A Short Review of MS

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Multiple Sclerosis

• An immune-mediated inflammatory disease of central nervous system (CNS) myelin (and axons)
• The neurological signs and symptoms of MS are variable
• The etiology of MS is unknown
• The diagnosis of MS is one of exclusion
Myelin Ultrastructure

I

II

Lazzarini et al. (2004) Myelin Biology and Disorders
The purpose of myelin is to increase the velocity of nerve conduction
Conduction Through a Demyelinated Nerve Fiber

Conduction Through a Myelinated Nerve Fiber
Common Symptoms of MS

- Optic Neuritis
- Sensory disturbance
- Weakness (hemiparesis or paraparesis)
- Coordination difficulties
- Fatigue /Endurance
- Cognitive / Mood disorder
- Bladder / Bowel disorder
- Sexual dysfunction
- Double vision
- Dysarthria
- Vertigo / Dizziness
Clinical patterns of MS

A  Relapsing-remitting

B  Progressive-relapsing

C  Secondary-progressive

D  Primary-progressive
Diagnosis of MS

- McDonald Diagnostic Criteria
  - Signs/symptoms of neurological disease disseminated in both time and space
  - Single neurological episode with MRI evidence of dissemination: Clinically isolated syndrome (CIS)

- MRI is critical for diagnosis: T2 signal abnormalities usually have a periventricular and/or juxtacortical distribution
  - Radiologically isolated syndrome (RIS)

- Lumbar puncture: evidence of immunoglobulin production in CNS

- Evoked potentials

- OCT
Lumbar Puncture Results

- Referral placed to see Dr. Kamholz
- July 2017: Patient has right-sided weakness, blurred vision in left eye, ambulation problems
- Presented to UIHC ER and MRI performed
Pathophysiology of MS

• Inflammatory components
  • Coincides with relapsing features of disease

• Neurodegenerative component (axons and neurons)
  • Progressive, slow, worsening of disease

• Permanent damage accumulates
  • Stable, untreated patients build damage

• Macroscopic and microscopic changes
  • Changes on MRI
  • White matter changes
Confocal Microscopic Images of Axonal Changes in MS Lesions

Axon with active demyelination

Axon ends in large terminal ovoids

Role of T Cells in MS

- Increased number of helper T cells in spinal fluid
- Increased number of activated T cells passing into brain from peripheral blood
- Presence of T cells in MS plaques
- Increased frequency of activated T cells against the myelin seen in MS patients compared to healthy controls

Most Meds Target T Cells

From http://austinpublishinggroup.com/multiple-sclerosis/fulltext/images/ajmsn-v2-id1009-g001.gif
Disease Modifying Therapies (DMTs) in MS

• All current disease modifying therapies (except one, Ocrelizumab) are to reduce relapses in relapsing-remitting MS; not for symptom management

• Documented clinical benefits of DMTs
  • ↓ number of relapses, severity
  • ↑ time between relapses
  • ↑ number of patients relapse-free
  • ↓ disability and worsening on neuro exam in short term
  • ↑ quality of life
  • ↓ MRI lesion formation, size, and severity

“The exact relationship between MRI findings and the clinical status of MS patients is unknown. The prognostic significance of MRI findings in these studies has not been evaluated.” – Rebif Package Insert (in all of the package inserts for DMTs)
Treatment of MS

- The currently available treatments of MS are all directed toward modulating the immune system.

- There are now at least 15 drugs currently approved by the FDA for MS. All of these compounds are effective for relapsing/remitting MS.

- There one drug, Ocrelizumab, approved for the treatment of primary progressive MS.
Some of the Disease Modifying Treatments

Beta interferons (Avovex, Betaseron, Rebif, Plegridy).
Glatiramer acetate (Copaxone; a mixture of peptides with properties similar to myelin basic protein).
Tysabri (natalizumab), a monoclonal antibody to alpha 4 integrin on the surface of white cells.
Ocrevus (ocrelizumab), a monoclonal antibody to CD20, a protein on the surface of B cells.
Gilenya, a sphingosine receptor agonist
Tecfidera (dimethylfumarate), activates the Nrf2 pathway
Disease Modifying Therapies (DMTs) in MS

• Although we know that DMTs reduce relapses and disability in the short term, we do not know their effect on disability in the long term

• Although we know when to begin DMT (early), we do not know when to stop therapy, or what criteria to use to change from one to another
Take Home Lessons

- MS is an inflammatory mediated demyelinating disease of the CNS of unknown etiology
- The signs and symptoms of MS are caused by inflammatory attack on myelin, leading to segmental demyelination, axonal transection and conduction block
- The long term disability in MS is probably a result of accumulated degeneration of axons.
Take Home Lessons (cont)

• The diagnosis of MS is a clinical one, based on the patient’s history, physical exam, laboratory studies and neuroimaging studies.

• The current treatments for MS are directed toward modulating the immune system and are effective for only the relapsing/remitting form of the disease.