TREATMENT OPTIONS IN MYASTHENIA GRAVIS

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OUTLINE

• Anatomy/physiology
• Pathophysiology
• Electrophysiology
• RNS
• SFEMG
• Presentation
• Treatment
  • Acetylcholinesterase inhibition
  • Immune modulation
  • Immune suppression
  • Corticosteroids
  • Long-term
  • Thymectomy
• Future
• Other neuromuscular junction disorders

ANATOMY/PHYSIOLOGY

ACTIVITY – NORMAL NMJ

1. Depolarization
2. Activation of voltage gated Ca channels
3. Calcium influx
4. Acetylcholine release
5. ACh binds receptors
6. Ion channels open
7. Local depolarization=EPP
8. EPP is proportional to amount of ACh
9. depolarization above threshold -> all-or-none MAF
10. safety factor

PATHOPHYSIOLOGY

PROTOTYPICAL AUTOIMMUNE DISORDER

• Antibodies to nicotinic acetylcholine receptor (AChR) cause the disease
• Specific T cells permit and modulate the synthesis of high affinity antibodies that cause AChR loss, NMJ damage, failed NMJ transmission
• Reduced number of receptors at the motor endplates of patients
• Disease can be transferred to mice if inject IgG of MG patient
• Active animal immunization w/ purified AChR caused experimental autoimmune myasthenia gravis
• Procedures to reduce AChR antibodies improve symptoms
• Thymus
THYMUS AND MG

- T cells reactive to AChR found in blood and thymus
- Thymus contains 1) muscle cells w/ AChR ag, 2)(apc, 3) T cells
- Thymic lymphocytes can produce antibody
- Abnormal thymus in MG
  - 10-15% tumor
  - 70% have hyperplastic changes
  - Thymectomy causes decrease in reactive T cells

TESTING THE NEUROMUSCULAR JUNCTION

REPETITIVE NERVE STIMULATION

RNS-DECREMENTAL RESPONSE

- Baseline:
  - 32% decrease compound muscle action potential (CMAP) amplitude
- Post exercise facilitation:
  - 8% decrease
- Post exercise exhaustion:
  - 44% decrease
  - 56% decrease 2 minutes post
  - 69% decrease 3 minutes post

SINGLE FIBER EMG BASICS

- Study 2 adjacent single muscle fibers, “pair”, from same motor unit
- All muscle fibers within one motor unit fire at approximately same time, following motor axon depolarization
- Variation in time interval b/t firing of adjacent single muscle fibers from same motor unit = jitter
SFEMG

- Sensitive
- Not specific
  - ALS, polymyositis with abnormal jitter
  - Neuromuscular or myopathic conditions with abnormal fiber density

SFEMG SENSITIVITY

<table>
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<tr>
<th>Authors</th>
<th>N</th>
<th>[EDC] abnormal</th>
<th>EDC + additional</th>
<th>Published</th>
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<td>Sanders &amp; Stalberg</td>
<td>788</td>
<td>85%</td>
<td>98%</td>
<td>1996</td>
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<tr>
<td>Oh et al</td>
<td>120</td>
<td>92%</td>
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<td>Gilchrist &amp; Sanders</td>
<td>10</td>
<td>90% (ADG)</td>
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<td>Sanders &amp; Howard</td>
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<td>85% (any one muscle – usually EDC)</td>
<td>99% (any 2 mm – usually forehead)</td>
<td>1986</td>
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SENSITIVITY

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<tr>
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<th>SFEMG Any muscle</th>
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<th>RNS Any muscle</th>
<th>AChR antibody any time</th>
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<td>MG type</td>
<td>Gen</td>
<td>Ocul</td>
<td>Gen</td>
<td>Ocul</td>
</tr>
<tr>
<td>% abn</td>
<td>99</td>
<td>97</td>
<td>89</td>
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BRIEF PRESENTATION

- **EYE** - >90%
  - Diplopia
  - Ptosis
- **LIMB** 10-25% of onset
  - Proximal weakness (initially present w/)
  - **BULBAR** 17-23% at onset
  - Dysarthria
  - Dysphagia
  - Facial
  - **RESPIRATORY**
  - **FATIGUABLE**
EVALUATION-GENERAL

• Endurance testing
• Exertional activities
• Ice pack—may block AChE activity

Laboratory
• AcetylCholine receptor antibodies
• MuSK antibodies
• Voltage-gated calcium channel Ab
• “Tensilon” test—edrophonium

ANTIBODIES

• Binding
  • High specificity
  • 80-90% of generalized MG (15% seroconversion 12 mos)
  • Seen in ALS, PM, LEMS
• Blocking
  • Fewer than 1% of pts have these w/o binding ab
• Modulating
  • Increase AChR degradation by cross-linking receptors
    • 8/508 (Chan et al 2007) [1.6%]
• Striational
  • Lack specificity
  • Seen in 10-15% of LEMs
  • 90% of thymoma patients

ANTIBODIES — ACETYLCHOLINE RECEPTOR

MUSCLE SPECIFIC KINASE ANTIBODIES (MUSK)

• Receptor tyrosine kinase that causes auto- phosphorylation followed by phosphorylation of rapsyn and AChR
• Up to 40-70% of “seronegative” MG
• Cranial and bulbar muscles more involved or mainly neck, shoulder
• Involvement of limb muscles less severe, inconsistent
• High frequency of respiratory crises

TENSILON (EDROPHONIUM CHLORIDE) TEST

• Before

• After 8 mg

TREATMENT
## TREATMENT TIERS

- Acetylcholinesterase inhibitor – pyridostigmine – eg (60 Q4-6h)
- Immune modulation
  - Plasma exchange
  - IVIg
- Immune suppression
  - Prednisone
  - Other
  - Thymectomy

## COST

- Prednisone 20mg #90 - $10.70
- Azathioprine 50mg #90 - $21.55
- Neoral, Cyclosporine 100mg #60 - $159.60
- Cellcept, Mycophenolate 500mg #120 - $351.75 (brand), $117.80 (generic)

- 2006: Prednisone 20mg #90 - $9.10
- Azathioprine 50mg #90 - $22.45
- Neoral, Cyclosporine 100mg #60 - $369.10
- Cellcept, Mycophenolate 500mg #120 - $686.10

## HIGHER END PRODUCTS

- IVIG, Rebagamma 30g/600mL - $6,896.34
- Plasma exchange
- Rituximab

## IMMUNE SUPPRESSION

- Prednisone
  - 1 – 1 ½ mg/kg/day or QOD until improvement/ambulation
- Long-term immune suppression
  - Azathioprine (2-3 mg/kg/d)
  - Methotrexate (up to 15 mg/wk)
  - Cyclosporine (dose per trough level <200)
  - Cyclophosphamide (0.7-1 mg/m2)
  - Mycophenolate mofetil (2-3 g/d)
  - Tacrolimus
  - Rituximab

## MONITORING

- Clinical response
- Adverse effects
  - CBC
  - LFT – azathioprine and MTX
  - Renal function – CyA, cytoxan
  - Mg – cyclosporine (CyA)
  - Trough levels – cyclosporine
  - Antibody level

## PLASMA EXCHANGE

- Removes antibodies
- Response within days
- Lasts only several weeks
- 4-6 exchanges, removing 3-5 L of plasma each treatment
- Hypotension
- MI in patients at risk
- plasma exchange shown as a treatment (Newcom, Davis et al., 1978), confirmed myasthenia is antibody-mediated
IVIG

- May neutralize autoantibodies,
- Attenuate complement-mediated tissue damage,
- Block Fc receptors on macrophages,
- Modulate cytokines,
- 60-70% response rate
- 2 g/kg over days
- Headache, myalgias
- Renal failure, MI, stroke reported
- Possible longer ventilation/prolonged respiratory recovery

IVIG VS PLEX

- Previous trials underpowered
- 84 patients randomized
- Close to 70% patients improved at 2 weeks
- Higher AChR antibody and worse at presentation predicted better outcome
- Treatments comparable in moderate to severe MG

CORTICOSTEROIDS

- Suppress humoral, cell-mediated and nonspecific arms of the immune system
- High dose initially then reduce to QOD
- Improvement over 10-30 days or more
- Estimated 90% response rate
- May precipitate weakness
- Multiple side effects
- Calcium +/- vitamin D

EPITOME

- Prednisone vs. pyridostigmine in ocular MG
- Modest dose prednisone
- Over 4 months
- Double blind
- Prednisone may reduce risk of progressing to generalized
- Record review*
  - 87 patients, 55 were in the prednisone-treated and 32 were in the untreated groups
  - GMG developed in 13% of the prednisone-treated and 50% of the untreated patients


AZATHIOPRINE

- Blocks cell proliferation; inhibition of T lymphocytes
  presumed mechanism for benefit
- Goal 2-3 mg/kg
- Up to 20% cannot tolerate
- Hepatic toxicity
- Leukopenia
- Weekly to monthly CBC, LFTs

CYCLOSPORINE

- Inhibits T lymphocyte-dependent immune responses by suppressing IL2 activity
- Response w/in 1-2 months
- Cost
- Renal toxicity
- Hypertension
- 5-6 mg/kg/day divided BID
- Goal level ~100-150 ng/L trough
- Monitor Mg, Cr
- Multiple drug interactions
CYCLOPHOSPHAMIDE

- Nitrogen mustard alkylating agent, blocks B and T cell proliferation
- Myelosuppression
- Hemorrhagic cystitis
- Increased risk of malignancy
- For resistant MG

MYCOPHENOLATE MOFETIL

- Suppresses T and B cell proliferation via selective block of purine synthesis
- Target 2000-3000 mg/day, divided BID
- Mean time to improvement 10 weeks
- Side effects GI
- Myelosuppression potential
- 2 recent trials – negative results (Siddique 2012)
  - 68% attained remission/minimal manifestation at mean 16 mos
  - Of remaining 32%, greater than half showed 50% improvement
  - Mean time onset definite improvement 6 months
  - A few pts worsened after treatment cessation

THYMECTOMY

Jaretzki

PAST DATA

- Comparison of unrelated statistical techniques
  - Life table analysis, using the Kaplan-Meier method, is considered the preferred statistic technique for the analysis of remission following thymectomy.
  - If provided comparative analysis using all follow-up information accumulated to the date of assessment, including information on patients substantially lost to follow-up and on those who have not yet reached the date of assessment or have not had any evidence of remission.

- Uncorrected crude rates have been primary form of analysis in the comparative evaluation of remissions and improvement following thymectomy. An uncorrected crude rate consists of the number of remissions divided by the number of patients operated upon or sometimes divided only by the number of patients followed. This form of analysis does not include in the evaluation all the follow-up information accumulated to the date of assessment, including the length of follow-up. As a result, patients evaluated many years after surgery may incorrectly appear to do as well or better than those followed for shorter periods as a result of their treatment.

- Retrospective studies are usually non-randomized.

FUTURE THERAPIES

FIGURE 2. COMPARATIVE KAPLAN-MEIER REMISSION RATES OF SIX THYMECTOMY TECHNIQUES. Kaplan-Meier Life Table Analysis Remission Rates of Six Thymectomy Techniques Employed in the Treatment of Nonthymomatous MG Are Compared
**ECULIZUMAB**

- Complement activation at NMJ associated with AChR loss and NMJ transmission failure
- Humanized monoclonal Ab blocks formation of terminal complement complex by selectively preventing enzymatic cleavage of C5
- Randomized, double-blind, placebo-controlled, crossover, phase II trial
  - 6/7 pts improved by 3 pts on QMG scale at 16 weeks
  - 4/7 had 8 pt improvement

**ANTISENSE TREATMENT**

- EN101
  - EN101 is a synthetic 20-base antisense oligodeoxy-nucleotide directed against the human AChE gene
  - Phase II double-blind crossover
  - Decreases AChE activity
  - All doses showed decrease in symptoms
  - Can suppress pro-inflammatory function

**METHOTREXATE**

- Selective inhibitor of dihydrofolate reductase and lymphocyte proliferation
- Effective immunosuppressive medication for autoimmune disease
- Randomized, double-blind, placebo-controlled multicenter trial
  - Up to 20 mg
  - 37 enrolled
  - Anticipated completion in one year

**RITUXIMAB**

- Anti-CD20 monoclonal antibody
- Targets circulating B cells
- Feasibility trial
  - 7 patients
  - Well-tolerated
  - All scores improved at 12 weeks

**DRUGS TO MINIMIZE**

Katirji (ed)
MGTX

• A multi-center, single-blind, randomized study comparing Thymectomy to No Thymectomy
• In non-thymomatous MG individuals
• On prednisone
• Two-arm trial

REFERENCES

• Bloemberg MB. "Myasthenia Gravis and Myasthenic Syndromes," in Motor Disorders, ed: David S. Younger, Lippincott Williams & Wilkins, 1999:77-118.

CASE 1

• 42 yo male with subtle leg weakness for 2 years: 2 months of double vision, subtle swallowing difficulties

EXAM AND CONDUCTION FINDINGS

• Decreased left eye abduction
• Inability to maintain upgaze
• Neck flexion, hip flexion weakness
• What type of testing?
• What area?

EXAM AND CONDUCTION FINDINGS

• Normal standard nerve conduction studies and EMG
• 2-3 Hz RNS 50% decrement CMAP amplitude
CASE 2

- A 59 yo woman with an 8 month history of progressive weakness of legs (climbing stairs)
- Dry mouth

EXAM & CONDUCTION FINDINGS

- Proximal arm and leg weakness
- Decreased reflexes
- Normal sensation
- NCS - Small amplitude motor responses on
- Normal sensory responses
- Normal needle exam (EMG)
- Additional testing? What would it show?

CASE 3

A 50 year old woman presented to the clinic with acute trouble swallowing and speaking, eyelid drooping, and moderate generalized weakness. Her symptoms seemed to fluctuate throughout the day.

Her examination revealed bilateral ptosis, mild tachypnea, dysarthria, and moderate proximal-distal weakness of both arms and legs symmetrically. She had no sensory loss.
REPETITIVE NERVE STIMULATION (RADIAL MOTOR)

Postexercise exhaustion  Recovery

LAMBERT EATON MYASTHENIC SYNDROME

JITTER

• Also called “mean consecutive difference”
• Variation in the “interpotential interval” between two time locked muscle fiber action potentials
• Increased in myasthenia gravis 92-95% of the time

Normal  Increased

LAMBERT EATON MYASTHENIC SYNDROME

- Reduced release of Ach
- IgG antibodies to voltage-gated calcium channel
- Interferes with calcium-dependent release of Ach
- Causes reduced end-plate potential

VOLTAGE GATED CALCIUM CHANNEL ANTIBODY

• P/Q type identified in 90%
• 1/3 also have N type
• P/Q type reported in SCLC, PCD
• ~20% misdiagnosed as MG*

*O’Neill. Brain 1988

Katirji B in Myasthenia Gravis and Related Disorders.
**TREATMENT**

- Pyridostigmine
- Guanidine
  - increases intracellular calcium through inhibition of mitochondrial calcium uptake
  - increased intracellular calcium enhances neurotransmitter release.
  - bone marrow suppression, nephrotoxicity, hepatotoxicity
- 3,4 diaminopyridine (DAP)
  - blocks potassium channels in nerve terminals resulting in prolonged nerve action potentials with increased calcium entry into presynaptic neurons.

**CONGENITAL MYASTHENIC SYNDROMES**

Defective synthesis or packaging of acetylcholine
Deficiency of acetylcholinesterase
Deficiency of acetylcholine receptors
Slow postsynaptic ion channel

**Review**