Multiple Sclerosis
ID: 20 yr old, previously healthy, university student
RFR: Query MS

TIME LINE:
April 2003 - viral URTI with rash, sore throat and coryza
May 2003 – Left hemi-numbness and paraesthesia
June 2003 – paraparesis, incontinence and vertigo
  O/E – nystagmus on right lateral gaze
  - extremity weakness, no spasticity
  - ↓ pain and temp sense in Left leg and arm
  - received several doses of Solumedrol

MRI (from Mississauga Hospital)
- hyper-dense lesions on T2, prominent involvement of peri-ventricular region and brain stem as well as basal ganglia

THEN.............
Developed hypercapnia and was intubated, transferred to MUMC and admitted to ICU

O/E
• Flaccid paraparesis lower extremities (0/5)
• Upper Extremity flaccidity (R > L)
• Reflexes absent at knees and ankles, Babinski down bilateral
• Able to discriminate light touch and pressure, but not vibration and light touch

Dx: ? Any thoughts?
Tx: Solumedrol and IvIg
Further Workup in ICU

**Serology**
- Anti Hep C Ab – Neg
- HBsAg - Neg
- HIV, WNV, Lyme Disease - ?

**LP**
- + Protein
- + Lymphocytes
- + Oligoclonal Bands

**Autoimmune Work-up**
- IgA 1.3
- IgG 30.60 ↑
- IgM 1.12
- pANCA <1.0
- cANCA <1.0
- ENA +
- Ribonuc Prot –
- Smith Ab –
- SSB (Latimer) Ab –
- SSA (Rose) Ab +
- JO-1 –
- Scleroderma Ab –
- Rheumatoid Factor 16.2
- Lactate 3.3
Required tracheostomy for 1 month, but was eventually extubated in early July. Also developed sacral ulcer in ICU.

**July 2003** – Transferred to 3Y
- Regaining motor function, improved mobility
- Vision improvements
- Increasing independency
- Overall improved cognitive function

Accepted as Candidate for Rehab at Chedoke (Aug 21) and all was going well……..

**UNTIL………..**
Sept 1 – weakness, slurred speech and difficulty swallowing
- found to have E.Coli in urine, sens to Cephazolin

Sept 2 – trachycardia (160), normotensive and ↓u/o

Sept 3 - ↑fatigue, ↓initiation, ↓speech
- AVSS, alert and oriented
- now requiring 2 person transfer (deteriorated)

Sept 4 - ↑spasticity, ↓LOC and ↓swallow
- MRI - ↑signal in left brainstem (new) and
  + gadolinium in R temporal and L occipital

Transferred back to MUMC
**Medications:**
- Solu-Medrol 1000ug IV OD x 3 days
- Cefazolin 1 mg IV q8h x 7 days
- IVIg 40g IV OD x 2 days
- Vit B12 1000mEq SC/IM x 1
- Potassium Citrate 25mEq PO OD
- Dalteparin 5000U PO OD
- Senna syrup 2 tabs qhs

**Allergies** – All Tapes
On Examination

Vitals  BP102/72   HR 96, reg   RR 18   Sat 98\(^\circ\)
General  tired but arousable
Neuro  alert, PEARL, bilat pupils 5mm
        able to follow step-wise commands
        ptosis R>L,   Left afferent pupillary defect
        slurred speech, poor swallow
Motor  L arm >4, R arm <3, L leg 2/5, R leg 0/5
        spasticity and clonus in legs
DTR’s 2+ in lower extrem, 1+ in upper extrem
        babinski’s – up on left, right questionable
CVS Normal S1, S2,pisa3,S4,m
Resp ↓B/S to Left Lung, shallow breathing, Øcrackles or wheezes, Øcyanosis
        Ø accessory muscle use
Abdo  eythematos rash RUQ (since putting on gown)
        flat, soft, Øtender, Ømasses, ØHSM, +BS
Labs

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<td>235</td>
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Urine Analysis from Sept 1 - E. Coli sens. to cefazolin
ESR 27 ↑
CRP 16.5 ↑
Thyroid Peroxidase Ab –neg
Thyroglobin Ab –neg
ACTH stim test – cortisol 404 – 995 (Normal)
Issues so far:
1. Neurologic → ADEM vs MS vs metabolic/genetic
   • Is this deterioration 2° to UTI?
   • Does not seem to be improving on IV steroids and IVIg
   • Repeat MRI showing new lesions
   • Being seen by neuromuscular and neurology
2. UTI – being treated with Abx
3. ↓ swallow – NG tube vs PEG tube
4. Sacral Ulcer – wound care and culture pending
Anatomy Review

- Nervous System
  - CNS
  - PNS
    - ANS
    - SNS
    - ENS
Cell Types

- Neurons
- Neuroglia
  - Astrocytes
  - Oligodenrocytes
  - Microglia
  - Ependymal cells
- Chemical Environment
  - Myelin Sheath
  - Engulfs microbes/debris
- Line ventricles
- Myelination
  - Schwann
  - Oligodendrocyte
Signal Transmission
Epidemiology

- 1/1000 in Northern European Countries/North America
- Median Age Of Onset 23.5-30
- Females > Males
Multiple Sclerosis

Demyelinating disorder characterized by distinct episodes of neurological deficits separated in time, attributable to white matter lesions that are separated in space
Pathophysiology

- **Environmental?**
  - Highest prevalence in northern climates even standardizing for ethnicity
  - Age 15 may be important
  - Twin Studies (monozygotic twins have 25% concordance rate)

- **Genetic?**
  - Migration studies show that low risk populations increase their risk when they move to northern climates but rates don’t reach peak
  - First degree relatives at increased risk (3-5% or 30-50x the background risk)

- **Immune Factors?**
Immune?

Hypothesized stimulus of the immune system

- Many viruses associated with MS although none conclusively linked (observational).
- EBV
  - Increased risk of MS following infections
  - Elevations in anti-EBV antibody titers before onset of MS (Nurses’ Health Study)
Experimental Allergic Encephalomyelitis

- Animal Model resembling MS
- Injection of MBP and Freund’s complete adjuvant into certain mice can induce EAE
- Cloned T cells then can be transferred to syngeneic mice and cause EAE
Autoimmune

Chronic Inflammatory Cells within and around MS plaques
- Both CD8+ and CD4+ T cells
- Macrophages
- Role for antibody mediated immunity as CSF immunoglobulin found in patients with MS
Pathophysiology

Multiple Sclerosis Pathogenesis

- Pre-existing myelin-reactive T-cells
- Peripheral activation - molecular mimicry? - superantigens? - other factors?
- Local activation proliferation
- Adhesion & penetration
- Secondary influx

- Antigen-presenting cell
- Plasma cell
- Astrocyte
- Neuron
- Antibody
- Complement
- Oligodendrocyte
- Myelin sheath

- Basement membrane
- Blood vessel

from Hohlfeld, Brain, 1997
Clinical Presentation

- Onset between ages 15-50
- Optic Neuritis
- Internuclear ophthalmoplegia
- Lhermitte’s Sign
- Fatigue
- Uhthoff’s Phenomenon
Optic Neuritis

- Unilateral eye pain accentuated by ocular movements, variable degree of visual loss, relative afferent pupillary defect.
- 90% regain vision over 2-6 months
- Reported risk of progression to MS after case of ON is 15-75%
  - About 50-70% of ON have cranial MRI findings consistent with MS
  - Of those about 50-60% go on to develop MS in 5 years
Optic Neuritis
Internuclear Ophthalmoplegia

- Abnormal horizontal ocular movements with lost or delayed adduction and horizontal nystagmus of abducting eye.
- Lesion of MLF
- Can be bilateral
Sensory Symptoms

Commonly described as numbness, tingling, pins and needles, tightness, coldness or swelling

- Varying degrees of vibration and joint position sense
- Decreased pain and light touch in extremities
- Patchy areas of decreased pain and light touch on trunk
# Clinical Presentation

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<th>Symptom</th>
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<th>Total</th>
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<td>Balance Problems</td>
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<tr>
<td>Sensory in Face</td>
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<td>Lhermitte’s Sign</td>
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<tr>
<td>Vertigo</td>
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<tr>
<td>Bladder Problems</td>
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<td>Limb Ataxia</td>
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<tr>
<td>Pain</td>
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<td>0.5</td>
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# Differential Diagnoses

## Inflammatory Diseases
- Acute disseminated encephalomyelitis
- Systemic Lupus Erythematosus
- Polyarteritis Nodosa
- Sjögren's Disease
- Behcet's Disease
- Granulomatosis angiitis
- Paraneoplastic encephalomyelopathies

## Infectious Diseases
- Lyme Neuroborreliosis
- HTLV-1
- HIV
- Progressive multifocal leukoencephalopathy
- Neurosyphilis

## Granulomatous Diseases
- Sarcoidosis
- Wegener's granulomatosis
- Lymphomatoid granulomatosis

## Diseases of Myelin
- Adult metachromatic leukodystrophy
- Adrenomyeloneuropathy

## Other
- Vitamin B12 Deficiency
- Arnold-Chiari Malformation
- Spinocerebellar Disorders
Features that are not quite in keeping with MS

- FmHx of neurological disease
- A well demarcated spinal level in the absence of disease above the foramen magnum
- Prominent back pain that persists
- S&S that can be attributed to one anatomical site
- Patients > 60 yrs or < 15 at onset
- Progressive disease
Workup

- CBC with differential, urinalysis, chemistry panel, ALT, ALP, total protein, Alb, Ca, serum glucose, Globulin, Phosphorous.
- Blood work should test for relevant infectious possibilities including HIV, HTLV, and syphilis.
- Autoimmune/idiopathic inflammatory blood serologies should also be checked, including sed rate, ANA, ENA, ANCA, paraneoplastic panel, and ACE.
- Metabolic blood parameters should be measured including B12, sensitive TSH, and free T4.
- CSF is usually examined for glucose, protein, cell count, cytology, immunoglobulin gamma index, oligoclonal bands, and relevant bacterial, mycobacterial, or fungal cultures.
- MRI looking for lesions and compressions.
Diagnostic criteria I
(Ann Neurol 2001; 50:121-127)

- 2 or more attacks
- 2 or more objective clinical lesions

What Is An Attack?
- Neurological disturbance of kind seen in MS
- Subjective report or objective observation
- 24 hours duration, minimum
- Excludes pseudoattacks, single paroxysmal episodes

Determining Time Between Attacks
- 30 days between onset of event 1 and onset of event 2
Diagnostic Criteria

Clinical lesions?
- Pyramidal (motor)
- Cerebellar (coordination)
- Brain stem (speech and swallowing)
- Sensory (touch and pain)
- Visual
- Mental
- Bowel and bladder

Example: Retrobulbar Neuritis x 2 wk 2/12 ago and now paraparesis x 4 hr. (N)
Diagnostic criteria II

- 2 or more attacks
- 1 objective clinical lesion

Plus

**Additional data needed:**
- Dissemination in space, demonstrated by:
  - MRI
  - Or
    - 2 or more MRI-detected lesions consistent with MS plus a positive CSF
- or await further clinical attack involving different site

Example: Retrobulbar Neuritis x 2 wk 2yr ago and now recurring. (N)
Diagnostic criteria II

MRI criteria
Three out of four:
- 1 Gadolinium-enhancing or 9 T2 hyperintense lesions if no Gd-enhancing lesion
- 1 or more infratentorial lesions
- 1 or more juxtacortical lesions
- 3 or more periventricular lesions

(1 spinal cord lesion = 1 brain lesion)
Positive CSF
- Oligoclonal IgG bands in CSF (and not serum)

or
- elevated IgG index

Example:
- Retrobulbar Neuritis x 2 wk 2yr ago and now recurring. MRI shows some lesions in spinal cord, many supratentorial lesions and a few infratentorial lesions. (Y)
- Retrobulbar Neuritis x 2 wk 2yr ago and now recurring. MRI shows many supratentorial lesions only and CSF is normal. (N)
3 Head MRI of patients with MS. 

A, T1-weighted sagittal image showing multiple hypointense periventricular lesions. 

B, Axial T2-weighted image showing confluent periventricular high-intensity lesions most prominent at the frontal and occipital horns. A focal lesion is also present in the posterior limb of the left internal capsule. 

C and D, Periventricular lesions suggestive of MS.
Diagnostic criteria III

- Only one attack
- 2 objective clinical lesions

Plus

**Additional data needed:**
- Dissemination in time, demonstrated by:
  - MRI
  Or
  - Second clinical attack

- Example: Retrobulbar Neuritis x 2 wk and incontinence x 1 wk 2 yr. MRI shows lesions in frontal lobes. (N)
What Provides MRI Evidence Of Dissemination In Time?

A Gd-enhancing lesion demonstrated in a scan done at least 3 months following onset of clinical attack at a site different from attack, or

In absence of Gd-enhancing lesions at 3 month scan, follow-up scan after an additional 3 months showing Gd-lesion or new T2 lesion.

Example: Retrobulbar Neuritis x 2 wk and incontinence x 1wk. MRI showed lesions in frontal lobes. MRI 4/12 later shows spinal cord lesions. (Y)
Diagnostic criteria IV

- Only one attack
- Only 1 objective clinical lesion (monosymptomatic presentation)

Plus

**Additional data needed:**
Dissemination in space by demonstrated by:
- MRI
- or positive CSF and 2 or more MRI lesions consistent with MS

**and** Dissemination in time demonstrated by:
- MRI
- or second clinical attack
Diagnostic criteria V

- Insidious neurological progression suggestive of MS (primary progressive MS)
  
  Plus **Additional data needed:**
  
  1) Positive CSF
  
  and 2) Dissemination in space demonstrated by:
  
  - MRI evidence of 9 or more T2 brain lesions
  - or 2 or more spinal cord lesions
  - or 4-8 brain and 1 spinal cord lesion
  
  or
  
  - positive VEP with 4-8 MRI lesions
  - or positive VEP with <4 brain lesions plus 1 spinal cord lesion
  
  and 3) Dissemination in time demonstrated by:
  
  - MRI
  
  or
  
  - continued progression for 1 year
**Diagnostic criteria V**

- **Visual Evoked Potential**
  - Pattern reversal stimulates a nerve transmission along
    - the optic nerve,
    - the optic chiasm
    - the optic tract to the lateral geniculate body.
    - From there a second axonal signal moves along the optic radiations
    - and the posterior periventricular white matter to the occipital cortex.
  - Normal total travel time < 100 milliseconds measured by EEG.
Natural History

- Most commonly characterized by acute or subacute onset of clinical dysfunction
- Frequency of relapses varies – average of 0.4 to 0.6 relapses per year
- Relapses more frequent during the first years of disease onset
- 15% will never experience second relapse
- Benign MS – patient remains fully functional in all neurologic systems 15 years after the disease onset
- Malignant MS – disease with rapid progressive course, leading to significant disability in multiple neurologic systems or death in a relatively short time after disease onset
Disease Progression

- Relapsing-remitting – clearly defined relapses with full recovery or residual deficit upon recovery
Disease Progression

- Primary progressive – disease progression from onset with occasional plateaus and temporary minor improvements
Disease Progression

- Secondary progressive – initial RR disease followed by progression with or without occasional relapses, minor remissions and plateaus
Progressive relapsing – progressive disease from onset, with clear acute relapses; progression continues between relapses.

Clinic-based study by Weinshenker: found that 66% had RR disease at onset, 15% had PR, and 19% had PP.
Disease Progression

- Disease progression measured by Kurtzke disability score
- Expanded version (EDSS) also commonly used
- Emphasis on ambulation capabilities with scores above 4
- Quantifying MRI scans (correlate poorly with disability because of silent lesions)

**Kurtzke Disability Status Scale**

1. No disability and minimal neurologic signs
2. Minimal disability (e.g., slight weakness or stiffness, mild gait or visual disturbance)
3. Moderate disability (e.g., monoparesis, mild hemiparesis, moderate ataxia, disturbing sensory loss, prominent urinary or eye symptom, or combination of lesser dysfunction)
4. Relatively severe disability but fully ambulatory without aid, self sufficient and able to be up around 12 hours/day, does not prevent the ability to work or carry on normal living activities, excluding sexual dysfunction
5. Disability is severe enough to preclude working, maximal motor function involves walking unaided up to 500 meters
6. Needs assistance with walking (e.g., cane, crutches, or braces)
7. Restricted to a wheelchair but able to wheel oneself and enter and leave chair without assistance
8. Restricted to bed or chair, retains many self care functions and has effective use of arms
9. Helpless and bedridden
10. Death due to multiple sclerosis (from respiratory paralysis, coma, following repeated or prolonged epileptic seizures)
Prognostic Factors

- More benign course in females
- Onset at early age more favourable
- Better prognosis with relapsing form vs progressive form
- Increasing disability with higher rate of relapses early in disease
- Impairment of pyramidal, brain stem and cerebellar symptoms have poor prognosis
- Patient with known benign course of 15 years will rarely evolve into severe course
- The APOE epsilon 4 allele associated with faster progression of disability
Symptom Management

- Cognitive deficits – support, coping strategies, Rx of depression, interferon-beta-1a (Avonex)
- Tremor – anticonvulsants (carbamazepine, valproic acid, gabapentin), propranolol, clonazepam
- Impotence – sildenafil, prostaglandin
- Fatigue – amantidine, methylphenidate, modafinil
- Bladder dysfunction – oxybutinin, imipramine, tolteridine
- Spasticity – baclofen, zanflex, dantrum, benzodiazepines
Treatment

Acute attacks – corticosteroids

- Short courses of IV methylprednisolone (with or without short prednisone taper)
- High dose oral methylprednisolone with tapering
- Oral vs IV steroids – which is better?
Treatment

Relapsing remitting disease:

- Interferon-beta-1b (Betaseron) - lower exacerbation rate and frequency of relapses
- Interferon-beta-1a (IM - Avonex and SC – Rebif)
- Glatiramer acetate (Copaxone) – daily SC injection
- Mitoxantrone (Novantrone) – chemotherapy agent
- No clear evidence for choosing one drug vs another
Treatment

Progressive disease

- Total lymphoid radiation, cyclosporine, methotrexate, cyclophosphamide, mitoxantrone, azathioprine, interferon, steroids, IVIG, plasma exchange, bone marrow transplant, anti-integrin antibodies

- Side effects in using immunosuppressive therapy for long-term
Acute Disseminated Encephalomyelitis (ADEM)

Classically, a monophasic inflammatory disorder of the CNS following acute measles infection or rabies vaccination

Substantiation of these associations require strong epidemiological data &/or a pathognomonic lab finding for ADEM

Difficult to distinguish ADEM from MS with hx of nonspecific viral illness
Pathophysiology of ADEM

Likely, transient autoimmune response towards myelin or other self-antigens via molecular mimicry or nonspecific activation of autoreactive T cell clones
Comparing ADEM and MS

- Onset
- Clinical Course
- Clinical Diagnostic Features
- Common Clinical Features
- Prognostic Factors
- Pathology
- MRI
- CSF
Onset

- ADEM rapid onset (abrupt or up to several hours)
- MS variable onset
Clinical Course

- ADEM patient reaches peak dysfunction within several days
- Recovery begins within days and continues for weeks to months (Complete recovery 50%)
- Relapses are rare
- Mortality 10-30%

- MS:
  - Relapsing-remitting
  - Primary Progressive
  - Secondary Progressive
  - Clinically Inactive
  - Mixed
**Clinical Diagnostic Features**

- **ADEM may have**
  - Lethargy to coma
  - Seizures
  - Hemiparesis
  - CN palsies
  - Paraparesis

- **MS diagnosis requires 2 lesions**
  (clinically or on investigations) that are separated in time and location

- **Age of onset between 15-50 years old**

- **Usually relapses and remits**
Common Clinical Features

- ADEM
- Simultaneous bilateral optic neuritis
- LOC
- Meningimus
- Loss of DTR with retained abdominal reflexes with Babinski’s reflex
- Temp. 37.8°C (100°F)

- MS
- Unilateral optic neuritis
- Preserved awareness
- Diplopia (INO)
- Hyperactive reflexes
- L’hermitte’s sign
- Uhthoff’s sign
Prognostic Factors

- ADEM
- Proceeding measles infection
- Rapidity and severity
- CSF with high protein and WBC

- MS
- High lesion load
ADEM perivascular inflammation, edema, and demyelination. These lesions usually show partial resolution after weeks without the appearance of new lesions.

MS multifocal areas of demyelination with surrounding edema, loss of oligodendrocytes, astroglial scarring.
ADEM may produce small perivenous lesions often uniform in size.

After weeks, disappearance of previous lesions without new lesions.

Cerebral or spinal plaques in the periventricular white matter, corpus callosum, centrum semiovale, and deep structures.
CSF

**ADEM**
- Normal pressure
- Normal cell count
- Modest ↑ in protein
- Usually no oligoclonal banding
- Myelin banding protein

**MS**
- Normal pressure
- WBC normal in 66 %
- ↑ IgG
- Oligoclonal banding in 85-95 %
- Myelin banding protein