 years
  2. Thymoma (15%)

- OMG w/o thymoma: not rec

- Response: months-years
Acute Therapies: IVIg and Plasmapheresis

- Short term – transient (days to weeks)
- Not indicated in OMG
- Indications in GMG
Alternatives to Medical Treatment

• Ptosis
  – ptosis crutches
  – ptosis surgery: not recommended

• Diplopia
  – patch
  – prisms: too variable
  – strabismus surgery: poor outcome
Drug Precautions

**Antibiotics:** aminoglycosides, neomycin, streptomycin, kanamycin, gentamicin, tobramycin, netilmicin, amikacin,

**Other:** tetracycline, ciprofloxacin, erythromycin

**Anticonvulsants:** dilantin

**Antimalarial:** chloroquine, quinine

**Cardiovascular:** quinidine, procainamide, verapamil, timolol, propanolol

**Ophthalmic:** betaxolol, timolol

**Psychotropic:** lithium, chlorpromazine

**Rheumatologic:** D-penicillamine, chloroquine
Most Common Problems

- Aminoglycosides
- Beta blockers
Studies in OMG

- Thyroid function tests
- CT Chest
- Review patient drug list
- Tuberculin skin test
- Rheumatologic screen
Future Options

• Vaccine

• Early immunosuppression
  – injury to NMJ occurs during years 1-3
    maximum weakness
    generalization
    prednisone treated OMG
  – trial: early IVIg
Future Options

• Vaccine
  – Araga and Blalock ’94
  – Anti-idiotypic antibodies
  – Prevention of experimental autoimmune myasthenia gravis
Future

- Early immunosuppression
  - injury to NMJ: year 1-3
    - maximum weakness
    - generalization
    - prednisone treated OMG
  - trial: early IVIg?