Chief Round
Multiple sclerosis

神經內科 R3 田怡婷
Date 2013/03/13
Outlines

- Introduction
- Pathophysiology
- Clinical manifestation
- Image findings
- Diagnostic criteria
- Treatment
Disease of myelin

Autoimmune
- Acute disseminated encephalomyelitis
- Acute hemorrhagic leukoencephalopathy
- Multiple sclerosis

Infectious
- Progressive multifocal leukoencephalopathy

Toxic/Metabolic
- Carbon monoxide
- Vitamin B12 deficiency
- Mercury intoxication (Minamata disease)
- Alcohol/tobacco amblyopia
- Central pontine myelinolysis
- Marchiafava-Bignami syndrome
- Hypoxia
- Radiation

Vascular
- Binswanger disease

Hereditary Disorders of Myelin Metabolism
- Adrenoleukodystrophy
- Metachromatic leukodystrophy
- Krabbe disease
- Alexander disease
- Canavan-van Bogaert-Bertrand disease
- Pelizaeus-Merzbacher disease
- Phenylketonuria
Age of onset

- Mean and median age of onset in relapsing forms of MS is age 29 to 32
  - the peak age of onset is approximately 5 years earlier for women than for men
  - female to male subjects was 1.77 : 1.00 (F > M)
- Primary progressive MS (PPMS) has a mean age of onset of 35 to 39 years
- The onset of MS can occur decade
- Perhaps as many as 5% of cases of MS have their onset before age 18
Epidemiology and genetics

- 350,000 in the US, > 1 million worldwide
- Genetic and environmental factors
  - risk of developing MS: 0.1% generally, 2%–4% if a first-degree relative had MS, 30% if monozygotic twins
  - northern latitude (esp >15y/o) → ??
  - race is a determinant of MS risk
  - human lymphocyte antigen alleles DR21501B1
  - low vitamin D levels
Natural history

- 10yrs- 50% use a cane, 15% wheelchair
- About 50% had acceleration of disability and a paucity of effective therapies
- More malignant clinical course in man
- Favorable prognostic factors:
  - Relapse ↓ 70% in 3rd trimester of pregnancy
  - Infrequent exacerbations, esp in the 1st yr
  - Sensory symptoms predominating over motor or cerebellar dysfunction
  - Good functional recovery from each exacerbation
Natural history

- The number of exacerbations in the earliest phase strongly influences level of disability
  - normal brain MRI at diagnosis: no accrue significant disability over 14 years
  - $\geq 10$ MR lesions or a change in lesion load within the first year: significantly more likely to progress to advanced disability (e.g., ambulation with a cane or walker)
Outlines

- Introduction
- Pathophysiology
- Clinical manifestation
- Image findings
- Diagnostic criteria
- Treatment
Pathophysiology

- The manifestations of the pathological process seen in the CNS
- demyelination and a moderate degree of axonal loss as evident from detailed pathological and advanced magnetic resonance imaging (MRI) techniques
Fig. 54.1 Schematic diagram of impulse conduction in normal (upper panel) and demyelinated (lower panel) regions of a nerve fiber. Solid arrow indicates the direction of impulse conduction; red area indicates the region occupied by the impulse. Current flow is indicated by broken arrows. In normally myelinated regions (upper), the high resistance, low capacitance directs the majority of action current to the next node of Ranvier. In contrast, in demyelinated regions (lower), action current is short-circuited through the damaged myelin sheath or denuded regions of the axon, so further propagation of the action potential is blocked.

Pathological hallmark of MS is the *cerebral or spinal plaque*

- discrete region of demyelination with relative preservation of axons

Heidenhain myelin stain

Holzer stain for gliosis
Neuropathology

- Histopathologic hallmark of MS: perivenous inflammation $\Rightarrow$ demyelination, axonal injury and transaction, neurodegeneration $\Rightarrow$ gliotic sclerosis
- unknown initial trigger of the immune cascade, maybe breakdown of myelin by an infectious agent or immune system dysregulation with failure to recognize and avoid immunologic reactions to self antigens
Outlines

- Introduction
- Pathophysiology
- Clinical manifestation
- Image findings
- Diagnostic criteria
- Treatment
Cognitive Impairment

- Only 5% of patients with MS suffered from cognitive impairment (1981, Kurtzke)
- The most frequently reported abnormalities are with working memory, attention, and speed of information processing
- Patients complain of memory loss, difficulties at work or with interpersonal relations, inability to multitask
  - Comorbid depression, anxiety disorders, and emotional lability
Cognitive Impairment

- The Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Rao et al., 1991)
- Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) (Benedict et al., 2002)
- Paced Auditory Serial Addition Test (PASAT) (Cutter et al., 1999)
Cognitive Impairment

- Lesions located in frontal and parietal lobes
  - processing speed, attention, and verbal memory
- Global and regional atrophy
- Thalamic atrophy
Cognitive Impairment

- Intramuscular (IM) interferon beta-1a showed a 47% reduction in cognitive decline (Fischer et al., 2000).
- L-amphetamine is associated with improved learning and memory in cognitively impaired MS patients (Benedict et al., 2008; Morrow et al., 2009)
- Modafinil may improve focused attention and dexterity and palliate fatigue.
Affective Disorders

- **Depression** is the most common manifestation
  - More prevalent in MS than in other chronic diseases (50% versus 12.9%) → suggesting an organic component
  - Frontal or subcortical white-matter disease may also be a contributory causative factor

- **Euphoria**, formerly considered to be common in MS, is actually infrequent and is usually associated with moderate or severe cognitive impairment

- Emotional “dyscontrol” is quite common
Cranial Nerve Dysfunction

- Optic neuritis (ON) is the most frequent type of involvement of the visual pathways
  - Relative afferent pupillary defect (RAPD) or Marcus Gunn pupil
  - 90% of patients regain normal vision → over a period of 2 to 6 months
- Bilateral simultaneous ON is rare in MS
  - Usually unilateral acute or subacute syndrome
- Mapping of visual fields reveals a central or cecocentral scotoma (central scotoma involving the physiological blind spot)
Cranial Nerve Dysfunction

- **Uhthoff phenomenon** → recurrence of a neurological symptom following an increase in body temperature
  - Hot weather, exercise, fever or saunas and hot tubs
Cranial Nerve Dysfunction

- Impairment of individual ocular motor nerves is infrequent in MS
  - vestibulo-ocular connections and internuclear connections
    > CN VI > CN III > CN IV
- Nystagmus is a common finding in MS
  - *acquired pendular nystagmus* → *oscillopsia*
- *Internuclear ophthalmoplegia* (INO)
  - abnormal horizontal ocular movements with lost or impaired adduction and horizontal nystagmus of the abducting eye
  - Lesion of MLF on the side of diminished adduction; Convergence is preserved
Cranial Nerve Dysfunction

- Impairment of facial sensation is a relatively common finding in MS
- *Facial myokymia*, a fine, undulating wavelike facial twitching, and hemifacial spasm can be caused by MS
- Vertigo is a reported symptom in 30% to 50% of patients with MS and is commonly associated with dysfunction of adjacent brainstem or cranial nerves
Impairment of Sensory Pathways

- Sensory manifestations are a frequent initial feature of MS
  - spinothalamic, posterior column, or dorsal root entry zone lesions
  - numbness, tingling, pins and needles, tightness, coldness, itching, or swelling of limbs or trunk
- A bilateral sensory level (ascending) is a more frequent finding than a hemisensory (Brown-Séquard) syndrome
Impairment of Motor Pathways

- Corticospinal tract dysfunction is common in MS
- Paraparesis or paraplegia occurs more frequently than significant weakness in the upper extremities
  - Deep tendon reflex exaggerated
  - Sustained clonus
  - Extensor plantar responses
Impairment of Cerebellar Pathways

- Cerebellar pathway impairment results in gait imbalance, difficulty performing coordinated actions with the arms, and slurred speech
  - dysmetria, decomposition of complex movements, and hypotonia
  - walking is impaired by ataxia
  - ocular findings of nystagmus, ocular dysmetria, and frequent refixation saccades
  - speech can be scanning or explosive in character
Impairment of Bladder, Bowel, and Sexual Functions

- The extent of sphincter and sexual dysfunction often parallels the degree of motor impairment in the lower extremities.
- Most common complaint related to urinary bladder dysfunction is urgency → uninhibited detrusor contraction.
- Involvement of sacral segments of the spinal cord, symptoms of bladder hypoactivity may evolve (e.g., decreased urinary flow, interrupted micturition, incomplete bladder emptying).
Impairment of Bladder, Bowel, and Sexual Functions

- Constipation is more common than fecal incontinence
- Sexual dysfunction
### Table 54.2  Common Clinical Features of Multiple Sclerosis

<table>
<thead>
<tr>
<th>Clinical Features Suggestive of Multiple Sclerosis</th>
<th>Clinical Features Not Suggestive of Multiple Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset between ages 15 and 50</td>
<td>Onset before age 10 or after age 60</td>
</tr>
<tr>
<td>Involvement of multiple areas of the CNS</td>
<td>Involvement of the PNS</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Hemianopsias</td>
</tr>
<tr>
<td>Lhermitte sign</td>
<td>Rigidity, sustained dystonia</td>
</tr>
<tr>
<td>Internuclear ophthalmoplegia</td>
<td>Cortical deficits such as aphasia, apraxia, alexia, neglect</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Deficit developing within minutes</td>
</tr>
<tr>
<td>Worsening with elevated body temperature</td>
<td>Early dementia</td>
</tr>
</tbody>
</table>

*CNS, Central nervous system. PNS, peripheral nervous system.*

**NICP 6th edition, Chapter 54**
Outlines

- Introduction
- Pathophysiology
- Clinical manifestation
- Image findings
- Diagnostic criteria
- Treatment
MRI

- Ovoid lesion perpendicular to the ventricles, particularly in sagittal T2-weighted

- **Dawson’s fingers**: emanate from the ependymal zone of the ventricles and extend upward into the white matter-corona radiata, corpus callosum, centrum semiovale, and juxtacortical areas and in gray matter

- The **spinal cord** lesions tend to be **cigar-shaped**, span one to two segments, and have a predilection for the **cervical** spinal cord

- MR lesions usually lasts only 2-4 wks in any lesion, but sometimes up to a few months
Fig. 2. A sagittal fluid-attenuated inversion recovery (FLAIR) MR image demonstrates subependymal hyperintensities radiating out into the deep white matter often referred to as “Dawson’s Fingers”.
Fig. 3. An axial fluid-attenuated inversion recovery (FLAIR) MR image shows juxtacortical gray matter hyperintensities (arrows). Gray matter involvement is underrepresented by routine MR imaging and is involved early in the disease course.
Fig. 4. Fluid-attenuated inversion recovery sequence on MR imaging is superior for the detection of MS plaques because the CSF appears black, which increases the contrast. On T2-weighted MRI, the MS plaques and CSF are white, which makes it more difficult to distinguish. (A) An axial FLAIR MR image demonstrates a periventricular MS plaque (arrow) with high contrast between black CSF and white MS plaque. (B) An axial T2-weighted MR image demonstrates low contrast between white CSF and white MS plaque (arrow).
Secondary progressive MS. A sagittal FLAIR image (A) reveals multiple periventricular white matter lesions consistent with MS. Note that many of the lesions are hypointense on the pregadolinium T1-weighted image (B). Persistent T1-hypointense lesions (“black holes”) represent areas of significant demyelination and axonal damage and have a stronger correlation with disability than T2-hyperintense lesions, especially in patients with secondary progressive MS.
**Fig. 54.11 A-B,** Areas of confluent demyelination in a severely affected progressive multiple sclerosis patient. Outlines show volume of interest selected for spectroscopy study. **C,** Spectra obtained with proton spectroscopy in this patient. **D,** Spectra of normal brain. Note reduced height of N-acetylaspartate (NAA) peak, with resultant reduction in the ratio of NAA to creatine (Cr). CHO, Choline; LA, lactic acid.
Outlines

- Introduction
- Pathophysiology
- Clinical manifestation
- Image findings
- Diagnostic criteria
- Treatment
Diagnostic Criteria

- CSF analysis
- Evoked potentials (EP)
- Neuroimaging

**Box 54.2 Paraclinical Evidence in Multiple Sclerosis Diagnosis**

**What Is a Positive MRI?**
Three out of four of the following:
- 1 gadolinium-enhancing brain or cord lesion or 9 T2 hyper-intense brain and/or cord lesions if there is no gadolinium-enhancing lesion
- 1 or more brain infratentorial or cord lesions
- 1 or more juxtacortical lesions
- 3 or more periventricular lesions

*Note: Individual cord lesions can contribute along with individual brain lesions to reach required number of T2 lesions.*

**What Provides MRI Evidence of Dissemination in Time?**
A gadolinium-enhancing lesion detected in scan at least 3 months after onset of initial clinical event at a site different from initial event

**OR**
A new T2 lesion detected in a scan done at any time compared to a reference scan done at least 30 days after initial clinical event

**What Is Positive CSF?**
Oligoclonal IgG bands in CSF (and not serum) or elevated IgG index

**What Is Positive VEP?**
Delayed but well-preserved waveform

*NICP 6th edition, Chapter 54*
CSF analysis

- Cell counts are typically normal but may be slightly elevated in 15% to 20% of patients (T lymphocytes predominant)
- It is common to see mild elevations of albumin in 20% to 30% of MS patients

| Table 54.5  Cerebrospinal Fluid Abnormalities in Multiple Sclerosis |
|----------------|--------|--------|--------|--------|----------------|
|                | Albumin | IgG/TP | IgG/Albumin | IgG Index | Oligoclonal Banding of Ig |
| Clinically definite multiple sclerosis | 23%     | 67%    | 60%-73%     | 70%-90%   | 85%-95%         |
| Normal controls          | 3%      | —      | 36%        | 3%        | 7%*             |
Diagnostic Criteria

- The common thread among all MS diagnostic criteria has been the requirement for symptoms and signs that are disseminated in time and space.

- Clinically isolated syndrome (CIS)
  - a monophasic neurological illness that is clinically consistent with MS
  - accompanied by typical multifocal white-matter lesions on MRI
### TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS

DIS Can Be Demonstrated by \( \geq 1 \) T2 Lesion\(^a\) in at Least 2 of 4 Areas of the CNS:

- Periventricular
- Juxtacortical
- Infratentorial
- Spinal cord\(^b\)

Based on Swanton et al 2006, 2007.\(^22,27\)

\(^a\)Gadolinium enhancement of lesions is not required for DIS.

\(^b\)If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count.

MRI = magnetic resonance imaging; DIS = lesion dissemination in space; CNS = central nervous system.

### TABLE 2: 2010 McDonald MRI Criteria for Demonstration of DIT

DIT Can Be Demonstrated by:

1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Based on Montalban et al 2010.\(^24\)

MRI = magnetic resonance imaging; DIT = lesion dissemination in time.

### TABLE 3: 2010 McDonald Criteria for Diagnosis of MS in Disease with Progression from Onset

PPMS May Be Diagnosed in Subjects With:

1. One year of disease progression (retrospectively or prospectively determined)

2. Plus 2 of the 3 following criteria\(^a\):

   A. Evidence for DIS in the brain based on \( \geq 1 \) T2\(^b\) lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)

   B. Evidence for DIS in the spinal cord based on \( \geq 2 \) T2\(^b\) lesions in the cord

   C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

\(^a\)If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the Criteria.

\(^b\)Gadolinium enhancement of lesions is not required.

MS = multiple sclerosis; PPMS = primary progressive MS; DIS = lesion dissemination in space; CSF = cerebrospinal fluid; IgG = immunoglobulin G.
<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 attacks*, objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack b</td>
<td>None c</td>
</tr>
<tr>
<td>≥2 attacks*, objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by: &gt;1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtaocular, infratentorial, or spinal cord) d; or Await a further clinical attack* implicating a different CNS site</td>
</tr>
<tr>
<td>1 attack*; objective clinical evidence of ≥2 lesions</td>
<td>Dissemination in time, demonstrated by: 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 Await a second clinical attack*</td>
</tr>
<tr>
<td>1 attack*; objective clinical evidence of 1 lesion (clinically isolated syndrome)</td>
<td>Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtaocular, infratentorial, or spinal cord) d; or Await a second clinical attack* implicating a different CNS site; and For DIT: 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 Await a second clinical attack*</td>
</tr>
<tr>
<td>Insidious neurological progression suggestive of MS (PPMS)</td>
<td>1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria d: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtaocular, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)</td>
</tr>
</tbody>
</table>
Diagnostic Criteria

- *Radiographically isolated syndrome (RIS)*
  - asymptomatic patients who have MRI-detected anomalies highly suggestive of MS
- The MAGNIMS 2010 updated criteria have slightly lower specificity but *much improved sensitivity* (79.2%) in predicting conversion from CIS to clinically definite MS (CDMS)
Course of MS

Fig. 54.8 The clinical courses of multiple sclerosis. (Data from Lublin, F.D., Reingold, S.C., 1996. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 46, 907-911.)
Course of MS

- **Relapsing-remitting (RR) MS**: Clearly defined relapses with full recovery or with sequelae and residual deficit on recovery. The periods between disease relapses are characterized by a lack of disease progression.

- **Secondary progressive (SP) MS**: Initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus.
Course of MS

- **Primary progressive (PP) MS:** Disease progression from onset, with occasional plateaus and temporary minor improvements allowed.

- **Progressive relapsing (PR) MS:** Progressive disease from onset, with clear acute relapses with or without full recovery. The periods between relapses are characterized by continuing progression.
**Differential diagnosis of MS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Characteristic</th>
<th>Distinction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MS VARIANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>Monophasic demyelination occurring with or just after an infection, vaccine, or other immune-altering event</td>
<td>No infallible method, but it occurs in the setting of an infection or a recent vaccine. Unusual neurologic symptoms, such as altered consciousness. MRI lesions may be hemorrhagic and involve gray matter.</td>
</tr>
<tr>
<td>NMO; Devic’s disease</td>
<td>Abrupt onset optic neuritis, transverse myelitis, brainstem tegmentum syndromes (vomiting, ocular motor, vestibular) 10%–50% may have brain lesions</td>
<td>Seropositive for NMO IgG antibody (sensitivity approximately 50%–75%). Presence of antibody is highly specific (approximately 90%) for NMO.</td>
</tr>
<tr>
<td><strong>INFLAMMATORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bechet’s disease</td>
<td>Oral/genital ulcers, arthritis</td>
<td>CSF pleocytosis without IgG elevation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mucocutaneous ulcer biopsy</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Systemic symptoms usually present, with organ involvement (lung, kidney)</td>
<td>Serum and CSF ACE levels may be elevated. Enhancement of meninges. Biopsy of skin, lymph node, or lung diagnostic. Octreotide body scanning.</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Systemic symptoms: dry eyes, dry mouth</td>
<td>+ serology for SS-A (Ro), SS-B (La) autoantibodies</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Multiple systemic involvement: kidney, skin, hematologic system, CSF may be positive for oligoclonal bands and IgG elevation</td>
<td>+ serology ANA, DS-DNA autoantibodies</td>
</tr>
<tr>
<td><strong>VASCULAR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute ischemic optic neuropathy</td>
<td>Usually painless vision loss</td>
<td>Older &gt; 50, infarction of the optic nerve, atherosclerotic risk factors. Normal CSF, MRI nonspecific aging changes.</td>
</tr>
<tr>
<td>Susac’s disease</td>
<td>Clinical triad: encephalopathy, branch retinal artery occlusion, hearing loss</td>
<td>Fluorescein angiography pathognomonic staining of arterioles proximal to retinal artery occlusion. Biopsy shows autoimmune endothelopathy of microvasculature (brain, retina, cochlea).</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>Recurrent brain ischemia Headache, seizures</td>
<td>Skin lesions, arthritis. High titers of antiphospholipid antibody IgG/IgM.</td>
</tr>
</tbody>
</table>
# Differential diagnosis of MS

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Migraine</th>
<th>INFECTIONOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Migraine</strong></td>
<td>Focal, transient neurologic deficit usually temporally associated with headache (30–90 min)</td>
<td>CSF and evoked potentials results should be normal. MRI may have some nonspecific white matter changes</td>
</tr>
<tr>
<td><strong>INFECTIOUS</strong></td>
<td></td>
<td>Course is progressive rather than relapsing. CSF PCR positive for JC virus. Brain biopsy may be necessary</td>
</tr>
<tr>
<td><strong>PML</strong></td>
<td>Usually patient is immunocompromised. Death within weeks to months without treatment</td>
<td>+ HTLV-I/II serology</td>
</tr>
<tr>
<td><strong>HTLV-I/II (tropical spastic paraparesis)</strong></td>
<td>Myelopathic symptoms dominate, sometimes associated with dementia. May have white matter lesions on MRI and CSF + oligoclonal bands</td>
<td></td>
</tr>
<tr>
<td><strong>Lyme disease (neuroborreliosis)</strong></td>
<td>Tick exposure, erythema migrans</td>
<td>Western blot positive serology/CSF + PCR</td>
</tr>
<tr>
<td><strong>Syphilis</strong></td>
<td>Usually patient is immunocompromised</td>
<td>MRI results usually normal; Negative FTA-ABS results rule out syphilis</td>
</tr>
<tr>
<td><strong>Human herpesvirus-6</strong></td>
<td>More commonly affects peripheral nervous system</td>
<td>Positive serology for human herpesvirus-6</td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td>Usually in setting of systemic infection (pneumonia)</td>
<td>Serum antibodies are positive There is usually active liver disease</td>
</tr>
<tr>
<td><strong>Mycoplasma</strong></td>
<td>Serum antibody positive for mycoplasma pneumonia</td>
<td></td>
</tr>
<tr>
<td><strong>METABOLIC</strong></td>
<td></td>
<td>Serum levels of B12/folate are low</td>
</tr>
<tr>
<td><strong>B12 deficiency</strong></td>
<td>Rarely cause abnormalities of brain MRI. Myelopathic symptoms dominate</td>
<td>24-h urine free copper excretion, serum copper level</td>
</tr>
<tr>
<td><strong>Copper deficiency</strong></td>
<td>Myelopathy, peripheral neuropathy, optic neuritis</td>
<td>Neutrophil zinc determination, 24-h urine zinc excretion</td>
</tr>
<tr>
<td><strong>Zinc deficiency</strong></td>
<td>Diminished taste and smell</td>
<td></td>
</tr>
<tr>
<td><strong>Celiac disease</strong></td>
<td>Ataxia and brainstem involvement dominate</td>
<td>Antigliadin antibody positive Spinal fluid is normal. &gt; 90% human lymphocyte antigen-DQ2 positive</td>
</tr>
<tr>
<td><strong>Vitamin E deficiency</strong></td>
<td>Progressive ataxia</td>
<td>Serum vitamin E low, retinal pigmentation</td>
</tr>
<tr>
<td><strong>GENETIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wilson's disease</strong></td>
<td>Prominent movement disorder (ataxia, tremor), dementia</td>
<td>Kayser-Fleischer rings on slit lamp. Serum copper elevated. Low serum ceruloplasmin &lt; 0.2 g/L, penicillamine challenge test, gene mutation ATP7B</td>
</tr>
</tbody>
</table>

(continued on next page)
Differential diagnosis of MS

| Condition                                      | Characteristic                                                                 | Distinction                                                                 |
|------------------------------------------------|-------------------------------------------------------------------------------|                                                                            |
| Hereditary spastic paraparesis                | Easily confused with primary progressive MS with progressive myelopathy      | Peripheral nerve involvement MRI and CSF results are usually normal. Genetic testing not yet reliable |
| Porphyria                                     | Progressive focal neurologic deficits usually including prominent ataxia      | Psychiatric and behavior symptoms prominent. 24-h urine elevated ALA and PBG |
| Cerebral autosomal dominant arteriopathy with  | Multifocal neurologic deficits, often associated with migraine and progressive| Family history Genetic testing available; AD mutation in notch-3 gene         |
| subcortical infarcts and leukoencephalopathy   | dementia                                                                      |                                                                            |
| **ONCOLOGY**                                  |                                                                               |                                                                            |
| CNS lymphoma                                  | Usually immunocompromised MRI lesions enhance and are highly sensitive to      | CSF results positive cytology CSF results negative for IgG                   |
|                                               | steroid treatment                                                             | Brain biopsy may be necessary to differentiate                              |
| Paraneoplastic syndrome                       | Abrupt onset of ophthalmoplegia, ataxia. CSF oligoclonal band often present   | MRI results usually normal Antibody serum positive Anti-Yo or Anti-Hu       |
| **STRUCTURAL**                                |                                                                               |                                                                            |
| Spondylosis                                   | Easily mistaken for primary progressive MS, myelopathic                       | CSF and VEP results are normal. MRI shows spinal cord compression           |
| Syringomyelia                                 | Myelopathic symptoms, may involve lower cranial nerves                        | MRI imaging shows syrinx. Brain MRI and CSF normal                         |
| Spinal vascular malformation                  | Rare, but relapsing or progressive myelopathic symptoms with intrinsic cord  | MRI of brain, VEP, CSF results normal. Spinal angiogram may be necessary    |
|                                               | abnormalities                                                                 |                                                                            |
| **ENVIRONMENTAL**                             |                                                                               |                                                                            |
| Toxin                                         | Drug/exposure specific                                                        | CSF results normal. Usually monophasic with exposure                       |

Abbreviations: NMO, neuromyelitis optica; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; VEP, visual evoked potential.
Outlines

- Introduction
- Pathophysiology
- Clinical manifestation
- Image findings
- Diagnostic criteria
- Treatment
Treatment

- Methylprednisolone 1g, for 3 days, followed by an 11-day oral prednisone taper -> 50% improvement in time to next relapse
- No difference in final visual acuity at 1 year comparing treated (high-dose versus low-dose steroid limbs) and untreated cases
Table 1. Treatment Options for Multiple Sclerosis.*

<table>
<thead>
<tr>
<th>Status</th>
<th>Treatment</th>
<th>Suggested Mechanism of Action</th>
<th>Uses and Range of Effects</th>
<th>Forms of Multiple Sclerosis Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved by the Food and Drug Administration</td>
<td>Interferon beta</td>
<td>Inhibits adhesion&lt;br&gt;Inhibits synthesis and transport of MMPs&lt;br&gt;Blocks antigen presentation</td>
<td>Treatment of relapses&lt;br&gt;Slows progression&lt;br&gt;Reduces lesions seen on MRI and brain atrophy&lt;br&gt;Potential cognitive benefit</td>
<td>Relapsing</td>
</tr>
<tr>
<td></td>
<td>Glatiramer acetate</td>
<td>Increases regulatory T cells&lt;br&gt;Suppresses inflammatory cytokines&lt;br&gt;Blocks antigen presentation</td>
<td>Treatment of relapses&lt;br&gt;Reduces lesions seen on MRI</td>
<td>Relapsing–remitting</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone</td>
<td>Reduces Th1 cytokines&lt;br&gt;Eliminates lymphocytes</td>
<td>Treatment of relapses&lt;br&gt;Reduces lesions seen on MRI&lt;br&gt;Slows progression</td>
<td>Relapsing–remitting&lt;br&gt;Secondary progressive&lt;br&gt;Progressive relapsing</td>
</tr>
<tr>
<td>Possible adjunctive therapy</td>
<td>Corticosteroids (intravenous or oral formulations)</td>
<td>Inhibit synthesis and transport of MMPs&lt;br&gt;Alter cytokine profile&lt;br&gt;Reduce CNS edema</td>
<td>Treatment and prevention of relapses</td>
<td>Relapsing</td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
<td>Inhibits purine synthesis, affecting B cells, T cells, and macrophages</td>
<td>Treatment of relapses&lt;br&gt;Slows progression</td>
<td>Relapsing–remitting&lt;br&gt;Secondary progressive</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>Acts as folate antagonist, affecting DNA synthesis in immune cells</td>
<td>Slows progression</td>
<td>Secondary progressive</td>
</tr>
<tr>
<td></td>
<td>Plasma exchange</td>
<td>Removes deleterious antibodies</td>
<td>Treatment of relapse</td>
<td>Relapsing</td>
</tr>
<tr>
<td></td>
<td>Intravenous immune globulin</td>
<td>Has antidiotypic effects&lt;br&gt;Blocks Fc receptors&lt;br&gt;Alters cytokine profile</td>
<td>Treatment and prevention of relapses</td>
<td>Relapsing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Rationale or Mechanism</th>
<th>Preliminary Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combinations of approved agents</td>
<td>Targets multiple injury mechanisms</td>
<td>Evidence of reduced activity on MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced relapses</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Depletes B cells</td>
<td>Clinical trials under way</td>
</tr>
<tr>
<td>Chemokine-receptor antagonists</td>
<td>Reduce entry of lymphocytes into CNS</td>
<td>Clinical trials under way</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Blocks N-methyl-D-aspartate and sodium channels</td>
<td>Reduced spinal-cord atrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced number of hypointense lesions on T1-weighted MRI</td>
</tr>
<tr>
<td>Phenytoin and flecainide</td>
<td>Block sodium channels</td>
<td>Neuroprotective in animals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical trials under way</td>
</tr>
<tr>
<td>Blockers of neurite outgrowth inhibitor</td>
<td>Promote axonal sprouting</td>
<td>Studies in animals under way</td>
</tr>
<tr>
<td>Blockers of NG2, LINGO-1, Notch, and Jagged</td>
<td>Promote oligodendrocyte differentiation</td>
<td>Studies in animals under way</td>
</tr>
<tr>
<td>Activation of oligodendrite transcription</td>
<td>Promotes oligodendrocyte differentiation</td>
<td>Under development</td>
</tr>
<tr>
<td>factor 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stem cells</td>
<td>Initiate myelin repair</td>
<td>Established efficacy in animal models</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Early trials in humans under way</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Promote neuronal survival</td>
<td>Under development</td>
</tr>
<tr>
<td>Antiapoptosis factors</td>
<td>Promote survival of neurons and oligodendrocytes</td>
<td>Studies in animals under way</td>
</tr>
</tbody>
</table>

* CNS denotes central nervous system, NG2 neuron-glia antigen 2, and LINGO-1 leucine-rich-repeat and immunoglobulin-domain-containing neurite outgrowth inhibitor receptor-interacting protein 1.
THANK YOU