Inflammatory Demyelinating Diseases

- **Devic's Disease aka Neuro Myelitis Optica**
  - Originally believed to be a variant of MS but MS drugs don't work so now considered its own entity
  - S/S: aggressive monophasic OR relapsing/remitting dz of upper spinal cord and optic nerve ONLY sparing rest of CNS
  - Dx: clinical, + NMO Ab, MRI, CSF (normal glucose, high protein, neutrophilic pleocytosis, NO other unique MS findings)
  - Tx: acute steroids/IVIG/Rituxan and then chronic immunosuppresants (Mayo Clinic Trials for new drugs)
- **Acute Disseminated EncephaloMyelitis (ADEM)**
  - Seen in young adults
  - Acute immune mediated multifocal monophasic demyelinating disease which follows 4-21d after a viral illnesses (URI, flu, chickenpox)
  - S/S: flu-like Sx, seizures, cognitive impairment w/ LOC, focal neurological deficits, meningeal signs
  - Different Than MS: abrupt onset, more acute, flu-like Sx, cognitive impairment w/ LOC
  - Dx: CSF (high ICP, neutrophilic pleocytosis, high protein, otherwise like MS), MRI (looks just like MS)
  - Tx: steroids, IVIG, plasma exchange, immunosuppressants
  - Complications: MS
  - Prognosis: 20% mortality in children or if they survive then 50% have some degree of permanent Sx
  - NB Acute Hemorrhagic Leukoencephalitis (like ADEM but with larger hemorrhagic lesions, high mortality)
- Autoimmune (SLE, Sjoogren's, Hashimoto's, Behcet's, Sarcoid, Vasculitis, etc)
- Metabolic (VitB12 def, Cobalamin Def, Copper/Zinc Def esp s/p gastric bypass, Central Pontine Myelinolysis, etc)
- Infection (post infectious HSV, Enterovirus, Mycoplasma, etc vs infectious PML, Lyme, HIV, HSV, etc)
- Genetic (Adrenoleuodystrophy, Wilson's, etc)
- **Multiple Sclerosis**

Epidemiology

- Incidence is increasing (maybe due to increased awareness)
- RFs: + 1° FHx (30x) NB 2% of population vs if +FHx then 4% but not directly genetic, higher latitudes (2x) where migration away before/after 15yo decreases/does not decrease your risk (2/2 settlement patterns of different ethnic groups, decreased production of immunosuppressive VitD, endemic infections, etc), 3F:1M, other autoimmune diseases
- Initial presentation ~25yo w/ most b/t 18-45yo but there have been cases in children <5yo and elders >60yo

Mechanism

- HLA-A3, B7, DR2, DW2
- **Autoimmune attack on myelin (White Matter NOT Grey Matter) in only CNS (Brain and Spinal Cord NOT PNS)** → Demyelination → Axonal Dysfunction → Axonal Loss → Wallerian Degeneration → Neurodegeneration
- Some association w/ infections (EBV, HHV-6, Chlamydia)
- Why do most pts worsen into a progressive disease? After each inflammatory attack sequestered Ags w/in the immunologically privileged CNS are slowly being released and recognized by immune cells aka "epitope spreading" leading to additional targets for the immune system
- Molecular Mimicry (immune response against foreign antigens cross react with self epitopes in myelin) and Super Antigens (foreign antigens promote a generalized nonspecific immune response) → inflammatory cells extravasate from vessels resulting in pervenular lymphocytes and white matter macrophages → macrophages eat up lipid rich myelin resulting in lipid laden macrophages → microglial proliferation and gliosis (scarring)
  - T-Helper-1 Lymphocytes: pro-inflammatory cytokines (IFN-γ, TNF, IL-1) the BAD!!!
  - T-Helper-2 Lymphocytes: anti-inflammatory cytokines (IFN-β, IL-4, IL-10) the GOOD!!!

Clinical Features

- "many different neurologic complaints separated by time and space that cannot be explained by a single lesion"
- Flares develop over hours to days to years (never suddenly or within minutes)
- Uhthoff's Phenomenon: originally Uhthoff found that pts who recovered from optic neuritis would subsequently experience reemergence of vision loss when exposed to excessive heat/physical exertion this phenomenon is actually seen in many other neurologic dysfunctions
- Brain
  - Cerebrum (usually manifests later on)
    - Fatigue (very common)
    - Dementia (memory, attention, slowing in processing speed, verbal fluency, reasoning, visual-spatial perception, language abnormalities)
    - Mood/Personality Changes
  - Cerebellum
    - Gait Problems, Ataxia, Vertigo, Nystagmus Balance Problems, Spatial Disorientation (illusion of self/environmental tilt), Sensory Rich Overload (problems with sensory rich environments like shopping malls)
      - Pts often present w/ head tilt and vertical eye misalignment
      - Also contributed by affected motor system, sensory system, visual system, and vestibular system
      - Sometimes pts have paroxysmal attacks which are quite disturbing, last 25-30 seconds, numerous times/day, treated with AEDs
    - Cerebellar/Rubral Outflow Intention Tremor (refer to Parkinson's notes)

        - Dysarthria
    - Visual Pathway
        - Optic Nerve (Optic Neuritis-refer)
            - Marcus Gunn Pupil aka Afferent Pupillary Defect
        - Any point in the visual pathway
            - Bitemporal Hemianopsia if at Optic Chiasm
            - Homonymous Hemianopsia/Quadrantanopsia if at posterior center
        - MLF (InterNuclear Ophthalmoplegia – INO)
            - Ipsilateral Eye Medial Rectus Palsy on Adduction w/ Contralateral Eye Horizontal Nystagmus on Abduction
            - Three Types: (1) No Limited Adduction just Slow Velocity – most common (2) Mild Limited Adduction w/ Slow Velocity (3) Completely Limited Adduction thus no Velocity to Measure
            - ~45% of MS pts will have clinical or subclinical INO
            - Bilateral INO is pathognomonic for MS (unilateral seen in CVAs)
            - "WEBINO" (Wall-Eyed and Bilateral INO) occurs when you have Bilateral INO + Lesion of the Medial Rectus Subnucleus resulting in inability to converge with eyes at rest appearing exotropic (pointing outward) aka "Wall-Eyed"
        - Extra Ocular Nerves CN III, IV, VI
            - Palsies esp CN VI
            - Intrusion of Unwanted Eye Movements
        - Peripheral Retina / Ciliary Body (Uveitis)
            - Cells and Debris in Vitreous along the Pars Plana of the Ciliary Body
            - Retinal Periphlebitis
            - Retinal Venous Sheathing
            - Leaking Fluorescein Angiography
    - Brainstem: dysarthria, dysphagia, ataxia, vertigo, N/V, etc
- Spinal Cord
    - Dorsal Spinal-Cerebral Columns (sensation) (most common initial symptom)
        - Neuropathic Pain, Paresthesia, Numbness
    - Pyramids/Cortico-Spinal Columns (motor)
        - + UMN Signs: Paresis, Babinski, Spasticity
    - Autonomic
        - Bladder
            - Urgency Incontinence: 2/2 to loss of descending inhibitory influence from higher centers therefore detrusor hyperreflexia, instability, poor storage capacity
            - Detrusor-Sphincter-Dyssynergia (DSD) aka Overflow Incontinence: uncoordinated contraction of the bladder wall simultaneous with the bladder neck preventing normal emptying leading to large post void residuals, r/o UTIs, r/o stones, and hydronephrosis
        - Bowel
            - Primarily Constipation
            - Sometimes Incontinence
        - Genitals
            - Male: Impotence, Diminished Sensation/Arousal, Orgasm/Ejaculation Problems
            - Female: Diminished Sensation/Arousal and Orgasm Problems
    - Transverse Myelitis
        - Combination of all above three
    - Lhermitte's Sign
        - electric pain in arms, back, legs precipitated by flexion/rotation of neck
    - Trigeminal Neuralgia
- NB Charcot Triad: Scanning Speech, Intention Tremor, Nystagmus
- NB Paroxysmal Phenomena: rapid, brief (<30sec), frequent (50x/d), episodes of dystonia, dysarthria, ataxia, akinesia, paresthesia, etc

Diagnosis

- It is very important to distinguish true relapses (no systemic Sx) vs pseudo relapses (have systemic Sx like F, 2/2 systemic infection esp UTI or meds, therefore Tx underlying cause w/ abx and tylenol and no steroids)
- McDonald's Criteria (complicated diagnostic criteria based on clinical findings and MRI)
- Clinical
- MRI (3/4: >1 GAD enhancing lesions, >1 non-enhancing infratentorial/cord lesions, >1 juxtacortical lesions, >3 periventricular lesions)
    - + GAD = active dz vs – GAD = inactive dz
    - 95% (Brain) and 75% (Spinal Cord) sensitivity but specificity is low w/ the following DDx: tumor, lymphomas, AVMs, mitochondrial cytopathies, VitB12 deficiency, HIV, HTLV Tropical Spastic Paraparesis, Vasculitis, SLE
    - NB the older the pt the less specific b/c MS lesions look very much like microvascular ischemic changes
    - Ovoid lesions perpendicular to posterior/lateral ventricles and corpus collosum, juxtacortical white matter, short cervical spinal cord lesions

- T2/Flair (hyperintense aka white, DDx: migraines, age, HTN, DM, smoking, DL, trauma, etc BUT note that these causes do not cause lesions in spinal cord unlike in MS hence always check cervical spine MRI) vs T1 (iso/hypointense)
  (1) White Matter Lesions in Both Brain and Spinal Cord (Chronic: T2 vs Acute: T1 suggesting vascular leakage)
    a. Dawson's Fingers: lateral periventricular plaques esp at corpus collosum and at angles perpendicular to ventricle
    b. Other white matter areas:
- CSF (80% sensitive but not specific, can be absent in early MS, check CSG when Dx if unclear, DDx: SLE, Sarcoidosis, Lyme Dz, Syphilis, Carcinomatous Meningitis, Tumors, HTLV Tropical Spastic Paraparesis, Adrenoleukodytrophy, Vasculitis
  - Increased IgG Index >0.77 (CSF-IgG/CSF-Albumin / Serum-IgG/Serum-Albumin) and Increased IgG Synthesis Rate
  - ≥2 Oligoclonal IgG Bands on Electrophoresis
  - Other: Normal Glucose, Normal or Mildly Increased Lymphocytic Pleocytosis, Normal or Mildly Increased Protein,
- Evoked Potentials (70% sensitivity but not specific)
  - Sensory pathways are stimulated and velocities down myelinated neurons are measured (demyelination = slower velocity)
  (1) Visual Evoked Response (VER)
  (2) NB Brain stem Auditory Evoked Response (BAER), SomatoSensory Evoked Response (SSER), etc not done anymore
- Lab: anti-myelin Ab (used for research purposes), ruling out other stuff (RPR, ESR, Lyme, B12, ANA, ACE, HTLV-1, ACL, LA, TSH)
- Histology
  (1) Pervenular Lymphocytes
  (2) White Matter Lipid Laden Macrophages
  (3) Microglial Proliferation
  (4) Gliosis (Scarring)
- Types of Diagnosis
  - Definite
    - Clinical: ≥2 episodes + ≥2 white matter lesions on MRI
    - Lab: ≥2 episodes + 1 white matter lesion on MRI + abnormal CSF
  - Probable
    - Clinical: ≥2 episodes + 1 white matter lesion on MRI
    - Lab: ≥2 episodes + abnormal CSF

Prognosis

- Flare (last 1-2d), Remission (>30d b/t episodes to be considered a remission), flares can be followed by incomplete recovery
- ? if flares are spontaneous or if triggered by environmental factors by 1/3 seem to be 2/2 viral infection and severe stress
- Dz begins w/ a flare w/ complete/incomplete remission aka Relapsing Remitting MS aka RR-MS (85%) and if pt's Sx worsen with subsequent flares then it is called Secondarily Progressive MS aka SP-MS (50% of RR-MS pts in 10yrs, important to note that most pts do not realize that there Sx are worsening)
- Dx begins w/ progressive disease aka Primary Progressive MS aka PP-MS (15%) and if pt's have superimposed flares then it is called Progressive Relapsing MS (SP-MS), NB unresponsive to DMAs
- 50% will require the use of an ambulation assistance device w/in 10yrs of onset
- Life expectancy is reduced by 7yrs 2/2 infectious complications of immobility
- Usual number of clinical attacks is 1/yr but is important to note that subclinical demyelination attacks occur much more often
- Only 1/3 develop debilitating disease most just have a chronic disease
  - Factors Increase Chances of Debilitating Disease
    - Frequent Attacks Early in Disease
    - Shorter Remission Intervals
    - Partial vs Complete Remissions
    - Onset at Older Age
    - Progressive Course
    - Early Cerebellar or Pyramidal Involvement
- AFTER FIRST DIAGNOSIS IF MULTIPLE MRI FINDINGS THEN 85% WILL PROGRESS TO FULL MS IN 2 YEARS
- Marburg / Balo's Concentric Sclerosis Variant (rare severe variant leading to death in months)

Treatment

- General
  - Acute
    - **corticosteroids**: IV methylprednisolone 1g/d divided BID x3-5d then PO prednisone tapered over 12d, do NOT alter the overall course of MS (except for optic neuritis in which pts treated were less likely to develop MS in the subsequent two years however beyond there was no statistical difference) but help accelerate recovery from each attack
    - **abx**: infections exacerbate Sx therefore always check UA, CBC, etc and Tx w/ abx
    - if really bad consider plasma exchange
  - Chronic
    - No Tx until 1993 when first IFN was developed!!!
    - Disease Modifying Agents (DMAs) takes 3mo to take effect
    - After pts are diagnosed with MS based on above they often enter into a clinically silent state and b/c of this many doctors argue not to start DMAs but the problem is that almost all of the pts enter in RR-MS and

eventually SP-MS and even though silent there is subclinical demyelination is still occurring therefore it is recommended that DMAs be initiated at diagnosis (also remember that frequency during the first two years is a risk factor for progressive disease)
- Some pts are never formally diagnosed with even probable MS but nevertheless other etiologies have been excluded therefore MS is still likely, in this case many doctors still treat based just based on one episode and one MRI/CSF findings
- RR-MS: IFN-β 1a or GA vs. SP-MS IFN-β 1a only b/c GA has not yet been shown to slow progression of disability (1a is first line agent b/c 1b has more significant SEs and bad scheduling/administration, however, if pt has been put on 1b and doing well do not switch to 1a b/c of cross-reactivity)
- Once initiated DMA treatment should be continued indefinitely unless severe SEs, lack of efficacy or newer agents then alternative agents, intermittent steroids, and adjuvants should be considered
- b/c clinically pts may be silent and still have MRI findings DMA efficacy should be assessed based on MRI even if a pt is clinically silent
- after awhile IFN doesn't work as well 2/2 production of NAbs (Neutralizing Antibodies) you can measure these to assess Tx failure but the question is what to do b/c Nabs are often transient
- High NAB titers likely decreases biological activity ultimately culminating in more disease therefore it is recommended that NAB titers be done Q1-2yrs, if <20 do not check unless there appears to be a major shift in the pts clinical course, if high then modify DMAs
- IFN works more quickly than glatiramir

(1) **IFN-β 1a** (Avonex) IM (Rebif) SQ Qwk (great)
   a. IFN suppresses T-cells production and CNS migration
   b. IFN-β has been shown to (1) decrease number of clinical relapses (2) decrease number of MRI lesions (3) slow progression of disability
   c. SEs: flu-like Sx, transient exacerbation of previous neurologic Sx, migraines, hepatoxicity, leucopenia, depression, seizures, injection site reaction, mod NAB production, cross reaction w/ IFN-β 1b
   d. Slowly titrate up and pre-Tx w/ Tylenol
   e. If persistent/severe SEs then: pentoxifylline, amantidine, or low-dose steroids on day of and day after injection
   f. Avoid in pts w/ HAs, liver dz, depression

(2) **IFN-β 1b** (Betaseron) IM Q every other day (bad)
   a. " "
   b. " "
   c. SEs: same + skin lesions w/ r/o abscesses/necrosis b/c IM injection and high NAB production
   d. " "

(3) **glatiramer acetate** (Copaxone) SQ Qd (alright)
   a. 4aa polypeptide similar to Myelin Basic Protein (MBP) which has the effect of blocking antigen presentation
   b. glatiramer acetate has been shown to only (1) decrease number of clinical relapses
   c. SEs: (best tolerated of the three agents with NO flu-like symptoms and NO NABs) injection site reactions w/ hives, non-cardiac chest pain/dyspnea/palpitations/anxiety, flu-like Sx, leucopenia
   d. Takes 9-12mos

(4) Second Line Agents
   a. mitoxantrone (Novantrone) IV, SEs: AML and CM (immunosuppressant, old chemo drug used for Tx of hairy cell leukemia)
   b. natalizumab (Tysabri) IV, SEs: PML (monoclonal Ab to alpha-4 integrin, suspended in 2005 but reintroduced in 2006 when it was determined that PML occurred when pts took both Tysabri AND other immunosuppresants)
   c. MTX/Azathioprine/Cytoxan (if refractory to above)
   d. Estrogens (b/c pregnant women have less Sx while they have flares after delivery)
   e. VitD (b/c higher latitudes means lower VitD levels)
   f. Statins (b/c on anti inflammatory effects)

(5) New Drugs: Fingolimod, Cladrabine, etc

- Adjuvants
  - Fatigue: rule out other causes, exercise, weight control, meds (amantadine, fluoxetine, protriptyline, 4-aminopyridine, methylphenidate)
  - Depression (refer)
  - Insomnia (refer)
  - Sensory: AEDs, neurontin/gabapentin
  - Motor
    - Spasticity/Jerking/Stiffness/Cramping/Weakness
    - PT/OT
    - Tremor: thalamotomy, thalamic stimulation, gabapentin, many other drugs
    - 4-aminopyridine (potassium channel antagonist that improves exercise tolerance)
    - General: baclofen (but many pts experience increased weakness when using this drug) if severe there are baclofen intrathecal pumps and surgical release procedures, new drugs are coming out (tizanidine)
    - Local: benzos, gabapentin, dantrolene, quinine, botulism
  - Bladder
    - Urgency: Tolterodine, Oxybutynin, Propantheline, Hyoscyamine Anticholinergics

- Overflow: Above + Mild: Intermittent/Continuous Catheterization vs Severe: Superpubic Catheter followed by Surgical Diversions, Sphincterotomy, or Sphincter Stent Prosthesis w/ Balloon Dilation