Multiple Sclerosis Update

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Disclosure

- Dr. Bagert has provided consulting services to Atara Biotherapeutics
Multiple Sclerosis

Commonest, disabling disease of young adults
Affects 1,000,000 people in the US
Multiple Sclerosis

Autoimmune attack on myelin in brain and spinal cord
Multiple Sclerosis: Quick Facts

Setting the record straight....

- FACT: MS is highly variable from one person to another
- FACT: MS is highly treatable
- FACT: MS is *not* uniformly disabling
Multiple Sclerosis

- Exact Cause of MS is unknown
- Thought to result from complex interplay of both environmental and genetic factors
MS is highly treatable

- Disease Modifying Therapies—13 approved therapies available
- Goal of treatment: Prevent disability
- Early diagnosis and treatment makes a difference
- Treat the individual
- Comprehensive care approach
A Revolution in MS Care over Past Two Decades

MS: Disease Modifying Therapies

- interferon beta-1b-1993
- interferon beta-1a (intramuscular) --1996
- glatiramer acetate—1996
- mitoxantrone --2000
- interferon beta-1a (subcutaneous)—2002
- natalizumab —2006
- fingolimod—2010
- teriflunomide—2012
- dimethyl fumarate--2013
- peginterferon beta-1a—2014
- alemtuzumab ——2014
- ocrelizumab ——2017
- siponimod--2019
Types of Multiple Sclerosis

- Relapsing Remitting
- Secondary Progressive
Primary Progressive MS

Time

Neurologic Impairment

Primary Progressive
Diagnosis of Multiple Sclerosis

- 2016 McDonald Criteria
- Dissemination of disease in space and time—still applies
- MRIs now used to achieve this criteria earlier
- MRI of brain and spinal cord
- Lumbar puncture (sometimes)
- Rule out alternative diagnoses
New concept of “Shared decision-making”

Important decisions about patient care should be *shared* between patient and MS care provider.
MS can cause many different types of neurological symptoms. All MS Symptoms are treatable.
Principals of MS Symptom management

- Avoidance of offending trigger of symptom
- Wellness - pro-active approach to symptom
- Medication as necessary
- Equipment / devices as necessary
Diet makes a difference in MS

- Whole Foods
- Low saturated fat
- Lots of fruits and vegetables
- Whole grains
- Limit processed foods
- Limit fried foods
- Limit salt
- Basically, a healthy diet
Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis

ABSTRACT

Background: Vascular comorbidity adversely influences health outcomes in several chronic conditions. Vascular comorbidities are common in multiple sclerosis (MS), but their impact on disease severity is unknown. Vascular comorbidities may contribute to the poorly understood heterogeneity in MS disease severity. Treatment of vascular comorbidities may represent an avenue for treating MS.

Methods: A total of 8,983 patients with MS enrolled in the North American Research Committee on Multiple Sclerosis Registry participated in this cohort study. Time from symptom onset or diagnosis until ambulatory disability was compared for patients with or without vascular comorbidities to determine their impact on MS severity. Multivariable proportional hazards models were adjusted for sex, race, age at symptom onset, year of symptom onset, socioeconomic status, and region of residence.

Results: Participants reporting one or more vascular comorbidities at diagnosis had an increased risk of ambulatory disability, and risk increased with the number of vascular conditions reported (hazard ratio [HR]/condition for early gait disability 1.51; 95% confidence interval [CI] 1.41-1.61). Vascular comorbidity at any time during the disease course also increased the risk of ambulatory disability (adjusted HR for unilateral walking assistance 1.54; 95% CI 1.44-1.65). The median time between diagnosis and need for ambulatory assistance was 18.8 years in patients without and 12.8 years in patients with vascular comorbidities.

Conclusions: Vascular comorbidity, whether present at symptom onset, diagnosis, or later in the disease course, is associated with a substantially increased risk of disability progression in multiple sclerosis. The impact of treating vascular comorbidities on disease progression deserves investigation. *Neurology*® 2010;74:1041-1047
2010 study showed that having a vascular risk factor was associated with a significantly greater risk of disability.

9,000 patients with MS participated—answered survey in NARCOMS registry.

People with 2 or more vascular risk factors had 200 times greater risk of disability from MS than people with no vascular risk factors!
Vitamin D

- Vitamin D receptor is present on lymphocytes.
- Vitamin D shifts the immune system in a direction that is beneficial for MS (away from Th1 phenotype and towards Th2)
- Vitamin D deficiency is risk factor for development of MS
- In those who have MS diagnosis, vitamin D deficiency drives autoimmunity
- Vitamin D level should be checked and managed
- Goal level in MS: 50-90 ng/mL
Vitamin D Makes MS Better

  - Followed 73 people with MS over 1.7 years
  - People whose vitamin D levels were less than 50 nmol/L **were twice as likely to experience a relapse** as those whose vitamin D level were greater than 100 nmol/L

- Most people need to take between 5,000 to 10,000 IU per day of vitamin D3 to have levels at higher end of normal range
Healthy lifestyle promotes wellness in MS

Guidelines for Healthful Eating

- 30% of calories from total fat
- 8-10% of calories from saturated fat
- 300 milligrams of cholesterol
- 2,400 milligrams of sodium

American Heart Association

Vitamin D

The body makes vitamin D when it is exposed to Ultraviolet (UV) rays from the sun.

Food Sources:
- Cheese
- Margarine
- Butter
- Fortified Milk
- Healthy Cereals
- Fatty Fish

NO SMOKING
Comprehensive MS Care Model

- New Model of MS Care
  - Treatment with all MS immunotherapy
  - Management of all MS symptoms
  - Diet, exercise, wellness counseling
  - Expert MS nursing
  - Clinical research trial opportunities
  - MS social worker--case management, psychological counseling
  - Group sessions to educate and support newly diagnosed
  - MS Yoga Classes
Future Research Directions

Remyelination
Repair
Precision Medicine
Conventional Model of MS Pathology

- MS is primarily a disorder of T-cells that target CNS myelin
- B-cells only bystanders in the conventional model
- Later stage of progressive MS is no longer inflammatory, but rather a degenerative one
CSF: Oligoclonal bands

- CSF in 90% of MS patients characterized by oligoclonal IgG bands
- Where do they come from?
- How are they explained by the T-cell model of MS pathophysiology.
New Model of MS Pathology

- Over past 18 years, new evidence from various fields of scientific inquiry--epidemiology, pathology and clinical trials--has challenged the conventional ideas of MS pathogenesis and pathophysiology.
- New model suggest Epstein-barr virus is etiologic to MS, and B-cells are central to MS pathology.
Epstein-barr virus--overview

- Human herpes virus 4
- Ancient virus that has co-evolved with hosts over the past 100 million years
- Establishes lifelong latency after primary infection
- Infects 95% of all humans
- Identified as the causative agent of infectious mononucleosis in 1968
- Transmitted via oral secretions
Epstein-barr virus--biology

- **EBV infects B-cells**
- **EBV clonally expands B-cells, and transforms them into latently and perpetually proliferating cell lines.**
- In healthy EBV carriers, infected B-cells restricted to lymph nodes by cell-mediated immunity, CD8+ T-cells.
- In EBV carriers with disease, B-cells escape control by cell-mediated immunity.
2012, Pakpoor et al.

Meta-analysis of 25 case-control studies looking at association between MS and EBV.

- OR of developing MS in EBV seronegatives was 0.00
- EBV present in 100% of MS patients
- Is EBV infection necessary before the development of MS?
2004, Serafini et al

First report showing that meninges of MS (post-mortem brains) patients with progressive MS filled with inflammation

Inflammation was largely observed to be B cells

Often very organized with germinal centers

These organized clusters of B cells are called “Ectopic B cell follicles”

Serafini et al. Detection of Ectopic B-cell follicles with Germinal Centers in the Meninges of Patients with Secondary Progressive MS. Brain Pathology 2004 Apr;14(2):164-74
Pathology—EBV in B-cell follicles


- EBV protein and RNA found in the ectopic B-cell lymphoid follicles in the meninges;
- Association between number of OCB and degree of EBV involvement in post-mortem brain
- No EBV infected B-cells in brains of patients with other inflammatory neuro disease was found

But…in the 11 ensuing years since this study was published, no one could replicate the results
In 2018, two independent researchers confirmed the 2007 study which found EBV protein and RNA in MS brain.
Clinical Trial--2008

- Phase 2, placebo controlled trial in relapsing MS; 104 patients treated with single course of rituximab
- 91% reduction in gad+ lesions as compared to placebo.
- Significant reduction in proportion of patients who were relapse free
- Led to a full re-assessment of role of B lymphocytes in MS pathophysiology

To Review...

- New robust sero-epidemiology suggest EBV infection is etiologic to MS.
- New pathology studies suggest MS brain has organized B-cell follicles in the meninges and the EBV is detected in these follicles.
- New clinical trial shows that anti-B cell therapy is highly effective for MS.
- Totality of evidence suggests that EBV infected B-cells may be integral to MS pathophysiology.
Theory of EBV Pathogenesis in MS

- Hygiene hypothesis
  - Late EBV infection (mononucleosis) in genetically susceptible individuals leads to immune dysregulation

- Cytotoxic T-lymphocyte (CD8+ T-cells) deficiency
  - MS occurs when cytotoxic T-cells (CD8+) cannot control EBV infected B-cells

- Immortalized B-cells damage CNS
  - Damage via T-cell activation and/or pathologic antibody production
MS—the future

- Unmet need for smarter approaches that address root cause of disease
- New understanding of the role of EBV in MS challenges us to create new therapies to treat and possibly cure MS
Phase-1 study of allogeneic EBV specific T-cells in MS

- Atara Therapeutics
- Multicenter, open-label, single-arm study in adult subjects with progressive forms of MS
  - Allogeneic EBV-specific T-cells specific for 3 latent EBV protein
  - Cells from EBV-positive healthy donors are stimulated and expanded in vitro and the resulting CD8-T cells are cryopreserved in T-cell library
  - Donor cells are HLA-matched to each individual MS patient to prevent rejection.
  - Not immunosuppressive
  - Expected to cross BBB
  - Ochsner is site for this study; Screened 3 patients so far
  - Phase-2 study planned
Thank you!