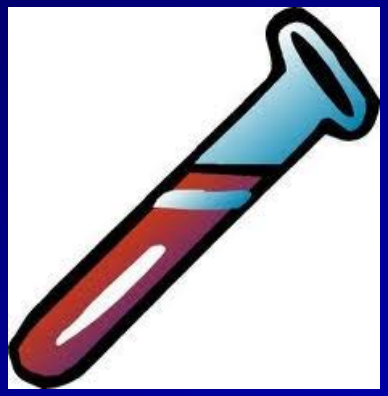
Evaluation of Neuromuscular Disorders

- Todd D Levine, MD
- Clinical Assistant Professor, University of Arizona
- Adjunct Professor of Neurology, Kansas University
- Phoenix Neurological Associates



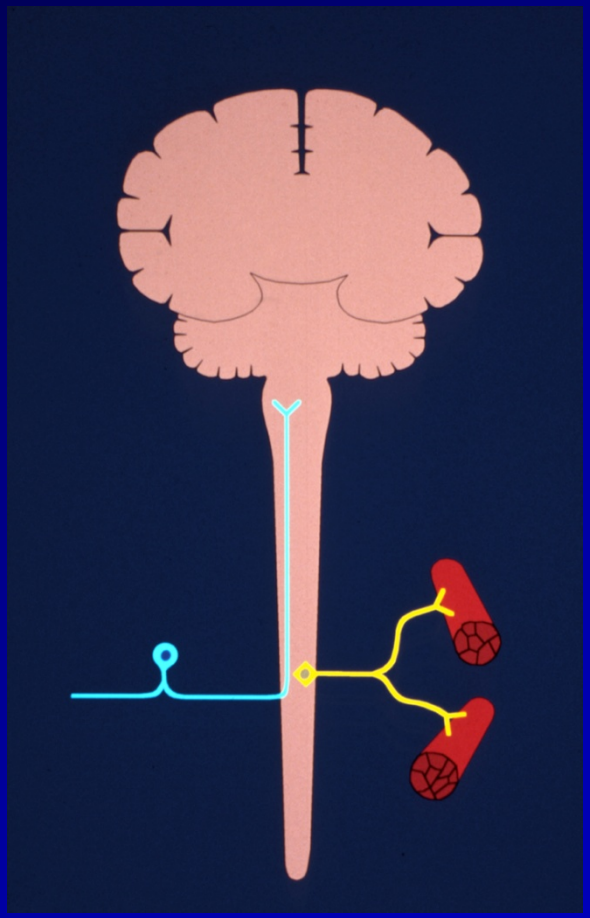
Approach to Neuromuscular Disorders

3 Goals

1. Determine the site of the lesion
2. Determine the cause of the lesion
3. Determine if there is a specific Rx therapy
   - If not, What is the best management?

GOAL 1: Determine the Site of the Lesion

- Brain
- Spinal Cord
- Neuronopathy (
- Neuropathy (root/plexus/nerve)
- Neuromuscular junction disorder
- Myopathy



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Localization of neurologic symptoms

Symptoms	Brain	Spinal Cord	Nerve	NMJ	Muscle
Motor	Unilateral	Bilateral	Distal	Proximal	Proximal
Sensory	Unilateral	Bilateral	Distal	None	None
Reflexes	Increased	Increased	Decreased	Normal	Normal
CN	Yes	No	Rare	Yes	Rare

What makes you think of nerve or muscle as the site for weakness?

Nerve

- Sensory
  - Tingling
  - Pain
  - Numb
- Asymmetric weakness
- Atrophy – esp. asymmetric
- Fasciculations
- Cramps

Muscle/NMJ

- Proximal weakness
- Hypertrophy
- Lifelong
- Ocular
  - Orb oculi
  - Ptosis
  - Ocular motility

Approach to the Patient with Neuropathy/Neuronopathy

KEY QUESTIONS:

1. What systems are involved?
   - Motor
   - Sensory
   - Autonomic
   - Combinations

Approach to the Patient with Neuropathy/Neuronopathy

KEY QUESTIONS

2. What is the distribution of weakness?
   - Only distal vs. proximal and distal
   - Focal/asymmetric vs. symmetric
   - Focal midline proximal symmetric
     - Neck/trunk/bulbar/diaphragm

Approach to the Patient with Neuropathy/Neuronopathy

KEY QUESTIONS:

3. Does sensory involvement consist of either:
   - Severe pain?
   - Severe proprioceptive loss?
     - ? Asymmetric without weakness
     - ? Symmetric

Approach to the Patient with Neuropathy/Neuronopathy

KEY QUESTIONS:

4. What is the temporal evolution?
   - acute (days to 4 weeks)
   - subacute (4 to 8 weeks)
   - chronic (> 8 weeks)
   - preceding events: infection, toxins

Approach to the Patient with Neuropathy/Neuronopathy

KEY QUESTIONS:

5. Is there evidence on the physical exam suggesting a hereditary neuropathy?

or

Is there a family history of neuropathy?

or

Do family members have abnormal exams?

Pes Cavus/ Hammertoes = Chronicity

Pattern Recognition of Neuropathic Disorders

Pattern NP1:

- Symmetric Proximal and Distal Weakness with sensory loss
  - Consider:
    - Acute- Guillan Barre
    - Chronic- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Pattern Recognition of Neuropathic Disorders

Pattern NP2:

- Symmetric Distal Sensory Loss With or Without Weakness
  - Consider:
    - cryptogenic sensory polyneuropathy (CSPN)
    - metabolic disorders
      - diabetic (DSPN)
    - drugs/toxins
    - hereditary
      - CMT

Pattern Recognition of Neuropathic Disorders

Pattern NP3:

- Asymmetric Distal Weakness With Sensory Loss
  - Single Nerves/Roots, consider:
    - CTS
    - Ulnar
    - Radiculopathy

Pattern Recognition of Neuropathic Disorders

Pattern NP4:

- Asymmetric Proximal and Distal Weakness With Sensory Loss
  - Consider:
    - polyradiculopathy or plexopathy

Pattern Recognition of Neuropathic Disorders

Pattern NP5:

- Asymmetric Distal Weakness Without Sensory Loss

  Consider:

  A. With upper neuron findings

     1. motor neuron disease/ALS

  B. Without upper motor neuron findings

     1. Progressive muscular atrophy
     2. Multifocal motor neuropathy
     3. Polio/post-polio/polio-like

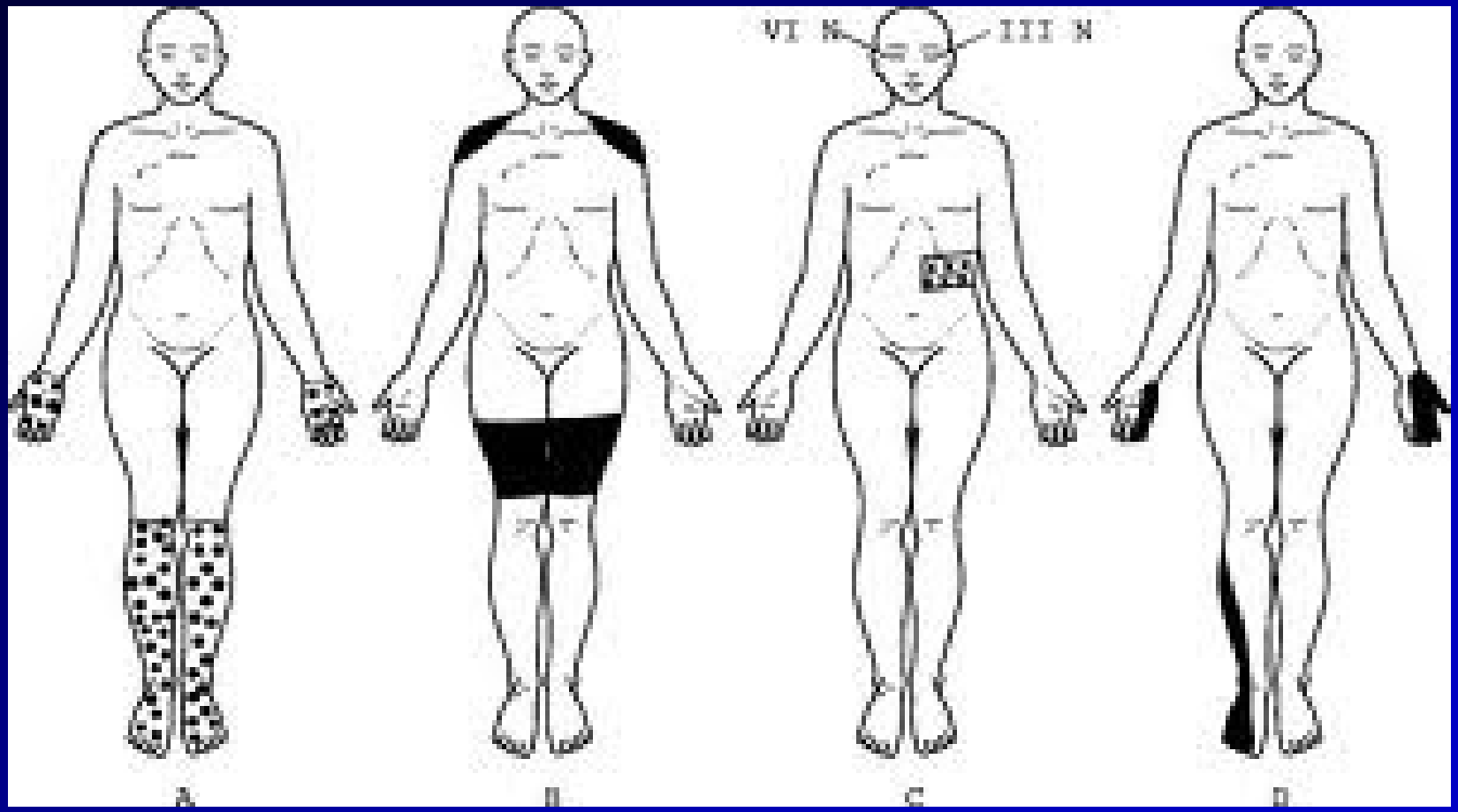
        - West Nile virus

Pattern Recognition of Neuropathic Disorders

Pattern NP6:

- Symmetric Sensory Loss and Upper Motor Neuron Signs
  - Consider:
    - B12 deficiency or other causes of combined system degeneration – esp. copper deficiency
    - Inherited disorders
      - Adrenomyeloneuropathy
      - Metachromatic leukodystrophy
      - Friedreich's
    - 2nd lesion, ex. Cervical spondylosis

Each of these things is not like the other
So our lab evaluation should be focused



Chronic Distal Symmetric Sensory Neuropathy

- Debate of IGT as cause of neuropathy
  - Should we do 2 hour glucose tolerance test
  - 15% of US has IGT
  - 2-3% of general population has PN
    - 8% of patients over age 55 have PN
    - 24% of patient over age 65 have PN

Is this merely an overlap of two very common disorders or is there a cause and effect

Answers are unknown

However for me it reflects another piece of evidence for end organ damage

So why not treat the patient: Diet, exercise, oral hypoglycemics

Chronic Distal Symmetric Sensory Neuropathy

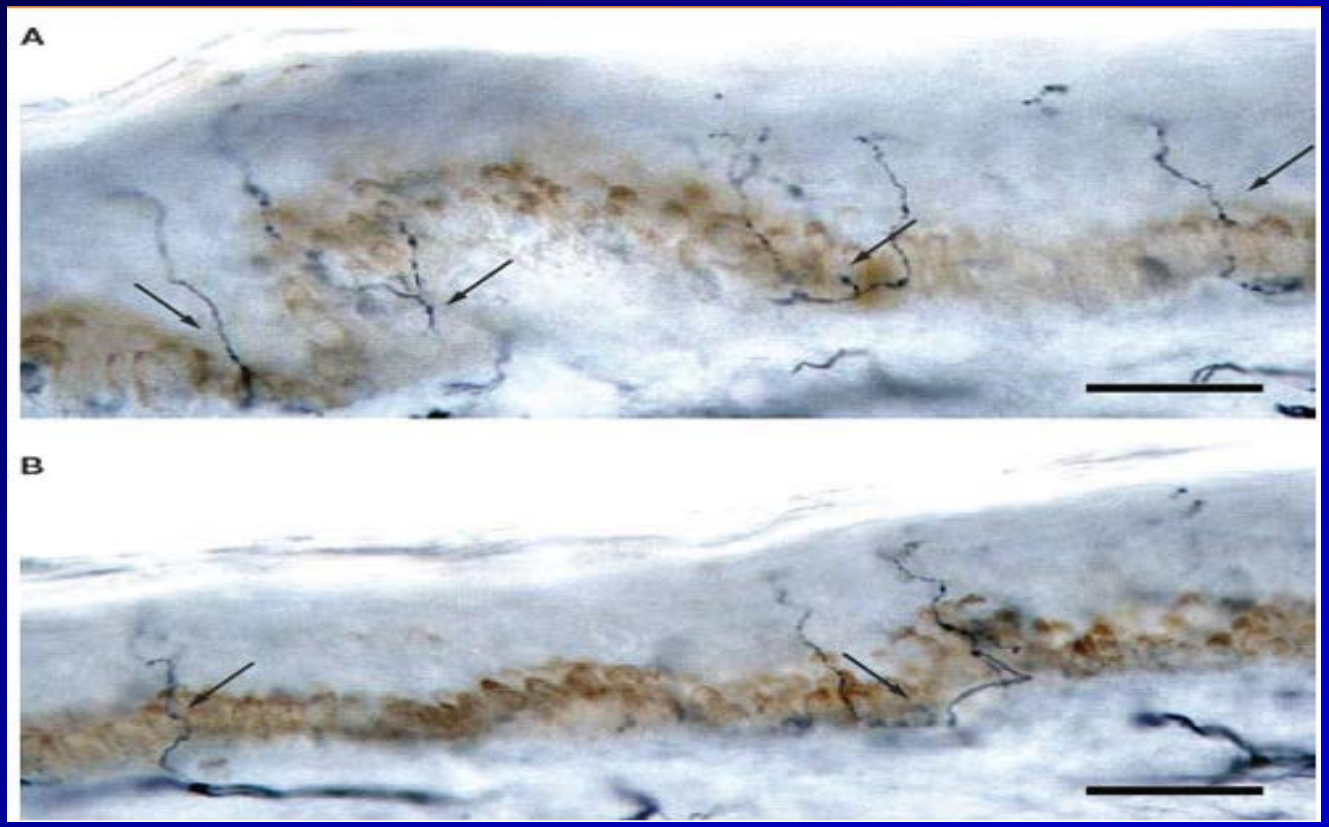
- **Vitamin B12**
  - B12 is an insensitive measure for B12 deficiency
    - B12 deficiency may be induced by metformin use greater than six months so screen frequently in your diabetics
      - Wille, DJ et al. Diabetes Care Jan 33(1) 156-61.
  - Methylmalonic acid is more sensitive test
  - Neuropathy progression may also relate to Homocysteine >13
    - 6 year prospective study. Progression of neuropathy related to HC- not B12.
      - Analysis of neuropathy symptoms as well as nerve conduction studies
        - Lesihear K et al. J Gerontol Biol Sci Med may 67(5) 537-543

Chronic Distal Symmetric Sensory Neuropathy

- **Paraproteins**
  - Serum immunofixation
  - Quantitative Immunoglobulin
  - Serum free light chains
  - No need for 24 hour urine
  - If IgM paraprotein is present test for MAG, GALOP
    - Gait Ataxia, Autoantibody, Late Onset Polyneuropathy
    - IgM vs Central Myelin Antibody
  - How and when to send to Heme/Onc.
    - Evaluate for lymphoma, Waldenstrom's Myeloma
    - If one is elevated and the others are depressed
    - If absolute level is very high: IGM >1000, IgG >2000.

Chronic Distal Symmetric Sensory Neuropathy

Epidermal nerve fiber density testing for small fiber neuropathy



Small Fiber Neuropathy

- Symptoms may be distal, proximal, or multifocal
- Symptoms may be persistent or intermittent
- In Isolated SFN- Exam and NCVs may be normal
- There may be significant overlap with other pain syndromes:
  - Fibromylagia
  - CRPS/RSD
- Reported sensitivity and specificity of skin biopsy is 88% and 92%
- It is the nature of the patients complaints that should prompt a skin biopsy
  - Neuropathic complaints with no other objective evidence for neuropathy
  - Unresolved debate as to whether IENFD is the gold standard
    - Could consider QSART where available

Small Fiber Neuropathy

Potential Etiology	Tests to Order
Diabetes Mellitus	*Fasting glucose, HgbA1c*
Impaired Glucose Tolerance	*2 hour glucose tolerance test*
Sjogren's syndrome	*SS-A, SS-B*
Primary Systemic Amyloidosis	*Serum Immunofixation* *Quantitative Immunoglobulins* *Serum free light chains* *Tissue biopsy: skin, fat pad, rectal*
Sarcoidosis	*Serum ACE*
Familial Amyloidosis	*Transthyretin gene sequencing*
Fabry Disease	*Alpha-galactosidase*

Acute/ Subacute Symmetric Sensory Neuronopathies

- Predominantly large fiber posterior column involvement with ataxia and dysmetria as main complaints
  - Psuedoathetosis found in many cases
- These may be non-length dependent because of effects on cell body rather than nerve process
- By NCS diffusely absent sensory responses with relative preservation of motor responses
- Higher likelihood for an autoimmune mediated process with neuronopathies than with neuropathies

Acute/ Subacute Symmetric Sensory Neuronopathies

Potential Etiology	Tests to Order
B12 deficiency	*Vitamin B12, methylmalonic acid*
Sjogren's syndrome	*SS-A, SS-B*
HIV	*HIV serology*
Paraneoplastic	*Hu serology*
Vitamin E deficiency	*Vitamin E levels*
Tabes Dorsalis	*RPR*
Vitamin B6 toxicity	*B6 levels*
CISP	*Evoked Potentials* *CSF analysis* *MRI of nerve roots*

Pure Motor Neuropathies

- These can present acutely, subacutely, or chronically
- Typically no sensory involvement and decreased reflexes
- Increased reflexes would raise concern for ALS or another central process and suggest spine or brain imaging
- Kennedy's Disease
  - Prominent gynecomastia
  - Prominent fasciculations
  - Androgen receptor gene mutation
    - CAG repeat. 40-65 repeats in symptomatic population

Acute Mixed Motor Sensory Neuropathies

- GBS
  - More common after upper respiratory infection
  - Examination of CSF for albuminocytologic dissociation
- AMSAN
  - More common after campylobacter infection
  - Examination of CSF for albuminocytologic dissociation

Acute Mixed Motor Sensory Neuropathies

Potential Etiology	Tests to Order
GBS	*CSF*
AMSAN	*CSF*
Mononeuritis Multiplex	*ESR, ANA* *Hepatitis B and C serologies* *cryoglobulins,* *HIV* *ACE* *Nerve biopsy*

Chronic Mixed Motor and Sensory Neuropathies

Potential Etiology	Tests to order
Diabetes	*Fasting glucose, HgbA1c*
Impaired glucose tolerance	*2 hour glucose tolerance test*
B12 deficiency	*Vitamin B12, methylmalonic acid*
Paraproteinemia	*Serum immunofixation, Quantitative Immunoglobulins, serum free light chains*
CMT1	*PMP duplication / deletion, Cx32, MPZ, MFN2*
CMT2	*EGR2, FIG4, GARS, GDAP1, HSPB1, LMNA, MFNA2, MPZ, Periaxin, RAB7*
Sjogren's syndrome	*SS-A, SS-B*
If tests are normal but disease is progressive	*CSF, sural nerve biopsy*

Conclusions

- Differential can be based on history alone
  - Exam to confirm history
  - Don't allow EMG/NCV to confuse you
- Rationalize aggressive testing with aggressiveness of the disease process
  - Idiopathic neuropathies are sensory and slowly progressive
  - If neuropathy is disabling and progressive than keep looking for cause
    - CSF: elevated protein, IgG synthesis rate would suggest a trial of empiric therapy
    - Nerve Biopsy
  - In face of progressive disease consider empiric trials of treatment
  - Most immune mediated neuropathies respond to steroids or IVIG within 3 months so don't flog a dead nerve and make the patient worse

Neuropathic Pain
Multidimensional Management

- Treatment of underlying cause of nerve damage
- Pharmacological therapy
- Non-pharmacological therapy

Painful Peripheral Neuropathy Treatment Goals

- Setting the expectation with emphasis on function: work, recreation & sleep
- This is in addition to significant reduction of pain scores by 30-50%
- Types of pharmacotherapies:
  - Antidepressants
  - Anticonvulsants
  - Topical agents
  - Analgesics
  - Opioid drugs

Antidepressants: TCAs & SSRIs

- >9 TCA and/or SSRI clinical trials in DPN or PHN
- Tricyclic antidepressants (TCAs) highly effective: amitriptyline, nortriptyline and desipramine
  - Br J Clin Pharmacol. 1990 Nov;30(5):683-91. Neurology. 2002 Oct 8;59(7):1015-21
- TCA effect independent of depression comorbidity
  - Neurology 1987 Apr;37(4):589-96
- Selective serotonin reuptake inhibitors (SSRIs) less effective than TCAs:
  - Fluoxetine no different than placebo in DPN
    - N Engl J Med 1992 May 7;326(19):1250-6.
  - Paroxetine less effective than imipramine in DPN
    - Pain 1990 Aug;42(2):135-44.
  - Escitalopram rs6318 *SNP* in the serotonin receptor 2C gene associated with 75% moderate or better pain relief
    - Eur J Clin Pharmacol 2011 Nov;67(11):1131-7

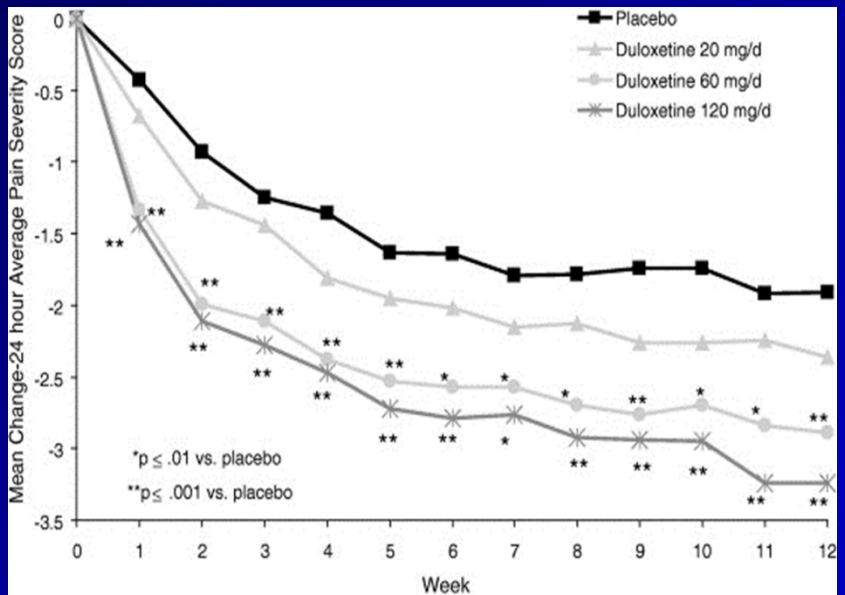
SNRI Antidepressants: Venlafaxine

- Increases synaptic serotonin/NE (SNRI) by inhibiting reuptake
- RCT: ER significantly reduces pain intensity in DPN
  - Pain 2004 Aug;110(3):697-706
- Doses of 150-225 mg a day, not 75 mg
- Useful as add on to GBP in DPN: improved pain, QOL, sleep and mood
  - J Clin Neuromuscul Dis 2001 Dec;3(2):53-62
- 112.5 mg bid may be as effective as imipramine 75 mg BID in a 3-way crossover, 4-wk RCT in DPN (n=15) and non-diabetic cases (n=17, CSPN = 11)
  - Neurology 2003 Apr 22;60(8):1284-9
- Relatively well tolerated; side effect of nausea and somnolence

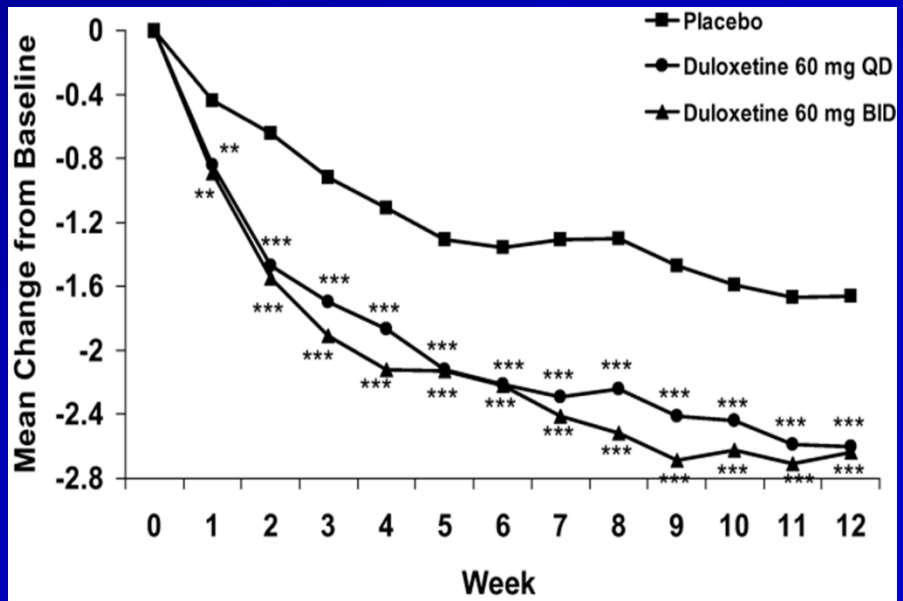
SNRI Antidepressants: Duloxetine

- SNRI released in Fall 2004 with higher, more balanced affinity for NE/5HT reuptake sites
- First FDA approved agent DPN (also approved for fibromyalgia)
- Effective at 60 and 120 mg/d not 20 mg/d
- Higher AE incidence with 120 mg dose

Pain. 2005;116(1-2):109-1



Pain Med. 2005;6(5):346-56



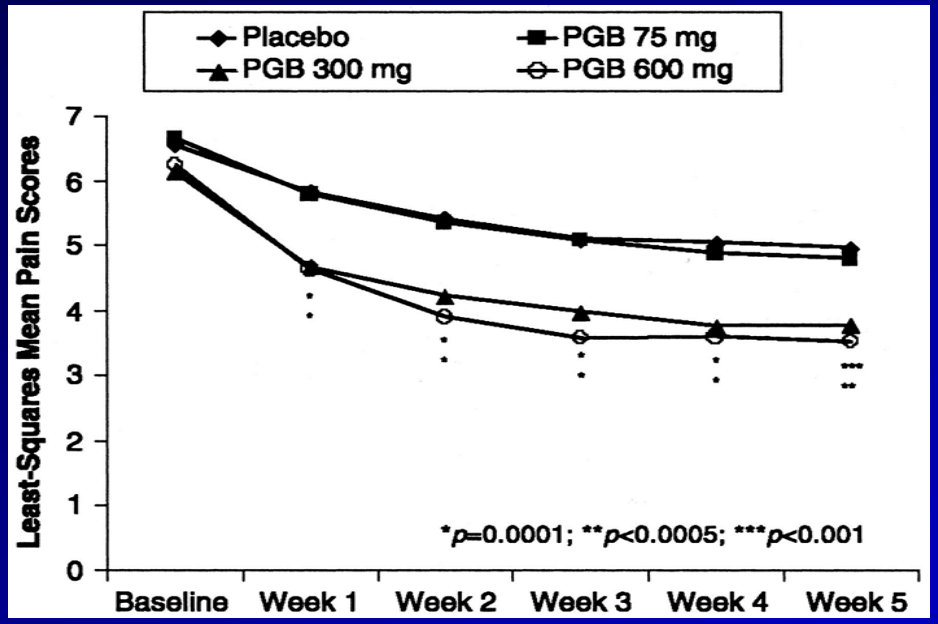
Anticonvulsants: Gabapentin

- Most commonly prescribed AED for pain
  - Does not bind to plasma proteins
  - Does not induce hepatic enzymes
  - Excreted unchanged in urine
- Mechanisms of action: binds to $\alpha_2\delta$ subunit of presynaptic voltage-dependent Ca channel
  - Life Sci 2007 May 8;80(22):2015-24
- Also increases CNS levels of GABA
  - Neurology 2002;58(3):368-72
  - Epilepsy Res 2002;49(3):203-210

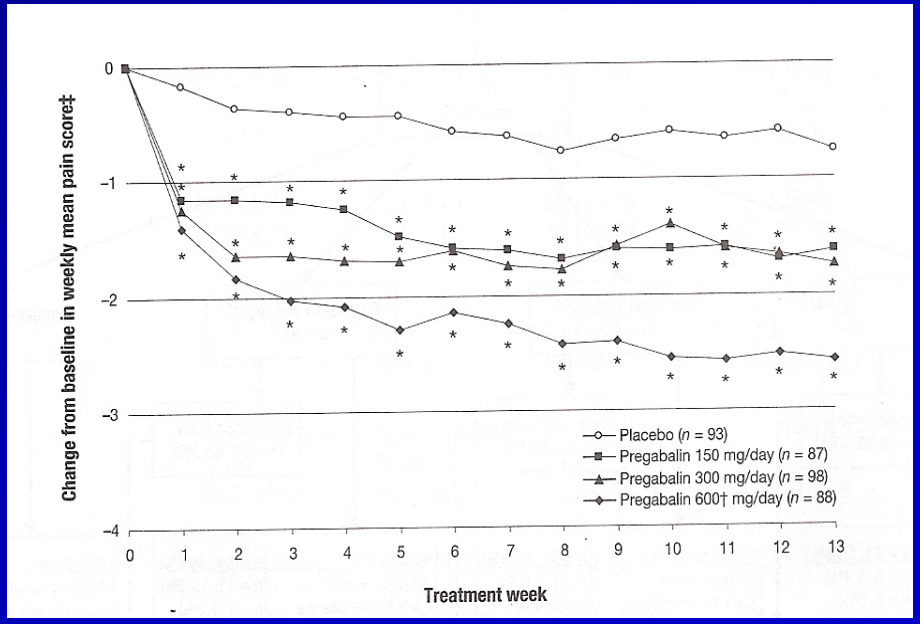
Anticonvulsants: Pregabalin

- Approved on 12/31/04:
  - DPN 50-100 mg TID
  - PHN 75-300 mg BID
  - Fibromyalgia 75-225 mg BID

Neurology 2004;63:2104-10

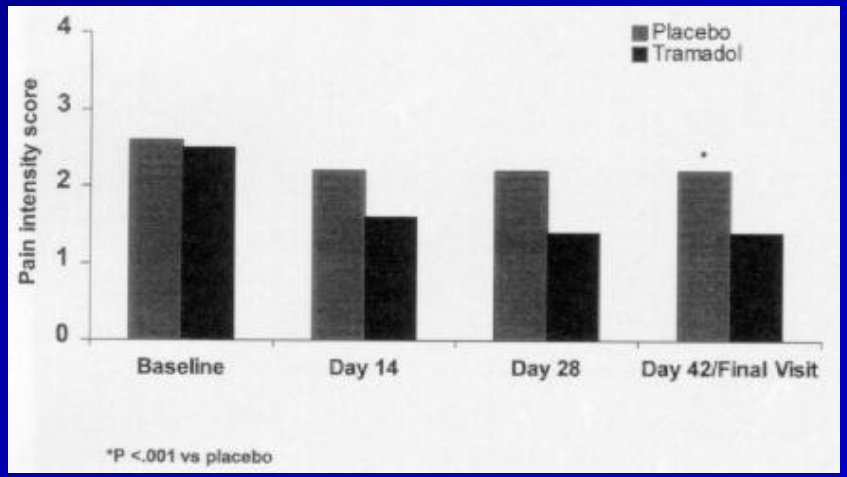


Curr Med Res Opin. 2006;22:375-84.



Tramadol in DPN

- Centrally-acting:
  - Binds μ-opioid receptors
  - Weak inhibitor of NEP/5HT reuptake
    - RCT tramadol (n=65; 50-400 mg) vs. PBO (n= 66):



  - Effective in DPN
  - Mean dose 210 mg/d
  - No effect on sleep
  - AEs: nausea, constipation, HA & somnolence

Neurology 1998;50:1842

Analgesics Opiate: Oxycodone CR in DPN

- RCT n=159
- Dose 10 mg BID increased Q 3 d to maximum 60 mg BID
- Primary efficacy was pain intensity at days 28 & 42
- Results at mean dose of 37 mg/d (10-100):
  - Effective in moderate to severe DPN pain
  - Adverse events in 96% vs. 68% on PBO!
    - Constipation 42%
    - Somnolence 40%
    - Nausea 36%
    - Dizziness 32%

Neurology 2003; 60:927-934

Neuromuscular Junction Disorders

Myasthenia Gravis
Tests for Diagnosis

- Edrophonium Test
- Serum Antibodies
- Repetitive Stimulation
- Single fiber EMG

Edrophonium Test
Quick/Easy Technique

- Now called Enlon (not Tensilon)
- Load 1 cc (10 mg) Enlon in TB syringe
- Inject directly in antecubital vein
- Inject in 3 Steps: 0.2 cc/0.2 cc/0.6 cc
- When patient feels effect of Enlon (fascics/sweating/nausea) - Stop Injection
- In general, no need for atropine, cardiac/blood pressure monitor, or placebo

Edrophonium Test

KEY POINTS

- Must have something to measure
  - Usually degree of ptosis
  - Occas dysarthria/dysphagia
  - Not extremity strength, fatigue or diplopia
- Not required in all MG patients
- Can rarely be “Positive” in other diseases

Acetylcholine Receptor Antibody (AChR-Ab)

- Most specific test for MG
- If positive, no other dx tests needed (usually)
- % positive:
  - 85% Gen MG
  - 50% Ocular MG
- “Binding” RIA most often used
  - NL < 0.03 to 0.5 nmol/l
- “Blocking”/ “Modulating” Assays – Don’t order or ignore
- Correlate poorly with severity
- Approach to AChR-Ab “Neg” patients is the same

AChR-Ab NEG Patients & MuSK Ab

- Muscle-specific kinase
  - Hoch 2001 *Nat Med*/ Plested 2002 *Neurology*
  - Abs to muscle-specific receptor tyrosine kinase
  - MuSK – agrin/agrin mediated signals @ NMJ
  - Approx 40% of AchR-Ab neg patients have Musk Ab
  - Phenotype – severe (bulbar), face/tongue atrophy

    female, less Rx resp

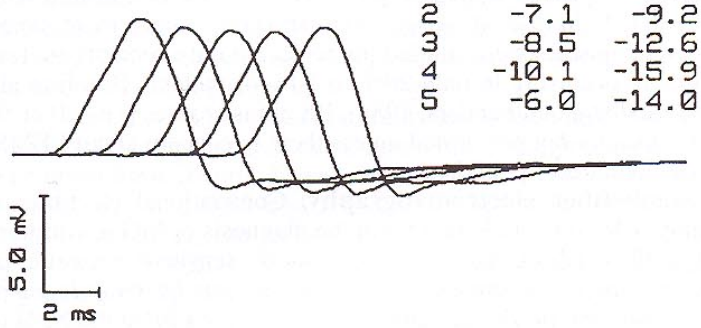
    never pure ocular
  - New Abs : LRP, rapsyn, agrin, dSNMG (cortactin) – still research tool

Repetitive Stimulation Key Points

- Decrement indicates neuromuscular blockade
- More likely in weak muscles (usually prox)
- Look for Post-Exercise Exhaustion and Post-Exercise Facilitation
- Perform at 2-3 Hz
- Not necessary on all MG patients

Baseline

A



Resp (#)	NPamp (%chg)	NParea (%chg)
1	0.0	0.0
2	-7.1	-9.2
3	-8.5	-12.6
4	-10.1	-15.9
5	-6.0	-14.0

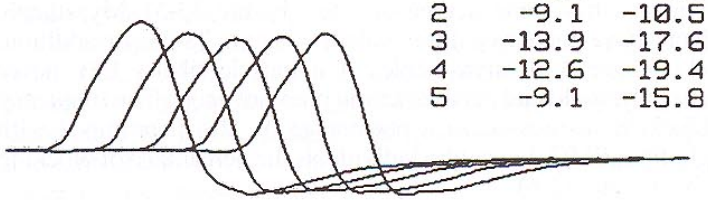
Immediately post-exercise

B

Resp (#)	NPamp (%chg)	NParea (%chg)
1	0.0	0.0
2	2.3	0.3
3	1.3	0.2
4	3.4	-0.8
5	7.0	2.8

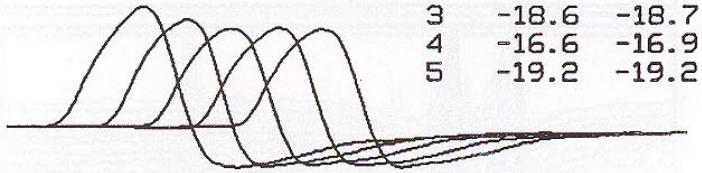
1 min post-exercise

C



Resp (#)	NPamp (%chg)	NParea (%chg)
1	0.0	0.0
2	-9.1	-10.5
3	-13.9	-17.6
4	-12.6	-19.4
5	-9.1	-15.8

2 min post-exercise

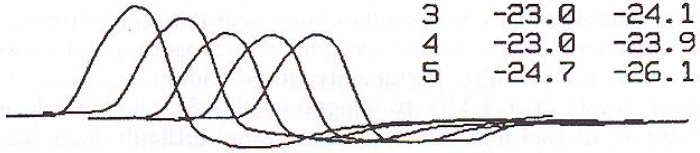


D

Resp (#)	NPamp (%chg)	NParea (%chg)
1	0.0	0.0
2	-11.0	-12.6
3	-18.6	-18.7
4	-16.6	-16.9
5	-19.2	-19.2

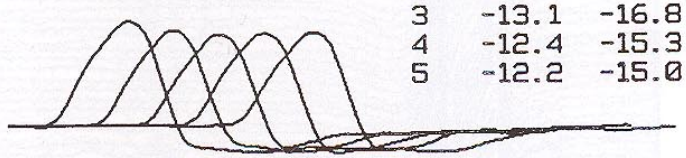
4 min post-exercise

E



Resp (#)	NPamp (%chg)	NParea (%chg)
1	0.0	0.0
2	-15.1	-16.1
3	-23.0	-24.1
4	-23.0	-23.9
5	-24.7	-26.1

Immediately post 10 sec exercise



F

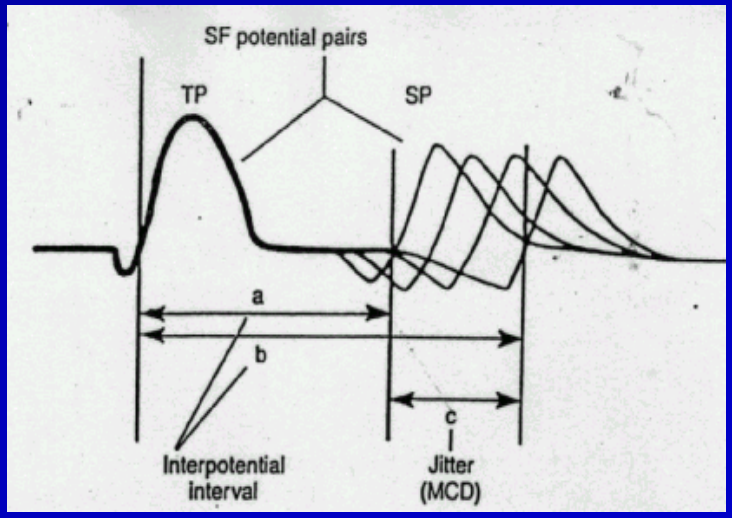
Resp (#)	NPamp (%chg)	NParea (%chg)
1	0.0	0.0
2	-9.6	-12.5
3	-13.1	-16.8
4	-12.4	-15.3
5	-12.2	-15.0

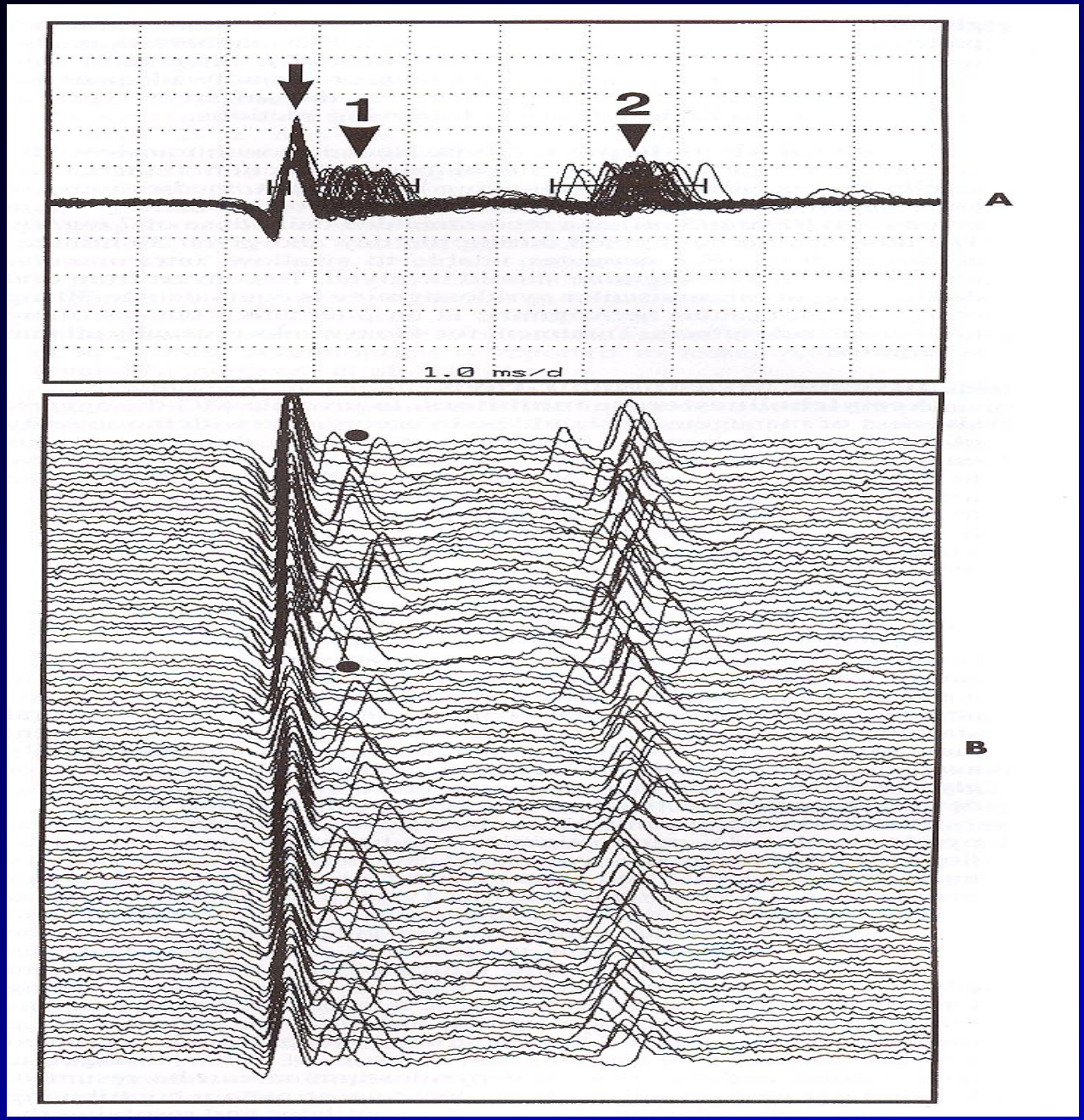
Yield Of Repetitive Stimulation

	Distal	Proximal
All generalized	65%	85%
Mild generalized	55%	75%
Ocular	35%	45%

Single Fiber EMG

- Records individual muscle fiber potentials
- Jitter Measures Variability of Rise-Time of End-Plate Potential to Reach Threshold
- Jitter measured in microseconds as the Mean Consecutive Difference - MCD





MCD #1 = 270 µsec
50% blocking

MCD #2 = 187 µsec

Single Fiber EMG

- Pros:
  - Most Sensitive Test for MG
    - 94% Generalized
    - 80% Ocular
- Cons:
  - Difficult, Time-Consuming, Tedious, Requiring Computerized EMG Machine, Software, SF Needles
  - Least Specific Test for MG
    - Abn in Denervating/Myopathic Disorders
  - Seldom required in an MG patient
  - Reimbursement issues

Myasthenia Gravis

- Mortality:
  - Prior to 1960: >30%-very grave!
  - Now: < 1%
  - Due to Mech Vent and Steroids & other Rx
- We now expect most patients to improve and some to go into remission

Treatment of Myasthenia Gravis

Typical Time to Clinical Effect After Initiating Therapy

THERAPY	TIME
Edrophonium	1-2 minutes
Pyridostigmine	10-15 minutes
Plasmapheresis	1-14 days
IVIg	1-4 weeks
Prednisone	2-8 weeks
Mycophenolate	2-6 months
Methotrexate	2-6 months
Cyclosporine	2-6 months
Azathioprine	3-18 months
Thymectomy	Several months to several years

Pyridostigmine (Mestinon)

- 1st line Rx for MG
- Don’t expect or use too much
  - 60 mg TID - QID
- If need more than this, immunosuppressive Rx needed
- Generic now available
- Avoid time-release form
- Anticholinergic meds useful for GI side effects:
  - Hyoscyamine sulfate 0.125 mg (Levsin/Anaspaz)

Corticosteroid Treatment for MG

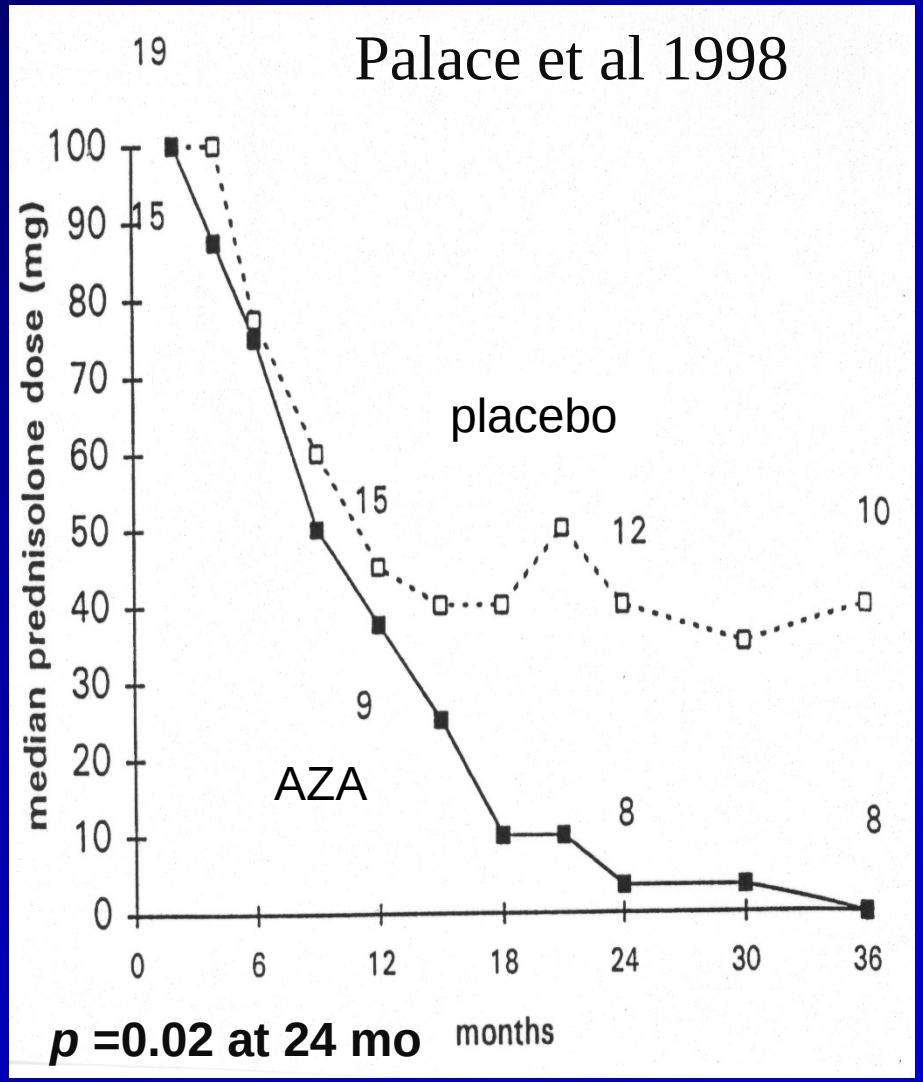
- Mechanism: inhibition NF-κB, Dec cytokines
  - Immune supp
- 1st line Rx for MG since 1970s
- Improvement begins in 2-4 weeks
- Maximum benefit in ~ 6 months
- Transient worsening occurs in 50% of pts during first week
- “Remission” is often steroid dependent

Prednisone Rx for MG

- High Dose
  - 60 to 100 mg/day x 2 weeks
  - Then 60 to 100 mg qod until much better
  - Then taper 5 mg q 2 wks
  - Requires initial inpatient admission
- Low / Slow Approach
  - Seybold & Drachman 1974
  - Gradual increase to avoid initial worsening
  - 10 mg/day; increase by 10 mg q 5-7 days
  - Then switch to qod
- In-between Approach
  - Mycophenolate trial protocol
    - Pred 20 mg/day

Azathioprine (Imuran)
Rx for MG

- Purine analog - blocks DNA/RNA synthesis and cell proliferation
- Response is slow - up to 18 months
- Dose: Begin 50 mg/day x 1 week, Then, 2-3 mg/kg/day
- Typical dose 150 mg/day (single dose)
- Toxicity
  - Systemic “flu-like” reaction
  - Leukopenia
  - Hepatotoxicity
- Monthly CBC/LFTs
- We do not use Thiopurine Methyltransferase (TPMT) test



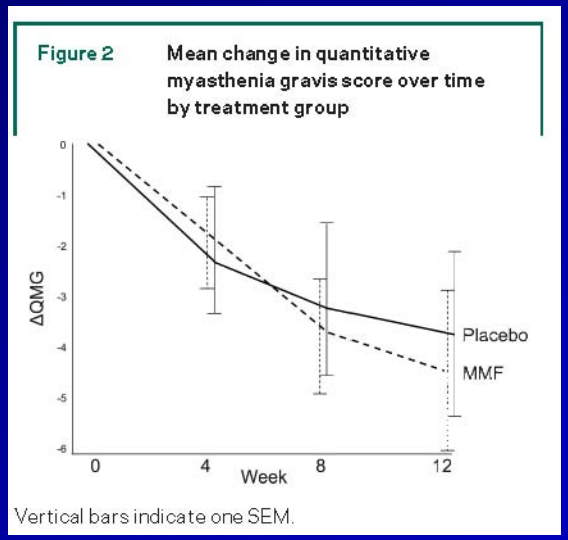
Cyclosporine in MG

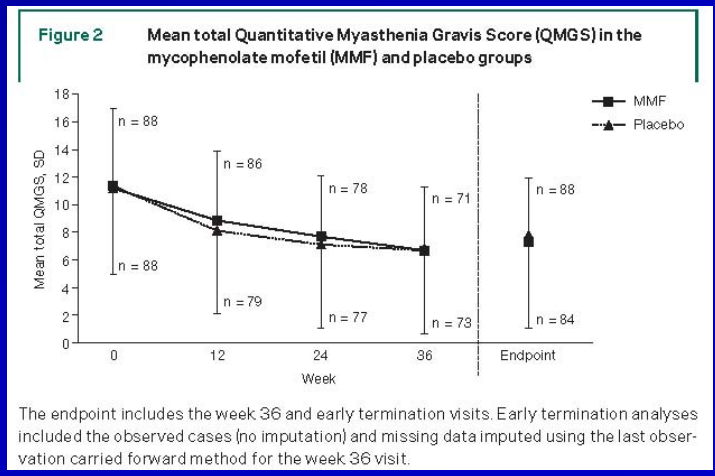
- Selective/reversible on T-cells
  - Inhibit IL-2 and interferon γ
  - Inhibits cytotoxic/express supp Ts
- 1987 - CSA Effective in non-immunosuppressed MG
  - 20 patients
- 1993 - CSA Effective in Steroid-Dep MG
  - 39 patients
- QMG - Primary End-Point
- In 1993 Study:
  - Mean Dec QMG 3.5 in CSA
  - Mean Dec QMG 0 in Placebo
- Sandoz industry study: results never released

Tindall et al 1987 & 1993

Mycophenolate Mofetil Rand/Control Trials in MG

- **Sanders & colleagues** (MSG *Neurology* 2008;71:394)
  - Investigator initiated funded by FDA-ODG
  - Must be AChR-Ab pos
  - No prior IS Rx
  - 2.5 gm MM vs. plac
  - All placed on pred 20
  - 1º – QMG 3 mos
  - 2º – MMT, MG-ADL
  - AChR-Ab, SFEMG
  - 80 subjects
- **Aspreva sponsored-138 subjects** (Sanders et al *Neurol* 2008;71:400)
  - Can already be on prednisone
  - 9 month trial





RESULTS FOR BOTH:
NO SIGNIFICANT DIFFERENCE!

IV Immunoglobulin in Patients with Myasthenia Gravis

- 51 pts IVIg vs. placebo
- QMG: Sig dif at day 14 (p=0.047)
- Persisted at day 28
- Change in
  - IVIg: -2.54
  - Placebo: -0.89
- Post intervention status at day 14
  - IVIg imp 25%
  - Placebo imp 6%
- RNS/SFEMG-no sig diff
- Meriggioli editorial:
  - Getting enough “bang for the buck”

Zinman, Eduardo, Bril *Neurology* 2007; 68:837-881

Comparison of IVIg & Plex in MG

Barth, et al *Neurology* 2011;76

- 84 pts to IVIg 1g/kg/d x 2 days
  - Or PE x 5
- QMG > 10.5 and "worsening"

Table 2 Mean ± SD change in QMGS for disease severity from baseline to days 14, 21, and 28[a]

	IVIg (n = 41)	PLEX (n = 43)	p Value[b]
Baseline QMGS	14.2 ± 4	14.4 ± 3.8	0.83
Δ QMGS			
Day 0-14[c]	3.2 ± 4.1	4.7 ± 4.9	0.13
Day 0-21	3.3 ± 3.6	5.3 ± 5.5	0.07
Day 0-28	2.6 ± 4.0	4.7 ± 5.7	0.08

Abbreviations: IVIg = IV immunoglobulin; PLEX = plasma exchange; QMGS = Quantitative Myasthenia Gravis Score for disease severity.
[a] This table demonstrates that the changes of QMGS for disease severity did not differ between the 2 treatment groups for the 28-day study duration.
[b] p Values are for QMGS differences from baseline with IVIg compared to PLEX.
[c] Primary efficacy parameter.

Improved: 69% IVIg and 65% PE
Conc: IVIg & PE both effective Rx

Plasmapheresis

- Directly removes humoral factors such as autoantibodies, immune complexes, complement and other nonspecific inflammatory mediators
- Remove 3-6 liters of plasma over several hours. Replace with albumin or purified protein fraction (PPF).
- Indications for MG:
  - crises
  - pre-thymectomy
  - severe MG (not in crises) when initiating or increasing oral immunosuppressive drugs
  - chronic Rx

MG Crises
Rx Caveats

- Begin plasmapheresis ASAP
  - Minimum of 5 exchanges
- Increase steroids to high dose
  - Solumedrol 60 to 100 mg/IV/Day
- Stop pyridostigmine
- Usually on ventilation at least 5 to 7 days

Special Article

Neurology 2000;55:7-15

Practice parameter: Thymectomy for autoimmune myasthenia gravis (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

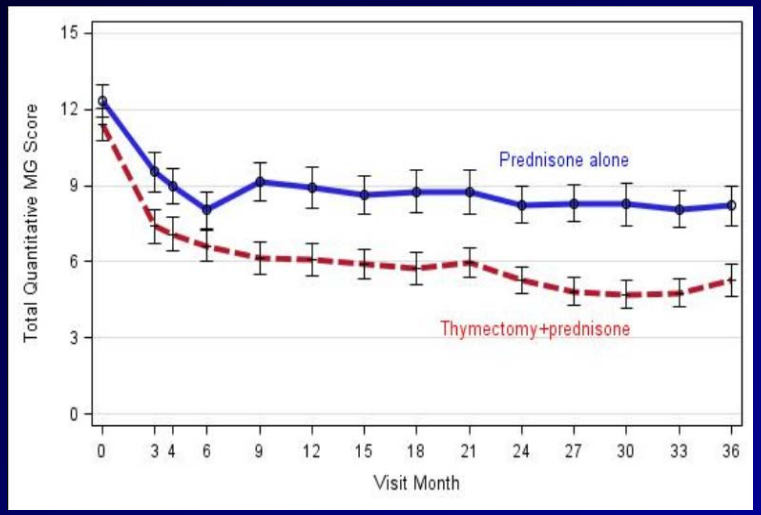
Gary S. Gronseth, MD; and Richard J. Barohn, MD

Randomized Blinded Trial of Thymectomy for MG

- Newsom-Davis, Wolfe, Cutter, Kaminski, Jaretski
- Randomized/controlled NIH trial
- REQ – gen, AChR Ab+
- All pts go on prednisone
- All get transternal thymectomy
- Blinded evaluations
- OUTCOME: Pred dose and QMG at 3 yrs
- QUESTION: Do THY pts do better than pred alone?
- Difficult/slow enrollment but enrollment complete (# 126 patients)
  - Most subjects outside USA
- Wolfe G, et al. NEJM 2016;375:511-522

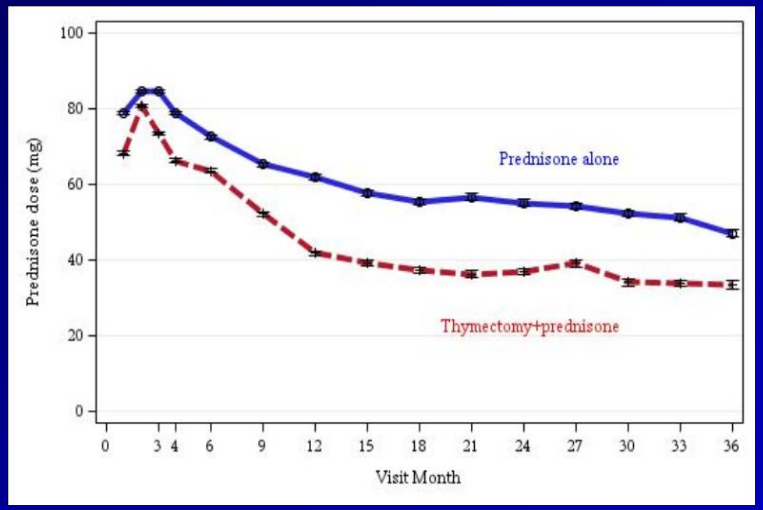
Wolfe et al. Thymectomy in MG

(New England Journal of Medicine 2016;375:511-522)



QMG Score (Mean±SE) by Treatment Group

- QMG difference: 2.85 pts (99.5% CI 0.47-5.22; p<0.001)



Time-Weighted Average AD Prednisone Dose (Mean±SE) by Treatment Group

- Prednisone dose difference: 44 mg vs 60 mg (95% CI 7-25 mg; p<0.001)

Thymectomy for MG Summary

- Now a Controlled Trial Exists! Positive study!
- But Response May Not be Immediate
  - Measured in Months to Years
- No Guarantee of Improvement
- Numerous Procedures
- Thymoma is an absolute indication
- Not rec for:
  - Ocular
  - Very young children
  - Greater than 60, or, ? > 70, or ? > 80
    - (Depends on how old the Rx Neurologist is)

Drugs to Avoid in MG

- Aminoglycosides – IV
- Curare – IV
- Don’t worry about others!
  - Concern about other antihistamines, anticholinergics, beta-blockers, calcium channel blockers, antibiotics – ALL unwarranted

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF ECULIZUMAB IN PATIENTS WITH REFRACTORY GENERALIZED MYASTHENIA GRAVIS

JAMES F. HOWARD, Jr., MD,[1] RICHARD J. BAROHN, MD,[2] GARY R. CUTTER, PhD,[3] MIRIAM FREIMER, MD,[4] VERN C. JUEL, MD,[5] TAHSEEN MOZAFFAR, MD,[6] MICHELLE L. MELLION, MD,[7] MICHAEL G. BENATAR, MD, PhD,[8] MARIA ELENA FARRUGIA, DPhil, MD,[9] JING JING WANG, MD, MS,[10] SUNEIL S. MALHOTRA, PhD,[10] JOHN T. KISSEL, MD,[4] and the MG Study Group

Muscle Nerve 2013;48:76-84

- 14 MG pts – 4 mo RTC crossover
- **Results**:
  - 86% on ecluz met QMG DOI (3 pt imp) (57% placebo)
  - QMG score sig less after ecluz ($p < 0.0001$)
  - MGADL: eculizumab 9/13 imp 2 pts placebo 3/13
- Plan – phase 3 study just completed

Eculizumab Phase 3 Trial Results

MG-ADL and QMG Worst-Rank ANCOVA

Change From Baseline Total Score at Week 26, As Analyzed by Worst-Rank ANCOVA P-value

Primary Endpoint
MG-ADL, p=0.0698

First Secondary Endpoint
QMG, p=0.0129

- 3 of 4 prospectively defined sensitivity analyses to validate the primary endpoint of MG-ADL achieved p-value < 0.05
- For QMG, 4 of 4 prospectively defined sensitivity analyses achieved p-value <0.05

Howard JF – REGAIN: A Randomized, Double-Blind, Placebo-Controlled Multi-Center Phase 3 Study of the Safety and Efficacy of Eculizumab in Subjects with Refractory Generalized Myasthenia Gravis

Lambert-Eaton Myasthenic Syndrome (LEMS)

CLINICAL FEATURES

- On Exam:
  - Proximal arm/leg weakness
  - Occasionally can demonstrate improvement after a few seconds of voluntary contraction
  - Poorly reactive pupils
  - Hypo or areflexia
  - Occasionally mild distal sensory loss in feet

LEMS

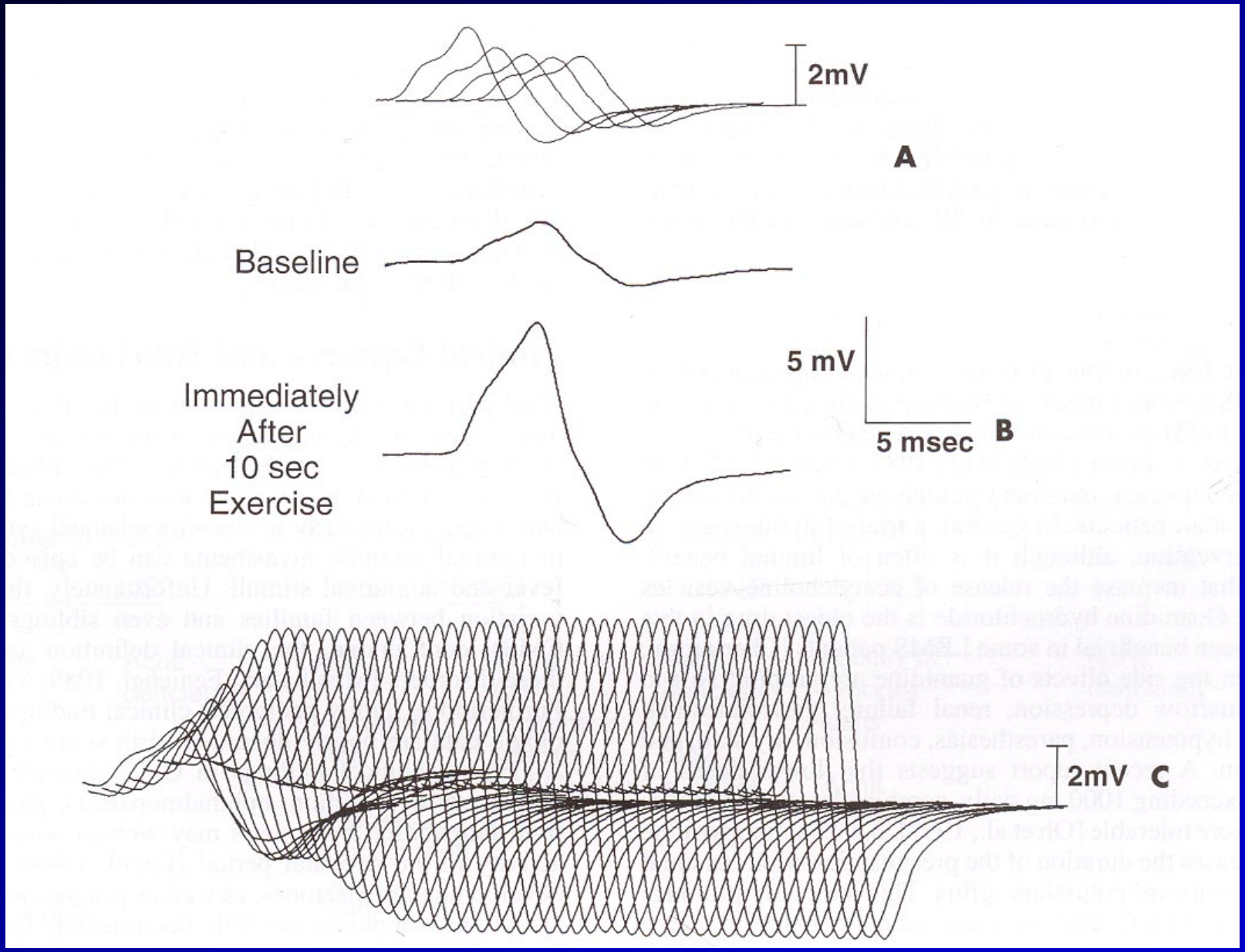
Malignancy/Non-malignancy Assoc.

- LEMS more common in men - 4.7:1 M:F
- Overall 50% have a malignancy
  - 75% Males
  - 25% Females
- Tumor usually small-cell lung CA
- 3% small cell lung CA pts develop LEMS
  - LEMS can proceed tumor detection by many months
- Most young women: non-malignant
- Most old men: malignant

Voltage-Gated Ca++ Channel Ab's

- 85% of patients
  - Cancer: 98%
  - No cancer: 90%

LEMS Neurophysiology



LEMS – Rx Recommendations

- Rx underlying cancer if present
- Try 3,4 DAP if available
- If need IS Rx:
  - Prednisone 1st line
  - IVIg 2nd line
  - then other po meds as needed
- PE if severely weak

Acquired Muscle Disorders

Todd D Levine, MD
Clinical Assistant Professor of Neurology
University of Arizona
Phoenix Neurological Associates
Phoenix, Arizona
Adjunct Professor of Neurology
University of Kansas Medical Center

Dr. Levine is a consultant and has received consulting fees from Baxter, CSL Behring, Corinthian Reference Labs, NuFactor, Pfizer, Questcor and Talecris. He has research grants from CSL Behring, Eisai, FDA and Questcor.

Symptoms of Inflammatory Myopathies

- Muscle weakness
  - Usually proximal more than distal (MP1)
- Swallowing problems
- GI symptoms
- Breathing problems
- Rash
- Muscle pain?

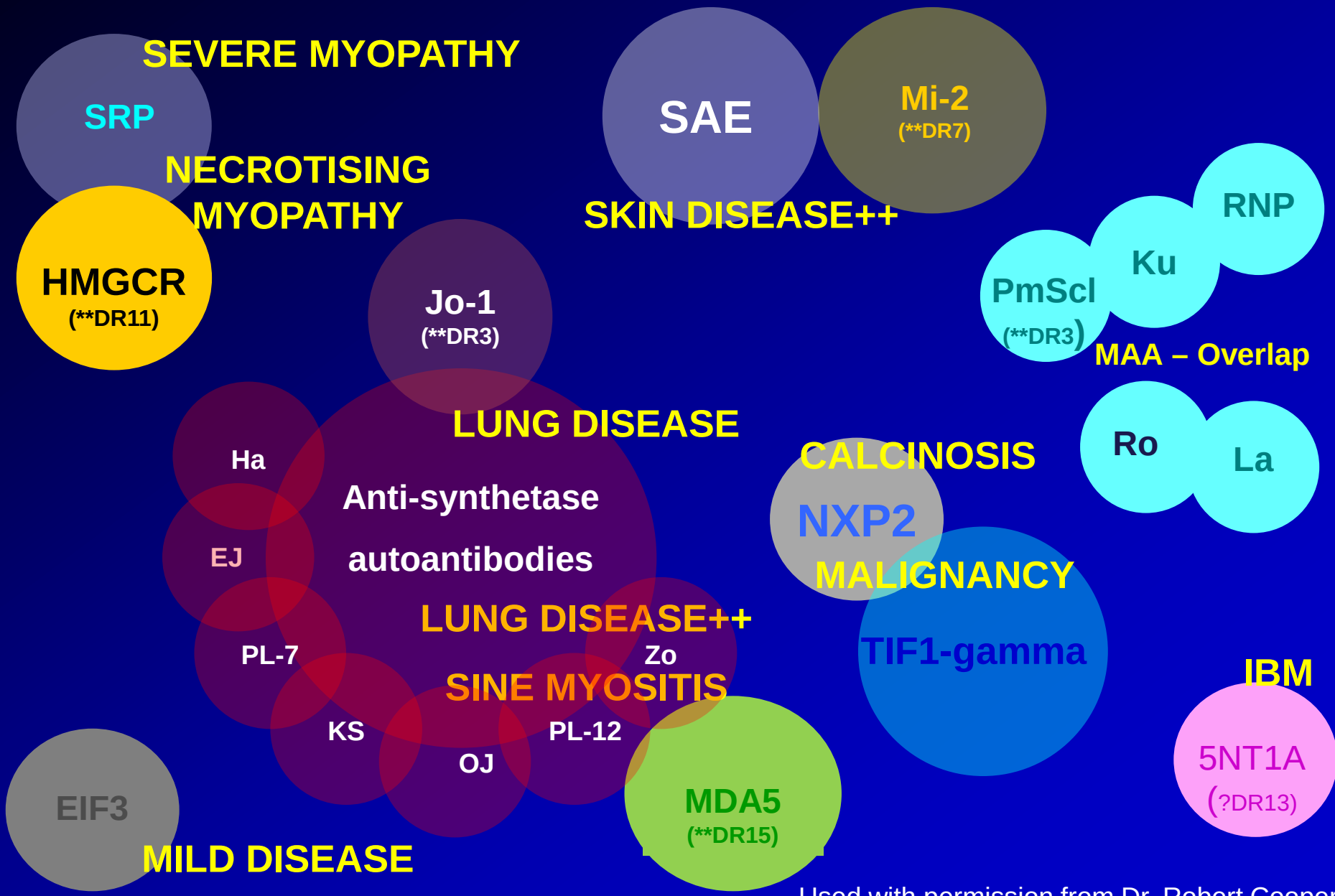
IIM

- Rare disorders with incidence 1-5/100,000
- Subacute to chronic presentation
- Limb-girdle distribution of weakness except IBM
- Neck flexors and pharyngeal
- Variable degree of CK elevation
- EMG/NCS: irritative myopathy (with IBM chronicity)
- May be associated with malignancy, ILD or CTD
- Most respond to immunosuppressive therapy

IIM Classification

- **Dermatomyositis (DM)**
- **Polymyositis (PM)**
- **Necrotizing myopathy (NM)**
- **Sporadic inclusion body myositis (IBM)**
- Granulomatous myositis
- Eosinophilic myositis
- Infectious myositis
- Overlap syndromes
- Non-specific myositis

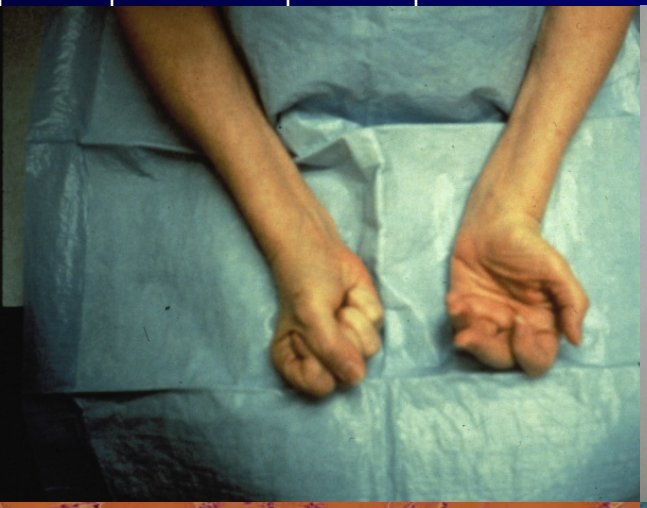
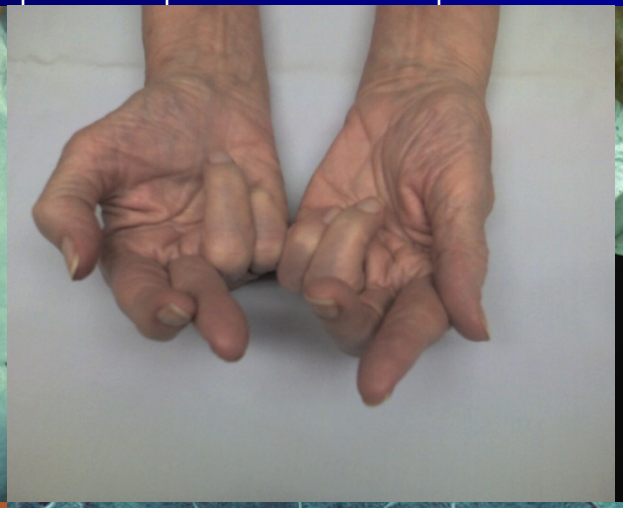
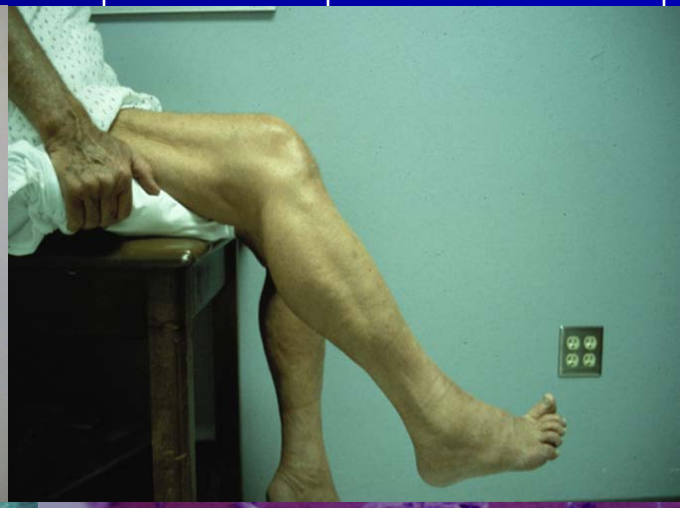
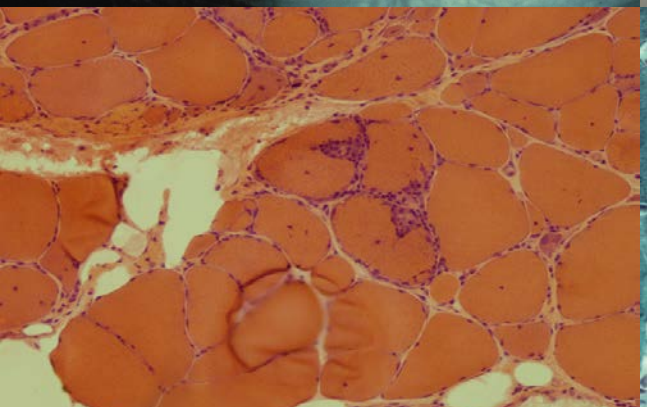
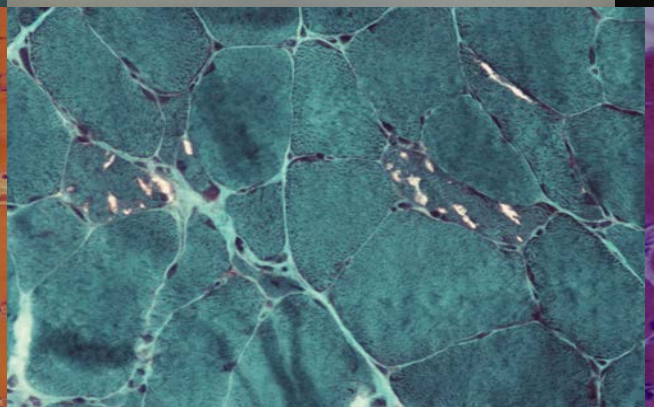
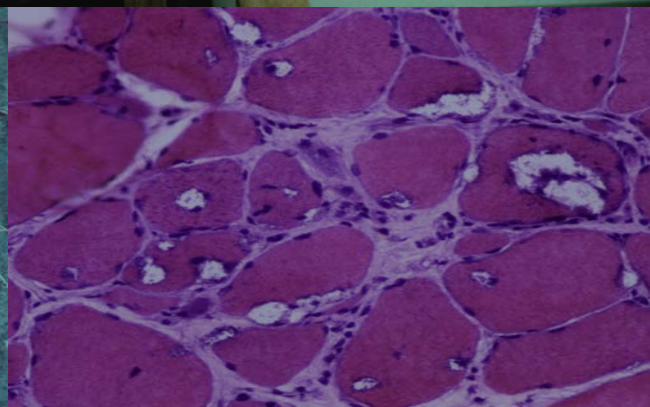
Serological Classification of Inflammatory Myopathies



Used with permission from Dr. Robert Cooper

IBM

	Age of Onset	Rash	Pattern of Weakness	CK	Muscle Biopsy	Cellular Infiltrate	Response to Therapy	Commonly Associated Conditions
IBM	Elderly (most of IIM >50)	No	Asymmetry Finger flexor, knee extensor, dysphagia	NL or up to 10xNL	Rimmed vacuoles; endomysial inflammation with invasion	CD8+T-cells; macrophage & Myeloid Dendritic Cells	No	Autoimmune disorder: SS, SLE, thrombocytopenia & sarcoidosis

Sporadic Inclusion Body Myositis Epidemiology

- IIM incidence 1-5/100,000
- IBM represents 16-30% of all IIM
- Symptom onset before age 60 in 18% to 20%
- IBM is the most frequent inflammatory myopathy in patients > 50 yrs old
- Age-adjusted (>50) prevalence > 3.5/100,000
- M/F = 2-3/1
- Sporadic

sIBM: Presentation

- Insidious onset with slow chronic progression
- Frequent diagnosis delay by mean of 5-8 yrs
- Proximal and distal weakness –Frequent falls & loss of dexterity
- Weakness is asymmetric in one third
- Atrophy of weak muscles especially late
- Dysphagia 40% earlier on, almost all later on
- Mild facial weakness
- Muscle stretch reflexes ↓ at the patella

sIBM: Laboratory Tests

- CK is NL or mildly increased 2 -10 x NL
- EMG/NCS:
  - irritative myopathy or “mixed pattern”
  - Mild distal sensory neuropathy in 30%
- 20% of IBM clinical phenotype mislabeled as PM due inflammation without vacuoles
- May need >1 biopsy to “prove” pathologically
- 30% of patients have large MUPs which can lead to misdiagnosis of ALS
- Highly specific antibody reaction to NT5C1A which is now commercially available

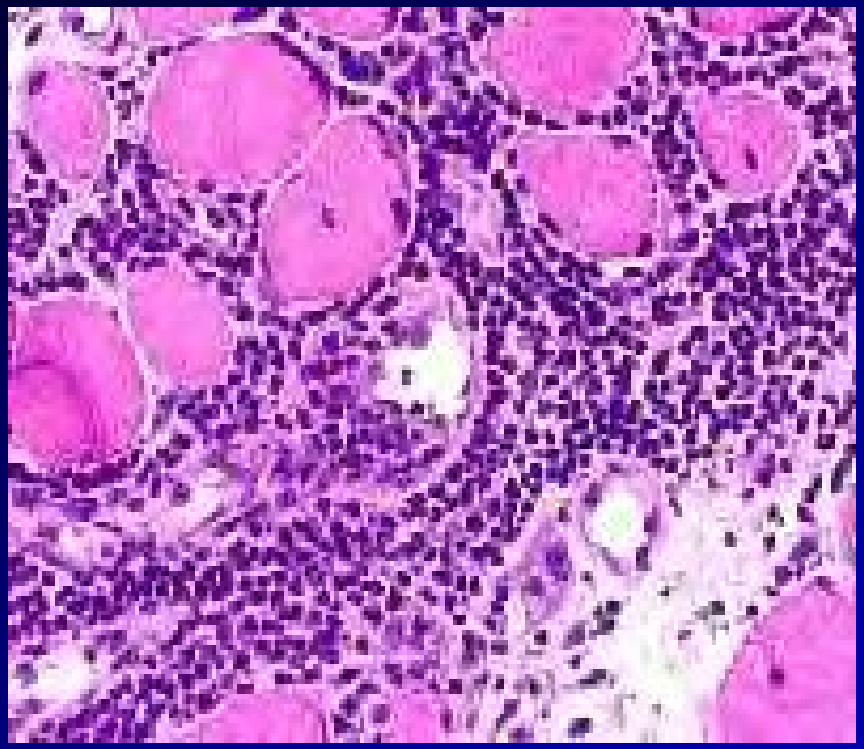
Chahin N 2008; Greenberg, 2013

Sporadic Inclusion Body Myositis Prognosis

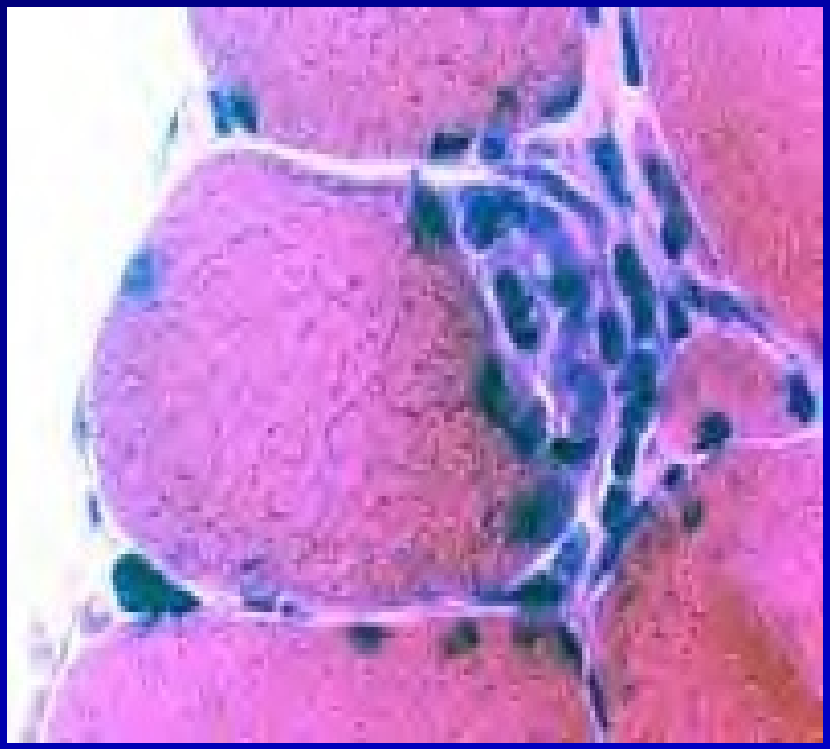
- Relentless progression
- Progression to disability more rapidly when symptoms begin > 60 years of age
- 10/14 patients with > 5 years symptoms required a cane or support for ambulation
- 3/5 patients with symptoms ≥ 10 years in wheelchairs
- No Rx at this time

Dalakas & Sekul 1993

Polymyositis



Endomysial Inflammation
CD8+ T cells Predominate



Focal Invasion by T cells

Polymyositis

- Cell-mediated autoimmune sporadic muscle disease
- Affects mainly adults over the age of 20
- IIM incidence 1/100,000
- PM represents 2% of all IIM (van der Meulen 2003)
- 63% of patients with PM pathology have clinical PM, 37% have IBM phenotype (Chahin 2008)
- Subacute to chronic onset of limb-girdle weakness –
- Neck flexors and pharyngeal muscles may be affected

PM - Laboratory Features

- Serum CK usually elevated 5-50 x LLN, aldolase increase
- May be associated with autoantibodies: Jo-1, PM-1 & SRP
- EMG/NCS: irritative myopathy as in DM and NM
- Muscle biopsy:
  - MHC expression on myocyte surface
  - Endomysial inflammation
  - APCs present Ag to naive CD8+ cells which mature to cytotoxic cells in an HLA-I/MHC restricted fashion
  - Surround & commonly (63%) invade non-necrotic fibers expressing MHC antigens
  - Necrosis, phagocytosis & regenerating myofibers
  - Granzyme, perforin and granulysin

Necrotizing Myopathy

- Immune-mediated myopathy vs. toxic
- Women/men = 3/1, onset age 30+
- Severe subacute progressive proximal weakness – **MP1**
- More rapid onset than PM & weakness severe in 1/3
- Triggers: drugs (**statins**, fibrates, zetia, cyclosporine, labetolol, EtOH, propofol), neoplasm, influenza or idiopathic
- More resistant to treatment than PM or DM especially when triggered by cancer or drug-induced
- SANAM – statin associated necrotizing autoimmune myopathy
  - weakness/increased CK, 2 months after stopping statins

NM: Laboratory Features

- CK is highly elevated 10 x or more
- MSA in 35%: HMGCoA, Jo1, SRP & Mi2
- EMG/NCS: irritative myopathy

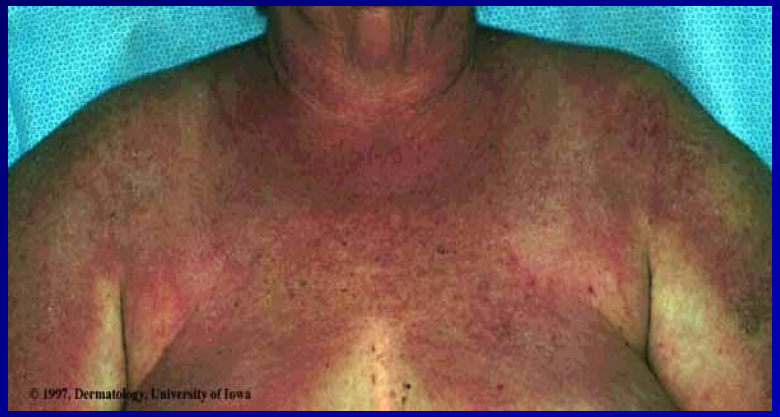
NM: Pathophysiology Update

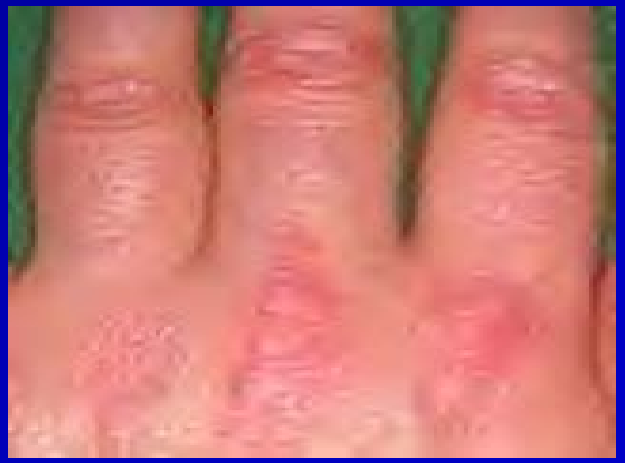
- Statins induce Ab to 200 & 100 kDa autoAg
- Statins up-regulate expression of HMGCR, the major target of autoantibodies in SANAM:
  - In vitro statin exposure of muscle cells induced expression of the 200/100 kDa autoantigens
  - HMGCR is the ~ 100 kDa autoantigen
- HMGCR Ab in 16/26 (63%) of NM cases
- High specificity approaching 100%
- 33% of antibody positive NM cases are statin-naïve!

Arthritis Rheum 2010;62(9):2757-66; Arthritis Rheum. 2011;63(3):713-21; Arthritis Care Res (Hoboken). 2012;64(2):269-72; Mamenn et al. Arthritis Rheum. 2010

Diagnosis of DM

- Proximal muscle weakness
- CK up to 30 times normal
- Irritative myopathy by EMG
- Associated myositis specific antibodies
- Skin changes





IIM
Dermatomyositis

- Complement-mediated autoimmune microangiopathy
- Affects both children and adults
- Subacute or chronic presentation
- May be associated with underlying malignancy
- Limb-girdle distribution of weakness with:
  - Erythema, scaling rash over malar area of face, extensor joints, MCP and IP joints (Gottrons papules)
  - Heliotrope rash, periorbital edema
  - Joint contractures
  - In children: calcinosis, vasculitis, “no” malignancy, remission

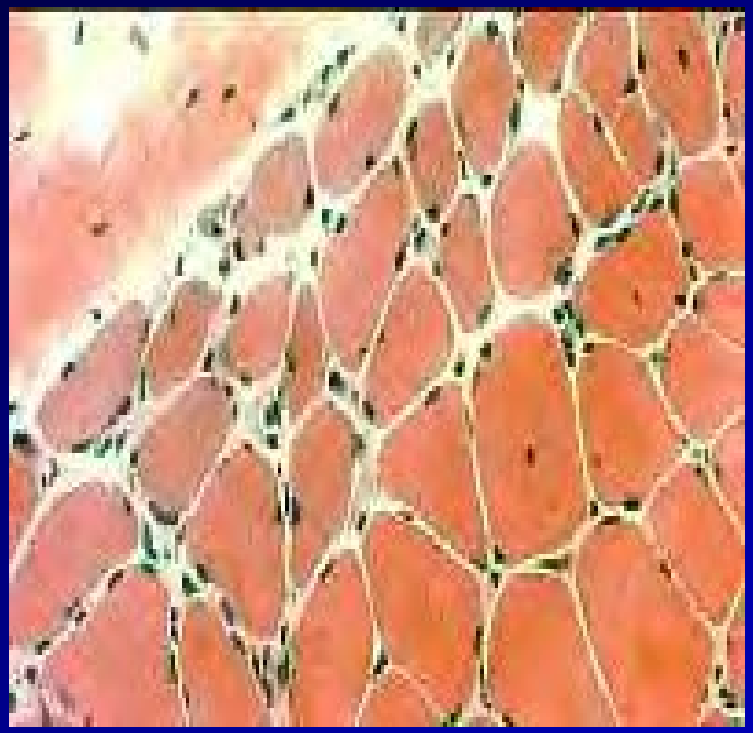
DM - Laboratory Features

- CK is usually elevated in 90% & up to 50 x ULN
- CK does not correlate with severity of weakness
- May be associated with autoantibody to Mi-2
- Anti-p155 in ¼ DM cases with cutaneous disease
- Most amyopathic DM have highly specific antibodies to the type I IF-inducible protein 1, IFIH1 Ab aka MDA-5
- FIH1 Ab predicts rapidly progressive ILD

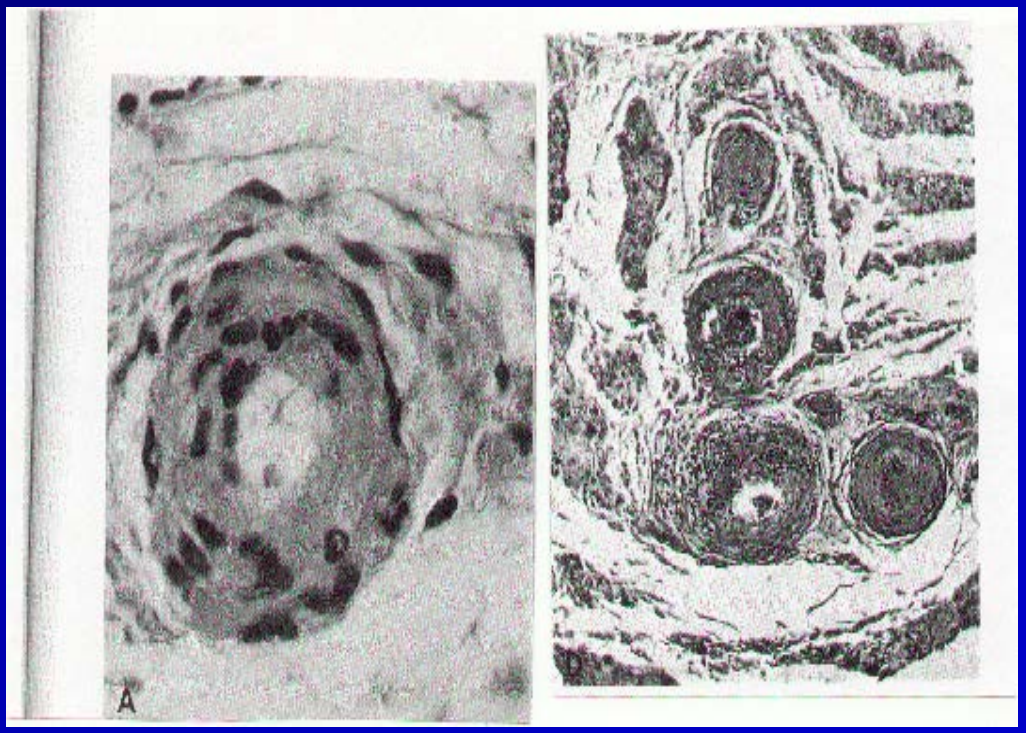
Gunawardena et al Rheum 2008
Sato et al Arth. Rheum 2009

Dermatomyositis: Muscle Biopsy

Perifascicular atrophy



B cell predominance in perivascular infiltrates perivascular deposits of IgM and complement



PM/DM/NM
Drug Therapy

- 1st Line
  - Prednisone
  - IV methylprednisolone
- 2nd Line
  - Methotrexate
  - Azathioprine*
  - IVIg*
  - Mycophenolate mofetil
- 3rd Line
  - Rituximab*(Oddis)
  - Cyclophosphamide
  - Etanercept* (Amato)
  - Tacrolimus (Oddis)
  - Cyclosporine
- 4th Line / Experimental
  - Chlorambucil
  - ? Infliximab
  - MEDI-545 completed
  - ?Tocilizumab

*RCT

Arthritis & Rheumatism 2012; Arthritis Care Res 2010;62(9):1328-34
MSG. Ann Neurol 2011;70(3):427-36