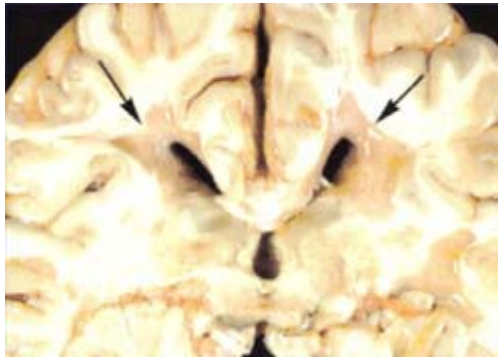
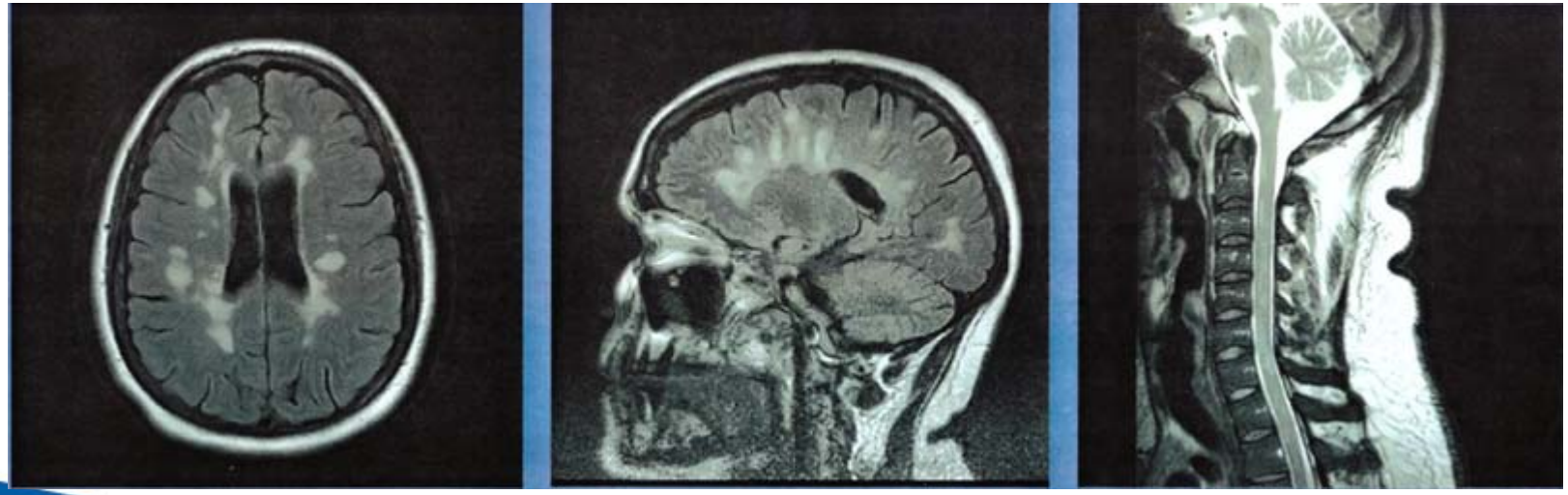
Multiple sclerose: clinical pearls

Dr. Bart Bruneel - neuroloog

Multiple sclerosis

- Chronic inflammatory condition of the CNS induced by an environmental trigger in a genetically sysceptible patient.
- CNS lesions disseminated in time and space without an alternative explanation





Multiple Sclerosis: significance

- The most common, non-traumatic cause of disability in young adults
- Estimated ~ 400,000 MS patients in the US
- More common in women: ~ 2:1
- Onset: 20-40 years old
- Treatable with > 10 FDA approved agents

- With increased emphasis on early DX en TX there is greater **risk of misdiagnosis**

Etiology: Nature vs. Nurture

- Genetics
  - Identical twins (20-30%)
  - Non-identical twins/Siblings (2-5%)
  - Racial clustering

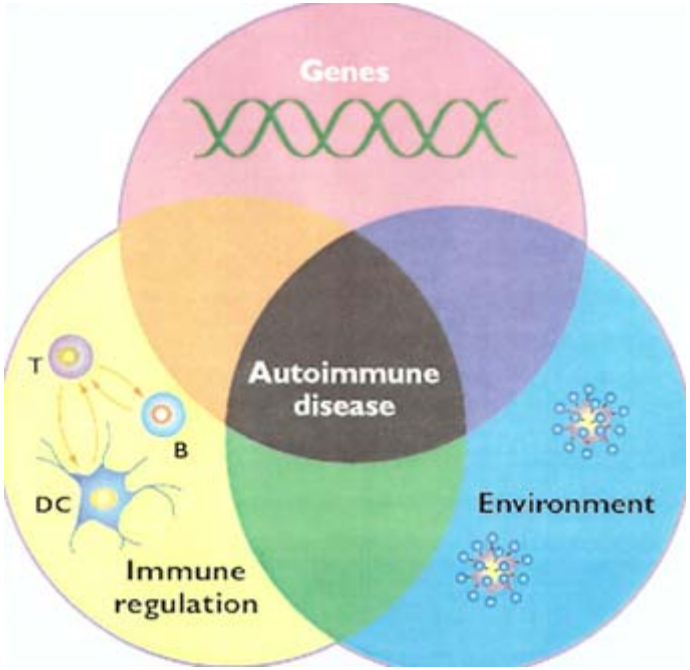
- Environment:
  - 20% have affected family member
  - Migration Studies

- The Search: virus, bacteria, nutrition, well water, exposure to animals, trauma, minerals, chemical agents, metals, organic solvents, geographical influences and occupational hazards.

Etiology of MS

Over > 100 Immune Gene SNPs implicated in the risk of MS: HLADR2, IL-2rec; IL-7 rec

Innate immune response (macrophages)
Adaptive immune response (T and B lymphocytes)

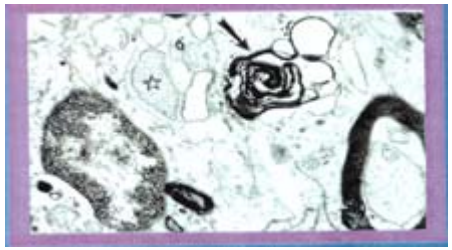


Viruses (EBV)
Vitamin D
Latitude
Smoking
Diet (salt)
Gut Microbiomen
Obesity

Disease Mechanism: 3 components

Inflammation

Demyelination

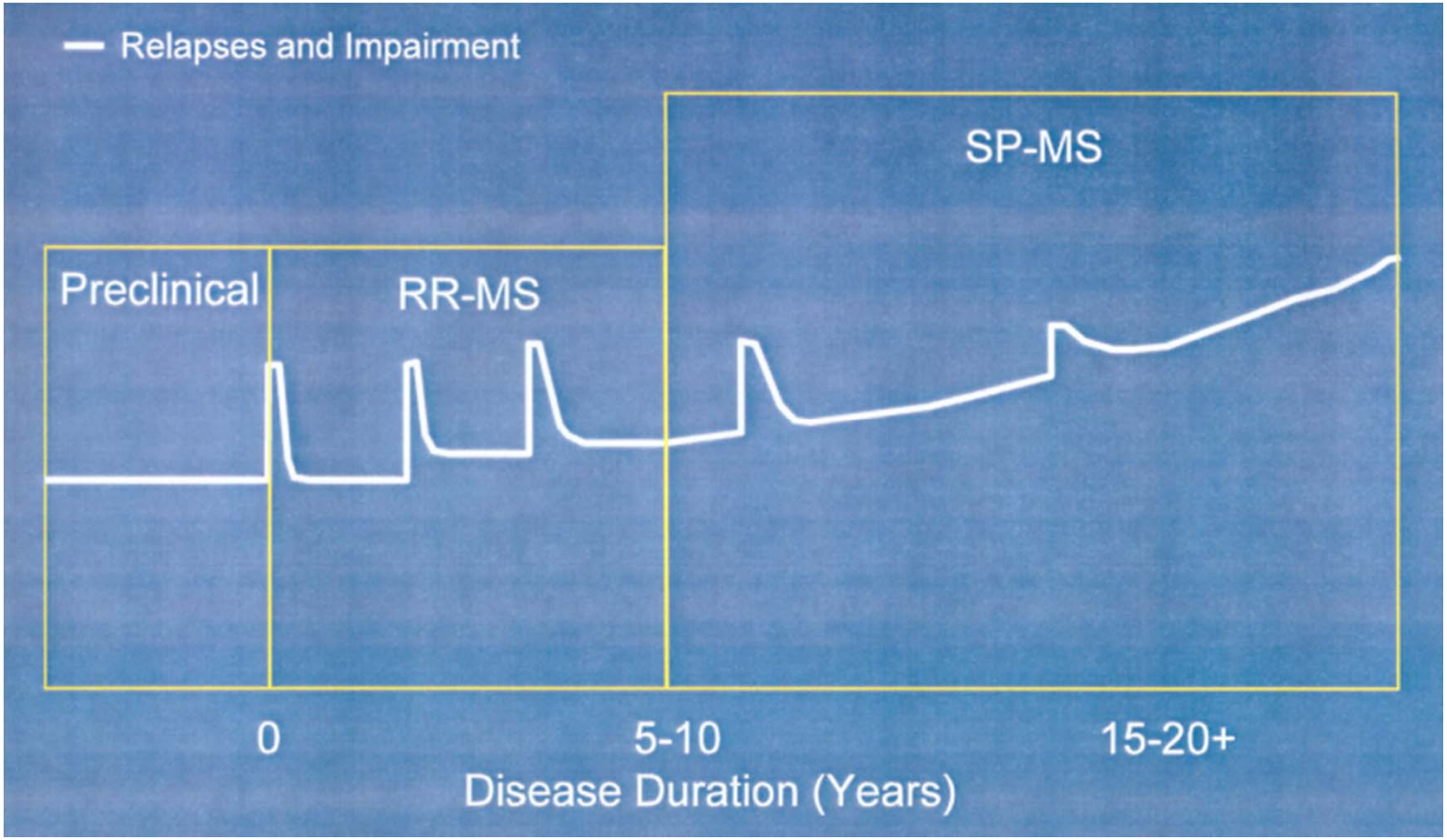


Neuron loss

Expression of MS Disease

- Clinical: Relapse, Residual Symptoms & Disability Accrual
- Sub-clinical: MRI changes
  - Acute -> Enhancement
  - Chronic -> T2 lesion burden, T1 “holes”, atrophy

Natural history of relapsing MS
Clinical and MRI measures



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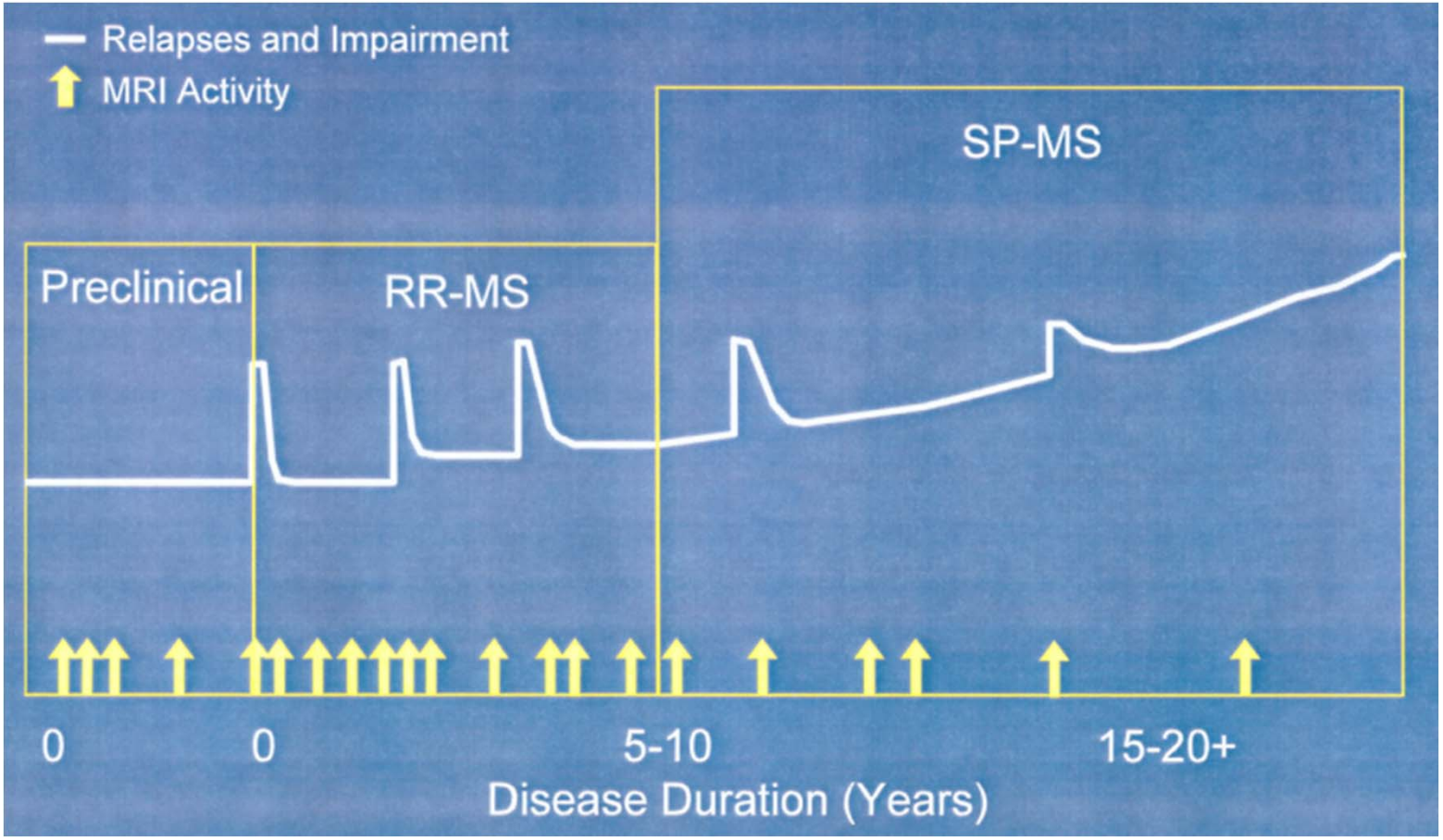

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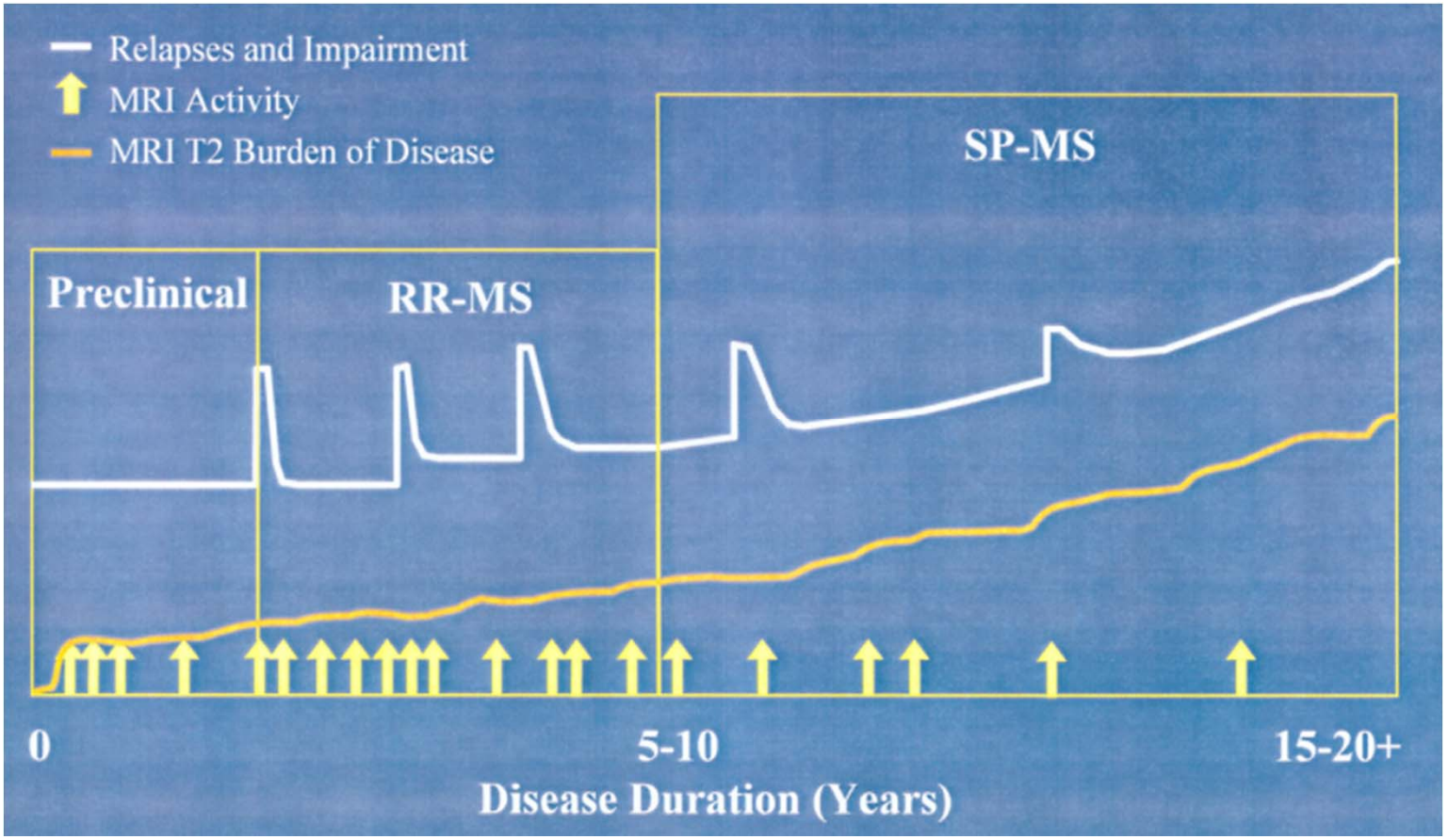

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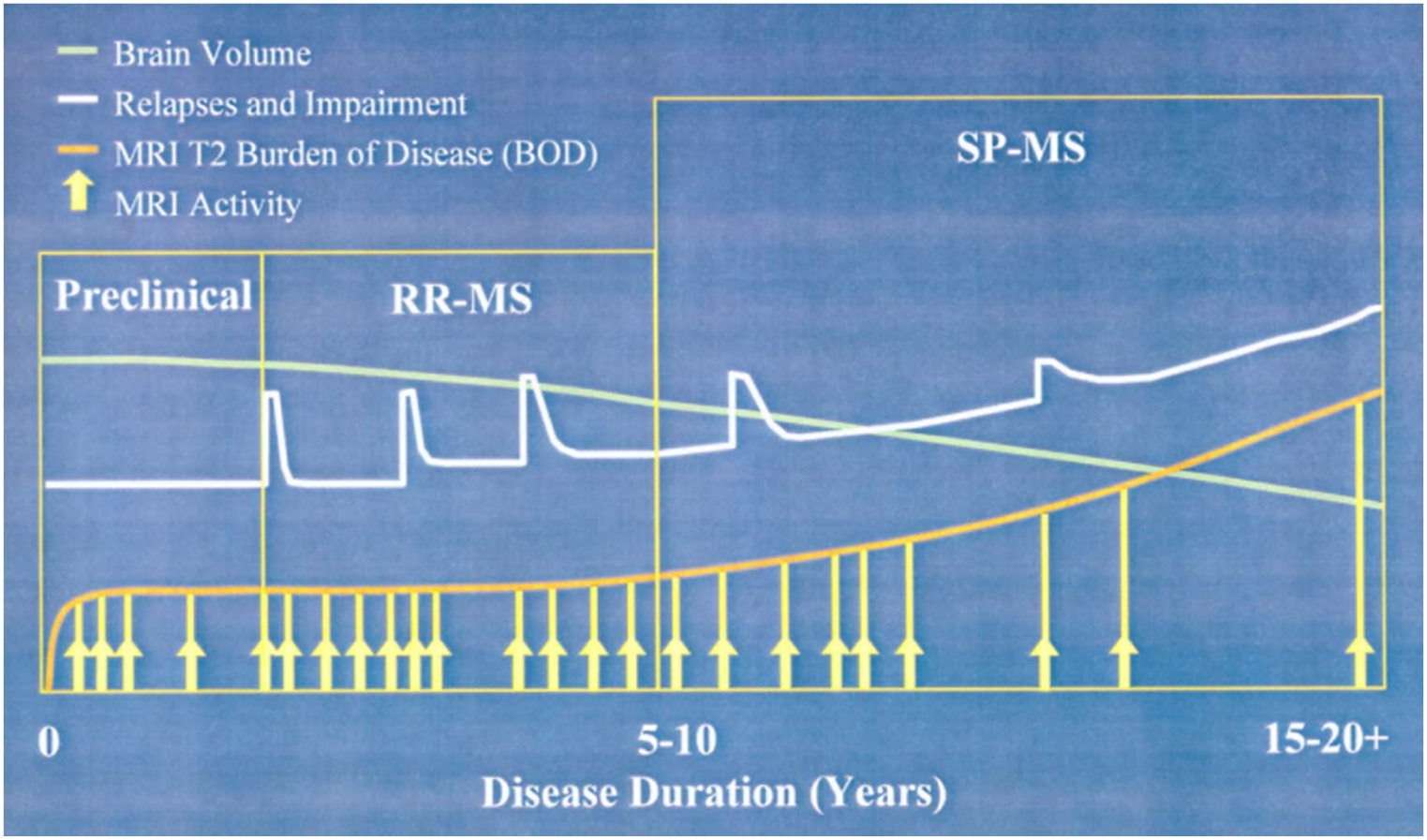

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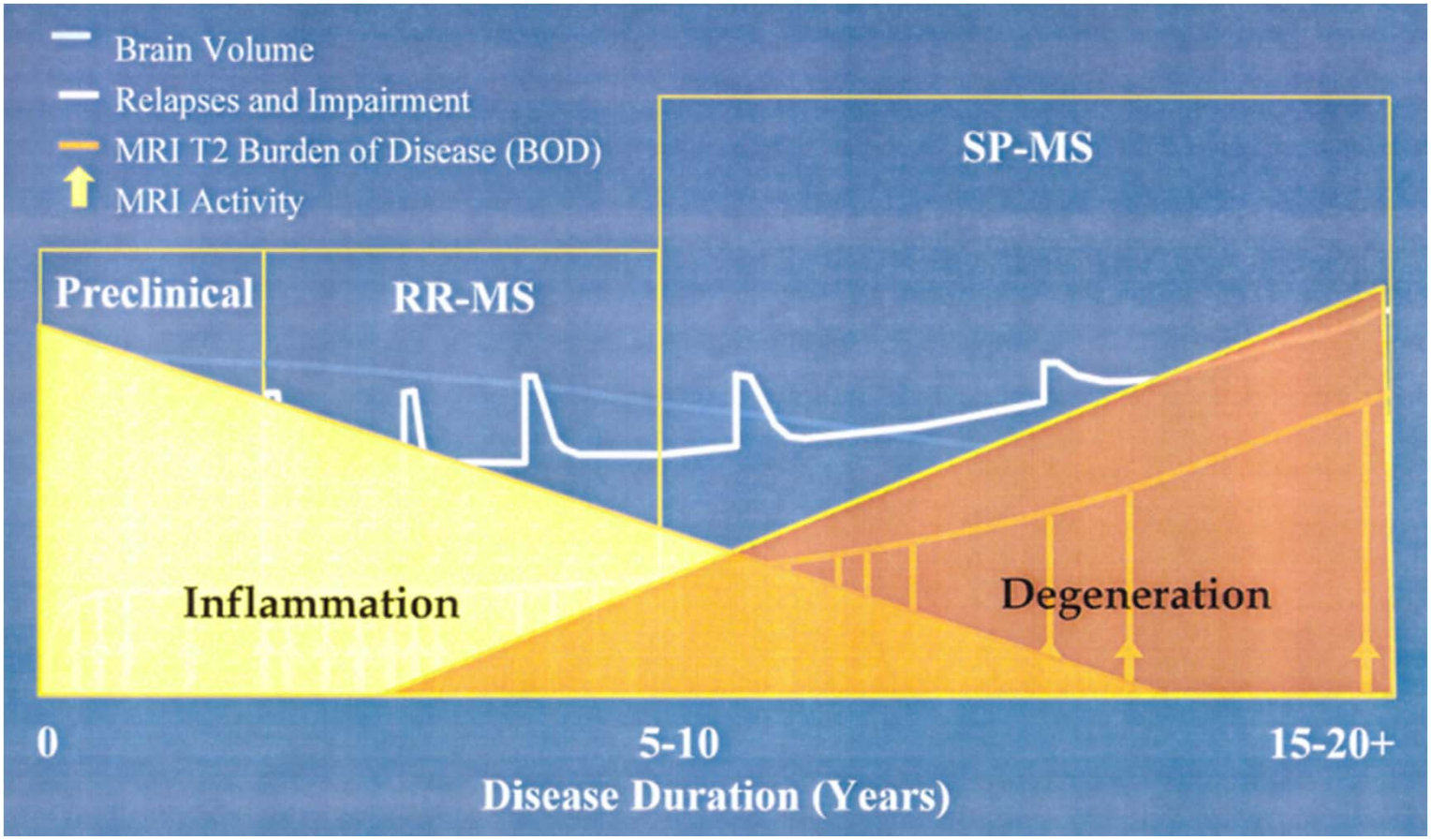
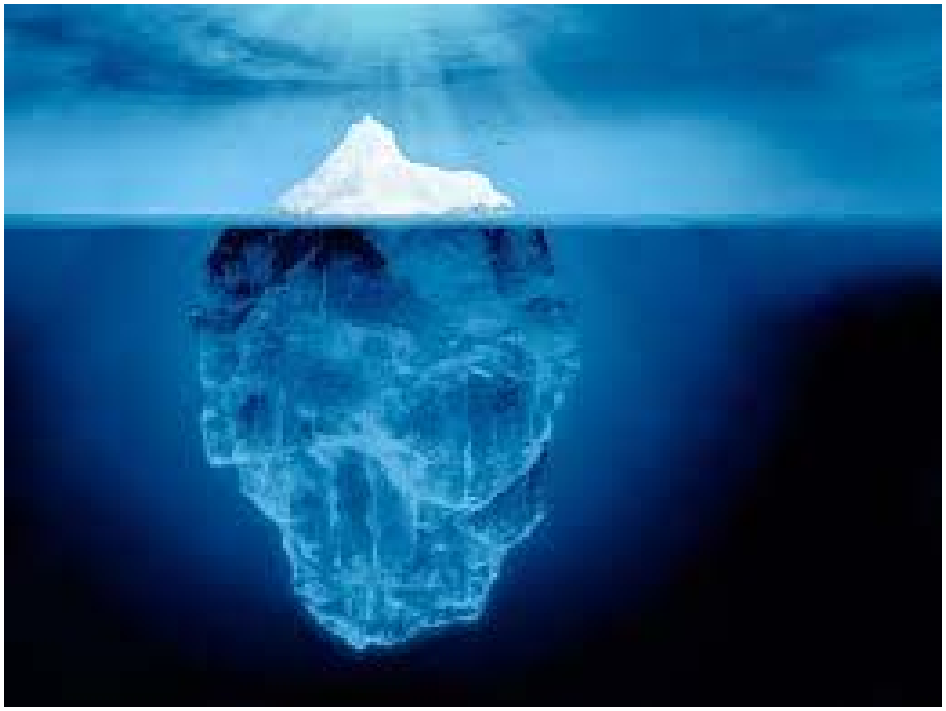


Relapses = tip of the Iceberg



azWest
Zorg op mensenmaat

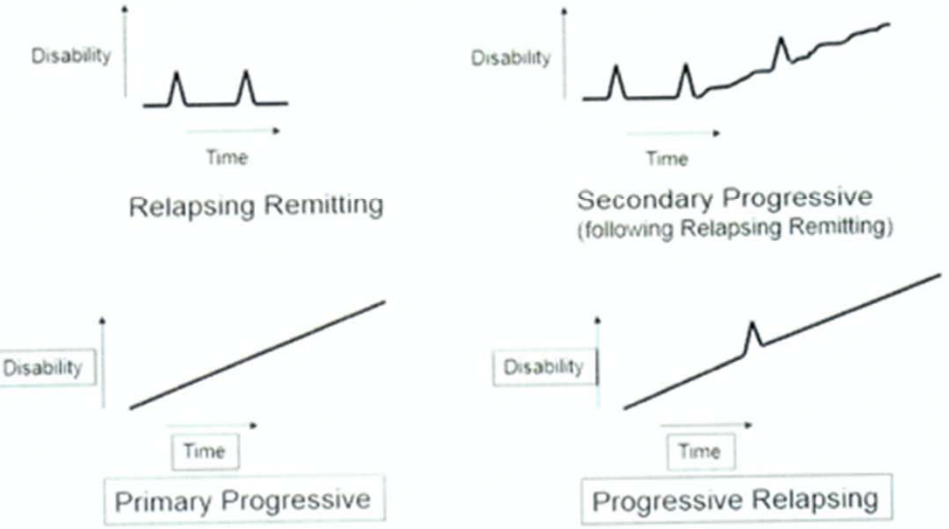
Clinical Courses of MS: Classification

- What is the pattern of disease?
  - Once patients are diagnosed with MS, defining their MS subtype is critical

- Why define the clinical course?
  - It may help to:
    - Guide treatment choices
    - Guide communication between the clinician and patient and help to set more appropriate, realistic expectations

Lublin FD, et al. Neurology. 2014; 83:278-286

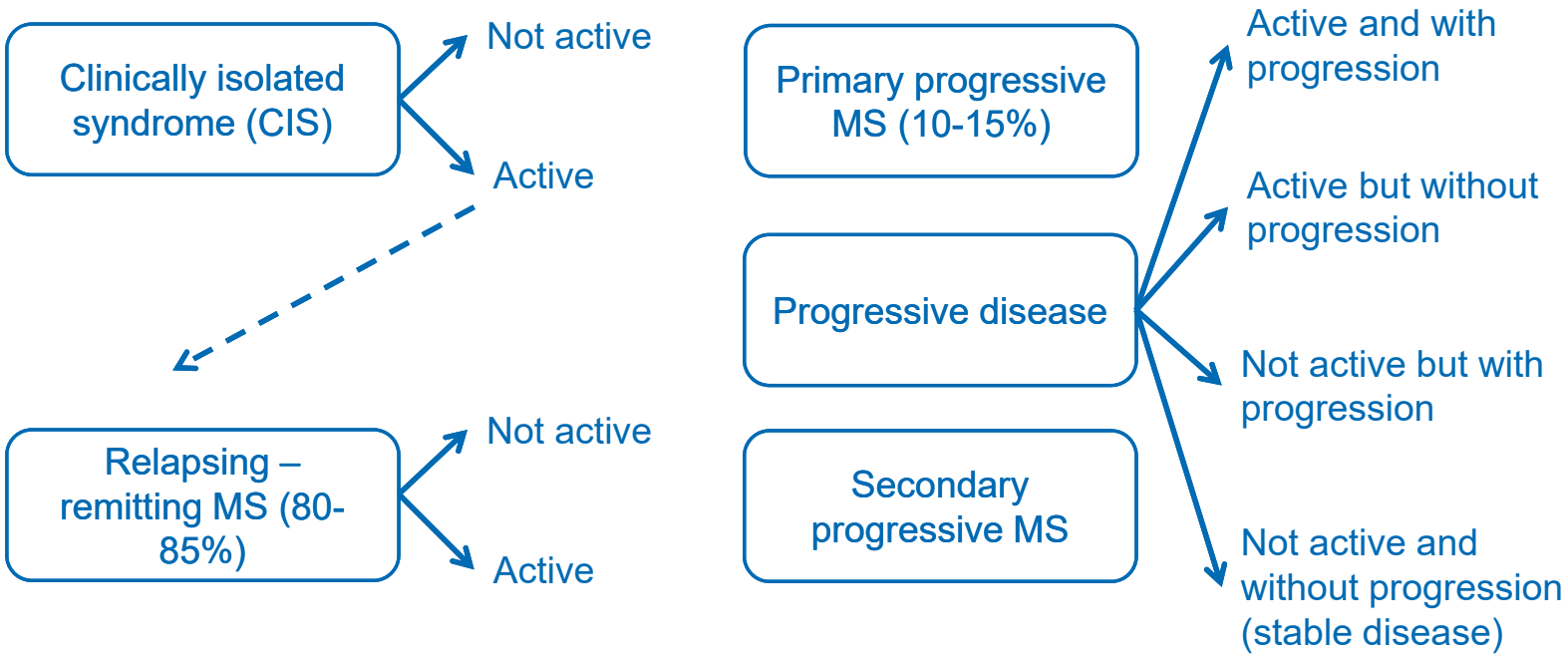
MS Disease Classification



Slide 30

Lublin and Reingold. Neurology 1996; 46:907-911

MS Disease Subtypes

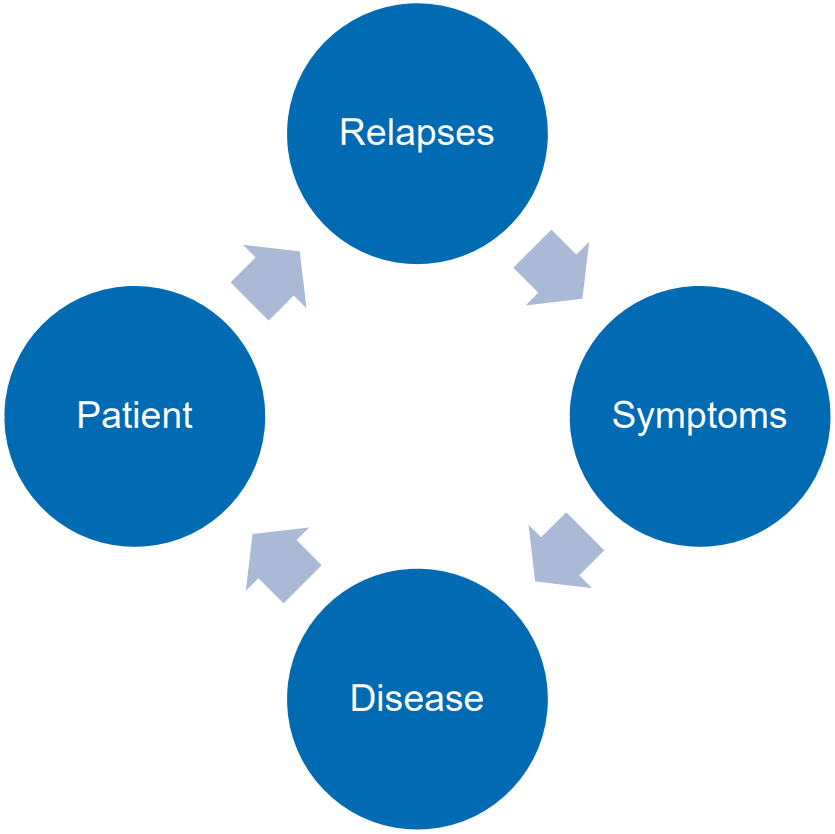


Radiologically isolated syndrome not included

Active = inflammatory activity measured by clinical relapses and/or MRI activity.
Progression = measured by clinical evaluation

Lublin FD et al. Neurology. 2014;83(3):278-286

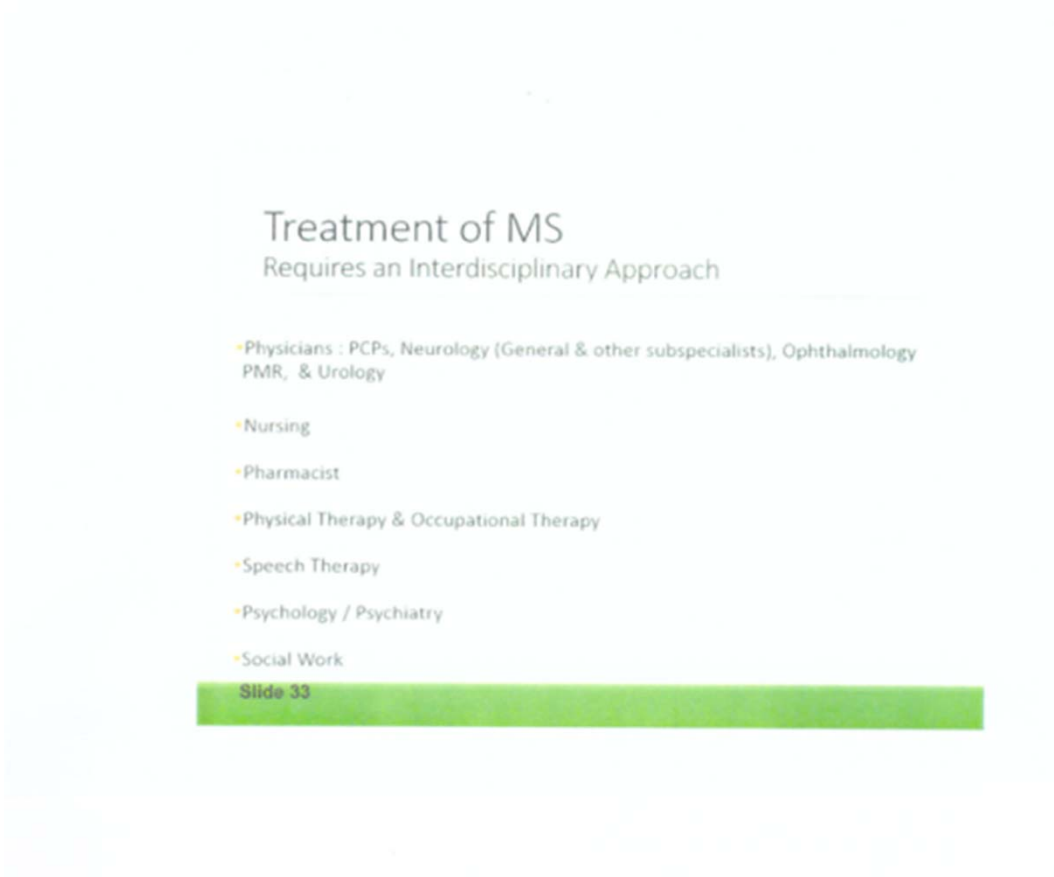
Treatment of MS



Treatment of MS
Requires an Interdisciplinary Approach

- Physicians: PCPs, Neurology (MS & Sleep), PMR & Urology
- Nursing
- Physical Therapy & Occupational Therapy
- Speech Therapy
- Psychology / Psychiatry
- Social Work

Treatment of MS
Requires an Interdisciplinary Approach



Consequences of MS: Symptoms

- Spasticity
- Weakness
- Gait dysfunction
- Pain
- Tremor
- Vertigo
- Bladder dysfunction
- Bowel dysfunction
- Sexual dysfunction
- Depression
- Cognitive impairment
- Fatigue

Typical Manifestations of MS

	Present at Onset (%)	Incidence Overall (%)
Visual loss or oculomotor	49	100
Weakness	43	88
Sensory loss	41	87
Incoodination	23	82
Bladder, bowel, sexual	10	63
Cognitive impairment	4	39

Adapted from Poser 1979

Disease that Minic MS

- Systemic autoimmune
  - Sjögren's syndrome
  - Systemic lupus erythematosus
  - Wegener's granulomatosis
  - Sarcoidosis
  - Behçet's disease
- Infectious
  - PML
  - HIV
  - Lyme disease
  - Syphillis
- Demyelinating
  - Neuromyelitis optica
  - ADEM
  - Optic neuritis
- Stiff person syndrome
- CNS neoplasms
  - Lymphoma
- Metabolic
  - Vitamin B12 & CU deficiency
- Cerebrovascular disease
- Migraine
- Vasculitis
- Genetic/hereditary
  - Adrenomyeloneuropathy
  - CASASIL

ADEM = acute disseminated encephalomyelitis; CADASIL= cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS = central nervous system; PML : progressive multifocal leukoencephalopathy

Burks j. Multiple Sclerosis: Diagnosis: Medical Management, and Rehabilitation, 2000.

Common Clinical Syndromes

- Acute Optic Neuritis/Optic Neuropathy
  - NMO, ADEM, nutritional deficiencies (B12, copper), genetic (Leber's, CMT2a), drugs, infections (lyme, syphilis), rheumatological (SLE, Sjogren's), Sarcoidosis, compressive tumors.
- Transverse Myelitis/Progressive Myelopathy
  - NMO, ADEM, SLE, Sjogren's, APL syndrome, compression, genetic (SCA), nutritional (as above), infectious (HIV, HTLV, Hepatitis C, syphilis), malignancy (paraneoplastic; CRMP5)
- Posterior Fossa Syndromes
  - Brainstem/cerebellar dominated presentations; rheumatological, genetic, infectious, structural

NMO:neuromyelitis optica; ADEM=acute disseminated encephalomyelitis; CMT=Charcot Marie Tooth; SLE=systemic lupus erythematosus; APL=antiphospholipid; SCA=spinocerebellar ataxia; HIV=human immunodeficiency; HTLV:human T-lymphotropic virus; CRMP5=collapsin response mediatro protein 5

MS Diagnostic Criteria

- Schumacher 1965
  - Clinical criteria
  - Dissemination in time and space

- Poser 1983
  - Incorporates paraclinical tests
  - No clearcut MRI criteria
  - Categories
    - Possible, probable, definite
    - Clinically – or laboratory - supported

Diagnosis of MS

- Dissemination **in Space**
  - Multifocal CNS process by history, exam, MRI, EP
- Dissemination **in Time**
  - Relapses or progression by history
  - New lesions by exam, MRI, EP
- Immune-mediated – CSF & MRI
- No other explanation by History, Exam, MRI, CSF of Blood Studies

Role of MRI in Early Diagnosis

- Can be used to confirm **dissemination in space** in patients with clinical evidence of only one lesion

- Can be used to confirm **dissemination in time** in patients with only a single clinical event

TABLE 4: The 2010 McDonald Criteria for Diagnosis of MS

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a second clinical attack[a] implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]

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McDonald 2010: DIS

DIS Can Be Demonstrated by ≥1 T2 Lesion[a] in at Least 2 of 4 Areas of the CNS:

- Periventricular
- Juxtacortical
- Infratentorial
- Spinal cord[b]

Based on Swanton et al 2006, 2007.[22,27]

[a]Gadolinium enhancement of lesions is not required for DIS.

[b]If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count.

MRI = magnetic resonance imaging; DIS = lesion dissemination in space; CNS = central nervous system.

McDonald 2010 - DIT

DIT Can Be Demonstrated by:

1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Based on Montalban et al 2010.[24]
MRI = magnetic resonance imaging; DIT = lesion dissemination in time.

McDonald 2010 - PPMS

PPMS May Be Diagnosed in Subjects With:

1. One year of disease progression (retrospectively or prospectively determined)

2. Plus 2 of the 3 following criteria[a]:

A. Evidence for DIS in the brain based on ≥1 T2[b] lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)

B. Evidence for DIS in the spinal cord based on ≥2 T2[b] lesions in the cord

C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

[a]If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the Criteria.
[b]Gadolinium enhancement of lesions is not required.
MS = multiple sclerosis; PPMS = primary progressive MS
DIS = lesion dissemination in space; CSF = cerebrospinal fluid; IgG = immunoglobulin G.

ORIGINAL ARTICLE

WILEY Neurologica

Multiple biomarkers improve the prediction of multiple sclerosis in clinically isolated syndromes

V. Martinelli[1] | G. Dalla Costa[1] | M. J. Messina[2] | G. Di Maggio[1] | F. Sangalli[1] | L. Moiola[1] | M. Rodegher[2] | B. Colombo[1] | R. Furlan[3] | L. Leocani[4] | A. Falini[5] | G. Comi[1]

MRI variables			
2010 DIS criteria	Fulfilled vs not fulfilled	3.52 (2.18-5.68)	<.001
2010 DIT criteria	Fulfilled vs not fulfilled	2.07 (1.43-3.00)	<.001
T2 lesions	1-SD increase	1.20 (1.03-1.39)	.01
	≥9 vs <9[b]	1.59 (1.05-2.41)	.02
T1 lesions	1-SD increase	1.46 (1.22-1.74)	<.001
	Present vs absent[b]	2.20 (1.42-3.40)	<.001
Gd-enhancing lesions	1-SD increase	1.18 (1.01-1.38)	.04
	Present vs absent[b]	1.41 (1.00-2.01)	.05
CSF variables			
Cells	1-SD increase	1.00 (0.84-1.18)	.99
	≥2/μL vs <2/μL[b]	1.32 (0.90-1.93)	.16
Proteins	1-SD increase	0.91 (0.76-1.08)	.27
	>40 mg/dL vs ≤40 mg/dL[b]	0.77 (0.37-1.59)	.47
Oligoclonal bands	Present vs absent	2.87 (1.81-4.56)	<.001

Red Flags for the potential Misdiagnosis of MS

- Normal neurological examination
- No dissemination over time and space
- Onset of symptoms before age 10 or after age 55
- Progressive course before age 35
- Unifocal manifestations (even if relapsing or progressive)
- Missing features (e.g. Normal vision, bladder/bowel function)
- Normal MRI, cerbrospinal fluid, or evoked potentials
- Progressive myelopathy
- Impaired level of consciousness
- Prominent uveitis
- Peripheral neuropathy
- Gray matter features (e.g. early dementia, seizures, aphasia, extrapyramidal features)
- Atypical or lack of response to treatment
- Implausibly rapid of dramatic response to corticosteroids or DMTs.

CONTEMPORARY ISSUES IN NEUROLOGIC PRACTICE

"Undiagnosing" multiple sclerosis

The challenge of misdiagnosis in MS

Andrew J. Solomon, MD
Fran P. Klein, MD, PhD
Dennis Bourdette, MD

ABSTRACT

Objective: To describe the clinical characteristics of encounters with patients misdiagnosed with multiple sclerosis (MS)

CONTEMPORARY ISSUES IN NEUROLOGIC PRACTICE

"Undiagnosing" multiple sclerosis

The challenge of misdiagnosis in MS

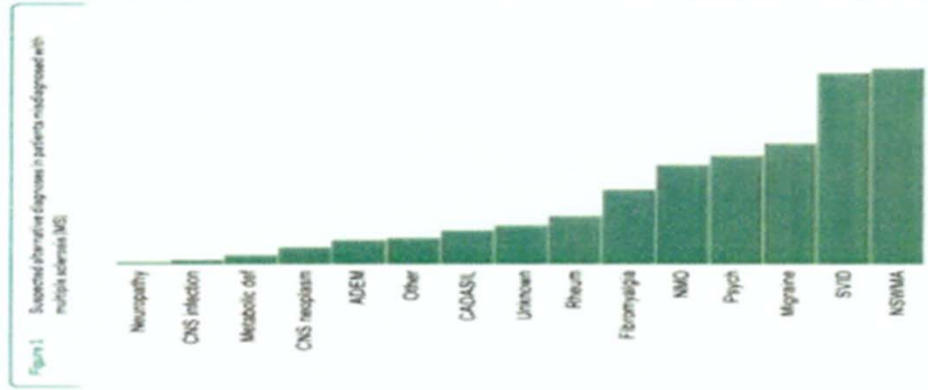


Figure 1 Suspected alternative diagnoses in patients misdiagnosed with multiple sclerosis (MS)

- Verkeerde diagnose:
- Een studie leerde dat 95 % van de bevraagde neurologen het laatste jaar een verkeerde diagnose hadden gesteld.

- Normaal voorkomende witte hersenstof.
- Small vessel disease.
- Migraine.
- Psychiatrisch.
- CADASIL.

Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial

Emmanuelle Le Page, David Veillard, David A Laplaud, Stéphane Hamonic, Blasko Wasik, Christine Lebrun, Fabien Zagnoni, Sandrine Wiertlewski, Véronique Deburghgraeve, Alain Créange, Gilles Edan, for the COPOUSEP investigators* and the Ward Network for Excellence in Neuroscience

AAN 2017: S31.008

A multi-centre, randomized, double-blind, non-inferiority clinical trial to compare the clinical and radiological efficacy of 625 mg versus 1250 mg of oral methylprednisolone in patients with relapse of MS: Oral-CORTEM trial

C. Ramo, F. Torres, G. Domenech, J. Capellades, et.al.

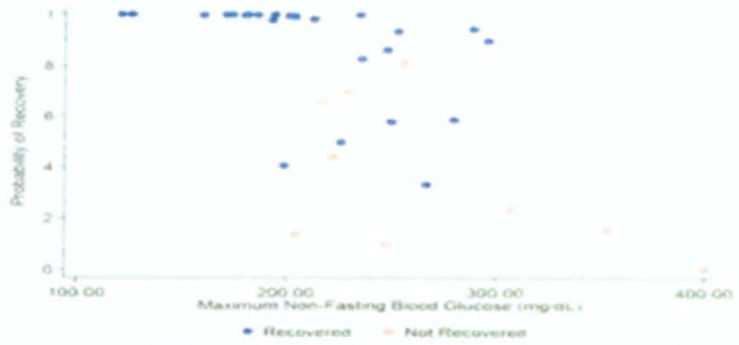
- Optimale dosis van de corticotherapie:

- Oraal niet inferieur t.o.v. IV.
- 625 mg niet inferieur t.o.v. 1250 mg PO.

Glucocorticoid-associated Blood Glucose Response and Multiple Sclerosis Relapse Recovery

Myla D. Goldman, MD, MSc; Scott Koenig, BS; Casey Engel; Christopher R. McCartney, MD; Min-Woong Sohn, PhD

Figure 1. Scatter plot of predicted probability of recovery from an acute MS relapse and maximum non-fasting blood glucose level (n = 36). Probability of recovery was estimated from Model 3 shown in Table 3



Neurology: Neuroimmunology & Neuroinflammation (*in press*)

- Corticotherapie en glycemie.
- Patiënten die bij een relaps volledig herstelden hadden een significant lagere glycemie dan deze die niet volledig herstelden.
- Minder dan 200 mg/dl.

MULTIPLE SCLEROSIS JOURNAL | MSJ

Topical Review

Urinary tract infections in multiple sclerosis

Véronique Phé, Mahreen Pakzad, Carmel Curtis, Bernadette Porter, Collette Haslam, Jeremy Chataway and Jalesh N Panicker

- Nitrates & Leukocyte esterase – 95% NPV, lower PPV (<76%)
- Culture is needed to confirm UTI, prior to Abx (>10^5 CFU/ml)
- Do not need to delay steroids when Tx UTI w/relapse
- Uncertainty around the benefit/risk of ABX prophylactics in PwMS
- Data does not support the benefit of Cranberry extract in UTI prevention
- D-Mannose may offer benefit and is under ongoing study.

- Urinaire infecties.

- Antibiotica hebben een effect op de darmflora. Is behandelen altijd goed?
- In elk geval moet de diagnose gesteld worden met een cultuur.
- Een urinaire infectie is geen reden om een corticotherapie uit te stellen.
- Het is niet zeker dat een antibiotica profylaxis gunstig is bij MS patiënten.
- Cranberry is niet nuttig.

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Fatigue and fluid hydration status in multiple sclerosis: A hypothesis

Molly C Cincotta, Matthew M Engelhard, Makela Stankey and Myla D Goldman

- Vermoeidheid en de hydratatiestatus.

- Bij een hoge hydratatiestatus is de vermoeidheid minder uitgesproken.
- Patiënten moeten hierop attent gemaakt worden.

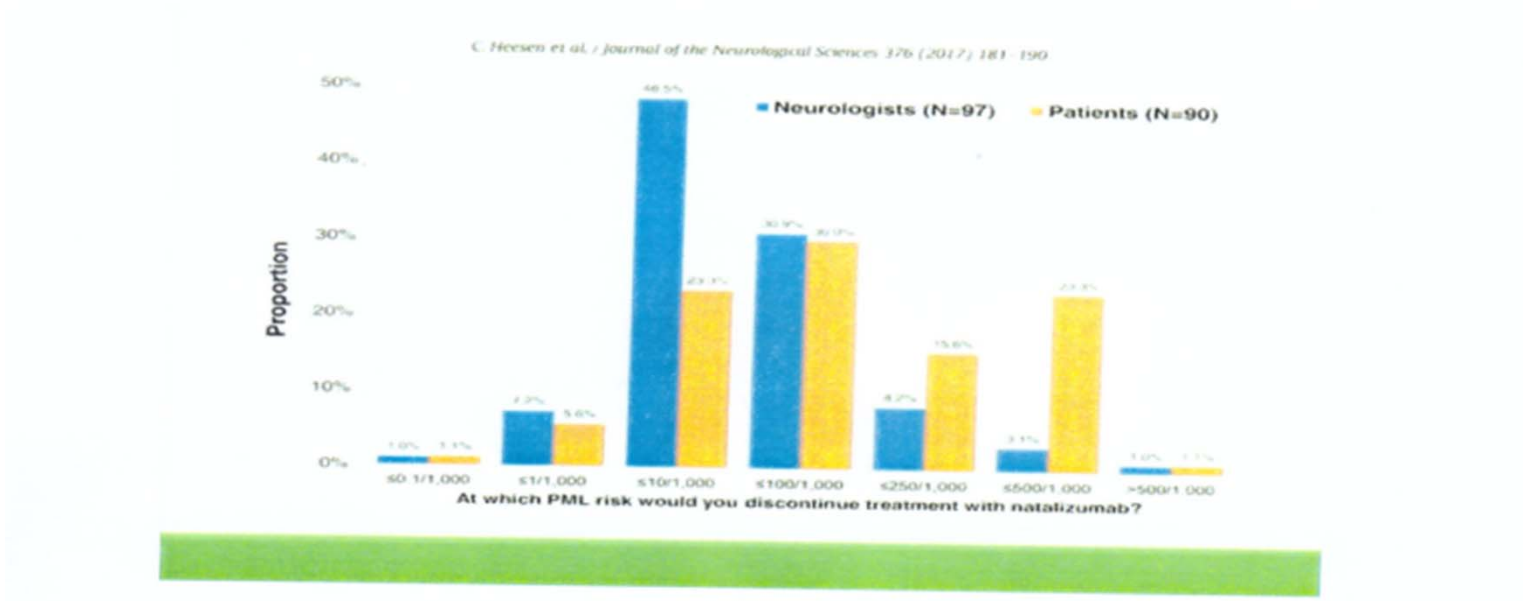
Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Benefit-risk perception of natalizumab therapy in neurologists and a large cohort of multiple sclerosis patients

Christoph Heesen [a,*,1], Ingo Kleiter [b,1], Sven G. Meuth [c], Julia Kramer [c], Jürgen Kasper [d], Sascha Köpke [e], Wolfgang Gaissmaier [f]


C. Heesen et al. / Journal of the Neurological Sciences 376 (2017) 181–190
Neurologists (N=97)
Patients (N=90)
Proportion
50%
40%
30%
20%
10%
0%
≤0.1/1,000
≤1/1,000
≤10/1,000
≤100/1,000
≤250/1,000
≤500/1,000
>500/1,000
At which PML risk would you discontinue treatment with natalizumab?

- Benefit-risk perception van een behandeling met Tysabri.

- Neurologen zouden een behandeling vlugger stoppen.
- Patiënten hebben een hogere risico tolerantie.

- Voldoende inzicht in de problematiek?

Zijn er nog vragen?

Dank u voor uw aandacht

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