XXVI World Congress of Neurology (WCN 2023)

October 17th 2023

Teaching Course: Practical Considerations on the Treatment of MS and other Demyelinating dDseases

Progressive Multiple Sclerosis

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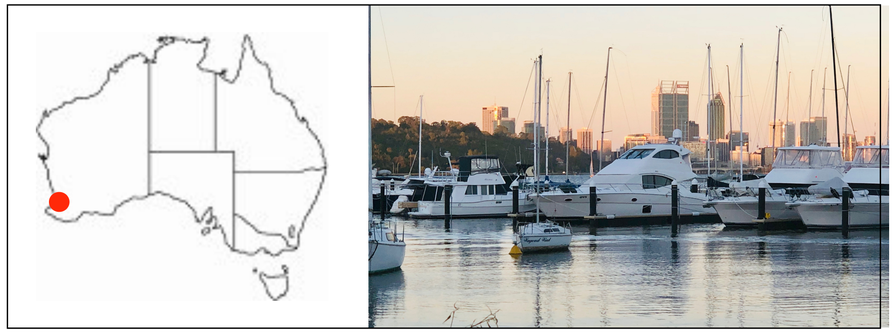

Disclosure:

Professor Carroll has been the recipient of travel assistance and honoraria for participation in industry sponsored meetings from, and has provided advice to, Bayer Schering Pharma, Biogen-Idec, Novartis, Genzyme, Sanofi-Aventis, CSL, Teva, Merck and Cellgene.

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Progressive Multiple Sclerosis

1. What is PMS?

2. What is “Progression”?

3. How to treat PMS?

Goals of teaching course:

To provide the attendee with an improved understanding of the recognition, mechanisms, measurement and treatment of Progressive MS

2017 McDonald criteria for diagnosis of multiple sclerosis in patients with a disease course characterised by progression from onset (primary progressive multiple sclerosis)

Primary progressive multiple sclerosis can be diagnosed in patients with:

- **1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse**

Plus two of the following criteria:

- One or more T2-hyperintense lesions* characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions* in the spinal cord
- Presence of CSF-specific oligoclonal bands

*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required.

Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

Alan J Thompson, Brenda L Banwell, Frederik Barkhof, William M Carroll, Timothy Coetzee, Giancarlo Comi, Jorge Correale, Franz Fazekas, Massimo Filippi, Mark S Freedman, Kazuo Fujihara, Steven L Galetta, Hans Peter Hartung, Ludwig Kappos, Fred D Lublin, Ruth Ann Marrie, Aaron E Miller, David H Miller, Xavier Montalban, Ellen M Mowry, Per Soelberg Sorensen, Mar Tintoré, Anthony L Traboulsee, Maria Trojano, Bernard M J Uitdehaag, Sandra Vukusic, Emmanuelle Waubant, Brian G Weinshenker, Stephen C Reingold, Jeffrey A Cohen

***Lancet Neurol* 2018; 17: 162–73**

Progression and worsening - a cause of confusion

Progression = a progressive phase of the disease during which disability accrues independent of relapses

Worsening = increasing disability due to residual effects of a relapse or during a progressive phase

Thompson AJ and Cicarelli O
NATURE REVIEWS | NEUROLOGY
https://doi.org/10.1038/s41582-020-00421-4

"driven by a continuum of diverse concurrent pathophysiological processes with contributions that vary across individuals and over time"

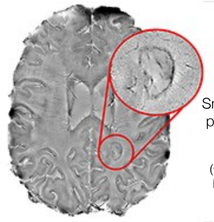
Kuhlman T et al
Lancet Neurol 2022
https://doi.org/10.1016/S1474-4422(22)00289-7

Multiple sclerosis progression: time for a new mechanism-driven framework

Causes of CNS injury in (P)MS

Focal inflammation

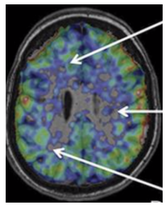
Perivenous plaque



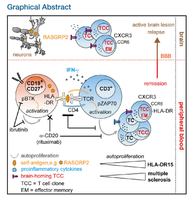
Smouldering plaque

(Credit: Reich lab, NIH/NINDS)

Diffuse inflammation



ug activation (PET)



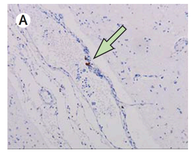
Autoproliferation.
Memory B-cells activate brain-homing auto reactive CD4⁺ T-cells

Cortical disease

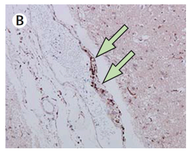
Cortical lesions

Meningeal Extra Lymphatic Follicles

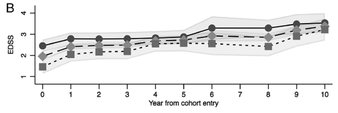
CD20⁺

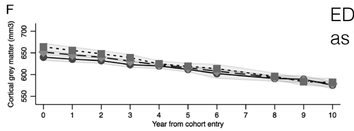


CD3⁺



Ageing and comorbidities



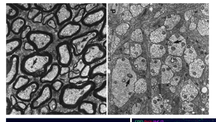


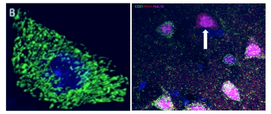
EDSS rises, and brain volume shrinks as **Telomeric age** increases

Telomere length T/S ratio 0.6
Telomere length T/S ratio 1
Telomere length T/S ratio 1.4

Secondary effects

Persistent demyelination
Mitochondrial mutations
Energy failure
(Length dependent) Axonal loss





Acta Neuropathologica (1998) 96: 139-143

3. How to treat PMS?

- **All DMTs approved for RMS are also approved for Progressive MS with activity (FDA)**
- **Ocrelizumab is approved for PPMS and SPMS as above Ofatumumab**
- **Siponimod specifically approved for SPMS and as above as are other S1P Receptor modulators**
- **Alemtuzumab**
- **Natalizumab**
- **Cladribine**
- **AHSCT**
- **Not specifically approved but in active use or with trial evidence of usefulness**

Rituximab

Alpha Lipoic acid

Ibudilast

Simvastatin

TK and BTK inhibitors

Treatment principles

Given the pathological features underlying MS disease processes and the risk from those recognised to predict later progression the following seem sensible:

1. **Use the most effective agents available at commencement of treatment**
2. **Where possible review efficacy of treatment against MRI parameters, clinical exam (and biomarkers)**
3. **When available add complementary agents that have plausible rationale**
4. **Disease activity is more important than (outdated) phenotypes**