MG 101: The Basics

MG 101: Curriculum

1. History of Myasthenia Gravis (MG)
2. What goes wrong?
   - Problems with the immune system
   - Normal muscle function
   - Muscle function in MG
3. How is MG diagnosed?
4. How is MG treated?
5. Living with MG.
6. The Future
1. History of MG

- *Myasthenia* (Greek – muscle illness)
- *Gravis* (Latin – “grave or serious”)
- First description in the 17th century
  - Sir Thomas Willis
    - “a woman who spoke freely and readily enough for a while, but after a long period of speech was not able to speak a word for one or two hours”

‘On the palsy’, persons who (translated) in the morning are able to walk firmly, to fling about their Arms hither and thither, or to take up any heavy thing, before noon the stock of Spirits being spent, which had flowed into the Muscles, they are scarce able to move Hand or Foot.
“Treatment of myasthenia gravis with physostigmine”

“Mrs. M.”

First thymectomy, 1939

- Alfred Blalock
- 21 year old woman with thymic tumor and MG
  - Able to stop prostigmin
  - No recurrence of symptoms over 3 year follow-up
  - “We wish to emphasize again the absence of conclusive proof that the improvement noted in our patient is due to removal of the tumor.”

Ann Surg 1939;110:544
“Guessing it Right”

- John A. Simpson, April 28, 1960
- "Myasthenia gravis: a new hypothesis"
  
  "...the ‘competitive-blocking’ substance must have the unusual property of persistence in the myasthenic baby for several weeks... Where, then, are we to look for a blocking substance which must be of competitive type, transmissible through the placenta, with persistence in the child for a few weeks only, but not transmissible to another adult? If one looks at the mechanism of attachment of acetylcholine to receptor protein one is immediately reminded of the Ehrlich theory of antibody action. Let us suppose that antibody was developed against the "receptor substance" of the end-plate protein. Would not this substance have exactly the properties described?"


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2. What goes wrong?

1. Normal Nerve-muscle triggering (neuromuscular junction)
2. The neuromuscular junction in MG
3. Immune system abnormality
The Neuromuscular Junction (1)

The Neuromuscular Junction (2)
Why does MG cause muscle weakness?

MG Damages the Muscle Endplate

A. Myasthenia Gravis

B. Destruction of neuromuscular connection (Myasthenia Gravis)
The Immune System and MG

- The Immune System’s Job:
  The body’s homeland defense.
  Must correctly recognize potential threats and distinguish “good” from “bad”
- The Neuromuscular Junction: Target of the immune system in MG

MG is an autoimmune disease
The Problem

Normal Immune system:
Protects against foreign invaders

Autoimmune Disease:
occurs when the immune system loses tolerance to self tissues

Fig. 1. The castle of health — an early twentieth century view of the healthy body protected behind castle walls. From J. W. Ritchie, Primer of Histology and Physiology (1918-Re).

Why do people get autoimmune disease?

Nature Immunology (9): 759-761 (2001)
Why do people get MG?

- Probably same reasons as previous slide
- We don’t really know
- Thymus gland

What is happening in the immune system in people with MG?

- APC
- T
- T
- B
- Plasma cell
- Anti-AChR Abs
- Nerve Terminal
- Postsynaptic membrane
- AChR
- MuSK
- Rapsyn
- AChase
- ACh
- Voltage-gated Na⁺ channel
- Voltage-gated Ca²⁺ channel
The Thymus Gland and the Origin of MG

The thymus gland is abnormal in many MG patients
- Thymectomy makes MG better (we think)
- Muscle-like cells express AChR
- BUT - What triggers immune attack?
  - Abnormal AChR?
  - Viral infection
3. How is MG diagnosed?

- Clinical features
- Tensilon test
- Antibody tests
- Electrical tests

Clinical features of MG

- Muscle weakness - fluctuating
- Fatigue with muscle use
- Double vision, droopy eyelids, trouble swallowing/chewing
- Facial weakness
- Shortness of breath
- No pain, numbness
MG weakness

MG: Initial presentation and progression

- Initial symptoms
  - Eye muscle weakness: 75%
  - Head/neck weakness: 15%
  - Limb weakness: 10%

- Within first year
  - ~75% develop head/neck +/- limb weakness
  - ~67% reach maximum MG severity
  - ~20% experience severe exacerbation/MG crisis
**Tensilon Test**

- Before
- After

**AChR antibody test**

- Positive in 85% of MG patients
- Antibody level does NOT correlate with disease severity between patients
- In an individual patient, changes in antibody levels do correlate
“Antibody negative” MG

- 40-50% of patients with ocular MG
- MuSK antibodies in 40% of AChR negative, generalized MG
- “Low-affinity” antibodies in “double negatives” ??

Electrical tests

- Repetitive nerve stimulation (RNS)
- Single fiber EMG
4. How is MG treated?

- Non-immune treatments
  - Mestinon, etc.
  - “Band-aid”

- Immune-directed treatments
  - Short-term
    - Plasmapheresis, IVIg
  - Long-term
    - Corticosteroids
    - Immunosuppressive drugs
    - Thymectomy?

Thymectomy?

- Does it Work?
- In which patients?
  - Thymoma
  - How old/young?
- Ongoing international trial
Treatment must be individualized

- Based on:
  - Age of onset
  - Status of thymus (CT scan)
    - Thymoma
    - Thymic hyperplasia
  - Antibody status
  - Severity/distribution of disease
  - Other medical problems

5. Living with MG

- Prognosis
  - Most patients do well with treatment
  - Little/no functional limitations
  - Your MG will likely not go away or be “cured”
  - You will probably need some drugs to control your MG (all have potential side effects)
Factors affecting MG

- Exercise
- Body Temperature
- Illness, infections, stress
- Menstrual cycle
- Less when MG controlled

What can you do?

- Avoid overexertion
- Avoid catching infections
- Avoid certain drugs
- Eat a well-balanced diet and get plenty of rest, and some exercise
What about exercise?

- Guided by your own strength / endurance
- Stop if you are fatigued, continue as you are if you are feeling good
- The bottom line is that exercise is good within sensible guidelines
- During “stable times,” you can follow as active a regime as anyone else
- During a exacerbation ease off, and titrate your level of exercise the point at which you feel most comfortable.

Everyone’s different

- Auburn's starting Quarterback from 2005-2007, he guided the Tigers to a 29-9 record
- 117.58 passer rating
Questions

- Is MG inherited?
- Is MG contagious?
- Why did I get MG?
- Will my MG go away?
- Will I be able to continue working?

Questions

- Can vaccination trigger or worsen MG?
- Are there vaccines that MG patients should not have?
- What is MG crisis?
Outlook is improving in MG!

6. The future

- Current
  - Best-characterized autoimmune disease
  - Treatment is effective in most (but non-specific)

- The future
  - What triggers MG?
  - What keeps it going?
  - What are the genetic factors?
  - Design a more specific treatment – CURE?
How is research in MG carried out?

- Experimental MG
- Patient-related research

Experimental MG

- Rabbits, rats, mice, etc.
- Immunize with AChR from electric organs of electric eels or fish.
- Weakness, Antibody responses
Experimental MG

Torpedo California

AChR

Baseline

MG – Clinical Trials

- **PHASE I TRIALS:** Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects, early evidence of effectiveness; may include healthy participants and/or patients.
- **PHASE II TRIALS:** Controlled clinical studies conducted to evaluate the effectiveness and safety of the drug in patients.
- **PHASE III TRIALS:** Expanded controlled trials provide and adequate basis for FDA labeling.
What would be the ideal treatment for MG?

- Treatment applied for a short time
- Long-lived result
- Target effects to autoreactive cells (Antigen-specific)
- No side-effects

The ideal immunotherapy
Obstacles

- Treatment of autoimmune disease occurs months or even years after the onset of the disease process
- Autoimmune response becomes more complex as disease progresses
- Benefit achieved by interfering with the immune system’s defense mechanisms

MG upsets the balance in the immune system
How do we restore the balance?

“The art of medicine consists in amusing the patient while nature cures the disease”

Voltaire (1694 - 1778)

How do we restore the balance?

- Expand regulatory immune cells
  - Use agents (drugs) that promote their mobilization and growth
  - ?Grow them in culture
    - Make them AChR-specific
    - ? Stem cells
Summary

- MG is caused by an abnormal immune response targeting the muscle (AChR, MuSK)
- Most people with MG do well with the right treatment (treatment must be individualized).
- You can live a normal life with MG.
- We know a lot about the immune system defect in MG, but there are key questions that remain unanswered.

Thank You