Updates in Multiple Sclerosis
2016
Ann C. Cabot, DO
Concord Neurology
MS Specialty Care Clinic
Dr. Cabot is a speaker for: Acorda, Pfizer, Biogen, Teva, Genzyme
Consultant: Genzyme, Biogen
Objectives

* Participant will be able to recognize common signs and symptoms of MS
* Participant will gain insight into treatment of MS and MS symptoms
* Participant will become aware of risks issues with MS disease modifying therapies
What is MS?

- A disease of the Central Nervous System with both inflammation and axonal degeneration
- Very heterogeneous
- Different types/stages
  - Relapsing Remitting
  - Secondary Progressive
  - Primary Progressive
  - Progressive-Relapsing
## Demographics of MS

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Description</th>
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<tbody>
<tr>
<td>Age at onset</td>
<td>15 to 45 years</td>
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<tr>
<td>Gender</td>
<td>70% women</td>
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<tr>
<td>Geography</td>
<td>Prevalence increases with latitude</td>
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<tr>
<td>Incidence</td>
<td>8,500 - 10,000 new cases per year in US</td>
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<td>US prevalence</td>
<td>250-350,000 (1/1000)</td>
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Syndromes Strongly Suggestive of MS

In Young Patients (Under 40)
* Acute optic neuritis
* Internuclear Ophthalmoplegia
* Trigeminal neuralgia
* Sensory useless hand syndrome
* Acute urinary retention or incontinence
* Impotence in males
* Bands of numbness or paresthesias

In Older Patients (Over 40)
* Progressive painless spastic paraparesis
* Abnormal gait
* Bladder dysfunction
Lhermitte’s Phenomenon

* Shock-like sensation traveling down the spine with neck flexion
* Pathophysiology: Mechanical stimulation of demyelinated axons can generate action potentials.
Uhthoff's Phenomenon

- Classically described as a decrease in visual acuity with a rise in body temperature
- Pathophysiology: “warmth” activates the Na+/K+ pump
Obtaining history

- Previous symptoms
- Memory change
- Bowel and bladder habits
- Uhthoff's Phenomenon
- Lhermitte's phenomenon
- Family history of MS
- History of painful visual loss
- History of “dropping things”
Exam

* Disc examination
* Visual Acuity
* Internuclear Ophthalmoplegia
* Marcus Gunn Pupil
* Single leg hop
* Eye movements

* Color desaturation
* Asymmetry of exam
* Hyper-reflexia
* Lhermitte's
* Plantar responses
* Cerebellar testing
* Sensory level
Routine rule-outs

- B12 & Methylmalonic acid
- ANA, RF
- Lyme
- Angiotensin converting enzyme (ACE)
- TSH, T4
- SSA, SSB
- RPR
- ESR and CRP
- Vitamin D level
MS Disease Type and Progression

Relapsing-remitting

Secondary-progressive

Primary-progressive

Progressive-relapsing

Pathology of MS

* Immune-mediated disease in susceptible individuals
* Demyelination occurs: Slowed conduction
* Axonal injury and destruction occur
  * Permanent neurological dysfunction
* Lesions in optic nerves, periventricular white matter, brain stem, cerebellum, SC

The Immunology of MS

- The innate immune response
- Adaptive immune response – production of specific antibody with immunologic memory
  - Lymphocytic B-cells produce Ab
  - T-cells release IL’s which balance the immune response

- The interaction between T-cells and APC’s are an important part of the AIS
- The pathway then chosen depends greatly on the stimulatory molecules presented – a system of checks and balances
Cytokine Imbalance in MS

**Normal**
- **Inflammatory**
  - IFN-γ
  - IL-12
  - TNF
- **Anti-inflammatory**
  - IL-4
  - IL-10
  - TGF-β

**MS**
- **Inflammatory**
  - IFN-γ
  - IL-12
  - TNF
- **Anti-inflammatory**
  - IL-4
  - IL-10
  - TGF-β
Extravasation

astrocytes BRAIN
TISSUE

MYELIN

oligodendrocyte

B cell

Rolling

Adhesion

Extravasation

Circulation

LUMEN OF VENULE

BLOOD FLOW

LUMEN OF VENULE

α4 Integrin
VCAM
LFA-1
ICAM

BLOOD FLOW

Activated T cell

Proteases (MMPs)

Antigen presenting cell (astrocyte or microglial cell)

Activated microglia/macrophages

Activated T cell

Cytokines and chemokines

IL-1, IL-12, chemokines

Antigen presenting cell

Circulation

Activated macrophage

Proteases

Axonal damage

O2•−

NO•−

excess glutamate

GluR

Oligodendrocyte

MYELIN

Autoantibodies

Complement

T CELL REACTIVATION
Use of MRI in Diagnosis

* MRI is used to improve confidence in a clinical diagnosis of MS or to make a diagnosis of MS in clinically isolated syndromes¹
* May show dissemination in space and time (eg, new lesions on follow-up MRI)¹
* Total lesion load at diagnosis tends to be predictive of future disability²

Sagittal FLAIR – Morphology Matters

Typical of MS

Perivenular

Unlikely MS

Random
Callosal Atrophy in MS

MS & Gd: Optimization

T1-non

T1-Gd immediate

T1-Gd 5-min delay
Goals of Disease Management

- Treating relapses
- Managing symptoms
- Modifying/reducing relapses and delaying progression to disability
- Facilitating an acceptable quality of life
Disease Modification

- Aim to alter the natural course of the disease
  - Decrease relapses
  - Delay disability
- Two classes of disease-modifying medications:
  - Immunomodulators
  - Immunosuppressants

Current DMT’s

- Betaseron, Extavia
- Avonex, Rebif, Plegridy
- Copaxone, Glatopa
- Novantrone
- Tysabri
- Gilenya
- Aubagio
- Tecfidera
- Lemtrada
Disease Measurements

- Relapse rate
- Sustained disability
- Lesion load
- Cognitive dysfunction
Potential Action of IFN-β

- Decreased MHC class II expression
- Apoptosis of auto reactive T cells
- Decreased Co-stim molecules
- Shift from pro inflammatory cytokines to anti-inflammatory

- Flu like Side effects
- Depression
- Injection site reactions
- Injection fatigue
- Adherence
Glatiramer Acetate MOA

* Competes with MBP for binding to MHC II sites
* Induction of anti-inflammatory Th2 cells
* Good long term safety data
* Now available 3 times a week
* Injection reactions, allergic reactions, and lipoatrophy ongoing issues
* Post injection reaction

Natalizumab MOA

- Recombinant humanized Ab
- Lymphocytes and monocytes express α4-β1 integrin
- The integrin binds VCAM-1
- Tysabri blocks α4-integrin binding to VCAM and therefore inhibits migration

- Allergic reactions
- PML progressive multifocal leukoencephalopathy, monitor JCV-ab
- Infections
Fingolimod - Gilenya

- Internalizes S1P receptor
- Traps circulating lymphocytes in lymph node
- Reduces T cells infiltrating the CNS

- FDO – first dose observation
- Screen for bradycardia, heart block, med interactions, macular edema, and varicella immunity
- Also PML
Teriflunomide (Aubagio)

Background

* Metabolite of Leflunomide (Arava), an oral therapy approved for the treatment of RA since 1998
* once a day oral

Check TB test and LFT, CBC prior to therapy
Monitor LFT monthly x months
GI, hair thinning (temporary) and Skin reactions

Dimethyl Fumarate (Tecfidera)

* Therapeutic mechanism of dimethyl fumarate in MS is speculative
  * inhibit pro-inflammatory cytokines
  * Possible anti oxidant pathway? Potential for repair (nrf2)
* Flushing and GI symptoms most common issues
* 4 cases of PML
* Monitor Lymphocytes

Alemtuzumab (Lemtrada)
Background and Mechanism of Action

* Alemtuzumab is a humanized antibody directed against CD52 antigen (anti-CD52 Ab)
* This is present on >95% of T cells and B cells
* Long-term depletion of B and T cells resulting in prolonged reduced white count and reduced inflammation in the CNS
* Monitor labs monthly x 4 years after 2nd course
* ITP, renal, thyroid (autoimmune conditions)

Acute MS Relapses

- Relapse
  - Focal disturbance of function >24 hr
  - Occur about once a year in untreated patients
  - In absence of infection
- Management: high-dose steroids
  - Common option: methylprednisolone IV for 5 days
  - Weakness, “MS hug”, Optic neuritis, Decreased coordination
Triggers for a Psuedoexacerbation

- Infection – urinary, pulmonary, skin, etc
- Stress – work, financial, relationships
- Poor or inadequate sleep
- Systemic illness
Symptom management

- Highly variable, depends on symptoms
- Spasticity – baclofen, tizanidine, baclofen pump, benzodiazepines
- Fatigue – amantadine, modafinil, stimulants
- Depression – SSRI’s, other antidepressants
- Cognition – variable
- Bladder – neurogenic bladder
- Bowel – constipation management
- Pain – avoid narcotics if possible
Figure 2. Multiple sclerosis symptoms can be related and interdependent.

Crayton H et al. Neurology 2004;63:S12-S18

Cycle of Symptoms

- Fatigue
- Depression
- Exercise
- Spasticity
- Bladder Problems
- Sleep
- Cognitive Function

Increase
Decreases
Decreases
InCREASE
Decreases
Dalfampridine

- To help improve walking in patients with MS
- Contraindicated in patients with history of seizure and renal impairment
- Side effects – may not work, dizziness, vivid dreams
* Smoking may increase the risk of getting MS
  * Twice as likely to get MS if smoke before age 17
    * Riise, Neurology 2003

* Smoking increases the rate of disease progression in MS
  * Three times the rate of disability for patients who smoke with MS
    * Hernan, Brain, March 9, 2005

* Meta-analysis reveals risk estimate for developing MS 1.5 for ever smoking vs never smoking

* Smoking and 2 HLA genes interact to increase the risk for MS
  * Hedstrom et al, Brain.2011;134(3):653-664
Pipeline for MS
Evidence-based medicine is the conscientious explicit and judicious use of current best evidence in making decisions about the care of individual patients."  

It is using the best information to make the best decisions.

It utilizes available data, sometimes there can be a plethora of data, and sometimes the data is sparse, making it more difficult.

Clinical Trial Phases

* Phase I: Metabolism, Pharm. Action on healthy volunteers (20-80) 6 m – 1 yr.
* Phase II: Effectiveness for indication and short term SE on several hundred patients with indications for 1-2 yrs
* Phase III: Overall risk benefit on several hundred to thousand for 2 -3 yrs
* Phase IV: New population or indication for 1 -2 years
Daclizumab

* A humanized antibody (90% human and 10% mouse) directed against a marker on T cells
* Therefore targeting activated T cells without causing general T cell depletion
* Immunosuppressant
* Once a month injection

B cells contribute to MS pathology in several ways:

- Production of autoantibodies
- Release immune stimulating substances
- Present antigen to T cells to stimulate “attack”

Ocrelizumab is a humanized antibody that eliminates a certain type of B cell.

Ibendenone

- Trial ongoing looking if effective at slowing down progressive forms of MS
- A man made drug similar to Co-Q10
- Study ongoing to see if safe and if can prevent ongoing disability
- May limit demyelination and death of brain cells, slow atrophy
Biotin

- 300mg/day dosed in 154 patients with PPMS and SPMS
- 166 patients, 154 randomized 2:1. Treated -103, placebo 51.
- Outcome measures: decrease in EDSS by 1 point if EDSS 4.5-5.5, and decrease by 0.5 if 6-7
- 13% met outcome measure, 0% in control group. Also, treated group: 13% progressed with EDSS, control group 41% progressed, with a difference of 67% in favor of Biotin.
- 16 centers involved
  Improvement seen in some patients up to 16 months from the start of trial.

- We still have a lot to learn, further studies ongoing
Anti-Lingo -1

- Anti-LINGO-1 blocks the LINGO-1 protein, which inhibits the production of myelin.
- It is felt this enhances myelin growth. It has consistently performed well in animal models and in human cells grown in culture.
- 82 patients with optic neuritis studied. The trial found that the antibody was no better than a placebo at improving vision. But it did speed up signaling in retinal nerves — a possible sign that the myelin sheath had been rebuilt — by 41% over placebo after eight months of treatment.
- Much we still don’t know, including long term safety, etc.
Team Approach

- Neurology and PCP
- Social work
- Peer support
- Speech and language
- Mental health
- PT/OT
- Psychiatry
- Patient