Multiple Sclerosis
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32nd Annual Board Review Course in PM&R
3/15/2015

Learning Objectives

› Review the basics of multiple sclerosis etiology, diagnosis, presentation and treatment
› Appreciate the complexity of presenting symptoms
› Appreciate the rapidly changing science related to multiple sclerosis

Outline

› What is MS?
  ◦ Pathology
› How do you get it?
  ◦ Etiology
› How does it present?
  ◦ Clinical types, diagnosis
› How do we treat it
  ◦ How do we treat it’s symptoms

What is MS?
What is multiple sclerosis?

- "dysimmune" disorder of neuroinflammation
- Scarring or plaques
- Central nervous system– brain and spinal cord
- Demyelination, axonal loss and brain atrophy
- Grey and white matter

Brain white and gray matter

1. T-cells migrate into CNS and become pathogenic
2. Pathogenic cells trigger inflammatory response
3. Cytokines released attract
4. And activate monocytes into macrophages
5. Which destroy myelin and sever axons
6. B cells (plasma cells) release antibodies which probably also participate in myelin destruction.
7. Regulator T cells decrease the inflammatory process

Spinal Cord White and gray matter

Pathology of inflammation

http://fieremans.diffusion-mri.com/phd/PRDv02.html

http://www.d.umn.edu/~lholmstr/Biol1761/LectureOutlinesCh13_000.htm
The immune system is attacking an infectious agent that looks like myelin or brain material. The immune system doesn’t recognize the brain and thinks it is foreign.

Cytodegeneration of oligodendroglia, their processes or myelin trigger the immune system. The immune system is destroying cells that are unhealthy.


Pathophysiology of MS


MS affects the brain and spinal cord causing an upper motor neuron lesion. Consequently, you would expect to see which of the following?

- 1. decreased reflexes
- 2. spasticity
- 3. weakness
- 4. increased tone
True or false

- MS causes upper motor neuron lesions therefore EMG will show positive sharp waves, fibrillation potentials and abnormal motor units only in weak muscles?

What causes MS?

- Environmental factors – Virus, smoking, vitamin D, gut microbes, latitude prior to age 15
- Genetic predisposition – Over 100 genes involved, HLA-DRB1*15:01 allele, identical twins 25%


What does MS look like?

- Estimated 350,000 people in the US
- Women 2–3x > men
- Northern latitudes
- Age of onset 20 to 40
- Common cause of disability in this age group
- Decreases life span 5 to 10 year
- Caucasians predominantly
 World wide prevalence of MS

MS presenting symptoms

- Optic neuritis
- Sensory changes
- Weakness
- Cognitive issues
- Bowel and bladder deficits
- Fatigue
- Lhermitte’s sign
- Heat sensitivity (Uhtoff phenomenon)
- Internuclear ophthalmoplegia
- Ataxia
- Intention tremor
- Spasticity
- Dizziness
- Pain
- Double vision
- Depression
- Sexual dysfunction

Signs & Sx based on CNS location

- Cerebellar and basal ganglia:
  - ataxia
  - intention tremor
  - dysarthria
- Dorsal columns:
  - sensory abnormalities
  - proprioception
  - deep sensation
- Corticospinal tract:
  - weakness
  - pain
- Frontal lobe:
  - cognitive deficits
  - memory
  - learning
  - impaired emotional responses
- Brainstem:
  - myokymia
  - deafness
  - tinnitus
  - vertigo
  - dysphagia
  - internuclear ophthalmoplegia

Figure 1 Voluntary eye movements (A) Right gaze.
**Internuclear ophthalmoplegia**

- Lesion of the medial longitudinal fasciculus (MLF)
- Lesion of the MLF on the affected side
- Decreased adduction
- Convergence intact

**Presenting symptoms**

- Monofocal
- Multifocal
- Come on abruptly or slowly
- Attacks that resolve
- Slow progression

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**Clinical Patterns**

- Relapsing remitting MS (RRMS)
- Secondary progressive MS (SPMS)
- Primary progressive MS (PPMS)
- Progressive relapsing (PRMS)
- Clinically isolated syndrome (CIS)
- Radiologically isolated syndrome (RIS)

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**Relapsing Remitting MS**

![Image of Relapsing Remitting MS]

Relapsing Remitting MS
- 85% of cases
- Worsening of condition with variable recovery
- Lasts weeks to months
- Typically relapse every 1–2 years without treatment

Secondary Progressive

Secondary progressive MS
- Started with RRMS but now progressing
- Typically without any or much reduced incidence of relapses
- Approximately 70% of RRMS will ultimately progress to SPMS
- Treatment is indicated especially if there is still evidence of inflammation

Primary Progressive
Primary Progressive MS (PPMS)

- Approx 10% of cases
- No evidence of acute exacerbation
- Current treatments not effective
- Typically later onset 30–40 years old
- Male = female
- No significant inflammation seen on MRI

Progressive Relapsing

MS presentations

- Clinically isolated syndrome
  - Only one episode
- Radiologically isolated Syndrome
  - Asymptomatic lesions found randomly
**MS Clinical Presentations**

- **Onset <35 yo**
- **Monosymptomatic**
- **Long remissions**
- **Onset symptoms sensory or optic neuritis**
- **Ambulation not affected**
- **Low disability**

**Prognosis**

- Better
  - Male, Onset >35 yo
  - Polysymptomatic
  - Rapidly progressive
  - Motor, ataxia or tremor
  - Non-ambulatory
  - High disability

- Poorer

**Progression of MS**

- **Highly variable**
- **PPMS progresses much faster than RRMS**

**MS Presentations**

- **Pre-symptomatic MS**
- **CIS**
- **RRMS**
- **SPMS**

**Prognosis**

**Better**

- Onset <35 yo
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**Poorer**

- Male, Onset >35 yo
- Polysymptomatic
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**Progression of MS**

- Highly variable
- PPMS progresses much faster than RRMS

**Reading:** Stellman, JP et al. PLoS One. 2014 Mar 20;9(3):e92761. Disease prediction not found in PPMS.
**Question**

- What is the most common type of MS
  1. relapsing remitting
  2. secondary progressive
  3. primary progressive
  4. Progressive relapsing

**Diagnosis**

- History and neuro exam
  - Two neurologic events separated by time and space
  - Abnormal exam consistent with white matter demyelination
- Studies
  - Brain/spinal cord MRI
  - Lumbar puncture
  - Evoked potentials
- Exclude other diagnosis

**Diagnosing MS**

- Disseminated in space
  - damage in at least two separate areas of the central nervous system (CNS)
    - Brain
    - spinal cord
    - optic nerves AND
- Disseminated in time
  - damage occurred at two different points in time
    - Can be met with acute and chronic MRI finding AND
- Rule out all other possible diagnoses.

**Neurologic event**

- Must last longer than 24 hours
- Must be at least 30 days from previous episode
- Must not be due to other issues (infection, heat, medication)

**McDonald Criteria 2010 MS Diagnosis – Disseminated in space**

<table>
<thead>
<tr>
<th>DIS Can Be Demonstrated by ≥1 T2 Lesion(^\text{a}) in at Least 2 of 4 Areas of the CNS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periventricular</td>
</tr>
<tr>
<td>Juxtacortical</td>
</tr>
<tr>
<td>Infratentorial</td>
</tr>
<tr>
<td>Spinal cord(^\text{b})</td>
</tr>
</tbody>
</table>

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

\(^\text{b}\)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.

**McDonald Criteria 2010 MS diagnosis: Disseminated in time**

**DIS 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; DIS = lesion dissemination in space.


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**McDonald Criteria 2010 MS Diagnosis – PPMS**

**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\(^c\):
   - A. Evidence for DIS in the brain based on ≥1 T2\(^\text{a}\) lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)
   - B. Evidence for DIS in the spinal cord based on ≥1 T2\(^\text{a}\) lesions in the cord
   - C. Positive CSF (i.e., oligoclonal bands and/or elevated IgG index)

\(^\text{c}\)If a subject has a brainstem or spinal cord syndrome, all asymptomatic lesions are excluded from the Criteria.

\(^\text{a}\)Gadolinium enhancement of lesions is not required.

MRI = multiple sclerosis; PPMS = primary progressive MS; DIS = lesion dissemination in space; CSF = cerebrospinal fluid; IgG = immunoglobulin.


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**MRI brain findings**

- Dawson’s fingers
- Brain atrophy
- Used to monitor progress and response to medications

[Image of MRI brain scan]

http://radiopaedia.org/g/images/482357
**MRI findings in MS**

**Brain**
- Location
  - Periventricular
  - Subcortical
  - Infratentorial
- Appearance
  - Ovoid
  - Hyperintense T2
  - Hypointense T1
- Acute lesions
  - Gad enhancing on T1
  - Last 30 to 40 days

**Spinal Cord**
- Little or no swelling
- Hyperintense on T2
- At least 3 mm
- Less than 2 vertebral lengths
- Focal
- Usu only part of the cord

www.nationalMSsociety.org

**MS Spinal cord lesions**

www.radiopaedia.org/articles/multiple-sclerosis

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**Cerebrospinal fluid in MS**

- Normal white blood cell count
- Normal protein
- Immunoglobulin oligoclonal bands 83% to 94% of patients
- No oligoclonal bands in the blood

http://www.mstrust.org.uk/information/publications/msexplained/images/bands.gif

**Other diagnostic tools**

- Visual evoked potentials (VEP)
- Brainstem Auditory Evoked response (BAER)
- Somatosensory evoked potentials (SSEP)
- Optical coherence tomography (OCT)
MS look alike: Neuromyelitis optica (NMO)

- Optic neuritis
- Spinal cord lesion > 3 segments
- NMO IgG positive (anti-aquaporin-4 Antibody)

Treatment
- Plasma exchange
- Rituximab, axathioprine + prednisolone, mycophenolate
- Mitoxantrone, cyclophosphamide, methotrexate

Differential diagnosis of MS

<table>
<thead>
<tr>
<th>Vascular</th>
<th>Multiple lacunar infarcts, CADASIL, spinal arteriovenous malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Infarction, stroke, multiple sclerosis, HIV myelopathy, PML, LRRF-1 myelopathy</td>
</tr>
<tr>
<td>T</td>
<td>Traumatic</td>
</tr>
<tr>
<td>A</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>M</td>
<td>Metabolic/toxic</td>
</tr>
<tr>
<td>I</td>
<td>Idiopathic/genetic</td>
</tr>
<tr>
<td>N</td>
<td>Neoplastic</td>
</tr>
<tr>
<td>S</td>
<td>Psychiatric</td>
</tr>
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</table>

How do we treat MS?

Treatment of MS exacerbation
**Acute exacerbation treatment**
- 500 to 1000 mg/day IV methylprednisolone for 3 to 5 days
- New sx or worsening sx lasting more than 24 hours and NOT due to infection, other illness or medication
- Improves recovery but does not alter disease progression
- Typically used for severe flare
- Long term use associated with increased risk of osteoporosis, cataracts, ulcers
- Side effects: edema, mood swings, increased/decreased appetite, dyspepsia, insomnia, aseptic necrosis

**Medication Treatments for MS prior to 1993**

**Treatments Goals**
- Reduce frequency of relapses
- Reduce MRI findings
- Reduce disability progression

**FDA Approved MS Disease Modifying Therapies – 1993 to 2015**
- Beta–interferon β1b (Betaseron) 1993
- Beta–interferon β1a (Avonex) 1996
- Glatiramer (Copaxone) 1997
- Mitoxantrone (Novantrone) 2000
- Beta–interferon β1 a (Rebif) 2002
- Natalizumab (Tysabri) 2006
- Fingolimod (Gilenya) 2010
- Teriflunomide (Aubagio) 2012
- Dimethyl Fumarate (Tecfidera) 2013
- Peginterferon β1a (Plegridy) 2014
- Alemtuzumab (Lemtrada) 2014
Disease Modifying Treatments: Injectables

- Interferon beta 1–a
  - Avonex®- IM q week
  - Rebif®- SC 3x/week
  - Plegridy®- SC q 2 weeks

- Interferon beta 1–b
  - Betaseron®- SC 3x/week

- Glatiramer acetate
  - Copaxone®- SC q day or three times per week

Interferon–beta 1 a and b agents

Mechanism: immune modulator
Adverse rxn: Injection site reaction
- Flu like symptoms
- Leukopenia
- Liver toxicity
- Depression
- Risk of antibodies
Safety Monitoring: CBC, hepatic panel at 1, 3, 6 mos then q 6 mos

Glatiramir Acetate

Mechanism: immune modulator
Adverse rxn: injection site rxn
- lipoatrophy
- systemic injection rxn
Pregnancy: safe
Safety monitoring: none

DMTs Orals

- Orals
  - dimethyl fumarate (Tecfidera®)
    - BID
  - terafslumomide (Aubagia®)
    - Q day
  - fingolomod (Gilenya®)
    - Q day
**Fingolimod**

Mech of action: Spingosine-1-phosphate receptor modulator. Prevents egress of lymphocytes from lymph nodes.

- **Adverse rxn:** leukopenia, infections - herpes, varicella, liver tox, macular edema, fetal risk, PML (2 cases)
- **Monitoring:** CBC, LFT, VZV titer, eye exam, EKG prior to starting.
  - First dose monitoring for bradycardia, AV block.
  - Ongoing CBC, LFTs, eye exam.

**Teriflunamide**

Mech of action: Blocks de novo pyrimidine synthesis pathway exerting a cytostatic effect on stimulated and proliferating T and B cells.

- **Black Box:** hepatotoxicity, teratogenicity.
- **Adv rxn:** lymphopenia, leukopenia, cholestyramine for expedited elimination peripheral neuropathy, acute renal failure/hyperkalemia, HTN, stevens-johnson-syndrome rare.
- **Monitoring:** CBC, LFT, TB test, pregnancy counseling prior.
  - LFTs q mos for 6 mos, then q 6 mos.

**Dimethyl fumarate**

Mech of action: Activates the nuclear factor 2 pathway which is involved in the cellular response to oxidative stress.

- **Adv rxn:** nausea, flushing, abd cramping, lymphopenia, PML (one case).
- **Monitoring:** CBC and LFT q 6 moths.

**DMTs: IV**

- Mitoxantrone (Novantrone®)
  - IV q 3 mos.
- Natalizumab (Tysabri®)
  - IV q 28 days (13/year).
- Alemtuzumab (Lemtrada®)
  - IV for 5 days year one, 3 days year 2.
Mitoxantrone
Mech of action: immunosuppression, disrupts DNA synthesis and repair
Black Box: cardiotoxicity, leukemia
Adverse rxn: nausea, vomiting, fatigue, infection, leukopenia, liver toxicity, amenorrhea, infertility
Monitoring: CBC, CMP, UA pre-infusion, Echo before and after each dose and annually for life. CBC after discontinuation to monitor for late leukemia.

Natalizumab
Mech of action: monoclonal antibody anti VLA-4, blocks movement of activated T cells into the CNS
Black Box: progressive multifocal leukencephalopathy (PML)
Adv rxn: liver toxicity, anti-natalizumab antibodies
Monitoring: FDA mandated REMS program TOUCH, MRI q 6 mos if JCV + and greater than 24 mos on tx, MRI q 3 to 6 mos

PML Risk Factors
- JC (John Cunningham) virus positive
- Time on natalizumab – greater than 2 years
- Prior immunosuppressive
  - cyclophosphamide (Endoxan®, Cytoxan®, Neosar®, Procytox®, Revimmune®)
  - Azathiaprine (Azasan®)
  - Mitozanthrone (Novantrone®)

Risk of PML on Natalizumab

<table>
<thead>
<tr>
<th>JCV Ab</th>
<th>Past Immuno</th>
<th>Overall</th>
<th>&lt;24 mos</th>
<th>&gt;24 mos</th>
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<tbody>
<tr>
<td>Neg</td>
<td>No</td>
<td>1.8,136</td>
<td>1.45,1841</td>
<td>1.5,180</td>
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<tr>
<td>Neg</td>
<td>Yes</td>
<td>1.2,869</td>
<td>1.15,935</td>
<td>1.1,827</td>
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<tr>
<td>Yes</td>
<td>No</td>
<td>1.203</td>
<td>1.1,130</td>
<td>1.1,29</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>1.72</td>
<td>1.398</td>
<td>1.46</td>
</tr>
</tbody>
</table>

PML risk and JCV titer without immunosuppressants

<table>
<thead>
<tr>
<th>Index results</th>
<th>1-24 mos</th>
<th>25-48 mos</th>
<th>49-72 mos</th>
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<tbody>
<tr>
<td>&lt;= 0.9</td>
<td>1 in 10,000</td>
<td>1 in 3333</td>
<td>1 in 2500</td>
</tr>
<tr>
<td>&lt;= 1.1</td>
<td>1 in 10,000</td>
<td>1 in 1429</td>
<td>1 in 1429</td>
</tr>
<tr>
<td>&lt;= 1.3</td>
<td>1 in 10,000</td>
<td>1 in 1000</td>
<td>1 in 833</td>
</tr>
<tr>
<td>&lt;= 1.5</td>
<td>1 in 10,000</td>
<td>1 in 833</td>
<td>1 in 769</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>1 in 1000</td>
<td>1 in 123</td>
<td>1 in 118</td>
</tr>
</tbody>
</table>

Barts and the London School of Medicine and Dentistry. ENS hot topic: JCV titres and PML risk. June 10, 2013

Alemtuzumab

Mech of action: monoclonal Ab that depletes CD52+ cells

Black Box: autoimmune disorders, infusion reactions and malignancies.

Adv rxn: Infusion related (fever, HA, rash, fatigue) Infection (Herpes) Autoimmune (thyroid, ITP, Goodpasture’s)

Monitoring: VZV, TSH, CBC, Cr, UA, skin no live vaccinations after tx REMS

Current therapy summary

- Amazing array of new treatments over the past 20 years
- Side effects can limit adherence
- No therapies are effective against progressive, non inflammatory types
- Copaxone best for pregnancy

Common problems in MS

- Gait impairment
- Depression
- Cognitive impairment
- Speech and swallow
- Heat regulation
- Social isolation
- Fatigue
- Vocational issues
- Tremor
- Pain
- Neurogenic bowel and bladder
- Spasticity
- Sleep problems
What is mobility?


Causes of altered Mobility in MS

Due to MS
- Weakness LE and UE
- Spasticity
- Balance problems
- Sensory loss
- Vision
- Cognition
- MS exacerbation
- Ataxia/coordination problems
- Fatigue +/-
- Contractures
- Cerebellar involvement

Non MS issues
- Infection/acute illness
- Osteoarthritis
- Back pain
- Osteoporosis
- Cardiovascular problems
- Depression

Treatments
- PT for functional restoration
- Spasticity management
- Bracing
- Pacing
- Walker
- Manual wheelchair
- Power wheelchair

Assistive Devices
Assistant Devices

Wheelchair  Scooter

Benefits of exercise in MS

- Improved functional capacity
- Decreased depression
- Decreased fatigue
- Increased quality of life
- Decreased cardiovascular disease, diabetes, osteoporosis, obesity

Dalfampridine: Blocks potassium channels on demyelinated nerves

Who Should Not Take Dalfampridine?

- History of seizures
- Moderate to severe kidney impairment – CrCl less than 50m/min
- Do not take extra or double up after missed doses

Dalgas U. Multiple Sclerosis 2008;14:35-53
Limitations of Dalfampridine
- Cost
- It does not work for everyone
- It has a limited degree of benefit
- It is not safe for everyone
- It does not change the course of MS

Dalfampridine: Side Effects
- Not everyone feels better taking it
- Urinary tract infection (12%)
- Insomnia (9%)
- Dizziness (7%)
- Headache (7%)

Fatigue in MS
- Invisible symptom
- One of most common MS symptoms
- Affects employment
- Cause unknown, not related to MRI lesion burden

Treatment of fatigue
- Rule out medical problems (hypothyroid, anemia, sleep apnea, B12)
- Screen for depression
- Energy conservation techniques
- Cognitive behavioral therapy
- Medications (amantadine, modafinil, methylphenidate)
- Cooling vests
- Evaluate polypharmacy
**Cognitive impairment**
- Invisible symptoms
- Up to 70% of MS patients affected (Chairavolloti ND. Lancet Neurol. 2008. 7:1139–1151)
- Processing speed, visual learning and complex sustained attention
- Correlates with cortical atrophy more than lesion load
- Can be impacted by fatigue, sleep, depression, medications
- Affects employability

**Treatment for cognitive impairment**
- Speech strategies
- Neuropsych testing
- Tx medical problems
  - Depression, fatigue, heat intolerance
- No medications FDA approved

**Depression in MS**
- Life time prevalence of 50%
- Anxiety affects 1/3 of people with MS
- Suicide at least 2 times the rate
- Can be evaluated with the PHQ9

**Treatment of depression**
- Cognitive behavioral therapy
- SSRIs
- Check for cognitive impairment
Heat Sensitivity

- Common symptom
- Can bring on weakness (Uhthoff phenomenon)
- Treated with cooling vest
- Air conditioning
- Cool climate

Pain in multiple sclerosis

- Variety of estimates on prevalence but up to 80%
- Impacts general health and mood
- Impacts ability to do rehab
- Occurs early and late
- Difficult to predict who will have pain
- Psychosocial factors may be more important than physical factors
- No association between site of lesion and presence of pain (Svendsen KB et al. 2011)

Pain and MS

Types of pain in multiple sclerosis

- Continuous central neuropathic pain
- Intermittent central neuropathic
  - Trigeminal neuralgia, Lhermitte's sign, glossopharyngeal neuralgia, optic neuritis
- Musculoskeletal/ nociceptive
  - Spasms, joint pain related to positioning, injection pain, visceral/bladder pain
- Mixed neuropathic and non-neuropathic
  - Headaches
Treatment of pain in multiple sclerosis

- Central neuropathic pain
  - Tricyclic antidepressants
  - Antiepileptic medications
  - Opiates
- Intermittent central neuropathic pain
  - Antiepileptic medications
- Musculoskeletal pain
  - Antiinflammatories
  - Antispasmetics

Social isolation and vocational issues

- Can be problematic due to symptoms associated with MS
- Encourage patients to participate in a support group
- Minimize bowel and bladder issues
- Neuropsych testing
- Accommodations at work

How is disability measured in MS?

EDSS: Expanded Disability Status Scale

- Developed to quantify disability
- Used in research
- Heavily weighted to ambulation
- May not be sensitive enough to catch small but meaningful changes

Overview of MS
- Definition – now includes white and grey matter, dysimmune, axonal destruction
- Etiology – T cells, B cells, environment, genetics
- Presentation – types, variability
- Diagnosis – much more use of MRI
- Treatment of acute exacerbations – unchanged
- Treatment ongoing – large changes
- Sx treatment – complex, benefits from multidisciplinary team

EDSS


Summary