Myasthenia: Is Medical Therapy in the Grave?

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Disclosures
Outline

History of Thymus

Anatomy of Thymus

Pathophysiology of Myasthenia Gravis

Medical Management of Myasthenia Gravis

Surgical Management of Myasthenia Gravis
History
Myasthenia

1672 - described by Thomas Willis

1895 - Term coined by Friedrich Jolly (Greek)

Prior beliefs of etiology

  CNS disease

  Metastatic disease from malignant thymus

  Primary disease of striated muscle
James Ewing

“No group of tumors has more successfully resisted attempts at interpretation and classification than those of the thymus.”
History

1892 - Hoppe reports association of MG with thymoma

1901 - Weigert reports thymic tumor with myasthenia gravis

1913 - Sauerbruch performs thymectomy in patient with MG

1936 - Blalock performs thymectomy, no tumor and long-term improvement
Myasthenia without Thymoma

“I am of the opinion that pathologic changes may be found in the thymus in cases of myasthenia gravis in direct ratio to the care with which they are sought.” - E.H. Norris
Mary Broadfoot Walker

1934 - Successfully treated weakness from MG with physostigmine
Anatomy
Thymus

Pyramid Shaped Bi-lobed gland with horns extending into the neck

Located in the Anterior Mediastinum

Posterior to sternum and anterior to pericardium

Descends from 3rd/4th pharyngeal pouches

Can extend from both pleural reflections, from hyoid to diaphragm, and as deep as the carina

Arterial supply from inferior thyroid artery

Venous drainage to innominate vein
Pathophysiology
Thymoma

Most common anterior mediastinal tumor (⅕ in adults)

⅓ - ½ of patients with thymomas have MG

10% of patients with MG have thymomas

70% of patients with MG have lymphoid follicular hyperplasia
Thymoma

Masaoka Staging

I - macroscopic, completely encapsulated; microscopic, no capsular invasion

IIA - macroscopic invasion in surrounding fatty tissues or mediastinal pleura

IIB - Microscopic invasion into the capsule

III - Macroscopic invasion into neighboring organ

IVA - Pleural pericardial dissemination

IVB - Hematogenous or lymphogenous metastases
Myasthenia Gravis

Autoimmune neuromuscular disease

Most common neuromuscular junction disorder

Incidence - 5.3 per million person years

Prevalence - 0.5 - 20.4 per 100,000

Females - 3rd decade, more common

Males - 5th decade, 2nd peak incidence, greater association with thymoma
Myasthenia Gravis

Anti-acetylcholine receptor antibody to nicotinic post-synaptic receptor

Detectable in 90% with generalized MG and 50% with ocular myasthenia

Increases AChR degradation, blocks binding sites, complement mediated damage of the post-synaptic membrane

Muscle specific Tyrosine Kinase implicated in some non-thymic disease

Anti-MuSK inhibits clustering of AChR on the post-synaptic membrane

Low density lipoprotein receptor related protein 4
Myasthenia Gravis

Symptoms: diplopia, ptosis, fatigue, dysphagia, limb weakness

Initial presentation: 50% ocular, 30% generalized, 10% bulbar, 10% limb

1 in 5 will develop crises, usually within the first two years

Diagnosis: Tensilon Test (edrophonium)

Prognosis

Death: historical mortality 33%

Remission: 30% ocular and 10% generalized within 10 years of onset

10-20% spontaneous
# Myasthenia Gravis Foundation of America

<table>
<thead>
<tr>
<th>Class</th>
<th>Features</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>any ocular muscle weakness; may have weakness of eye closure; all other muscles are normal</td>
</tr>
<tr>
<td>II</td>
<td>mild weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity</td>
</tr>
<tr>
<td>III</td>
<td>moderate weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity</td>
</tr>
<tr>
<td>IV</td>
<td>severe weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity</td>
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<tr>
<td>V</td>
<td>intubation with or without mechanical ventilation (exception: intubation for routine perioperative management)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>predominantly affects the limb muscles, axial muscles or both; may have lesser involvement of the oropharyngeal or respiratory muscles</td>
</tr>
<tr>
<td>B</td>
<td>predominantly affects the oropharyngeal muscles, respiratory muscles or both; may have lesser or equal involvement of the limb or axial muscles</td>
</tr>
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</table>
Medical Management
Medical Management

Anticholinesterases (pyridostigmine): first line therapy

Prolongs ACh availability at the NMJ

Steroids (prednisone): added for chronic treatment

Plasma exchange, IVIG: used for crisis
Medical Management - second line

Azathioprine: most frequently used immunosuppressant, reduce steroid dose

Ciclosporin: efficacious with and without steroids

Cyclophosphamide: for MG unresponsive to steroids

Mycophenolate Mofetil: for MG unresponsive to steroids

Rituximab: chimeric monoclonal antibody, anecdotal
## Medical Therapies

<table>
<thead>
<tr>
<th>Good Evidence</th>
<th>Weak Evidence</th>
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<tbody>
<tr>
<td>Anticholinesterases</td>
<td>Mycophenolate Mofetil</td>
</tr>
<tr>
<td>Steroids</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Plasma Exchange</td>
</tr>
<tr>
<td></td>
<td>Intravenous Immunoglobulin</td>
</tr>
<tr>
<td></td>
<td>Hematopoietic Stem Cell Transplantation</td>
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</tbody>
</table>
Surgical Management
Surgical Technique

Remove all B-cell reservoir secreting antibodies

Approach

Trans-sternal, extended trans-sternal

Most-commonly employed

Minimally Invasive: Videoscopic, Trans-Cervical, Robotic

Questionable extent of resection

Equivocal remission rates, shorter LOS

M&M
Surgical Outcomes

Time to surgery longer in non-thymomatous MG

Most studies have shown increased remission rates vs MM

  13-46% in symptomatic patients

  70% pharmacologic reduction

Young women have higher remission rates than older men

Results in patients with thymoma are less consistent than those with thymic hyperplasia
Traditional Indications

Not used for ocular myasthenia

  Unless failure of medical therapy

Indicated for those with thymoma

  50% increased survival at 5 years

More commonly for those less than 60 years old with generalized MG

For non-thymomatous MG

  Variable clinical practice

No definitive study for thymectomy
Based on these findings, we conclude that the benefit of thymectomy in nonthymomatous autoimmune MG has not been established conclusively. For patients with nonthymomatous autoimmune MG, thymectomy is recommended as an option to increase the probability of remission or improvement (Class II).
Figure 1. Study flow diagram.

Records identified through database searching using first strategy (upto November 2011):
- MEDLINE 360
- EMBASE 453
- LILACS 12
- CENTRAL 22
- Cochrane Neuromuscular Disease Group Specialized Register 10

Records identified through database searching using second strategy (date of search May 2013):
- MEDLINE 59
- EMBASE 6
- LILACS 22
- CENTRAL 1
- Cochrane Neuromuscular Disease Group Specialized Register 3

No additional records identified through other sources

948 records
182 duplicates removed

766 records screened using title and abstract

31 full-text articles assessed for eligibility
31 full-text articles excluded, with reasons

0 studies included in qualitative or quantitative synthesis
Randomized Trial of Thymectomy in Myasthenia Gravis

Randomized Trial of Thymectomy in Myasthenia Gravis

Multi-center (36)

Randomized Trial

Single-blind (rater-blinded)

Comparing thymectomy plus prednisone with prednisone alone

Between 2006 - 2012

Follow-up at 3 years

Funded by the National Institute of Neurological Disorders and Stroke
Randomized Trial of Thymectomy in Myasthenia Gravis

Inclusion criteria:

Myasthenia gravis without thymoma for less than 5 years

Age 18-65 years old

Taking no immunosuppressants, except prednisone

MGFA Stage II to IV

Positive AChR antibodies

Primary Outcomes

Quantitative Myasthenia Gravis Score
Randomized Trial of Thymectomy in Myasthenia Gravis

Randomized 126 patients

Group A: extended trans-sternal thymectomy with alternate day prednisone

Group B: alternate day prednisone
Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prednisone Alone (N = 60)</th>
<th>Thymectomy plus Prednisone (N = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex — no. (%)</td>
<td>39 (65)</td>
<td>50 (76)</td>
</tr>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Range</td>
<td>18–64</td>
<td>18–63</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4 (7)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (10)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17 (28)</td>
<td>17 (26)</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>30 (50)</td>
<td>31 (47)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (5)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Therapy at enrollment — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>56 (93)</td>
<td>60 (91)</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>47 (78)</td>
<td>49 (74)</td>
</tr>
<tr>
<td>Previous therapy — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous immune globulin</td>
<td>13 (22)</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>7 (12)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>MGFA class — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>25 (42)</td>
<td>25 (38)</td>
</tr>
<tr>
<td>IIB</td>
<td>14 (23)</td>
<td>18 (27)</td>
</tr>
<tr>
<td>III</td>
<td>20 (33)</td>
<td>21 (32)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Duration of disease — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.14</td>
<td>1.08</td>
</tr>
<tr>
<td>Range</td>
<td>0.13–4.38</td>
<td>0.02–4.41</td>
</tr>
<tr>
<td>QMG score\textsuperscript{f}</td>
<td>12.35±4.90</td>
<td>11.40±5.12</td>
</tr>
<tr>
<td>Prednisone use at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>47 (78)</td>
<td>49 (74)</td>
</tr>
<tr>
<td>Dose — mg</td>
<td>42.49±23.52</td>
<td>43.43±28.92</td>
</tr>
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\textsuperscript{a}Quantitative Myasthenia Gravis scores range from 0 to 39, with higher scores on each of 13 items indicating more severe disease; a reduction of 2.3 points correlates with improved clinical status. I bars indicate standard errors.

Figure 1. Quantitative Myasthenia Gravis Score and Prednisone Dose, According to Treatment Group.
Randomized Trial of Thymectomy in Myasthenia Gravis

Primary Outcomes

Thymectomy group had lower Quantitative Myasthenia Gravis Score (p<0.001)

QMG: diplopia, facial muscle weakness, strength of arm/leg muscles

Increased score is increased disease severity

Thymectomy group had lower average prednisone requirement (p<0.001)
Randomized Trial of Thymectomy in Myasthenia Gravis

Surgery group had less need for azathioprine (17% vs 48%, p<0.001)

Surgery group had less need for hospitalization (9% vs 37%, p<0.001)

No difference in treatment related complications, but Surgery group had fewer treatment related symptoms and fewer distress related to disease symptoms.
Concluded that thymectomy improved clinical outcomes over a 3 year period in patients with nonthymomomatous myasthenia gravis
Questions
References

Greenfield’s Surgery, Chapter 80 Mediastinum, SCORE, 2016

Blalock, Myasthenia Gravis and Tumors of the Thymic Region, Annals of Thoracic Surgery 1939

Mayor, Thymectomy improves outcomes in myasthenia gravis, trial shows, BMJ 2016

Cea, Thymectomy for non-thymomatous myasthenia gravis, Cochrane Database 2013

Wolfe, Randomized trial of thymectomy in myasthenia gravis, 2016

De Roxas, Clinical Profile and Outcome of Postthymectomy versus Non-Thymectomy Myasthenia Gravis Patients in the Philippine General Hospital: A 6-Year Retrospective Study, 2016

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Gronseth, Practice Parameter: Thymectomy for Autoimmune Myasthenia Gravis (An Evidence-Based Review), 2000.

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Conclusions

Myasthenia Gravis is a rare auto-immune neuromuscular disease

Surgical therapy is recommended for thymomatous MG

Surgical therapy is likely to be recommended with increasing frequency for non-thymomatous MG

Longer term follow up is needed
Thank You
Have a Spooktacular Day