Myasthenia Gravis

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A detailed history often reveals evidence of early, unrecognized myasthenic features:

Intermittent diplopia
Frequent purchases of new glasses to correct blurry vision, difficulty focusing and/or early onset of convergence insufficiency of a need for prism correction
Use of dark glasses to reduce diplopia or hide drooping eyelids
Avoidance of certain foods that become difficult to chew and swallow

Cessation of activities that require prolonged use of muscle activity
Myasthenia Gravis

Clinical Classification

I. Ocular alone

IIa. Mild generalized

IIb. Moderately severe generalized plus usually some bulbar involvement

III. Acute severe over weeks-months with severe bulbar involvement

IV. Late severe with marked bulbar involvement
Ocular Myasthenia Gravis

Because the majority of patients with myasthenia gravis present with ocular manifestations, the ophthalmologist plays an essential role in the diagnosis of this condition and a high index of suspicion facilitates the diagnosis.
Muscle groups involved at onset

Analysis of 295 cases

Ocular alone 34%
Bulbar alone 8%
Extremities alone 15%
Ocular and bulbar 7%
Muscle group analysis continued.

Ocular and extremities 7%
Bulbar and extremities 6%
Ocular, bulbar and extremities 21%

Simpson et al, Acta Neurol. Scand. 1966 suppl. 23 pl
## Extraocular Muscles

Analysis of 295 cases

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral ptosis</td>
<td>37</td>
</tr>
<tr>
<td>Bilateral ptosis</td>
<td>36</td>
</tr>
<tr>
<td>Unilateral EOM paresis</td>
<td>8</td>
</tr>
<tr>
<td>Bilateral EOM paresis</td>
<td>32</td>
</tr>
</tbody>
</table>
Extraocular muscles continued

Bilateral ptosis and EOM paresis  57
Unilateral ptosis and EOM paresis  16
Unilateral ptosis and bilateral paresis  13

Simpson et al, Acta Neurol. Scand. 1966 suppl. 23 pl
Eyelids

The findings on examination of the lids may simulate:

Congenital ptosis
Senile ptosis
Horner’s syndrome
Levator dehiscence
Superior division 3\textsuperscript{rd} nerve palsy
Nuclear 3\textsuperscript{rd} nerve palsy
Mitochondrial myopathy
Ptosis

Unilateral (partial or complete), alternating with or without paradoxical lid retraction, or see-saw ptosis

Bilateral and asymmetric, variable in severity

Lid twitch – Cogan sign

Variable levator function
Ptosis continued.

Weakness of the orbicularis oculi

Increased ptosis with repetitive eye closure

Recovery of ptosis with gentle eye closure
To Document Ptosis

Measure the palpebral fissure before testing EOM, giving Tensilon, or using sympathomimetic drugs

Increase of *ptosis on fatigue*

Myasthenic lid twitch

Recovery of ptosis following gentle eye closure
To document ptosis continued.

Range of levator function

± Weakness orbicularis oculi

Photograph and compare with family snapshots

Measure response to IV Tensilon
<table>
<thead>
<tr>
<th>Myopathy</th>
<th>Myasthenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric</td>
<td>Asymmetric</td>
</tr>
<tr>
<td>No</td>
<td>Ptosis on fatigue</td>
</tr>
<tr>
<td>No</td>
<td>Lid twitch</td>
</tr>
<tr>
<td>No</td>
<td>Recovery w/ eye closure</td>
</tr>
<tr>
<td>Constant</td>
<td>Range lev. function</td>
</tr>
<tr>
<td>Yes</td>
<td>Weak orb. oculi</td>
</tr>
<tr>
<td>Negative</td>
<td>Tensilon test</td>
</tr>
<tr>
<td>50%</td>
<td>Family history</td>
</tr>
<tr>
<td>Slowly Progressive Course</td>
<td></td>
</tr>
</tbody>
</table>
Saccades
Examination may show:

Intrasaccadic fatigue (slow in midflight)
Decrescendo from saccade to saccade
Hypermetria of small saccades
Hypometria of large saccades
Quiver movements and “hyperfast” saccades
Fatigability of quick phases on OKN
Myasthenia Gravis

Myasthenia gravis is a disease of skeletal muscle acetylcholine receptors. The chemical transmitter, acetylcholine (ACh) is unable to bind to the receptors (AChR) on the postsynaptic membrane to transmit the nerve impulse to muscle fibers to produce a muscle contraction.
Presentation (I)

MG occurs at any age, involves either sex and begins insidiously.

Second and third decades commonest age of onset in women. Seventh and eighth decades in men.

Patients complain of specific muscle weakness, not generalized fatigue.
Presentation (II)

Ptosis or diplopia – initial symptoms in 65% of patients

Oropharyngeal muscle weakness – difficulty in swallowing and talking
initial symptoms in 17% of patients

Limb weakness presenting symptom in only 10% of cases
Presentation (III)

Characteristically, severity of weakness fluctuates during the day, least in the morning, worsening as the day progresses, especially after prolonged use of affected muscles.

In the era before corticosteroid treatment, approximately one-third of patients improved spontaneously, one third became worse and one third died.
Presentation (IV)

Ocular myasthenia – if progressing to generalized MG usually does so within the first two years after onset

After 15 to 20 years, weakness becomes fixed. The Burnt-Out-Stage + muscle atrophy
Edrophonium Chloride Tensilon Test (10 Mg in 1 cc)

Precautionary Steps:

List all medications being taken
History of drug allergy and previous reaction to Tensilon
Perform the test in the ER with an ambu bag, atropine and adrenalin available in elderly patients and those with cardiac disease
Administration Procedure

The ideal dose of Tensilon cannot be predetermined
Give a 0.1 cc test dose and monitor pulse, blood pressure and clinical state
Follow with 0.3 cc aliquotes examining for a response in ptosis, EOM or Lancaster strabismus screen test after each one
Once improvement is seen -- STOP
The defect in neuromuscular transmission in Myasthenia Gravis is due to:

The muscle end-plate membrane is distorted

Acetylcholine receptors are lost from the tips of the folds, and antibodies attach to the postsynaptic membrane

Ach is released normally but absence of receptors prevents the transmitter binding to the muscle membrane
Acetylcholine Receptor Antibodies

75% of cases generalized MG have serum antibodies (Ab) that bind to huma AChR
54% with ocular MG have antibodies 10%
MG cases with no binding antibodies have other antibodies
The AChR Ab tit varies widely among patients with similar degrees of weakness.
The amount of Ab in the serum does not predict the severity of the disease in individual patients
Antibodies continued.

The Ab level may be low at onset on MG and gradually become elevated in late stage.

Worthwhile to repeat test when initial values normal.
The Presence of AChR Antibody is not diagnostic for MG, also present in:

- Systemic lupus erythematosus
- Inflammatory neuropathy
- Amyotrophic lateral sclerosis
- Rheumatoid arthritis in patients taking D-penicillamine
- In cases of thymoma without MG
Association of MG with other diseases

- Hyperthyroidism: 6%
- Rheumatoid arthritis, less than: 2%
- Systemic lupus erythematosus: 2%
- Diabetes mellitus: 7%
- Non thymus neoplasm: 3%
Differential Diagnosis

Graves ophthalmopathy
Progressive External Ophthalmoplegia (PEO)
Oculopharyngeal Dystrophy
Myotonic Dystrophy
The Lambert-Eaton Myasthenic Syndrome (LEMS)
Guillain Barre Syndrome – Miller Fisher variant
Factors that Aggravate MG

Emotional stress
Systemic illness e.g. viral URI
Thyroid disease, hyper or hypo
Pregnancy
Menstrual Cycle
Increase in body temperature
Drugs
Treatment decisions are based on the predicted response to a specific form of therapy.

Treatment goals must be individualized according to the severity of the disease, the patient’s age and sex, and the degree of functional impairment.
The response to any form of treatment is difficult to access because the severity of symptoms fluctuates. Spontaneous improvement, even remissions, occur without specific therapy, especially during the early stages of the disease.
CHE Inhibitors (I)

Mestinon (Pyridostigmine bromide) first choice, dose 30-60 mg q 6-8 h/daily

Prostigmine (Neostigmine bromide) 7.5 – 15.0 mg q 6-8 h/daily

No fixed dosage schedule suits all patients
CHE Inhibitors (II)

The need for ChE inhibitors varies from day to day and during the same day. Different muscles respond differently with any dose, certain muscles get stronger, others do not change and still others become weaker. The drug schedule should be titrated according to the patient's work load and muscle activity.
ChE Inhibitors (III)

Many patients assume responsibility for their own drug dose

The goal is to keep the dose low enough to provide definite improvement 30 to 40 minutes later and allow the effect to wear off before the next dose

Advise patients re: adverse effects of ChE inhibitors
Prednisone

Marked improvement or complete relief of symptoms occurs in 75% of cases. Improvement in first 6 to 8 weeks, but strength may increase to total remission over months. Best responses in patients with recent onset MG, but chronic disease may also respond.
Prednisone continued.

The severity of the disease does not predict the ultimate improvement.

Patients with thymoma have an excellent response to prednisone before or after thymectomy.
Dose

Prednisone 60 to 80 mg/day given until sustained improvement (usually 2 weeks) then alternate days beginning with 100-120 mg tapered over months to lowest dose necessary (usually less than 20 mg alternate days)
<table>
<thead>
<tr>
<th>Table 83.7: Plasma exchange in myasthenia gravis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>Produces rapid improvement in most patients</td>
</tr>
<tr>
<td>No known chronic side effects</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>Expensive</td>
</tr>
<tr>
<td>Requires concomitant immunosuppression, corticosteroids, or thymectomy for long-lasting benefit</td>
</tr>
<tr>
<td><strong>Major role</strong></td>
</tr>
<tr>
<td>Adjunctive therapy, most useful in</td>
</tr>
<tr>
<td>Producing rapid improvement before thymectomy or other surgery or in myasthenic crisis</td>
</tr>
<tr>
<td>Initiating improvement that may be maintained by other forms of immunotherapy</td>
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<tr>
<td>Patients who have failed to respond to other forms of treatment</td>
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</tbody>
</table>
Table 83.4: Corticosteroids in myasthenia gravis

<table>
<thead>
<tr>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produce rapid improvement in most patients</td>
</tr>
<tr>
<td>Produce total remission or marked improvement in 90% of patients (high-dose, daily corticosteroids)</td>
</tr>
<tr>
<td>Predictable time of response</td>
</tr>
<tr>
<td>Relatively simple drug schedule</td>
</tr>
<tr>
<td>Reduce the morbidity and mortality of subsequent thymectomy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid side effects</td>
</tr>
<tr>
<td>Exacerbation of weakness soon after initiation</td>
</tr>
<tr>
<td>Require chronic administration for maximum benefit</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major role</th>
</tr>
</thead>
<tbody>
<tr>
<td>As an initial definitive therapy</td>
</tr>
<tr>
<td>For producing rapid, virtually complete improvement in the majority of patients</td>
</tr>
<tr>
<td>For permitting subsequent thymectomy to be performed with greater safety</td>
</tr>
<tr>
<td>As secondary treatment in most patients who fail to respond to thymectomy or other immunosuppressive therapy</td>
</tr>
</tbody>
</table>
Table 83.5: Immunosuppressant drugs in myasthenia gravis

<table>
<thead>
<tr>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produce marked, sustained improvement in most patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long delay before improvement</td>
</tr>
<tr>
<td>Serious side effects</td>
</tr>
<tr>
<td>Expense</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major role</th>
</tr>
</thead>
<tbody>
<tr>
<td>As initial definitive therapy in patients with late-onset myasthenia gravis or in whom corticosteroids are contraindicated</td>
</tr>
<tr>
<td>As secondary treatment in patients who fail to respond to corticosteroids or thymectomy</td>
</tr>
<tr>
<td>In combination with prednisone to enhance the response or permit more rapid reduction of prednisone dose</td>
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</tbody>
</table>
http://www.library.med.utah.edu/NOVEL