Neuroimmune Disorders
AKA
Neurologic manifestations of autoimmune diseases

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Objectives

• Review neurologic conditions that have an underlying autoimmune etiology
• Discuss initial diagnostic work-up to determine what could be causing the neurologic symptoms
• Review neurologic manifestations of specific autoimmune diseases that I care for
• Discuss briefly treatment of neurologic manifestations of specific autoimmune diseases
• Review briefly the most common autoimmune neurologic diseases (GBS, MS, MG)
Disclaimer

I am a rheumatologist not a neurologist or a magician so.....I will do my best and try to focus on a more primary care approach to these neurologic problems.
Immune-mediated neuropathies:

**Acute**

- Guillain-Barré syndrome (GBS)-is an acute monophasic illness resulting from an immune response to a preceding infection that cross-reacts with peripheral nerve components because of molecular mimicry. The immune response can be directed towards the myelin or the axon of peripheral nerve, resulting in demyelinating and axonal forms of GBS.

**Chronic**

1. Multiple Sclerosis
2. Myasthenia gravis
3. Chronic inflammatory demyelinating polyneuropathy (CIDP) (prototype)
4. Multifocal motor neuropathy (MMN)
5. POEMS syndrome (osteosclerotic myeloma: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes)
6. Anti-myelin associated glycoprotein (MAG)-related neuropathies

Note: # 4,5 & 6 are distinct from classic CIDP on the basis of clinical, electrodiagnostic, and therapeutic differences.
What did I get myself into?
Other possible neuroimmune syndromes

Those w/ likely or possible immune mediated mechanism

- Classic, idiopathic CIDP
- Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) or Lewis–Sumner syndrome
- Chronic immune sensory polyradiculopathy (CISP)
- Sensory-predominant CIDP
- Distal acquired demyelinating symmetric (DADS) neuropathy
- Demyelinating neuropathy with central nervous system demyelination
- Gait ataxia with late onset polyneuropathy (GALOP) syndrome
- Multifocal motor neuropathy
- Neuromyelitis Optica (mixed axonal and demyelinating)

Systemic disorders that may be associated w/ neuroimmune Dx

- Monoclonal gammopathy of undetermined significance (MGUS)
- Multiple myeloma
- Waldenstrom macroglobulinemia
- Mixed cryoglobulinemia
- Systemic disorders (eg, diabetes mellitus, thyrotoxicosis, neoplasms, SLE, RA, Sjogren’s, systemic vasculitides,
So where to begin?
Presenting symptoms (Important but poor diagnostic accuracy)

<table>
<thead>
<tr>
<th>Sensory</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness/tingling</td>
<td>Weakness</td>
</tr>
<tr>
<td>Burning</td>
<td>– Symmetric vs asymmetric</td>
</tr>
<tr>
<td>Ants crawling</td>
<td>– Proximal vs distal</td>
</tr>
<tr>
<td>Pain/Lancinating</td>
<td>Balance</td>
</tr>
</tbody>
</table>

Dysautonomia
Respiratory
Ophthalmoplegia
Bulbar

Physical Exam Findings-
Better predictor than Symptoms (especially if > 1 abnormality)

**Sensory exam**
- Distal sensation
- Pin Prick / Light touch/Temp
- Vibratory
- Position
- DTRs/Babinski

**Motor Exam**
- Strength
- Atrophy?
- Fasciculations?

**Autonomic**
- Postural hypotension
- Impotence
- Bladder dysfunction

Mendell JR, Sahenk Z, NEJM, 2003;348:1243
Rutkove SB Up to Date, Sept 2016, Shefner JM ed.
Electro-diagnostic Testing
EMG/NCS

Axonal Disorders
Demyelinating

Radicular, denervation/reinnervation, Neuromuscular Junction

Labs - Ideally should be based on Electro-diagnostic testing

Other: CSF, Imaging, Genetics, Tissue biopsy

Diagnostic approach to polyneuropathy from Up to Date Sept 2016

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Extensive diagnostic testing is probably not necessary in a patient with mild symptoms who has a known underlying cause of neuropathy (e.g., diabetes mellitus, alcohol abuse, or chemotherapy). However, a diagnostic evaluation is warranted in patients with no clear etiology or in whom symptoms are severe or rapidly progressive. In addition, a full diagnostic evaluation should be pursued in patients with atypical features, including asymmetry, non-length dependence, motor predominance, acute onset, or prominent autonomic involvement.

Abs: antibodies; ANA: antinuclear antibodies; CIDP: chronic inflammatory demyelinating polyneuropathy; EMG: electromyography; HIV: human immunodeficiency virus; SPEP: serum protein electrophoresis; IVIG: intravenous immune globulin; RPR: rapid plasma reagin; SPEP: serum protein electrophoresis; TSH: thyroid stimulating hormone; UPEP: urine protein electrophoresis; VDRL: venereal disease research laboratory.

* Including sympathetic skin response, Valsalva maneuver.
$ In patients with borderline normal serum B12.
Polyneuropathy

**Axonal**
- Axonal neuropathies cause symptoms and signs related to axon loss:
- Sensory, some weakness, pain
  - DM, HIV, Uremia, Vitamin Deficiency, alcohol, chemotherapy, most common chronic problems
  - Toxin, Porphyria often more fulminant and may be painful
  - Type of acute GBS

**Demyelinating**
- Most Autoimmune neuropathies are predominantly demyelinating -Humoral and cell Mediated- which damage myelin & or myelin producing Schwann cells.
  - Weakness, sometimes sensory loss, reduced vibratory & proprioception more than pinprick & temp.

**Neuromuscular Junction** - Myesthenia

Rutkove SB, Overview of Polyneuropathy, Up to date, Sept 2016, Shefner JM, Ed.
Lang D, Robinson-Papp J, Immune mediated neuropathies, Up to Date, Sept 2016, Shefner JM, Ed.
**What diagnostic labs should be done**

* tests with highest yield

<table>
<thead>
<tr>
<th>Predominantly Axonal</th>
<th>Predominantly Demyelinating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose, HGA1C *</td>
<td>SPEP/UPEP*</td>
</tr>
<tr>
<td>SPEP/UPEP *</td>
<td>Immunoelectrophoresis</td>
</tr>
<tr>
<td>Vitamin B12*</td>
<td>Hepatitis B &amp;C</td>
</tr>
<tr>
<td>ESR/CRP</td>
<td>Spinal tap</td>
</tr>
<tr>
<td>RPR</td>
<td>If clinical suspicion then:</td>
</tr>
<tr>
<td>ANA- caution</td>
<td>– Antimyelin associated glycoprotein (MAG if mainly sensory sx), AntiGM1 (if mainly motor sx), HIV, genetic testing if ? Charco-Marie-Tooth Dx, Aquaporin-4 (AQP4-IgG - NMO),</td>
</tr>
<tr>
<td>If clinical suspicion then:</td>
<td></td>
</tr>
<tr>
<td>– HIV, Heavy metals, RF, Sjogren’s SSA/SSB, Vit B1, Lyme, Hepatitis, Methylmalonic acid and homocystein levels *, urine/blood porphyrins</td>
<td></td>
</tr>
<tr>
<td>– I add ANCA, CPK/Aldolase if weakness</td>
<td></td>
</tr>
</tbody>
</table>

Acetylcholine Receptor (AChR) and Muscle-Specific receptor Tyrosine Kinase (MuSK)

Dale Lange, MD, Jessica Robinson-Papp, MD Immune-mediated neuropathies, Up to Date Sept 2016 updated, Ed : Jeremy M Shefner, MD, PhD
Bird SJ, Clinical manifestations of Myasthenia gravis, Up to Date Sept 2016
Anti-Nuclear Antibody -ANA

• Screening ANA- high rate of false + (5-30% or more depending on age). If one assumes that the prevalence of ANA-associated diseases in the population is 1 percent, the majority of these patients will have a false positive result.

• Order if pretest probability high

• MUST ORDER A TITER- not just a screen. If screen is + must f/u with a titer and should be >1:40 to be considered significant

## Conditions where ANA can be +

### Systemic Auto-immune
- SLE: 98-100%
- Scleroderma: 95%
- MCTD: 100%
- Drug Induced: 80-95%
- Sjogren’s: 60-90%
- Rheumatoid Arthritis: 45%
- Raynauds: 40%
- Polymyositis/DM: 35%
- Juvenile Idiopathic arthritis (JIA): 15-40%

### Organ Specific Autoimmune
- Hashimotos Thyroiditis: 50%
- Graves’ Disease: 50%
- Autoimmune Hepatitis: 70%
- Primary Biliary Cirrhosis: 50-70%

### Other diseases:
- Infections: EBV, HIV, Parvovirus 19
- Bacterial: SBE, Syphilis
- Malignancies: Lymphoproliferative, paraneoplastic syndromes
- Inflammatory Bowel Disease
- Interstitial Pulmonary Fibrosis

Block DB, Up to date, Sept 2016, Ed: Schmerling RH
Follow-up Auto-Antibodies if ANA is > 1:40

- Anti-dsDNA antibodies: caution also high false + rate recently. Level > 20 likely significant.
- Anti-Smith antibodies
- Anti-RNP
- Anti-Histone (if concern for drug induced lupus)
- Antineuronal antibodies if neurologic symptoms
- Antiphospholipid antibodies-clotting/stroke
- Anti-ribosomal P antibodies (lupus psychosis and depression)
- Others: anti-neurofilament, GFAP, endothelial cell, lymphocytotoxic, anti-SSA/SSB, anti 50 kDA (seizures) N-Methyl-D-Aspartate
- C3,C4, CBC w/ diff, Plts, renal, Urinalysis, LFTs

Schur, PH Neurologic Manifestations of SLE, Up to date, Sept 2016
# Neuropsychiatric Manifestations of SLE

## Central
- Cognitive dysfunction \(20-80\%\)
- Cerebrovascular disease \(19+\%\)
- Seizure disorder \(10-20\%\)
- HA-migrain 31%, tension 23.5%
- Lupus Cerebritis
- Aseptic Meningitis
- Demyelinating syndrome
- Movement disorder
- Myelopathy/transverse myelitis
- Acute Confusional state
- Mood disorder-Psychosis

## Peripheral
- Guillain-Barre syndrome
- Autonomic Neuropathy
- Mononeuropathy
- Myasthenia Gravis
- Cranial Neuropathy
- Plexopathy
- Polyneuropathy \(10-15\%\)

ACR nomenclature & case definitions for neuropsychiatric SLE, Arthritis & Rheum 1999;42:599
Schur P Up to Date Sept 2016, Florica B et al. Semin Arth & Rheum 2011;41:203
Pathophysiology of neurologic manifestations in SLE

- Vasculopathy
- Clotting disorders
- Autoantibodies
- Secondary factors
  - Infections associated w/ immunosuppression
  - Metabolic complications of other organ failures (eg. Uremia)
  - HTN
  - Toxic effects of therapy (eg. Corticosteroids, Plaquenil)
- Other factors: cytokines, chemokines, neuropeptides, oxidative stress, nitric oxide, interference w/ neurotransmission.
Pathophysiology of neurologic manifestations in SLE

- **Vasculopathy** - not vasculitis- thought to cause direct injury to blood brain barrier thereby allowing antibodies to enter the nervous system.
- Small to moderate perivascular accumulation of mononuclear cells w/o fibrinoid necrosis of vessel
- Possible small infarcts due to luminal occlusion
- Antiphospholipid antibodies may play a role
- Accelerated atherosclerosis may play a role

Treatment for the most common neurologic manifestation of SLE

- **Cognitive**
- **Stroke Syndromes**
  - If aPL then anticoagulation (if no stroke then just ASA 81mg)
  - If HTN control BP
  - If atherosclerotic disease- Tx appropriately and limit steroids if possible
- **Seizures**- antiepileptic medication, new onset seizures possible steroids short course 1mg/kg and one study cyclophosphamide and methylprenisolone IV
- **Headache**- no difference from non-SLE pt
- **Peripheral neuropathy**- predinsone 30-60mg/d to start, possible IVIG if GBS, other immune suppression if severe
Neurologic manifestations of RA

Central Nervous System

• Cervical Myelopathy
• CNS Vasculitis
• Rheumatoid nodules in CNS
• Meningitis
• Progressive multifocal leukoencephalopathy (JC virus)
• Hyperviscosity Syndrome
• Stroke (OR 1.64 CI 1.16-2.3)

Peripheral Nervous System

• Compression or Entrapment
  – Carpal tunnel
  – Tarsal tunnel
• Non-compression neuropathies
  – Distal Sensory Neuropathy
  – Combined Sensorimotor Neuropathy

Neuromuscular Disorders

-Myopathy (disuse, steroid induced)
-Myositis
-Amyloid

Solomon DH et al, Ann Rheum Dis, 2006;65:1608; Piecyk ML & Schur PH, Up to Date, Sept 2016
Anterior subluxation of C1 on C2 in RA

*Non-forced* flexion/extension

Magnified view 12 mm separation

Nakano KK et al. Ann Neurol 1978;3:144; Schur PH & Currier BL, Up to Date 2016
Anterior subluxation C1 on C2 w/ pannus causing impingement of cord

Schur PH & Currier BL, Up to Date 2016
Combined Sensorimotor Neuropathy in RA

• Long standing, Seropositive RA
• Nodules
• Male > female
• Other extra-articular involvement
• Signs of vasculitis
  – Palpable purpura
  – Livido reticularis
  – Nailfold and digital infarcts
  – Skin ulcerations
• Acute, painful paresthesias, weakness (wrist/foot drop)
Combined Sensorimotor Neuropathy in RA

More severe, presents more acutely
EMG/NCS – can be axonal or severe demyelinating
Sural Nerve Biopsy- Nerve damage due to acute necrotizing arteritis
Treatment- Aggressive immune suppression- steroids, Cytoxan, Rituxan if + ANCA
Neurologic manifestations of Sjögren's Syndrome

- **Mild Inflammatory Myopathy (2.5-47%)**
  - Rare inclusion body
  - If aggressive myositis may be overlap syndrome

- **Peripheral neuropathies (2-25%)**
  - May precede diagnosis of SS
  - Axonal sensory and sensorimotor- may be painful, small or large fiber neuropathy
  - Sensory ataxic neuropathy (< 5%)
  - Pure sensory trigeminal neuropathy, axonal
  - Mononeuritis multiplex, suggestive of vasculitis, axonal and perivascular inflammation on biopsy
  - Multiple cranial neuropathies: Bell’s Palsy most common, VIII, III, IV, VI

- **Rare:** Radiculoneuropathy, Autonomic neuropathy

- **CNS involvement- variable:** diffuse, focal or multifocal recurrent episodes, disease free periods, NMO, cognitive issues
Neurologic Manifestations of Various Vasculitis Syndromes

Neurologic Manifestations of Various Vasculitis Syndromes

• Large Vessel
  – Headache, Stroke, amaurosis fugax- GCA
  – Claudication-Takayasu/s

• Medium vessel
  – Mononeuritis multiplex
  – Sensory neuropathy
  – Cranial neuropathy
  – CNS
  – External ophthalmoplegias and sensory neural hearing loss

• Small Vessel
  – Clinically significant neuropathy uncommon
  – Mainly sensory neuropathy
No talk on autoimmune neurologic conditions would be complete without:

- Guillain Barre Syndrome
- Multiple Sclerosis
- Myasthenia Gravis
Multiple Sclerosis

- Most common immune-mediated inflammatory demyelinating disease of the CNS
- No clinical features unique to MS, but some more suggestive
  - Relapses & Remissions
  - Onset between 15-50 years
  - Subacute motor symptoms
  - Optic neuritis
  - Lhermitte's sign - a sudden electric shock like sensation that travels from your neck to your spine. Can be seen in other conditions
  - Internuclear ophthalmoplegia - characterized by total or partial failure to adduct one eye in lateral gaze and a monocular nystagmus of the abducting eye. It may be unilateral and bilateral
  - Sensory changes in limbs

Olek MJ Clinical course and classification of multiple sclerosis, Up to Date sept 2016
## Suggestive and atypical features of multiple sclerosis

<table>
<thead>
<tr>
<th>Features suggestive of multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapses and remissions</td>
</tr>
<tr>
<td>Onset between ages 15 and 50 years</td>
</tr>
<tr>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Lhermitte sign</td>
</tr>
<tr>
<td>Internuclear ophthalmoplegia</td>
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<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Heat sensitivity (Uhthoff phenomenon)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Features atypical for multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady progression</td>
</tr>
<tr>
<td>Onset before age 10 or after age 50 years</td>
</tr>
<tr>
<td>Cortical deficits such as aphasia, apraxia, alexia, or neglect</td>
</tr>
<tr>
<td>Rigidity or sustained dystonia</td>
</tr>
<tr>
<td>Convulsions</td>
</tr>
<tr>
<td>Early dementia</td>
</tr>
<tr>
<td>Deficit developing within minutes</td>
</tr>
</tbody>
</table>
Diagnosis of MS

- Predominantly Clinical
- Demonstration of CNS lesions dissemination in time and space
- MRI
- CSF
- Other
Ancillary testing in multiple sclerosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Percent abnormal in patients with multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual evoked responses</td>
<td>50 to 90</td>
</tr>
<tr>
<td>Brainstem auditory evoked responses</td>
<td>20 to 55</td>
</tr>
<tr>
<td>Somatosensory evoked potentials</td>
<td>50</td>
</tr>
<tr>
<td>Cerebrospinal fluid oligoclonal banding</td>
<td>85 to 95</td>
</tr>
<tr>
<td>Cerebrospinal fluid IgG index</td>
<td>75</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>70 to 95</td>
</tr>
</tbody>
</table>

Data from:
Treatment of MS

- Refer to Neurology
- Up to Date has nice Algorithm
- Glucocorticoids for acute attacks 3-7 day courses 500-1,000 methylpred
- Immune suppressing/disease modifying
  - Interferon beta-1a-Avonex
  - Interferon beta-1b-Betaferon
  - Glatiramer - induce and activate T lymphocyte suppressor cells specific for myelin antigens. It is a mixture of random polymers similar to myelin basic protein.
  - Activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway - monomethyl fumerate
  - Monoclonal antibody against the alpha-4 subunit of integrin molecules, limits adhesion and transmigration of leukocytes-Natalizumab
  - Alemtuzumab - binds to CD 52 – immunomodulatory on some lymphocytes
  - Teriflunomide - an immunomodulatory agent inhibiting pyrimidine synthesis - antifnflamamtory and ant proliferative effects
  - Fingolimod - phosphate - binds to sphingosine 1 phosphate receptors and blocks lymphocytes ability to emerge from lymph nodes - CNS lymphocytes decrease

Sominanda A et al, Mult Scler, 2007;13:208, Package inserts, Olek MJ Up to date
Myasthenia Gravis

• The most common disorder of neuromuscular transmission
• Autoimmune disorder
• Hallmark is fluctuating weakness in ocular, bulbar, limb and respiratory muscles in varying degrees and combinations
• Weakness is the result of an antibody-mediated, T cell dependent immunological attack directed at the proteins in the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors & or receptor associated proteins)
Myasthenia Gravis Clinical Forms

- Ocular Myasthenia- weakness limited to eye lids and extra-ocular muscles (ptosis, diplopia >50%)
- Generalized- weakness ocular muscles but also combination of bulbar (15%), limb (<5%) and respiratory
- Specific muscle weakness and not generalized fatigue
Myasthenia Gravis - Diagnosis

• Refer to Neurologist
• Bedside Edrophonium (Tensilon) Test and ice pack test (bad of ice on closed lid for 2 minutes then ptosis re-evaluated – sensitivity 80%)
• Serologic
  – Acetylcholine receptor antibody (AChR-Ab)
    • 90% generalized form
    • 50% ocular form
  – Muscle specific tyrosine kinase antibody (MuSK-Ab)
    • 38-50% generalized MG w/ negative AChR-Ab
• Electrophysiologic (repetitive nerve stimulation study and single fiber EMG)

Bird SJ Diagnosis of Myasthenia gravis, Up to Date, Sept 2016
Myasthenia Gravis-Treatment

• Symptomatic- Anticholinesterase agents
  – Pyridostigmine bromide (Mestinon)

• Chronic Immunomodulating
  – Glucocorticoids
  – Other immunomodulating

• Rapid Immunomodulating
  – Plasmapheresis
  – IVIG

• Surgical-Thyroidectomy

Bird SJ, Treatment of myasthenia gravis, Up to Date, sept 2016
Guillain-Barré syndrome (GBS)

Etiologies

- Campylobacter jejuni infection is the most commonly identified precipitant of GBS.
- Cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus (HIV) infection have also been associated with GBS.
- A small percentage of patients develop GBS after another triggering event: immunization, surgery, trauma, and bone-marrow transplantation.

Types of Acute GBS

- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) (most common in NA, Europe)
- Acute motor axonal neuropathy (AMAN) (Japan and China)
- Acute motor and sensory axonal neuropathy (AMSAN)
- Miller Fisher syndrome (MFS) - ophthalmoplegia with ataxia and areflexia
The cardinal clinical features of GBS

- Progressive, mostly symmetric muscle weakness and absent or depressed deep tendon reflexes.
- The weakness can vary from mild to severe, with nearly complete paralysis of all extremity, facial, respiratory, and bulbar muscles.
- Severe respiratory muscle weakness necessitating ventilatory support develops in about 30 percent, and dysautonomia occurs in 70 percent of patients.
- GBS usually progresses over a period of about two weeks.
Clinical Findings predictive of Respiratory Failure in GBS

French prospective study 722 patients w GBS not ventilated on admission but needed in 313

- Time of onset to admission < 7 days
- Inability to cough
- Inability to stand
- Inability to lift eyebrows
- Inability to lift head
- Elevated liver enzymes
- Abnormal PFts
  - FVC < 20mL/kg
  - Max inspiratory pressure < 30 cmH2O
  - Max expiratory pressure < 40 cm H2O

Sharshar et al. Crit Care Med 2003;31:278; Vriesendorp FJ Up to Date, Sept 2016
Diagnosis of GBS

• **Clinical presentation** – index of suspicion

• Dx confirmed by **cerebrospinal fluid (CSF) analysis** –
  – An increased cerebrospinal fluid (CSF) protein with a normal CSF white blood cell count, called albuminocytologic dissociation
  – Found in 50 to 66 percent of patients with GBS in the first week after the onset of symptoms and in ≥75 percent of patients in the third week.

• **Neurophysiology studies / Electrodiagnostic studies help determine type**
  – Acute polyneuropathy with either predominantly demyelinating (ie, AIDP)
  – Axonal (ie, AMAN or AMSAN) features.
  – Testing for serum IgG antibodies to GQ1b is useful for the diagnosis of Miller Fisher syndrome.
Guillain-Barré syndrome-Treatment

• Plasma Exchange or IVIG hastens recovery
  – Equivalent effects
  – Combination not beneficial
  – Plasma exchange for non-ambulatory adults who start treatment in 4 weeks or ambulatory starting in 2 weeks
  – IVIG recommended for non-ambulatory adults within 2-4 weeks

• Glucocorticoids not recommended

• Supportive Care (30% develop respiratory failure)

Patwa HS et al. Guidelines from American Academy of Neurology Neurology 2012;78:1009
Hughes RA et al, Neurology 2003;61:736; Vriesendorp FJ Up to Date, Sept 2016, Shefner JM Ed.
Summary

- Neuroimmune disorders or Neurologic manifestations of Autoimmune diseases is **not for the faint of heart**
- Basic good clinical practice will guide most evaluation and treatment/referral decisions ie- a good Hx and Px
- Consider EMG/NCS before labs testing (although I am not certain how cost effective that is. I usually do basics)
  - At least glucose, HGA1C, Vitamin B12, Homocysteine and methylmeonic acid, SPEP/UPEP, basic chem and CBC panel and would get UA to check for protein
  - ANA w/ caution, ANCA, Hep B& C, cryoglobulins, C3,C4 and CRP/ESR if suspect vasculitis (If obese ESR and CRP less reliable)
  - Other: based on clinical suspicion (HIV, RPR, Heavy metals. Ro/La)
- Neurology referral – pick up to phone or admit if concern