Multiple Sclerosis: Current Trends in Treatment

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19th Annual Mud Season Symposium

Disclosure Statement

- Member of Speaker's Bureau
  Biogen Idec
- Will discuss non FDA approved therapies

Multiple Sclerosis

- The most common chronic disease affecting the central nervous system (CNS) in young adults
- The hallmark of MS is inflammatory, demyelinating plaques in the CNS
- Immune-mediated, chronic, inflammatory disease, precipitated by unknown environmental factors in genetically susceptible individuals

Compston A, Coles A. *Lancet*. 2002;359:1221-1231.

Epidemiology of MS

- Approximately 400,000 cases in the United States[1] & 2.5 million world wide
- The chances of developing MS are 1:1000 in the general population[2]
- Estimated 2.5 million cases worldwide[3]
- Higher prevalence in those with northern European ancestry[4]
- Highest incidence in Caucasians
- Higher incidence in women (>2:1)[4]

1. National MS Society Information Sourcebook. www.nationalmssociety.org/sourcebook. Accessed March 6, 2007.
2. Compston A, Coles A. *Lancet*. 2002;359:1221-1231.
3. Frohman EM. *Med Clin North Am*. 2003;87:867-897.
4. Hogancamp WE, et al. *Mayo Clin Proc*. 1997;72:871-878.

Genetics of MS

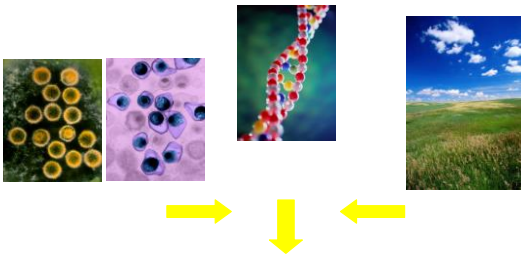
- No gene has been identified yet
- Virtually unseen in certain populations
  - 1/1000 risk of MS in the general population
  - 2-5/100 for person with a close relative with MS
    - 1/50 for daughter of a mother with MS
    - 1/100 for son of a father with MS
    - 1/20-50 for a sibling of a person with MS
- Fraternal twins- 4%
- Identical twins- 30%
- Multiple chromosome changes seen
- Multiple factors-genetic, environmental

Viral Link to MS

- Epstein Barr virus- mononucleosis
- 90 % of Americans have antibodies
- Higher levels associated with greater likelihood of developing MS
- ? Predictive value

JAMA- March 2003- Ascherio/Harvard

Potential Triggers for Multiple Sclerosis



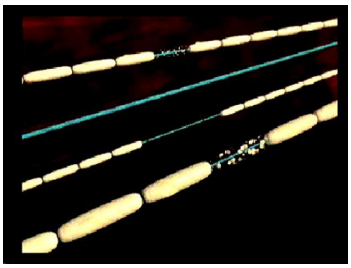
Pathophysiology of MS

- The pathologic hallmarks of MS lesions include breakdown of the blood brain barrier (BBB), multifocal inflammation, demyelination, oligodendrocyte loss, gliosis, and axonal degeneration
- Although the primary pathology is immune-mediated destruction of CNS myelin and oligodendrocyte loss, the major cause of neurologic disability is axonal loss

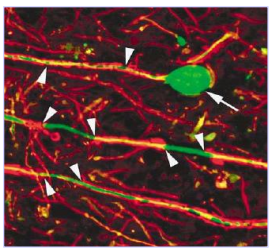
Pathophysiology of Multiple Sclerosis

- MS is an inflammatory demyelinating disorder of the the central nervous system.
- The cells that form myelin, the oligodendrocytes, are the targets of attack.
- The cause of MS in unknown but probably stems from an infectious and/or autoimmune origin.
- MS is characterized by areas of focal demyelination (plaques) throughout the white matter and the spinal cord. These can be seen on MRI.

Mild to Moderate Demyelination



Pathophysiology: Axonal Loss



Arrowheads=areas of active demyelination. Arrow=terminal axon ovoid.

Trapp BD, et al. *N Engl J Med.* 1998;338:278-285.

Pathophysiology/ Etiology/ Epidemiology

- Chronic, neuroimmunologic disease of the central nervous system (CNS)
- Inflammatory attacks (relapses, exacerbations) vary in number and frequency
- Myelin damage and scarring
- Irreversible axonal damage may result

Pathophysiology of MS

- The axons become irreversibly damaged. This slows conduction and/or may cause a total conduction block over time. This results in much of the permanent disability we see over time. Transient loss of function with fever and fatigue is attributable to conduction failure in demyelinated fibers.
- Attacks, cause some permanent damage. It is the accumulation of damage from repeated demyelinating events that accounts for long term disability.
- Every attack, even subclinical is important

Immunology

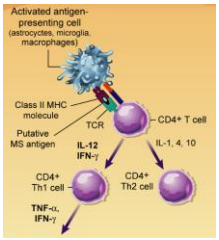
- It is highly likely that multiple mechanisms participate in demyelination and axonal injury.
- The immunologic aspects of MS are complex requiring consideration not only of immune system responses but also of the intricacies of immune-CNS interaction.
- These include dynamics at the level of the BBB:
  - the effects of the CNS responses on the biology of invading inflammatory cells

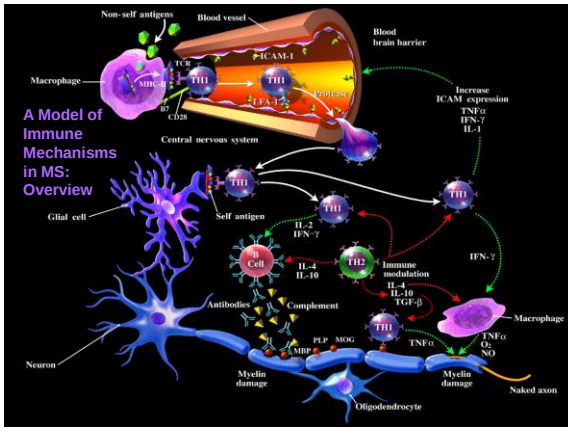
Immune Cells: Key Players

- Antigen-presenting cells (APCs)
  - Macrophages, microglia, etc.
- T cells (T lymphocytes)
  - Responsible for cell-mediated immune response
  - T Helper cells
- B cells (B lymphocytes)
  - Responsible for the production of antibodies

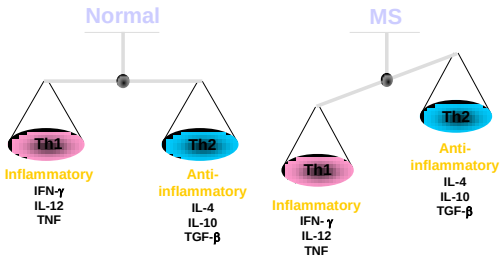
Activation of Immune Cells in the CNS

- Upon antigen presentation in CNS, CD4+ T cells differentiate into autoreactive Th1 cells that release proinflammatory cytokines
- This process leads to an inflammatory cascade and immune-mediated demyelination





Cytokine Imbalance in MS



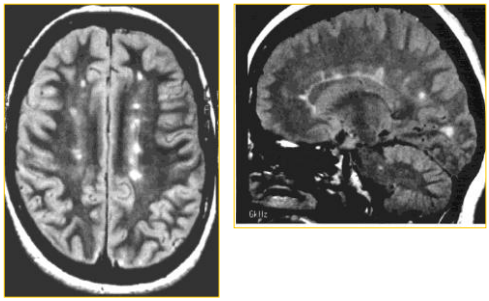
Immunopathogenesis of MS Summary

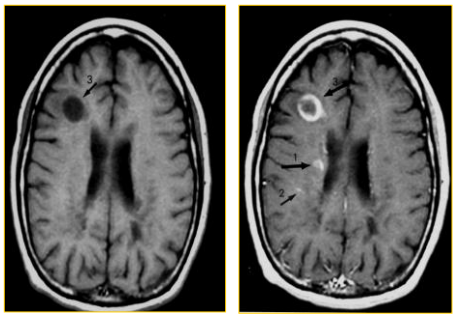
MS is an immune-mediated disease characterized by inflammation of the central nervous system (CNS)

- Breakdown of the blood-brain barrier (BBB)
- CNS inflammation facilitated by activation and migration of autoreactive T cells into the CNS
- Production of demyelinating autoantibodies

Central nervous system injury

- Demyelination
- Axonal injury
- Brain atrophy





Course of the Disease

- Unpredictability is a hallmark of disease
- Natural history data describes a pattern of increasing disability if untreated
- The early disease course in characterized by acute inflammation
- Prognostic indicators can suggest a disease pattern

MS: Clinical Subtypes

- Clinically isolated syndrome (CIS)
- Four established clinical courses differ by the time course of relapse and progression
  1. Relapsing-Remitting MS (RRMS)
  2. Secondary Progressive MS (SPMS)
  3. Primary Progressive MS (PPMS)
  4. Progressive Relapsing MS (PRMS)

Goodin DS, et al. *Neurology.* 2002;58:169-178. Craig J, et al. *J Neurol Neurosurg Psychiatry*. 2003;74:1225-1230.

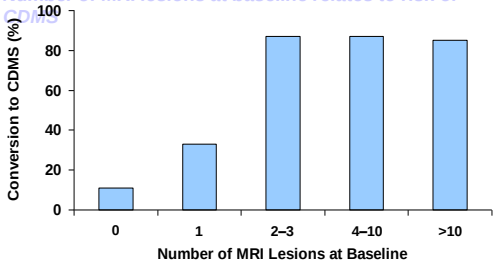
CIS

- First neurologic episode lasting at least 24 hours
- Caused by inflammation/demyelination in 1 or more sites in the CNS
- A person with CIS can have a single neurologic sign or symptom:
  - An attack of optic neuritis caused by a monofocal lesion
- Or more than 1 sign or symptom
  - An attack of optic neuritis accompanied by weakness on 1 side caused by multifocal lesions

National MS Society: CIS. The MS Information Sourcebook. www.nationalmssociety.com. Accessed December 2006.

CIS: Risk of Developing MS

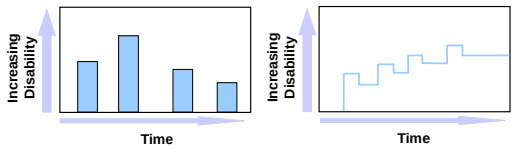
Number of MRI lesions at baseline relates to risk of CDMS



O'Riordan JI, et al. *Brain*. 1998;121:495-503.

Relapsing-Remitting MS

No disease progression between relapses



Acute relapses with full recovery

Acute relapses with sequelae and residual deficit upon recovery

Lublin FD, Reingold SC. *Neurology*. 1996;46:907-911.

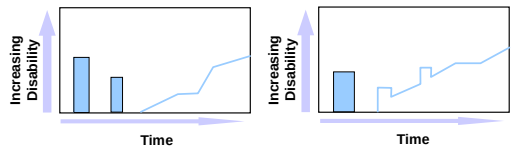
Clinical Subtypes of MS

- Secondary Progressive MS (SPMS)
  - Begins as RRMS
  - At some point the attack rate is reduced
  - The course is then a steady deterioration in function unrelated to acute attacks

Goodin DS, et al. *Neurology.* 2002;58:169-178.

Secondary Progressive MS

Patients with an initial RRMS course convert to SPMS, which is characterized by continuous progression



Without relapses

With relapses

Lublin FD, Reingold SC. *Neurology*. 1996;46:907-911.

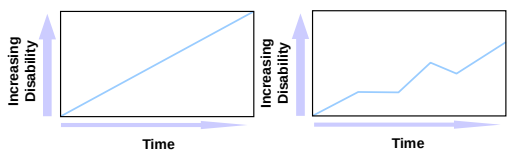
Clinical Subtypes of MS

- Primary Progressive (PPMS)
  - Characterized by steady decline in function without acute attacks
- Progressive Relapsing (PRMS)
  - Begins with a progressive course, but acute attacks develop occasionally

Goodin DS, et al. *Neurology.* 2002;58:169-178.

Primary Progressive MS

PPMS is characterized by progression of disability from ons



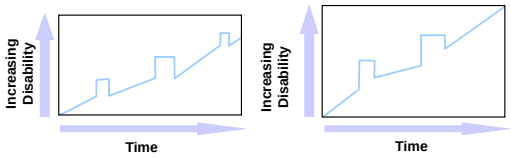
Without plateaus or remissions

With occasional plateaus and temporary minor improvements

Lublin FD, Reingold SC. *Neurology*. 1996;46:907-911.

Progressive Relapsing MS

PRMS is characterized by disease progression from onset v the occurrence of clear acute relapses

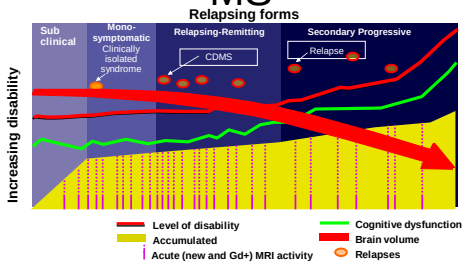


Full recovery following relapse with progression between relapses

Without full recovery following relapse with progression between relapses

Lublin FD, Reingold SC. *Neurology*. 1996;46:907-911.

Natural Progression of MS



Diagnosis of MS: McDonald Criteria (2005)

- Objective evidence of dissemination in time and space of lesions is essential
- All other explanations for clinical features must be excluded prior to diagnosis of MS
- Clinical evidence must be based on objective clinical signs
- MRI, CSF, and visual evoked potentials (VEPs) are helpful for diagnosis when clinical presentation is not characteristic of a particular disease
- Following evaluation, diagnosis will be MS, not MS, or possible MS

McDonald WI, et al. *Ann Neurol.* 2001;50:121-127.

Revised McDonald Diagnostic Criteria for MS

Polman CH, et al. *Ann Neurol.* 2005;58:840-846

Clinical Presentation	Additional Data Needed for MS Diagnosis
2 or more attacks; objective clinical evidence of 2 or more lesions	None
2 or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by MRI *or* 2 or more MRI-detected lesions consistent with MS + positive CSF *or* Await further clinical attack implicating a different site
1 attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by MRI *or* Second clinical attack
1 attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by MRI *or* 2 or more MRI-detected lesions consistent with MS + positive CSF AND Dissemination in time, demonstrated by MRI *or* Second clinical attack
Insidious neurological progression suggestive of MS	One year of disease progression (retrospectively or prospectively determined) AND 2 out of 3 of the following: Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive visual evoked potentials; Positive spinal cord MRI (2 or more focal T2 lesions); Positive CSF

Favorable Prognostic Indicators

- Early age of onset
- Female sex
- Optic neuritis as presenting episode
- Sensory symptoms as presenting episode
- Acute onset of symptoms
- Little residual disability after each exacerbation
- Long interexacerbation period

Lublin FD. *Neurol Clin*. 2005;23:1-15.

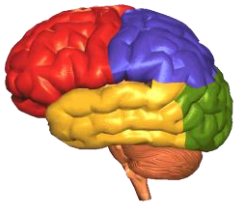
Unfavorable Prognostic Indicators

- Later age of onset
- Progressive course from onset
- Male sex
- Frequent exacerbations
- Poor recovery from exacerbations
- Involvement of cerebellar or motor functions

Lublin FD. *Neurol Clin*. 2005;23:1-15.

The Goal in Treating MS

To positively affect all aspects of the disease
- Disability
- Relapses
- Inflammation and lesions shown on MRI
- Atrophy
- Cognition



MS: Treatment Approaches

- Treatment of acute attacks
- Symptom management
- Disease modification
- Psychosocial interventions/Education
- Rehabilitation

Relapses

- Synonyms:
  - Attack, flare, exacerbation
- Definition:
  - sudden worsening of any MS symptom or the appearance of new symptom
  - last at least 24 hours
  - are separated from a previous exacerbation by at least 1 month
  - occur in absence of environmental, metabolic, or infectious processes

National MS Society: CIS. The MS Information Sourcebook. www.nationalmssociety.com. Accessed December 2006.

Relapses - Etiology

- Caused by an area of inflammation in the CNS
- Exacerbations are correlated with focal areas of inflammation of the CNS caused by immune system over-activity

National MS Society: CIS. The MS Information Sourcebook. www.nationalmssociety.com. Accessed December 2006.

Relapses
Impact on Quality of Life

- May be mild or may significantly interfere with the individual's daily life
- Exacerbations usually last from several days to several weeks, although they may extend into months
- Occur about once every year in untreated patients

Pseudo-exacerbations

- Last less than 24 hours
- Occur in the setting of illness, overheating, febrile state, heat and humidity, flu-like reactions to interferons, exercise, or infections
- Usually self-limited and rarely require intervention beyond cooling measures and treatment of any underlying infection or inflammation

Clinical Subtypes of MS

- Relapsing-Remitting MS (RRMS)
  - Characterized by self-limited attacks of neurological dysfunction
  - Attacks develop acutely, evolving over days to weeks
  - Over the next several weeks to months, the majority of patients experience a recovery of function that is often (but not always) complete
  - In between attacks, the patient is neurologically and symptomatically stable

Goodin DS, et al. *Neurology.* 2002;58:169-178.

Treatment of Acute Attacks

- High dose intravenous corticosteroids, e.g., methylprednisolone
- Most often a 3–5 day course usually as an outpatient
- May or may not be followed an oral steroid (taper), e.g., prednisone
- Short course of steroids usually well tolerated; mood changes may occur
- Long term use side effects: hypertension, diabetes, osteoporosis, cataracts, ulcers, weight gain

Treatment Options for MS

FDA-approved therapies for relapsing forms of MS

Avonexâ (Interferon beta-1a IM injection)
Rebifâ (Interferon beta-1a SC injection)
Betaseronâ (Interferon beta-1b SC injection)
Extaviaâ (Interferon beta-1b SC injection)
Copaxoneâ (Glatiramer acetate SC injection)
Tysabriâ (Natalizumab IV-therapy)
Gilenyaâ (first approved oral medication)

Treatment Options for MS

FDA-approved therapy for worsening MS

– **Novantrone (Mitoxantrone IV-therapy)**

Disease Modification—Immunomodulators

- Avonex®, Betaseron®, Copaxone®, Extavia®, Gilenya® , Rebif® , Tysabri®
- Reduce the frequency and severity of relapses
- Reduce MRI lesions
- Slow progression of disability
- Different side effect profiles, dosing schedule, mode of administration

How Interferon-β Drugs Work

- Interferon-β drugs can help limit the immune response and control damage to the neurons
- These drugs bind to specific receptors on target cells
- Migration across the BBB is inhibited
- They turn down the signal that promotes the immune response, and turn on the signal that stops this response
- As a result, the attack on the cell is called off

Proposed Copaxone Mechanism of Action in MS

- Synthetic protein that stimulates myelin basic protein
- Seems to block myelin-damaging T cells by acting as a decoy
- Copaxone must pass the BBB to be effective

Administration Schedules

• AVONEX® (Interferon beta 1-a)	• IM weekly
• Betaseron® (Interferon beta 1-b)	• SC every other day
• Extavia® (Interferon beta 1-b)	• SC every other day
• Rebif® (Interferon beta 1-a)	• SC three times a week
• Copaxone® (Glatiramer acetate)	• SC every day

Corticosteroids

- Potent anti-inflammatory agents that can reduce the inflammation in brain & spinal cord
- Methylprednisolone 1g/day qd x 3-5 days
- Some providers follow IV with an oral taper
- Regular schedule – Pulsed steroids

Mitoxantrone

- Chemotherapeutic agent that suppresses the activity of WBCs
- FDA approved for clinical worsening MS
- Lifetime use is restricted to 140mg/m^2
  12mg/m^2 IV q 3 mos for 2-3 years
- Due to immune suppression-avoid contact with sick people and dental procedures for 2-3 weeks after each infusion

Cyclosphosphamide

- Used off label for the treatment of MS
- Suppresses white blood cells
- Modest improvement (at best) in patients with progressive MS
- Dose varies based on WBC
  Administered by induction
  Pulse therapy

Natalizumab/Tysabri

- Monoclonal antibody that reduces the movement of active immune cells into the CNS
- Approved monotherapy for RRMS
- Generally recommended for patients who had an inadequate response or unable to tolerate other MS therapies
- Increases the risk for progressive multifocal leukoencephalopathy (PML)

Proposed Tysabri Mechanism of Action in MS

- At the BBB Tysabri binds with alpha4-integrin
- Interaction with VCAM-1 is inhibited
- Thus migration of immune cells across the BBB is inhibited

Natalizumab

- Wash out period from immunomodulators
- Dose-300mg as a 1 hour infusion q 4 wks
- TOUCH program enrollment is mandatory
- Significantly reduces relapse, disability progression, new lesion development as seen on MRI

Progressive Multifocal Leukoencephalopathy

- TOUCH program is a comprehensive risk-management program
- PML is a rare and progressive demyelinating disease of the brain
- PML often leads to permanent disability or death
- Believed dormant is 80% of population

Progressive Multifocal Leukoencephalopathy

- PML characterized by weakness in one side of body or limbs, blurred or loss of vision, fatigue, language impairments, memory loss, confusion, disorientation or loss of balance
- MRI at baseline & s/s suggestive of PML
- Screening prior to each infusion
- CSF analysis for JC viral DNA
- Documentation carefully tracts infusions

Other Treatment Options for MS

- Other potential MS therapies
  - Intravenous immunoglobulin G (IVIG)
  - Monoclonal antibodies
  - Plasmapheresis
- Additional immunosuppressive therapies
  - Azathioprine -Imuran
  - Cyclophosphamide-Cytoxan
  - Methotrexate
  - Mycophenolate-CellCept

Symptoms

- Fatigue
- Impaired ambulation
- Bowel/bladder dysfunction
- Visual disturbances
- Pain
- Imbalance
- Incoordination
- Sensory changes
- Dysarthria
- Cognitive impairment
- Tremor
- Spasticity
- Weakness
- Dysphagia
- Sexual dysfunction
- Emotional changes (depression, bi-polar disorder)

How are MS symptoms treated?

- Symptoms caused by inflammation are likely to disappear as the inflammatory attack subsides.
- Symptoms caused by scarring and damage to the nerve cells themselves are likely to remain.
- There a variety of medications and management strategies available to manage the many types of symptoms that can occur.

Symptom Management Summary

- Symptom management is a major part of MS care
- Majority of symptoms are not unique to MS
- While symptoms may be unpredictable, most show good response to intervention
- Encouraging the practice of good health habits is an important strategy

Psychosocial Support

- Factors that impact emotional response to MS
  - **Uncertain diagnosis**
  - **Unpredictable course**
  - **Invisible symptoms**
  - **Potential disability**
  - **Diminished self-esteem**
  - **Altered relationships**
  - **Uncertain financial future**

Psychosocial Interventions

- Disease-related education to enhance people's understanding of the disease, adaptive coping strategies, and available resources
- Encouragement to remain active and productive
- Assessment and treatment of emotional and/or cognitive problems

Psychosocial Support

- Support family members' coping
- Promote productivity, including transition from employment to other satisfying roles
- Help individuals with MS and their families access available resources

Rehabilitation

Structured, problem-focused, inter-disciplinary interventions to:

- **Enhance function following exacerbations**
- **Identify appropriate assistive devices and environmental modifications**
- **Identify and instruct in behavior modification**
- **Prevent injuries and unnecessary complications**
- **Empower individual and family**

The central challenge facing persons with MS is to “find a place for the illness while keeping the illness in it’s place”.

Gonzales et al., 1989