Progressive MS

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Disclosures

Dr. Bagert serves as Principapal Investigator on clinical trials with Atara Biotherapeutics, Roche, Sanofi, Genentech, Jazz Pharmaceuticals and Biogen.

Outline

- Cases
- Phenotypes
- Pathophysiology
- Clinical features
- Treatment
  - DMT
  - Symptom management
  - Lifestyle
- Research directions
- Back to cases
- Final thoughts

Objectives

There is an unmet need for effective treatments for progressive MS

Understanding the distinct pathophysiology of progressive MS is critical

Future therapies for progressive MS must:

- Be CNS penetrant
- Target smoldering inflammation
- Address EBV infection
- Address remyelination and repair

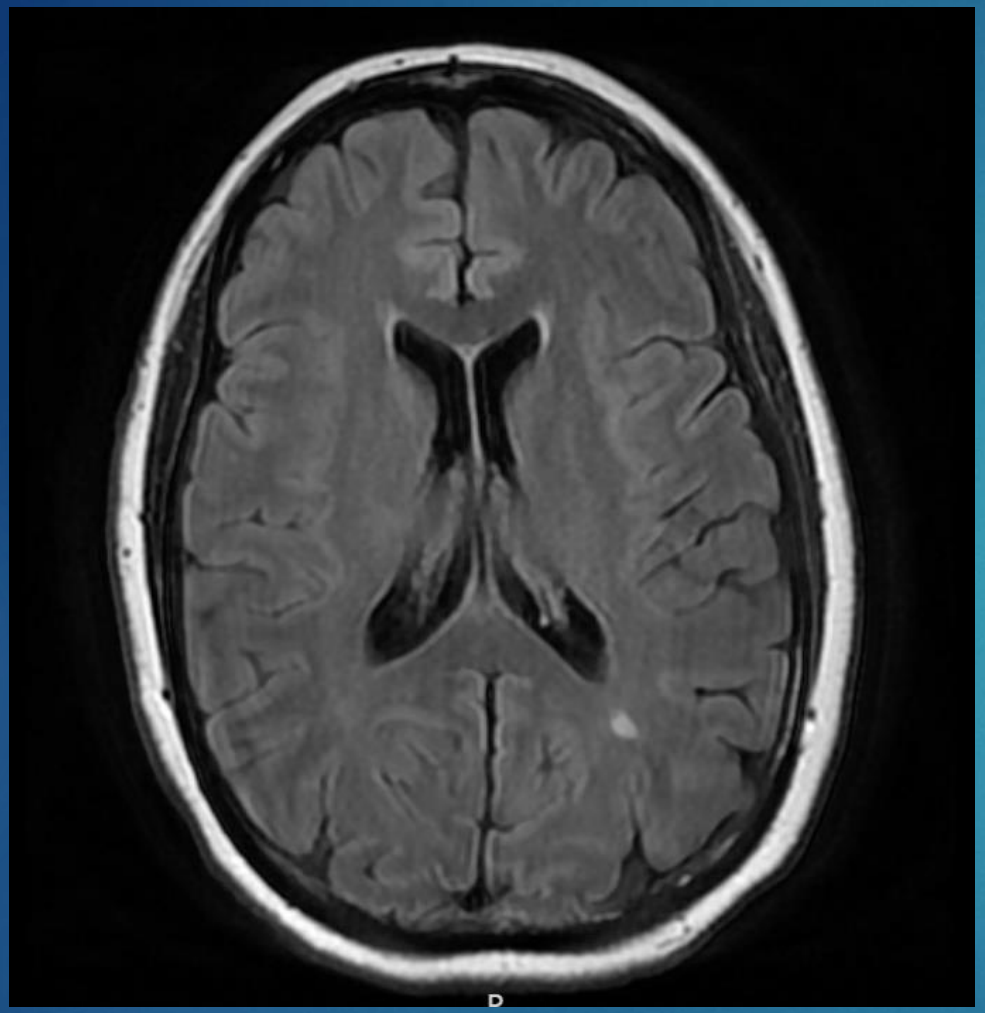
Attention to symptom management and lifestyle is also fundamental to comprehensive MS care for the progressive MS patient.

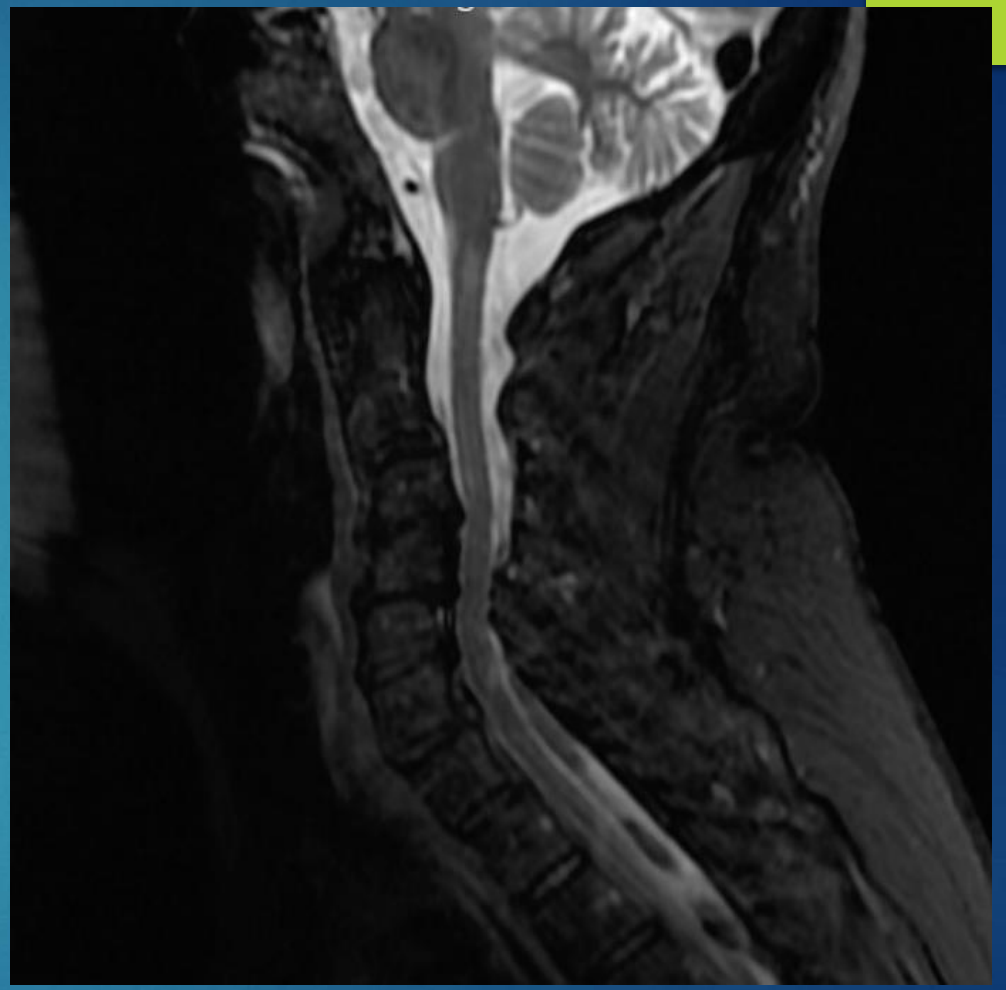
Case 1

- 52 y/o woman referred to MS with gradual onset of gait disturbance in 2014
- MRI with only a few lesions typical of MS in the brain
- LP with 12 OCB unique to CSF
- mimics negative
- DX: Primary progressive MS

Case 1

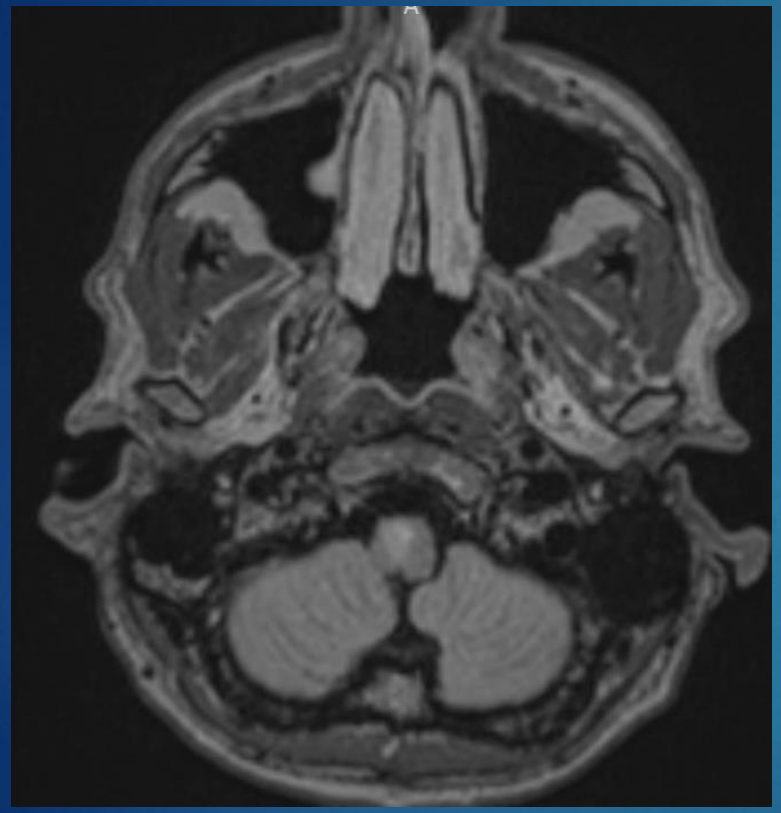
- 25 foot timed walk in November 2014: 8.2 seconds without assist
- Started on Copaxone
- In October 2015, 25 foot timed walk was 15 seconds
- DMT switched to Rituxan

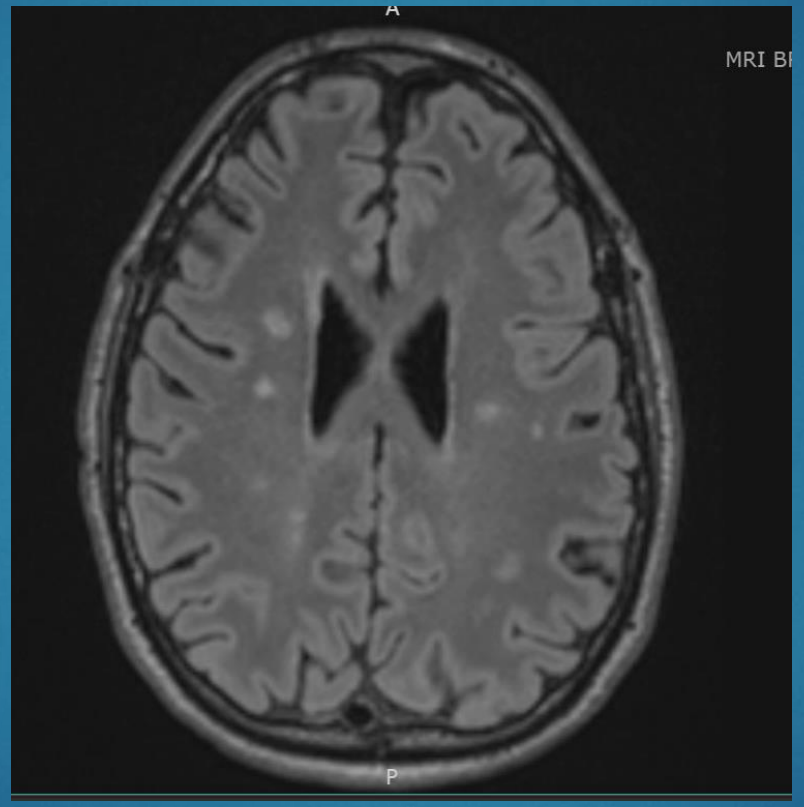


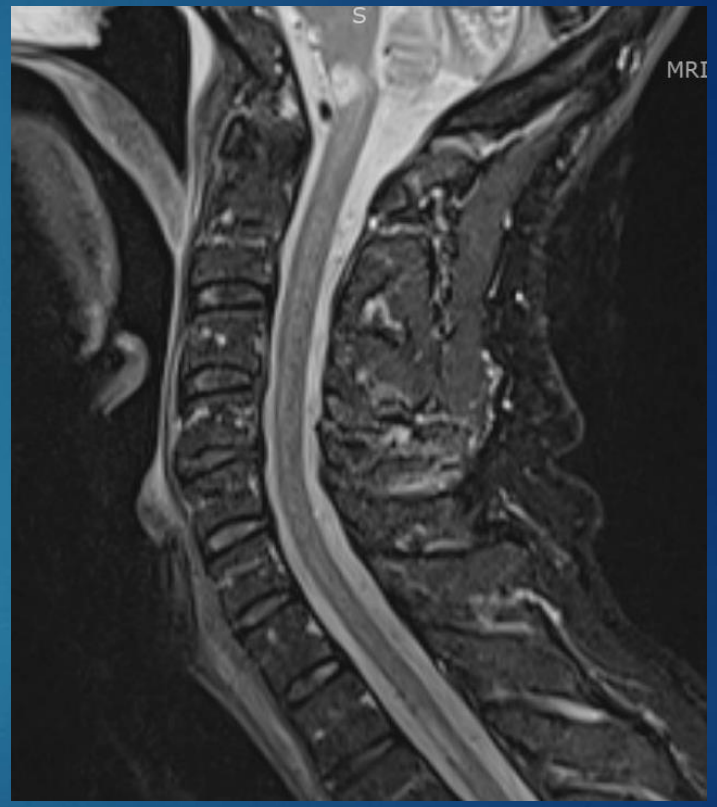


Case 2

- 52 y/o man diagnosed with RRMS by me in 2009
- Had severe initial relapse affecting medulla but had significant improvement.
- Started on Rebif and did well for 5 years.
- Did not have any future relapses, but did start to progressively worsen in 2014
- in 2012, 25 ft timed walk was 3.5s
- in 2014, 25 ft timed walk was 6 seconds
- **Secondary progressive MS**

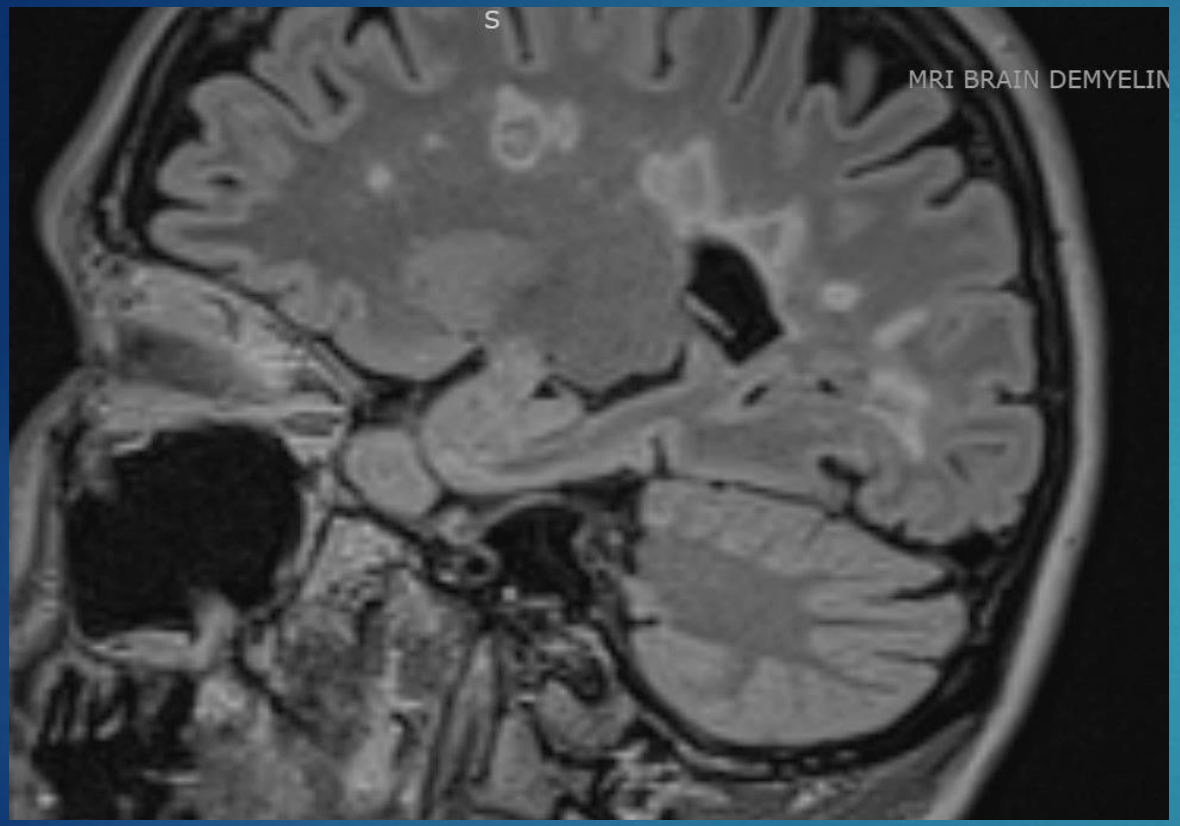



A
MRI BI
P


S
MRI

Case 3

- 50 y/o woman referred for evaluation for possible MS in September 2019
- In January 2019, developed blurry vision that progressed to double vision
- In May 2019, developed gait imbalance
- exam with bilateral INO, ataxia and 25ft timed walk 7.2 seconds
- LP with 2 OCB unique to CSF and elevated IgG index
- VEPs slow bilaterally
- MRI brain with demyelination t/o
- Started on Ocrevus
- **Either SPMS or PPMS**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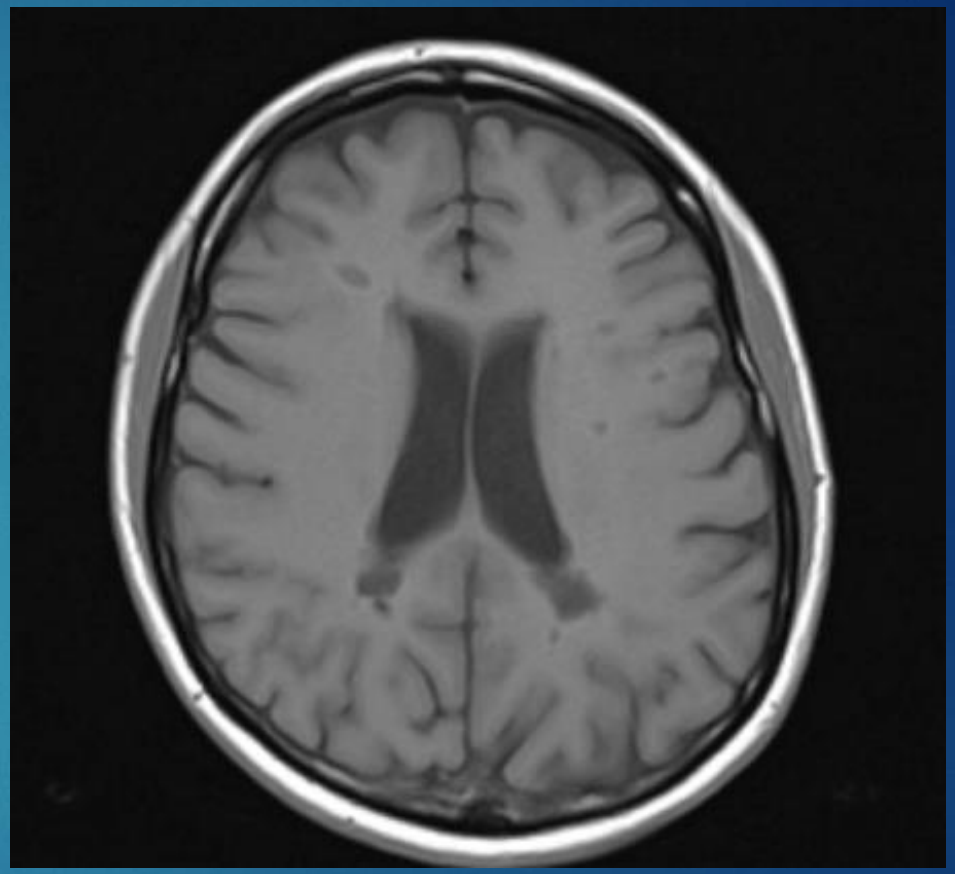
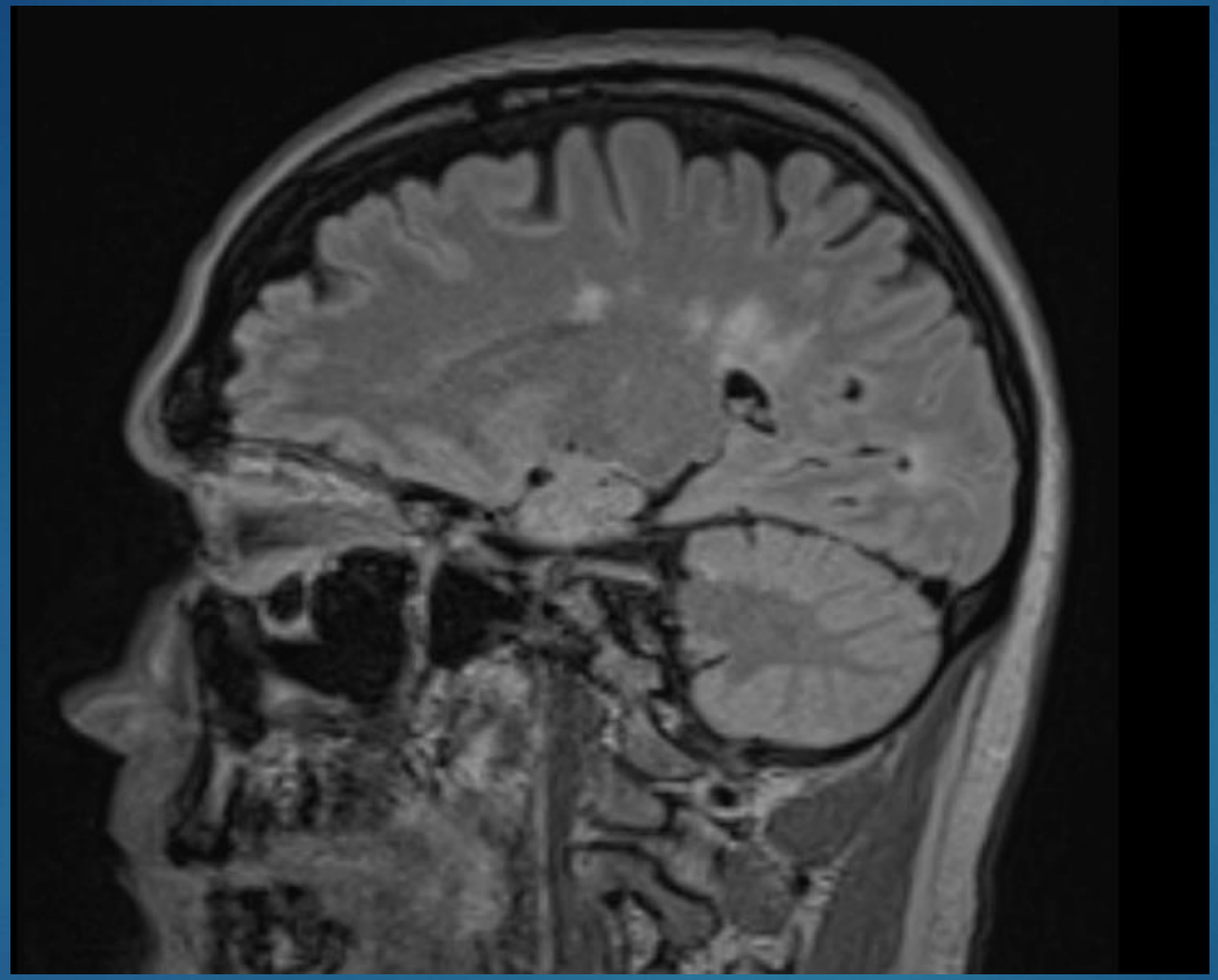
MRI BRAIN DEMYELIN

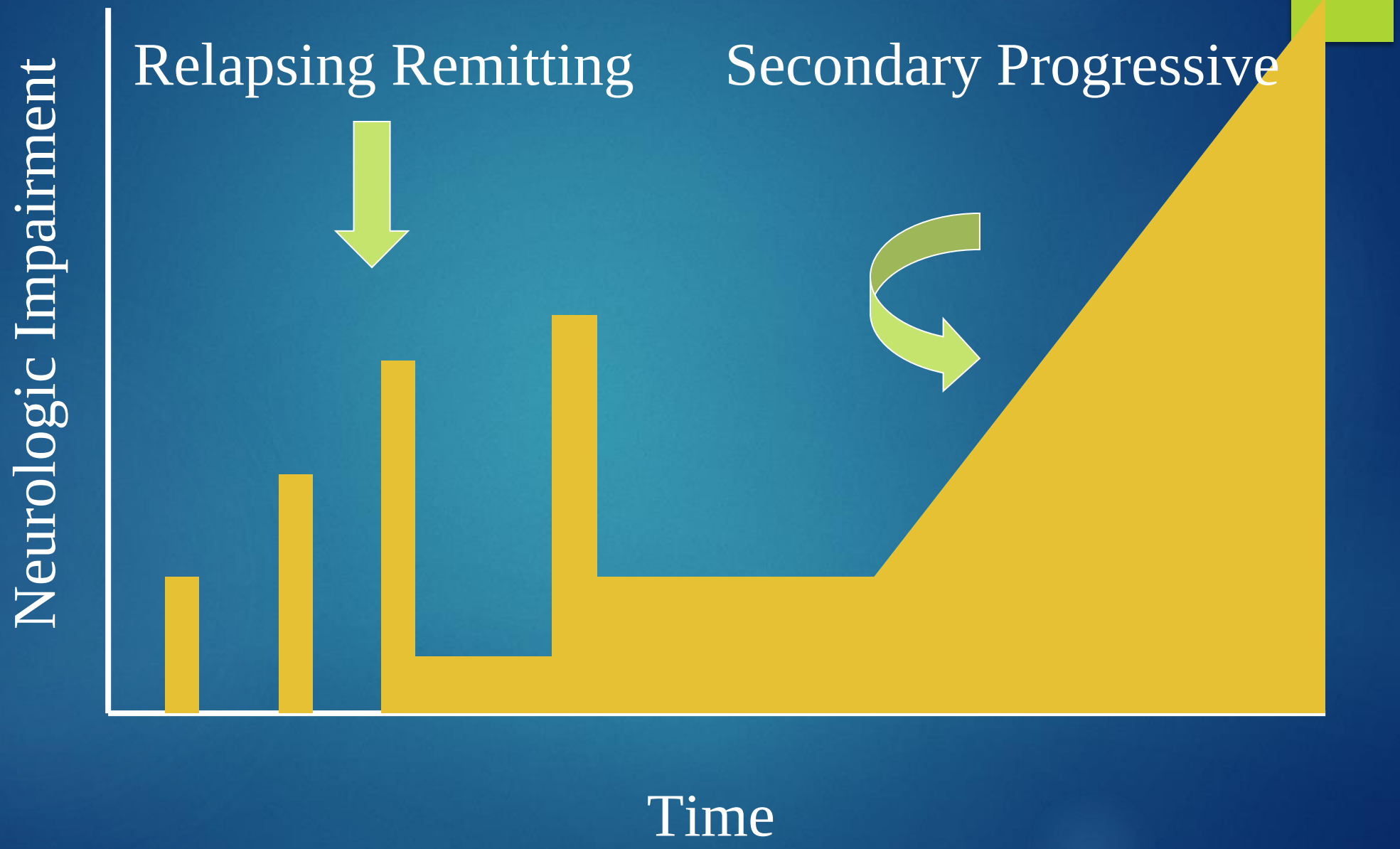


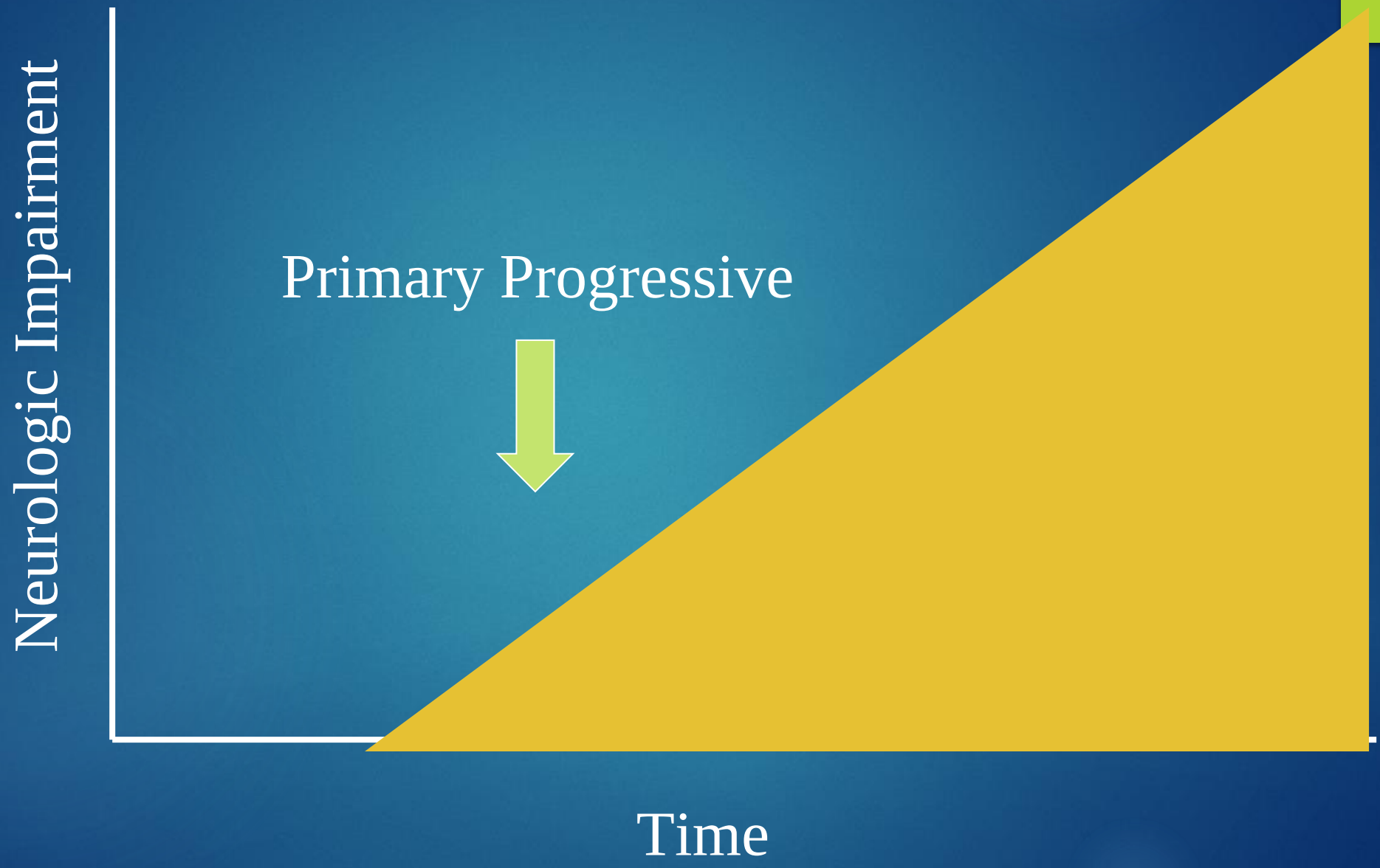
Case 4

- 51 y/o man presented to our MS Center in 2017 to establish care.
- Initially had optic neuritis 1989--confirmed by ophthalmologist; improved slightly.
- Then developed leg numbness in March 1991. No LP was done. No DMT at first. Improved again
- Describes a progressive course t/o the 1990s.
- **Secondary progressive MS**
- Finally started Betaseron 1999 (10 years after initial demyelinating event).
- Stopped betaseron in 2005 after cellulitis associated with injection–no DMT since
- Started Rituxan in 2017

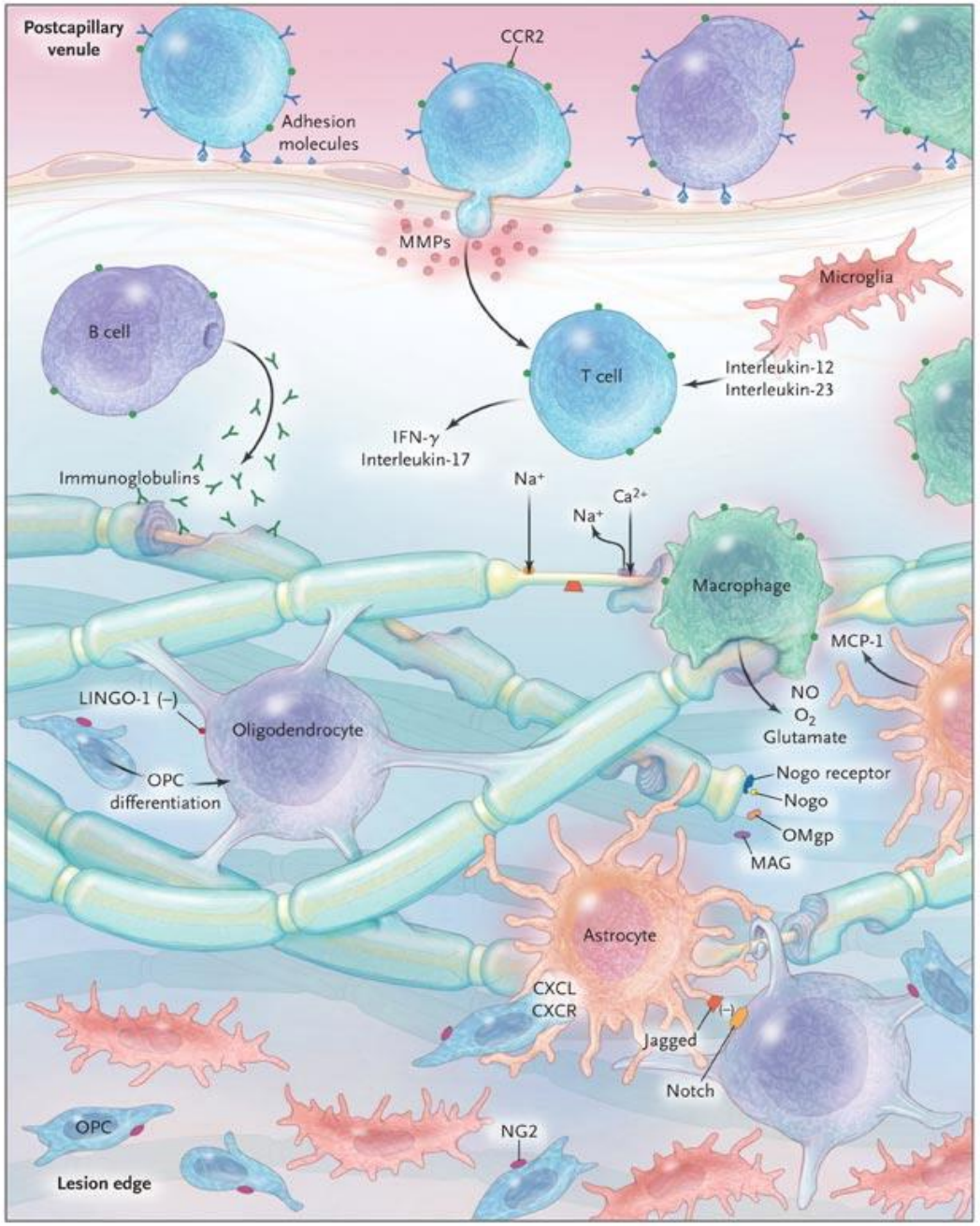


Phenotypes of Multiple Sclerosis


Relapsing Remitting
Secondary Progressive
Neurologic Impairment
Time


Neurologic Impairment
Primary Progressive
Time

Pathophysiology



PROGRESSIVE MS PATHOLOGY

Compartmentalized inflammation behind an intact blood-brain barrier

Cortical demyelination

Meningeal lymphoid follicles

Microglial activation

Reactive oxygen species which are toxic to axons and neurons

Axonal mitochondria become injured by reactive O2 species and NO

Energy deficiency in the mitochondrial respiratory chain leads to axonal degeneration and cell death

FROHMAN EM ET AL. N ENGL J MED 2006;354:942-955.

Pathology of Progressive MS

- Compartmentalized inflammation with B cell follicles
- Closed BBB
- Axonal degeneration
- Activated microglia
- Mitochondrial injury, oxidation byproducts, glutamate excitotoxicity all which lead to further demyelination and cell death

- 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. Brain Pathology 2004 Apr;14(2):164-74

RESEARCH ARTICLE

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

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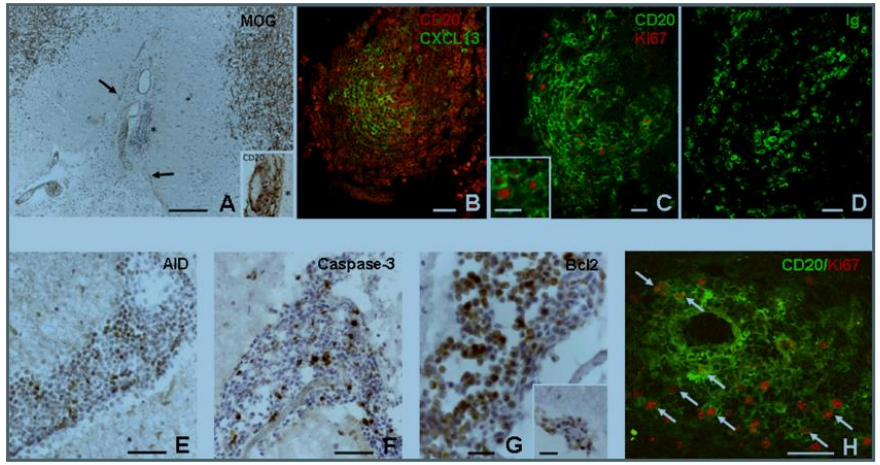
Multiple sclerosis (MS) is characterized by synthesis of oligoclonal immunoglobulins and the presence of B-cell clonal expansions in the central nervous system (CNS). Because ectopic lymphoid tissue generated at sites of chronic inflammation is thought to be important in sustaining immunopathological 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



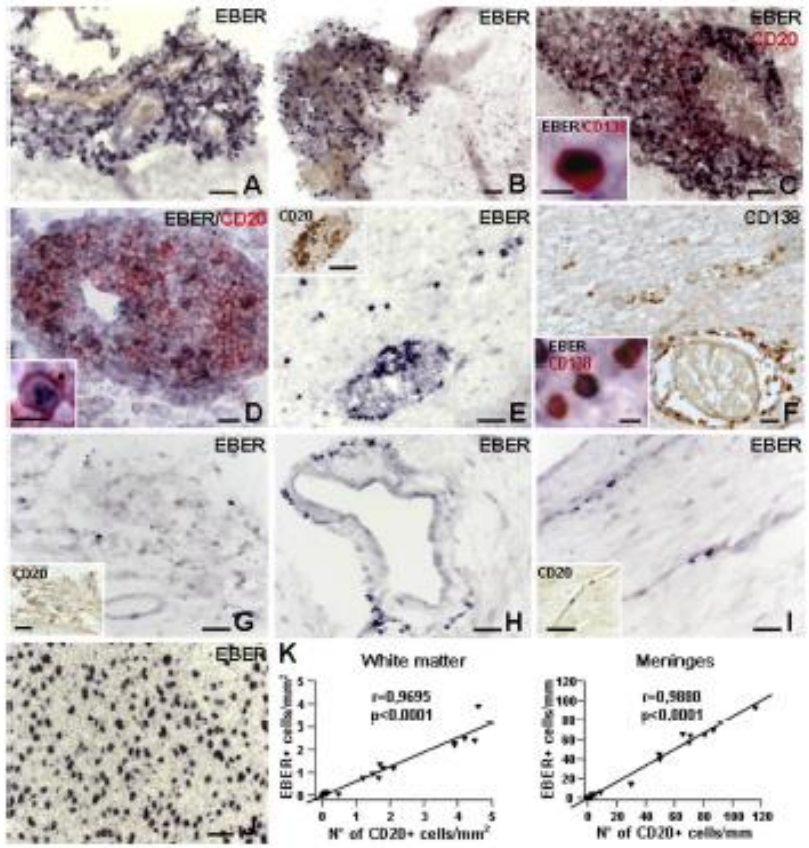


Figure 2. Detection of EBER⁺ cells in the MS brain by in situ hybridization. (A–E) EBV-high MS cases. In situ hybridization for EBER shows enrichment of EBER⁺ cells (blue-black nuclei) in ectopic B cell follicles located in the meninges of two different MS cases (A and B). Combined in situ hybridization for EBER and immunostaining for CD20 (red surface staining) reveals a high frequency of EBER⁺ B cells in an ectopic B cell follicle (C) and a lower percentage of B cells expressing EBER in the large perivascular cuff of an acute white matter lesion (D; the same lesion stained for CD20 and Ki67 in an adjacent section is shown in Fig. 1 H). In the insets in C and D, an EBER⁺/CD138⁺ plasma cell and an EBER⁺/CD20⁺ B cell are shown, respectively, at higher magnification. Perivascular EBER⁺ (E), CD20⁺ B cells (inset in E), and CD138⁺ plasma cells (F) in a large periventricular white matter lesion (E), and some intraparenchymal infiltration by EBER⁺ cells (E) and plasma cells (F) in the same region. The inset in F shows CD138⁺ plasma cells positive for EBER inside the parenchyma. (G–I) EBV-low MS cases. EBER⁺ cells in the meninges (G) and around scarcely infiltrated blood vessels (H and I) in chronic active white matter lesions. The insets in G and I show CD20 immunostaining of the corresponding areas in adjacent sections. In situ hybridization for EBER in a control, EBV-associated B cell lymphoma (J). Bars: A–C, E, G, J, and insets in E, G, and I, 50 μm; D and F, 20 μm; insets in C, D, and F, 10 μm. (K) Statistically

PATHOLOGY—2007
SEREFINI B ET AL. DYSREGULATED EPSTEIN-BARR VIRUS INFECTION IN THE MULTIPLE SCLEROSIS BRAIN. J EXP MED. 2007. NOV 26; 204(12): 2899-912

REPORT

MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1]†, Marianna Cortese[1]†, Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[6], Stephen J. Elledge[6], David W. Niebuhr[9], Ann I. Scher[9], Kassandra L. Munger[1]‡, Alberto Ascherio[1,10,11]*‡

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. The demyelination in the brain and spinal cord is an immune-mediated process (*1*) possibly triggered by a relatively rare disease, has until now impeded such an investigation. Over the course of a 20-year collaboration with the US military, we have identified cases of MS in a cohort composed of active-duty US military personnel between 1993 and 2013, a racially

race/ethnicity, branch of military service, and dates of collection of blood samples who were on active military duty when the case was diagnosed (Fig. 1A and fig. S1). There were 801 MS cases and 1566 controls with samples available to assess EBV infection status. Most of the individuals in our study were <20 years of age at the time of their first blood collection (Fig. 1B), and those who developed MS had symptom onset a median of 10 years after time of first sample (Fig. 1C).

Only one of the 801 MS cases occurred in an individual who was EBV-negative in the last sample, which was collected at a median of 1 year before MS onset [hazard ratio (HR) for MS comparing EBV-positive versus EBV-negative = 26.5; 95% confidence interval (CI): 3.7 to 191.6; $P = 0.001$, conditional logistic regression]. At baseline, 35 MS cases and 107 controls were EBV-negative. All but one of these 35 EBV-negative MS cases became infected with EBV during the follow-up, and all seroconverted before the onset of MS (fig. S3). The median time from the first EBV-positive sample to MS onset was 5 years (range: 0 to 10 years), and the median time from estimated EBV seroconversion, defined as the midpoint between the last seronegative sample and the first seropositive sample, to MS onset was 7.5 years (range: 2 to 15 years),

Diagnosis of Progressive MS

Summary of 2017 McDonald Criteria for the Diagnosis of MS

- ✓ *Requires elimination of more likely diagnoses*
- ✓ *Requires demonstration of dissemination of lesions in the central nervous system in space and time*

DIT = dissemination in time **DIS** = dissemination in space	**CNS** = central nervous system **CSF** = cerebrospinal fluid	**T2 lesion** = hyperintense lesion on T2-weighted MRI

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
…in a person who has experienced a typical attack/CIS at onset	
• 2 or more attacks and clinical evidence of 2 or more lesions; OR • 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location	None, DIS and DIT have been met
• 2 or more attacks and clinical evidence of 1 lesion	DIS shown by <u>one</u> of these criteria: - additional clinical attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial, or spinal cord
• 1 attack and clinical evidence of 2 or more lesions	DIT shown by <u>one</u> of these criteria: - Additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
• 1 attack and clinical evidence of 1 lesion	DIS shown by <u>one</u> of these criteria: - Additional attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial, or spinal cord **AND** DIT shown by <u>one</u> of these criteria: - additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
…in a person who has steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least <u>two</u> of these criteria: - 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical, or infratentorial) - 2 or more T2 spinal cord lesions - CSF oligoclonal bands

TABLE 5-1 **Clinical Characteristics of Multiple Sclerosis Subtypes**

	Relapsing	Secondary progressive	Primary progressive
Mean age	20-40 years	10-15 years after initial disease presentation	≥40 years
Female:male	3:1	3:1	1:1
Presenting event	Optic neuritis, acute partial transverse myelitis, brainstem syndromes	Progressive myelopathy, brainstem or cerebellar syndrome	Progressive myelopathy, brainstem or cerebellar syndrome
Frequency of presentation at start	85%	Not applicable	10-15%
Course	Episodes of acute worsening of neurologic functioning with total or partial recovery	Gradual neurologic deterioration following a relapsing course with or without relapses	Steady functional decline from disease onset without relapses or remission
Conventional brain MRI	Lesion load burden is more compared with primary progressive MS; active lesions are common, cortical lesions less common	Rare active lesions; subpial demyelination and cortical atrophy are more common	Lesion load burden is less compared with relapsing multiple sclerosis; rare active lesions; subpial demyelination and cortical atrophy are more common
Conventional spinal cord MRI	Lower lesion load	Higher lesion load	Higher lesion load

MRI = magnetic resonance imaging.

Amezcua, L. *Continuum*, 2022

Treatment of Progressive MS

Disease Modifying Therapies

MS: Disease Modifying Therapies

1993-2018

- interferon beta-1b (Betaseron)-1993
- interferon beta-1a (Avonex) --1996
- glatiramer acetate (Copaxone)—1996
- mitoxantrone (Novantrone)--2000
- interferon beta-1a (Rebif)—2002
- natalizumab (Tysabri)–2006
- fingolimod (Gilenya)–2010
- teriflunomide (Aubagio)–2012
- dimethyl fumarate (Tecfidera)--2013
- peginterferon beta-1a (Plegridy)–2014
- alemtuzumab (Lemtrada)—2014
- ocrelizumab (Ocrevus)—2017

2019-2021

- siponimod (Mayzent) 2019
- cladribine (Mavenclad) 2019
- diroximel fumarate (Vumerity)--2019
- monomethyl fumarate (Bafiertam)–2020
- ozanimod (Zeposia)—2020
- ofatumumab (Kesimpta)—2020
- ponesimod (Ponvory)—2021
- ublituximab (Briumvi) - 2022

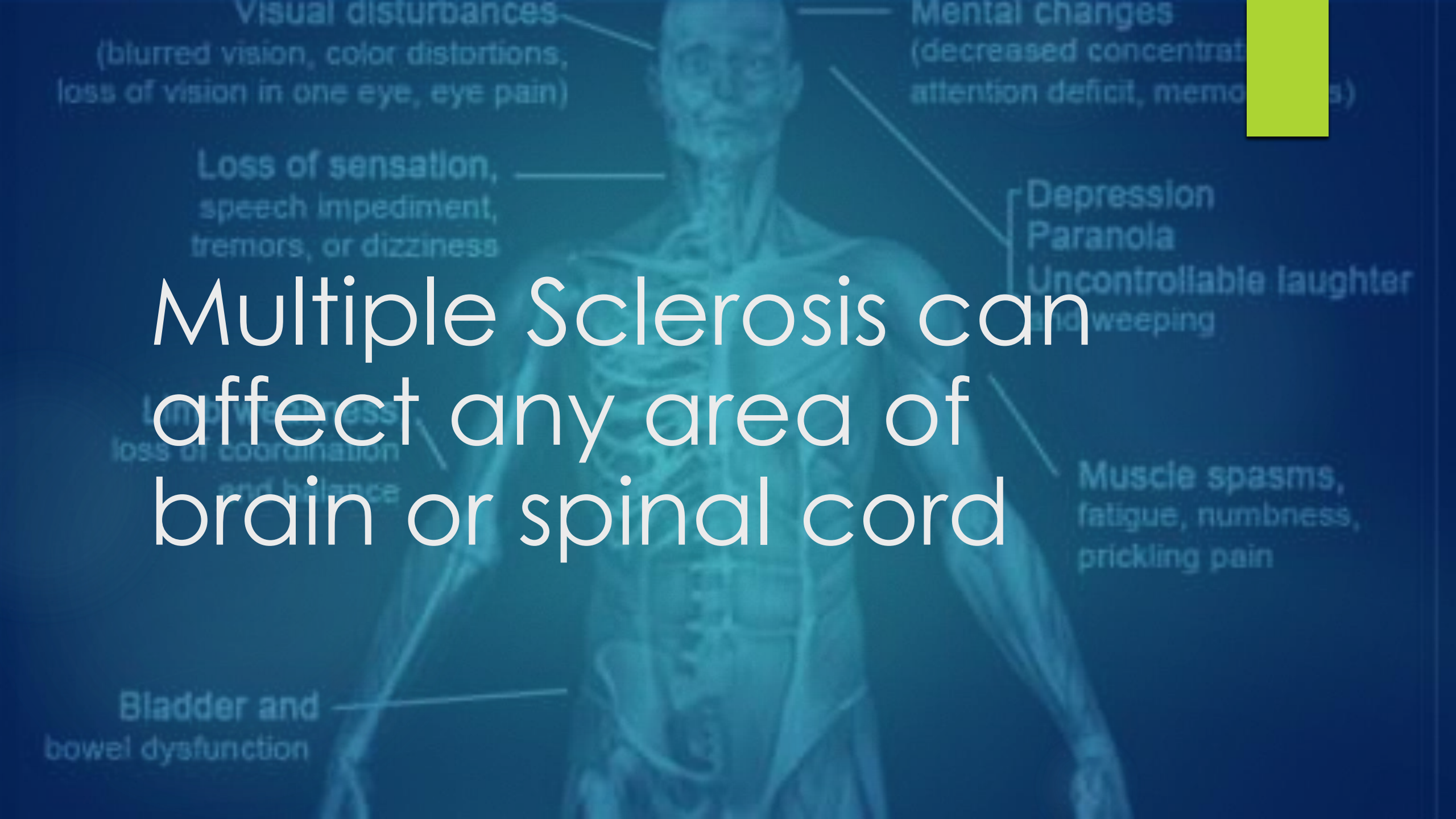
Common features of DMT trials that showed efficacy in PMS

- Patients were younger in age
- Disease duration was shorter
- More evidence of MRI activity (gad + lesion or new or expanding T2 lesions)
- Progressive phase more recent in onset

Ideal characteristics of PMS treatments

- Targets smoldering inflammation
- CNS penetration
- Anti-EBV
- Remyelination
- Neuroprotection
- Prevention—EBV vaccine?

Symptom Management

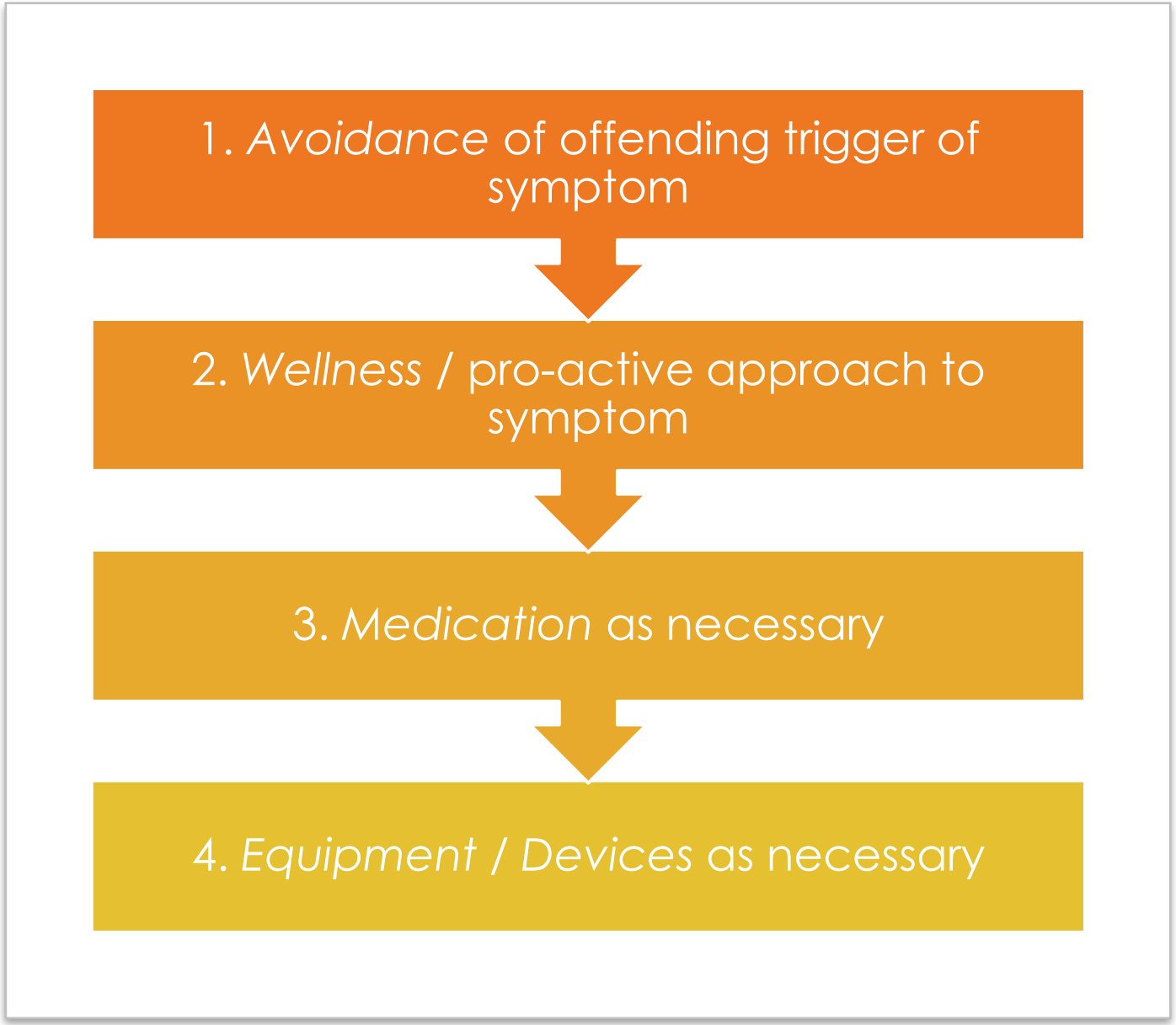


Multiple Sclerosis can affect any area of brain or spinal cord

Symptoms of MS

- Fatigue
- Spasticity
- Gait Disturbance
- Depression
- Tremor
- Sexual Dysfunction
- Cognitive Issues
- Pain
- Swelling
- Pressure Sores
- Bone Health
- Bladder and Bowel
- Involuntary Emotion

Principals of MS Symptom management



Lifestyle in Progressive MS

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.
- Several other studies have since shown similar relationship between vascular risk factors and increased disability in MS

Smoking

J Neurol (2009) 256:577–585
DOI 10.1007/s00415-009-0120-2

ORIGINAL COMMUNICATION

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Smoking is associated with progressive disease course and increased progression in clinical disability in a prospective cohort of people with multiple sclerosis

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Abstract *Background* Multiple sclerosis has a variable disease course. The contribution of modifiable lifestyle factors to disease course has not been well studied, although one cohort has reported that smoking is associated with conversion to secondary progressive MS course and another that smoking is not. *Methods* We conducted a prospective cohort study of people with MS in Southern Tasmania from 2002 to 2004 with 78 % (203/259) of eligible participating and 198 with one or more reviews and confirmed MS. The cohort had a high retention rate (90 % (183/203)). The median follow-up time was 909 days. Smoking data were collected at baseline and six-monthly reviews. Clinical disability assessments were conducted annually in conjunction with a real time clinical notification system for relapses. A repeated measures analysis and other statistical methods were used. *Results* Cumulative pack-years (p-y) smoked after cohort entry was associated with an increase in longitudinal MSSS ($p < 0.001$). Relative to the 0 pack years (p-y) category (in the year prior to the MSSS measure) those in the 0 to 1 p-y category had an adjusted mean difference in MSSS of 0.34 (95 % CI 0.28, 0.66); those in the 1 to 2 p-y category had a 0.41 (95 % CI −0.03, 0.85) increase; and those in the 2 or more p-y category had a 0.99 (95 % CI 0.41, 1.58) increase in MSSS. Similar results were found using a variety of statistical approaches or EDSS as a clinical outcome. Smoking during the cohort period was not associated with relapse (cumulative pack years smoked after cohort entry, HR 0.94 (0.69, 1.26) per pack year). *Conclusion* A better understanding of the mechanisms underlying smoking and multiple sclerosis, particularly progressive forms of the disease, may provide new insights for the eventual goal of better treatment and prevention of multiple sclerosis.

Key words multiple sclerosis · tobacco smoke · prospective cohort · repeated measures · disability

Abbreviations

25(OH) D	25 hydroxy vitamin D
AOR	adjusted odds ratio
CI	confidence interval
DNA	deoxyribonucleic acid
EDSS	expanded disability status scale
HR	hazard ratio
OR	odds ratio
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSSS	multiple sclerosis severity score
PP	primary progressive course

Exercise

- Researches from French and German MS Centers performed functional MRI looking at functional connectivity before and after an exercise program
- RESULTS: After 3 months of exercise program, patients had significant increase in connectivity on brain MRI
- presented ECTRIMS in October 2017

Diet

- Several diets studied including modified paleo and plant based. Unclear which is better at this point.
- I recommend a Mediterranean diet –high in fruits, vegetables and healthy fats. Low in sugar and red meat. No highly processed foods.
- And vitamin D supplementation

Research in Progressive MS

Ideal characteristics of PMS treatments

- Targets smoldering inflammation
- CNS penetration
- Anti-EBV
- Remyelination
- Neuroprotection
- Prevention—EBV vaccine?

PMS Phenotype	Intervention	Phase / Design	MOA
PPMS	Intrathecal AUOC-01	1a, open label	Cells from umbilical cord blood remyelination
PPMS	**Tolebrutinib**	**3, randomized, placebo**	**BTKi**
PPMS,	Long-acting glatiramer acetate IM -- monthly	2, two dosing arms	IM delivery of GA via microspheres
PPMS,SPMS	**ATA188 IV**	**2, placebo first year**	**Allogeneic, EBV-specific CD8+ T-cells**
PPMS	Oral Fenebrutinib	3, double blind, double dummy (Ocrevus)	BTKi
PPMS, SPMS	Metformin 500mg QID	1, placebo	Neuroprotection

PMS Phenotype	Intervention	Phase / Design	MOA
SPMS	Simvastatin 80mg daily	3, placebo	Neuroprotection
SPMS	Masitinib oral	3, placebo	Tyrosine kinase, targets mast cells and microglia
SPMS, PPMS, RRMS	Ixazomib oral	1, placebo	Proteasome inhibitor, Targets plasma cells
SPMS	OCH-NCNP1 3mg	2, placebo	Suppress Th1 and induce Th2
PPMS, SPMS	N-acetyl cysteine	2, placebo	Neuroprotective

ATA-188

- Atara Biotherapeutics
- Phase-1,2 study in progressive multiple sclerosis
- First cellular therapy trial in MS
- Rationale based on new theory that a failure to manage Epstein-barr virus leads to MS
- Donor T-cells stimulated against EBV, expanded in vitro, and stored in a cellular, HLA-sorted “library”
- HLA-matched, EBV-specific T-cells given to research participants with progressive MS
- We have enrolled 8 patients with PMS into this study

Lipoic Acid in SPMS

- Lipoic Acid is a potent antioxidant, available OTC
- Improves MS in mouse model
- Study: 2 years, 1200mg/day of Lipoic Acid compared to placebo
- 51 patients, secondary progressive MS
- Lipoic Acid group had reduction in brain atrophy
- Larger study being planned

Case 1

- 25 foot timed walk in November 2014: 8.2 seconds without assist
- Started on Copaxone
- In October 2015, 25 foot timed walk was 15 seconds
- DMT switched to Rituxan
- At the next visit, 25 foot timed walk was 9 seconds and she stabilized on Rituxan for 3 years, but then has steadily progressed since.
- **Non-ambulatory for past 5 years**

Case 2

- 52 y/o man diagnosed with RRMS by me in 2009
- Had severe initial relapse affecting medulla but had significant improvement.
- Started on Rebif and did well for 5 years.
- Did not have any future relapses, but did start to progressively worsen in 2014
- in 2012, 25 ft timed walk was 3.5s
- in 2014, 25 ft timed walk was 6 seconds
- **in 2023, 25 ft timed walk was 18s with walker**
- **Has been on multiple DMTs including Rituxan, Cladribine, Tecfidera**
- **Filed for disability in 2014**

Case 3

- 50 y/o woman referred for evaluation for possible MS in September 2019
- In January 2019, developed blurry vision that progressed to double vision
- In May 2019, developed gait imbalance
- exam with bilateral INO, ataxia and 25ft timed walk 7.2 seconds without assist
- LP with 2 OCB unique to CSF and elevated IgG index
- VEPs slow bilaterally
- MRI brain with demyelination t/o
- Sarted on Ocrevus
- **In 2023, 25ft timed walk 8.3s with rollator**
- **Still working full time**

Case 4

- 51 y/o man with SPMS diagnosed in 1991
- Started Rituxan which he took for few years that made no difference
- **Referred for IT baclofen pump-very helpful**
- Now largely bedbound with stage 4 pressure ulcers, SP catheter.
- Virtual care has been invaluable
- Focus on supportive and comprehensive care – social workers, equipment, home health, palliative care, home provider visits, NMSS support.
- Still working as a college professor

Final thoughts

- Unmet need to find effective treatments for progressive MS
- Treatments that are highly effective for RRMS are only marginally effective for progressive forms of MS
- Treatment of various MS symptoms is critical in patients with progressive MS
- Attention to lifestyle also very important
- Future therapies must:
  - Be CNS penetrant
  - Target smoldering inflammation
  - Address EBV infection
  - Address remyelination and repair

Thanks!