Optic Neuritis
Differential Diagnosis Including MS and NMO and their Treatments

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Colorado Vision Summit - July 15th, 2017
Disclosures

- Consulted for Biogen, Genzyme, Genentech, Novartis, and TG pharmaceuticals.

- Received research funding from Biogen, Novartis, Acorda, and Rocky Mountain MS Center.

- Off-label use of medications will be noted when mentioned.
Objectives

- Optic neuritis (ON) and its differential diagnosis
- Acute treatment of optic neuritis
- Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO)
- Long term treatment options
  - Macular edema with fingolimod
Optic Neuritis

- A type of optic neuropathy
- Inflammation of the optic nerve.
- DDx:
  - Idiopathic
  - Demyelinating diseases: multiple sclerosis (MS) and neuromyelitis optica (NMO)
  - Systemic autoimmune diseases: SS, SLE, sarcoidosis
  - Infections: syphilis, Lyme disease, HIV, herpes zoster, mononucleosis, and mycoplasma pneumonia
  - Metabolic: B12 deficiency
<table>
<thead>
<tr>
<th>Category</th>
<th>Disease (Select Examples)</th>
<th>Clinical Features</th>
<th>Paraclinical Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory/vasculitic</td>
<td>Sarcoidosis</td>
<td>Scleritis or uveitis may be present</td>
<td>ESR</td>
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<td></td>
<td>SLE</td>
<td>Multiorgan involvement possible</td>
<td>ANA</td>
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<td></td>
<td>Behçet</td>
<td>Often bilateral or sequential</td>
<td>ACE</td>
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<td>Wegener granulomatosis</td>
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<td>CXR</td>
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<td></td>
<td>Immunocompetent</td>
<td>Often bilateral</td>
<td>Chest CT</td>
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<td></td>
<td>Syphilis</td>
<td>Fundoscopy: may reveal papillitis, retinal exudates, and macular edema</td>
<td>Specific PCR and/or serologic testing</td>
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<td></td>
<td>Lyme disease</td>
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<td>Lumbar puncture</td>
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<td>Cat scratch disease (Fig. 1)</td>
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<td>CXR</td>
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<td>HSV</td>
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<td>PPD</td>
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<td>Immunocompromised</td>
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<td>Tuberculosis</td>
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<td>Toxoplasmosis</td>
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<td>Toxocara</td>
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<td>CMV</td>
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<td>HSV</td>
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<tr>
<td></td>
<td>Fungal infections</td>
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<tr>
<td>Ischemic</td>
<td>AION</td>
<td>Often older age group (&gt;50 yr)</td>
<td>ESR</td>
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<tr>
<td></td>
<td>PION</td>
<td>Fundoscopy: may show a pale swollen disc</td>
<td>CBC</td>
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<tr>
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<td>Diabetic papillopathy</td>
<td>Contralateral optic disc crowding, with small cup may be present</td>
<td>Lipid panel</td>
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<td></td>
<td></td>
<td>Poor visual recovery</td>
<td>Measure blood pressure</td>
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<td>Blood dyscrasia</td>
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<td></td>
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<td></td>
<td>Vitamin B12</td>
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<td></td>
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<td>Folic acid</td>
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<td></td>
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<td>Thiamine</td>
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<td></td>
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<td>Screen for toxin exposure</td>
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<tr>
<td>Toxic/Metabolic</td>
<td>Nutritional deficiency</td>
<td>History of undernutrition, alcohol or nicotine abuse</td>
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<td></td>
<td>Toxins/methanol</td>
<td>Bilateral visual loss on presentation</td>
<td></td>
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<td></td>
<td>Radiation</td>
<td>Fundoscopy: may have disc swelling in acute toxicity but frequently normal</td>
<td></td>
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<tr>
<td></td>
<td>Medications (ethambutol, amiodarone, or isoniazid)</td>
<td>appearing optic nerves initially with later development of optic nerve pallor</td>
<td></td>
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<tr>
<td>Traumatic</td>
<td>Trauma</td>
<td>Usually frontal or midfacial trauma</td>
<td>CT/MRI of orbit.</td>
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<td></td>
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<td>Orbital or skull fractures, optic nerve sheath hematoma, or optic nerve sheath</td>
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<td></td>
<td></td>
<td>arachnoid cyst</td>
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<tr>
<td>Hereditary</td>
<td>Leber hereditary optic neuropathy</td>
<td>Predominately young males affected</td>
<td>Genetic analysis for mitochondrial point mutation (11778, 14484, 3460)</td>
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<td></td>
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<td>Sequential, bilateral visual loss</td>
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<td>Fundoscopy may reveal peripapillary telangiectasian</td>
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<tr>
<td>Compressive/neoplastic</td>
<td>Intracranial mass</td>
<td>May have proptosis</td>
<td>CT/MRI of orbit and brain with contrast</td>
</tr>
<tr>
<td></td>
<td>Optic nerve tumor (meningioma, glioma, metastasis, lymphoma)</td>
<td>Fundoscopy: disc swelling can be seen early on, atrophy is seen chronically</td>
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<tr>
<td></td>
<td>Abscess</td>
<td>Optochoroidal collateral vessels may be present</td>
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<tr>
<td>Parainfectious/autoimmune</td>
<td>Postinfectious</td>
<td>Usually bilateral</td>
<td>MRI brain</td>
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<tr>
<td></td>
<td>Postvaccination</td>
<td></td>
<td>Paraneoplastic antibodies</td>
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<tr>
<td></td>
<td>Paraneoplastic</td>
<td></td>
<td></td>
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<tr>
<td>Demyelinating</td>
<td>Idiopathic</td>
<td>Pain with eye movement</td>
<td>MRI brain and orbits</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
<td>Fundoscopy: 1/3 with swollen optic nerve</td>
<td>NMO antibody</td>
</tr>
<tr>
<td></td>
<td>Neuromyelitis optica</td>
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</table>

SLI: indicates systemic lupus erythematosus; ESR, erythrocyte sedimentation rate; ANA, antineutrophil antibody; ACE, angiotensin converting enzyme; CXR, chest x-ray; CT, computed tomography; HSV, herpes simplex virus; CMV, cytomegalovirus; PCR, polymerase chain reaction; PPD, purified protein derivative; AION, anterior ischemic optic neuropathy; PION, posterior ischemic optic neuropathy; MRI, magnetic resonance imaging; NMO, neuromyelitis optica.
Optic Neuritis

• Bilateral Optic Neuritis – DDx
  – MS (Most common)
  – NMO (More commonly bilateral)
  – Lyme
  – Syphilis
  – B12 deficiency
  – HIV
  – Sarcoid
Differential Diagnosis of CNS inflammation

- Multiple Sclerosis (MS)
  - Clinically Isolated Syndrome (CIS) (?RIS)
  - Optic neuritis (ON)
  - Transverse myelitis (TM)
- Acute Disseminated Encephalomyelitis (ADEM)
- Neuromyelitis Optica (NMO) – Devic’s disease
- Sarcoid
- Collagen Vascular diseases (Lupus, Sjögren's, RA)
- Vasculitis
  - Primary CNS angiitis
  - Secondary vasculitis: ANCA +, Behçet's disease
- Paraneoplastic antibodies
Initial Symptoms of MS

- Limb Weakness - 40%
- Decreased vision/ Optic neuritis - 22%
- Tingling and unusual sensations such as electrical, itching or ‘sunburned’ / Paresthesias - 21%
- Double Vision/ Diplopia - 12%
- Dizziness/ Vertigo - 5%
- Urinary Bladder urgency, frequency, hesitancy - 5%

Also
- Pyramidal signs (Hyperreflexia, clonus, spasticity)
- Posterior column sensory deficits (vibration > proprioception)
- Cerebellar (intention tremor, dysmetria)

McAlpine, 1972
Intranuclear Ophthalmoplegia

- Localizes to the Medial Longitudinal Fasciculus connecting the VI (pons) and III (midbrain) nuclei.
- Have patient look quickly to side and observe adducting eye for lag.
- Abducting eye may develop nystagmus
Evidence of past optic neuritis

- Optic disk temporal pallor
- Afferent pupil defect
- Red desaturation
- Decreased contrast
- Central scotoma
- Abnormal VEP
Visual Evoked Potential

- Can be abnormal in asymptomatic patients.
- See a latency because of demyelination. Axonal loss will cause a loss of amplitude.
Role of MRI in evaluating ON

- Brain MRI in our patient did not show any lesions.
- Get orbital MRI if trying to evaluate ON
Role of MRI in evaluating ON

- Do you see white matter lesions?
- Rule out
  - Stroke
  - ?Vasculitis
  - ?Sarcoid

Beck et al Arch Neurol 2008
Acute Relapses

• Rule out pseudorelapses
  – “This is one of my typical relapses”
  – No fever, URI, UTI....
• Do you need to treat?
  – Are symptoms worsening?
  – When did symptoms begin?
• How aggressively to treat?
• Acuity recovers faster, but no long term effects.

Beck et al. ONTT, NEJM 1992
Steroid Treatment of MS “Attacks” or “Relapses” or “Exacerbations”

- Shortens attacks
- Does not alter severity of neurologic impairment
- Older studies indicated steroids do not affect ultimate recovery or course of MS
- Oral methylprednisolone may be equivalent to IV
- *IV methylprednisolone may transiently delay further attacks in pts with Optic Neuritis
- **? if periodic pulse IV steroids may slow clinical and MRI progression

**Zivadinov et al Neurology 2001; 57:1239-47
**Acute Treatment**

- **Steroids**
  - Decrease inflammation
  - 3-5 days of IV methylprednisolone (1 gr) or dexamethasone (200 mg)
  - Side effects: Anxiety, problems sleeping, high FSBG, worsen stomach ulcers, ...

- **Plasmapheresis**
  - Similar to dialysis
  - Side effects: hypotension, blood clots, and infection.

- **Cyclophosphamide**
  - Chemotherapy (800–1000 mg/m²)
  - Used in severe relapses
Acute Treatment

- Severe transverse myelitis

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>ΔEDSS</th>
<th>ASIA A (acute)</th>
<th>Non ASIA A (acute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV MP (n = 66)</td>
<td>0.3 ± 0.2</td>
<td>2.1 ± 0.2*</td>
<td></td>
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<tr>
<td>PLEX (n = 32)</td>
<td>0.5 ± 0.2</td>
<td>4.1 ± 0.4*</td>
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<tr>
<td>IV CP (n = 13)</td>
<td>3.0 ± 1.3</td>
<td>4.9 ± 0.5</td>
<td></td>
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<tr>
<td>PLEX + IV CP (n = 11)</td>
<td>4.4 ± 0.7</td>
<td>2.8 ± 0.6</td>
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</tbody>
</table>

Greenberg et al. Neurology 2007
Transverse Myelitis

• Inflammatory lesion of the spinal cord
• At the first occurrence, ≥2 brain lesions = 88% chance of conversion to MS in 20 years. 0 lesions = 19% risk of MS
• Presents typically with:
  – sensory (spinal level),
  – motor,
  – autonomic (bladder, bowel, sexual) dysfunction.
  – Lhermitte’s (paresthesias that radiate down the spine or limbs with neck flexion)
  – Paroxysmal tonic spams (involuntary dystonic contractions of limb and trunk muscles).
<table>
<thead>
<tr>
<th>Cord Syndrome</th>
<th>Clinical Signs</th>
<th>Characteristic Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transection</td>
<td>Loss of all motor, sensory, and autonomic function below lesion</td>
<td>Trauma, severe compression, necrotizing myelitis</td>
</tr>
</tbody>
</table>
| Anterior cord | Bilateral flaccid weakness  
Pain/temperature sensory loss  
Autonomic dysfunction | Anterior spinal artery occlusion |
| Dorsal column | Bilateral reduced vibration, proprioception, touch | | Tabes dorsalis  
Some cases of MS  
or B12 deficiency |
| Brown-Séquard | Ipsilateral pyramidal weakness and vibration/proprioception loss; contralateral pain loss | Multiple sclerosis  
Compression |
| Central       | "Dissociated" sensory loss  
Pain/temperature loss with spared vibration and proprioception | Syrinx  
Neuromyelitis optica |
| Tract-specific | Corticospinal tracts  
Corticospinal tracts and dorsal columns | Paraneoplastic myelitis  
B12 or copper deficiency |
Transverse Myelitis

• Causes
  – Post Infection/vaccination (60% in children)
  – Demyelination (MS, NMO, ADEM)
  – Idiopathic (15-30%)
  – Systemic inflammatory/autoimmune diseases (SLE, Behcet’s disease, Sjogren’s, sarcoid)
  – Paraneoplastic, neoplastic
  – compressive,
  – postradiation,
  – vascular.
Radiologically Isolated Syndrome

Asymptomatic patients with classic MS findings on MRI. Will they go on to develop MS?

- 1/3 will develop clinical MS over 2-5 yrs.
- 91% develop radiographic dissemination over 6-30 mos

42% - MRI for Headache
30% at 5 years in ONTT
194/300 (64.7%) with + OCBs
51% if 3+ brain MRI lesions

Radiologically Isolated Syndrome

Time to a first clinical event by (A) + spinal cord lesions, (B) age at first MRI suggestive of demyelinating disease, (C) sex, and (D) stratified based on the presence of 0, 1, 2, or 3 risk factors.

Multiple Sclerosis
What is MS?

• “Multiple sclerosis is a chronic, often disabling disease that attacks the central nervous system. MS is thought to be an autoimmune disease.” – National MS Society

• “Multiple sclerosis is a potentially debilitating disease in which your body's immune system eats away at the protective sheath that covers your nerves.” - Mayo

• “Multiple sclerosis is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms.” – Wikipedia

• “Multiple sclerosis is a nervous system disease that affects your brain and spinal cord. It damages the myelin sheath, ...It may be an autoimmune disease” – MedlinePlus (NIH)
What is MS?

- Autoimmune
- Inflammatory
- Demyelinating???
- Affects the Central Nervous system

> Sensitive but not specific
## 2010 International Panel Criteria

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS diagnosis</th>
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</thead>
<tbody>
<tr>
<td>Two or more attacks; objective clinical evidence of 2 or more lesions</td>
<td>None</td>
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<tr>
<td>Two or more attacks; objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by . . .</td>
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<tr>
<td>One attack; objective clinical evidence of 2 or more lesions</td>
<td>Dissemination in time, demonstrated by . . .</td>
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<tr>
<td>One attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)</td>
<td>Dissemination in space, demonstrated by . . .</td>
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<td></td>
<td>And dissemination in time, demonstrated by . . .</td>
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<tr>
<td>Insidious neurological progression suggestive of MS</td>
<td>One year of disease progression, and dissemination in space, demonstrated by two of the following . . .</td>
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Polman et al, Ann Neurol 2011
Multiple Sclerosis Diagnosis

- Diagnosis of relapsing MS requires multiple discrete neurological events, arising from lesions in CNS white matter, disseminated over time, without an alternative explanation.

- Newer criteria, magnetic resonance imaging (MRI), spinal fluid studies, and evoked potential studies are allowed to demonstrate lesion dissemination in space and time.

- In progressive-onset MS, dissemination in time is increasing symptoms or signs over a one-year period.
Definitions

• A flare (relapse, attack, bout, episode, exacerbation) – ≥1 symptom from MS with objective neurological deterioration lasting ≥24 hours in the absence of fever and following a neurologically stable period of ≥30 days.

• Dissemination in Space – 2 or more of the following: 1) juxtacortical, 2) periventricular, 3) infratentorial, 4) spinal cord. Optic Nerve is not included yet...

• Dissemination in Time – 1) new T2 lesion on a scan done ≥30 days after the onset of the initial clinical event, or 2) asymptomatic contrast enhancing lesion
Demographics of MS

- Main age of onset: 15 to 45 years
- Gender: ~70% women
- Geography: Incidence increases with distance from equator in both directions
- Incidence: 12,000 new cases per year
- Prevalence: 0.1% of US population (400,000)
- Race: Caucasians > other ethnic groups

Prognosis – ALL MS courses (data from before current therapies)

- 50% will require aid to walk within 10 years
- 50% will develop cognitive deficits
- 50%-80% will not be working in 10 years
- Loss of lifetime earnings
- Loss of productivity
Prognostic Indicators

**Good:**
- Optic neuritis at onset
- Sensory onset
- Little disability at 5 years
- Relapsing/remitting course
- Full recovery from attacks
- Few OCB at diagnosis

**Bad:**
- Cerebellar dysfunction
- Motor symptoms at onset
- High attack rate
- Progressive course
- African Americans
- Baseline MRI with many lesions.
Four Basic Disease Courses of MS: Most Common Is Relapsing-Remitting

Adapted with permission from Lublin FD and Reingold SC. *Neurology*. 1996;46:907-911.
Diagnostic Tests in MS

- Magnetic resonance imaging (MRI)
- Spinal fluid analysis
- Visual Evoked potentials
MRI Use in MS

• Useful in making the diagnosis of MS and in ruling other diagnoses out. Establish dissemination in Space (>1 of the following: 1) juxtacortical, 2) periventricular, 3) infratentorial, 4) spinal cord).

• Useful in monitoring MS therapies as many MS lesions (plaques) are clinically silent.

• There is often a huge disconnect between the MRI appearance and the clinical appearance
MRI use in MS

Typical
• Multiple T2/FLAIR white matter lesions
• Lesions >3 mm
• Often periventricular (*) or juxtacortical (#)

FLAIR lesions result from:
• Gliosis (Sclerosis)
• Inflammation
• Demyelination
• Edema (rare)

*T2 Lesions correlate poorly with disability
MRI use in MS

Typical

- Often ovoid and perpendicular to ventricles (Dawson’s Fingers)
MRI use in MS

• Lesions can coalesce and be quite extensive

• Note – Not even that bad.
Typical

- T1 black holes can be seen in the acute setting with gadolinium enhancement (sometimes ring-enhancing) and in lesions causing atrophy.
- Black Hole burden correlates with disability ($r^2 = 0.05$)
MRI use in MS

Typical

• Atrophy of the corpus callosum (←) and cortex (↓) is common in advanced disease
Typical

- Short (<3 Segment) Spinal Cord Lesions. Acutely show cord swelling and later atrophy of cord if damage is permanent.
MRI use in MS

Not Typical in MS

• Tumor-like mass Lesions with edema (tumefactive MS, but MS pts do get brain tumors!!!)
• Exclusively Punctate (<3mm) Lesions (leukoariosis – vascular ischemic changes, migraine)
• Anterior Temporal Lobe & occipital lobe lesions (CADASIL)
• Longitudinally Extensive Spinal Cord Lesions (>3 Segments – NMO, post infectious, vascular TM)
• Sparing of Corpus Callosum
• Diffusion Restriction (MS pts do get strokes!!!)
• Gray Matter Lesions (Cortex, Thalamus) Maybe not!!
Percent of patients (n=109) after 14 years with EDSS ≥6 (need unilateral assistance to walk 100m)

Cerebrospinal Fluid in CSF

- Nucleated cell count - < 5/mm$^3$ in 75% of MS
  < 40 /mm$^3$ in 90% of patients
- Glucose – normal
- Protein – normal in 60%
  > 100 mg/dl – very rare
- ↑ myelin basic protein – not specific
- Intrathecal IgG, IgM synthesis
  - Oligoclonal Bands in CSF
  - Increased IgG Index (>0.68)

\[
\text{IgG CSF/ IgG serum} = \frac{\text{IgG CSF}}{\text{IgG serum}}
\]
\[
\text{albumin CSF/ albumin serum}
\]
Differential Diagnosis of Oligoclonal Bands

- Viral encephalitis
- CNS Lyme - >70%; also + Abs in CSF to B. burgdorferi,
- HIV (CNS AIDS)
- Subacute sclerosing panencephalitis (SSPE, measles)
  - Highest number of OCB
- S/P Gastric bypass surgery
- Acute disseminated encephalomyelitis (ADEM)
  - Transient
Pathology
Hallmarks of MS Pathology

- Mononuclear inflammatory cells
- Demyelination
- Relative axon sparing
- Astrocyte hypertrophy
- Cervical spinal cord disproportionately involved
- Periventricular lesions

Demyelinated axons

Transected Axons

Most MS Lesions Center on Blood vessels (Perivenular)
What Causes MS?

MS is a multifactorial disease caused by the interplay of environmental, genetic, and immune factors.
MS Rate Estimates
(\(\lambda\)s indicates risk ratio compared with general population)

Reprinted with permission from Compston A and Coles A. Lancet. 2002;359:1221-1231.
Genetic Susceptibility

- MHC association: HLA-DR2 for those of northern European descent
- Relative risk of \( \approx 2 \) to \( 3 \times \) for DRB1*1501 and DRB1*1503
- Genetic susceptibility explained by the MHC locus is estimated at between 20% and 50%\(^1\)
- Homozygosity for DRB1*1501 \( \rightarrow \) more severe course, earlier onset\(^2\)
- Human chromosome 6p21.3

Other MS Susceptibility Genes

- Genome-wide analysis of SNPs in studies in ≈1000 subjects, validated in UK Wellcome Trust samples and National Institute of Mental Health samples.
- Identified alleles of IL-2RA gene and IL-7RA gene associated with MS susceptibility risk, as well as HLA-DRA region on chromosome 6.

IL = interleukin; RA = receptor α; SNP = single-nucleotide polymorphism.
MHC Linkages

• HLA DRB1*1501 increases susceptibility to MS
• HLA A*02 and HLA B*44 reduce susceptibility with the later possibly reducing FLAIR lesions and preserving brain volume.
• HLA C*05 may play a role.

Healy et al., Neurology 2010
What Causes MS?

MS is a multifactorial disease caused by the interplay of environmental, genetic, and immune factors.
Evidence for Immune System Involvement in MS

- Spinal Fluid Antibodies
- HLA (major histocompatibility) associations (because they are involved in T lymphocyte function) - HLA DR2 (15), DR4
- Female predominance is typical of autoimmune diseases
- Autoimmune Animal model (EAE)
- Response to drugs that act on the immune system
What Causes MS?

MS is a multifactorial disease caused by the interplay of environmental, genetic, and immune factors.
Evidence for a role of viruses/other infectious agent

- Epidemiologic evidence
- Geographic clustering
- Migration data
- Demyelinating animal models, e.g. visna in sheep, where viruses (lentiviruses) have long incubation periods
Geographic Variation

High risk (>30 per 100,000): northern Europe, northern United States, Canada, southern Australia, New Zealand

Medium risk (5–30 per 100,000): southern Europe, southern United States, northern Australia

Low risk (<5 per 100,000): Asia, South America, uncharted regions

Vitamin D and Risk of MS

• Sun exposure decreases with higher latitudes.

• MHC vitamin D response element (VDRE) in the promoter region of HLA-DRB1

• In a prospective study:
  – The risk of developing MS significantly decreased with increasing baseline levels of serum vitamin D
  – Patients taking high doses 14,000 IU daily had 41% fewer relapses than controls who took 1,000 IU daily and 17% had a relapse.

Break/Questions
Confirmed Diagnosis of MS

- Treat Relapse
  - Steroids, PLEX

- Treat Symptoms
  - Medications, Rehab, Counseling, etc

- Treat Disease
  - Disease-modifying therapies

- Address comorbidities
  - Smoking cessation, Weight loss, BP control, Vit D
Immunomodulatory vs Immunosuppressive Agents
The Evolving MS Treatment Landscape

<table>
<thead>
<tr>
<th>Year</th>
<th>Therapy Name</th>
<th>Type</th>
</tr>
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<tbody>
<tr>
<td>1995</td>
<td>Betaseron® (IFNβ-1b)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2000</td>
<td>Avonex® (IFNβ-1a)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2005</td>
<td>Copaxone® (glatiramer acetate)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2005</td>
<td>Novantrone® (mitoxantrone)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2005</td>
<td>Rebif® (IFNβ-1a)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2005</td>
<td>Tysabri® (natalizumab)</td>
<td>Infusion</td>
</tr>
<tr>
<td>2010</td>
<td>Extavia® (IFNβ-1b)</td>
<td>Infusion</td>
</tr>
<tr>
<td>2010</td>
<td>Gilenya® (fingolimod)</td>
<td>Oral</td>
</tr>
<tr>
<td>2011</td>
<td>Aubagio® (teriflunomide)</td>
<td>Oral</td>
</tr>
<tr>
<td>2012</td>
<td>Gilead® (dimethyl fumarate)</td>
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</tr>
<tr>
<td>2012</td>
<td>Plegridy® (Pegylated IFNβ-1a)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2012</td>
<td>Glatiramer acetate 40 mg SC TIW</td>
<td>Injectable</td>
</tr>
<tr>
<td>2013</td>
<td>Tecfidera® (Daclizumab)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2013</td>
<td>Rebif® (Daclizumab)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2014</td>
<td>Lemtrada® (Alemtuzumab)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2015</td>
<td>Zinbryta® (Daclizumab)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2015</td>
<td>Ocrevus® (Ocrelizumab)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2016</td>
<td>Glatopa® (Ocrelizumab)</td>
<td>Injectable</td>
</tr>
<tr>
<td>2017</td>
<td>Laquinimod</td>
<td>Injectable</td>
</tr>
<tr>
<td>2017</td>
<td>Siponimod</td>
<td>Injectable</td>
</tr>
</tbody>
</table>

**TIW = 3x/weekly.**
Probability of Developing SPMS

Hazard Ratio 0.38, \( p<0.0001 \)

Trojano et al. Ann Neur 2007. 1500 MS patients on either Beta-interferon (~1100) or nothing (~400) for up to 7 years. Followed by protocol at one of two MS centers in Italy. Not randomized. Not blinded.
MRI in disease monitoring

- Diagnostic MRI
- Month 0: Treatment Start
- Month 6: Monitoring MRI
- Month 12: Monitoring MRI

- New T2 lesions appearing on Month 6 MRI may have occurred anytime since diagnostic MRI and may not be taken as definite evidence of breakthrough disease.
- Gadolinium-enhancing lesions on Month 6 MRI may be a sign of breakthrough disease.
- By 12 months on therapy, any Gad+ lesions or new T2 lesions compared to Month 6 MRI may be a sign of breakthrough disease.

Monitor every 6-24 months based on disease activity and results of prior monitoring MRI.

Bermel RA, Nasmith RT. Curr Opin Neurol. 2015;28:244-249.
New T2 lesion Number at 1 Year Predicts EDSS Worsening

Prosperini et al. *Eur J Neurol* 2009
Comparing across trials...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative reduction Relapse Rate vs Pb (%)</th>
<th>% Relapse Free at two years</th>
<th>Reduction Disability vs Pb (3 mo/6mo)(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon B-1b</td>
<td>34</td>
<td>31</td>
<td>29* at 3 mo</td>
</tr>
<tr>
<td>Interferon B-1a (Avonex)</td>
<td>32</td>
<td>38</td>
<td>37 6</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>29</td>
<td>34</td>
<td>12* 3</td>
</tr>
<tr>
<td>Interferon B-1a (Rebif)</td>
<td>32</td>
<td>32</td>
<td>31 3</td>
</tr>
<tr>
<td>Natalizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFFIRM</td>
<td>68</td>
<td>67</td>
<td>42 3</td>
</tr>
<tr>
<td>SENTINEL (add on vs Avonex)</td>
<td>55</td>
<td>54</td>
<td>24 3</td>
</tr>
<tr>
<td>Fingolimod</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freedoms I</td>
<td>54</td>
<td>70</td>
<td>30 3</td>
</tr>
<tr>
<td>Freedoms II</td>
<td>48</td>
<td>72</td>
<td>17*/28 3/6</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEMSO 14mg</td>
<td>32</td>
<td>57</td>
<td>30 3</td>
</tr>
<tr>
<td>TEMSO 14mg</td>
<td>36</td>
<td>52 (1.5y)</td>
<td>32 3</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEFINE</td>
<td>53</td>
<td>73</td>
<td>38 3</td>
</tr>
<tr>
<td>CONFIRM</td>
<td>44</td>
<td>71</td>
<td>21 3</td>
</tr>
</tbody>
</table>

* Not statistically significant
Relapse Rate Varies Over Time

Relapses varied depending on sex, disease duration, and age

Kalincik et al, Brain, 136; 12. 2013
Escalation Therapy Approach

Escalation of therapy undertreats early, and over treats later
Risk Appropriate Approach

Risk appropriate approach may match disease activity better
Things to Consider

• Relative efficacy
• Side effects
  – injection site reactions
  – flu-like symptoms
  – transaminase elevations
  – Infections – HSV, PML
  – QT prolongation
  – Macular edema
• Compliance
• Cost - >$60,000 per year
• Patient assistance programs
Injection Site Reaction from Copaxone
Macular Edema with Fingolimod

- 0.2% of patients will develop
- Increases 5-10x if diabetic or higher if uveitis
- <10% occurs after 4 months. Monitor at baseline and 3 months.
- R/O in fingolimod patients with blurred vision.
ENROLLMENT FORM

1-800-887-8100 Fax: 1-800-775-5834

PATIENT INFORMATION
(Please print)

Sex: M [ ] F [ ] Date of Birth: __________

Name (First, Mi, Last, Suffix):

Street Address:

City/State/Zip:

Home Phone: OK to leave message? Yes [ ] No [ ]

Cell/Pager: OK to leave message? Yes [ ] No [ ]

Work Phone: OK to leave message? Yes [ ] No [ ]

Email Address:

OK for Shared Solutions® contact by email? Yes [ ] No [ ]

Social Security Number:

INSURANCE INFORMATION (Check all that apply)

[ ] Patient has no insurance

[ ] Patient needs assistance with benefits


[ ] Patient is awaiting Medicare coverage. Expected date for coverage to begin:

Primary Insurance: Member ID:

Group Number: Subscriber's Name:

Insurance Co. Phone: Employer:

Prescription Drug Card Name:

Prescription Drug Card Phone:

Please include copies of patient's insurance cards (front and back) when faxing referral to expedite benefit clearance.

©2005 Teva Neuroscience 05262411/050720

PHYSICIAN INFORMATION

Physician's Name: Office Contact:

Hospital/Clinic: Nurse Contact:

Phone: Fax:

Address:

City/State/Zip:

Statement of Medical Necessity: Primary Diagnosis ICD-9 CM 340 Treatment of Relapsing Remitting form of Multiple Sclerosis

CHECK FOR PRESCRIPTIONS REQUIRED

☐ COPAXONE® (glatiramer acetate injection) 20 mg SC QD (once per day) 30 day supply with ancillary supplies Refills: 11 months

OR

☐ COPAXONE® (glatiramer acetate injection) 20 mg SC QD (once per day) 90 day supply with ancillary supplies Refills: 3

☐ autoject® 2 for glass syringe injection device/PRN Device with instructions for use and travel pouch (Free of charge)

INJECTION TRAINING ORDERS

Injection training will be/has been conducted by the physician's office? Yes [ ] No [ ] Date:

First dose of medication will be/has been administered by physician's office? Yes [ ] No [ ] Date:

Shared Solutions® to refer/coordinate injection training? Yes [ ] No [ ]

PATIENT AUTHORIZATION AND RELEASE

I authorize Teva Neuroscience, Inc. to enroll me in the Shared Solutions® program. I understand that this enrollment form will be sent to Shared Solutions® so I may be enrolled and that someone from Shared Solutions® will contact me soon about the program. I further authorize the designated Specialty Pharmacy that receives my prescription for COPAXONE® to release and communicate to Teva any and all information about my prescription for and my use of COPAXONE® so that Teva may continue to provide me with products, supplies and/or services through the Shared Solutions® program, aggregate data, conduct market analysis and provide me with educational and additional information regarding COPAXONE® and multiple sclerosis. I understand that this information, once released, may be redisclosed by Teva. I also understand that receipt of COPAXONE® is not conditioned on my signing this authorization. I further understand that this authorization is revocable by me in writing, except to the extent action has been taken in reliance on it, by giving written notice to Teva Neuroscience, Inc., 501 East 104th St., Suite 900, Kansas City, Mo. 64131-4509. Unless revoked by me in writing, this authorization will be effective for as long as I take COPAXONE®.

Patient's (or Authorized Representative's) Signature __________________________ Date __________________________

Prescriber's Signature __________________________ Date __________________________

(Mid Level Practitioner requires license # and responsible/directing physician's name in item #3 of form)
MS Variants
(or are they?)
Acute Disseminated Encephalomyelitis (ADEM)

- An acute or subacute inflammatory process of the CNS.
- Histology - multiple foci of perivascular demyelination.
- May occur after an acute viral or bacterial infection, immunization, or without a preceding cause.
- Quick onset with encephalitis-like symptoms such as fever, fatigue, headache, nausea and vomiting, and in severe cases, seizures and coma.
- The incidence rate is ~8 per 1,000,000 people per year.
- Children > adults - average age around 5 to 8 years old
- Monophasic. Recurrent cases do occur - ?MS
- Treatment is IV steroids.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ADEM</th>
<th>Childhood Multiple Sclerosis&lt;sup&gt;52&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence or prevalence</td>
<td>~ 0.4-0.8/100,000/y</td>
<td>~ 1.5-4/100,000 prevalence</td>
</tr>
<tr>
<td>Age, median, y</td>
<td>6.5*</td>
<td>14.25</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>Possible male preponderance</td>
<td>1.7:1 to 2:1 (F/M)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Preceding infection/vaccination</td>
<td>Monosymptomatic presentation</td>
</tr>
<tr>
<td></td>
<td>Headaches, fever, lethargy</td>
<td>Pyramidal signs</td>
</tr>
<tr>
<td></td>
<td>Polysymptomatic presentation</td>
<td>Mononuclear optic neuritis</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td>Brainstem symptoms</td>
</tr>
<tr>
<td></td>
<td>Brainstem symptoms</td>
<td>Transverse myelitis</td>
</tr>
<tr>
<td></td>
<td>Altered mental state†</td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>Lymphocytic pleocytosis</td>
<td>Lymphocytic pleocytosis</td>
</tr>
<tr>
<td></td>
<td>Raised albumin or protein levels</td>
<td>Intrathecal immunoglobulin synthesis</td>
</tr>
<tr>
<td></td>
<td>Oligoclonal banding in 12.5%†</td>
<td>Oligoclonal banding in 40%-67%&lt;sup&gt;38,53&lt;/sup&gt;</td>
</tr>
<tr>
<td>MRI</td>
<td>Extensive lesion load§</td>
<td>Sole presence of well-defined lesions</td>
</tr>
<tr>
<td></td>
<td>Confluent and ill-defined lesions§</td>
<td>Corpus callosum long axis perpendicular</td>
</tr>
<tr>
<td></td>
<td>Bilateral deep gray matter lesions (thalamus, basal ganglia)§</td>
<td>lesions (Dawson fingers)</td>
</tr>
<tr>
<td></td>
<td>Perifocal edema and mass effect</td>
<td>Periventricular lesions</td>
</tr>
<tr>
<td></td>
<td>Absence of previous demyelinating activity</td>
<td>Hypointense “black holes” on T1-weighted images</td>
</tr>
<tr>
<td>Follow-up MRI</td>
<td>Status quo or lesion resolution; new lesions are not compatible with ADEM</td>
<td>Dissemination in time and space; evolution of clinically silent lesions possible</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Recovery over 1-6 months</td>
<td>Relapse remission usually in weeks</td>
</tr>
<tr>
<td></td>
<td>60%-80% of cases fully recover</td>
<td>Relapse rate lower than in adult MS</td>
</tr>
<tr>
<td></td>
<td>Monophasic disease course</td>
<td>Median time to reach EDSS 4.0 is 20 years&lt;sup&gt;‖&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Bickerstaff brainstem encephalitis vs Miller Fisher syndrome

• Bickerstaff as the name implies affects the brainstem and can lead to confusion and coma
• May be on a spectrum with Miller Fisher syndrome with a triad of ophthalmoplegia, ataxia and areflexia.
• Miller Fisher syndrome is associated with serum anti-GQ1b IgG antibody
• Good prognosis
• Treatment usually with plasmapheresis or IVIG
Weston-Hurst syndrome

- Acute hemorrhagic leukoencephalitis (AHL, or AHLE), acute necrotizing hemorrhagic leukoencephalitis (ANHLE), acute necrotizing encephalopathy (ANE), or acute hemorrhagic encephalomyelitis (AHEM)
- Hyperacute and frequently fatal form of ADEM.
- Characterized by necrotizing of venules and edema.
- Treat aggressively with IVIG, cyclophosphamide, plasma exchange, and corticosteroids.
Marburg (Acute MS)

• severe, acute MS
• ? If on a spectrum with RRMS
• monophasic illness
• malignant course with death as a possible outcome
• Poorly responsive to steroids
Balo’s concentric sclerosis

- Unknown why the concentric circles develop
- Can be seen in RRMS
- Tends to be associated with Marburg MS
Tumefactive MS

• Size greater than 2 cm
• Presence of a mass effect, edema, or ring enhancement
• May be associated with better prognosis
• Rule out:
  – gliomas
  – metastases
  – abscesses
Neuromyelitis Optica (NMO)
Davic’s Disease
Background

- Neuromyelitis optica (NMO) – is also known as Devic’s disease and optic-spinal MS.
- Mainly affects the optic nerves and spinal cord and both the gray and white matter.

A. NMO lesion affecting gray and white matter

B. KiM1P stain – macrophages

Lucchinetti et al 2002
History of NMO

• Allbutt (1870) recognized an association of spinal cord disease with vision loss.
• Erb (1880) provided the first thorough description of NMO.
• Eugene Devic (1894) presented a review of 16 cases of NMO – mostly severe, monophasic illness.


Wingerchuk et al 1999
Diagnosis requires all absolute criteria and one major supportive criterion or two minor supportive criteria.

**Absolute criteria**
1. Optic neuritis
2. Acute myelitis
3. No evidence of clinical disease outside of the optic nerve or spinal cord

**Supportive criteria**

**Major**
1. Negative brain MRI at onset (does not meet criteria of Paty et al.\(^9\)) (25/28 patients)
2. Spinal cord MRI with signal abnormality extending over ≥3 vertebral segments (21/23 patients)
3. CSF pleocytosis of $\geq 50$ WBC/mm\(^3\) OR $\geq 5$ neutrophils/mm\(^3\) (20/54 patients)

**Minor**
1. Bilateral optic neuritis (59/71 patients)
2. Severe optic neuritis with fixed visual acuity worse than 20/200 in at least one eye (31/69 patients)
3. Severe, fixed, attack-related weakness (MRC grade ≤2) in one or more limbs (32/71 patients)

*Wingerchuk et al 1999*
Variant of Multiple Sclerosis???

- Until recently, it was thought that NMO was a more severe variant of MS.
- The pathology differs between MS and NMO as do treatments. NMO responds better to immunosuppression (worse with interferons) and MS to immunomodulation.

<table>
<thead>
<tr>
<th></th>
<th>T cells</th>
<th>MO</th>
<th>Ig</th>
<th>C9neo</th>
<th>E</th>
<th>N</th>
<th>Hyalinized vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMO (n = 8)*</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>56</td>
<td>56</td>
<td>100</td>
</tr>
<tr>
<td>Multiple sclerosis (n = 73)</td>
<td>100</td>
<td>100</td>
<td>52</td>
<td>52</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>ADEM (n = 3)</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spinal cord infarction (n = 3)</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*The single autopsy case with no actively demyelinating lesions was not included in this analysis; †21 of 21 early active NMO lesions contained eosinophils. MO = macrophages; Ig = immunoglobulin deposition; E = eosinophils; N = neutrophils.

Lucchinetti et al 2002
Pathology suggested a humoral autoimmune component in NMO with vasculocentric deposition of complement (A, E), IgG (B), and IgM (C).

*Lucchinetti et al 2002*
Autoimmune antibody in NMO

NMO-IgG outlines CNS microvessels, pia, subpia, and Virchow-Robin space.
- Sensitivity 73% (95% CI 60-86)
- Specificity 91% (95% CI 79-100)

Lennon et al 2004
Staining of sera from patients with NMO is similar to Aquaporin-4

- Brain – Virchow-Robin space (pial-astrocyte interface) in mouse cerebellar cortex and midbrain. Pia, subpia and microvessels.
- Kidney – distal collecting tubules of medulla
- Stomach – basolateral membrane of gastric mucosa

Green: IgG from NMO patients.
Red: Aquaporin-4
Yellow: Colocalization

Lack of staining by NMO IgG in Aquaporin-4 null mice

Lennon et al 2005
New NMO guidelines

- Optic neuritis
- Myelitis
- At least two of the following three criteria:
  - MRI evidence of a contiguous spinal cord lesion 3 or more segments in length
  - Brain MRI nondiagnostic for multiple sclerosis
  - NMO-IgG seropositivity

* CNS involvement beyond the optic nerves and spinal cord is compatible with NMO.

Wingerchuk et al 2006
- Symmetric diffuse white matter lesions

- Symmetric periaqueductal lesions

- Symmetric diencephalic lesions

Pittock et al 2006
Diagnosis of NMO

Diagnostic criteria for NMOSD with AQP4-IgG
1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)
Diagnosis of NMO—seronegative

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status
1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over $\geq 3$ contiguous segments (LETM) OR $\geq 3$ contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)
anti-AQP4 titer after high-dose IV methylprednisolone (HIMP)

Takahashi et al, 2007
Treatment of NMO

• An International Consensus Group\textsuperscript{1} recommends
  – Azathioprine, mycophenolate, rituximab, or prednisone first line therapy
• ABC-R therapies are usually ineffective (IFN$\beta$ probably worsens NMO)
• There are reports of natalizumab and fingolimod exacerbating NMO
• Trials underway with antiCD19 and IL6.
• Tocilizumab may be an option if nonresponsive to antiCD20.\textsuperscript{2}

Overlap of ON with Lupus and Sjogrens

System Lupus Erythematosus

A. Peripheral nervous system manifestations
   1. Acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome)
   2. Autonomic disorder
   3. Mononeuropathy (single/multiplex)
   4. Myasthenia gravis
   5. Neuropathy (cranial)
   6. Plexopathy
   7. Peripheral neuropathy
B. Central nervous system manifestations
   1. Acute confusional syndrome
   3. Cerebrovascular disease
   4. Cognitive dysfunction
   5. Demyelinating syndrome
   6. Headache
   7. Movement disorder
   8. Myelopathy
   9. Seizure
C. Psychiatric manifestations
   1. Anxiety disorder
   2. Mood disorder
   3. Psychosis

Sjögren's syndrome

Sicca symptoms:
dry mouth/eyes

Testing:
+ Schirmer's test,
+ Salivary gland bx
+ SSA/SSB

*Adapted with permission from Lupus, 2003;12:872–876.
MS vs NMO

- **MS**
  - Short Spinal cord lesions (<2 vertebral segments)
  - Affects white matter in the periphery of cord
  - + brain MRI

- **NMO**
  - >3 vertebral segments
  - Located centrally within the cord affecting both white and gray matter.
  - May extend into brainstem (hiccups, N/V)
  - +NMO-IgG
Thank You!!

Any questions???

Did anybody call for a dogtor?