Multiple Sclerosis Update

Bridget Bagert, MD, MPH

Director, Ochsner Multiple Sclerosis Center

Disclosure

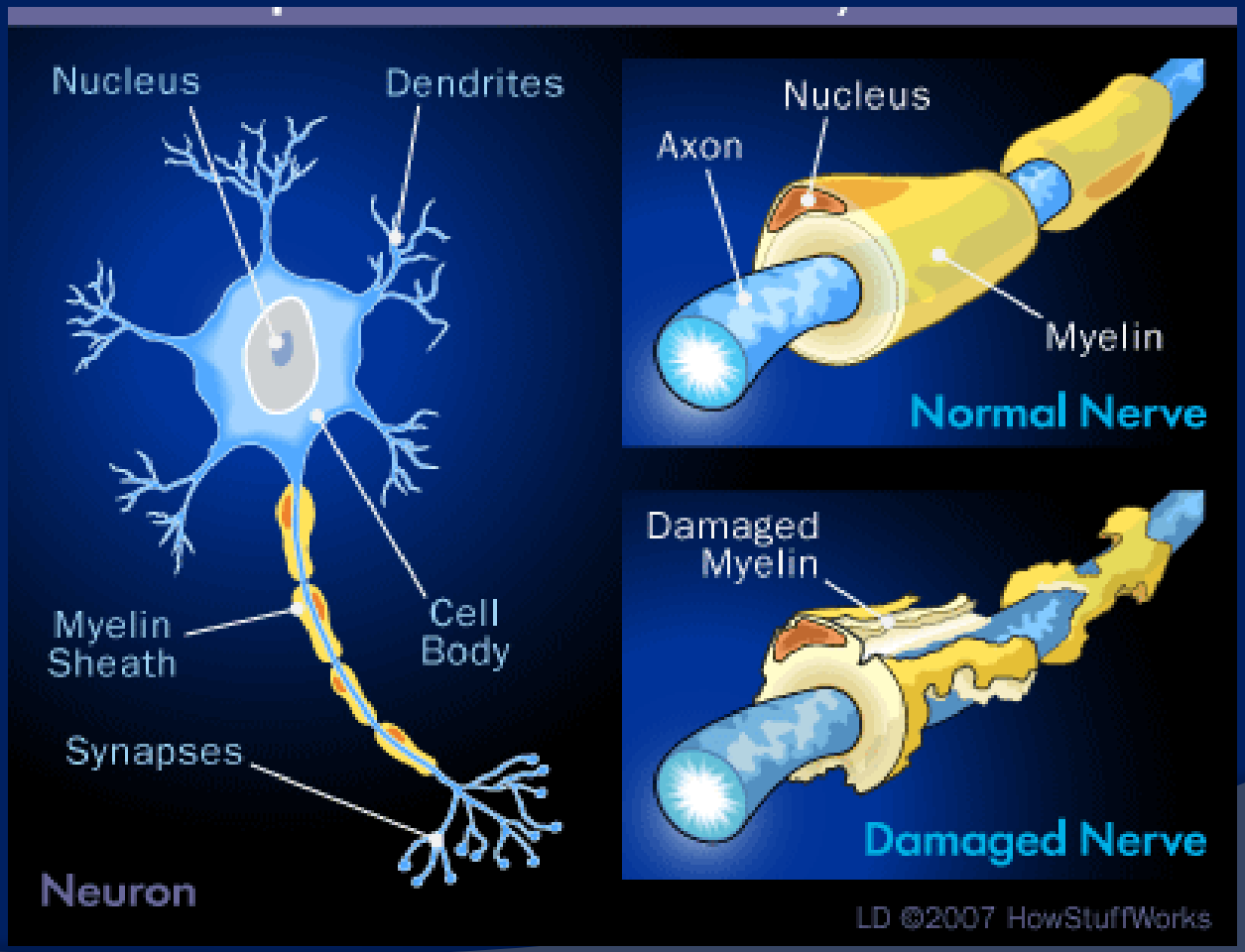
- Dr. Bagert has provided consulting services to Atara Biotherapeutics

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

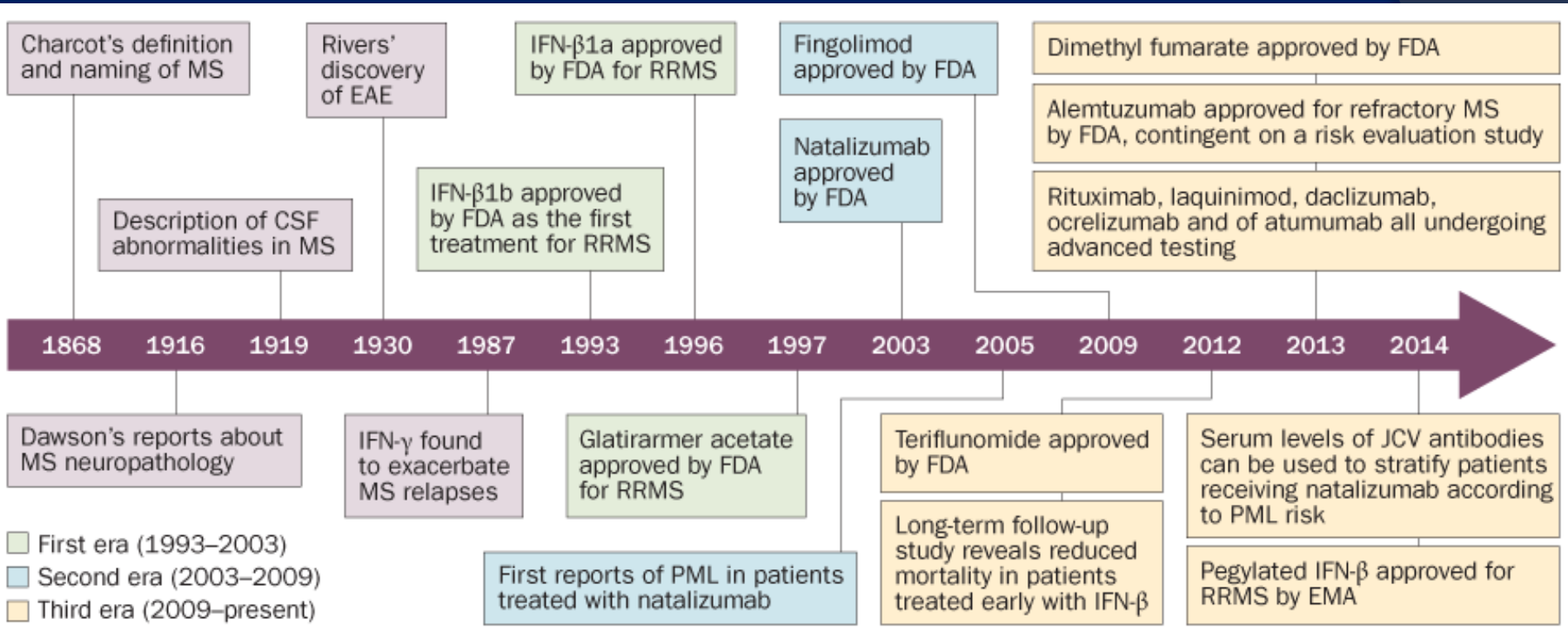
Multiple Sclerosis

- 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

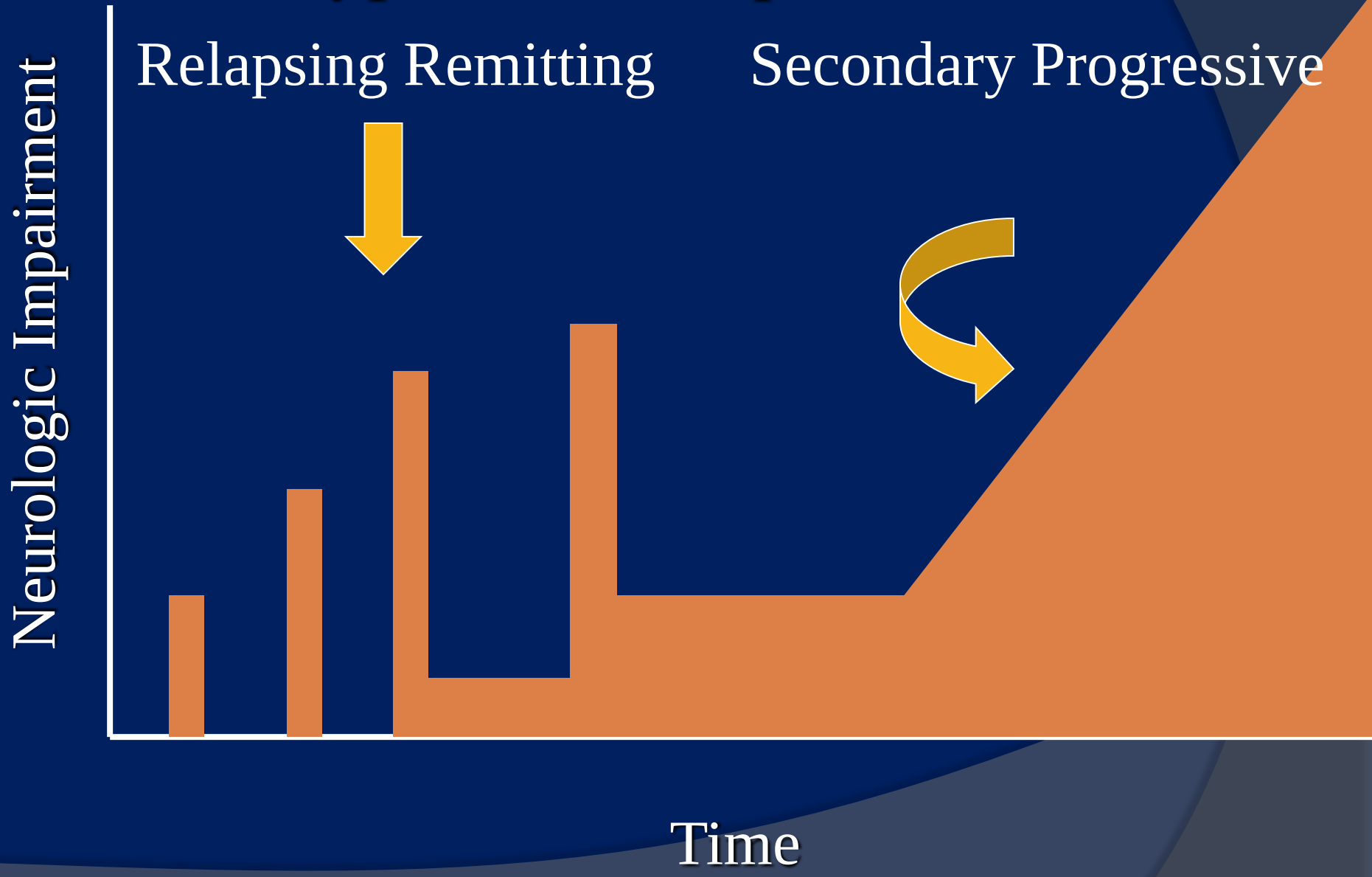


Ransohoff et al. Nat Rev Neurol.2015 March; 11(3): 134-142..

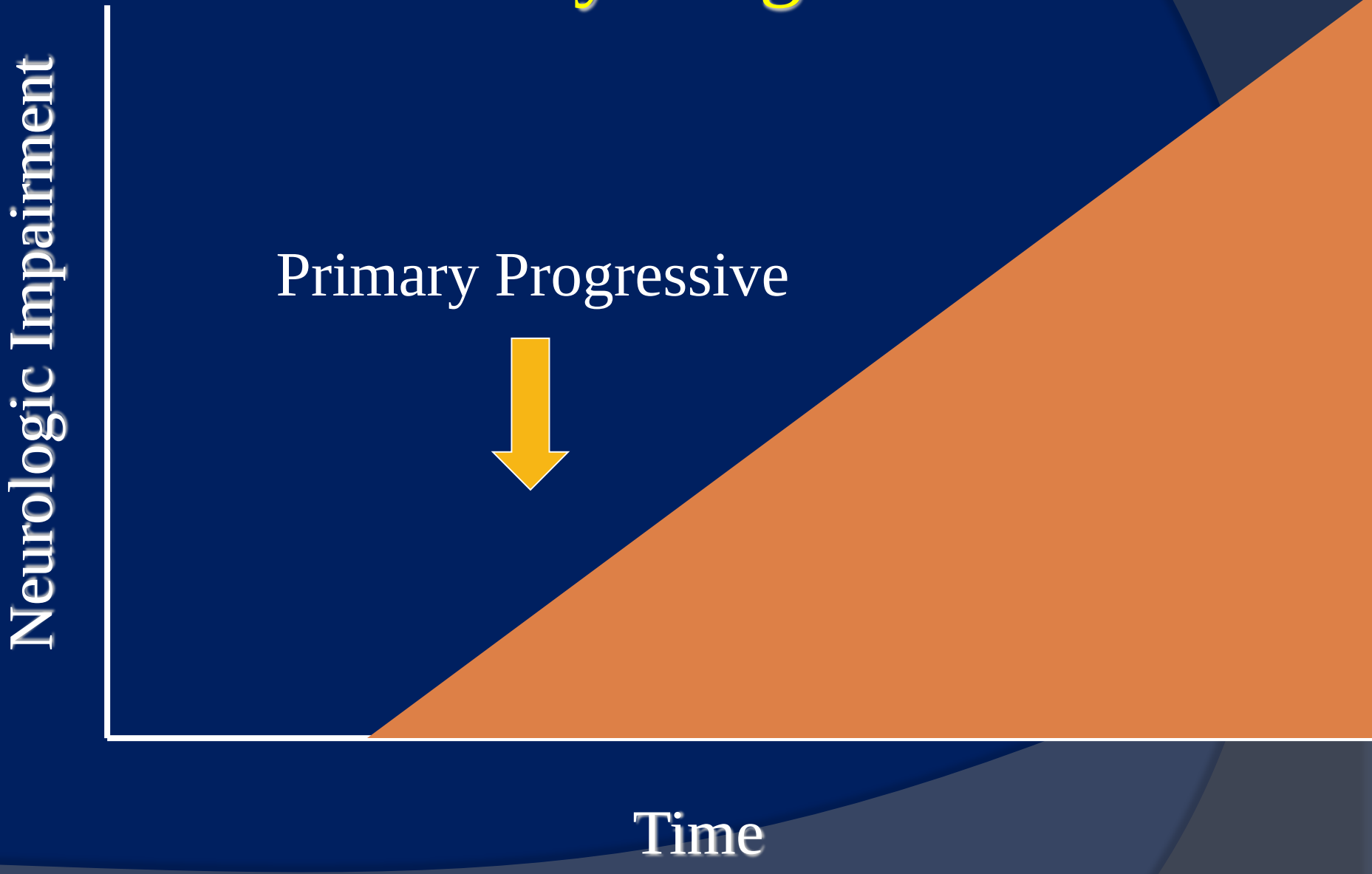
MS: Disease Modifying Therapies

- 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

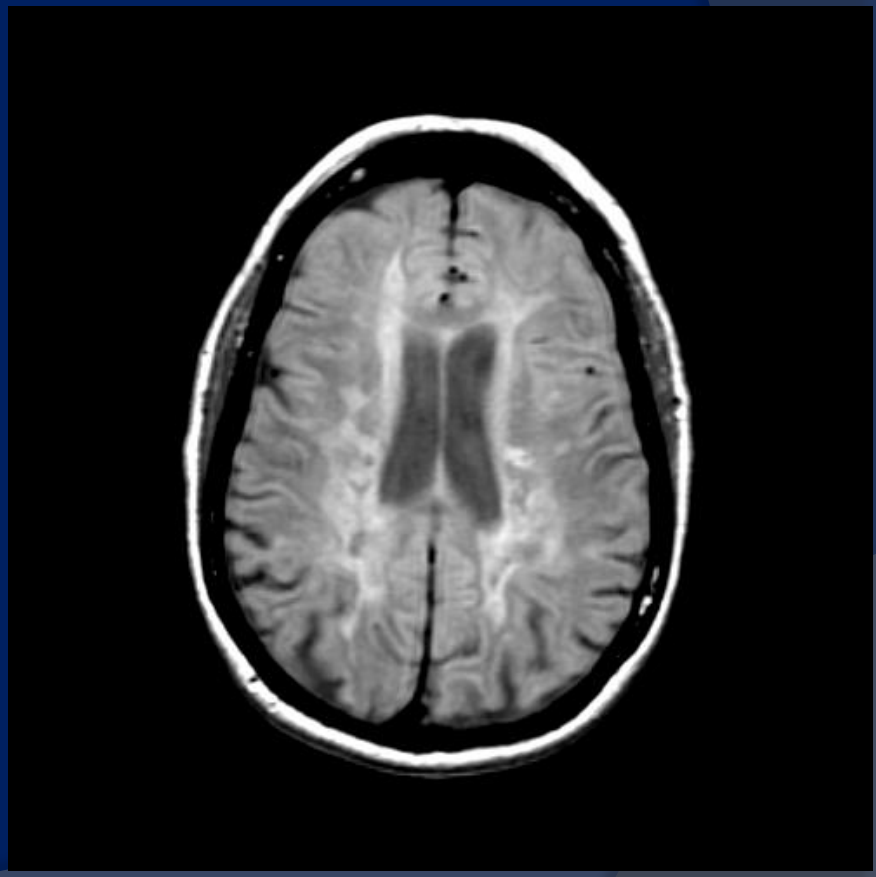


Primary Progressive MS

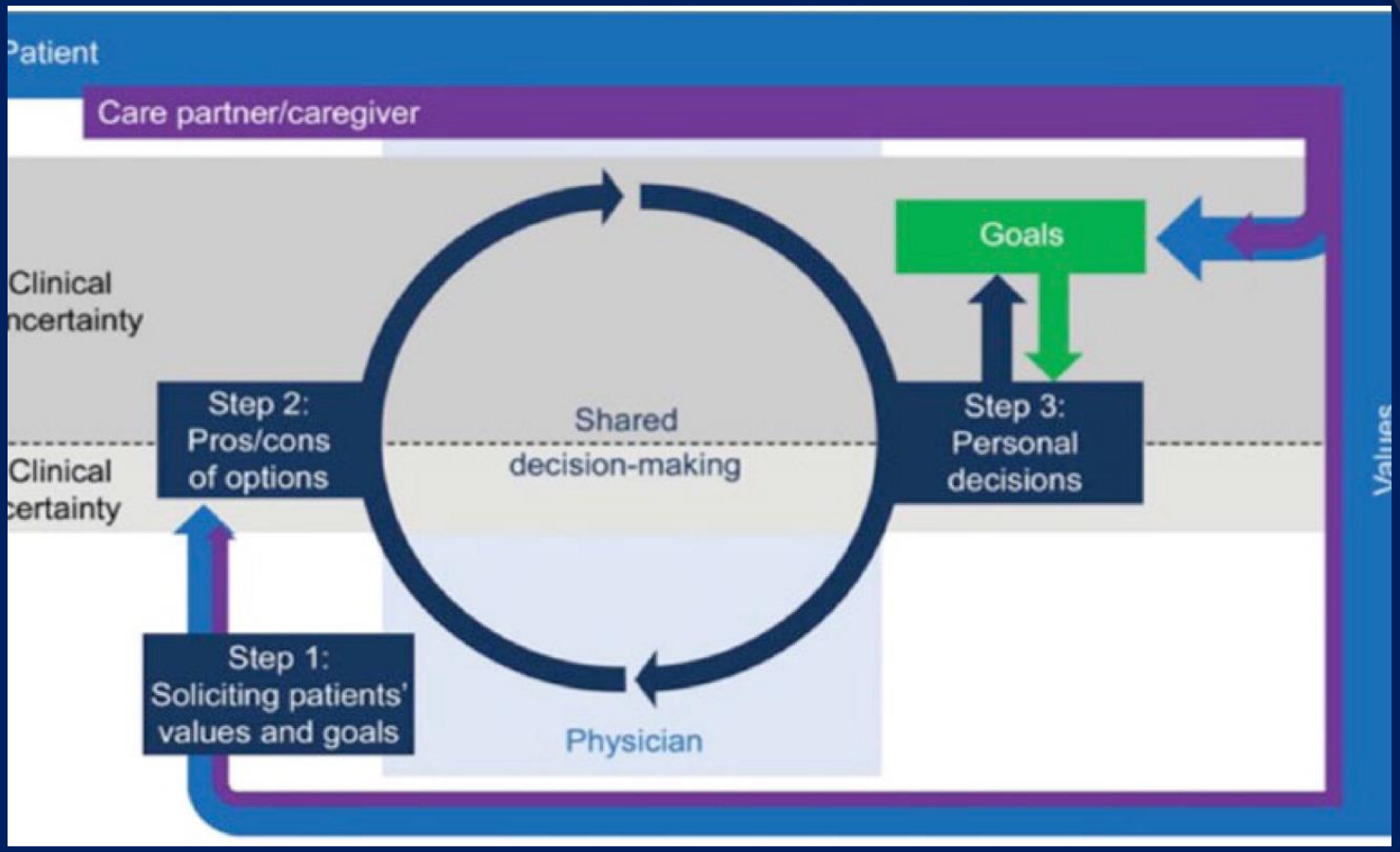


Diagnosis of Multiple Sclerosis

- 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



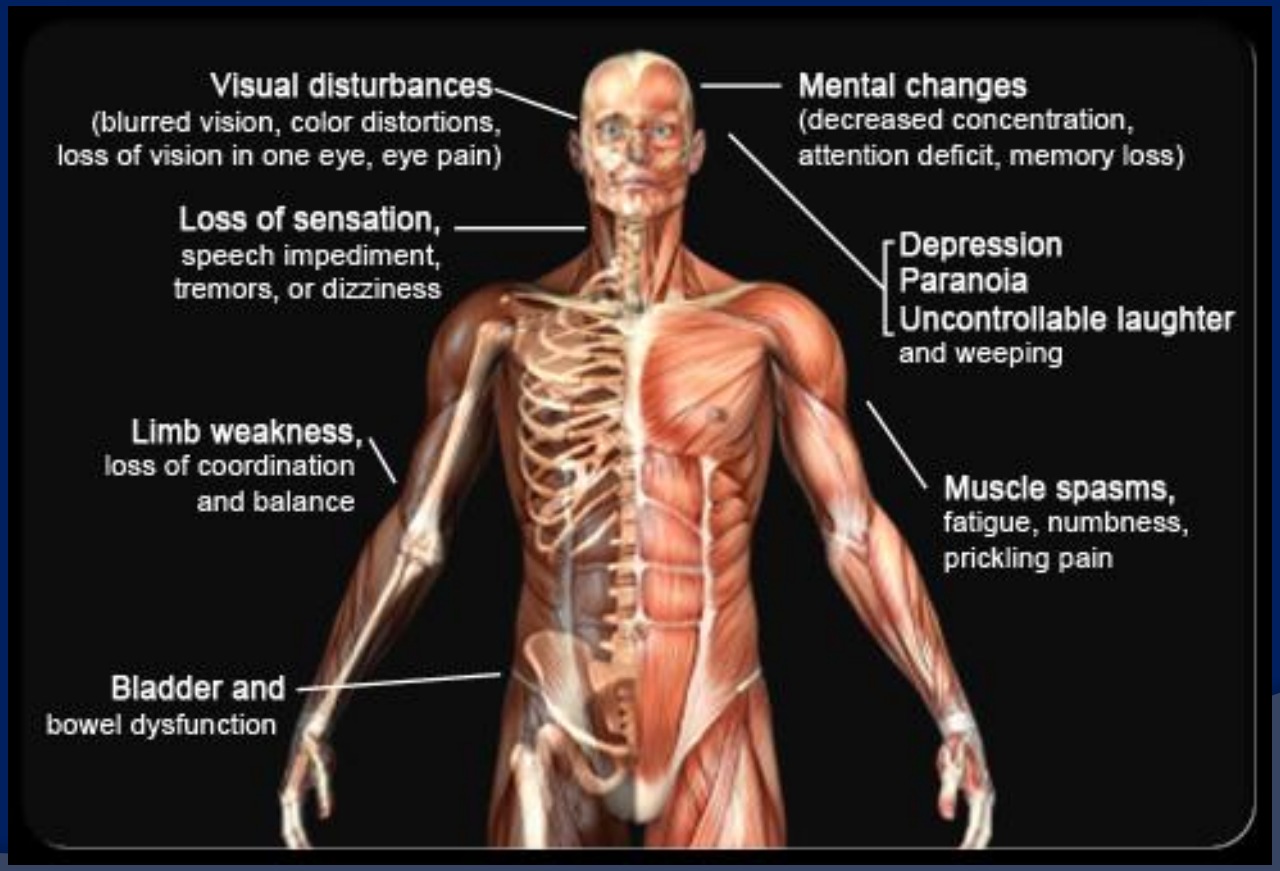
New concept of "Shared decision-making"



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 heart healthy diet

Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis

R.A. Marrie, MD, PhD
R. Rudick, MD
R. Horwitz, MD
G. Cutter, PhD
T. Tyry, PhD
D. Campagnolo, MD
T. Vollmer, MD

Address correspondence and reprint requests to Dr. Ruth Ann Marrie, Health Sciences Center, GF-533, 820 Sherbrook Street, Winnipeg, MB R3A 1R9, Canada
rmarrie@hsc.mb.ca

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

Vascular Risk Factors

- 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 did people with no vascular risk factors!

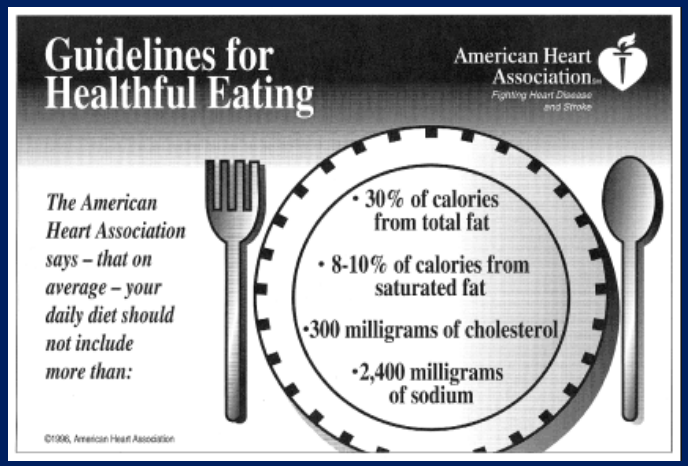
Vitamin D

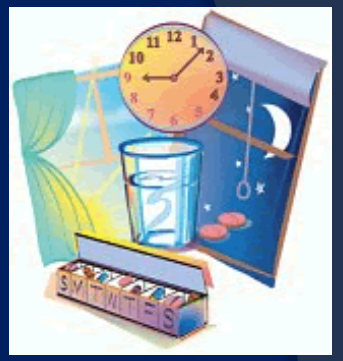
- Vitamin D receptor is present on lymphocytes.
- Vitamin D shifts the immune system in a direction that is beneficial for MS (away from Th1 phenotype and towards Th2)
- Vitamin D deficiency is risk factor for development of MS
- In those who have MS diagnosis, vitamin D deficiency drives autoimmunity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

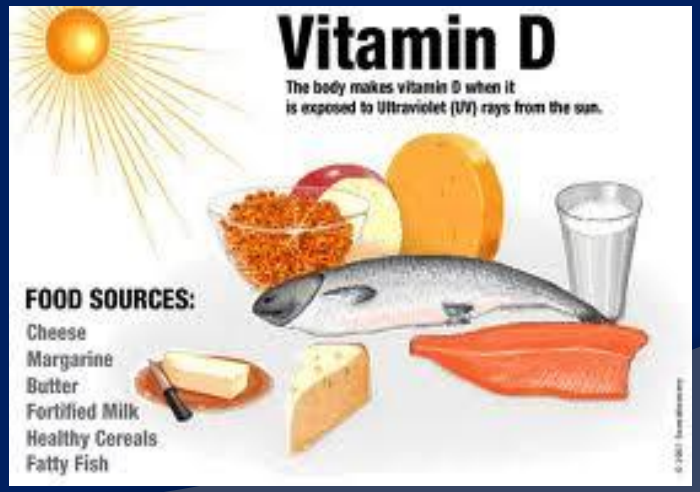
Vitamin D Makes MS Better

- *Runia, et al, Neurology 2012 79: 261-266*
  - 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







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

Ochsner™
Multiple Sclerosis Program

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

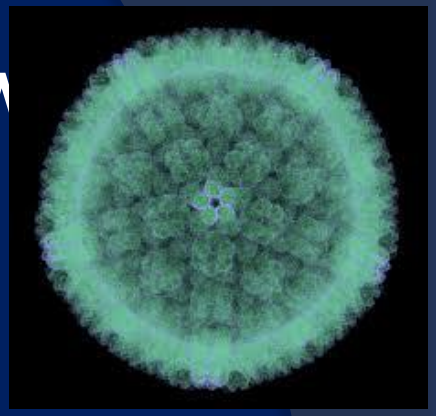
CSF: Oligoclonal bands

- CSF in 90% of MS patients characterized by oligoclonoal 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.

Epidemiology

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

The risk of developing multiple sclerosis in individuals seronegative for Epstein-Barr virus: a meta-analysis

Multiple Sclerosis Journal
19(2) 162–166

DOI: 10.1177/1352458512449682
msj.sagepub.com
SAGE

Julia Pakpoor[1,2], Giulio Disanto[1,2], Jennifer E Gerber[3], Ruth Dobson[4], Ute C Meier[4], Gavin Giovannoni[4] and Sreeram V Ramagopalan[1–4]

Abstract

Background: Epstein-Barr virus (EBV) infection is widely considered to be a risk factor for multiple sclerosis (MS). A previous meta-analysis estimated an odds ratio (OR) for MS in individuals seronegative for EBV of 0.06. Given the potential importance of this finding, we aimed to establish a more precise OR for adult and paediatric onset MS in EBV seronegative individuals.

Methods: PubMed and EMBASE searches were undertaken to identify studies investigating the association between MS and EBV. Twenty-two adult and three paediatric studies were included. ORs were calculated using a fixed effects model. A sub-group analysis based on the method of EBV detection was performed.

Results: The OR for developing adult MS in EBV seronegatives was 0.18 (95% confidence interval (CI) 0.13–0.26)) and for paediatric MS was 0.18 (95% CI 0.11–0.30). Sub-group analysis on EBV detection method showed that studies which used immunofluoresence generated an OR=0.07 (95% CI 0.03–0.16); for those that used enzyme-linked immunosorbent assay (ELISA) OR=0.33 (95% CI 0.22–0.50) and for studies which used ELISA and immunofluoresence OR=0.00 (95% CI 0–0.43).

Conclusion: The sensitivity and specificity of the assay used to measure EBV antibody titres have an influence on the association between MS and EBV. Looking at studies where two independent methods are used and therefore are likely to be the most robust, EBV appears to be present in 100% of MS patients. This has implications for future studies of EBV in MS. MS patients without EBV infection, if they truly exist, should be studied in more detail.

Keywords
Multiple sclerosis, Epstein-Barr virus, meta-analysis, case-control studies

Date received: 1st January 2012; revised: 25th April 2012; accepted: 26th April 2012

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?**

RESEARCH ARTICLE

Detection of Ectopic B-cell Follicles with Germinal Centers in the Meninges of Patients with Secondary Progressive Multiple Sclerosis

Barbara Serafini[1]; Barbara Rosicarelli[1]; Roberta Magliozzi[1]; Egidio Stigliano[2]; Francesca Aloisi[1]

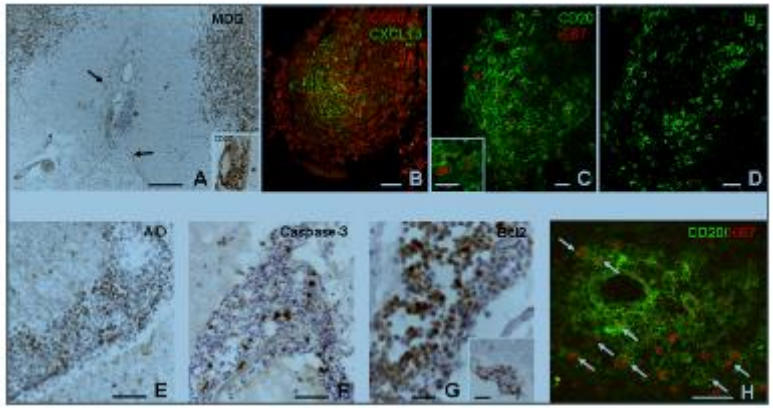
[1] Department of Cell Biology and Neuroscience, Istituto Superiore di Sanità, Rome, Italy.
[2] Institute of Pathological Anatomy, U.C.S.C. Policlinico A. Gemelli, Rome, Italy.

Corresponding author:
Dr Francesca Aloisi, Department of Cell Biology and Neuroscience, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Roma, Italy (E-mail: fos4@iss.it)

Multiple sclerosis (MS) is characterized by synthesis of oligoclonal immunoglobulins and the presence of B-cell clonal expansions in the central nervous system (CNS). Because ectopic lymphoid tissue generated at sites of chronic inflammation is thought to be important in sustaining immunopathological processes, we have investigated whether structures resembling lymphoid follicles could be identified in the CNS of MS patients. Sections from post-mortem MS brains and spinal cords were screened using immunohistochemistry for the presence of CD20$^+$ B-cells, CD3$^+$ T-cells, CD138$^+$ plasma cells and CD21$^+$, CD35$^+$ follicular dendritic cells, and for the expression of lymphoid chemokines (CXCL13, CCL21) and peripheral node addressin (PNAd). Lymphoid follicle-like structures containing B-cells, T-cells and plasma cells, and a network of follicular dendritic cells producing CXCL13 were observed in the cerebral meninges of 2 out of 3 patients with secondary progressive MS, but not in relapsing remitting and primary progressive MS. We also show that proliferating B-cells are present in intrameningeal follicles, a finding which is suggestive of germinal center formation. No follicle-like structures were detected in parenchymal lesions. The formation of ectopic lymphoid follicles in the meninges of patients with MS could represent a critical step in maintaining humoral autoimmunity and in disease exacerbation.

antibody producing plasma cells, or expand and mature locally mimicking a germinal center reaction, remains to be determined.

The germinal center of lymphoid follicles is the microenvironment where antigen-activated B-cells undergo clonal expansion and selection to differentiate into memory B-cells or into plasma cells secreting high affinity antibodies (23). These events require interactions of B-cells with T-cells and follicular dendritic cells (FDCs). The latter cells have a critical role in presenting intact antigen to B-cells and in providing B-cell survival and proliferation signals (21, 52). Moreover, FDCs produce the



- 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

In 2007, landmark pathology study of 22 post-mortem brain of MS patients and 7 brains of other inflammatory neuro disease *(Serafini et al. J Exp Med 2007, 204: 2889-2912)*.

- 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

Pathology 2018

- In 2018, two independent researchers confirmed the 2007 study which found EBV protein and RNA in MS brain.

PLOS ONE

RESEARCH ARTICLE

Epstein-Barr virus is present in the brain of most cases of multiple sclerosis and may engage more than just B cells

Asma Hassani[1], John R. Corboy[2], Suhail Al-Salam[3], Gulfaraz Khan[1]*

1 Department of Microbiology and Immunology, College of Medicine and Health Sciences, Tawam Hospital Campus, United Arab Emirates University, Al Ain, UAE, **2** Department of Neurology, University of Colorado School of Medicine, Rocky Mountain MS Center at University of Colorado, Aurora, United States of America, **3** Department of Pathology, College of Medicine and Health Sciences, Tawam Hospital Campus, United Arab Emirates University, Al Ain, UAE

* g_khan@uaeu.ac.ae

Check for updates

OPEN ACCESS

Citation: Hassani A, Corboy JR, Al-Salam S, Khan G (2018) Epstein-Barr virus is present in the brain of most cases of multiple sclerosis and may engage more than just B cells. PLoS ONE 13(2): e0192109. https://doi.org/10.1371/journal.pone.0192109

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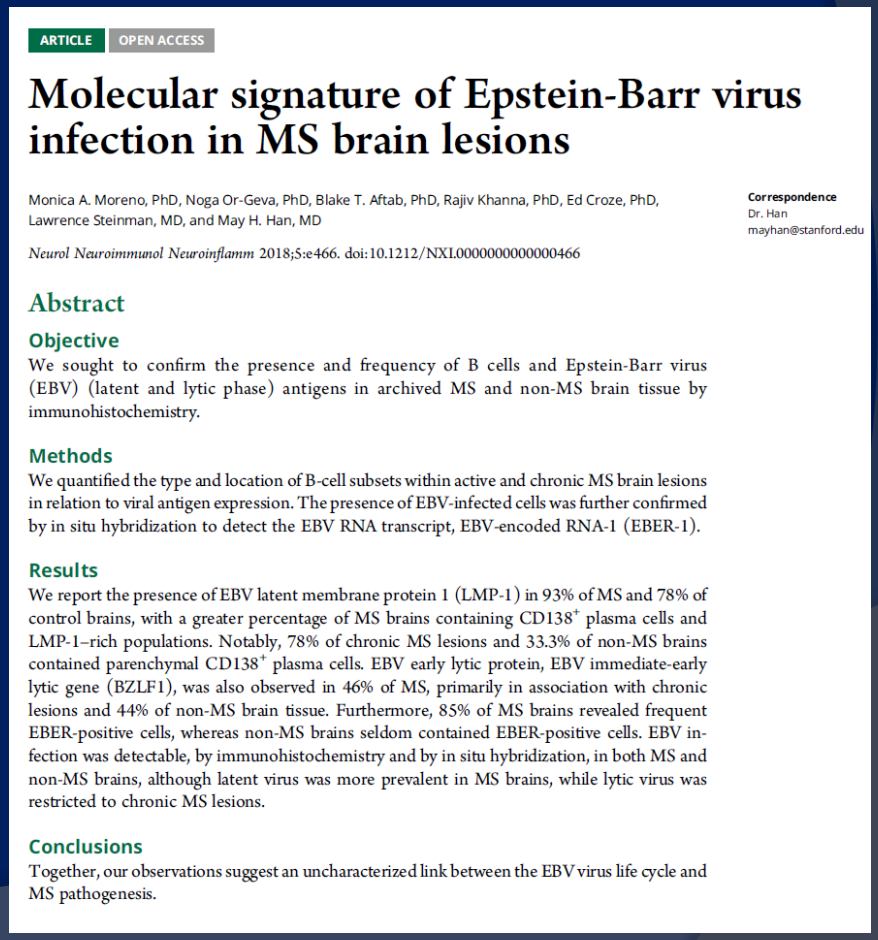
Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Abstract

Multiple sclerosis (MS) is a chronic neuroinflammatory condition of the central nervous system (CNS). It is a major cause of neurological disability in young adults, particularly women. What triggers the destruction of myelin sheaths covering nerve fibres is unknown. Both genetic and infectious agents have been implicated. Of the infectious agents, Epstein-Barr virus (EBV), a common herpesvirus, has the strongest epidemiological and serological evidence. However, the presence of EBV in the CNS and demonstration of the underlying mechanism(s) linking EBV to the pathogenesis of MS remain to be elucidated. We aimed at understanding the contribution of EBV infection in the pathology of MS. We examined 1055 specimens (440 DNA samples and 615 brain tissues) from 101 MS and 21 non-MS cases for the presence of EBV using PCR and EBER-*in situ* hybridization (EBER-ISH). EBV was detected by PCR and/or EBER-ISH in 91/101 (90%) of MS cases compared to only 5/21 (24%) of non-MS cases with other neuropathologies. None of the samples were PCR positive for other common herpesviruses (HSV-1, CMV, HHV-6). By quantitative PCR, EBV viral load in MS brain was mainly low to moderate in most cases. However, in 18/101 (18%) of MS cases, widespread but scattered presence of EBV infected cells was noted in the affected tissues by EBER-ISH. Immunohistochemical analysis of EBV gene expression in the 18 heavily infected cases, revealed that the EBV latent protein EBNA1, and to a lesser extent the early lytic protein BZLF1 were expressed. Furthermore, using double-staining we how for the first time that astrocytes and microglia, in addition to B-cells can also be infected. To the best of our knowledge, this is the most comprehensive study demonstrating that EBV is present and transcriptionally active in the brain of most cases of MS and supports a role for the virus in MS pathogenesis. Further studies are required to address the mechanism of EBV involvement in MS pathology.



ARTICLE OPEN ACCESS

Molecular signature of Epstein-Barr virus infection in MS brain lesions

Monica A. Moreno, PhD, Noga Or-Geva, PhD, Blake T. Aftab, PhD, Rajiv Khanna, PhD, Ed Croze, PhD, Lawrence Steinman, MD, and May H. Han, MD

Correspondence
Dr. Han
mayhan@stanford.edu

Neurol Neuroimmunol Neuroinflamm 2018;5:e466. doi:10.1212/NXI.0000000000000466

Abstract

Objective

We sought to confirm the presence and frequency of B cells and Epstein-Barr virus (EBV) (latent and lytic phase) antigens in archived MS and non-MS brain tissue by immunohistochemistry.

Methods

We quantified the type and location of B-cell subsets within active and chronic MS brain lesions in relation to viral antigen expression. The presence of EBV-infected cells was further confirmed by in situ hybridization to detect the EBV RNA transcript, EBV-encoded RNA-1 (EBER-1).

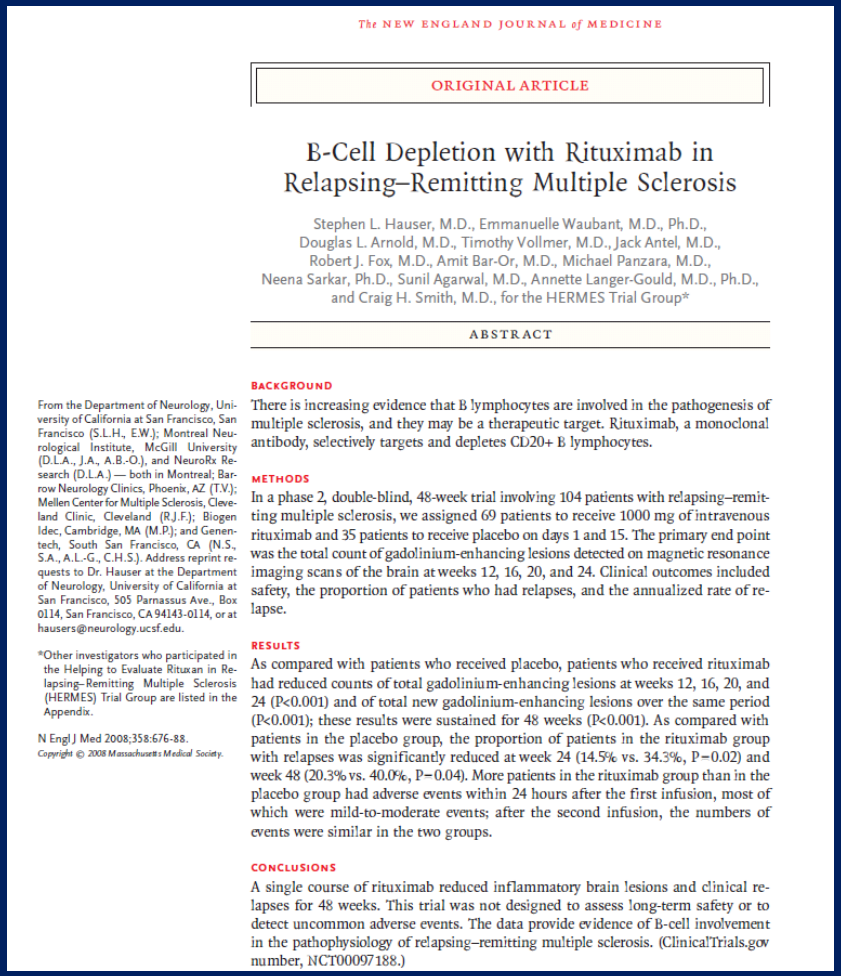
Results

We report the presence of EBV latent membrane protein 1 (LMP-1) in 93% of MS and 78% of control brains, with a greater percentage of MS brains containing $CD138^+$ plasma cells and LMP-1–rich populations. Notably, 78% of chronic MS lesions and 33.3% of non-MS brains contained parenchymal $CD138^+$ plasma cells. EBV early lytic protein, EBV immediate-early lytic gene (BZLF1), was also observed in 46% of MS, primarily in association with chronic lesions and 44% of non-MS brain tissue. Furthermore, 85% of MS brains revealed frequent EBER-positive cells, whereas non-MS brains seldom contained EBER-positive cells. EBV infection was detectable, by immunohistochemistry and by in situ hybridization, in both MS and non-MS brains, although latent virus was more prevalent in MS brains, while lytic virus was restricted to chronic MS lesions.

Conclusions

Together, our observations suggest an uncharacterized link between the EBV virus life cycle and MS pathogenesis.

Clinical Trial--2008



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

Stephen L. Hauser, M.D., Emmanuelle Waubant, M.D., Ph.D., Douglas L. Arnold, M.D., Timothy Vollmer, M.D., Jack Antel, M.D., Robert J. Fox, M.D., Amit Bar-Or, M.D., Michael Panzara, M.D., Neena Sarkar, Ph.D., Sunil Agarwal, M.D., Annette Langer-Gould, M.D., Ph.D., and Craig H. Smith, M.D., for the HERMES Trial Group*

ABSTRACT

BACKGROUND

There is increasing evidence that B lymphocytes are involved in the pathogenesis of multiple sclerosis, and they may be a therapeutic target. Rituximab, a monoclonal antibody, selectively targets and depletes CD20+ B lymphocytes.

METHODS

In a phase 2, double-blind, 48-week trial involving 104 patients with relapsing–remitting multiple sclerosis, we assigned 69 patients to receive 1000 mg of intravenous rituximab and 35 patients to receive placebo on days 1 and 15. The primary end point was the total count of gadolinium-enhancing lesions detected on magnetic resonance imaging scans of the brain at weeks 12, 16, 20, and 24. Clinical outcomes included safety, the proportion of patients who had relapses, and the annualized rate of relapse.

RESULTS

As compared with patients who received placebo, patients who received rituximab had reduced counts of total gadolinium-enhancing lesions at weeks 12, 16, 20, and 24 ($P<0.001$) and of total new gadolinium-enhancing lesions over the same period ($P<0.001$); these results were sustained for 48 weeks ($P<0.001$). As compared with patients in the placebo group, the proportion of patients in the rituximab group with relapses was significantly reduced at week 24 (14.5% vs. 34.3%, $P=0.02$) and week 48 (20.3% vs. 40.0%, $P=0.04$). More patients in the rituximab group than in the placebo group had adverse events within 24 hours after the first infusion, most of which were mild-to-moderate events; after the second infusion, the numbers of events were similar in the two groups.

CONCLUSIONS

A single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks. This trial was not designed to assess long-term safety or to detect uncommon adverse events. The data provide evidence of B-cell involvement in the pathophysiology of relapsing–remitting multiple sclerosis. (ClinicalTrials.gov number, NCT00097188.)

From the Department of Neurology, University of California at San Francisco, San Francisco (S.L.H., E.W.); Montreal Neurological Institute, McGill University (D.L.A., J.A., A.B.-O.), and NeuroRx Research (D.L.A.) — both in Montreal; Barrow Neurology Clinics, Phoenix, AZ (T.V.); Mellen Center for Multiple Sclerosis, Cleveland Clinic, Cleveland (R.J.F.); Biogen Idec, Cambridge, MA (M.P.); and Genentech, South San Francisco, CA (N.S., S.A., A.L.-G., C.H.S.). Address reprint requests to Dr. Hauser at the Department of Neurology, University of California at San Francisco, 505 Parnassus Ave., Box 0114, San Francisco, CA 94143-0114, or at hausers@neurology.ucsf.edu.

*Other investigators who participated in the Helping to Evaluate Rituxan in Relapsing–Remitting Multiple Sclerosis (HERMES) Trial Group are listed in the Appendix.

N Engl J Med 2008;358:676-88.

- 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

Hauser SL, et al; HERMES Trial Group. N Engl J Med. **2008** Feb 14;358(7):676-88.

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!