THE MANY FACES OF MULTIPLE SCLEROSIS

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Multiple Sclerosis Program
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 adherence 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

- Age at onset: 15 to 45 years
- Gender: 70% women
- Geography: Prevalence increases with latitude
- Incidence: 8,500 - 10,000 new cases per year in US
- US prevalence: 250-350,000 (1/1000)

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
Pathology of MS: Demyelination

- Areas of demyelination
- Followed by partial remyelination and gliotic scarring

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Number of Transected Axons Increases With Level of Activity in the MS Lesions

(NAWM: normal-appearing white matter)
Pathophysiology: Gray Matter


Early MRI Events and Disease Progression

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”
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
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

2010 Revised McDonald Criteria for MS

• Simplification of the criteria:

  • DIS can be demonstrated by \( \geq 1 \) T2 lesion in at least 2 of 4 areas of the CNS:
    • Periventricular, Juxtacortical, Infratentorial, and Spinal cord

  • DIT can be demonstrated by:
    • A new T2 or Gd+ lesion on fup MRI, with reference to baseline scan irrespective of the timing of the baseline scan
    • Simultaneous presence of asymptomatic Gd+ lesion and non-enhancing lesions at any time

• Annals of Neurology 2011;69:292-302
Importance of MRI

- Monitoring treatment effect
- Diagnosis
  - CIS
  - CDMS
- Standardized criteria
- Predicting disability
- Future role of MRI in MS
Sagittal FLAIR – Morphology Matters

Typical of MS

Unlikely MS

Perivenular

Random
Callosal Atrophy in MS

MS & Gd: Optimization

T1-non

T1-Gd immediate

T1-Gd 5-min delay
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 or oral taper
  - Weakness, “MS hug”, Optic neuritis, Decreased coordination
Patients who present with clinically isolated syndrome (CIS) should be managed based on their risk of progression to MS:

- In the Optic Neuritis Trial, risk at 10 years was:
  - 56% for patients with $\geq 1$ lesion
  - 22% for patients with no lesions

- In patients with CIS and no lesions, risk of MS at 14 years was:
  - 19% for clinically definite (CD) MS
Differential Diagnosis of TM

- **Infectious** — Lyme, syphilis, HIV, HTLV-1
- **Vascular** — arteriovenous malformation (AVM)
- **Malignancy** — intramedullary or extrinsic tumor
- **Metabolic** — $B_{12}$
- **Inflammatory/autoimmune** — SLE, Sjögren's, sarcoidosis, APLS, MS, NMO
- **Structural** — cervical spondylosis
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
• Avonex
• Copaxone
• Rebif
• Novantrone
• Tysabri
• Extavia
• Aubagio
• Tecfidera
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**
- Th1
  - Inflammatory
    - IFN-γ
    - IL-12
    - TNF
  - Anti-inflammatory
    - IL-4
    - IL-10
    - TGF-β

**MS**
- Th2
  - Inflammatory
    - IFN-γ
    - IL-12
    - TNF
  - Anti-inflammatory
    - IL-4
    - IL-10
    - TGF-β
Kasper, L. H. et al. Neurology 2010;74:S2-S8
Caring for the Whole Patient

- Identify the disease process
- Treating the disease
- Managing symptoms
- Maintaining optimal health
  - Physical
  - Mental

- Multidisciplinary team concept

- Patients have the disease for decades – how can we prevent complications?
What is our multi-disciplinary team?

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

- 27 year old diagnosed with MS at another institution after developing right ON, abnormal MRI consistent with demyelinating disease
- Treated with high dose INF
- Intolerant, transitioned to GA
- Stayed on (?) for a couple of years, but when came to her initial appointment, she hadn’t taken it for >9 months
- Presents to initial appointment with ascending numbness, banding sensation across her chest x 1 week.
M.B. 4/09 spine MRI Gd+
M.B. Exam

- Healthy appearing, pleasant, obese woman
- Neurologic findings:
  - Pallor OD
  - Normal strength
  - Sensation abnormal mild loss vibration bilaterally in LE
  - Coordination normal
  - Gait wide based, difficulty tandem
  - Reflexes brisk at knees, but symmetric, plantars equivocal
M.B. plan

- She underwent a course of IVMP for acute treatment and her symptoms improved
- Long discussion ensued about treatment failures and options
- She elected to restart a different high dose INF

- Counseled on diet, exercise, adherence, stress management.
- Offered patient access to the multidisciplinary team, but she didn’t think she really needed it at the time.
Adherence

- Medication for chronic illness is only taken by 50-60% of patients as prescribed.
- After 6 months, between 9-27% of MS patients have discontinued therapy.
- In specialized MS centers, rates were 1.7% at 6 months and 8% at 2 years.

Adherence

• Why patients don’t take their meds
  • Side effects or fear of side effects
  • Injection anxiety
  • Cost of therapy, either co-pay too high or not covered
  • No current symptoms
  • Inappropriate expectations of therapy “I felt worse on the treatment than I did from my MS”
  • Depression

• Lower education levels and increased alcohol consumption predictive of missed doses
• Missed doses correspond to higher relapse rates
M.B. 10/09

- She restarts INF-beta in August
- Getting married in 2 weeks, excited but stressed, worried she’ll have a flare on the honeymoon
- Dislikes her job, long irregular hours in a restaurant

- Complains of fatigue, new left sided numbness involving arm and leg.
- Exam reveals mild hyperreflexia on the left, left gaze evoked nystagmus, and mild pallor (old) right
Disease Measurements

- Relapse rate
- Sustained disability
- Lesion load
- Cognitive dysfunction
M.B.

- Starts a course of pulse steroids in addition to INF-B for 3 months
- She followed up 12/09 and was doing well, symptoms improved. Still has fatigue.
- Routine screening revealed a low vit D level, and high glucose, and borderline HTN.
- She is overweight (320lbs) and was referred to her PCP for further evaluation.
Fatigue – Krupp et al

- 1. My motivation is lower when I am fatigued.
- 2. Exercise brings on my fatigue.
- 3. I am easily fatigued.
- 4. Fatigue interferes with my physical functioning.
- 5. Fatigue causes frequent problems for me.
- 6. My fatigue prevents sustained physical functioning.
- 7. Fatigue interferes with carrying out certain duties and responsibilities.
- 8. Fatigue is among my three most disabling symptoms.
- 9. Fatigue interferes with my work, family, or social life.
Managing Fatigue in MS

• Rule out other causes
  • OSA?
  • Poor sleep hygiene?
  • Insomnia/anxiety?
  • Depression?
  • Medications?
  • Heat intolerance?
  • Other underlying medical condition? (thyroid, anemia, etc)

• Treatment options
  • Exercise, PT, OT (energy conservation)
  • Amantadine
  • Modafinil (Provigil)
  • Stimulants
  • Anti-depressants
Links between Vit D and MS

• It has long been observed that MS is more prevalent the further you get from the equator
• Many studies link low vit D levels as a risk factor for developing MS.
• Acts as a hormone which regulates activity of cells in our body
• An immune system modulator
• Actions via the Vit D receptors (VDR’s)
Immunomodulatory effects of Vit D

- CD4+ T-cells and MBP-specific T cells are inhibited by Vit D

- Activated Vit D enhances development of IL-10 and reduced IL-6 and IL-7 secreting cells.

- High levels have been shown to promote T-cell regulation and promote a more anti-inflammatory status.

- Correale et al, Brain, 2009 May;132:1146-60
- Smolders et al, Multiple sclerosis. 2008 Nov;14(9):1220-4
M.Z. Follow up May 2010

- Comes in complaining of headaches, moderate bifrontal, squeezing
- Fatigue a component, working long hours, trouble falling asleep
- Paracervical spasm on exam
- No bladder or bowel complaints
- On questioning, skips doses of INF, did not follow through with PCP on weight loss or exercise
On giving patients advice about diet and exercise....

What we say to dogs

Okay, Ginger! I've had it! You stay out of the garbage! Understand, Ginger? Stay out of the garbage, or else!

What they hear

Blah blah GINGER blah blah blah blah blah blah...
Nutrition and MS

- Much of the research is anecdotal, watch out for poorly controlled studies
- Low saturated fat, high in Omega 3 and 6.
- Adequate protein, calcium, vitamins, hydration, fiber, etc.

- Weight – being overweight can lead to sleep apnea, joint disease, poor general health
- Constipation is another common complaint in MS
- Role of food allergens potentiating MS symptoms

- Be open to discussion
Exercise

• Don’t let patients use MS as an excuse not to exercise!
• Remind patients, this is a neurodegenerative disease with no cure and only partial response to pharmacology – particularly symptom management
• Numerous studies implicate exercise as a means of reducing fatigue, improving gait, overall QOL.
• Resistance training has been shown to improve gait
• Pool therapy
• Wii Fit program
• Yoga or Tai Chi
• The important aspect of exercise is that it is tailored to the patients needs and abilities
M.Z. August 2010

- Relapse, symptoms of right lower extremity numbness, weakness, and spasticity
- No underlying triggers discovered, admits to not taking INF despite encouragement from physician, husband, other family members
- Treated with 3 days IVMP
- She skips her MRI and her next follow up.
- Comes back in November, wants to stay on INF, restart titration.
- Encouraged to come to our team meeting. Declines.
Mental health and Multiple Sclerosis

- Depression
- Functional status
- Suicide

- Treatment options
  - Always review options for patient
  - Consider how it affects the disease, how they treat themselves, relationships, work, etc.
M.Z. follow up

• Meets with therapist who discovers a history of abuse, self-neglect, low self-esteem.
• Begins a program, connects with the therapist, and is making progress.

• Examining adherence, self image.
**Pseudo exacerbation**

- If patient presents with ‘old’ symptoms which have become more apparent
- Important to recognize so we don’t over treat patients
- Just as important to treat underlying condition so as not to exacerbate with immunosuppressive treatments
Triggers for a Pseudoexacerbation

- **Infection** – urinary, pulmonary, skin, etc
- **Stress** – work, financial, relationships
- **Poor or inadequate sleep**
- **Systemic illness**
M.Z. follow up MRI FLAIR
M.Z. MRI Gd+
M.Z. Asks About Alternative Therapies

- Marijuana – Honarmand et al looked at street cannabis in MS pts. Users vs. Non-users
  - Users performed more poorly on processing speed
  - Working memory
  - Executive function
  - Visuospatial perception
  - 2x more likely to be classified as globally cognitively impaired
Instead of marijuana, I recommended:

- Mindfulness meditation – looked at 150 pts. in an 8 week program.
  - Improved HRQOL
  - Depression
  - Fatigue
- Total of 150 patients randomized to treatment or usual care
- Results positive up to 6 months post-intervention
  - Grossman et al in Neurology 75, Sept 28 2010
Tobacco $$$

- 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
M.Z. Treatment options

- Admits she can no longer be trusted to take her medication, she has been promising to do shots since 4/09 with little success.
- Has questions about options
- Discuss Natalizumab (Tysabri) and Fingolimod (Gilenya) risks and benefits reviewed
- She has elevated blood glucose, being evaluated for diabetes
- Patient chooses Tysabri
- Enrolls in Stratify-2 study and is JCV-Ab negative
Family Planning MZ

• Wants to improve her disease state and her overall health first, but also thinking of starting a family.

• What are the risks of the baby developing MS?
  • Genetic predisposition – several genes implicated
    • MHC on chromosome 6 – strongest association
    • Interleukin 7 receptor alpha (IL7RA)
    • Interleukin 2 receptor alpha (IL2RA)
    • CD58 genes
    • C-type lectin domain family 16, member A (CLEC16A)

• First degree relatives have a risk of 3-5%
  • Reproduced on a number of studies (adoptee, step, marriage, etc) and twin studies
Family planning MZ

- Tolerating pregnancy
  - 70% decline in relapses during pregnancy, inverse is true for post-partum relapse rate
  - Managing without medication for symptoms
- After delivery, managing a child if fatigue is still an issue

- Planning is key, don’t want to have an ooops moment!
MB/MZ

- If I had been successful in getting her in to the team clinic early on, would it have made a difference?
- What troubles could have been averted?
  - Adherence
  - Depression
  - Nutrition
  - Peer support
  - Educational
- She will have this disease for DECADES, and what choices we make NOW will predict her future
- MZ has more ‘right’ than ‘wrong’
ICAP

• Identification, causation, alleviation, and prevention of symptoms in patients with MS
  • Identify the symptoms that arise during various stages of the disease
  • Symptoms result in disability and have a negative effect on the QOL
  • Early symptomatic intervention may mitigate risks of later morbidity
    • Examples – cognitive impairment, fatigue, sexual dysfunction, bladder and bowel issues
  • Causation – result of disease itself or a secondary consequence
    • Patients with MS often blame all of their symptoms on MS
Figure 2. Multiple sclerosis symptoms can be related and interdependent.
Symptom management medications

- Highly variable, depends on symptoms
- Spasticity – baclofen, tizanidine, baclofen pump, benzodiazepines
- Fatigue – amantadine, modafinil, stimulants
- Depression – SSRI’s
- Cognition – variable
- Bladder – neurogenic bladder
- Bowel – constipation management
- Pain – avoid narcotics if possible
Symptom management medications

• Ampyra

\[ K^+ = \text{potassium} \]
MZ is a great example of why we need coordinated care!
What are we trying to avoid?

• Poor adherence leads to untreated MS
• Neglecting to treat depression leads to untreated MS
• Patients that are not engaged in addressing lifestyle issues (exercise, tobacco, diet, relationships, etc) should realize that they are not treating the disease to full benefit
• Symptom management can be as important as a DMT
• Time constraints on physicians make this a daunting task, locate good resources, and refer patients appropriately
THANK YOU

- MS is a highly variable disease with many possible presentations
- Disease modification and symptom management available
- Engaging the patient in their treatment is paramount!

- Enjoy the day!