HARVARD MEDICAL SCHOOL
DEPARTMENT OF NEUROLOGY
MASSACHUSETTS GENERAL HOSPITAL

Myasthenia Gravis

Shirley H. Wray, M.D., Ph.D.
Professor of Neurology, Harvard Medical School
Director, Unit for Neurovisual Disorders
Massachusetts General Hospital

History

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 insufficnecy of a need for prism correction
- Use of dark glasses to reduce diplopia or hide drooping eyelids

History continued.

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

	Number
Unilateral ptosis	37
Bilateral ptosis	36
Unilateral EOM paresis	8
Bilateral EOM paresis	32

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 3rd nerve palsy
- Nuclear 3rd 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

Ptosis

Myopathy		**Myasthenia**
Symmetric	Appearance	Asymmetric
No	Ptosis on fatigue	Yes
No	Lid twitch	Yes
No	Recovery w/ eye closure	Yes
Constant	Range lev. function	Varies
Yes	Weak orb. oculi	Yes
Negative	Tensilon test	Positive
50%	Family history	Rare
Slowly Progressive	Course	Fluctuates

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)
- Guillian 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

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

Treatment continued.

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 schedle suits all aptients

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 pateints 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 theeffect 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 83.7: Plasma exchange in myasthenia gravis

- Advantages
  - Produces rapid improvement in most patients
  - No known chronic side effects
- Disadvantages
  - Expensive
  - Requires concomitant immunosuppression, corticosteroids, or thymectomy for long-lasting benefit
- Major role
  - Adjunctive therapy, most useful in
    - Producing rapid improvement before thymectomy or other surgery or in myasthenic crisis
    - Initiating improvement that may be maintained by other forms of immunotherapy
    - Patients who have failed to respond to other forms of treatment

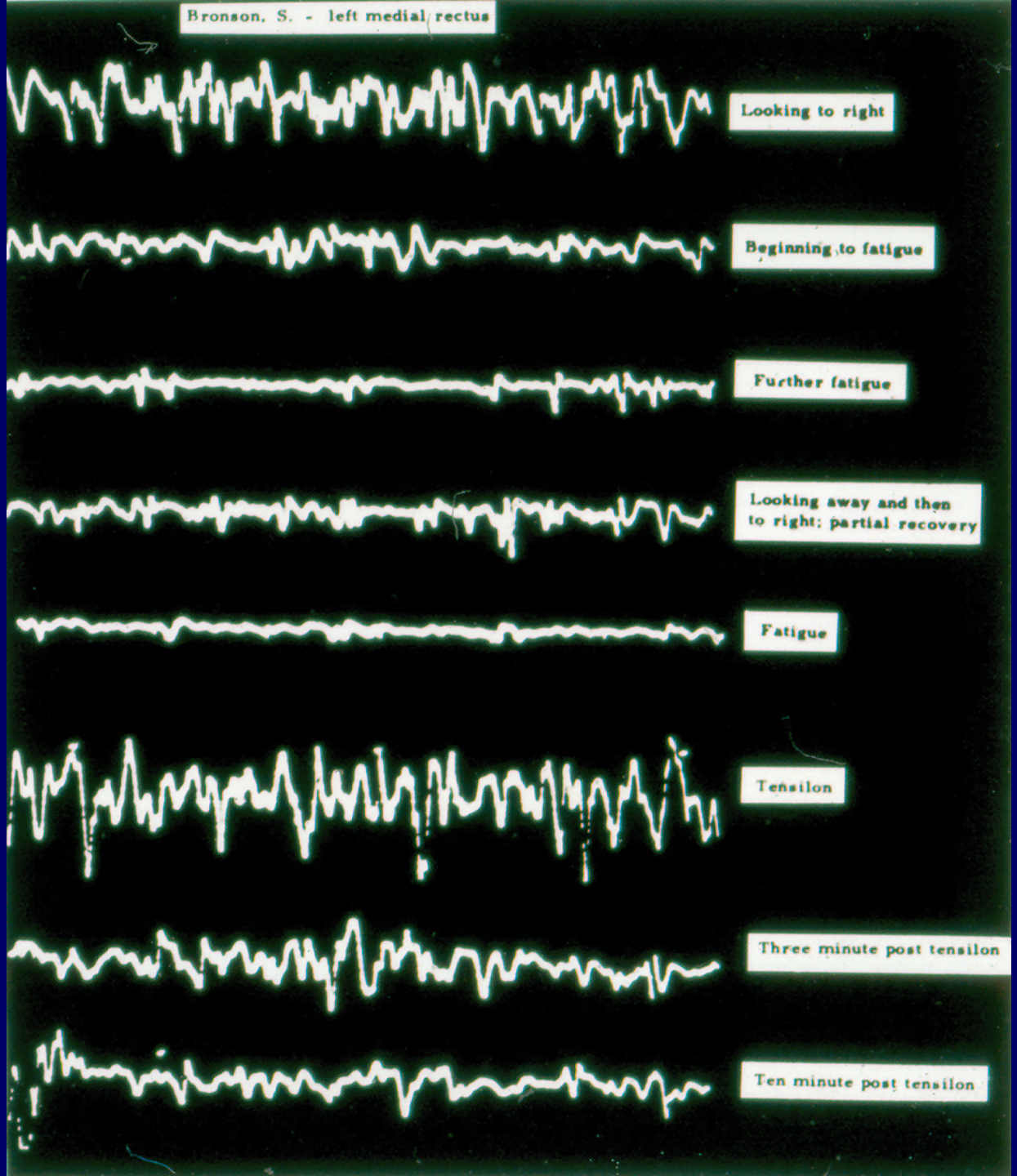
Bronson, S. - left medial rectus
Looking to right
Beginning to fatigue
Further fatigue
Looking away and then to right; partial recovery
Fatigue
Tensilon
Three minute post tensilon
Ten minute post tensilon

Table 83.4: Corticosteroids in myasthenia gravis

Advantages
Produce rapid improvement in most patients
Produce total remission or marked improvement in 90% of patients (high-dose, daily corticosteroids)
Predictable time of response
Relatively simple drug schedule
Reduce the morbidity and mortality of subsequent thymectomy
Disadvantages
Corticosteroid side effects
Exacerbation of weakness soon after initiation
Require chronic administration for maximum benefit
Major role
As an initial definitive therapy
For producing rapid, virtually complete improvement in the majority of patients
For permitting subsequent thymectomy to be performed with greater safety
As secondary treatment in most patients who fail to respond to thymectomy or other immunosuppressive therapy

Table 83.5: Immunosuppressant drugs in myasthenia gravis

Advantages
Produce marked, sustained improvement in most patients
Disadvantages
Long delay before improvemen
Serious side effects
Expense
Major role
As initial definitive therapy in patients with late-onset myasthenia gravis or in whom corticosteroids are contraindicated
As secondary treatment in patients who fail to respond to corticosteroids or thymectomy
In combination with prednisone to enhance the response or permit more rapid reduction of prednisone dose

http://www.library.med.utah.edu/NOVEL