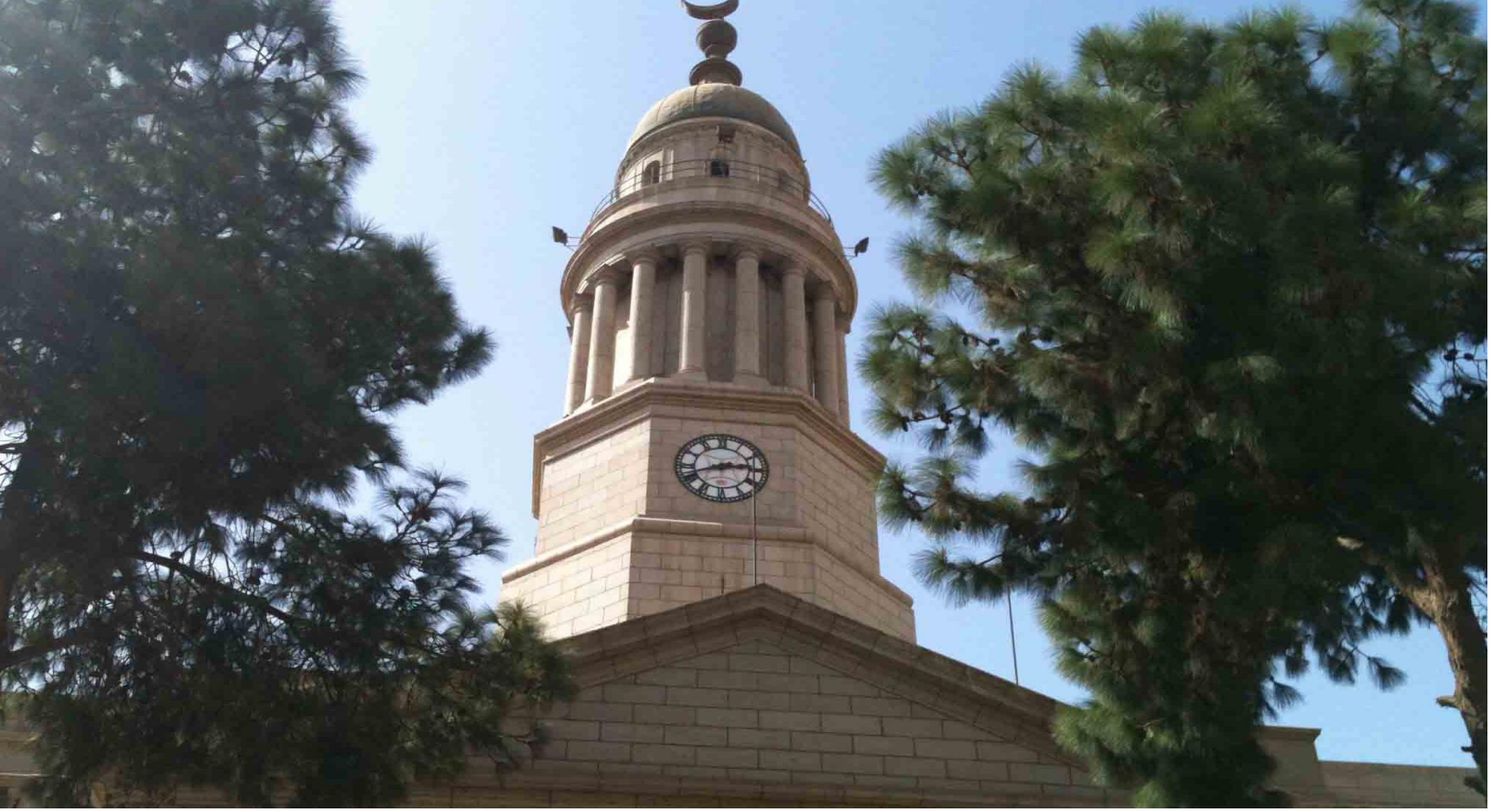
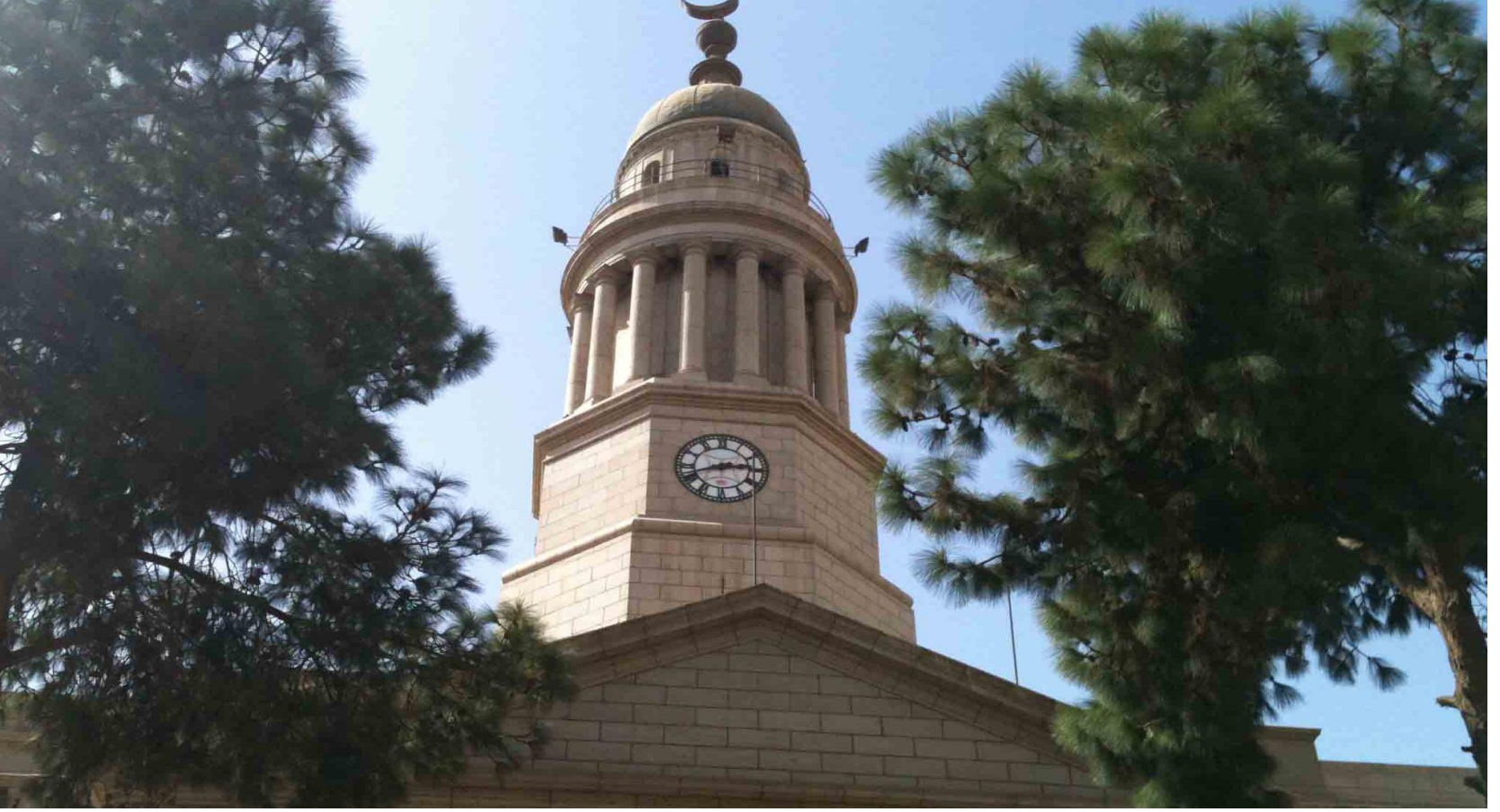


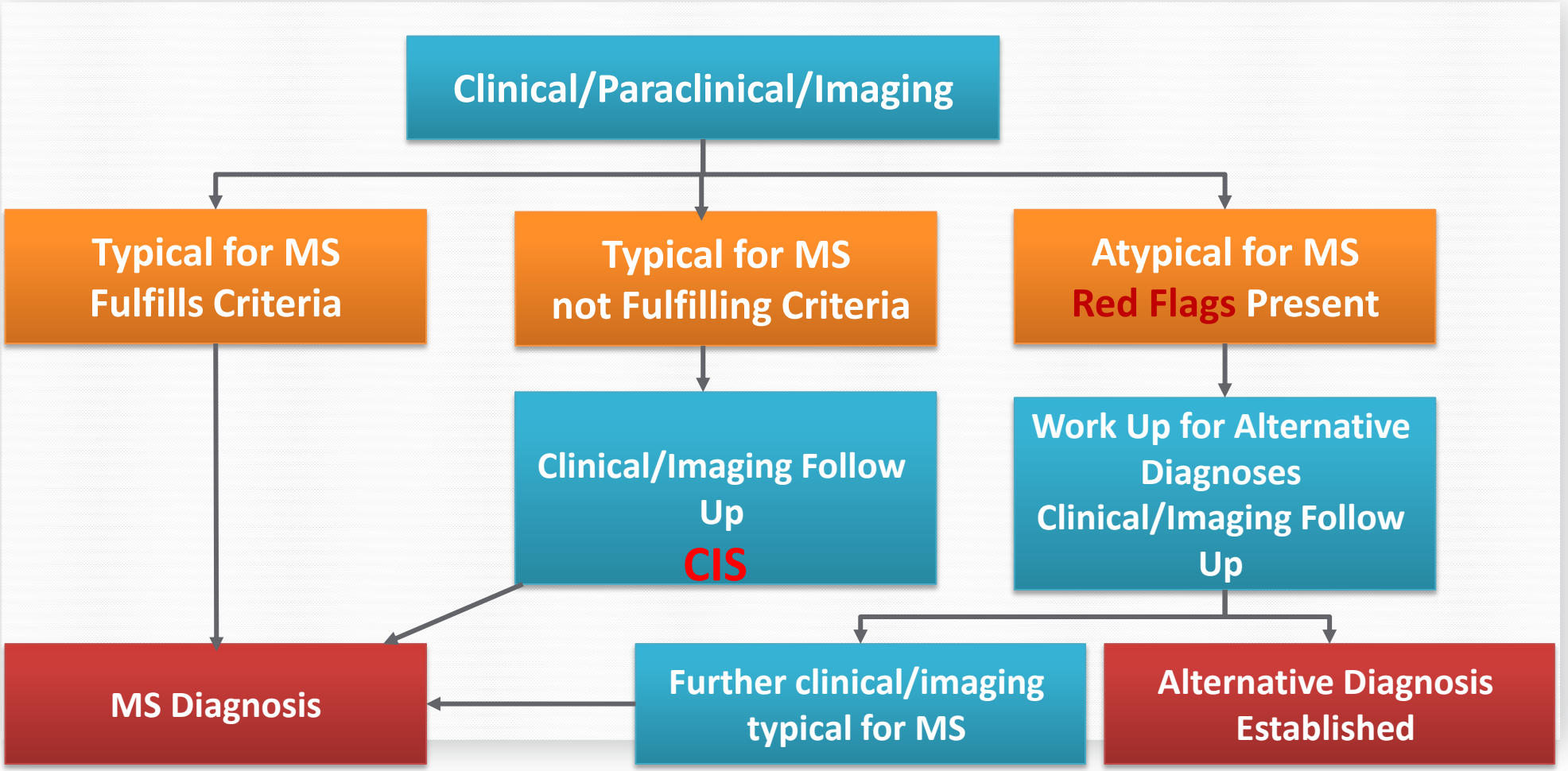
Clinically Isolated Syndromes



Amr Hasan, MD,FEBN

Associate Professor of Neurology - Cairo University

Mental map for diagnosis of MS



Clinically Isolated Syndromes

Definition

Clinical features

1- Optic neuritis
2- Spinal cord syndrome
3-Brain stem syndromes
4-Less common CIS

Risk factors for conversion to MS

1-Demographic, environmental and genetic factors
2-Abnormal MRI imaging
3- Biomarkers
4-OCT

Management

1- Acute treatment
2- Disease modifying therapy
3- Vitamin D supplementation

Definition

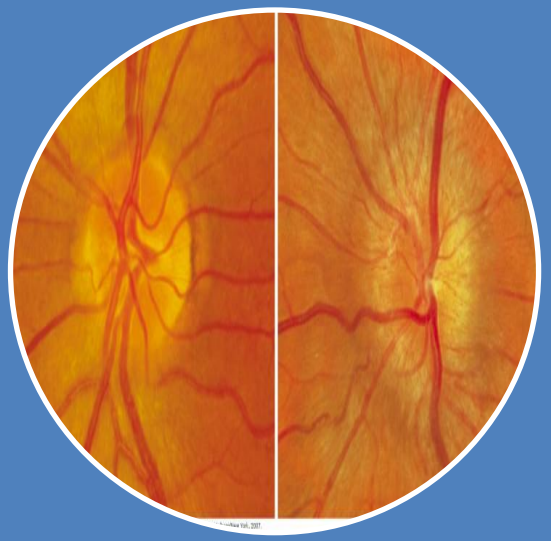
CIS definition

- A first neurologic symptom episode "ATTACK" of an acute inflammatory demyelinating event in the central nervous system lasting at least 24 hours in the absence of fever or infection ***(Polman et al, 2011).***
- **This definition also provides No DIS nor DIT by MRI Brain and Cervical Cord.**

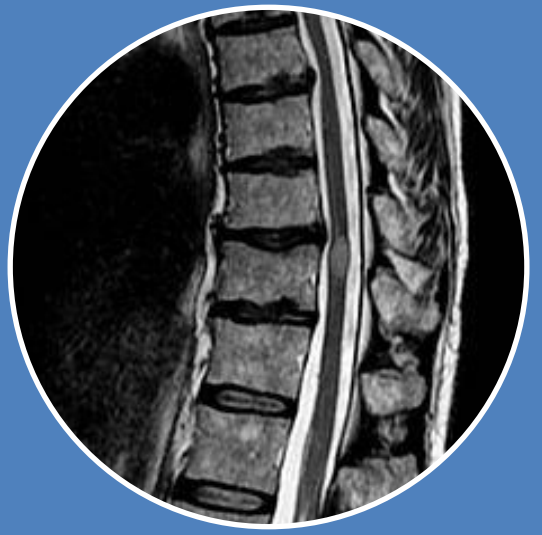
•**Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS**. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011 Feb; 69(2):292-302.

Clinical features

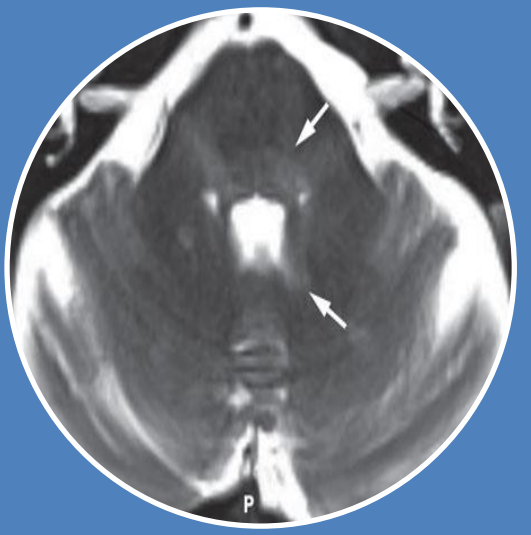
Clinically Isolated Syndrome (CIS)



ON



TM



BS

Clinically Isolated Syndrome (CIS) : less common

- Hemiparesis or homonymous hemianopia that may be mistaken for an acute stroke.
- Cognitive dysfunction
- Seizures, attributable to a demyelinating lesion in the cerebral cortex.

Clinically Isolated Syndrome (CIS)

ONSET:

Could be "subacute" ***(Miller et al. 2012)***, after which patients may progress to MS without showing evidence of relapses

TYPES:

- Monofocal episode: single neurologic sign or symptom.
- Multifocal episode: more than one sign or symptom.

• Miller DH, Chard DT, Ciccarelli O. clinically isolated syndromes. Lancet Neurol. 2012 Feb;11(2):157-69.

Optic Neuritis : Common Symptoms

- Monocular
  (Central Vision loss)
- Pain
  (eye movement)
- Altered colour vision
- Uhthoff’s symptom
- Flashes

Optic Neuritis : Common Symptoms

Optic neuritis in multiple sclerosis

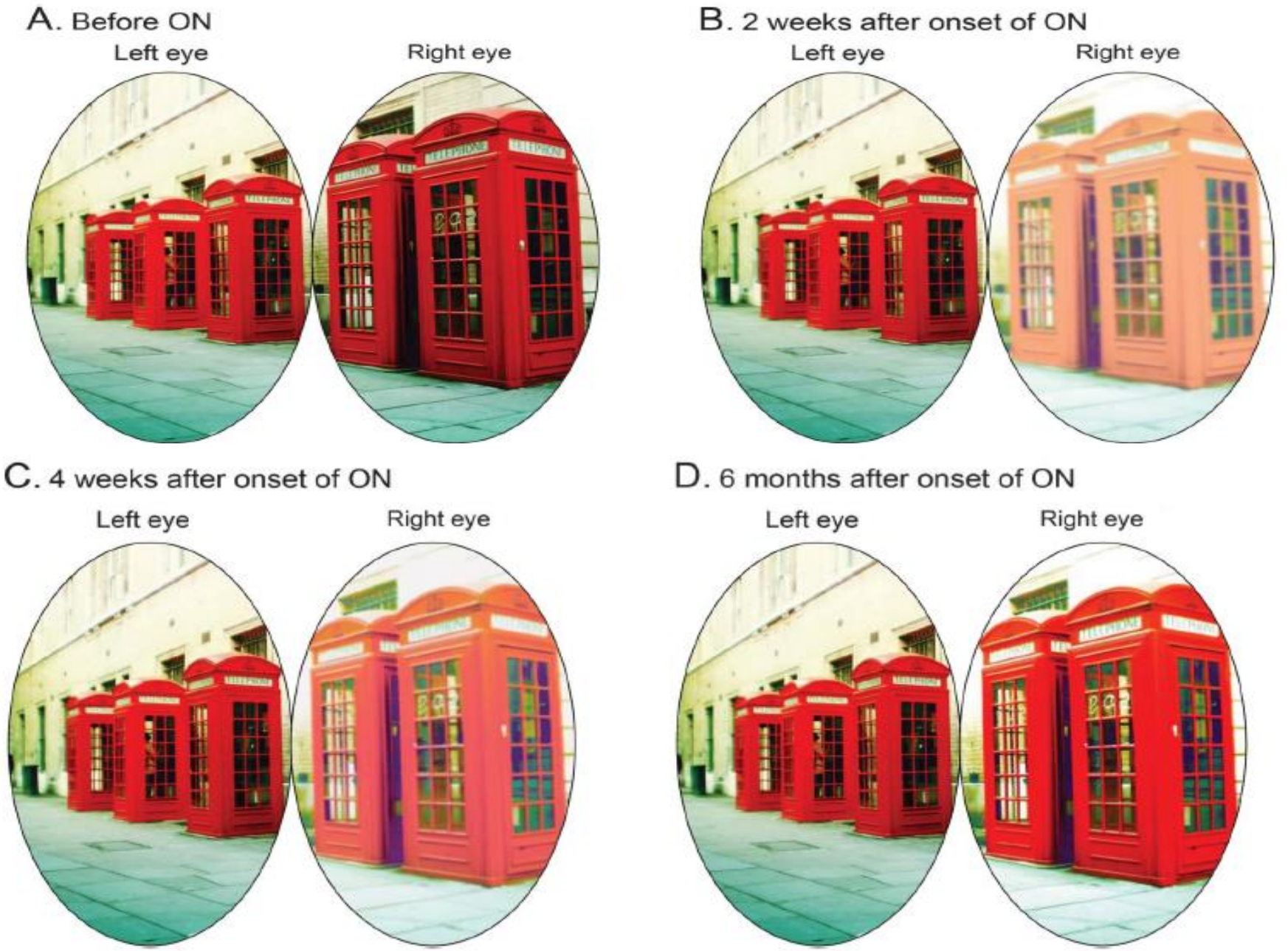
Looking from a patient's eyes

Paolo Preziosa, MD, Giancarlo Comi, MD and Massimo Filippi, MD

+ SHOW AFFILIATIONS | + SHOW FULL DISCLOSURES
Correspondence to Prof. Filippi: filippi.massimo@hsr.it

doi: http://dx.doi.org/10.1212/WNL.0000000000002869
Neurology July 19, 2016 vol. 87 no. 3 338-339

Figure A photograph taken in London by a patient with multiple sclerosis



An Egyptian Patient

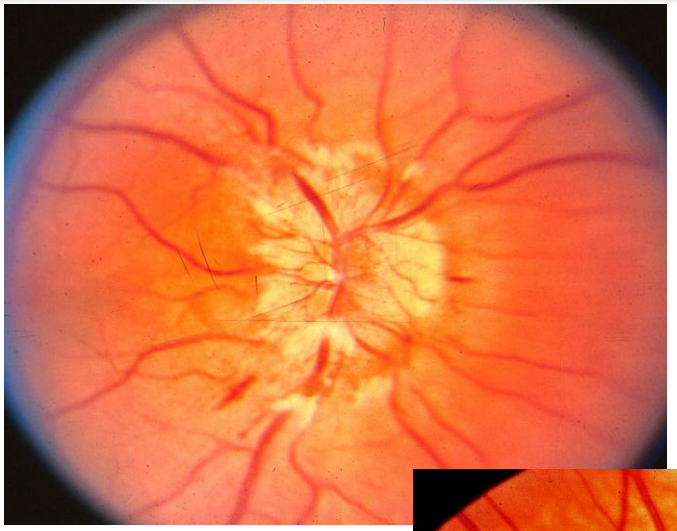
Optic Neuritis: Physical signs

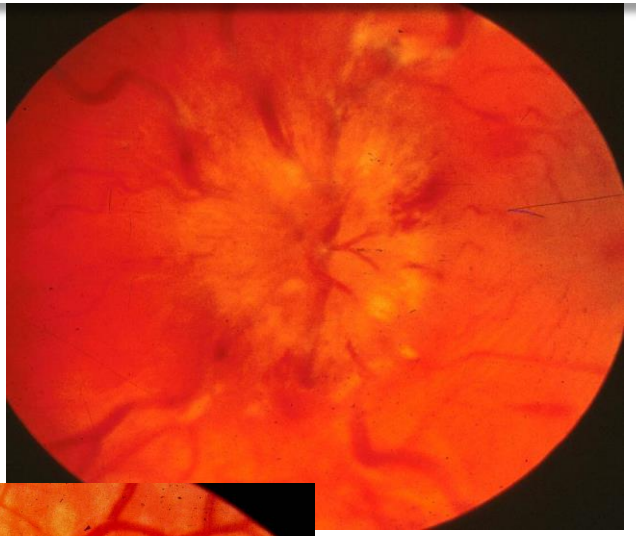
- Decreased visual acuity
- VF defect

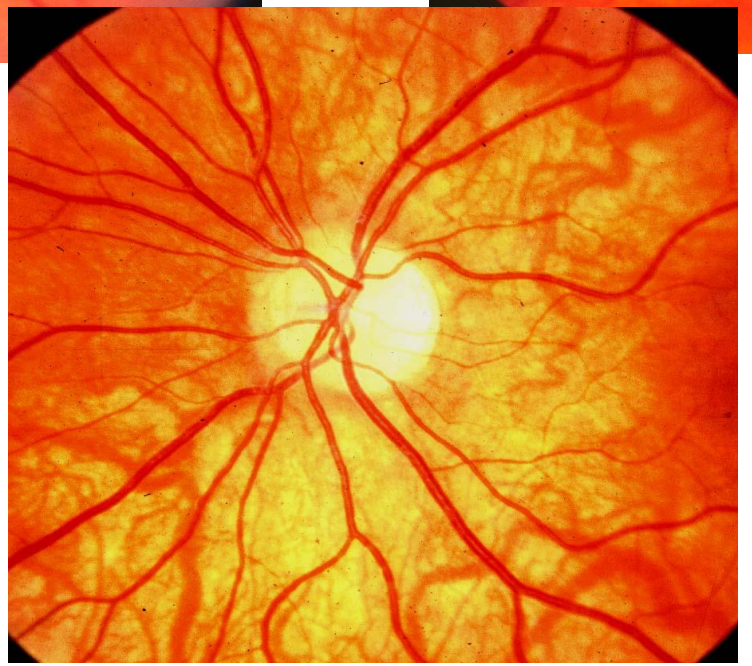
(Central/Altitudinal 29%)

- Dyschromatopsia
- Afferent Pupil Defect (RAPD)
- Optic disc swelling 35%
- Abnormal Contrast Sensitivity
- Abnormal VEP
- Altered Flicker Perception
- Altered depth perception
- Optic disc pallor

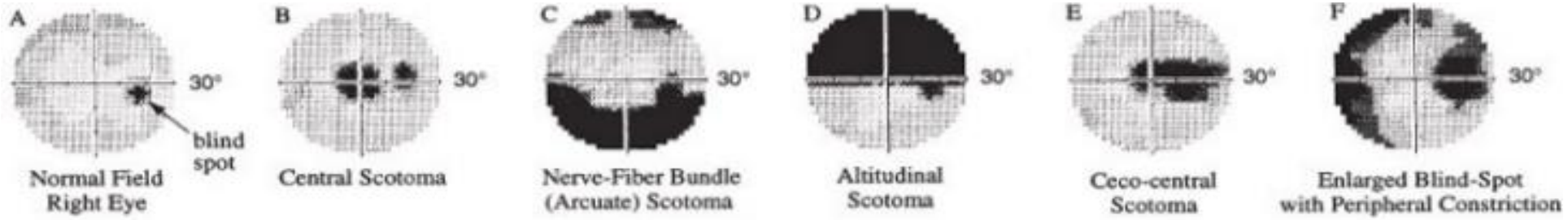
Optic Neuritis: Optic Disc







Optic Neuritis: VF defect



Macula damage

Glaucoma
Optic neuritis

(destroy axon of optic disc)

Turkish scimitar

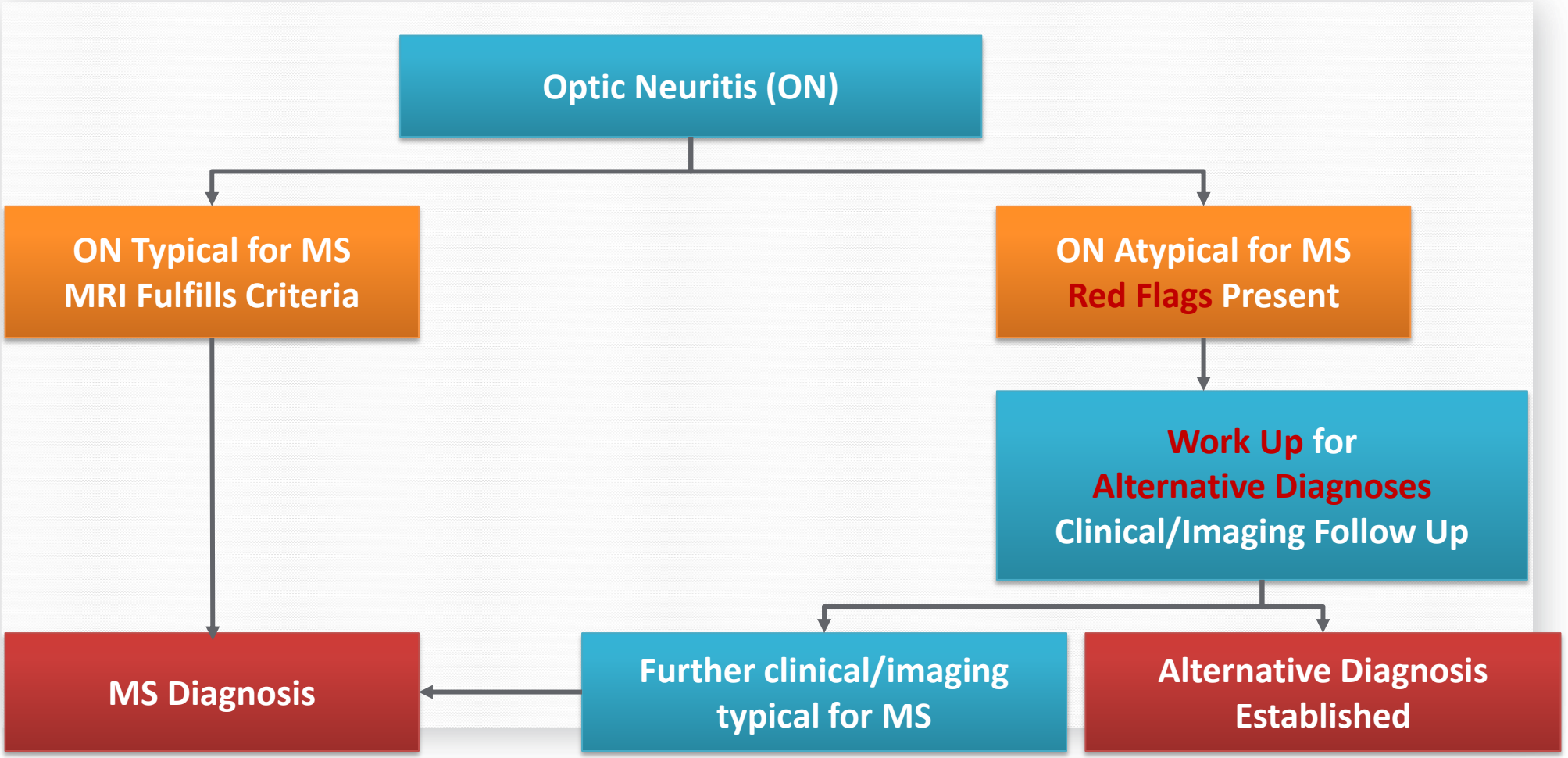
Ischemic optic neuropathy

Horizontal meridian

Optic neuritis
Toxic metabolic nutrition

macula

Mental map for diagnosis of ON



Optic Neuritis: Typical Vs Atypical

Typical	Atypical
• Acute or subacute attack	• Progressive disease
• Mostly young adults (age 20-55 y)	• Age group < 12 and > 50 y
• Unilateral visual acuity loss	• Bilateral visual loss
• Improvement with/without treatment	• No spontaneous visual improvement
• Continued improvement after corticosteroid withdrawn	• Deterioration after corticosteroid are discontinued
• Mild pain that worsens with eye movement	• Following loss of vision, painless to severe pain
• The optic disc appears normal or mildly swoll	• Severe swelling and hemorrhage in optic disc
• Variable visual field defects may occur	• Variable signs and symptoms, depending on etiology
• Altered perception of motion (the pulfrich phenomenon)	
• Vision blurs when body temperature rises (Uhthoff's phenomenon)	
• Bright, fleeting flashes of light (phosphenes)	

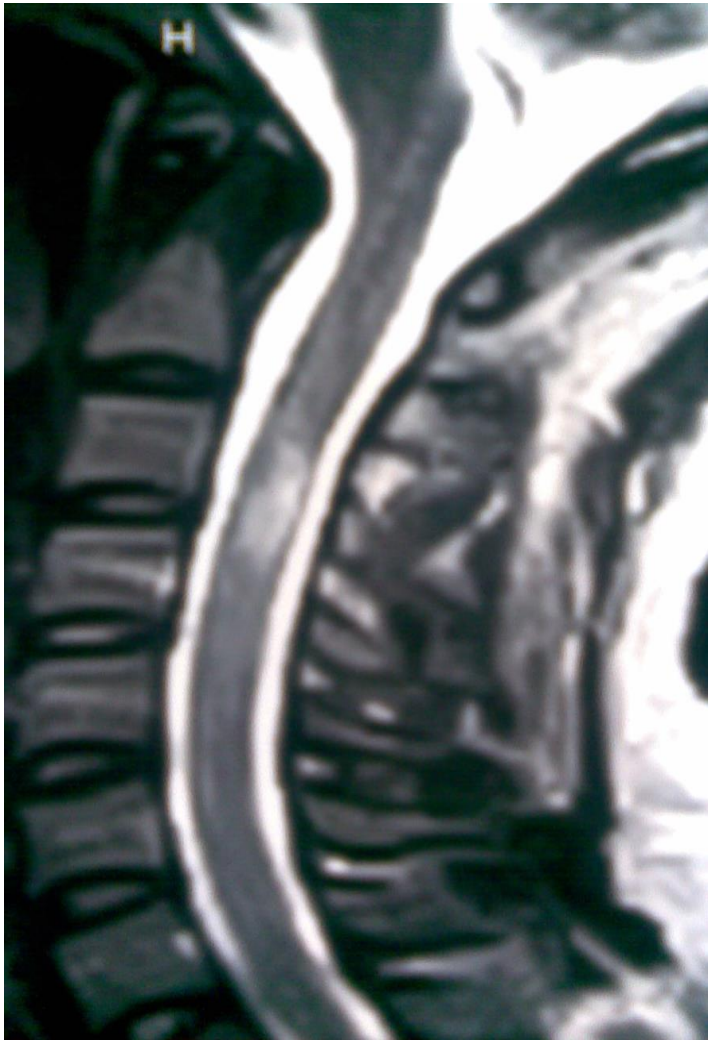
Optic Neuritis: D.D.

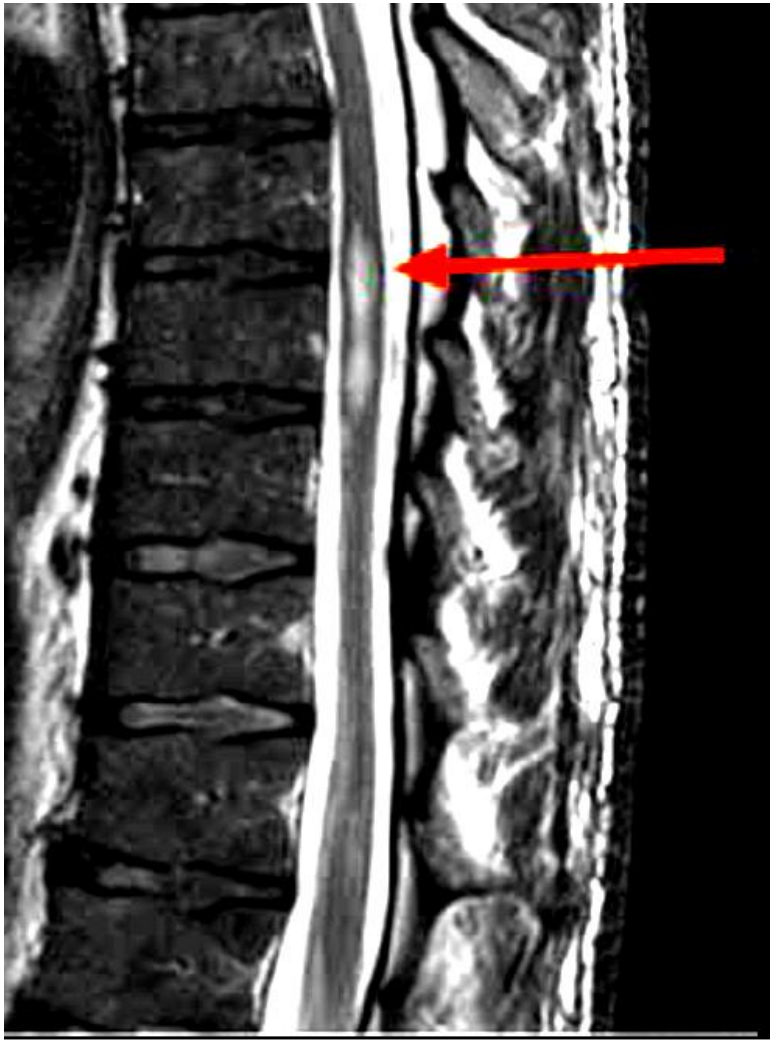
- AION (Ischemic Optic Neuropathy)
- Vasculitic Disorders (i.e. SLE)
- Hereditary (i.e. Leber's)
- Toxic/Nutritional (ETOH)
- Infectious (i.e.Bartonella, Lyme)
- Inflammatory (i.e. Sarcoid)
- Neoplastic/Paraneoplastic (i.e. lymphoma)
- Compressive (i.e.Tumours, Grave's orbitopathy)
- Multiple Evanescent White Dot Syndrome [MEWDS]
- Acute Idiopathic Blind Spot Enlargement Syndrome [AIBSE]).

Optic Neuritis: D.D.

- NMO
- CRION
- ADEM
- anti-Myelin oligodendrocyte glycoprotein–associated (MOG) optic neuritis

TM





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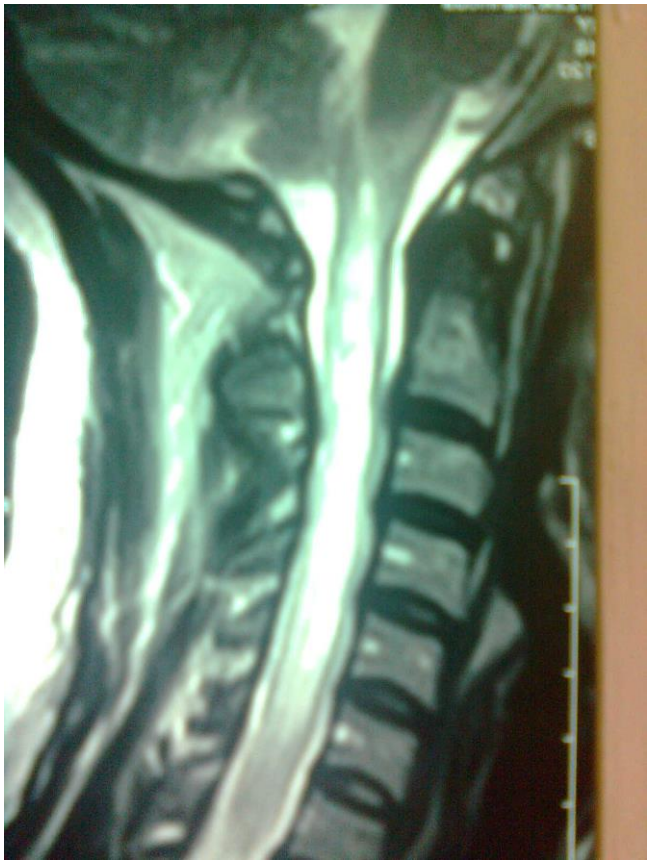
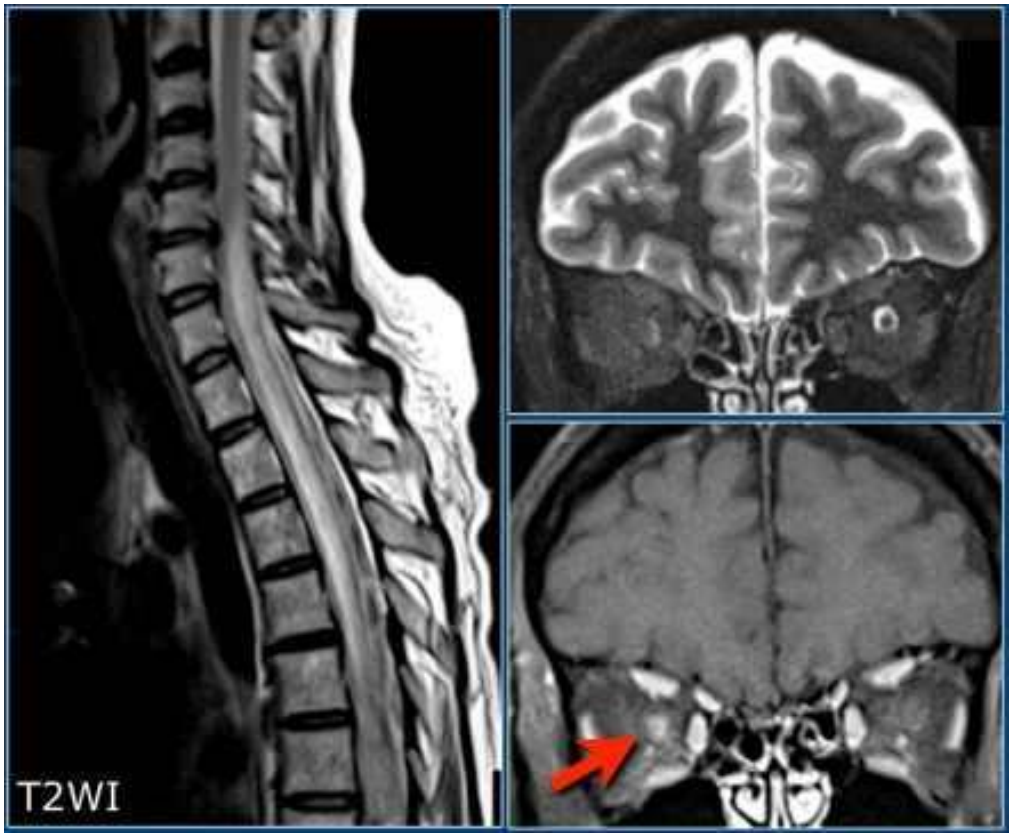


NMO



Isolated Spinal Cord Syndrome

Typical for MS

- Evolution over hours to days
- Partial myelitis
- Purely sensory
- Deafferented upper limb
- Lhermitte's sign
- Partial Brown-Sequard
- Spontaneous remission

Brain and spinal cord MRI

MRI clearly indicates a non-MS diagnosis e.g. spinal cord compression

Normal

Abnormal
Lesions consistent with demyelination

Low risk for MS (20%)

High risk for MS (60-90%)
Review McDonald criteria

Atypical for MS

- Hyperacute onset or insidiously progressive
- Complete transverse myelitis
- Sharp sensory level
- Radicular pain
- Areflexia
- Failure to remit

Consider other diagnosis

- **Compression** e.g. intervertebral disc, tumor
- **Ischemia/infarction**
- **Other inflammatory** e.g. neuromyelitis optica, sarcoid, lupus, Sjogren's
- **Infection** e.g. syphilis, lyme, viral, tuberculosis
- **Toxic/nutritional/metabolic.** E.g B12 deficiency, nitrous oxide toxicity, copper deficiency
- **Arteriovenous malformation**
- **Non-cord "mimics"** e.g. Guillain-Barre syndrome, Myasthenia gravis

MRI, CSF neurophysiological, serologic and other studies as appropriate

Isolated Brain Stem Syndrome

Typical for MS

- Internuclear opthalmoplegia
- 6th nerve palsy,
- multifocal signs e.g. facial sensory loss and vertigo or hearing loss

Atypical for MS

- Hyperacute onset
- vascular territory signs e.g. lateral medullary syndrome
- age>50
- isolated trigeminal neuralgia/ fluctuating ocular/bulbar weakness
- non-remitting, fever, meningism

Brain and spinal cord MRI

MRI clearly indicates a non-MS diagnosis e.g. Hge

Normal

Abnormal
Lesions consistent with demyelination

Low risk for MS (20%)

High risk for MS (60-90%)
Review McDonald criteria

Consider other diagnosis

- **Ischemic/hemorrhagic** (cavernous angioma)
- **Infiltrative**
- **Inflammatory** (Sarcoid, lupus)
- **Infection** (Syphilis, listeria, lyme, viral)
- **Toxic**
- **Nutritional**
- **Central pontine myelinolysis**
- **Neuromuscular** (myasthenia gravis)

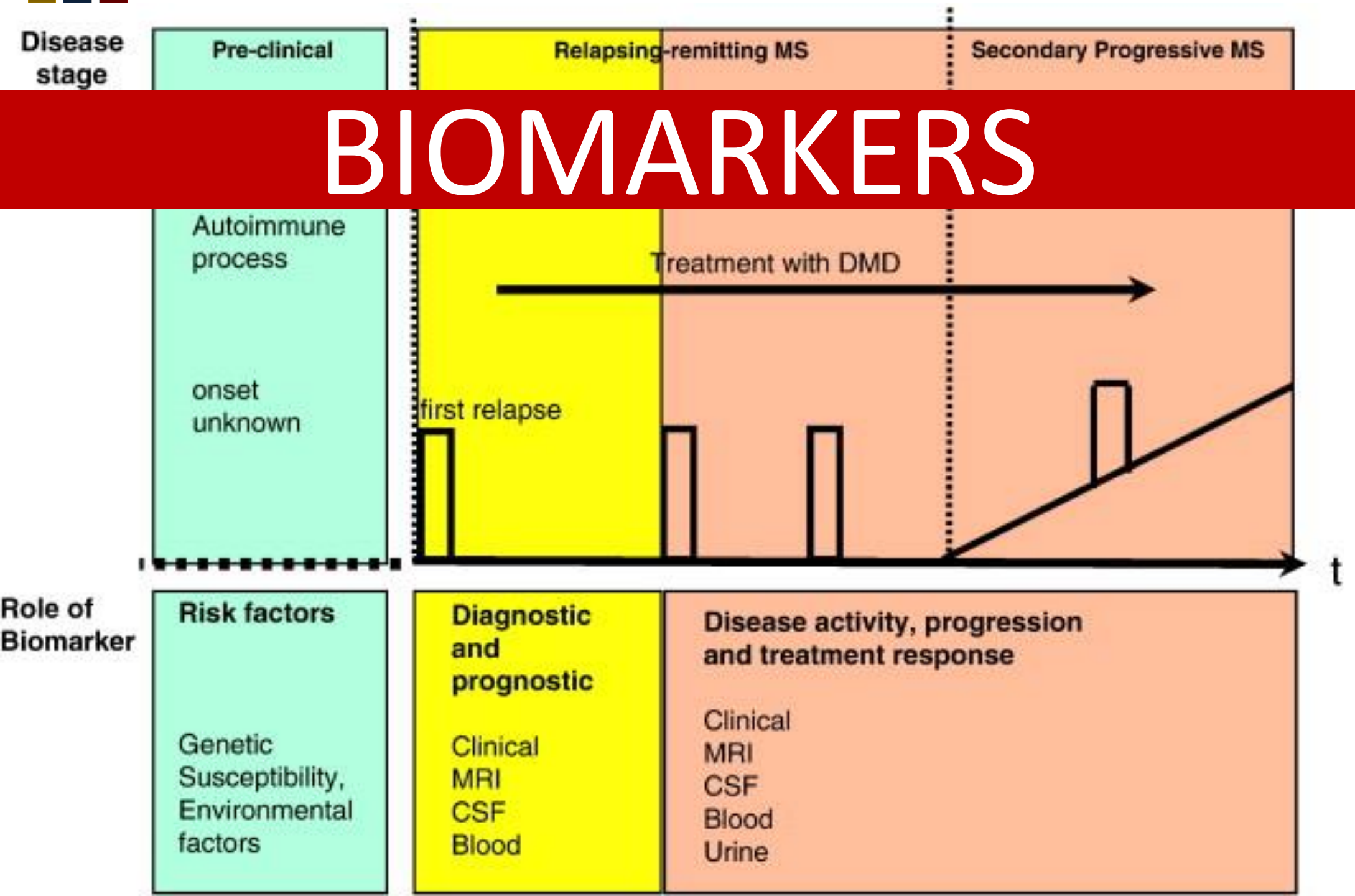
MRI, CSF, OCT neurophysiological, serologic and other studies as appropriate

Risk factors for conversion to MS

Demographic and environmental risk factors

- Younger age of onset.
- Cognitive impairment.
- Vitamin D deficiency.
- Smoking.
- Increased EBV encoded nuclear antigen.

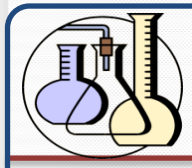
BIOMARKERS


Disease stage
Pre-clinical
Relapsing-remitting MS
Secondary Progressive MS
Autoimmune process
onset unknown
Treatment with DMD
first relapse
t
Role of Biomarker
Risk factors
Genetic Susceptibility, Environmental factors
Diagnostic and prognostic
Clinical
MRI
CSF
Blood
Disease activity, progression and treatment response
Clinical
MRI
CSF
Blood
Urine

BIOMARKERS

GENETIC/IMMUNOGENETIC:

- Biomarkers specified via genomics and immunogenetic techniques.



LABORATORY:

- All other biomarkers that can be measured in body fluids.

IMAGING:

- Biomarkers provided by imaging techniques.

BIOMARKERS

A. GENETIC AND IMMUNOGENETIC BIOMARKERS

HLA-DRB1*1501

TOB-1

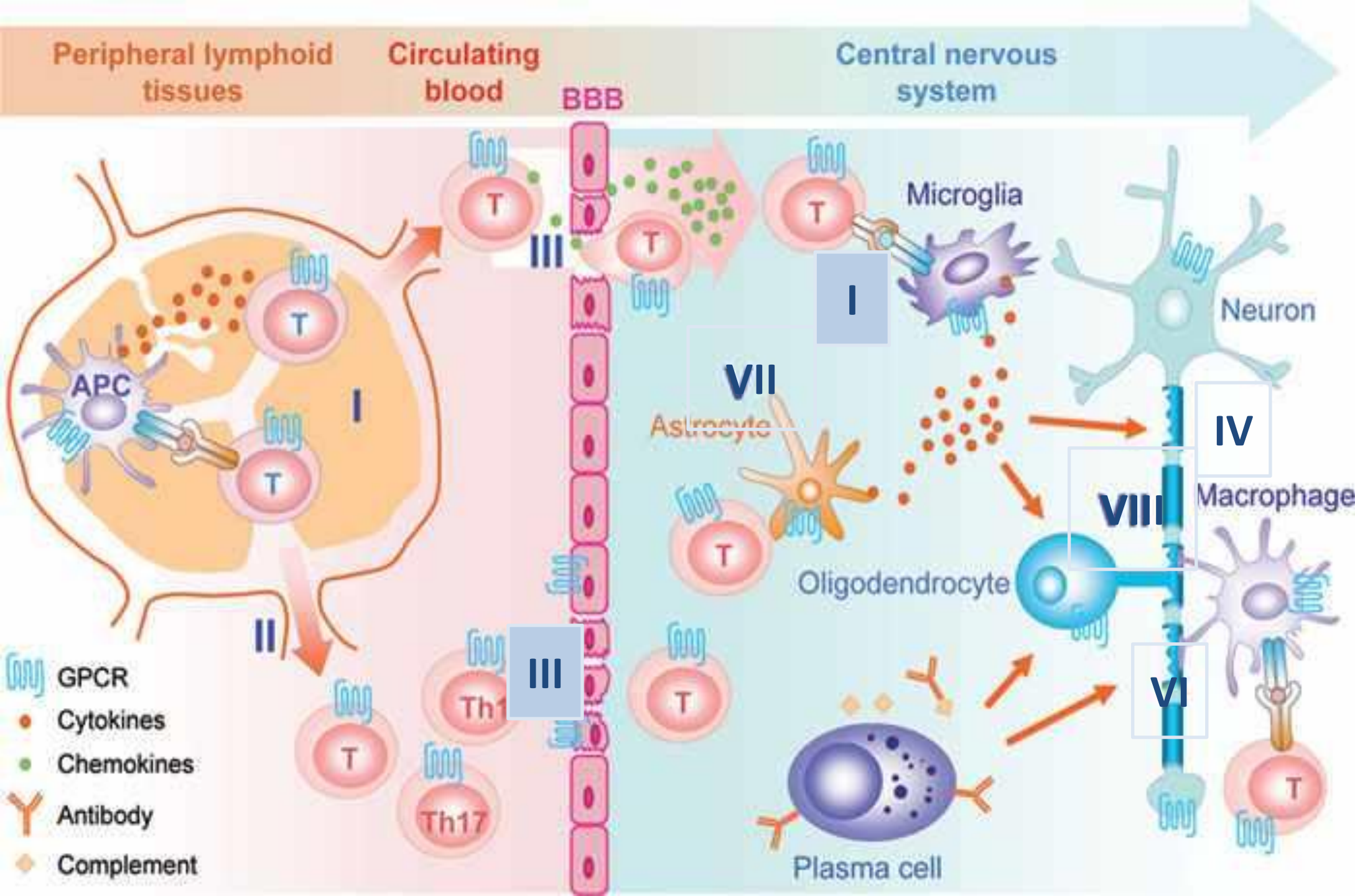
Apo lipoprotein-E

BIOMARKERS

B. LABORATORY BIOMARKERS

B. Laboratory Biomarkers

I. Biomarkers of Immunological Activation
II. Biomarkers of Neuroprotection
III. Biomarkers of BBB disruption
IV. Biomarkers of demyelination
V. Biomarkers of Oxidative Stress
VI. Biomarkers of Axonal Damage
VII. Biomarkers of Glial Activation Dysfunction
VIII. Biomarkers of Remyelination Repair
IX. Biomarkers of Therapeutic Response
X. Prognostic Biomarkers
XI. Emering biomarkers


Peripheral lymphoid tissues
Circulating blood
BBB
Central nervous system
APC
T
I
II
III
Th1
Th17
Microglia
Neuron
VII
Astrocyte
IV
VIII
Macrophage
Oligodendrocyte
VI
Plasma cell
GPCR
Cytokines
Chemokines
Antibody
Complement

BIOMARKERS

Brain. 2015 Apr;138(Pt 4):918-31. doi: 10.1093/brain/awv017. Epub 2015 Feb 13.

Chitinase 3-like 1: prognostic biomarker in clinically isolated syndromes.

Cantó E[1], Tintoré M[1], Villar LM[2], Costa C[1], Nurtdinov R[1], Álvarez-Cermeño JC[2], Arrambide G[1], Reverter F[3], Deisenhammer F[4], Hegen H[4], Khademi M[5], Olsson T[5], Tumani H[6], Rodríguez-Martín E[2], Piehl F[5], Bartos A[7], Zimova D[7], Kotoucova J[7], Kuhle J[8], Kappos L[8], García-Merino JA[9], Sánchez AJ[9], Saiz A[10], Blanco Y[10], Hintzen R[11], Jafari N[11], Brassat D[12], Lauda F[6], Roesler R[6], Rejdak K[13], Papuc E[14], de Andrés C[15], Rauch S[16], Khalil M[17], Enzinger C[17], Galimberti D[18], Scarpini E[18], Teunissen C[19], Sánchez A[20], Rovira A[21], Montalban X[1], Comabella M[22].

development of disability (hazard ratio = 3.8; P = 2.5 × 10(-8)). High CHI3L1 levels were associated with shorter time to multiple sclerosis (P = 3.2 × 10(-9) using Poser criteria; P = 5.6 × 10(-11) for McDonald criteria) and more rapid development of disability (P = 1.8 × 10(-10)). These findings validate cerebrospinal fluid CHI3L1 as a biomarker associated with the conversion to multiple sclerosis and development of disability and reinforce the prognostic role of CHI3L1 in patients with clinically isolated syndrome. We propose that determining cerebrospinal fluid chitinase 3-like 1 levels at the time of a clinically isolated syndrome event will help identify those patients with worse disease prognosis.

BIOMARKERS

C. IMAGING BIOMARKERS

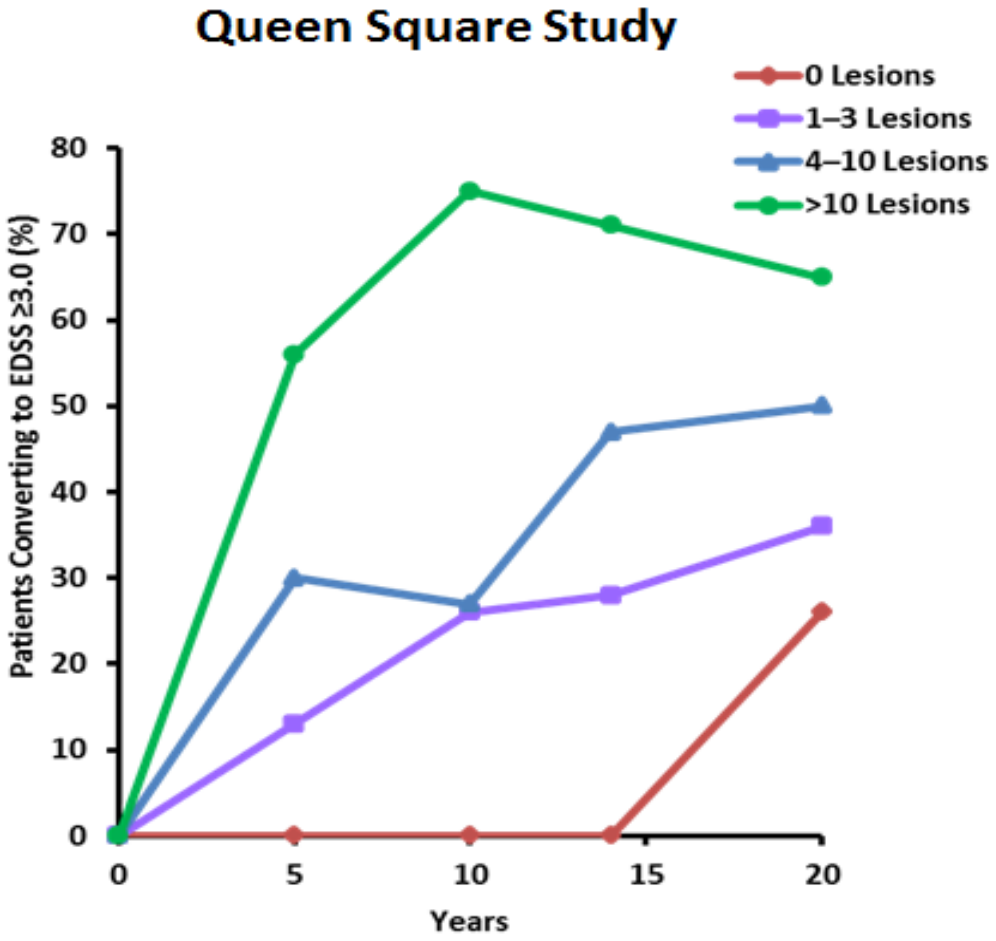
BIOMARKERS

CLINICAL

OCB

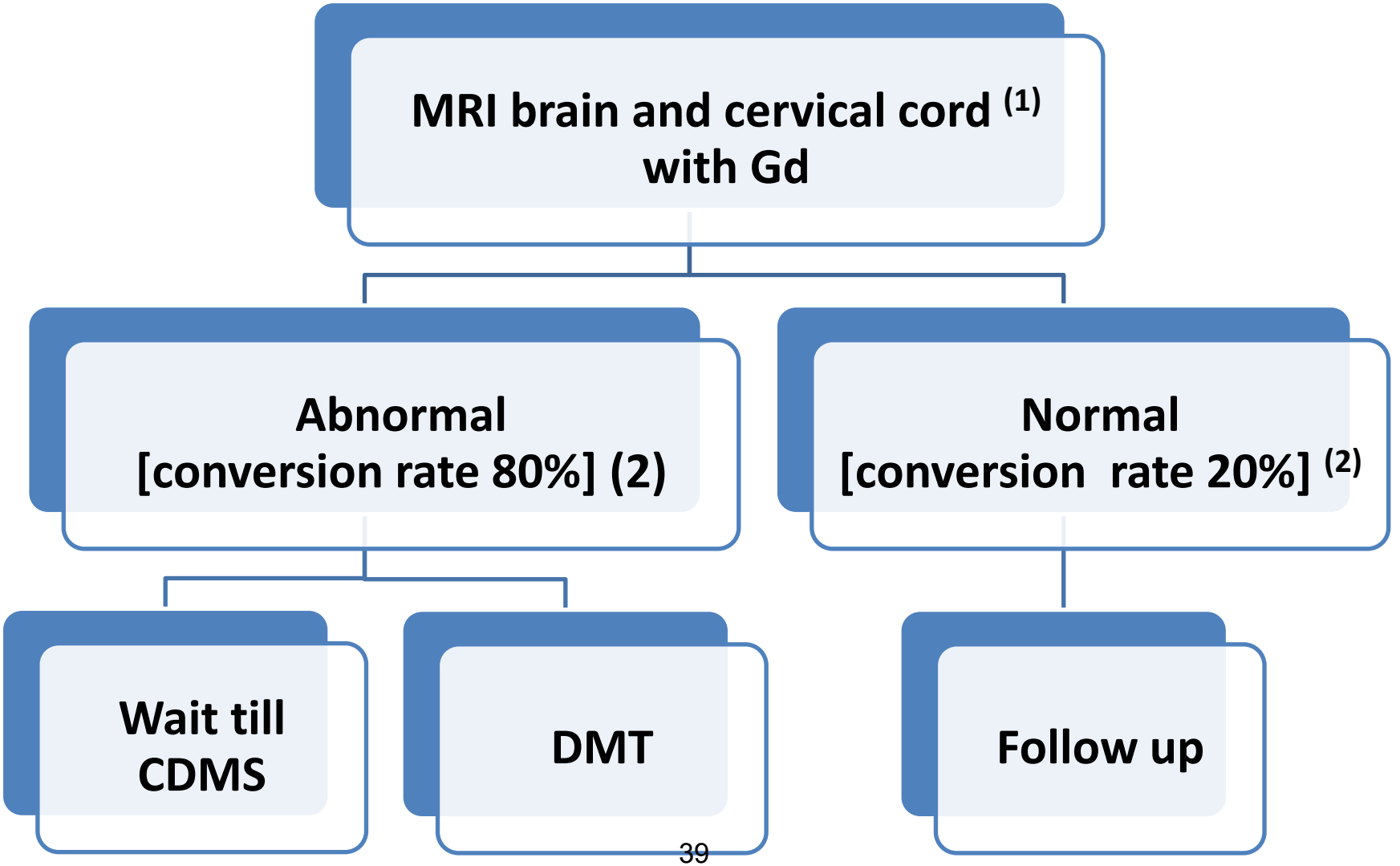
MRI

Baseline number of brain lesions predicts progression to EDSS Score ≥3.0



The data presented for years 5, 10, 14, and 20 were obtained from different publications based on the same longitudinal study.
The exact relationship between MRI findings and the clinical status of the patient is unknown.
Fisniku LK et al. *Brain*. 2008;131:808-817; Morrissey SP et al. *Brain*. 1993;116:135-146; O'Riordan JI et al. *Brain*. 1998;121:495-503; Brex PA et al. *N Engl J Med*. 2002;346:158-164.

Conversion of CIS to CDMS



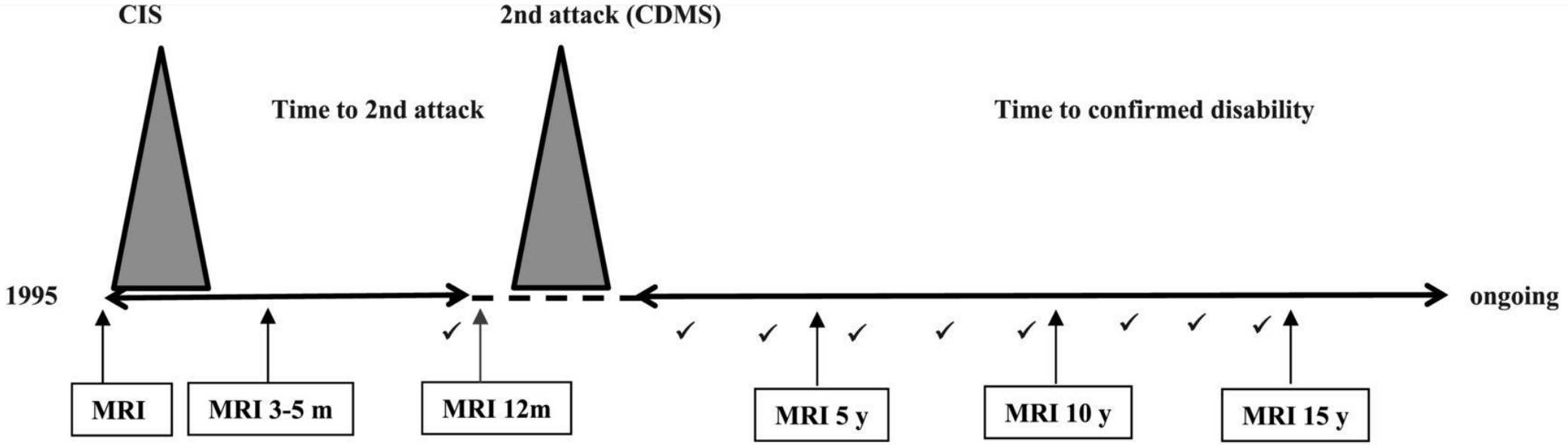
Conversion of CIS to CDMS

Patients who present with clinically isolated syndrome (CIS) should be managed based on their risk of progression to MS:

- In the Optic Neuritis Trial, risk at 10 years was:
  - 56% for patients with ≥1 lesion
  - 22% for patients with no lesions
- In patients with CIS and no lesions, risk of MS at 14 years was:
  - 19% for clinically definite (CD) MS

Brex et al. *N Engl J Med*. 2002;346:158-164.
Optic Neuritis Study Group. *Arch Ophthalmol*. 2003;121:944-949.

Conversion of CIS to CDMS



Baseline variables:
1. Demographic
2. Clinic and biological
3. MRI

Follow-up variables:
1. Clinical assesment: EDSS and relapses
2. MRI at 12 months and every 5 years

Mar Tintore et al. Brain 2015;138:1863-1874

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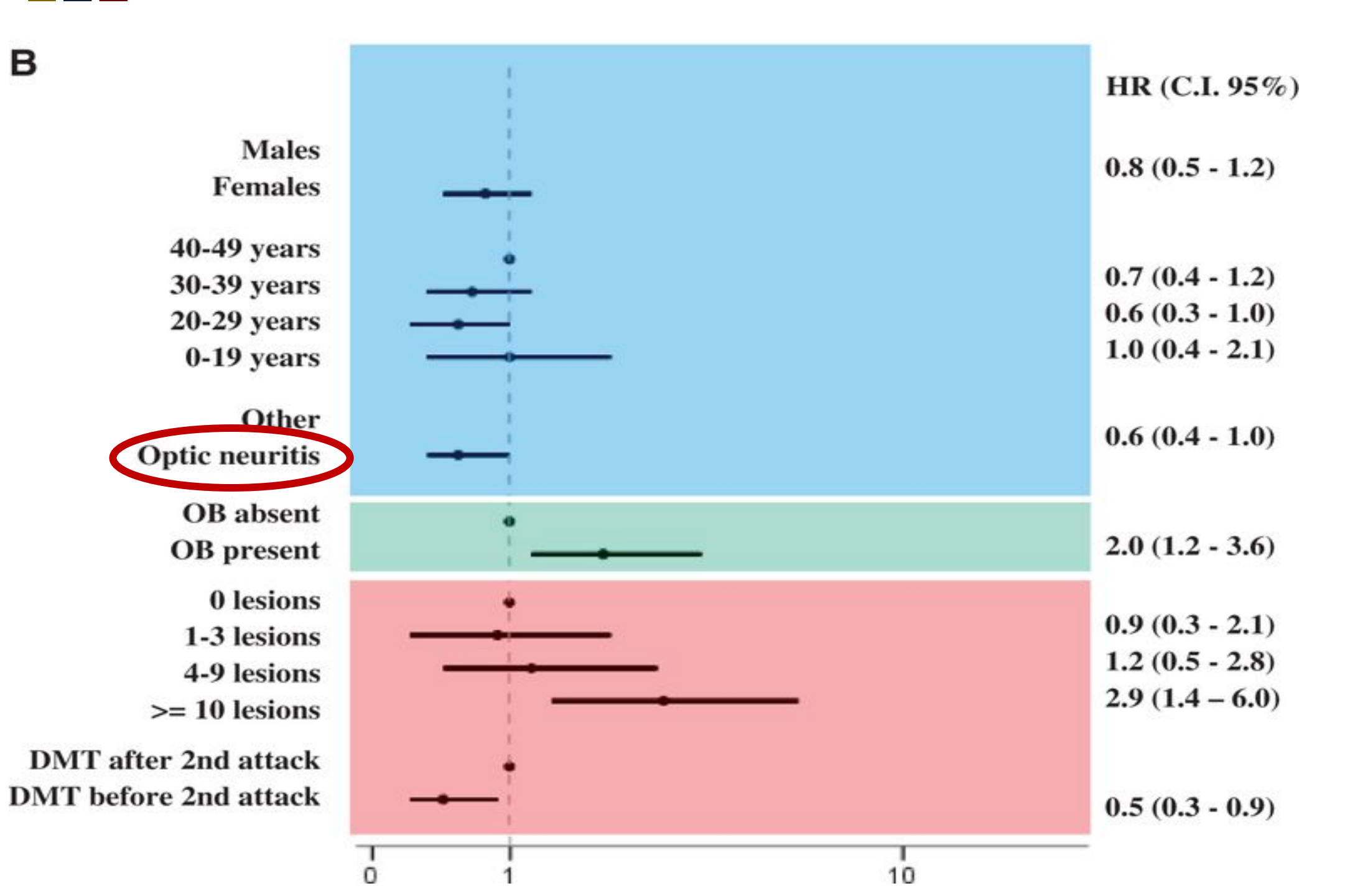
BRAIN A JOURNAL OF NEUROLOGY


B
HR (C.I. 95%)
Males
Females
0.8 (0.5 - 1.2)
40-49 years
30-39 years
20-29 years
0-19 years
0.7 (0.4 - 1.2)
0.6 (0.3 - 1.0)
1.0 (0.4 - 2.1)
Other
Optic neuritis
0.6 (0.4 - 1.0)
OB absent
OB present
2.0 (1.2 - 3.6)
0 lesions
1-3 lesions
4-9 lesions
>= 10 lesions
0.9 (0.3 - 2.1)
1.2 (0.5 - 2.8)
2.9 (1.4 – 6.0)
DMT after 2nd attack
DMT before 2nd attack
0.5 (0.3 - 0.9)
0
1
10

Management

Acute treatment

PLEASE

ORAL STEROIDS FOR ON

PLEASE

The ONTT was a prospective, randomized, multicenter placebo-controlled clinical trial designed to compare the benefits of treatment with

(1) intravenous methylprednisolone (IVMP) (250 mg administered every 6 h for 3 days followed by oral prednisone [1 mg/kg/day] for 11 days);

(2) oral prednisone (1 mg/kg/day); or

(3) oral placebo in 457 patients with acute optic neuritis.

Beck RW, Cleary PA, Anderson MM Jr, Keltner JL, Shults WT, Kaufman DI. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. *N Engl J Med*. 1992 Feb 27. 326(9):581-8.

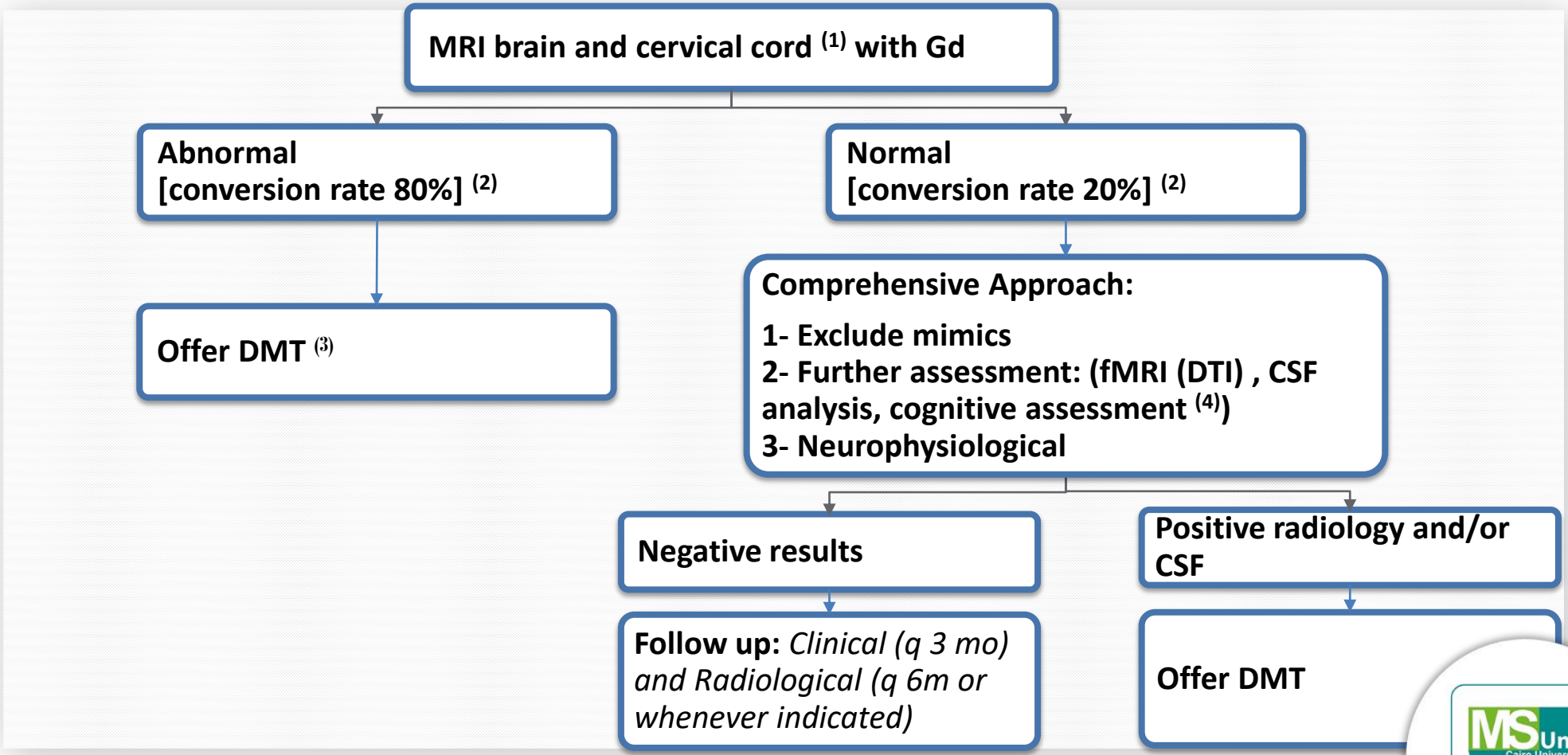
PLEASE

- The ONTT showed that treatment with standard-dose oral prednisone was associated with an increased rate of new attacks of optic neuritis.

- After 5 years, the recurrence rate was found to be higher in the oral prednisone (1 mg/kg) group (41%) than in those who received IVMP or oral placebo (25%).

1. Costello F, Burton JM. An approach to optic neuritis: the initial presentation. *Expert Rev Ophthalmol*. 2013. 8(6):539–551.
2. Shams PN, Plant GT. Optic neuritis: a review. *Int MS J*. 2009 Sep. 16(3):82-9.

Kasr Alaini Protocol of Manangement of CIS



Kasr Alaini Protocol of Manangement of Multiple Sclerosis

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- ***Brownlee W, Miller D.*** Clinically isolated syndromes and the relationship to multiple sclerosis. J Clin Neurosci; 2014 Dec;21(12):2065-2071.
- ***Reuter F., Zaaraoui W., Crespy L., Faivre A., Rico A., Malikova I., Soulier E., Viot P., Ranjeva J., Pelletier J., Audoin B.*** Frequency of cognitive impairment dramatically increases during the first 5 years of multiple sclerosis J Neurol Neurosurg Psychiatry 2011;82:1157-9.
- ***Loitfelder M, Fazekas F, Petrovic K, Fuchs S, Ropele S, Wallner-Blazek M, Jehna M, Aspeck E, Khalil M, Schmidt R, Neuper C, Enzinger C.*** Reorganization in cognitive networks with progression of multiple sclerosis: insights from fMRI. Neurology. 2011 Feb 8;76(6):526-33

Kasr Alaini Protocol of Manangement of Multiple Sclerosis

Studies that support treatment of CIS patients

- ***Jacobs L. D. et al.*** Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N. Engl. J. Med.* **343**, 898–904 (2000).
- ***Kappos, L. et al.*** Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurolog* 67, 1242–1249(2006).
- ***Comi, G. et al.*** Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomized, double-blind, placebo-controlled trial. *Lancet* **374**, 1503–1511 (2009).
- ***Comi, G. et al.*** Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomized controlled trial. *Lancet Neurol.* **11**, 33–41 (2012).
- ***Morrissey, S. P. et al.*** The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis. A 5-year follow-up study. *Brain* **116**, 135–146 (1993).
- ***Brex, P. A. et al.*** A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N. Engl. J. Med.* **346**, 158–164 (2002).

Vitamin D supplementation

- A small randomized control trial conducted by Derakhshandi et al. 2013, suggested that supplementation with cholecalciferol 50,000 units weekly in patients with optic neuritis who were vitamin D deficient reduced the risk of conversion to MS and had favourable effects on a number of MRI outcomes.

- The PreVANZ study being conducted in Australia and New Zealand is a randomised, double-blind controlled trial investigating three different doses of vitamin D versus placebo in patients with CIS, irrespective of baseline vitamin D levels. Results are expected in 2017.


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THANK YOU