Emerging Therapies in Multiple Sclerosis

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Objectives

1. Discuss and characterize the four main subtypes of Multiple Sclerosis.
2. Define the pathophysiologic process of Multiple Sclerosis as well as the suspected etiology of disease.
3. Review the symptoms and features involved in patients with Multiple Sclerosis.
4. Describe the protocol for making an accurate diagnosis using the most recent guidelines.
5. Identify the types of lesions found on MRI emphasizing the use of gadolinium and comparing differences between T1-weighted and T2-weighted imaging.
6. Explain the typical disease course of Multiple Sclerosis and prognosis for most diagnosed patients.
7. Discuss strategies for managing acute exacerbations and chronic symptoms in Multiple Sclerosis.
8. Discuss the long term disease modifying therapies used to treat Multiple Sclerosis.

The Strange Disease of Virgin Lidwina (1380-1433)

• Neurologic disease for over 38 years characterized by attacks and miraculous recoveries
• Developed progressive disease ataxia, fell down ice skating on February 2, 1396 progressive paralysis Death
• Patroness saint of the USA artistic ice skating team
Introduction

• Most commonly dx cause of progressive neurologic disability
• Patients exp acute attacks of neurological compromise, or are afflicted with steadily progressive deterioration
• Inflammation is the hallmark of MS
• Inflammation > Demyelination > Tissue scarring > Axonal injury/ transection > Neurodegeneration
• Loss of myelin sheaths surrounding axons results in abnormal patterns of interruption of neural conduction which leads to clinical signs & symptoms of MS

Epidemiology

• MS estimated to affect 400,000 in the US, 2.5 million worldwide.
• Diagnosed often in ages 20-50 year olds
• Women (2:1) >> Men
• Caucasian especially those of western European ancestry
• More progressive in African Americans
• Further from equator, increased prevalence
• 1% general population
• 4% if first-degree relative is affected
• 30-40% if twin affected

What causes Multiple Sclerosis?

• Genetic/ environment/ EBV?/ stress/ Vitamin D deficiency
• Trafficking of T Lymphocytes into the CNS
• Antigen-specific T-helper cells, CD4, recognize myelin proteins
• CD8 T-cells - major function is direct cytotoxicity
• B-cells specifically proliferate to produce a particular antibody; antibody proteins from the spinal fluid of MS patients = oligoclonal
Neurophysiology of MS

Types of Multiple Sclerosis

4 Main Subtypes:

- Relapsing-Remitting MS – most common
- Primary Progressive MS – 10%
- Secondary Progressive MS
- Progressive-Relapsing MS – 5%

Relapsing-Remitting MS
Typical Features of MS

- Optic Neuritis
- Afferent Pupillary Defect (APD)
- Internuclear ophthalmoparesis (INO)
- Trigeminal Neuralgia
- Cranial nerve palsies - facial weakness, facial numbness, diplopia, vestibulopathy
- Rubral tremor
- Myelitis → spinal cord = sensory disturbance, spasticity, weakness, bowel/ bladder/ sex dysfunction

Clinical Manifestations

- McDonald Criteria

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<tr>
<th>CLINICAL FEATURES</th>
<th>LESIONS</th>
<th>ADDITIONAL CRITERIA TO MAKE MS</th>
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Note: Clinical picture alone or sufficient additional evidence does not in itself establish a diagnosis of MS.
Neuroimaging

Cerebrospinal Fluid (CSF)

- Oligoclonal bands
- IgG index elevation
- Increased IgG synthesis rate
- Suggests immune mediated cause
- Similar patterns in other conditions (i.e. infectious, inflammatory, collagen vascular, neoplastic, etc.)
- NOT necessary for diagnostic confirmation of MS
- About 90% + patients with clinically definite MS
Differential Diagnosis

- Neuromyelitis Optica (NMO)
- Sarcoidosis
- Sjogren’s syndrome
- Systemic Lupus Erythematosus (SLE)
- HIV
- Neurophilis
- Lyme disease
- Neoplasms
- Nutritional deficiency (B-12, folic acid, copper)
- Zinc excess
- Age-related white matter changes
- Acute Disseminated Encephalomyelitis (ADEM)
- Vascular malformation
- Stroke
- CADASIL (Cerebral Autosomal Dominant Arteriopathy, Subcortical Infarcts, and Leukoencephalopathy)
- Primary CNS vasculitis (or other)
- Migraine
- Cervical stenosis

Clinical Course

- Patients do better when sensory symptoms predominate over motor or cerebellar dysfunction.
- Attacks arise as exacerbations, can produce any neurological sx which may persist for > 24 hours, followed by period of partial and in some cases nearly complete, recovery.
- Patients progress less when there is good functional recovery

We’ve come a long way baby!

- Jean-Martin Charcot 1860s
- Saw patients with “hysteria” and “exaggerated physical efforts”
- Treatments included:
  - Absolute bed rest
  - Electric shocks
  - Silver nitrate
  - Gold salts
  - Strychnine
- All without positive effects—only 5 years survival from onset
**Immunomodulators**

Injectons
- Betaseron (interferon beta-1b)
- Avonex (interferon beta-1a)
- Copaxone (glatiramer acetate)
- Rebif (interferon beta-1a)

Oral Medications
- Gilenya (fingolimod) 2010
- Aubagio (teriflunomide)
- Tecfidera (dimethyl fumarate)

Infused medications
- Novantrone (mitoxantrone)
- Tysabri (natalizumab)
- Lemtrada (alemtuzumab)

**Treatment of Acute Exacerbations**

- High-dose intravenous Solu-Medrol® (methylprednisolone)
- High-dose oral Deltasone® (prednisone)
- H.P. Acthar Gel (ACTH) is an option for those who are unable to cope with the side effects of high-dose corticosteroids, have been treated unsuccessfully with corticosteroids, do not have access to intravenous therapy, or have trouble receiving medication intravenously because of difficulty accessing the veins.

**Gait Dysfunction**

- 4-aminopyridine (4-AP)
- Ampyra
**Pseudobulbar Affect (PBA)**

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<th>Clinical Dimension</th>
<th>Hypo</th>
<th>Hyper</th>
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<td>Emotional lability</td>
<td>Crying, laughing</td>
<td>Crying, laughing</td>
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<td>Marked emotional lability</td>
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<td>Rapidly changing mood</td>
<td>Mood swings</td>
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<td>Marked changes in mood</td>
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<td>Inappropriate laughter</td>
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<td>Emotional lability</td>
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<td>Emotional overactivity</td>
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<td>Emotional underactivity</td>
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<td>Emotional flatness</td>
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<td>Emotional withdrawal</td>
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<td>Emotional numbness</td>
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<td>Depressed affect</td>
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<td>Inappropriate cynicism</td>
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<td>Humorless, inappropriate laughter</td>
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<td>Emotional flattening</td>
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<td>Emotional blunting</td>
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**Treatment** - Nuedexta

**Complementary and Alternative Medicine**

- Bee venom therapy: 20-40 bees are used, tweezers, stinger remains 10 to 15 minutes.
- Apamin, one component of bee venom, has theoretically beneficial effects. It acts to inhibit the potassium channel, the same part of the nerve cell inhibited by the experimental drug 4-aminopyridine (4-AP).
- Vitamin D3

**It takes a village...**

- MD/ PA
- Nurses
- Physical therapy
- Occupational therapy
- Speech Therapy
- Ophthalmology
- Urology
- Pain Management
- Psychotherapy
- Neuropsychology
- Social Worker
References


Fox M.D., Edward J. and Robert P. Lisak, M.D. Clinician's Primer on Multiple Sclerosis: Immunology and the Basic Mechanisms of Action of Pharmacological and Therapeutic Agents. Medical Education Resources and Consensus Medical Communications; 2010.

Frohman PA-C, Teresa C., O'Donoghue PA-C, Daniel L., and Dorothy Northrop, MSW. Multiple Sclerosis for the Physician Assistant. AAPA, 2011.


