

Neuroimmune Disorders

AKA

Neurologic manifestations of autoimmune diseases

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Objectives

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

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)

Sensory

- Numbness/tingling
- Burning
- Ants crawling
- Pain/Lancinating
- Tightness

Motor

- Weakness
 - Symetric vs asymetric
 - Proximal vs distal
- Balance

Dysautonomia

Respiratory

Ophthalmoplegia

Bulbar

Callaghan B et al, Review JAMA 2015;314:2172; England JD et al, Neurology 2005;64:199; Neurology 2009;72:186; England JD, Asbury AK Lancet 2004;363:2151; Rutkove SB, Overview of polyneuropathy, Up to date Sept 2016, Shefner JM Ed.

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.

Diagnostic approach to polyneuropathy from Up to Date Sept 2016

Symptoms suggestive of Polyneuropathy

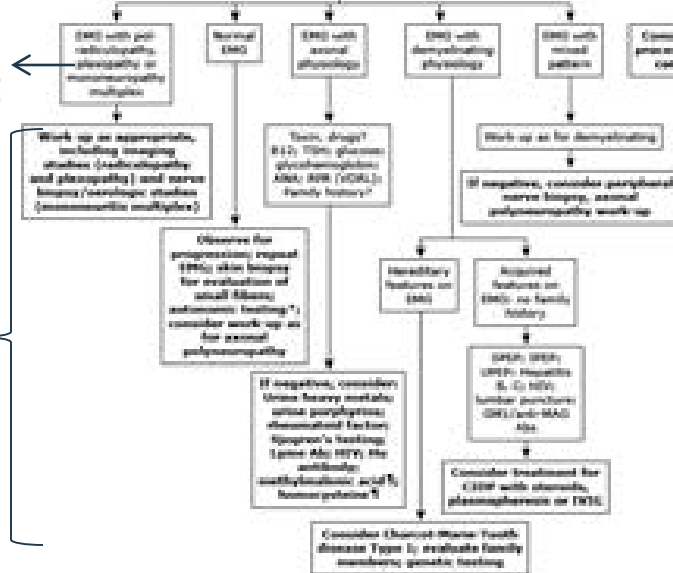
Hyporeflexia, sensory loss, atrophy or weakness

Hyperreflexia, increased tone

EMG/ NCS results

Consider central or spinal cord process

Suggested work-up based on EMG/NCS



**Rutkove SB,
Overview of
polyneuropathy,
Up to date Sept
2016, Shefner JM
Ed**

Extensive diagnostic testing is probably not necessary in a patient with mild symptoms who has a known underlying cause of neuropathy (eg, 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.

Ab: antibodies; ANA: antinuclear antibodies; CIDP: chronic inflammatory demyelinating polyneuropathy; EMG: electromyography; HIV: human immunodeficiency virus; IEP: immunoglobulin protein electrophoresis; IVIG: intravenous immune globulin; AHA: rapid plasma regain; SIEP: serum protein electrophoresis; TSH: thyroid stimulating hormone; UPEP: urine protein electrophoresis; VHL: von Recklinghausen's disease research laboratory.

* Including sympathetic skin response, TR, T4, B4 interval testing, valsalva maneuver.

† In patients with borderline-normal serum B12.

UpToDate®

Electro-diagnostic Testing-EMG/NCS

Gold standard

Axonal Disorders

Demyelinating

Radicular, Denervation/ Reinnervation, Neuromuscular Junction

Labs- Ideally should be based on Electro-diagnostic testing

Other: CSF, Imaging, Genetics, Tissue biopsy, angiogram

Callaghan B et al, Review JAMA 2015;314:2172; England JD et al, Neurology 2005;64:199; Neurology 2009;72:186; England JD, Asbury AK Lancet 2004;363:2151; Rutkove SB, Overview of polyneuropathy, Up to date Sept 2016, Shefner JM Ed **Great Algorithm.**

Polyneuropathy

Axonal

- Axonal neuropathies cause symptoms and signs related to axon loss:
- Sensory, some weakness, pain
 - Most common chronic problems: DM, HIV, Uremia, Vitamin Deficiency, alcohol, chemotherapy, 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

Handout from Up to date and data from Fauci AS et al, Harrison's Principles of internal Medicine 14th ed, 1998, page 2460

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

Predominantly Axonal

- Serum Glucose, HGA1C *
- SPEP/UPEP *
- Vitamin B12*
- Methylmalonic acid and homocystein levels *
- ESR/CRP
- RPR
- **ANA- caution**
- If clinical suspicion then:
 - HIV, Heavy metals, RF, Sjogren's SSA/SSB, Vit B1, Lyme, Hepatitis B & C, urine/blood porphyrins

Predominantly Demyelinating

- SPEP/UPEP*
- Immuno-electrophoresis
- Hepatitis B & C
- Spinal tap
- I add ANCA, CPK/Aldolase if weakness, cryoglobulins
- If clinical suspicion then:
 - 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),

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

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 Arth. 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- Viral: EBV, HIV, Parvovirus 19

Bacterial SBE, Syphilis

Malignancies: Lymphoproliferative,
paraneoplastic syndromes

Inflammatory bowel Ds

Interstitial Pulmonary Fibrosis

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-chromatin (nucleosome), 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

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%

Pathophysiology of neurologic manifestations in SLE

- Vasculopathy- not vasculitis
- 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/ neuro-transmission.

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**- Rx SLE, mild immune suppression, low dose steroids, Plaquenil
 - Make certain not just fibromyalgia and mild lupus causing problem
- **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 methylprednisolone IV
- **Headache**- no difference from non-SLE pt
- **Peripheral neuropathy**- prednisone 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

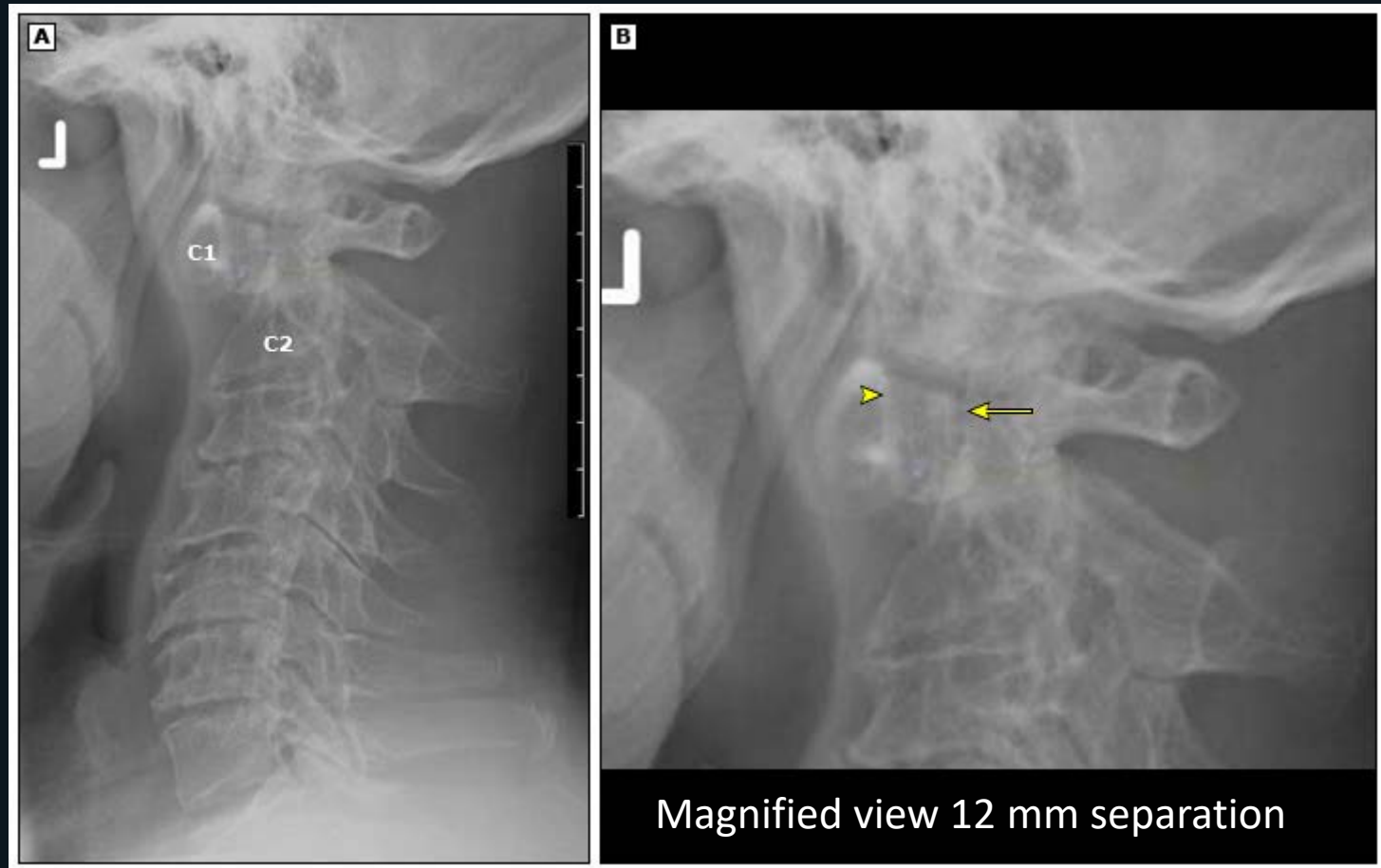
- Myopathy (disuse, steroid induced)
- Myositis
- Amyloid

Chang DJ & Paget SA, Rheum Dis Clin North Am, 1993;19:955

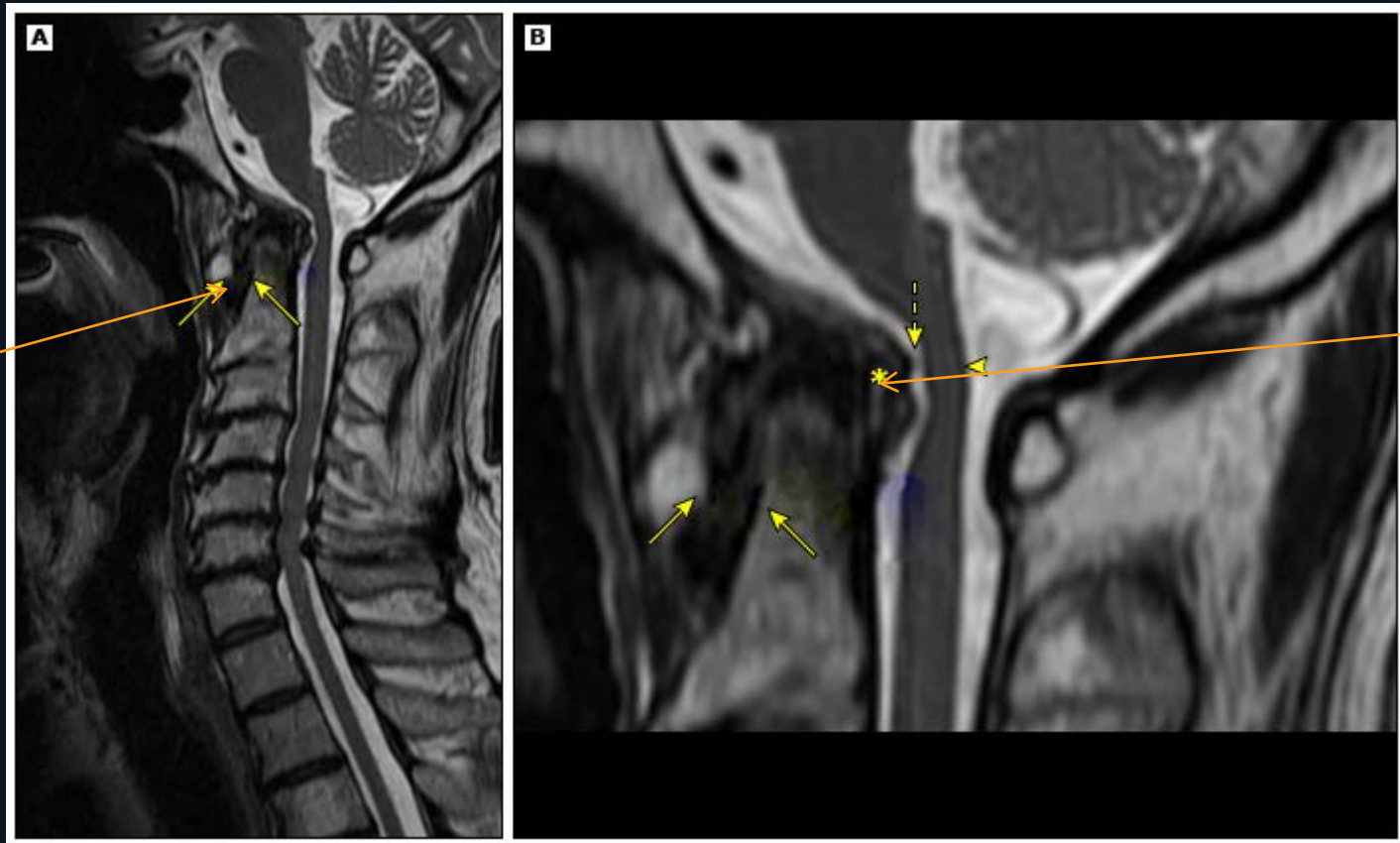
Solomon DH et al, Ann Rheum Dis, 2006;65:1608; Piecyk ML & Schur PH, Up to Date, Sept 2016

Anterior subluxation of C1 on C2 in RA

Non-forced flexion/extension



Anterior subluxation C1 on C2 w/ pannus causing impingement of cord



Combined Sensorimotor Neuropathy in RA

Very Serious

- 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 paresthesia, weakness (wrist/foot drop)

Combined Sensorimotor Neuropathy in RA



More severe, presents more acutely

EMG/NCS – can be axonal or severe demyelinating

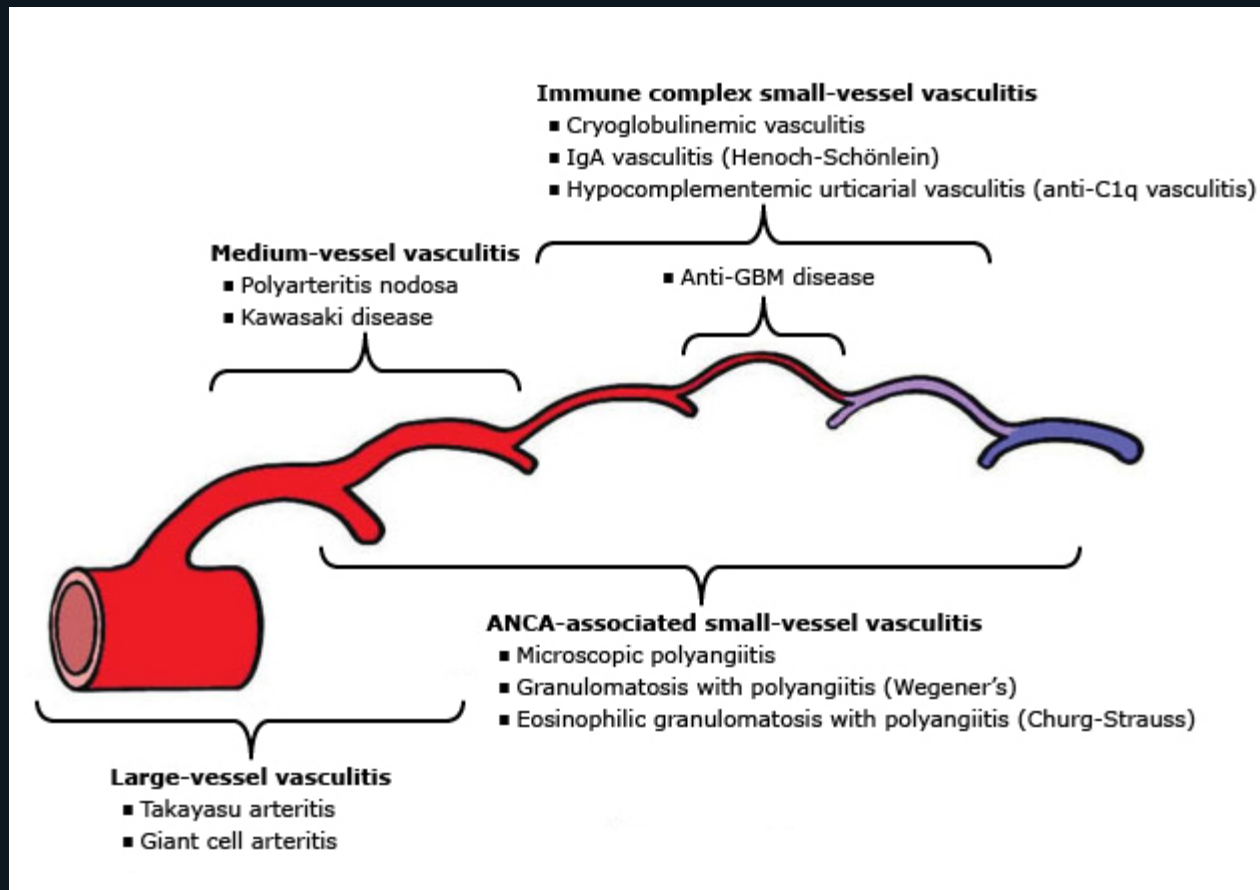
Sural Nerve Biopsy- Nerve damage due to acute necrotizing arteritis

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



Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65:1. Reproduced with permission from John Wiley & Sons, Inc. Copyright © 2013 by the American College of Rheumatology, Up to Date, Google Images

Neurologic Manifestations of Various Vasculitis Syndromes

- **Large Vessel**
 - Headache, Stroke, amaurosis fugax- GCA, PMR
 - 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

Myositis/Dermatomyositis

- Myopathy not neuropathy
- Proximal muscle weakness, not pain
- CPK/Aldolase elevated, ESR & CRP usually elevated
- MRI classic findings (Myositis Protocol)
- NCS/EMG classic findings
- Muscle biopsy gold standard
- If skin changes consider malignancy w/u
- Rx steroids and immune suppression

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
- If on TNF inhibitors and new neurologic sx could be MS related to med

Suggestive and atypical features of multiple sclerosis

Features suggestive of multiple sclerosis
Relapses and remissions
Onset between ages 15 and 50 years
Optic neuritis
Lhermitte sign
Internuclear ophthalmoplegia
Fatigue
Heat sensitivity (Uhthoff phenomenon)

Features atypical for multiple sclerosis
Steady progression
Onset before age 10 or after age 50 years
Cortical deficits such as aphasia, apraxia, alexia, or neglect
Rigidity or sustained dystonia
Convulsions
Early dementia
Deficit developing within minutes

Diagnosis of MS

- Predominantly Clinical
- McDonald Criteria: Demonstration of CNS lesions dissemination in time and space
- MRI changes
 - **Dissemination in space** is demonstrated -one or more T2 lesions in at least **two of four** MS-typical regions of the central nervous system (**periventricular, juxtacortical, infratentorial, or spinal cord**) or by the development of a further clinical attack implicating a different central nervous system site.
 - Brainstem or spinal cord syndromes, symptomatic MRI lesions are excluded from the criteria and do not contribute to lesion count.
 - **Dissemination in time** :simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time, or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan, or by the development of a second clinical attack.
- CSF
- Other

Need neurology evaluation

Olek MJ, Up to Dat Sept 2016

Ancillary testing in multiple sclerosis

Test	Percent abnormal in patients with multiple sclerosis
Visual evoked responses	50 to 90
Brainstem auditory evoked responses	20 to 55
Somatosensory evoked potentials	50
Cerebrospinal fluid oligoclonal banding	85 to 95
Cerebrospinal fluid IgG index	75
Brain MRI	70 to 95

Data from:

1. Giesser BS. *Diagnosis of multiple sclerosis. Neurol Clin* 2011; 29:381.
2. Dobson R, Ramagopalan S, Davis A, Giovannoni G. *Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. J Neurol Neurosurg Psychiatry* 2013; 84:909.

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 fumarate
 - 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 - >>antiflamamtory and ant proliferative effects
 - Fingolimod-phosphate-binds to sphingosine 1 phosphate receptors and blocks lymphocytes ability to emerge from lymph nodes- CNS lymphocytes decrease

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)

Myasthenia Gravis-Treatment

- Symptomatic- Anticholinesterase agents
 - Pyridostigmine bromide (Mestinon)
- Chronic Immunomodulating
 - Glucocorticoids
 - Other immunomodulating
- Rapid Immunomodulating
 - Plasmapheresis
 - IVIG
- Surgical-Thyroidectomy

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

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)

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 labs)
 - At least glucose, HGA1C, Vitamin B12, Homocysteine and methylmalonic 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

TGIO



Almost.....
Questions?