The Landscape of Prevention in Multiple Sclerosis and related disorders: Current Status and Future Directions

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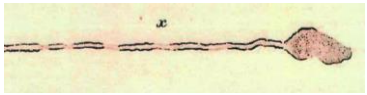
Disclosures

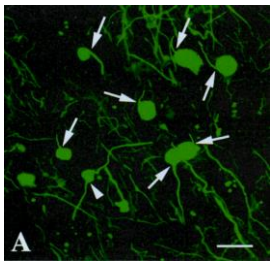
- EKH: has received honoraria/research support from Biogen, Merck Serono, Novartis, Roche, and Teva; has served as a member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, Sanofi Genzyme, and Zenas; has been supported by the Czech Ministry of Education – project Cooperatio LF1, research area Neuroscience, and the project National Institute for Neurological Research (Programme EXCELES, ID project No LX22NPO5107) – funded by the European Union-Next Generation EU.

Short history : Our understanding MS

- 1866 Jean-Martin Charcot: description of MS
- 1872 Froman, 1915 Doinikov: axonal transsection
- 1885 Babinski – correlation between inflammation and axonal transsection

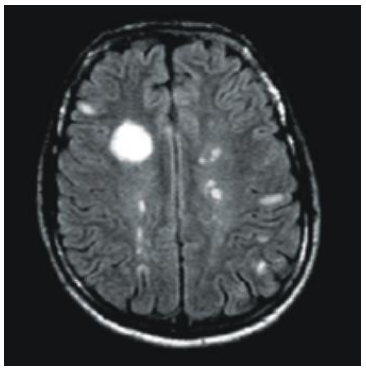


- 1933 experimental animal model of MS
- 1958 – Discovery of oligoclonal bands in CSF



1997

- 1981 development of MRI (since 1973)
- Hans Lassmann – description of MS pathology
- McDonald diagnostic criteria 2001, 2005, 2010, 2017, 2024



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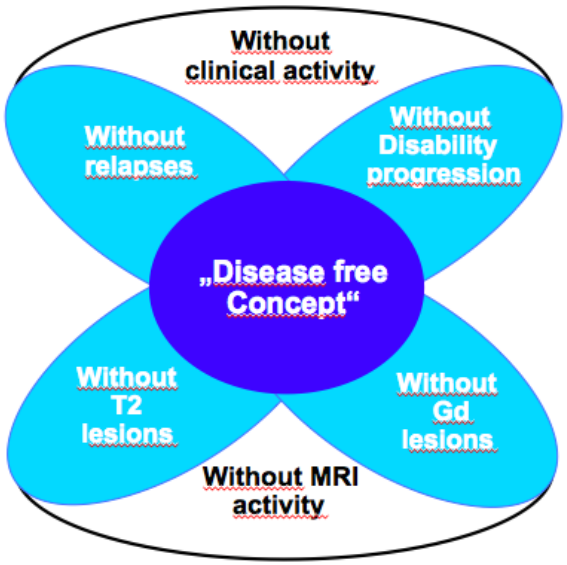
MS has mostly been treated late

- 1952 Corticotropin (Miller)
- 1982 double blind trial methodology accepted
- 1993 Interferon beta – first clinical study published
- 1996 Glatiramer acetate approved
- 2002 Mitoxantrone
- 2007 Natalizumab
- 2010 Fingolimod
- 2013 Dimethyl fumarát, Alemtuzumab, Teriflunomide
- 2017 Cladribin
- 2018 Ocrelizumab, 2020 Ofatumumab
- 2005 first drug for clinically isolated syndrome (first attack): IFNB



NEDA

Treatment goal: No Evidence of Disease Activity (NEDA) 2009

Concept of highly effective treatment (HET) from the beginning of MS

Havrdová E et al. Lancet Neurol 2009

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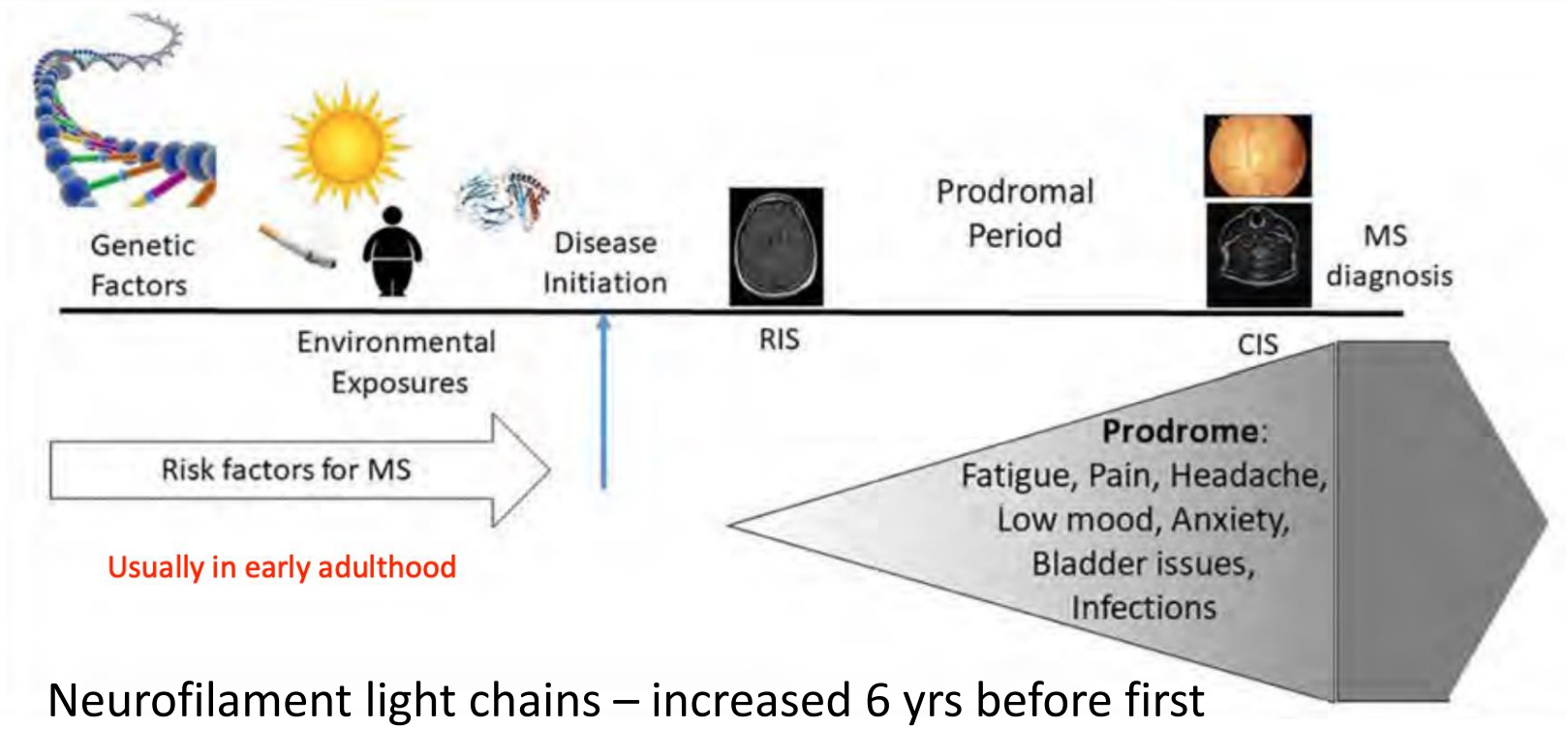
If we want to prevent MS we need to know:
When MS starts?



Neurofilament light chains – increased 6 yrs before first symptom
High titers of anti-EBV antibodies
Low vitamin D level

Tremlett H et al. Front Neurol. 2022 Jan 31;12:761408.

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What is RIS? Definition:

- 2009: the presence of asymptomatic, incidentally identified demyelinating-appearing white matter lesions in the CNS within individuals lacking symptoms typical of multiple sclerosis.

- 2023: Class I evidence that subjects with fewer lesions than required in the 2009 RIS criteria evolve directly to a first clinical event at a similar rate when additional risk factors are present (spinal cord lesion, new T2 or Gd+ lesion, CSF OCBs).

Lebrun-Frénay C, Okuda DT, Siva A, Landes-Chateau C, Azevedo CJ, Mondot L, Carra-Dallière C, Zephir H, Louapre C, Durand-Dubief F, Le Page E, Bensa C, Ruet A, Ciron J, Laplaud DA, Casez O, Mathey G, de Seze J, Zeydan B, Makhani N, Tutuncu M, Levraut M, Cohen M, Thouvenot E, Pelletier D, Kantarci OH. The radiologically isolated syndrome: revised diagnostic criteria. Brain. 2023 Aug 1;146(8):3431-3443.

Dx criteria for MS 2024 (not yet published): preclinical MS

- At least 1 lesion in 2 out of 5 typical locations +
- One out of 3 conditions:
  - At least 6 lesions with CVS
  - New T2 or Gd+ lesion
  - Presence of OCBs
- Skilled neuroradiologist, MR diagnostic protocol
- Why is it important? Can we do anything (except councelling on lifestyle modification)?

Lebrun-Frénay C, Okuda DT, Siva A, Landes-Chateau C, Azevedo CJ, Mondot L, Carra-Dallière C, Zephir H, Louapre C, Durand-Dubief F, Le Page E, Bensa C, Ruet A, Ciron J, Laplaud DA, Casez O, Mathey G, de Seze J, Zeydan B, Makhani N, Tutuncu M, Levraut M, Cohen M, Thouvenot E, Pelletier D, Kantarci OH. The radiologically isolated syndrome: revised diagnostic criteria. Brain. 2023 Aug 1;146(8):3431-3443.

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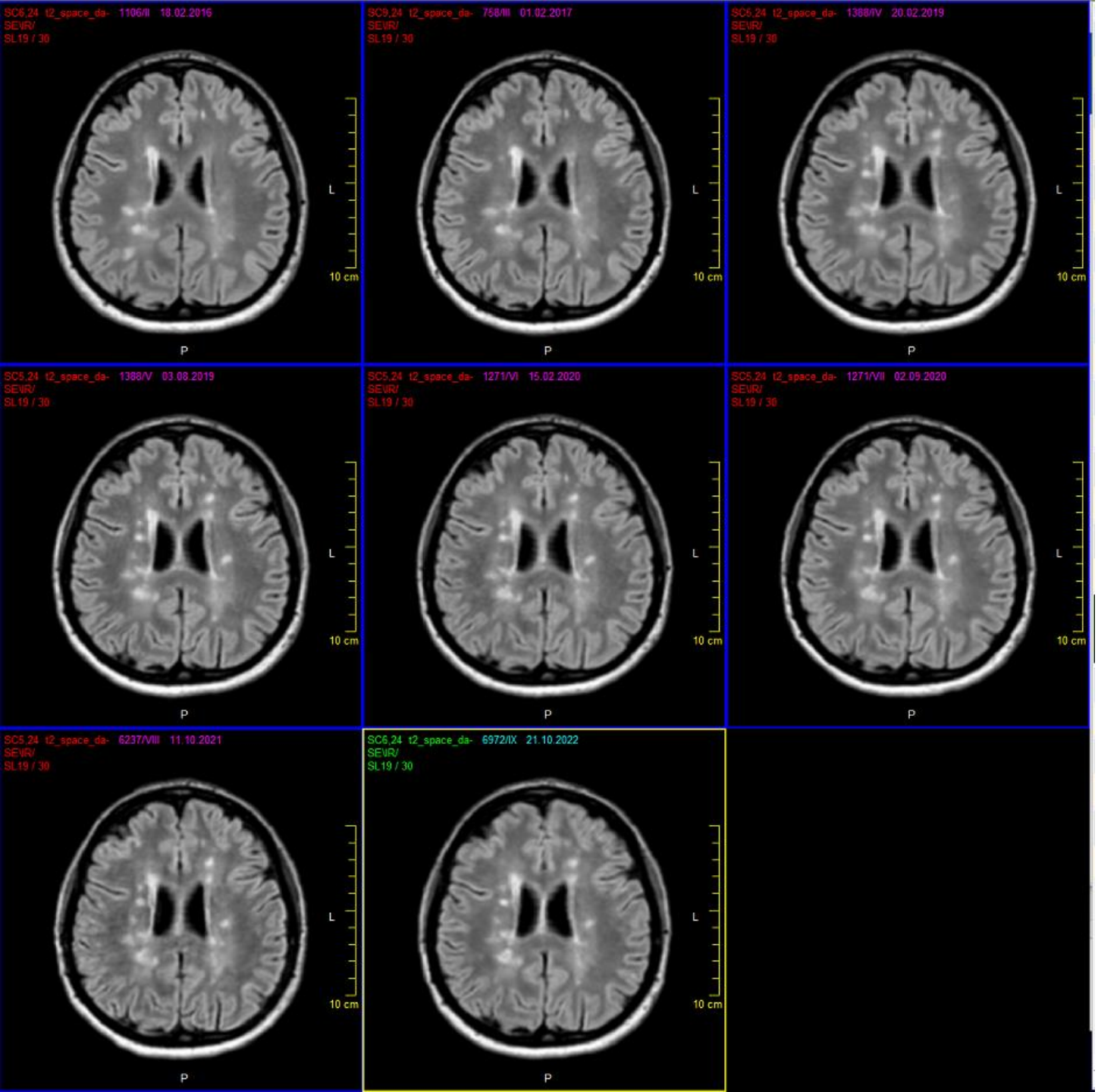
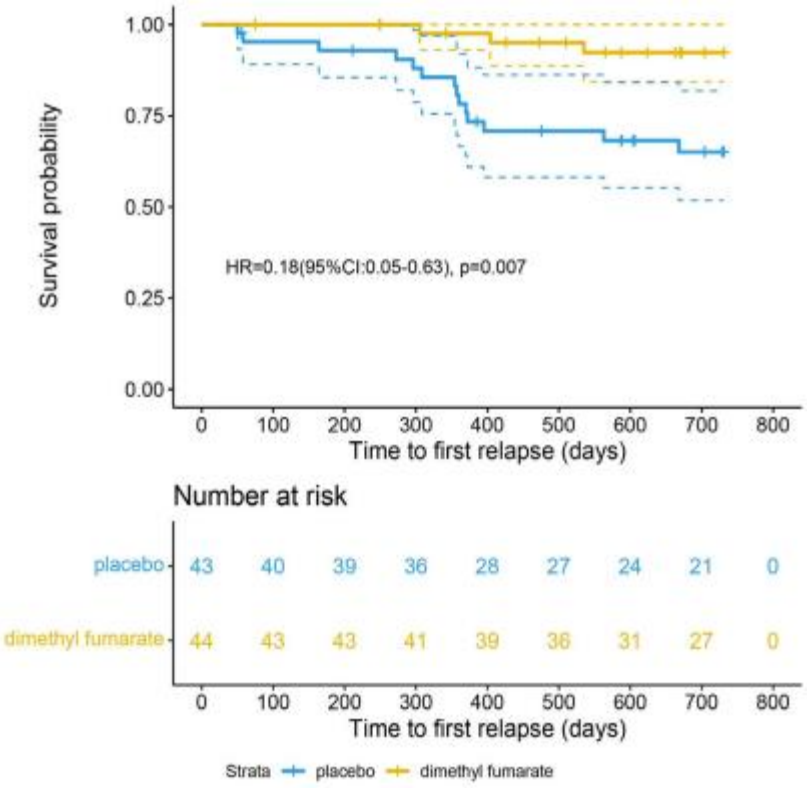


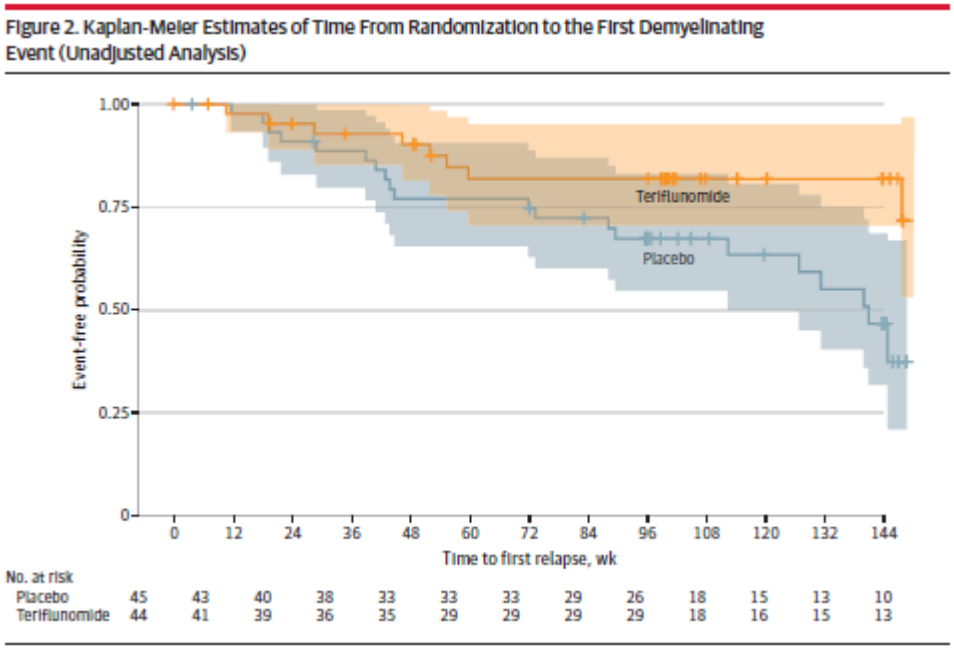
VB, f, 1984

History: experimenting with drugs, developed psychosis 2015, hospitalised in psychiatric ward, MRI showed lesions suspected from MS, she was sent to our center, we examined CSF 2017: 12 OCBs. Started Tx with teriflunomide after new MRI activity in 2019

DMF and TERI



DMF



Teri

Okuda D et al.: ANN NEUROL 2023;93:604–614
Lebrun-Frenay Ch. JAMA Neurol. 2023 Oct 1;80(10):1080-1088.

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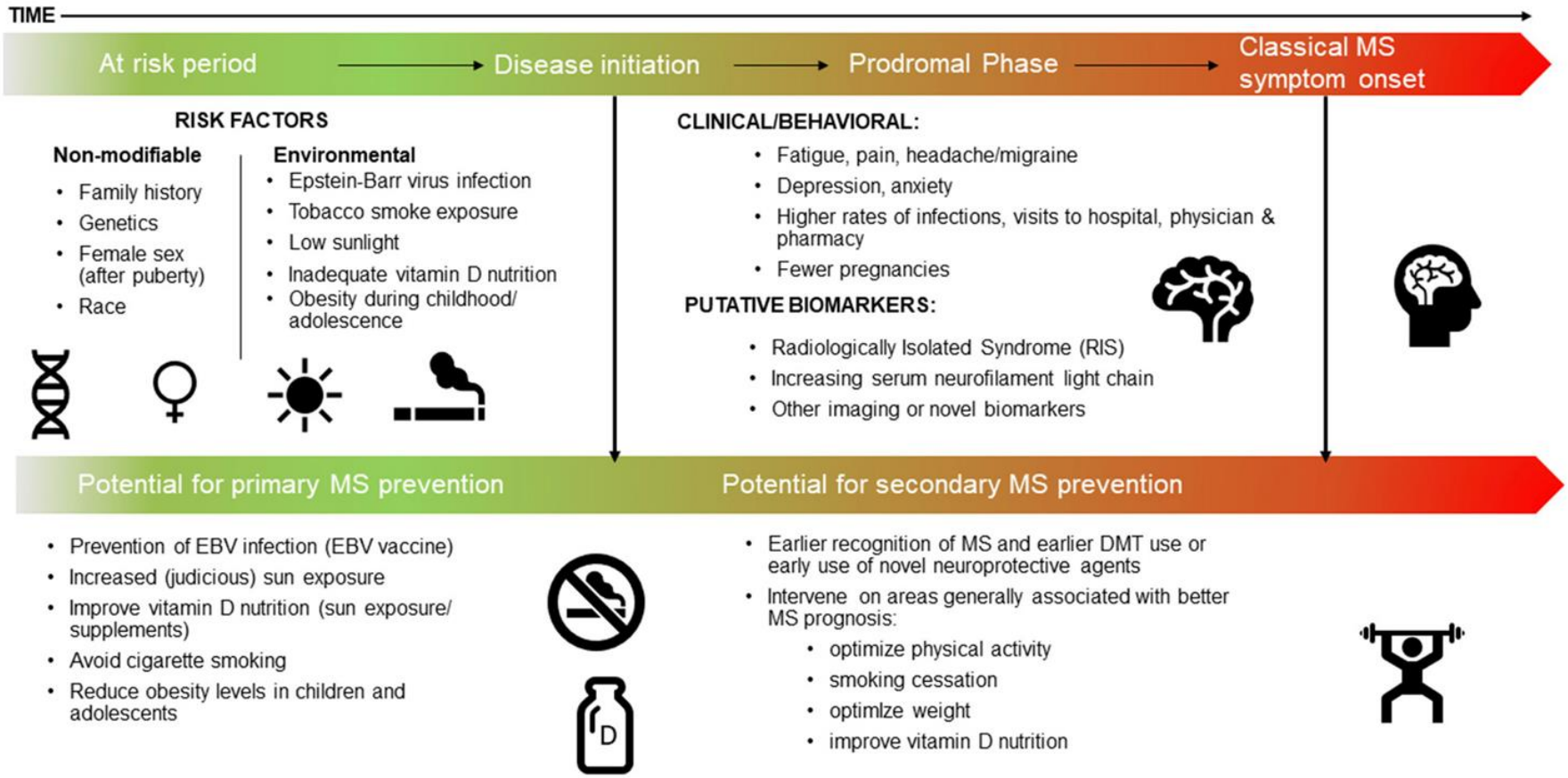

FIGURE 1 | The MS continuum, a proposed timeline: the at risk period, the prodrome, and potential for prevention.

Tremlett H et al. The Multiple Sclerosis Prodrome: Evidence to Action. *Front Neurol Jan 2022, vol 12:761408*

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Why to treat? – 1.

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Cognitive impairment, the central vein sign, and paramagnetic rim lesions in RIS

Jiwon Oh, Suradech Suthiphosuwan, Pascal Sati, Martina Absinta, Blake Dewey, Melanie Guenette, Daniel Selchen, Aditya Bharatha, Emily Donaldson, Daniel S Reich and Anthony Feinstein

Multiple Sclerosis Journal

2021, Vol. 27(14) 2199–2208

DOI: 10.1177/13524585211002097

Correspondence to:
J Oh
Division of Neurology, Department of Medicine, St. Michael's Hospital, University of Toronto, 30 Bond Street, Shuter 3-019, Toronto, ON M5B1W8,

Abstract

Objective: The central vein sign (CVS) and "paramagnetic rim lesions" (PRL) are emerging imaging biomarkers in multiple sclerosis (MS) reflecting perivenular demyelination and chronic, smoldering inflammation. The objective of this study was to assess relationships between cognitive impairment (CI) and the CVS and PRL in radiologically isolated syndrome (RIS).

Results: processing speed impaired: 40,7% pts.
memory impaired: 33,3%, executive function impaired: 14,8%

Why to treat? – 2.

› Neurology. 2013 Jun 4;80(23):2090-4. doi: 10.1212/WNL.0b013e318295d707. Epub 2013 May 1.

Brain metabolic changes suggestive of axonal damage in radiologically isolated syndrome

Maria Laura Stromillo [1], Antonio Giorgio, Francesca Rossi, Marco Battaglini, Bahia Hakiki, Gianmichele Malentacchi, Mario Santangelo, Claudio Gasperini, Maria Letizia Bartolozzi, Emilio Portaccio, Maria Pia Amato, Nicola De Stefano

Affiliations + expand

PMID: 23635962 DOI: 10.1212/WNL.0b013e318295d707

Abstract

Background: The MRI incidental finding in asymptomatic subjects of brain white matter (WM) changes meeting the Barkhof criteria for the diagnosis of multiple sclerosis (MS) has been recently characterized as the radiologically isolated syndrome (RIS). This entity needs to be more specifically defined to allow risk stratification of these subjects. We used brain proton magnetic resonance spectroscopic imaging (1H-MRSI) to assess metabolic changes in an RIS population.

Decreased brain NAA/Cr levels in a group of RIS subjects indicates that brain metabolic abnormalities suggestive of axonal damage can be significant even at this early disease stage.

Why to treat? – 3.

Early CNS neurodegeneration in radiologically isolated syndrome

OPEN

Christina J. Azevedo, MD, MPH
Eve Overton, BS
Sankalpa Khadka, BS
Jessica Buckley, BS
Shuang Liu, PhD
Mehul Sampat, PhD
Orhun Kantarci, MD
Christine Lebrun Frenay, MD
Aksel Siva, MD
Darin T. Okuda, MD
Daniel Pelletier, MD

ABSTRACT

Objective: Increasing evidence indicates that the thalamus may be a location of early neurodegeneration in multiple sclerosis (MS). Our objective was to identify the presence of gray matter volume loss and thinning in patients with radiologically isolated syndrome (RIS).

Methods: Sixty-three participants were included in this case-control study. Twenty-one patients with RIS were age- and sex-matched to 42 healthy controls in a 1:2 ratio. All participants underwent brain MRIs on a single 3T scanner. After lesion segmentation and inpainting, 1 mm^3-isometric T1-weighted images were submitted to FreeSurfer (v5.2). Normalized cortical and deep gray matter volumes were compared between patients with RIS and controls using *t* tests, and thalamic volumes were correlated with white matter lesion volumes using Pearson correlation. Exploratory cortical thickness maps were created.

Results: Although traditional normalized total gray and white matter volumes were not statistically

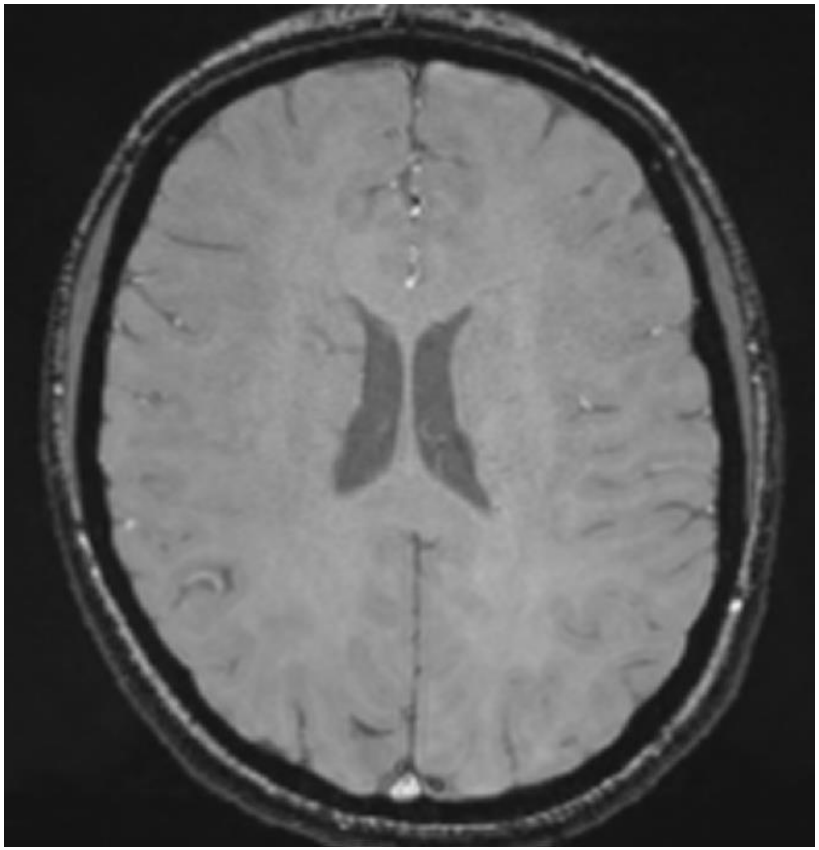
Thalamic volume loss is present early in CNS demyelinating disease

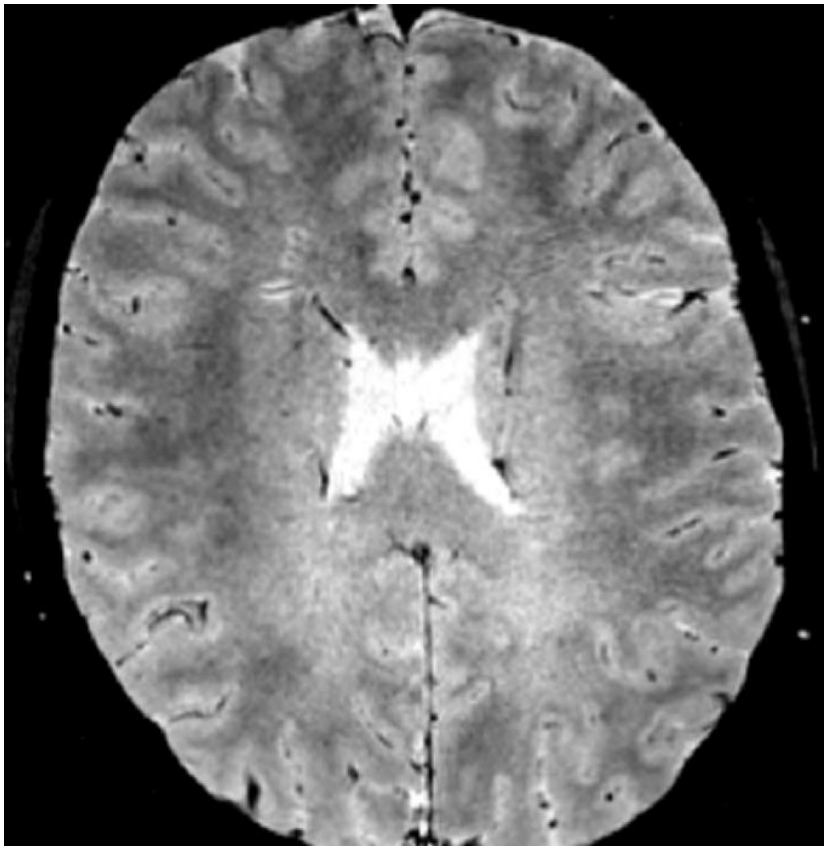
+ Okuda: ECTRIMS 2024 presentation on microstructural changes in the brainstem

When we should treat RIS?

- **It is true RIS** (not only some 2-3 small white spots in deep white matter on MRI)
  - Co-operation with a skilled neuroradiologist able to help establish the diagnosis (right MRI protocol incl. spinal cord MRI and gadolinium administration)
  - hands on training of radiologists working with our 15 tertiary MS Centers is currently being organized in Czech Republic

Central vein sign (CVS)





Different sensitivity - scanner 3T x 1.5T and sequence parameters

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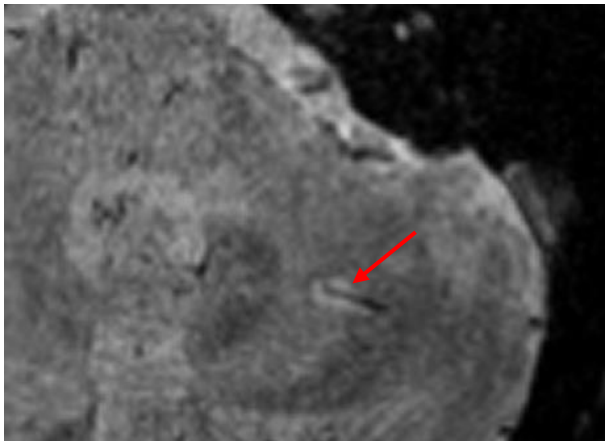
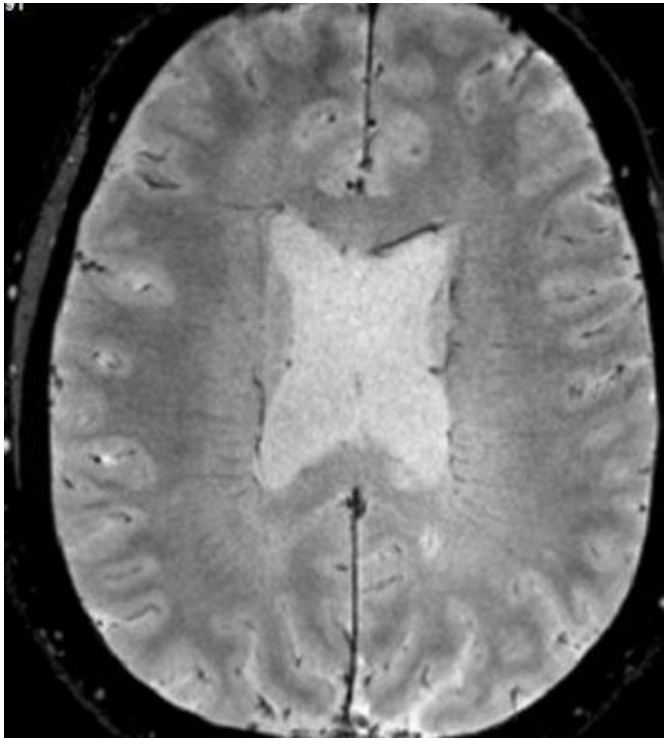
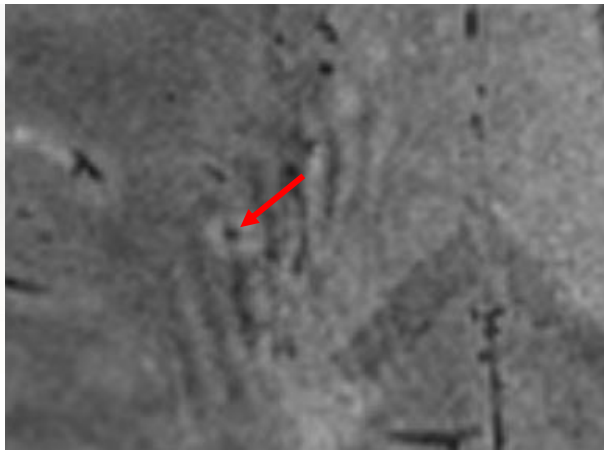
Central vein sign (CVS)







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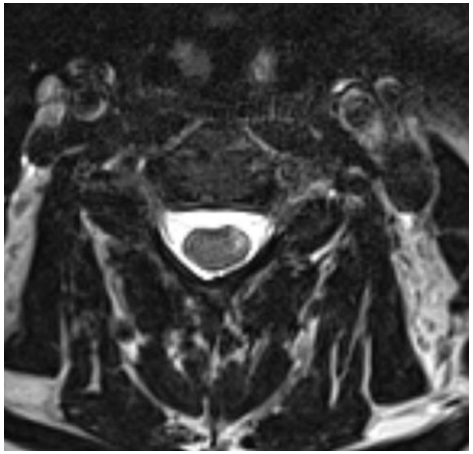
Nonspecific lesions on standard MRI ?

spinal cord lesions may be subclinical and if a standardized protocol was not used, the patient would not meet the diagnostic criteria; furthermore, it is an important prognostic sign indicating a more severe course.



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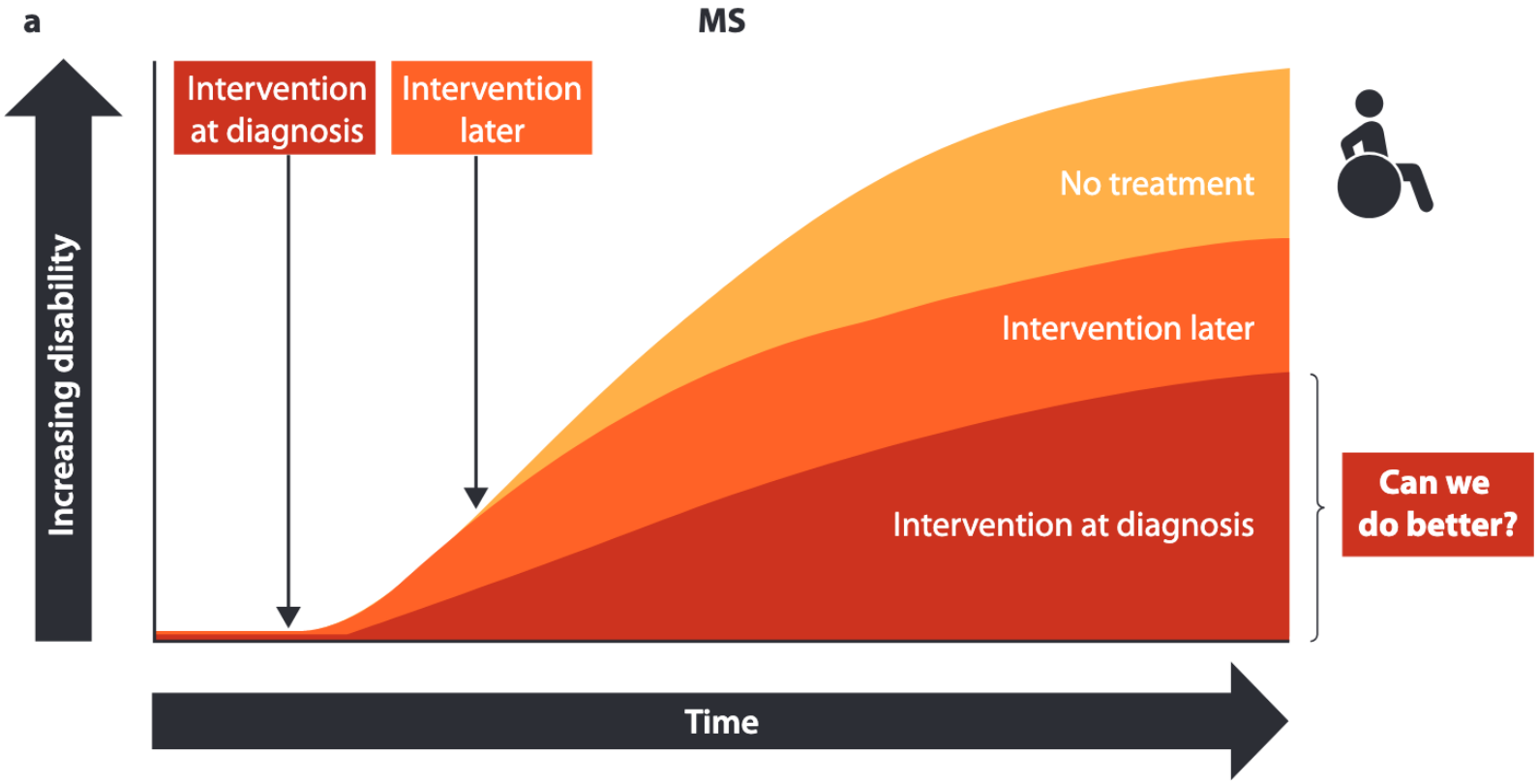
When we should treat RIS?

- **You are sure it is true RIS** (not only some 2-3 small white spots on MRI)
  - Co-operation with a skilled neuroradiologist able to help you establish the diagnosis (right MRI protocol)
  - You are able to check for all prognostic markers
- The patient is fully informed and agrees
- The treating neurologist is willing to monitor the patient (clinically, MRI, side effects)

Previous concept

often starting with “watch and wait“ strategy



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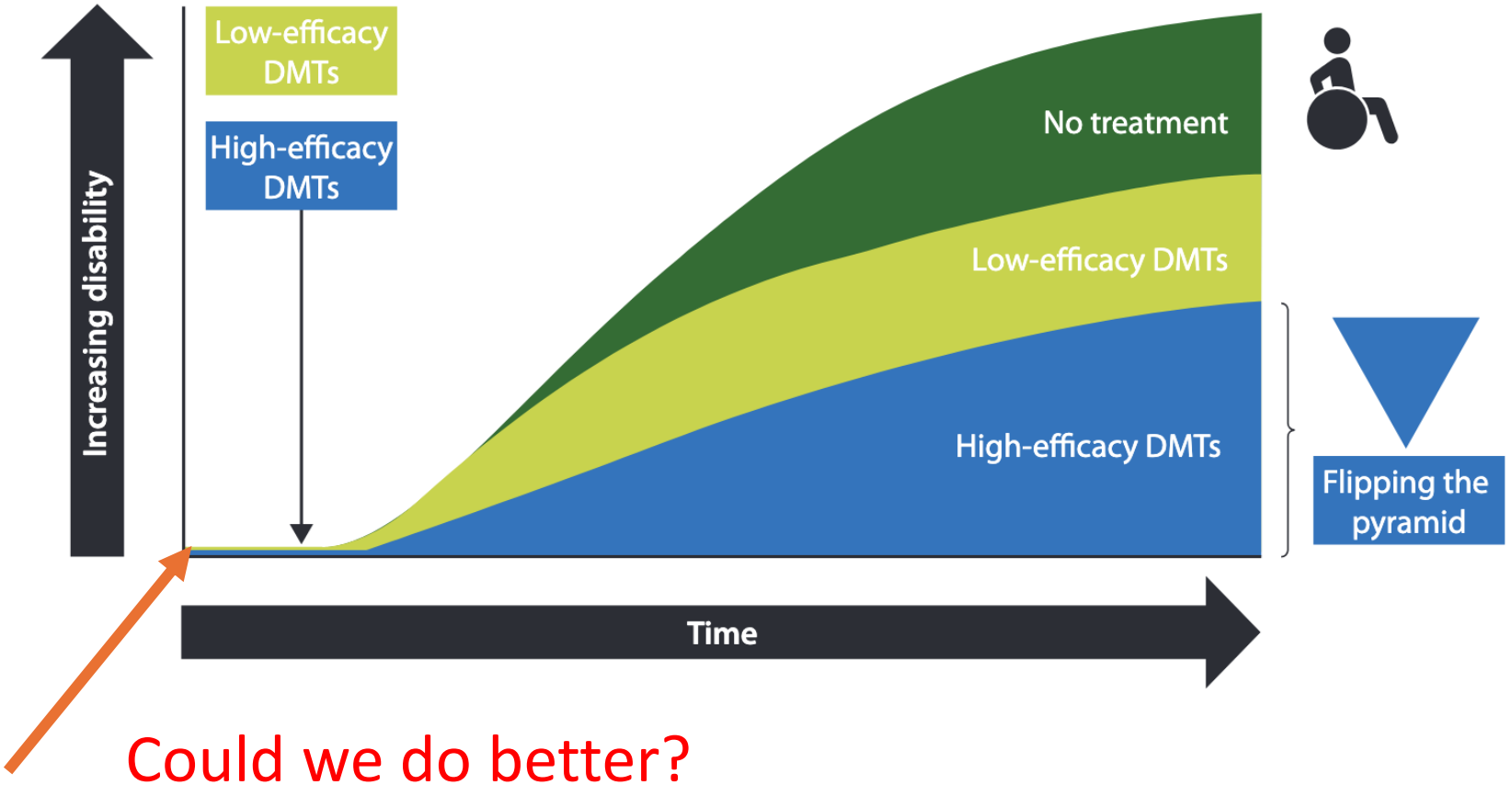
Contemporary concept



Could we do better?

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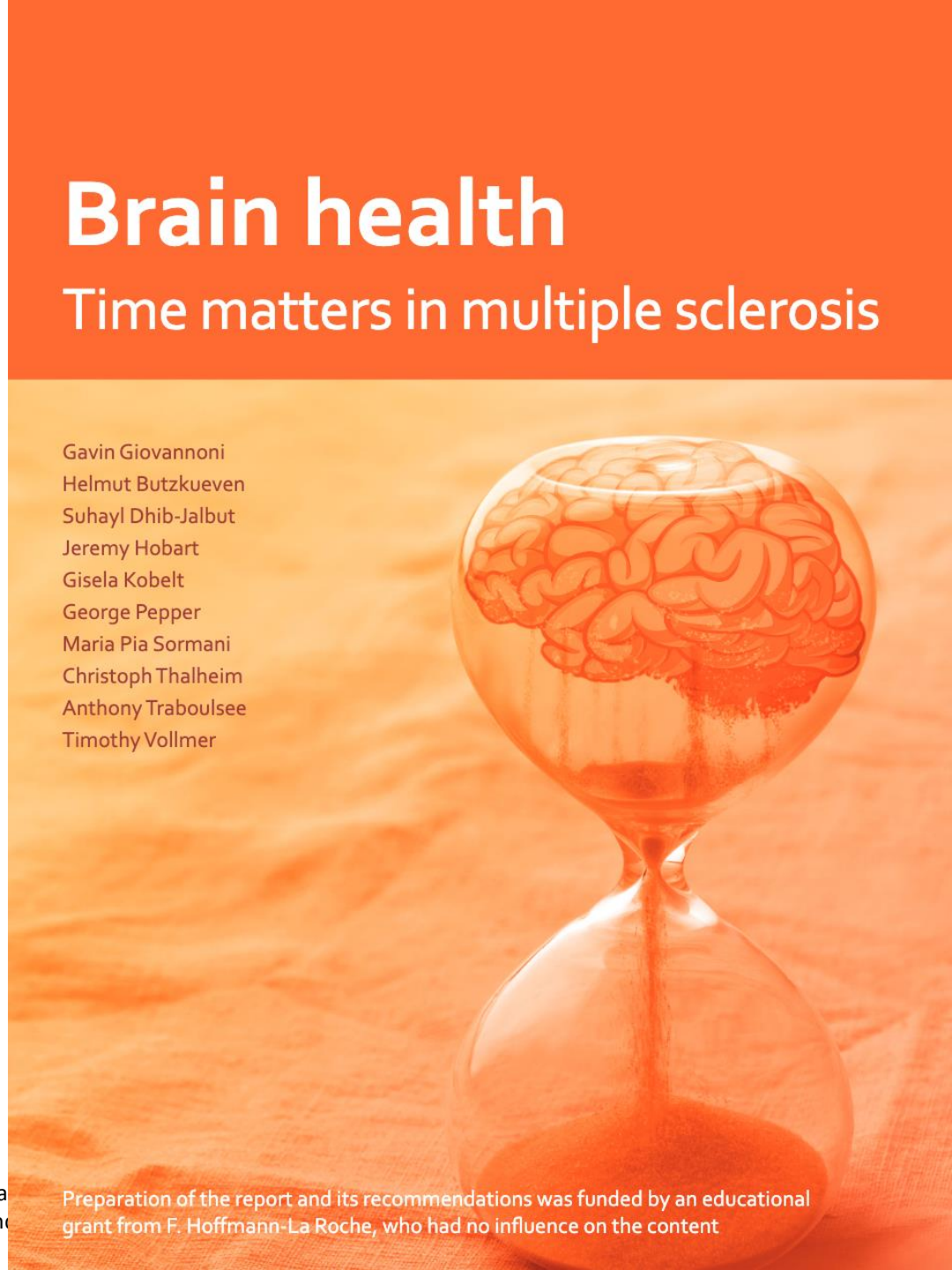
TASK FOR THE PATIENT

- 2015 launched at ECTRIMS



Live a brain-healthy lifestyle

Optimizing physical health to support treatment outcomes

MS Brain Health

OXFORD HEALTH POLICY FORUM

Brain health – time matters

Multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and related conditions

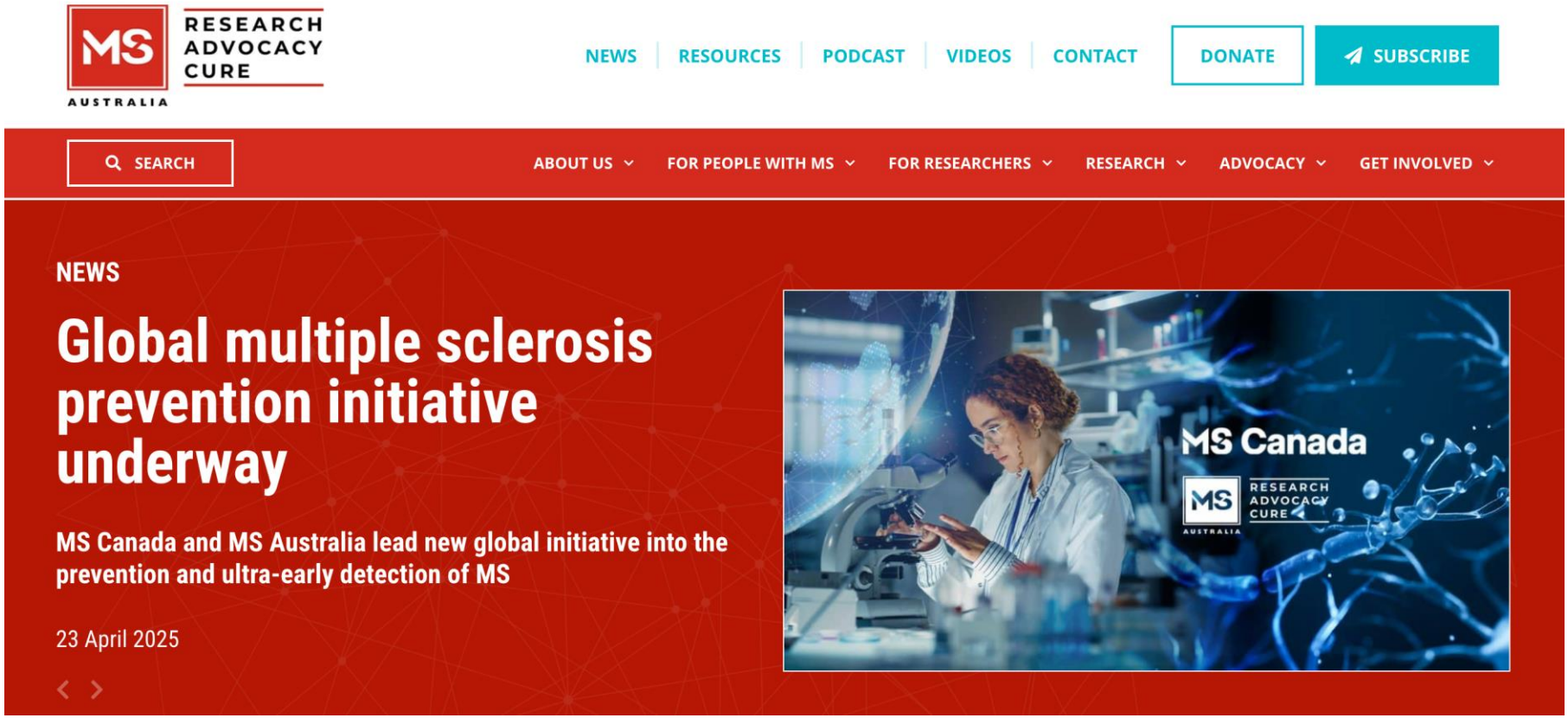
2024 Report

Helmut Butzkueven
Gavin Giovannoni
Sofia Arkelsten
Giancarlo Comi
Kathleen Costello
Michael Devlin
Jelena Drulovic
Emma Gray
Jodi Haartsen
Anne Helme
Jana Hlaváčová
Elisabeth Kasilingam
Yaou Liu
Thomas Mathew
Saúl Reyes
Jérôme de Sèze
Mitzi J Williams

MS prevention summary

- D vitamin supplementation
- Obesity prevention, healthy diet taking care of gut microbiota
- Smoking cessation
- Physical activity
- Cognitive training, psychotherapy
- Treatment of comorbidities

EMSP should join this initiative



- the future of MS care needs an active patient

Thanks for your attention

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