Klinikum rechts der Isar
Technische Universität München

Neuro-Kopf-Zentrum
Neurologische Klinik und Poliklinik

Klinikum rechts der Isar
Technische Universität München

Diagnosis and Treatment of Multiple Sclerosis and related diseases

Bernhard Hemmer

Case history

38 years old women. 20 years ago she developed unilateral vision loss. Vision improved after corticosteroid treatment. Within the next five years she developed 4 additional relapses affecting the spinal cord, cerebellum and the optic nerve. Recovery was incomplete after the last two relapses. 5 years ago she noticed that her walking distance decreased, 2 years ago she became dependent on a crane and now she requires a wheelchair for longer distances. She suffers from fatigue, incontinence and mild cognitive impairment. She has stopped working two years ago.

Overview

- MS prevalence and course
- Clinical symptoms & findings
- Diagnostic criteria
- Pathogenetic concepts
- Treatment strategy
- Related diseases

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Prevalence of MS in Germany

- Onset between the age of 20 and 50 years
- Most common non traumatic cause of disability in young adults

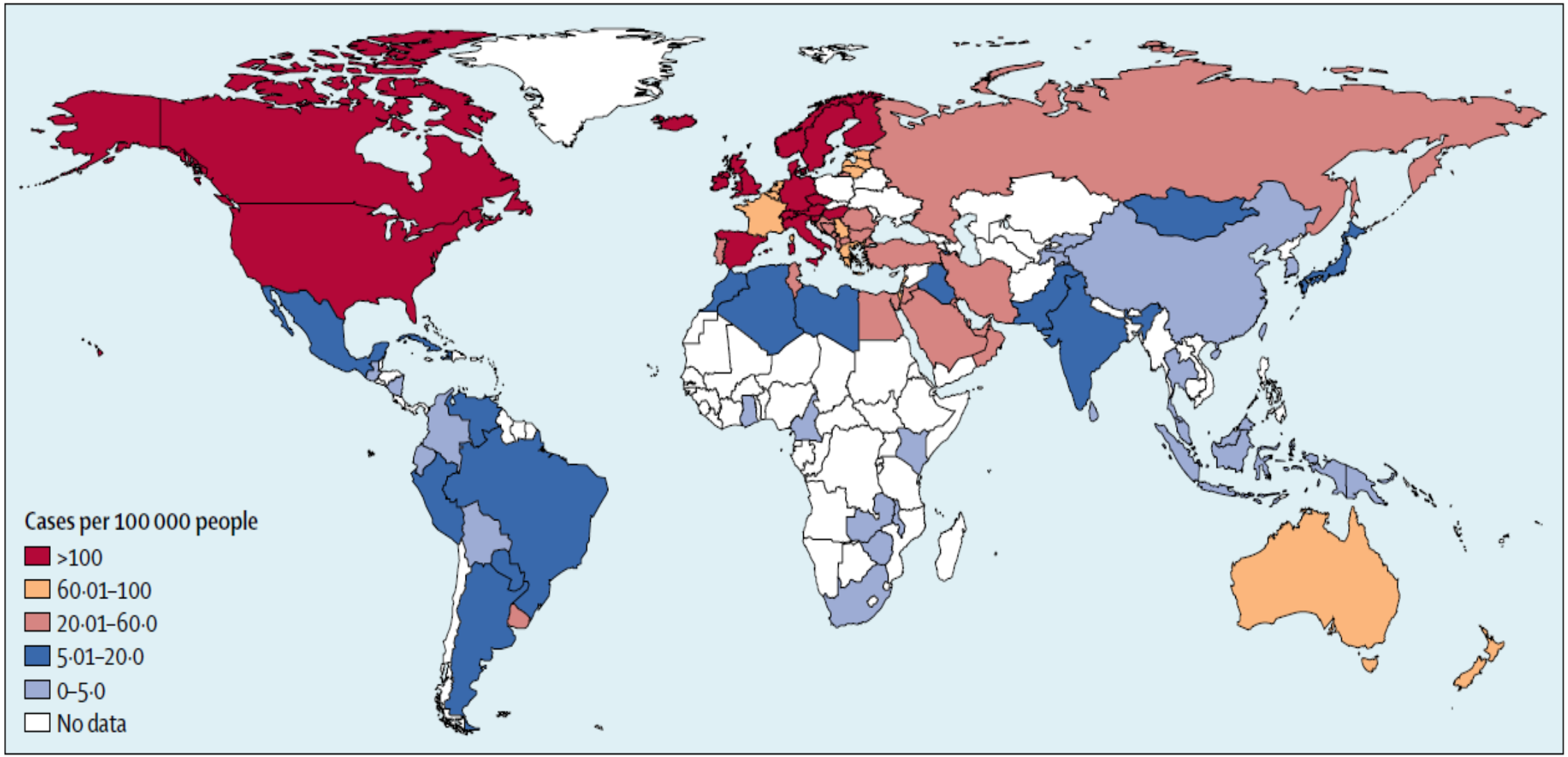
1 of 250

1 of 600

- Currently more than 250,000 people affected in Germany
- Prevalence will increase over the next two decades

Daltrozzo, Front Neurol 2018

Prevalence of MS worldwide



34TH CONGRESS OF THE EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

ECTRIMS

10 – 12 OCTOBER

2018

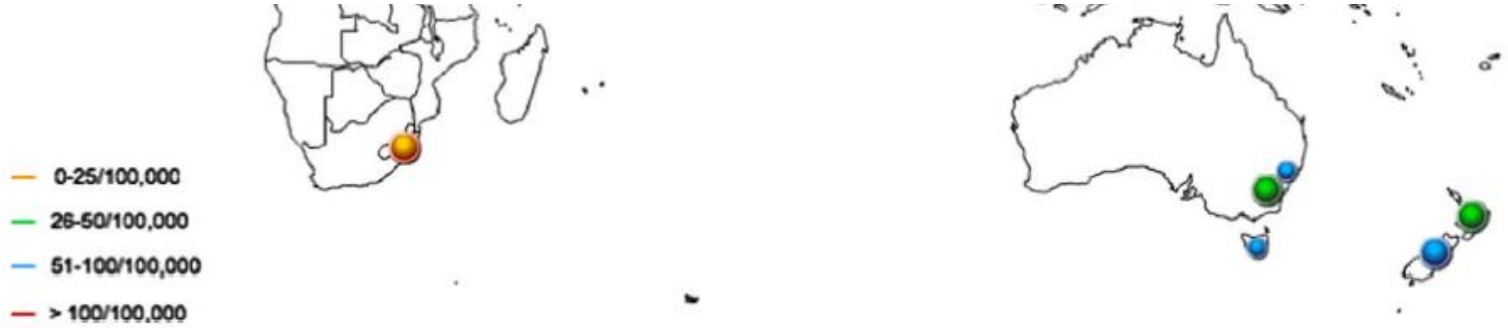
BERLIN, GERMANY

Prevalence of MS in Africa

Table 2 Crude and age adjusted prevalence rates in the over 15 year age group per 100 000 in the different racial groups

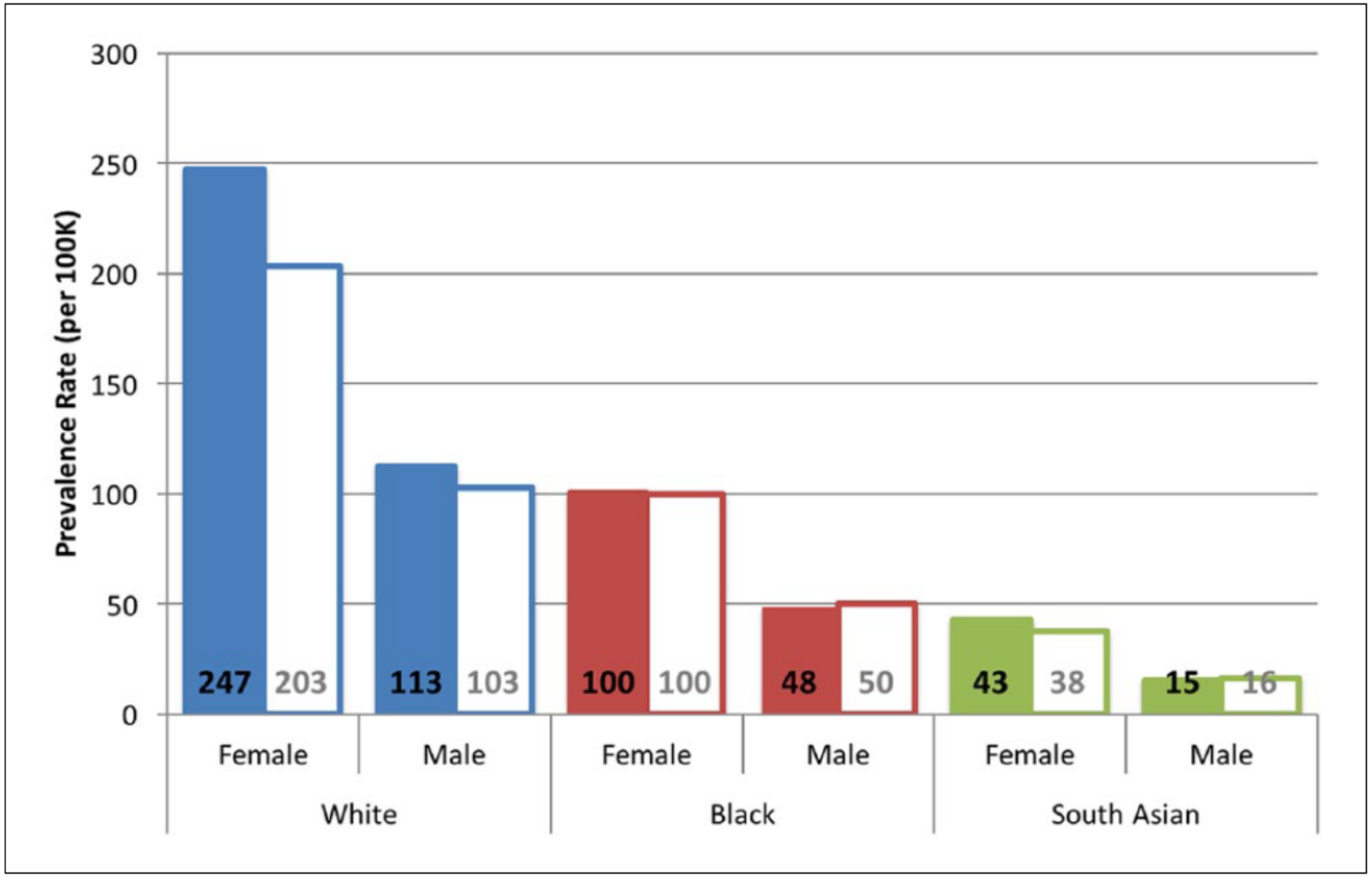
Population group	Number of people >15 years	Crude prevalence per 100 000 (95%, CI)	Age standardized rate per 100 000 to the world Segi population
Whites	409 554	25.63 (20.97–31.04)	25.64
Indians	632 262	7.59 (5.60–10.07)	7.15
Coloureds	102 663	1.94 (0.24–7.04)	1.72
Blacks	5 316 060	0.22 (0.12–0.40)	0.23

CI = confidence intervals.



Bighjee MSJ 2007, Makahni, MS and related dis. 2013

Prevalence of MS in different ethnic groups in London



Albor, MSJ 2017

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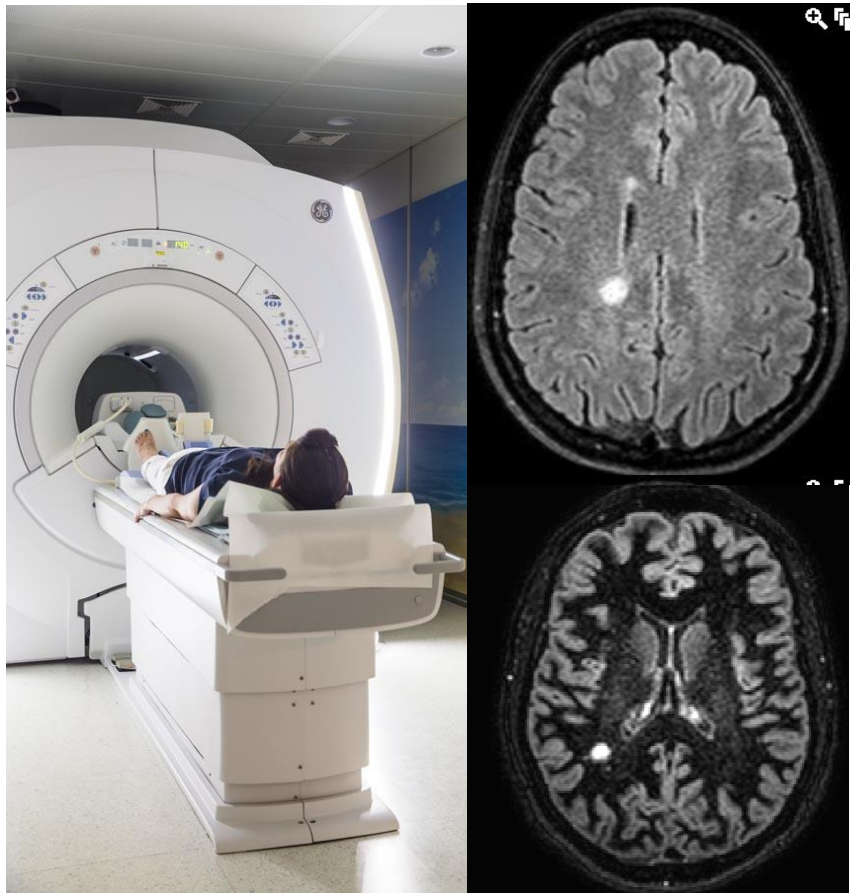
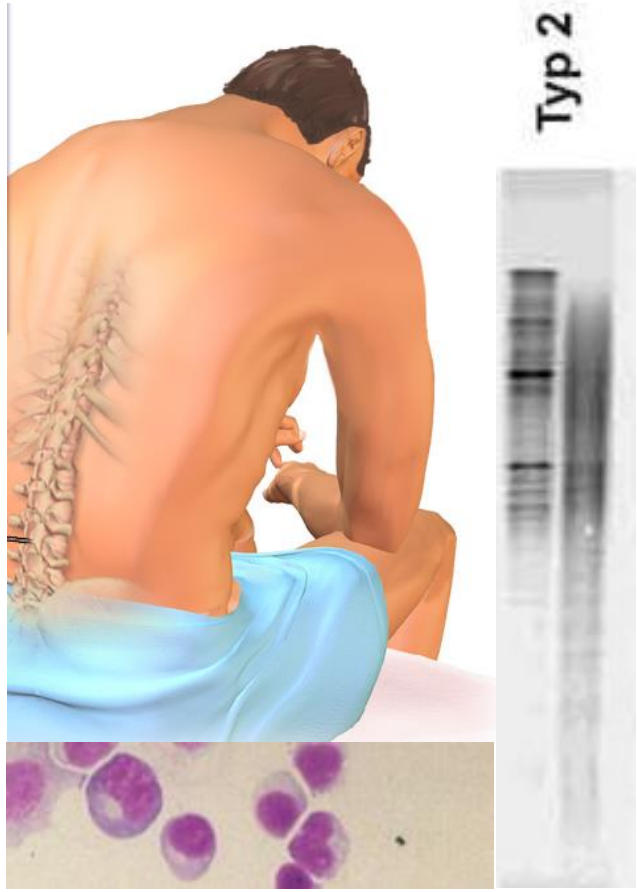
Diagnosing Multiple Sclerosis

Neurological symptoms

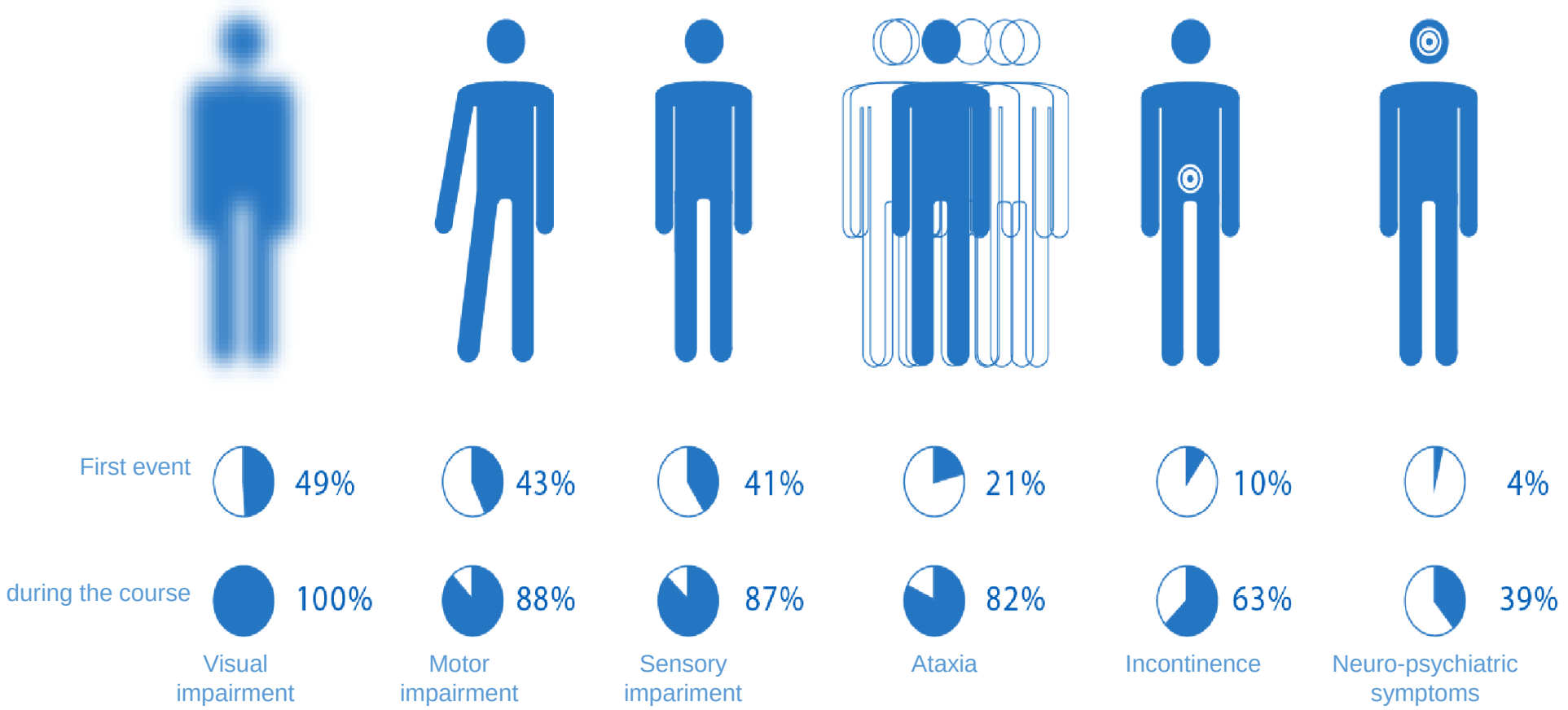
Imaging of brain and spine



CSF



Symptoms of Multiple Sclerosis



Uncommon: Aphasia, Seizures, Hemianopia, Neglect

Classical findings in MS

Lhermitte Sign
Electric sensation along the spine with neck movements

Uthoff Sign
Impairment gets worse with higher body temperature (e.g. fever, high sun exposure)

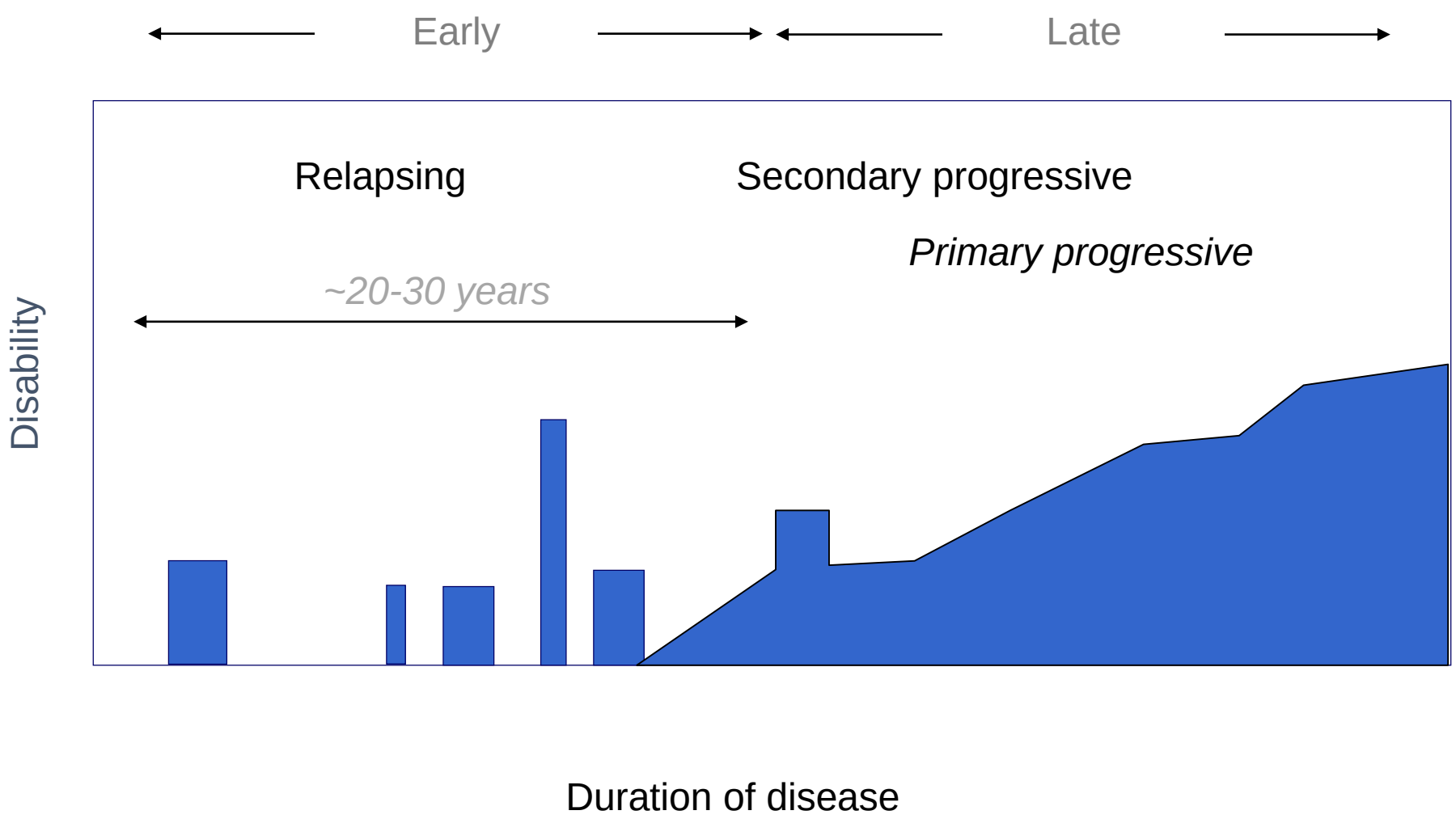
Internuclear Ophtalmoplegia
Ipsilateral impairment of adduction and contralateral dissociated nystagmus

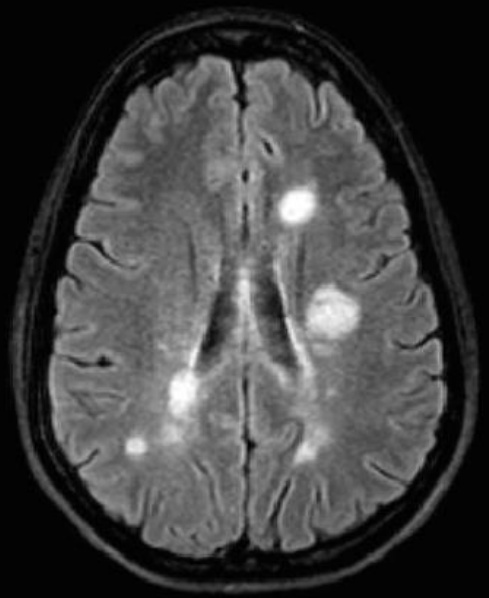
www.hegasy.de/dwnlds/09_Hegasy_Multiple_Sklerose.pdf, aufgerufen am 11.04.2018

Course of MS

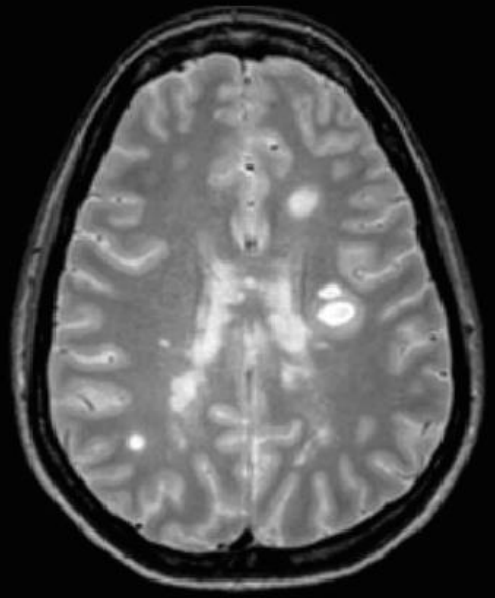
Onset of disease

Course of MS


Early
Late
Relapsing
Secondary progressive
Primary progressive
~20-30 years
Disability
Duration of disease



FLAIR axial

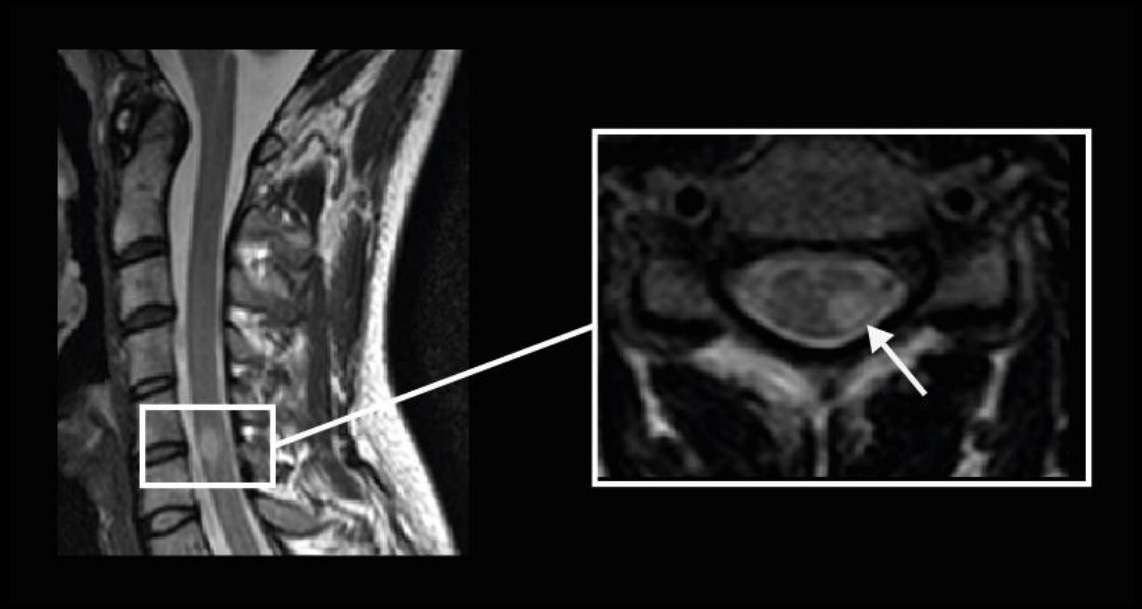


T2 axial

FLAIR sagittal

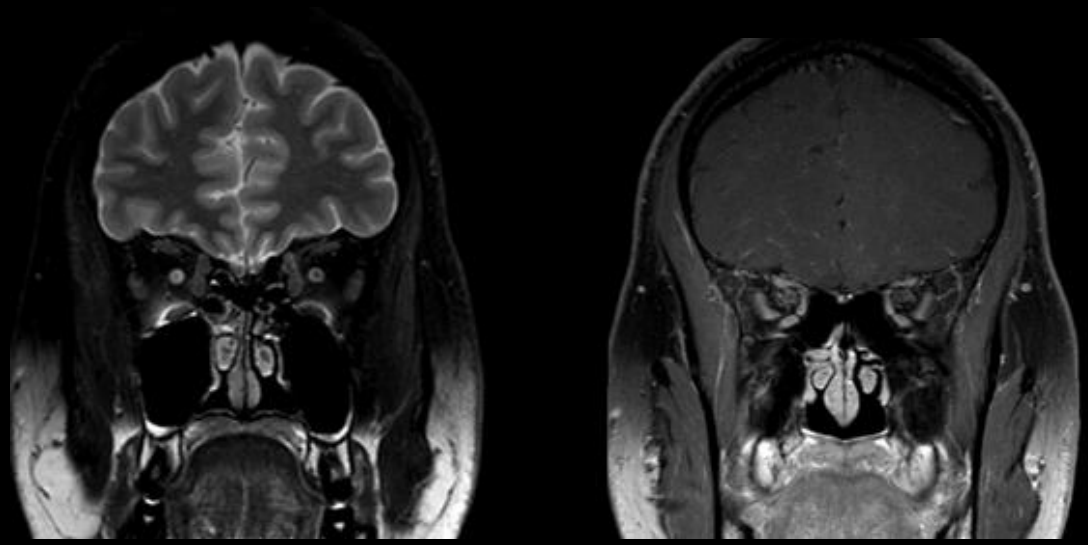
- Cerebral lesions in characteristic locations periventricular, juxtacortical und infratentorial
- Corpus callosum: „Dawson-Fingers“
- ± Gadolinium enhancement

T1 + Gadolinium



Spinal cord lesions

- cervical >thoracic cord
- usually not in central location
- not extending > 3 spinal segments



Optic nerve in the context of optic neuritis

Diagnostic workup

Cerebrospinal fluid

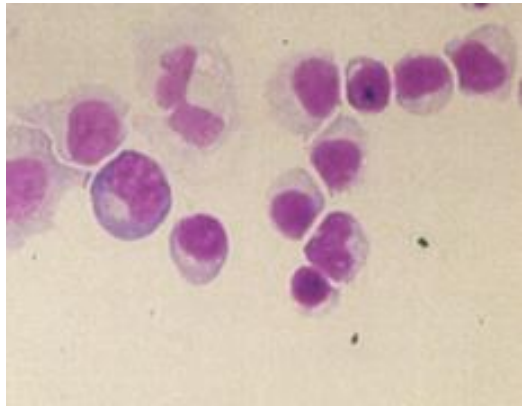
- Supports the diagnosis, Prognostic marker, DDx

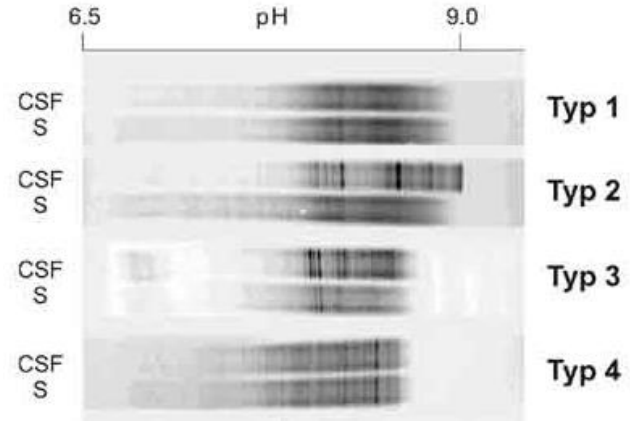
<u>Cellular compartment</u>

- 50% milde pleocytosis up to 50/µl
- lympho-mononculear cells

<u>Proteins</u>

- Protein levels: normal – slightly elevated
- 70% intrathecal IgG-synthesis (Reiber-scheme)
- 95% oligoclonal bands





http://www.uke.de/extern/dgln/interpret_oligo.htm (aufgerufen am 14.01.2014)

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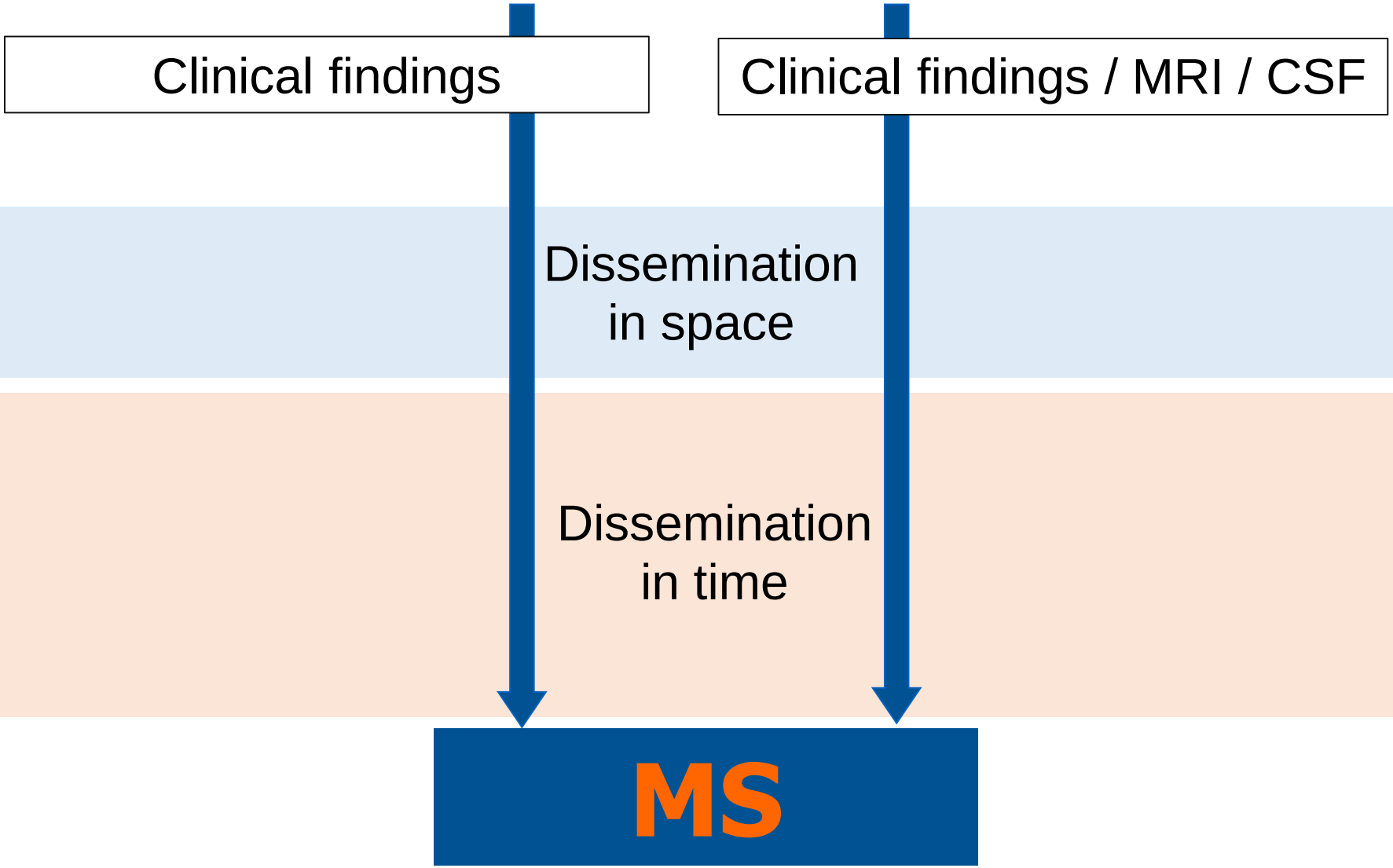
MS diagnostic criteria: revision 2017

Objective evidence for the occurrence of lesions disseminated in space and time typical for MS, which cannot be explained by other diseases or conditions

Thompson et al, Lancet Neurol 2018

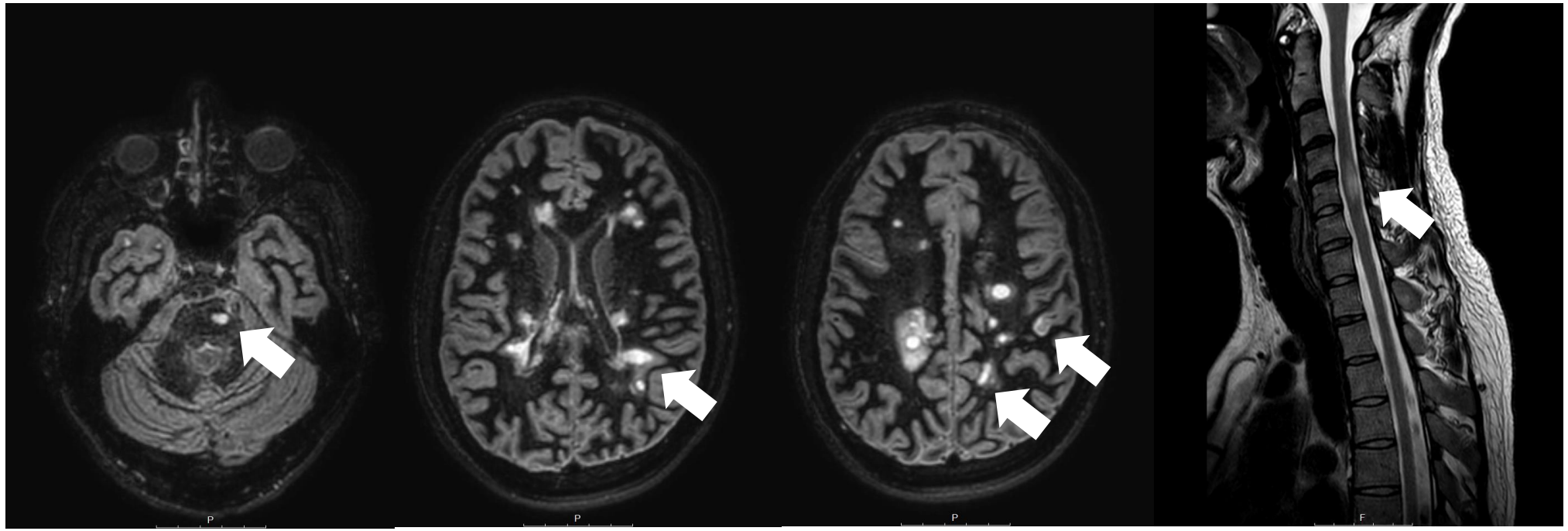
Diagnostic criteria



MRI criteria for dissemination in space

at least 1 lesion in 2 of 4 regions

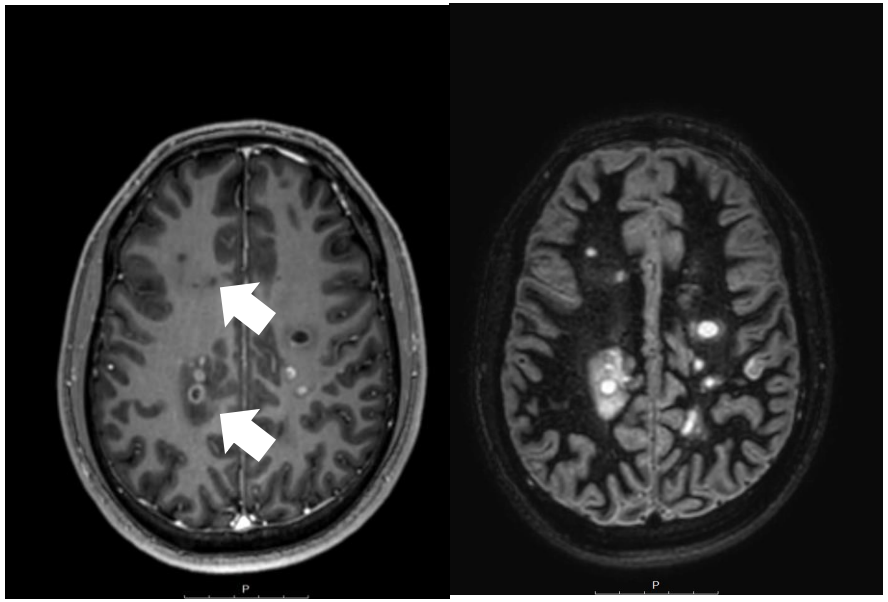
infratentorial | periventricular | juxtacortikal cortikal | spinal



MRI/CSF criteria for dissemination in time

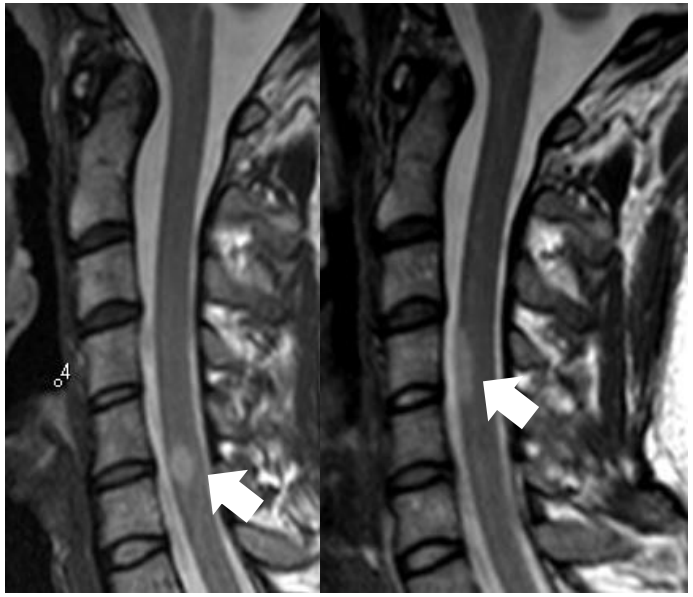
Relapse *and* 1 dissociation criterion

Gadolinium + and -. lesions



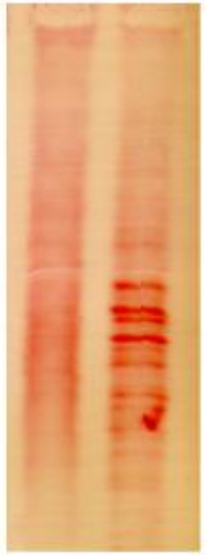
or

a new lesion in a follow up scan



or

OCBs in CSF



Differential diagnosis

- ADEM, Neuromyelitis Optica
- Susac‘s Syndrome
- Mb. Behcet, Neurosarkoidosis
- Lupus, Mb. Wegener, mPAN, Sjögren Syndrome, CNS-vasculitis
- CADASIL, MELAS, LHON
- Mb. Fabry, recurrent strokes
- HIV, syphilis, lyme disease, tuberculosis
- Herededitary leukodystrophies

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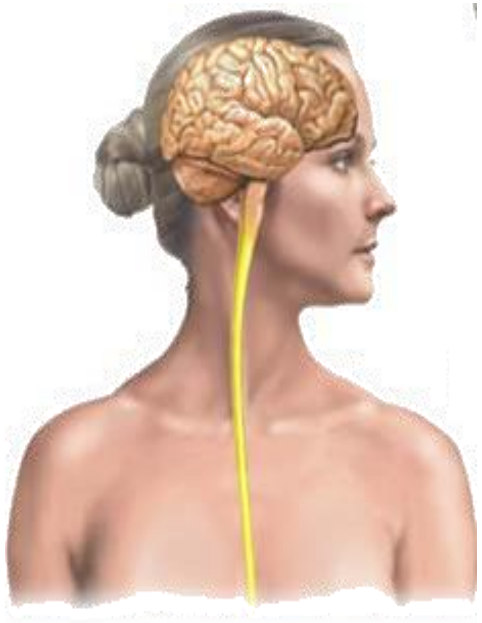
MS risk factors

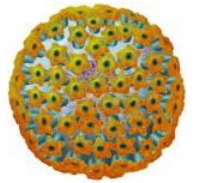
HLA-DR15, 3, 13

> 200 genetic risk factors

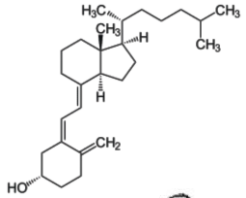
Genes



Environment



Infections
Epstein-Barr Virus?
others?

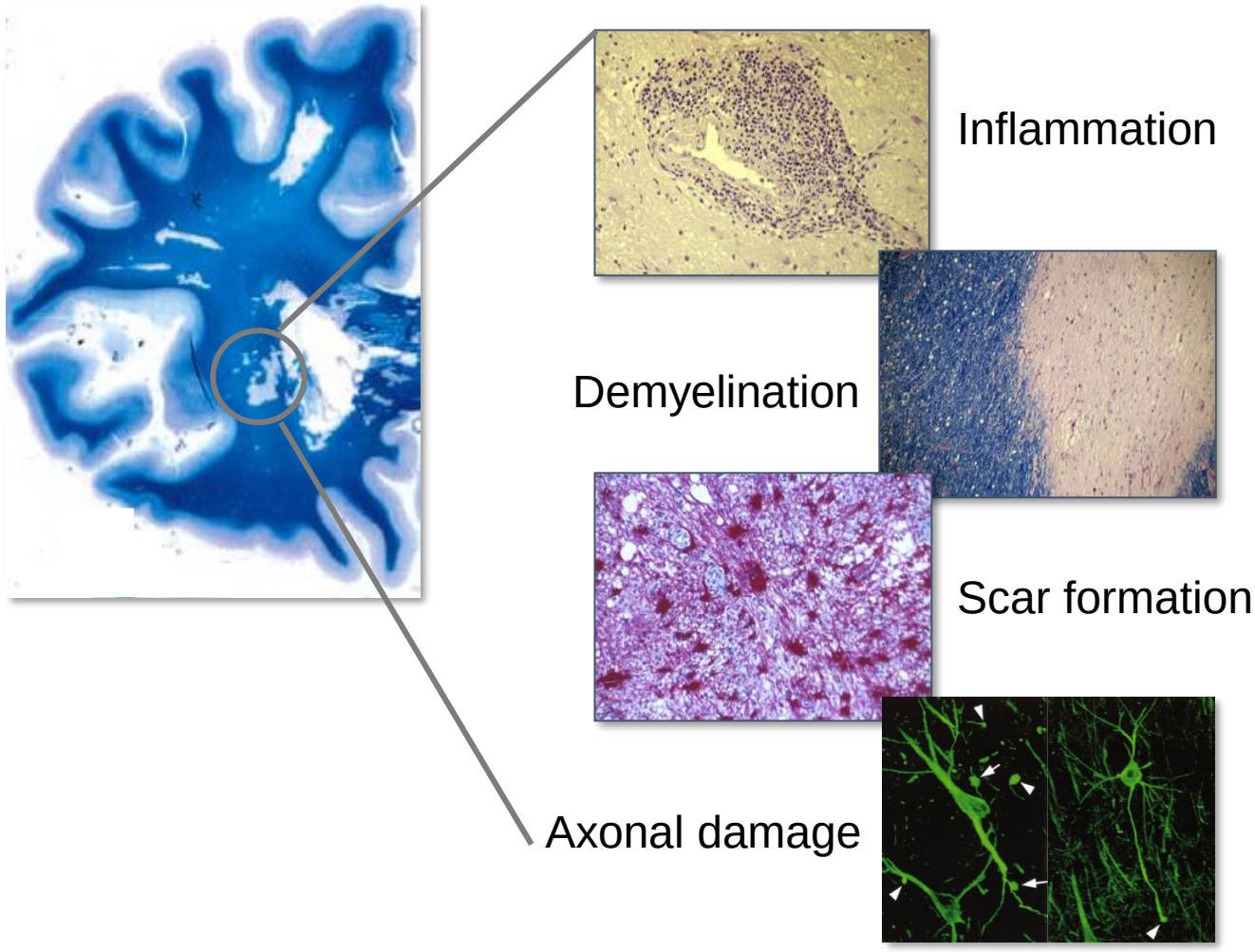


Low Vitamin D level?

Obesity?

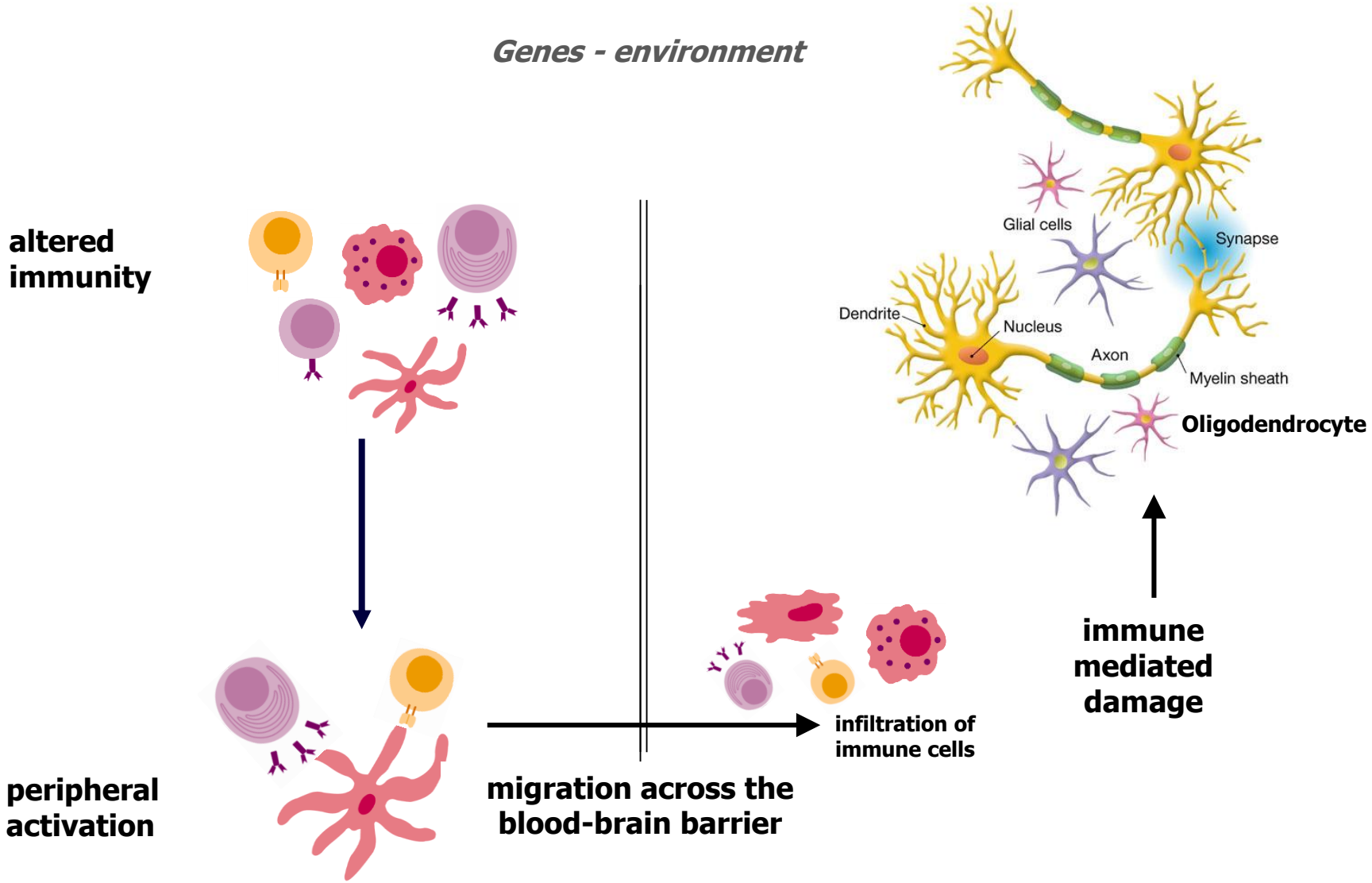
Smoking?

MS pathology



Lucchinetti C, *et al. Ann Neurol* 2000;47:707–717; Trapp B, *et al. Ann Neurol* 2001;50:389–400.

Pathogenesis of MS



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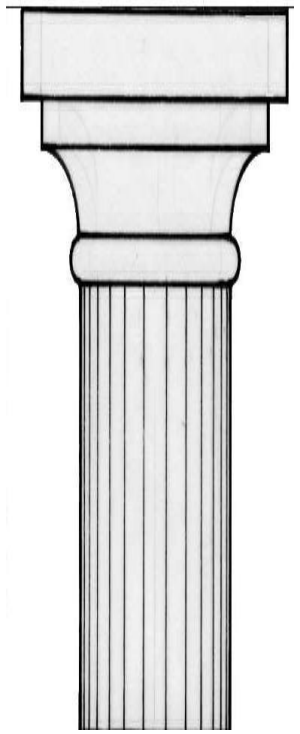
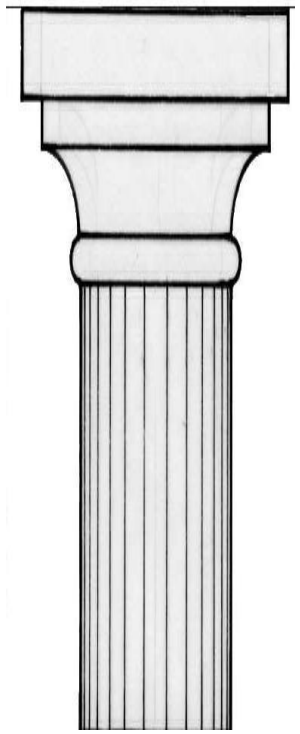
MS treatment strategies

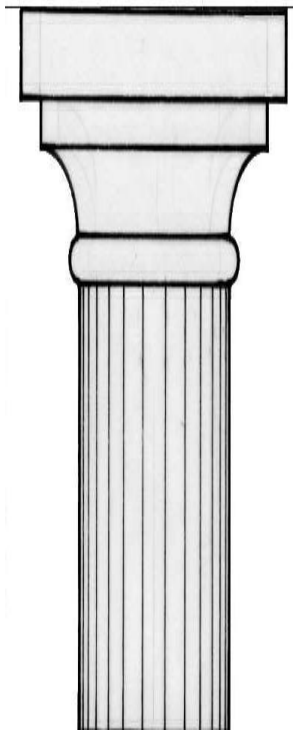
Revert clinical symptoms from relapse



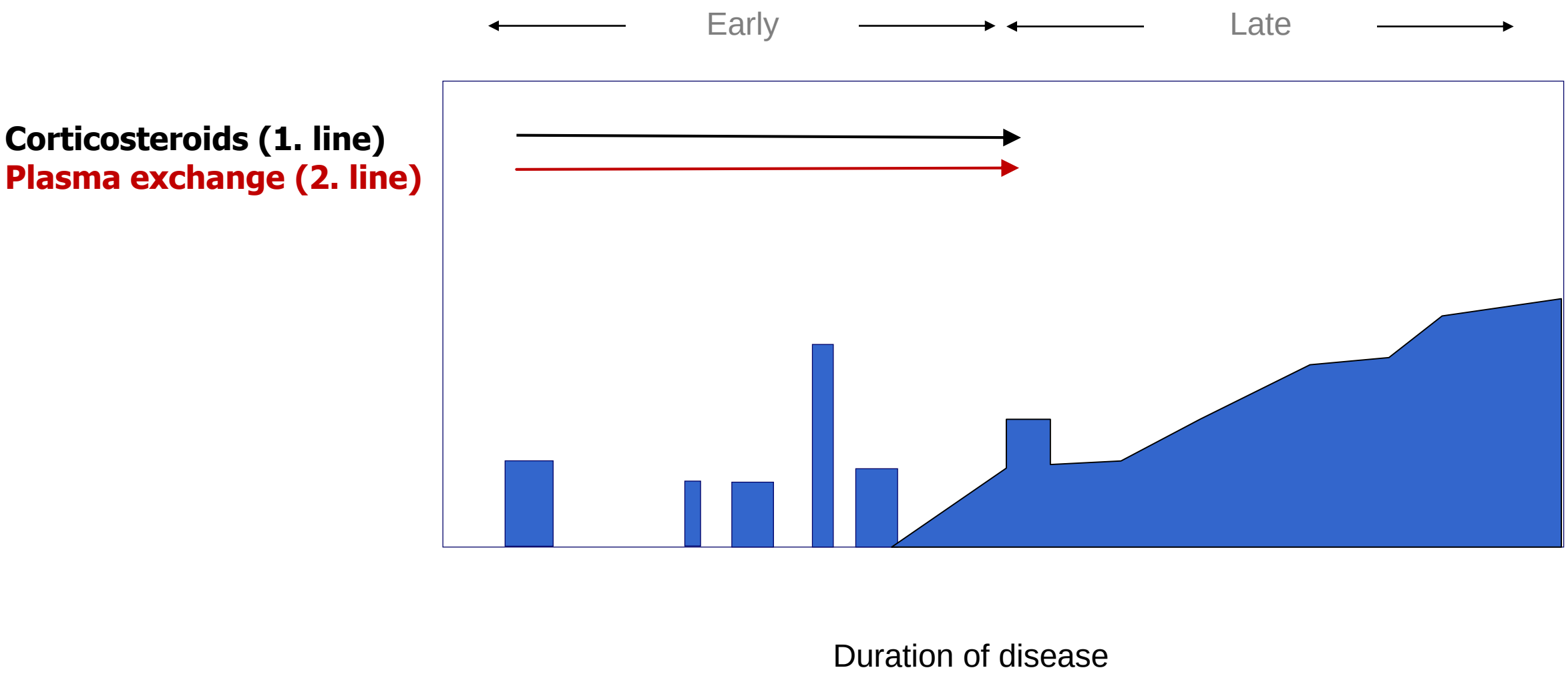
Prevent relapses and disease progression



Treatment of symptoms



Relapse treatment

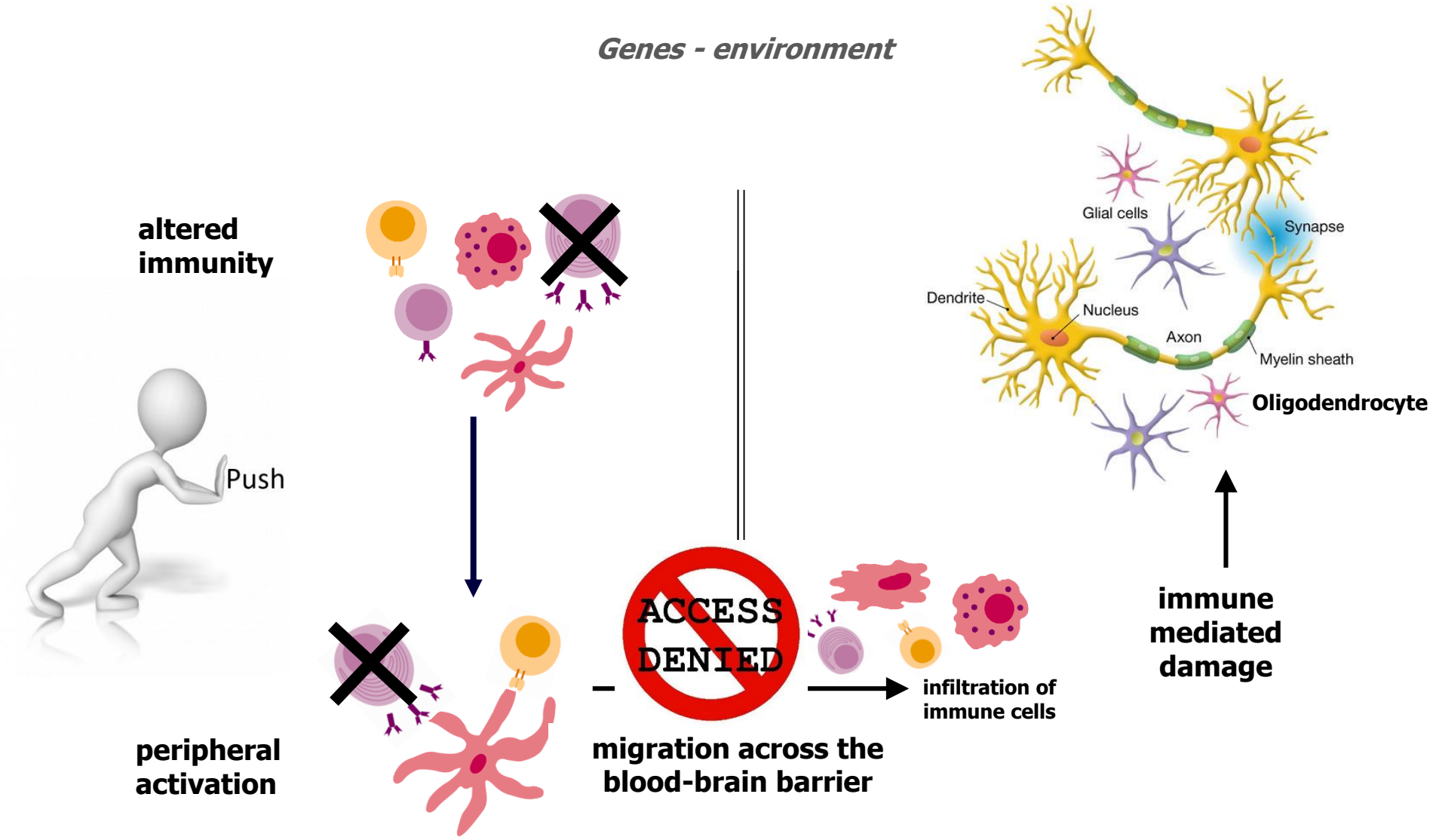


Relapse treatment

Methylprednisolon 500-1000mg/day, oral or i.v. for 3-5 days, taper possible

Plasma exchange or immunabsorption, 5 (-8) times

Preventing new relapses and progression



Immunotherapies for relapsing MS

Class I
moderate efficacy

Betainterferons
Dimethylfumarate
Glatirameroide
Teriflunomide
(Azathioprine)

Class II
Moderate -high efficacy

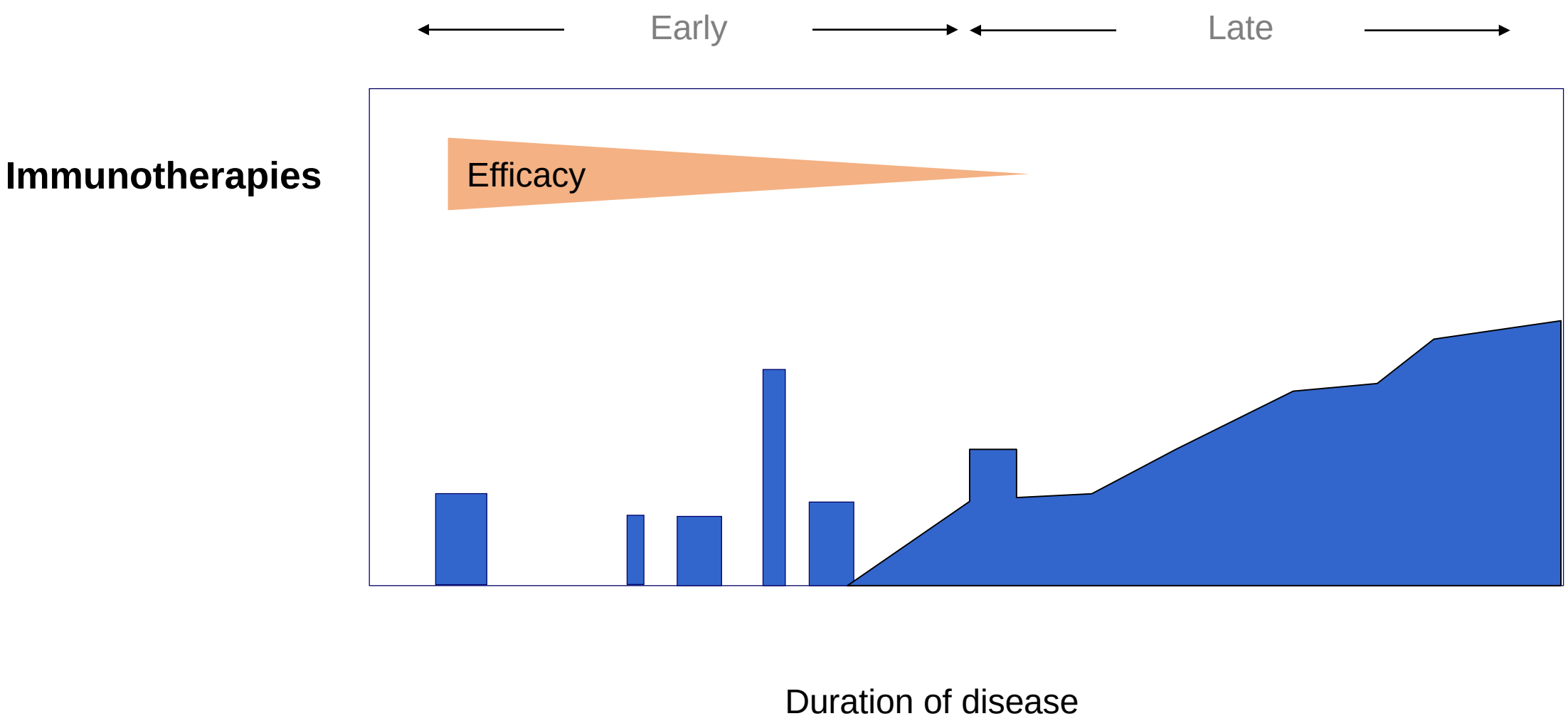
Fingolimod
Cladribin

Class III
high efficacy

Alemtuzumab
CD20 antibodies*
Natalizumab
(Mitoxantrone)

* Ocrelizumab or Rituximab (off label!)

Immunotherapies

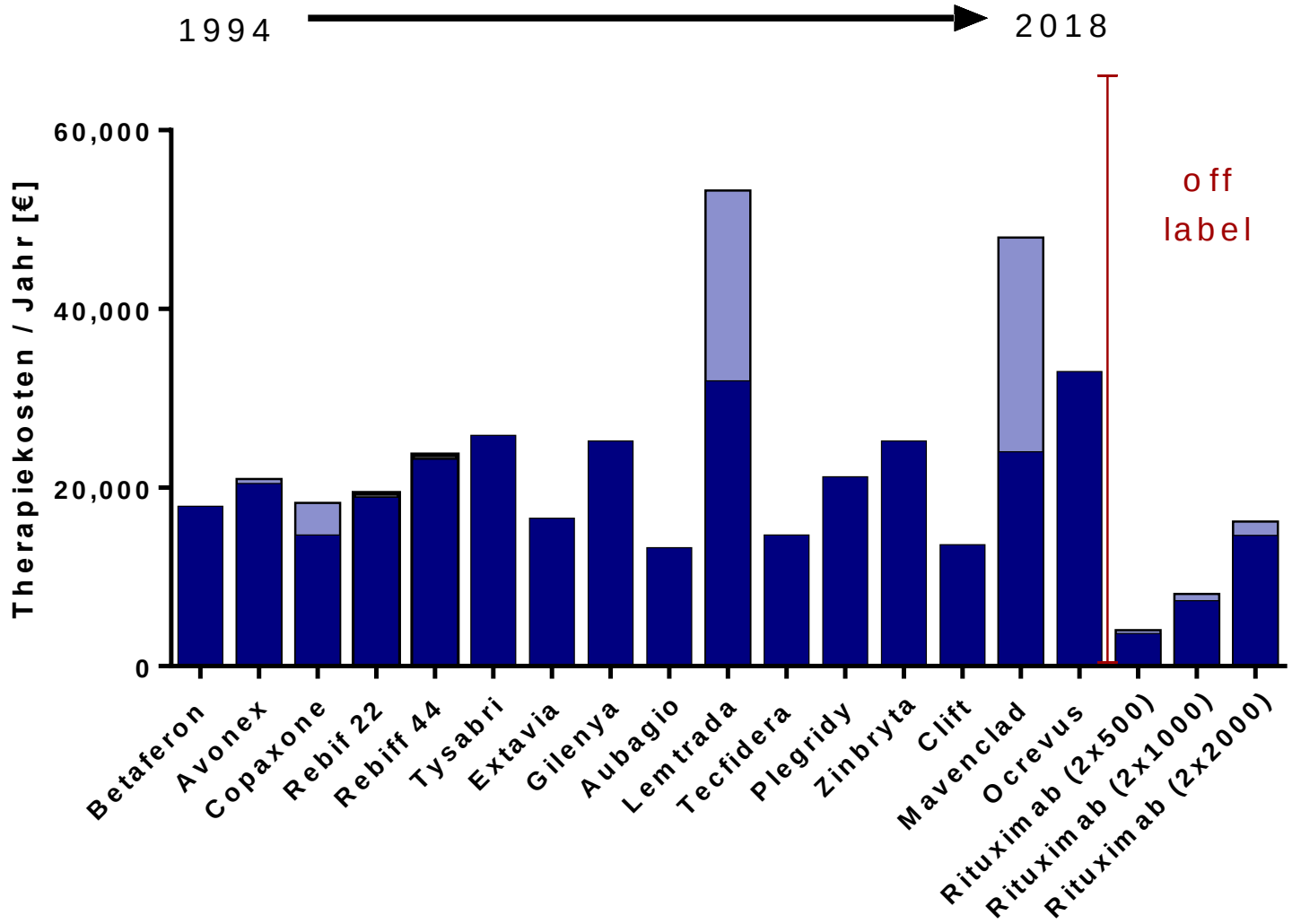


Immunotherapies for relapsing MS

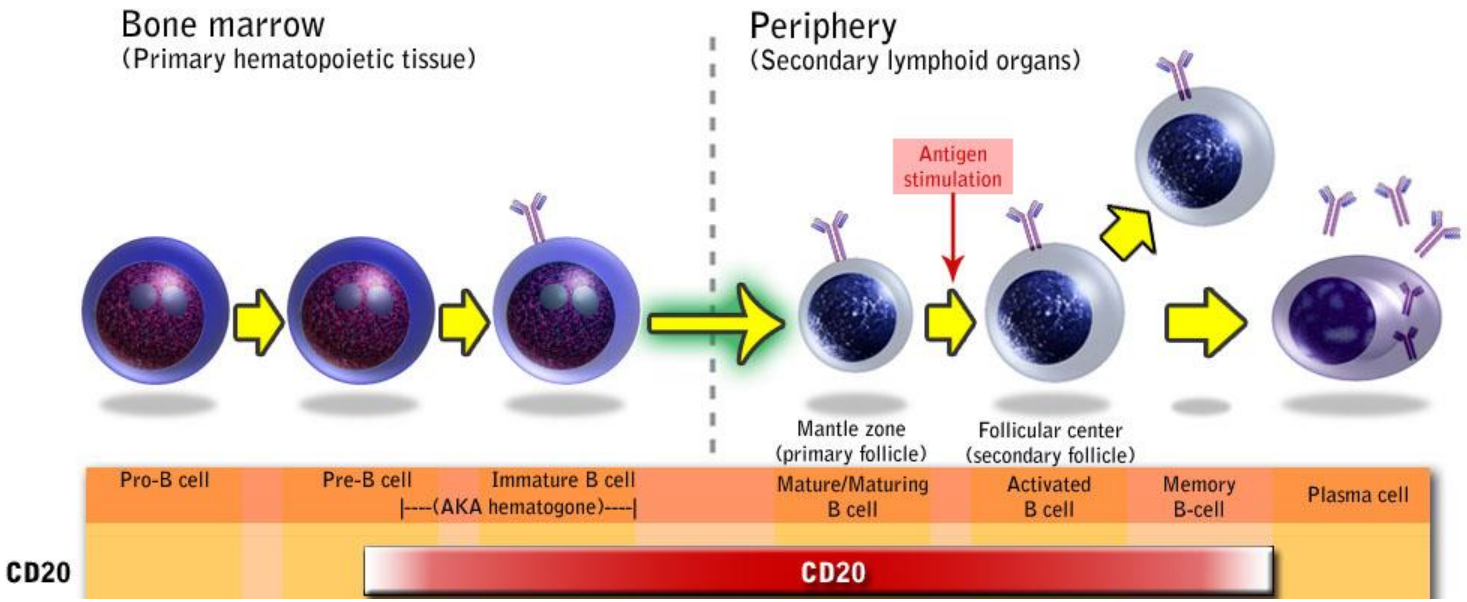
- Fewer new brain and spinal cord lesions (▼ 60-98%)
- Fewer relapses (▼ 30-80%(?))
- Less disability progression (▼ 10-50% (?))

- Some drugs have rare but severe side effects
- Some drugs impact on quality of life
- Some drugs require intense monitoring
- The efficacy of the drugs decreases with disease duration and age
- All approved drugs are very expensive

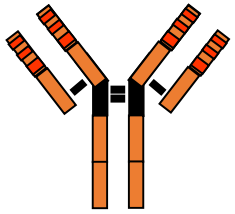
Costs of immuntherapy



CD20 antibodies in MS



Rituximab
Ocrelizumab
Ofatumumab



4 phase II studies
2 phase III studies
„Real world data“

Hauser NEJM 2008, Hawker Ann Neurol 2009, Kappos Lancet 2011, Sorensen Neurology 2014, Alping Ann Neurol 2016, Hauser NEJM 2017, Montalban NEJM 2017, Spelman MSJ 2017

Immunotherapy of MS in countries with limited resources

Rituximab (e.g. Rituxan but also several others): every 6 months 500mg i.v.

Good safety profile (so far at least in Europe), convenient and well tolerated by patients

Low treatment cost in Germany 3000€/year, in India 300€/year

Not licensed for MS but works very well in daily practice (e.g. most used drug in MS in Sweden)

But should only be given to patients with established diagnosis and proven disease activity

Should not be given to patients with chronic infections (e.g. HIV, Hepatitis)

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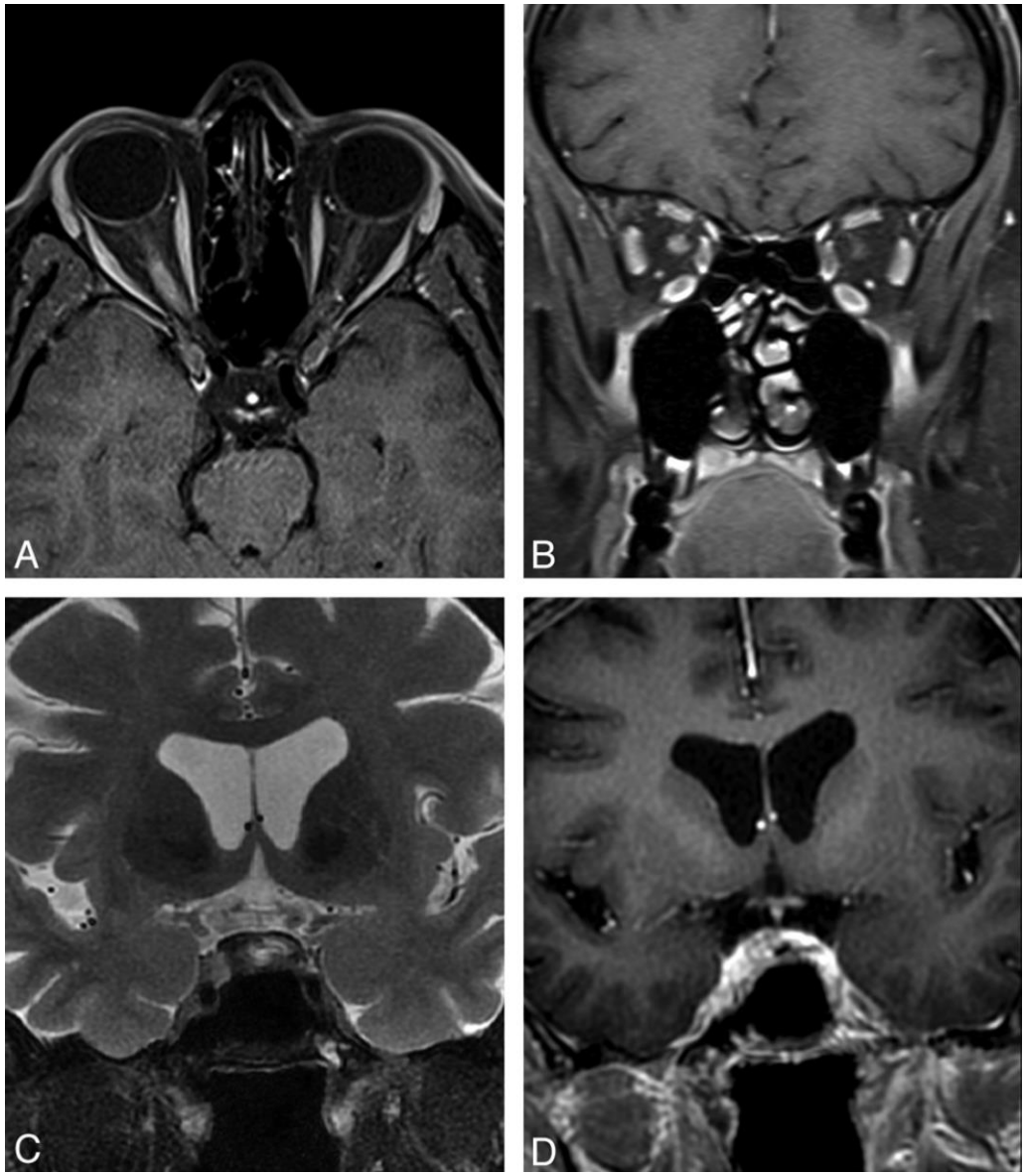
Case history

41 years old women. 5 years ago she developed unilateral vision loss. Vision did not improved after corticosteroid treatment. Over the next five years she developed 5 additional relapses affecting 3 times the optic nerves and twice the spinal cord. The relapses affecting the spinal cord led to sever motor and sensory impairment of both legs and were accompanied by severe pain. After the last relapses the patient remained impaired by moderate paraparesis and unilateral vision loss.


Philips
F

NMO: optic nerve



Barnett 2013

Diagnostic criteria of Neuromyelitis optica (2006)

Optic neuritis und acute myelitis

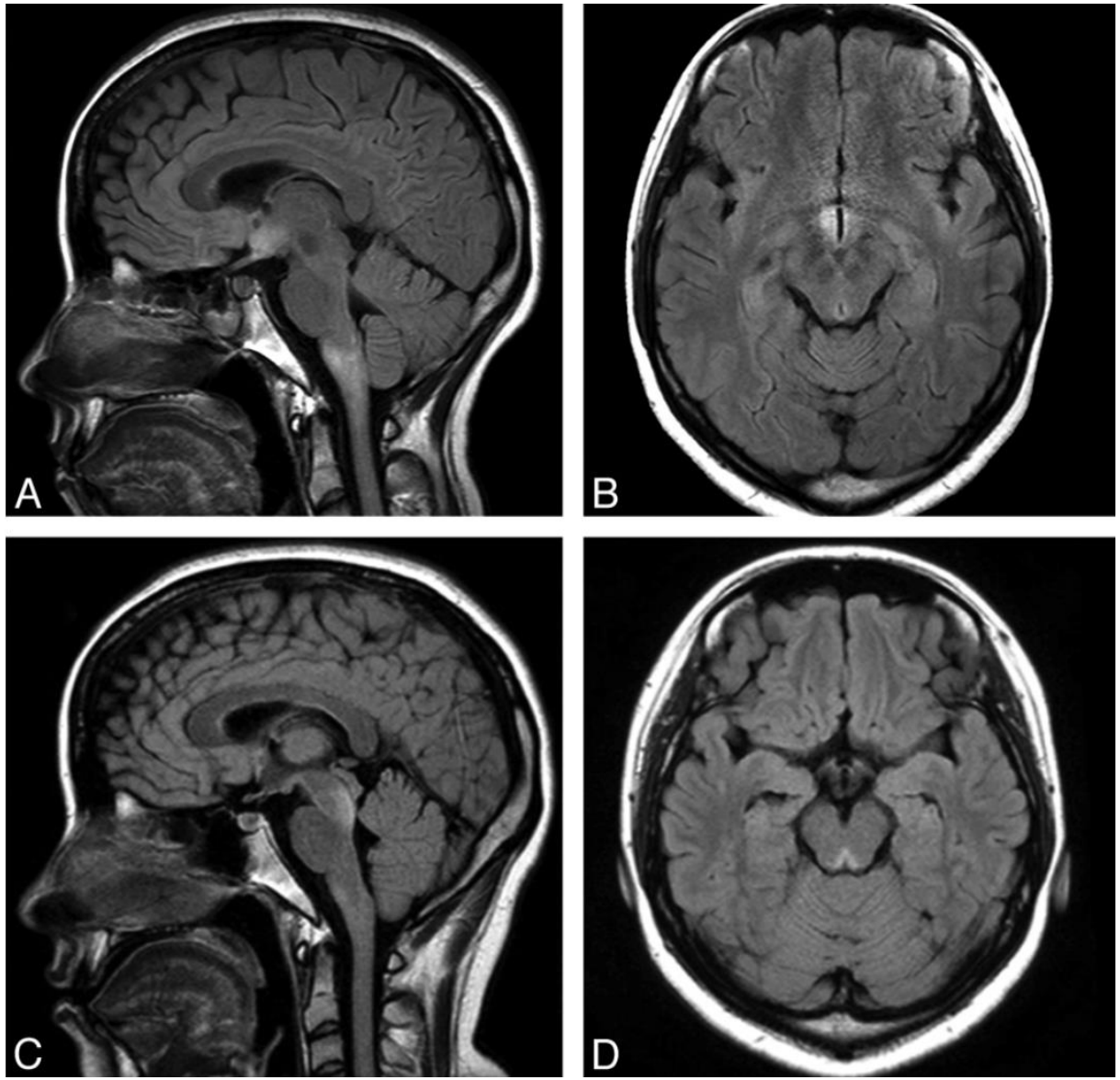
+ two of the three following criteria

1. cMRI does not fulfill the criteria for Multiple Sclerosis

2. Spinal MRI with a lesion that extends over 3 or more spinal segments

3. NMO-IgG antibodies in serum

Wingerchuk et al., Neurology 2006



Barnett 2013

NMO: brain lesions

typical:
periependymal lesions

Barnett 2013

Diagnostic criteria of Neuromyelitis optica (2015)

2015 IPND Neuromyelitis Optica Spectrum Disorder (NMOSD) Diagnostic Criteria

NMOSD With AQP4-IgG

1. At least 1 core clinical characteristic (at right)
2. Positive test for AQP4-IgG*
3. Exclusion of alternative diagnoses**

NMOSD Without AQP4-IgG or Unknown AQP4-IgG Status

1. At least 2 core clinical characteristics (at right) resulting from 1 or more clinical attacks and satisfying all of the following requirements:
   a) At least 1 of: ON, acute myelitis with LETM, or APS
   b) Dissemination in space (≥2 different core characteristics)
   c) MRI requirements, if applicable (at right)
2. Negative test(s) for AQP4-IgG* or testing unavailable
3. Exclusion of alternative diagnoses**

* Using best available detection method (cell-based assay strongly recommended).

Core Clinical Characteristics of NMOSD

Most common:

1. Optic neuritis (ON)
2. Acute myelitis
3. Area postrema syndrome (APS): episode of otherwise unexplained hiccups or nausea and vomiting

Less common:

4. Acute brain stem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Supporting MRI Requirements for NMOSD Without AQP4-IgG

1. **Acute optic neuritis:** brain MRI normal or demonstrating only nonspecific white matter lesions; OR optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm

Wingerchuk et al., Neurology 2015

Immunotherapy of NMO

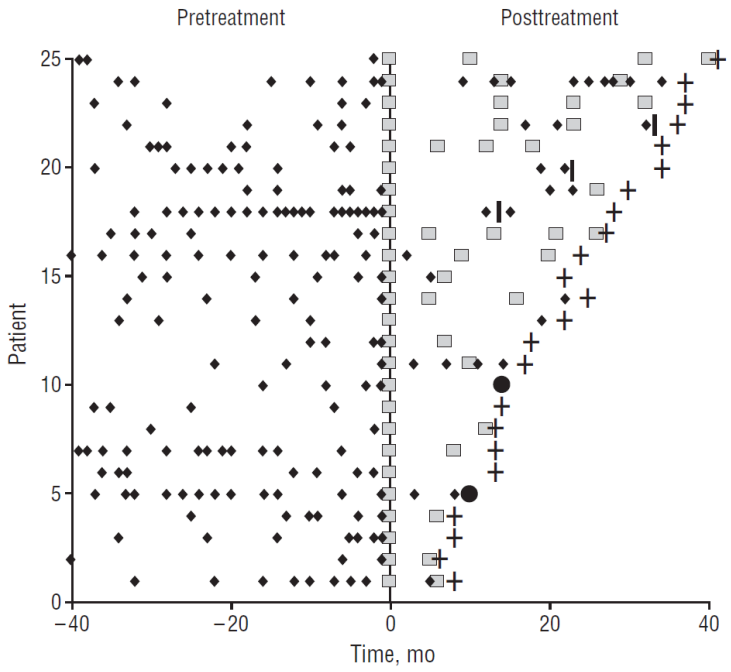
Trials supporting the use of immunosuppressive drugs in the treatment of NMO.

Drug	Date	Lead Author	Location	Population size
Azathioprine	1998	Mandler	United States	7
	2008	McKeon	United States	10
	2010	Bichuetti	Brazil	25
	2010	Sarhaian	Iran	28
	2011	Constanzi	United States	99
Mycophenolate	2009	Jacob	United States	24
Rituximab	2005	Cree	United States	8
	2008	McKeon	United States	8
	2008	Jacob	United States	25
	2011	Bedi	United States	23
	2011	Pellkofer	Germany	10
	2011	Kim	Korea	30
Methotrexate	2000	Minagar	United States	8
Oral corticosteroids	2007	Watanabe	Japan	11
Mitoxantrone	2006	Weinstock-Guttman	United States	5
	2011	Kim	Korea	20

Multiple Sclerosis and Related Disorders 1 (2012) 180–187

Rituximab in NMO

n=25



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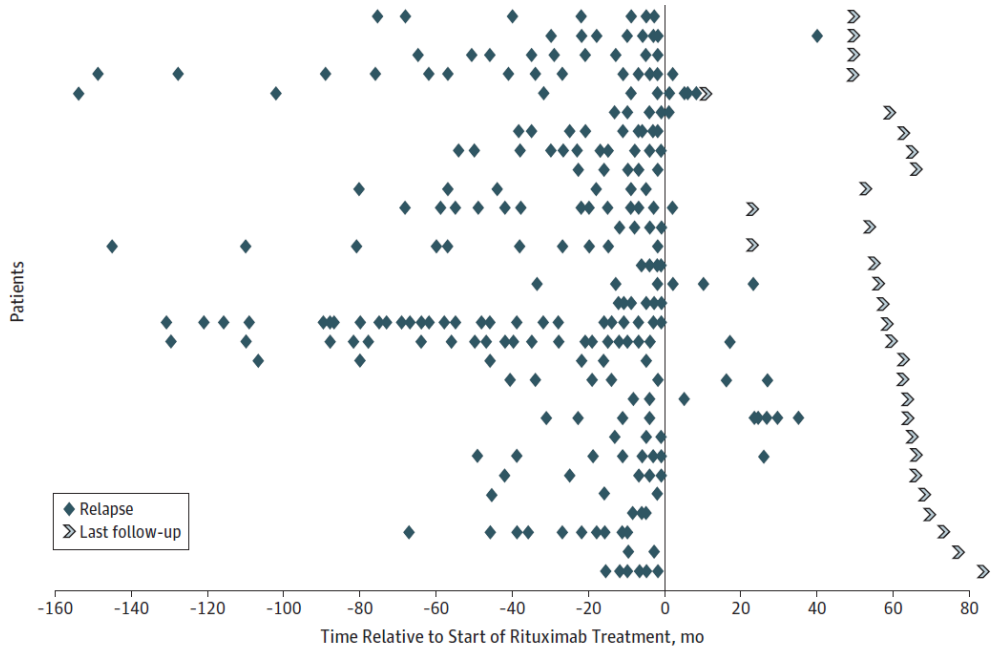


Jacob, *Arch Neurol* 2008

Kim, *Jama Neurol* 2014

New drugs in NMO

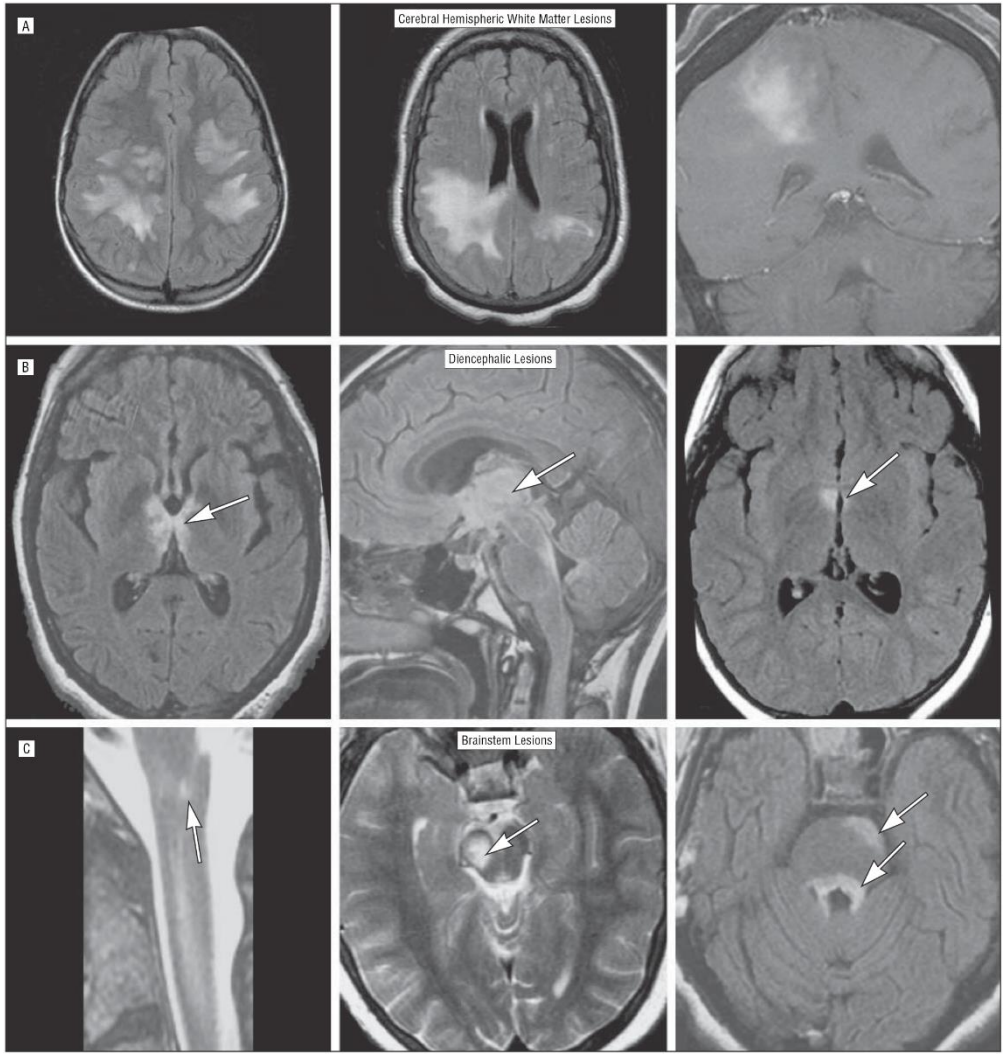
- Complement inhibitor Eculizumab (Solaris ®)
- Interleukin-6 receptor blocker (e.g. Tocilizumab®, Satralizumab® (SA 237)
- CD19 antibody

Summary

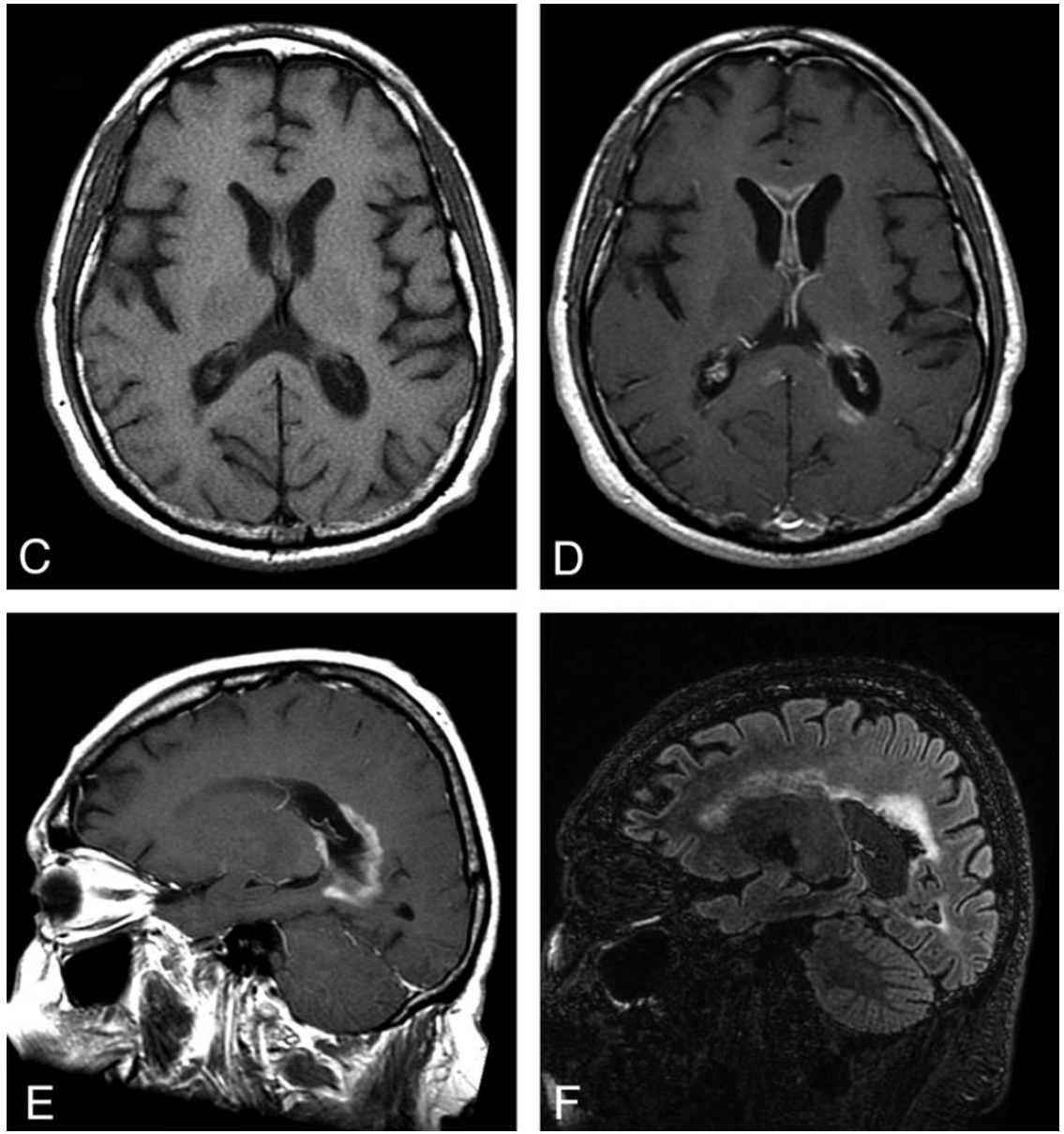
- Multiple sclerosis is the most prevalent autoimmune disease of the nervous system in Europe and will most likely become much more prevalent in Africa in the future.
- The criteria of dissemination in space (DIS) and time (DIT) have to be met to diagnose MS.
- MS relapses can be treated with high dose corticosteroids or plasma exchange.
- Many drugs are approved for immunotherapy of MS. CD20 antibodies are a new treatment option with particular interest for countries with limited financial resources.
- Neuromyelitis optica differs from MS with respect to phenotype and pathophysiology. NMO relapses are treated similar to MS relapses. Rituximab and immunosuppressants are the most widely used drugs for treatment of NMO.


Thanks for your attention!

Atypical lesions in Neuromyelitis optica (2015)



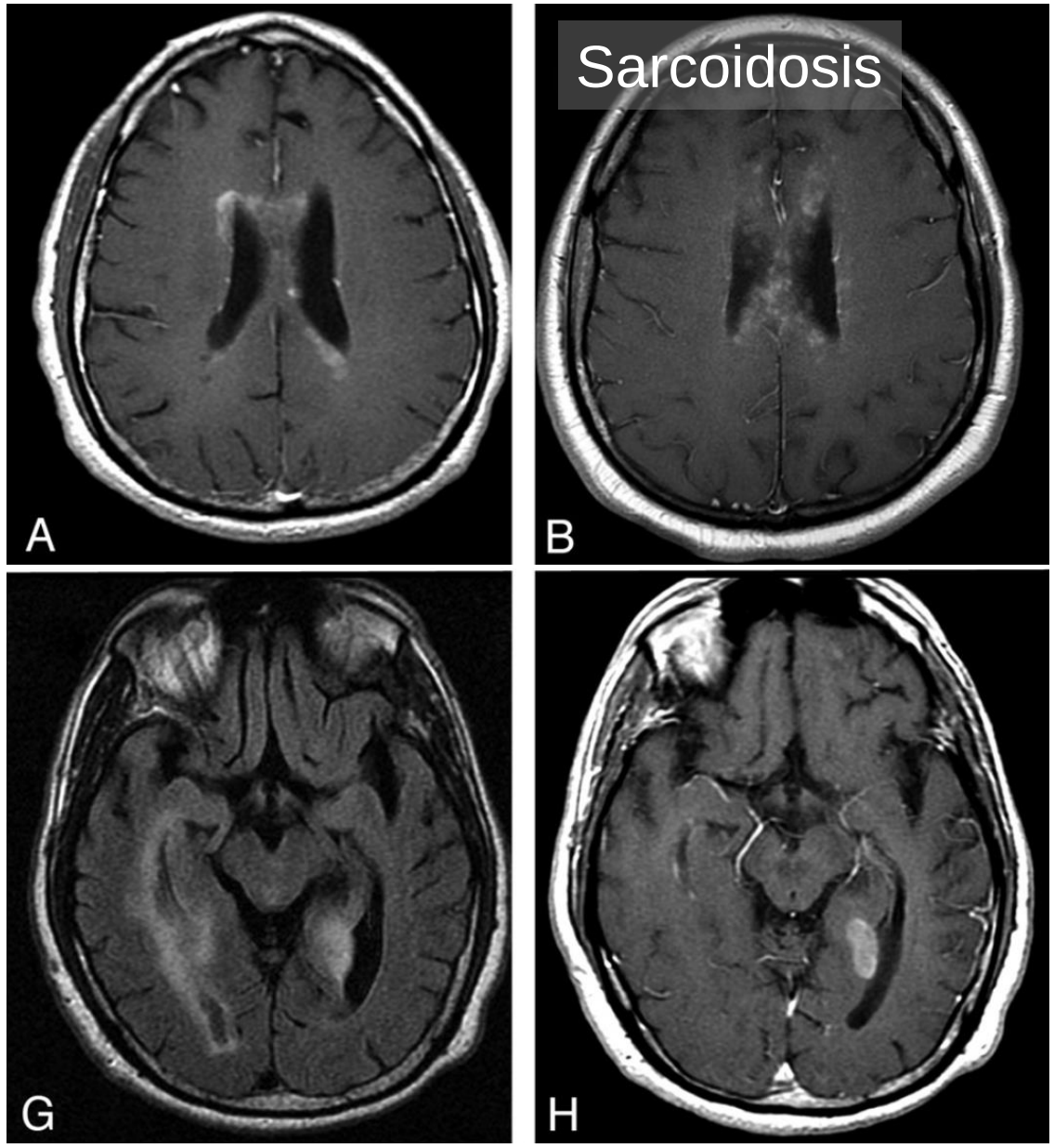
◂ Lesions in regions with strong AQP4-expression (Pittock 2006)



NMO: brain lesions

typical?:
periependymal lesions of lateral ventricles

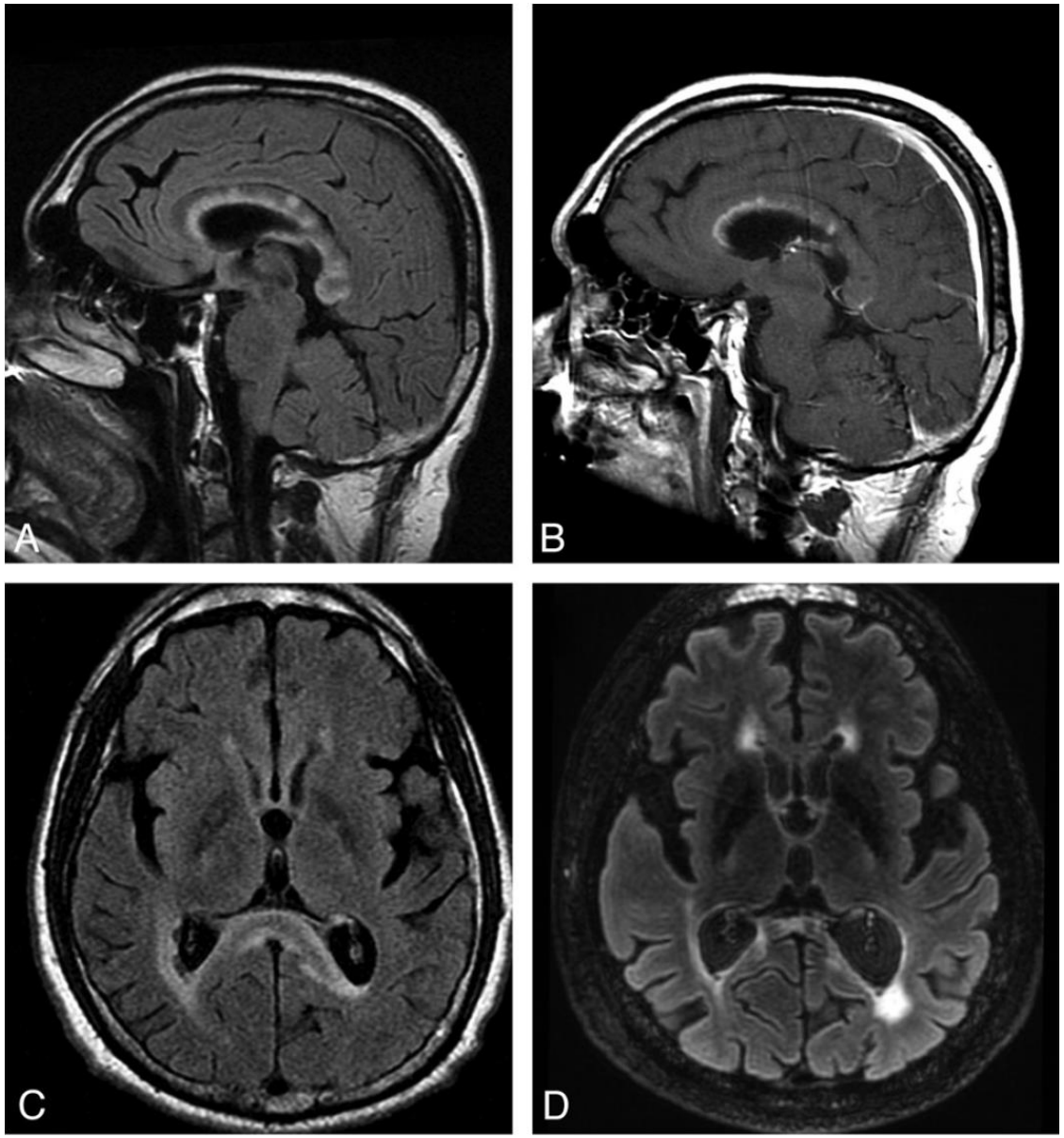
Barnett 2013



NMO: brain lesions

periventricular lesions

Barnett 2013

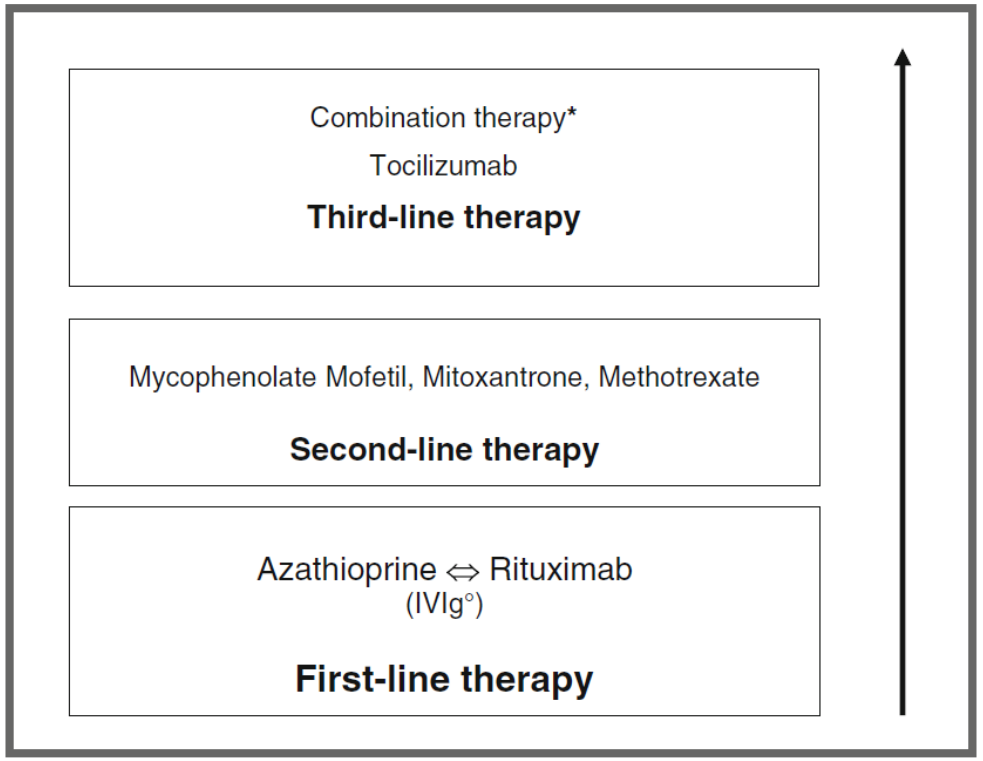


NMO: brain lesions

callosal lesions

Barnett 2013

Therapie der NMO



*Includes:

a) combination of steroids plus cyclosporin A or methotrexate or azathioprine

b) combination of immunosuppression plus intermittent plasma exchange

c) combination of rituximab with methotrexate or intravenous immunoglobulins (IVIg)

Trebst, *J Neurol* 2014