Brain MRI in optic neuritis
MAGNIMS symposium, EUNOS

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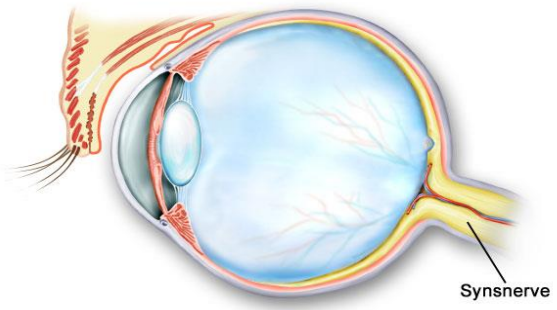
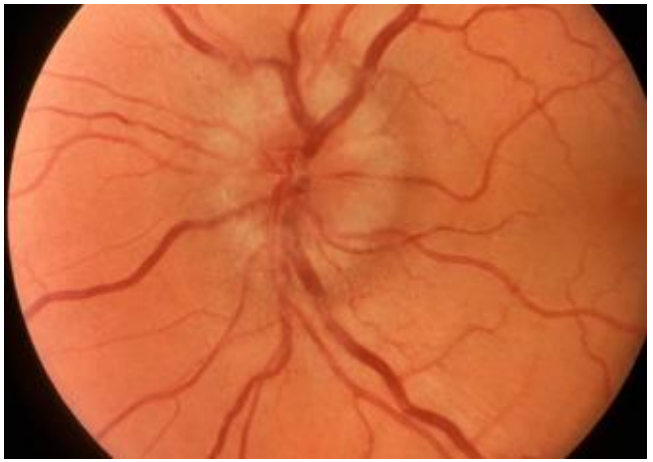
Optic neuritis

- Unilateral (in 90%) painful visual impairment



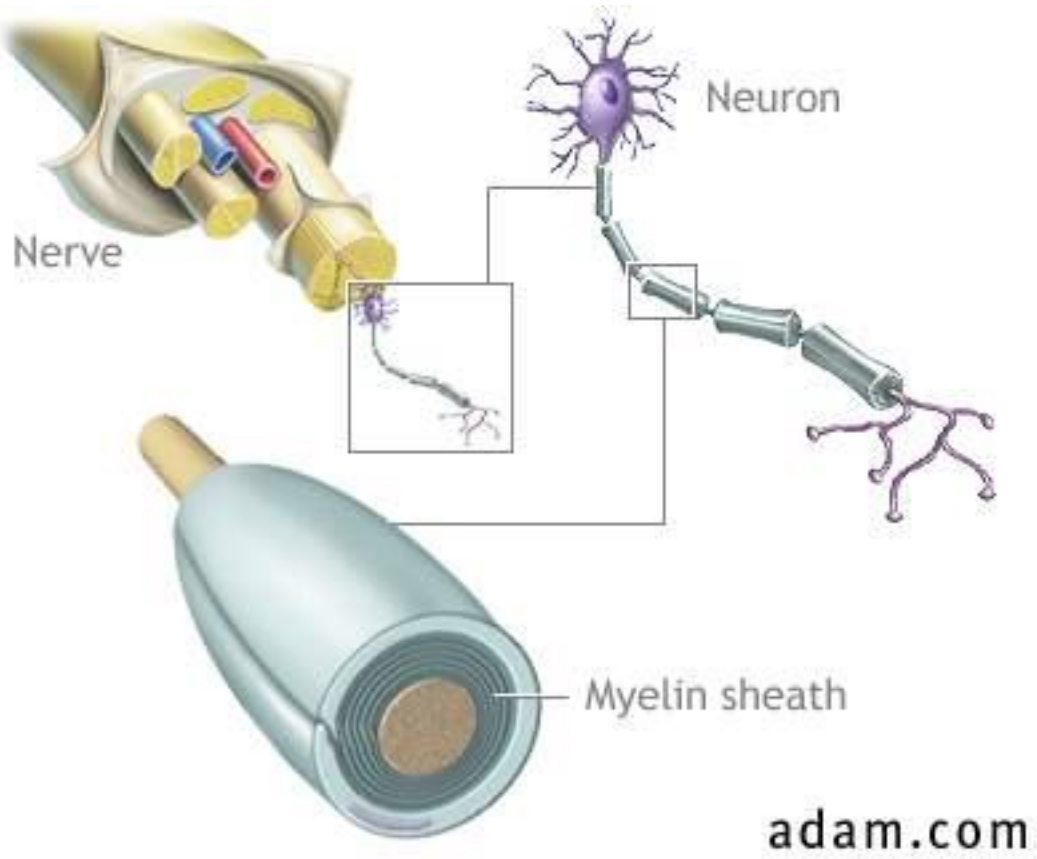
- Acute/subacute onset with progression in 2 days - 2 weeks



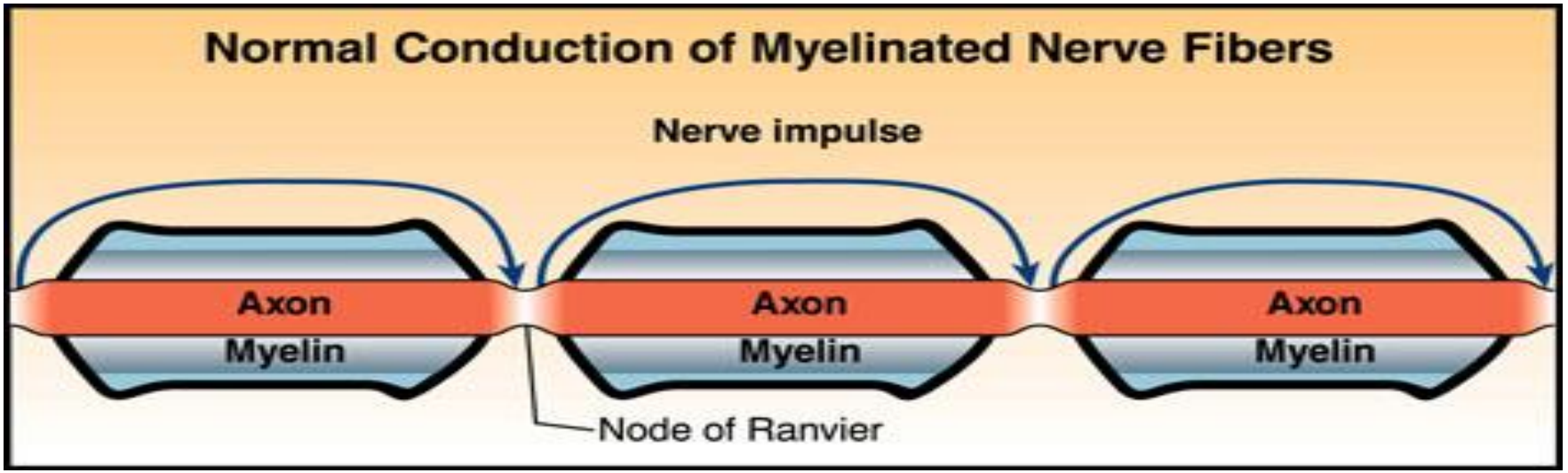
Definition af optic neuritis

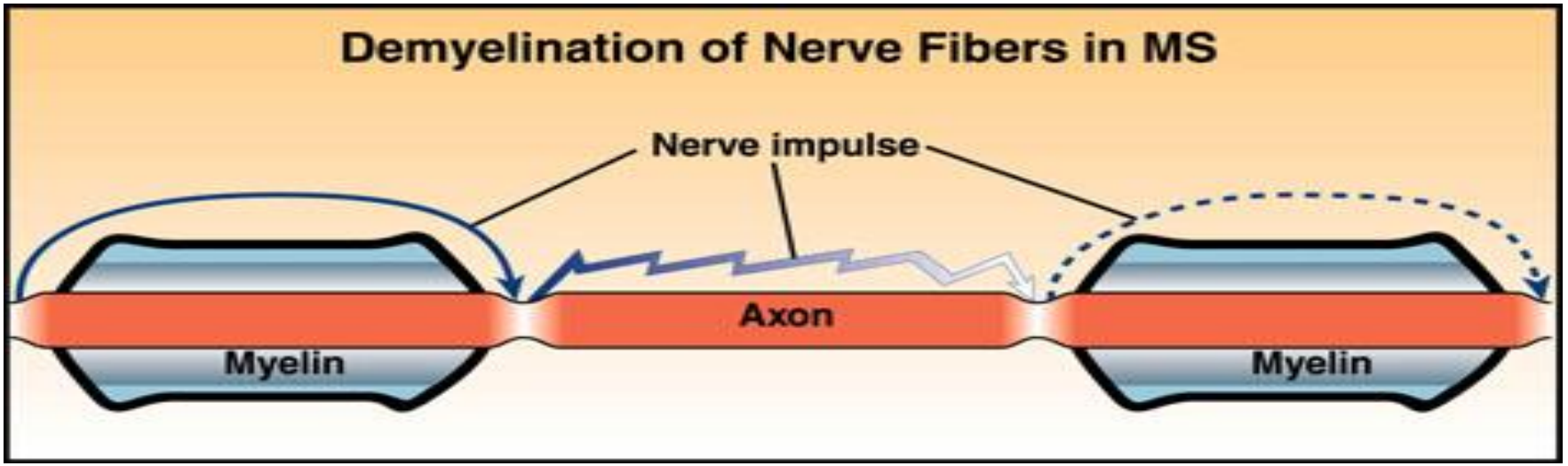
- IHS:
- A) Dull pain behind one or both eyes, worsened by eye movement and fulfilling criteria C and D
- B) Visual impairment due to a central or paracentral scotoma
- C) Onset of pain and onset of visual impairment separated by <4 weeks
- D) Pain resolves within 4 weeks
- E) A compressive lesion has been ruled out

Disease mechanisms



Disease mechanisms





OPTIC NEURITIS

- ON onset symptom for Multiple Sclerosis (MS) (20%)
- Same pathogenesis as MS in typical ON
- Well-characterized symptoms: ideal as a research model for a MS attack
- Fast progressing visual loss and pain
- Impact on colour perception
- 90% mono-ocular
- Spontanious remission within a few months
- 60 % complain of abnormal vision after 1 year

Atypical ON (aetiology)

- Infectious, post-viral and parainfectious
- Granulomatous and perineuritis
- Autoimmune
- Contiguous inflammation of sinuses, meninges or orbit

Post-viral, parainfectious, and infective optic neuropathy

- Chickenpox, rubella, infectious mononucleosis, mumps in particular (children, bilateral, simultaneous)
- Treatment with interleukin-2, interferon alpha, bee-stings, and MMR vaccination

Granulomatous and steroid dependent optic neuropathy

- Visual loss and disc swelling is characteristic
- Syphilis, Tb, cryptococcus, sarcoidosis, lymphoma, Wegener, and idiopathic orbital inflammatory disease

SLE and systemic vasculitis

- SLE, Sjogren, polyarteritis nodosa, Churg-Strauss syndrome, Bechet.

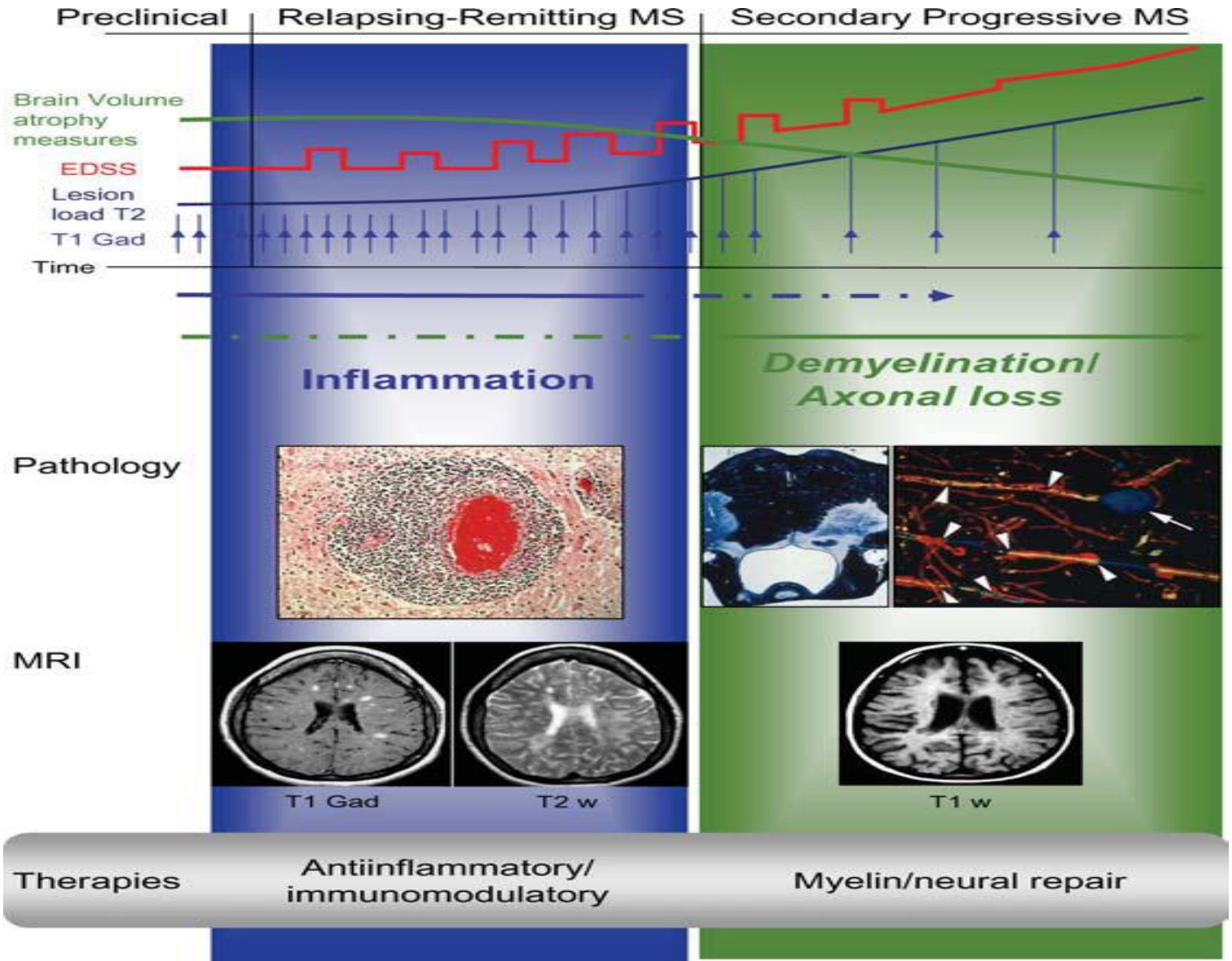
Paranasal sinus disease

- Mucocoeles and pyomucocoeles
- orbitalcellulitis

ON: relation to MS

Optic neuritis (ON) is an inflammatory condition of the optic nerve presumably of autoimmune origin, and more than 50 % of cases herald development of MS.

MULTIPLE SCLEROSIS
overview of the disease progression



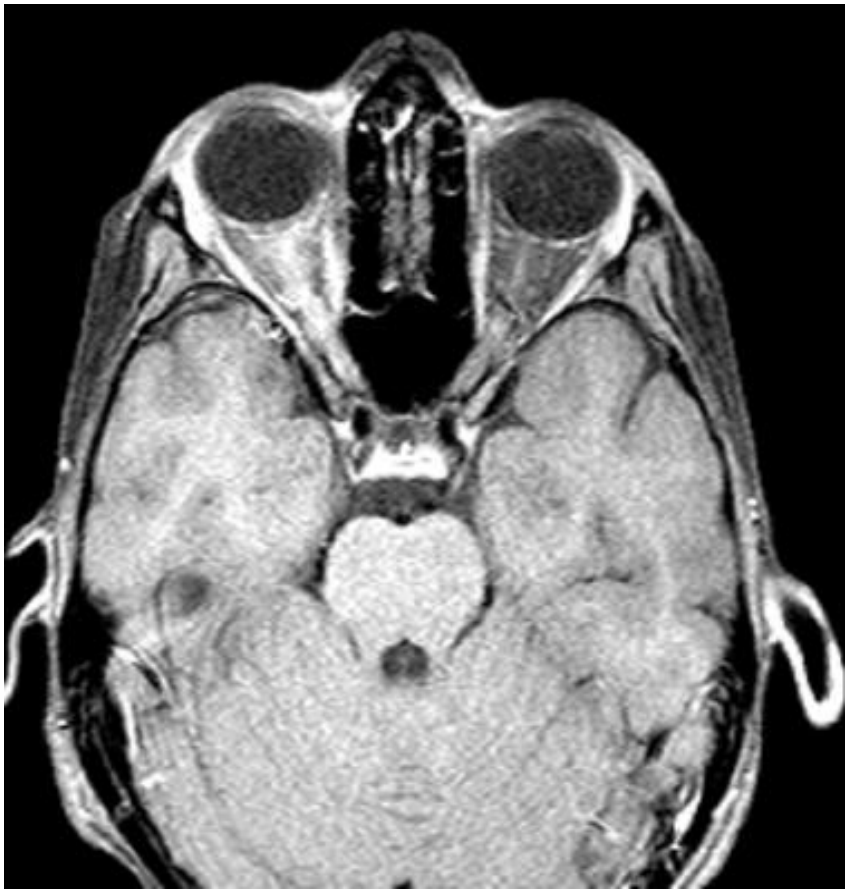
Optic neuritis

Risk of MS after 5 years

- Normal brain MR 16%
- 1-2 lesions 37%
- More than 3 lesions 51%

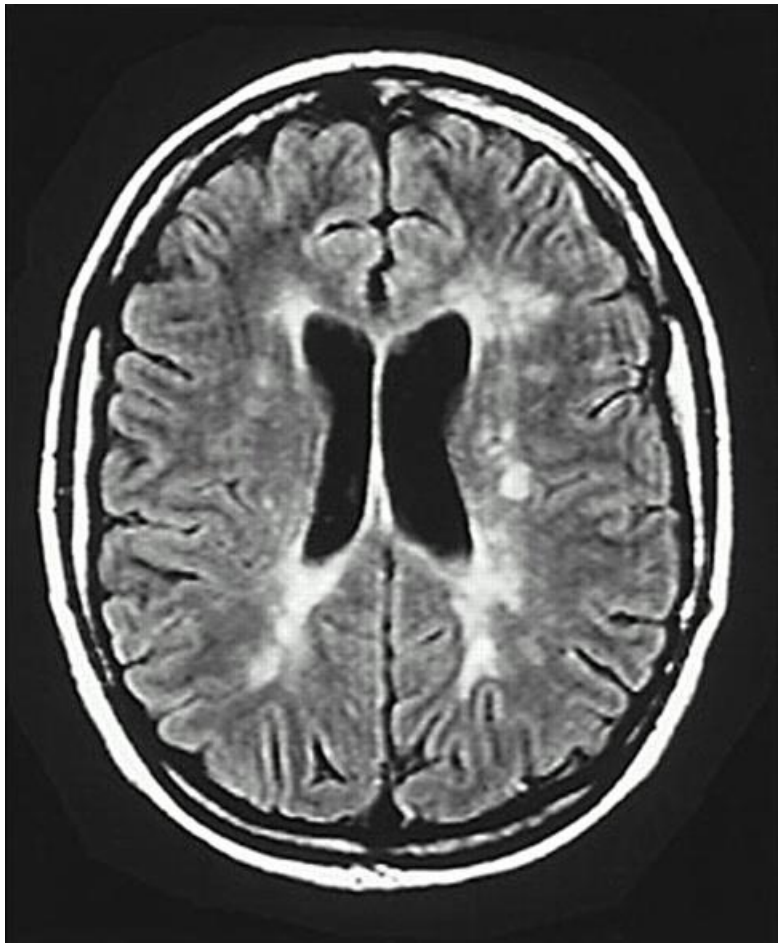
Risk of MS after 15 year

- Normal brain MR 25%
- White matter lesions 75%

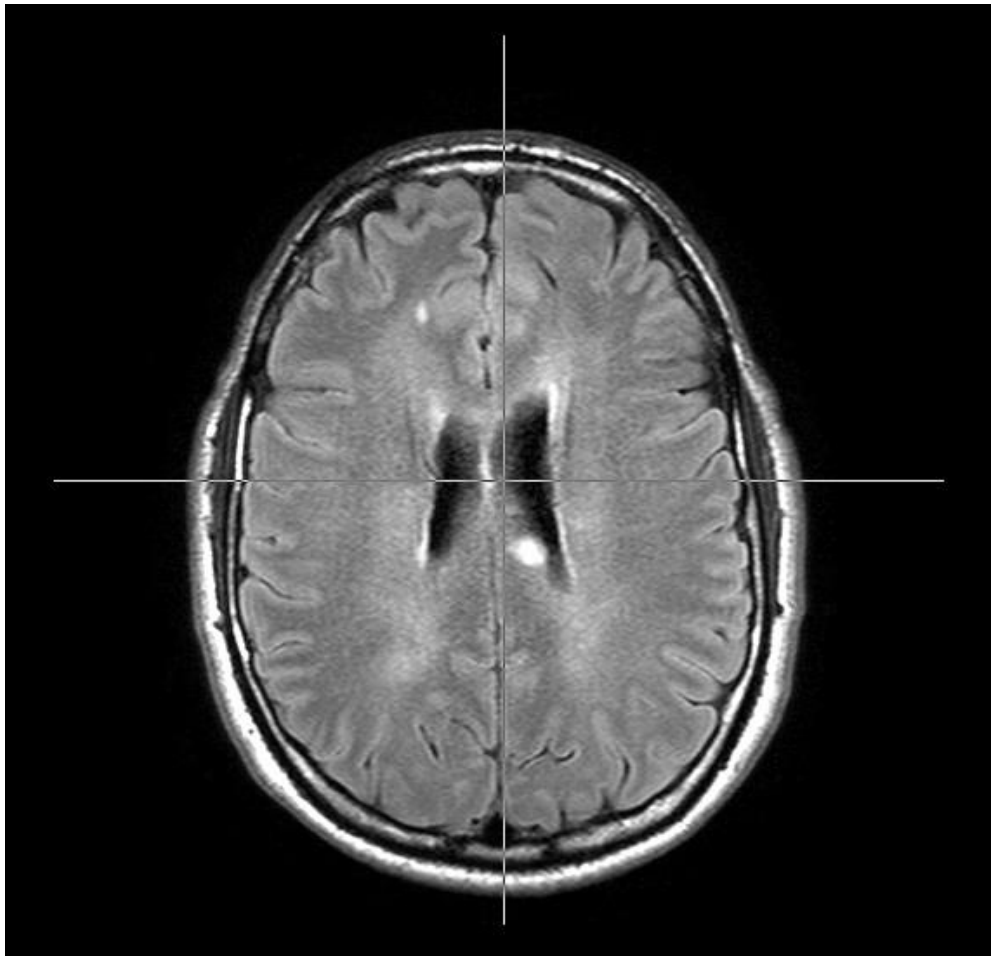


Typical MR changes in MS

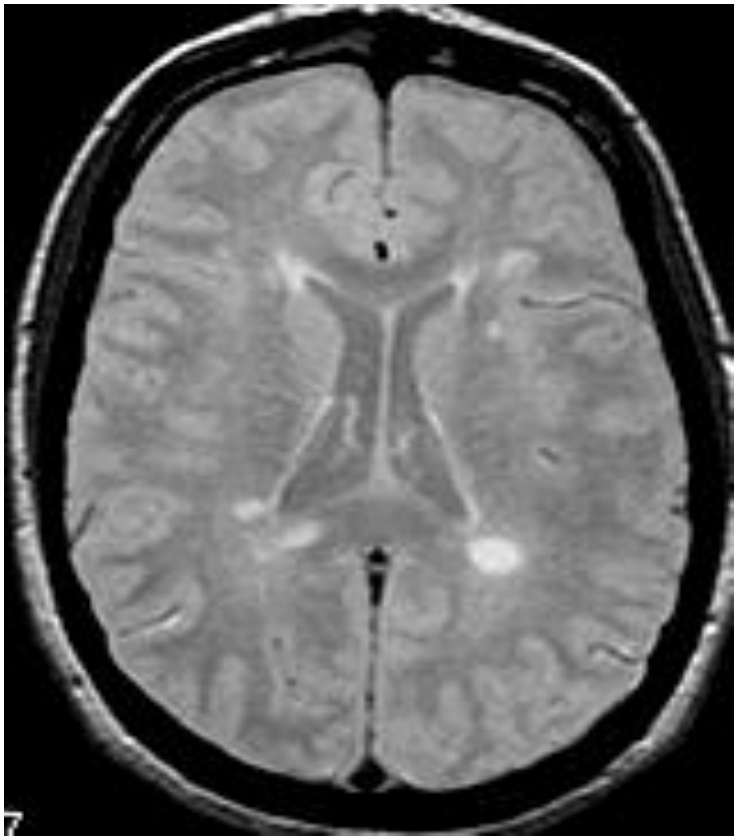
- Multiple WM lesions
- Oval
- Lesions > 3 mm
- Corpus callosum involvement
- Directed perpendicularly on the ventricles
- Localized perpendicularly juxta-cortical or infratentorial
- Often contrast enhancing

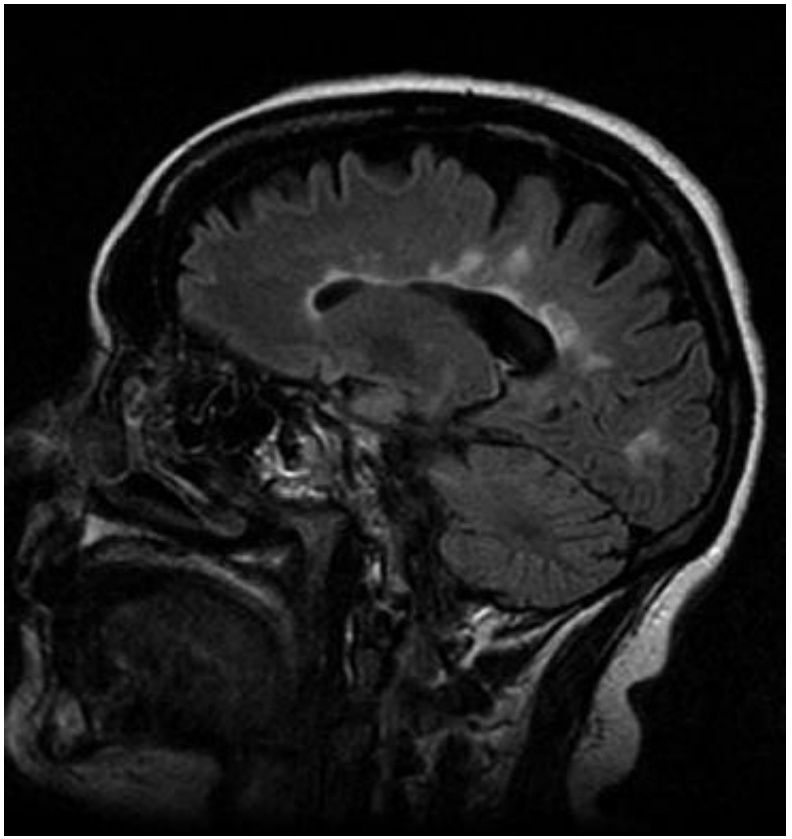


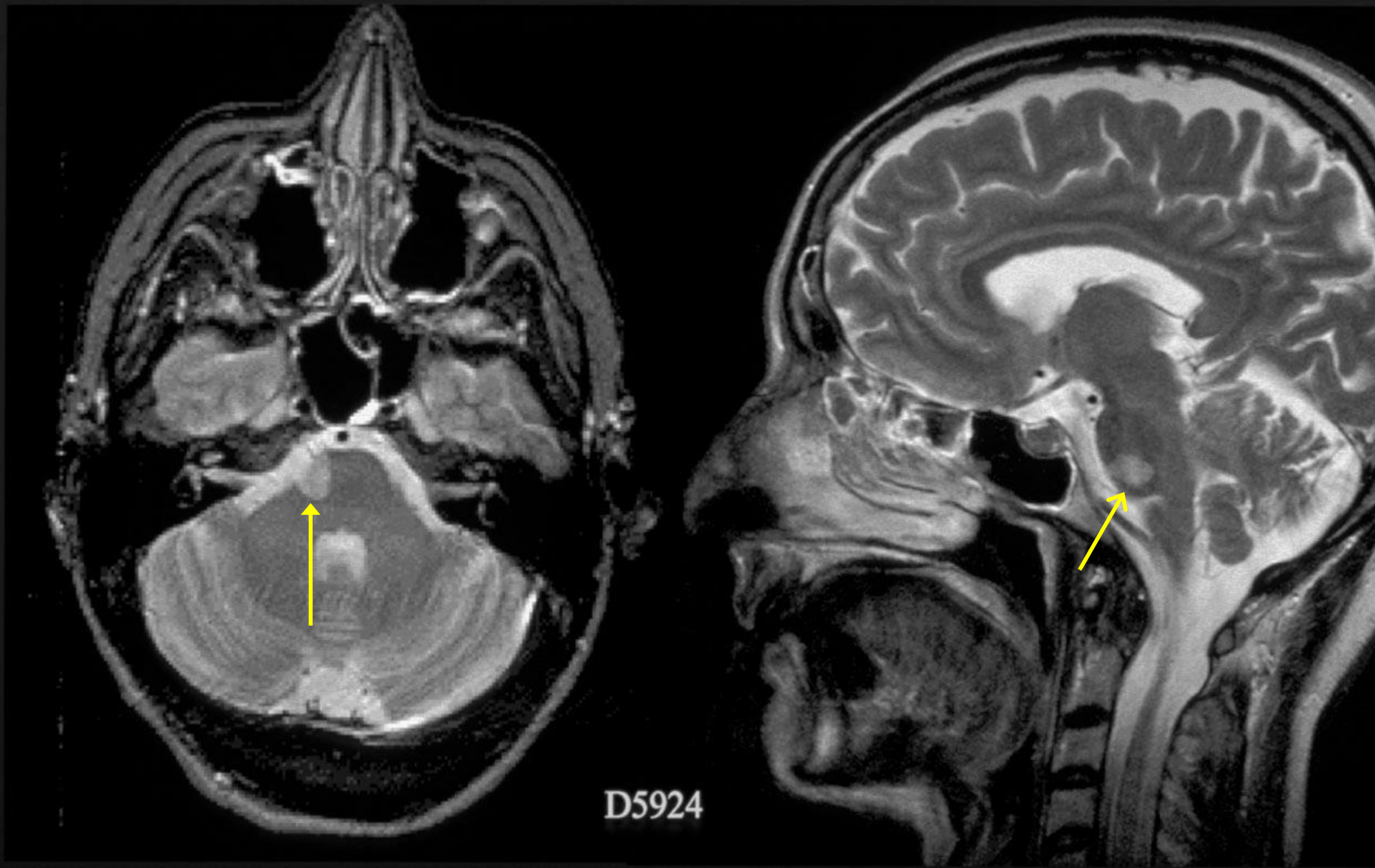
Periventricular lesion



Classical demyelinating lesions



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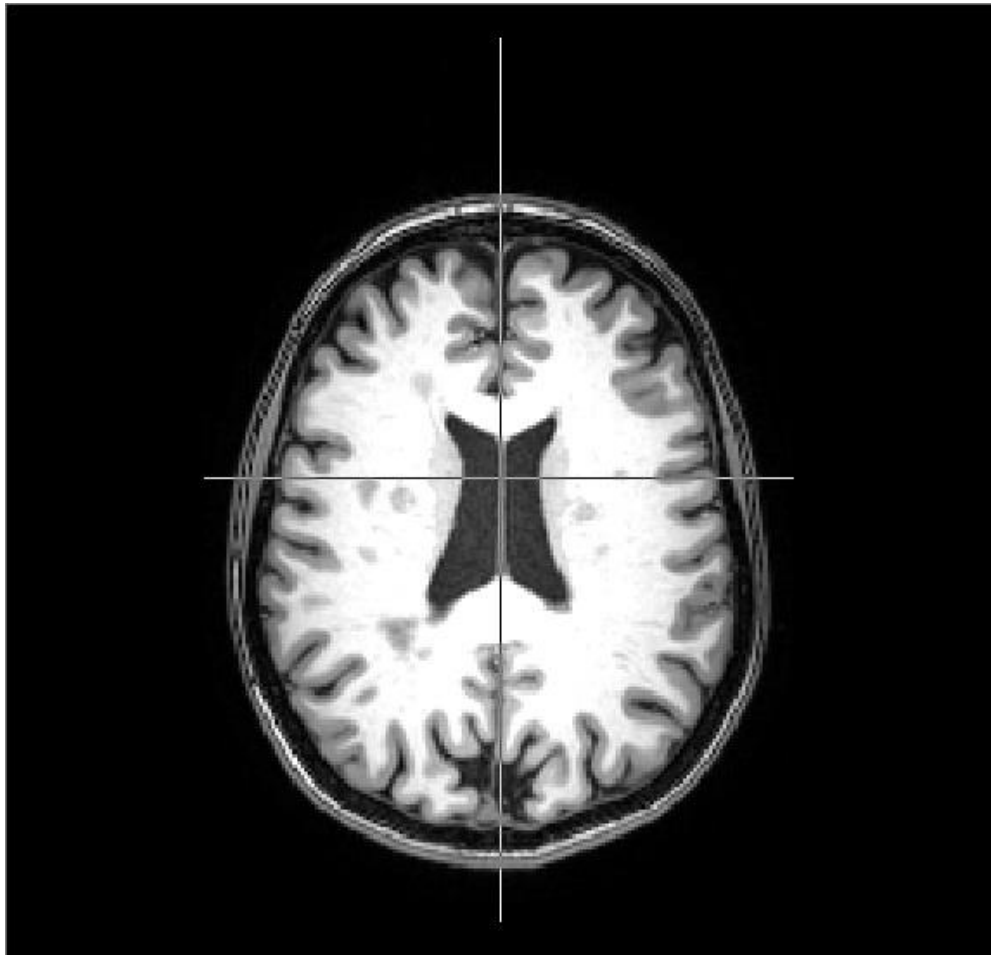

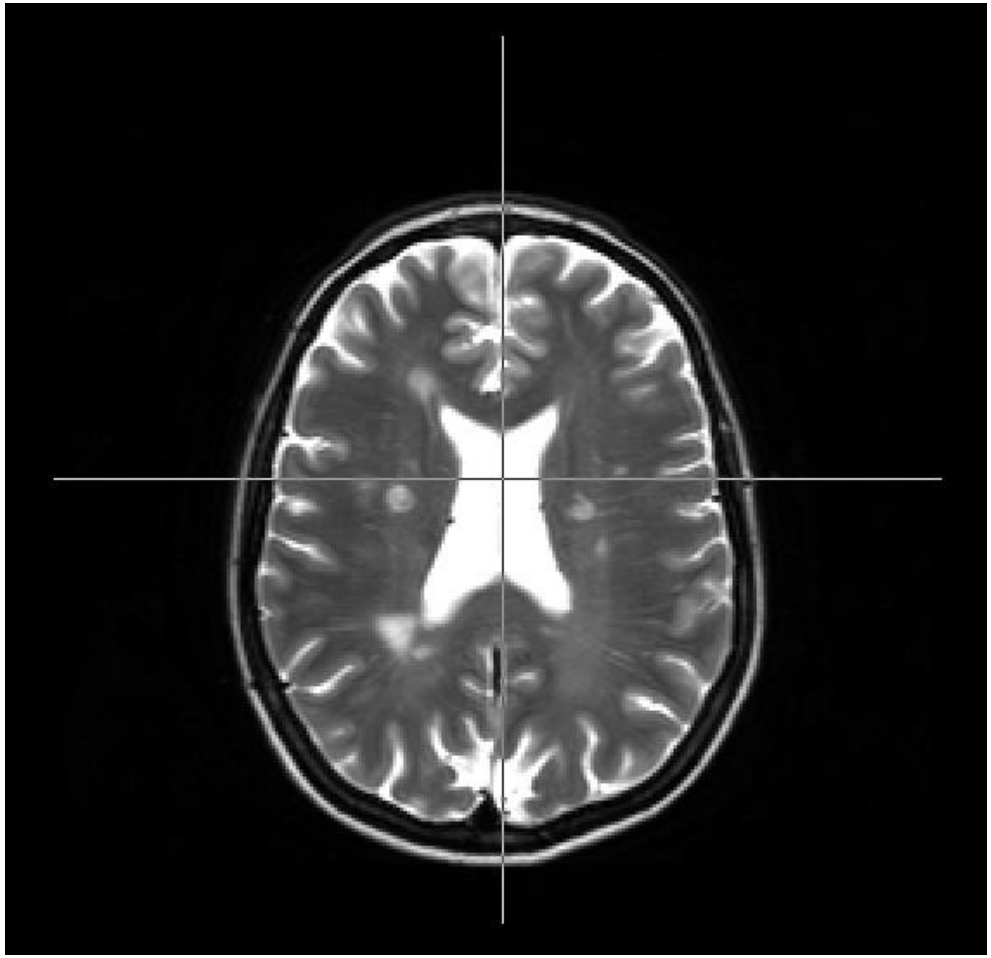

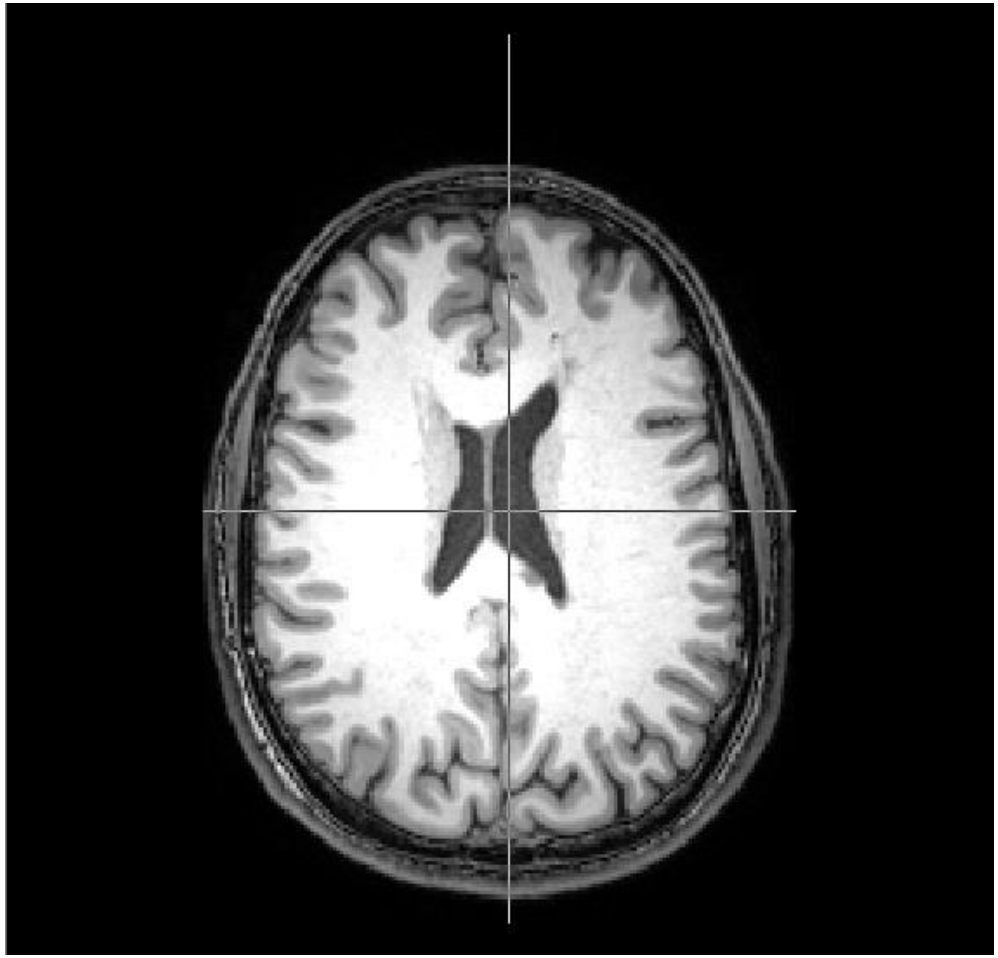

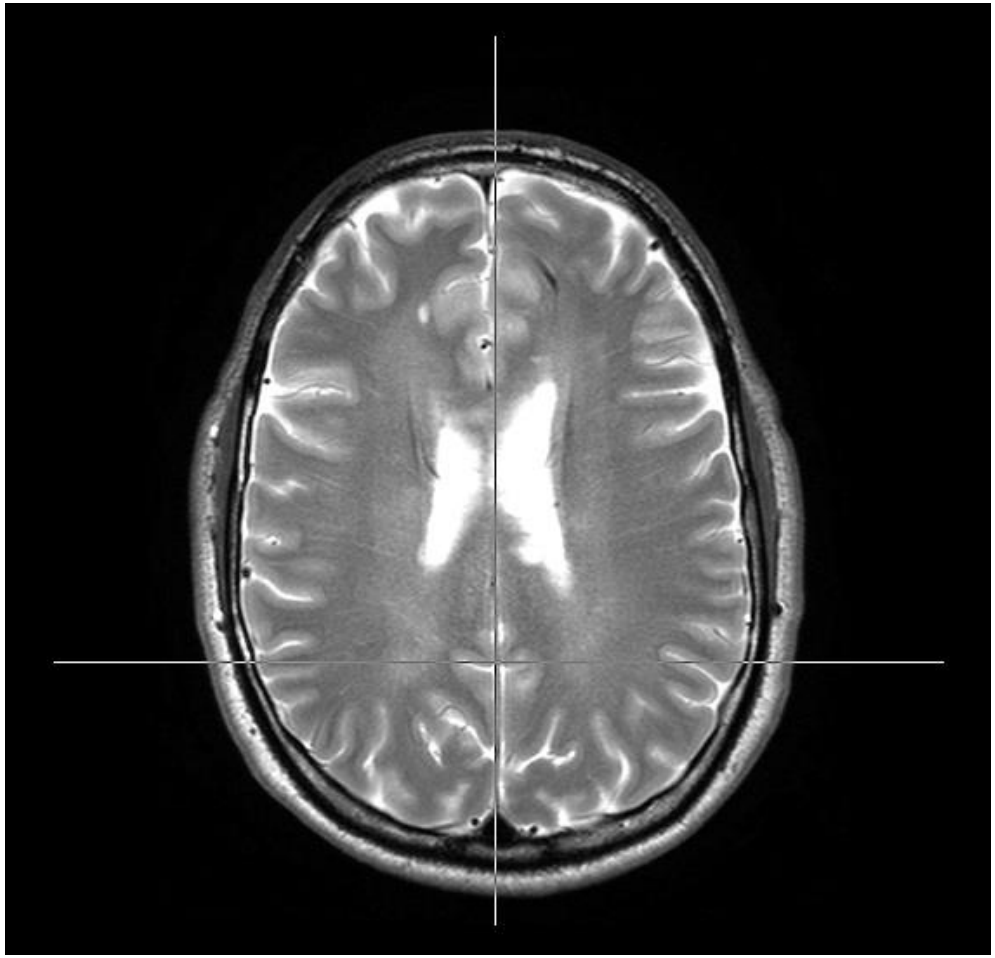

TABLE 4: The 2010 McDonald Criteria for Diagnosis of MS

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]
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is "MS"; if suspicious, but the Criteria are not completely met, the diagnosis is "possible MS"; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is "not MS."

[a]An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory

The value of high field MRI in multiple sclerosis and CIS

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Background

- MRI
  - Important for diagnosing MS
  - More high field scanners available
- High field
  - Better image quality
  - More and better visible lesions?
  - Earlier diagnosis?
  - Earlier treatment?

Metods

- PubMed searches
  - ”Multiple sclerosis + MRI + 3.0 T”, ”Multiple sclerosis + MRI + high field”; also as MeSH terms.
  - CIS and ON replacing multiple sclerosis
- 167 papers
  - Including 5, only those with direct comparison of low and high field strength.
- References included one more paper.

Background

- MRI
  - Important for diagnosing MS
  - More high field scanners available
- High field
  - Better image quality
  - More and better visible lesions?
  - Earlier diagnosis?
  - Earlier treatment?

Wattjes et al.

- Cohort
  - 40 patients with CIS, 18-55 years, steroid treated.
  - Disease duration 12-67 days, EDSS 0-3
- MR protocol
  - 1.5 T and 3.0 T
  - T2 turbo spin echo, T1 +/- Gd., FLAIR
  - MRI within 1-3 dage, randomised order.
- 2 radiologists evaluating

Wattjes et al.

- Number of lesions
  - FLAIR and T2: More lesions at 3.0 T
  - Significant for total number of lesions
  - FLAIR: 35/40 patients with lesions
  - T2: 33/40 patients with lesions
- T1, Gd+ læsioner
  - 43 at 3.0T
  - 40 at 1.5 T
- Vilibility score
  - FLAIR/T2: significantly better at 3.0 T
  - T1: Numerical best at 1.5 T, not significant

Nielsen et al.

- Cohort
  - 28 untreated patients, 18-52 years, EDSS 1-5
  - Disease duration: ON = 5-70 days, RRMS = 0.2-20 years
- MR protocol
  - 1.5 T and 3.0 T
  - FLAIR, T2 turbo spin echo, T1 +/- Gd., MPRAGE
  - MRI within one hour, randomised order.
- One person evaluating

Nielsen et al.

- Number of lesions:
  - FLAIR: 23/28 patients with lesions at 1.5 T
  - FLAIR: 25/28 patients with læsions at 3.0 T
  - T2: Fossa posterior lesions best visible
- T1, Gd+ lesions
  - 11/28 patinets with lesions at 1.5 T
  - 12/28 patients with lesions at 3.0 T
  - No significant differences in number and volume of lesions
- MPRAGE lesions
  - No significant differences in number and volumen per patient

Discussion

- All studies are relatively small.
- Patient cohorts are inhomogeneous.
- Wattjes et al.; biggest of 2 studies of CIS and
  - 30 % af patients fulfil 1 extra Barkhof criteria at 3.0T
  - Do no influence DIT
  - Only minor influence at DIS
  - MS diagnosis not made earlier
- Nielsen et al. Also include a CIS cohort, but do not relate it to diagnosing MS.

Conclusion and perspective

- High field strength reveals more, bigger and better visible lesions
- More lesions, but not earlier diagnosis of CDMS
- More and bigger studies of patients with CIS needed.
- Shall the next revision of the McDonald criteria include recommendation of field strength?
- Visualisation of grey substance and its MS pathology?

Strengths of study

- Uniform and stringent set-up
  - One type of first demyelinating event
  - Anatomic limited area (n. opticus) where inflammation and axon damage take place

  → Avoid that differences in MRI is due to different symptomatology and cause of disease

- MRI performed <30 days from onset

- Study population
  - Clinic of Optic Neuritis has specialized function for ON and get patients from all over the Eastern Denmark – representative group
  - Consecutive and prospective included

Gadolinium-DTPA enhancing lesions on MRI in patients with acute optic neuritis

a comparison of findings in patients with and without enhancement

Professor, DMSc Jette L. Frederiksen
based on Master's Thesis by Amanda Lamer Schjetlein, Spring 2015

Background

Optic neuritis (ON) is an inflammatory condition of the optic nerve presumably of autoimmune origin, and more than 50 % of cases herald development of MS.

ON patients were chosen for the present study to achieve a homogenous patient group in which complete diagnostic work up performed in the acute phase, within one month from onset.

Examination program

- Magnetic Resonance (MR) scanning and other diagnostic methods
- MR with Gadolinium contrast
- Visual Evoked Potentials (VEP)
- Cerebrospinal fluid (CSF): Oligoclonal bands (OCBs), IgG index and leucocytes
- Expanded Diability Status Scale (EDSS)

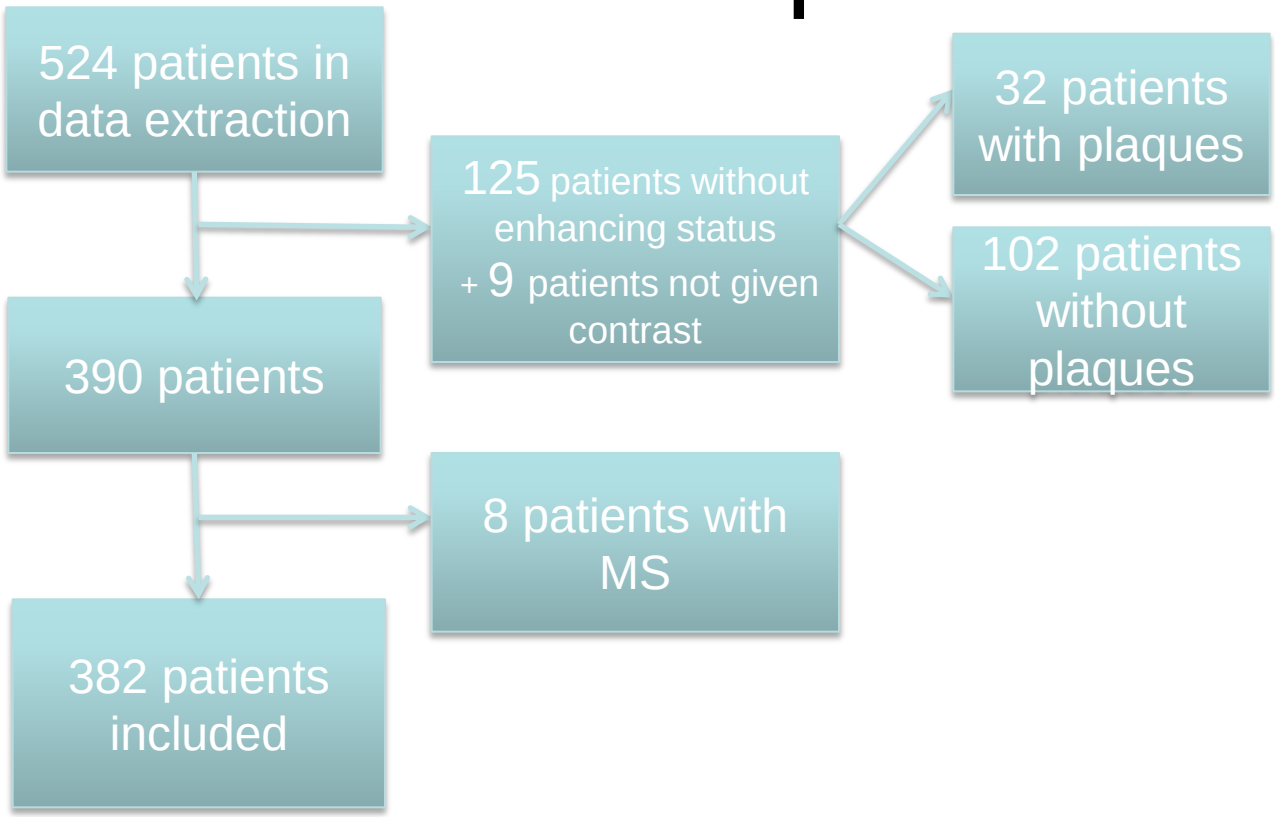
Goals

- Frequency of Gd-DTPA enhancing lesions
- Comparison between groups with and without enhancement
- Symptoms and severity of symptoms

Materials and methods

- From 2001 to 2014
- Population and field
- MR scanning: Tesla intensity and contrast administration
- LBP, VEP and EDSS
- Article search
- Statistical analysis: Chi-square, t-test, ANOVA and Tukey post hoc

Included patients



Results – Table 1

	Total	÷ enhancing lesions	+ Enhancing lesions	
	n=382	n=325	n=57	p
Enhancing lesions, n (%)	382	325 (85.1)	57 (14.9)	
Age, median (Q1-Q3)	37 (29-46)	38 (29-47)	37 (30-45)	0.612
Women n (%)	272 (71.2)	233 (71.7)	39 (68.4)	0.615
Non-enhancing lesions > 0, n (%)	229 (60.0)	181 (55.7)	48 (84.2)	<0.05
Non-enhancing lesions > 3, n (%)	119 (31.3)	89 (27.4)	30 (52.6)	<0.05
	n=372	n=318	n=54	
Days between onset and scan, median (Q1-Q3)	19 (12.8-32.3)	19 (13-37)	17.5 (11.3-26)	0.391
	n=369	n=313	n=56	
VEP, n (%)	302 (81.8)	247 (78.9)	55 (98.2)	<0.05
	n=335	n=285	n=50	
OCBs, n (%)	149 (44.4)	121 (42.5)	28 (56.0)	0.075
	n=323	n=278	n=45	
Leucocytes ≥ 5 cells/µl, n (%)	117 (36.2)	93 (33.5)	24 (53.3)	<0.05
	n=261	n=226	n=35	
EDSS, median (Q1-Q3)	1 (1-2)	1 (1-2)	2 (0-2.75)	0.354
	n=225	n=196	n=29	
FS6, median (Q1-Q3)	1 (1-2)	1 (1-2)	2 (0-3)	0.363

Results – Table 2

	Total	Cerebrum	N.opticus	Cerebrum and n.opticus	p
	n=57	n=35	n=13	n=9	
Age, median (Q1-Q3)	37 (30-45)	37 (30-43.5)	30 (27-47)	43 (38-50)	0.150
Women, n (%)	39 (68.4)	24 (68.6)	7 (53.8)	8 (88.9)	0.221
Non-enhancing lesions, n (%)	48 (84.2)	34 (97.1)	5 (38.5)	9 (100)	<0.05
	n=56	n=35	n=12	n=9	
VEP, n (%)	55 (98.2)	35 (100)	12 (100)	8 (88.9)	0.071
	n=55	n= 34	n=12	n=9	
Days from onset to scan, median (Q1-Q3)	18 (11.5-28)	19.5 (11.3-30.8)	15 (10.8-20)	18 (12-20)	0.534
	n=50	n=30	n=12	n=8	
OCBs n (%)	28 (56.0)	23 (76.7)	2 (16.7)	3 (37.5)	<0.05
	n=45	n=26	n=11	n=8	
Leukocytes ≥ 5 cells /µl, n (%)	24 (53.3)	16 (61.5)	5 (45.5)	3 (37.5)	0.410
	n=35	n=22	n=7	n=6	
EDSS, median (Q1-Q3)	2 (0-2.75)	2 (0-2.75)	1 (1-1.75)	2 (0.5-3.5)	0.849

Discussion

- Frequency of Gd-enhancing lesions: 15 %
- - Review: 30-59%
- - Swanton et al. 26 %
- - RRMS 50-65%
- CIS
- Disease burden
- Development of clinical definite MS
- - Risk factors: non-enhancing lesions and OCBs
- VEP
- EDSS

Strengths

- Consecutive inclusion
- Free admission and free of charge
- Homogeneous and well-defined geographical area
- Short time from onset to MRI
- Relatively large data

Weaknesses

- Number of excluded patients, but nearly only without lesions
- Retrospective study with prospective follow-up
- MR: Tesla 1.5 or 3.0 and contrast dose
- Change of criteria for MS, mono vs poly-symptomatic debut
- EDSS was not registered in all patients
- Few patients in group with enhancement and optic oedema
- Median age calculated from time of keying

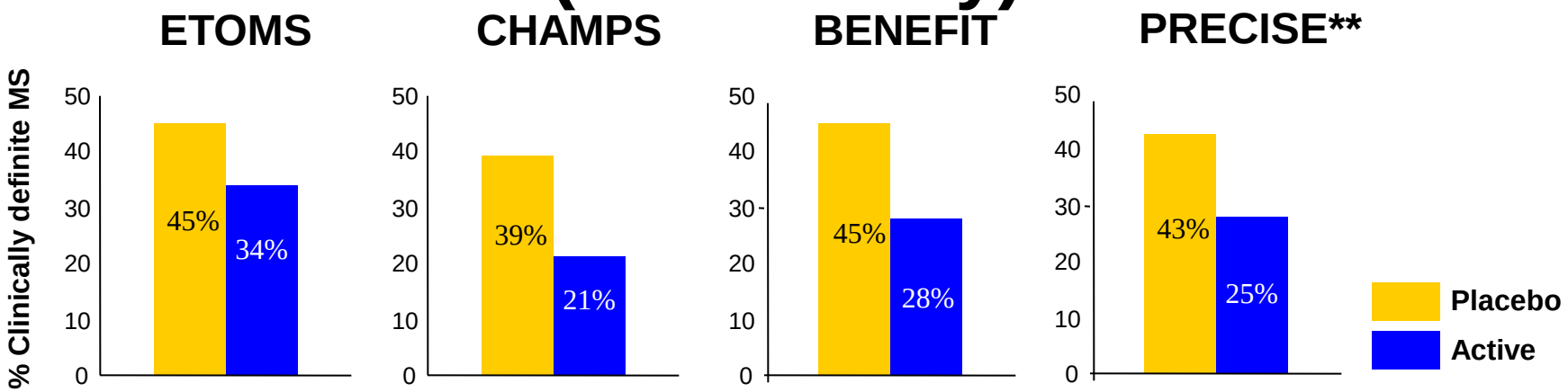
Conclusion and perspectives

- Possible lower disease burden
- Prospective study?
- Risk factors for MS development

CHAMPS 2000[1]	ETOMS 2001[2]	BENEFIT 2006[3]	PRECISE 2009[4]
Avonex 30 mcg IM q week	Rebif 22 mcg sc q week	Betaseron 250 mcg sc qod	Copaxone 20mg sc daily
1:1 randomization	1:1 randomization	5:3 randomization	1:1 randomization
Age 18-50	Age 18-40	Age 18-45	Age 18-45
Exit study after confirmed CDMS	Could remain in study on open label Rx after CDMS	Offered active medication after confirmed CDMS	Offered active medication after confirmed CDMS
First acute demyelinating event of ON, BS/Cerebellum, SC within 27 days of randomization	First clinical syndrome indicative of unifocal or multifocal involvement of the CNS within 90 days of randomization.	Clinical isolated syndrome: first neurologic event with symptoms or signs indicative of monofocal or multifocal involvement of the CNS within 60 days of randomization	Single unifocal clinical attack within 90 days of enrolment
≥ 2 asymptomatic T2 lesions ≥ 3mm, at least 1 PV or ovoid	> 4 T2 lesions or at least 3 T2 lesions if one was infra or Gd +	≥ 2 asymptomatic T2 lesions ≥ 3mm, at least 1 PV or ovoid or infratentorial	Positive Brain MRI at screening (≥ 2 lesions, ≥ 6mm in diameter)
IV Steroids within 14 days of onset +oral taper and Baseline MRI on steroids	+/- steroids with no std regimen	+/- steroids with no standard regimen	+/- steroids with no standard regimen

[1]Jacobs LD et al .*NEJM* 2000;343: 898-904; [2]Comi G, et al. *Lancet* 2001;357:1576-1582; [3]Kappos L et al. *Neurol 2006;67:* 944-53; [4]Comi G et al *Lancet Neurol* 2009; 374: 1503-11

CIS 2 year data (PreCISe 3 y)



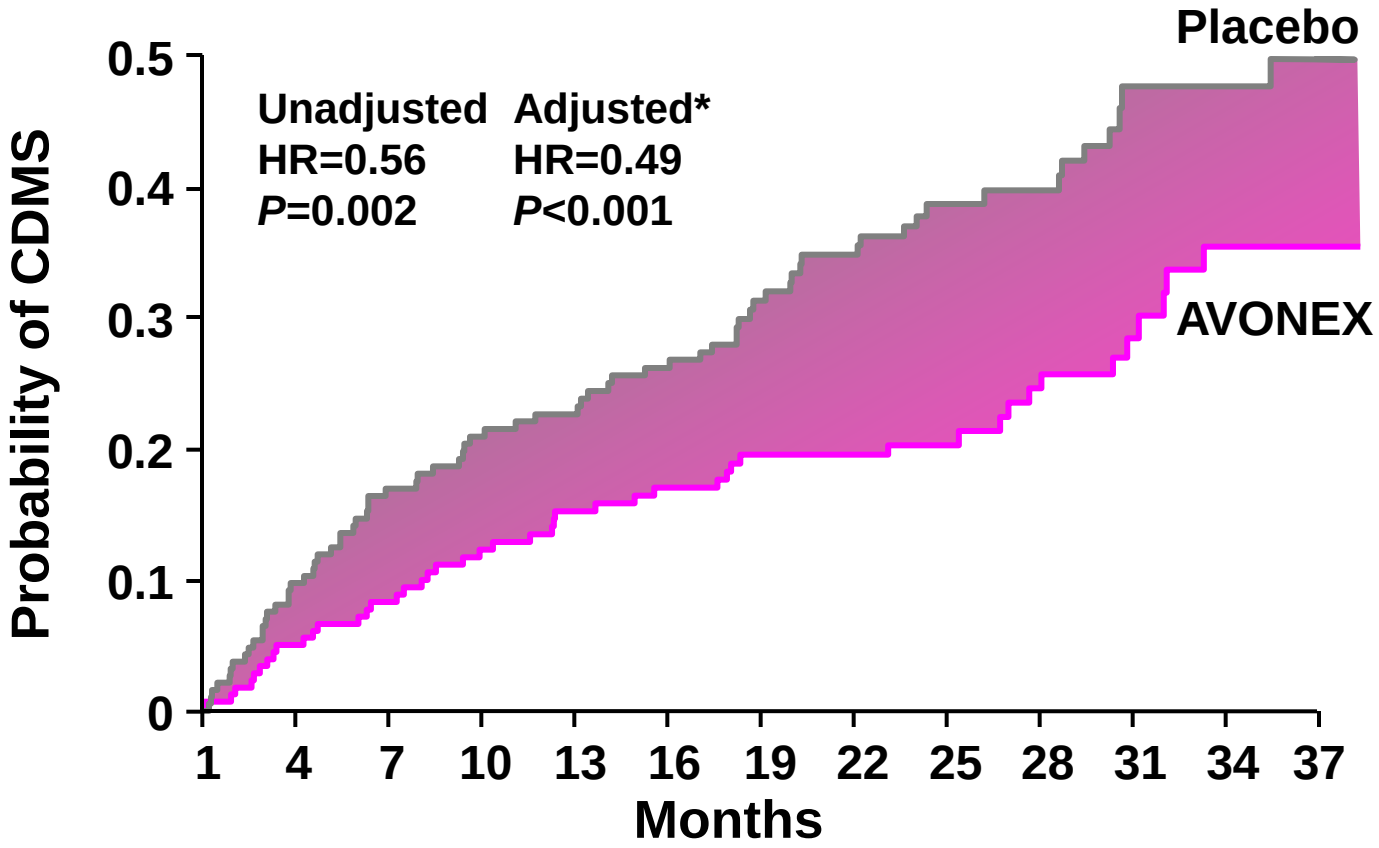
	Placebo	IFN	Hazard ratio*	RR
ETOMS[1]	45%	34%	0.65	35%
CHAMPS[2]	39%	21%	0.45	55%
BENEFIT[3]	45%	28%	0.50	50%
PRECISE**[4]	43%	25%	0.55	45%

*Adjusted hazard ratio. ** upto 3 years

1.Comi G, et al. Lancet. 2001;357:1576-1582; 2. O'Connor P et al Mult Scler 2009; 15: 728-34; 3.Kappos L, et al. Neurology. 2006;67:1242-1249; 4. Comi G et al Lancet Neurol 2009; 374: 1503-11

CHAMPS: Effect of AVONEX on the Risk of CDMS Development

Over 3 Years



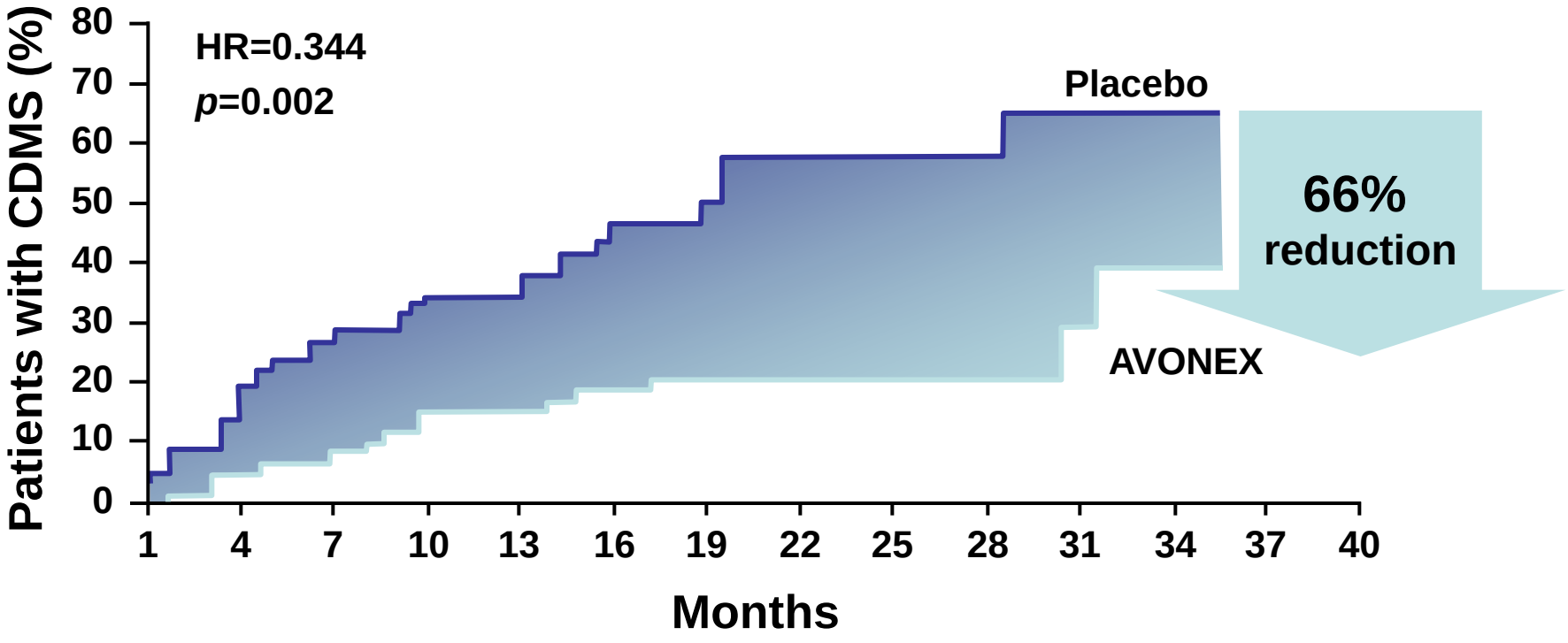
Unadjusted 44% Reduction

Adjusted* 51% Reduction

*Adjusted for age, type of initial event, volume of T2 lesions, and number of Gd+ lesions

Jacobs et al. *N Engl J Med.* 2000;343:898.

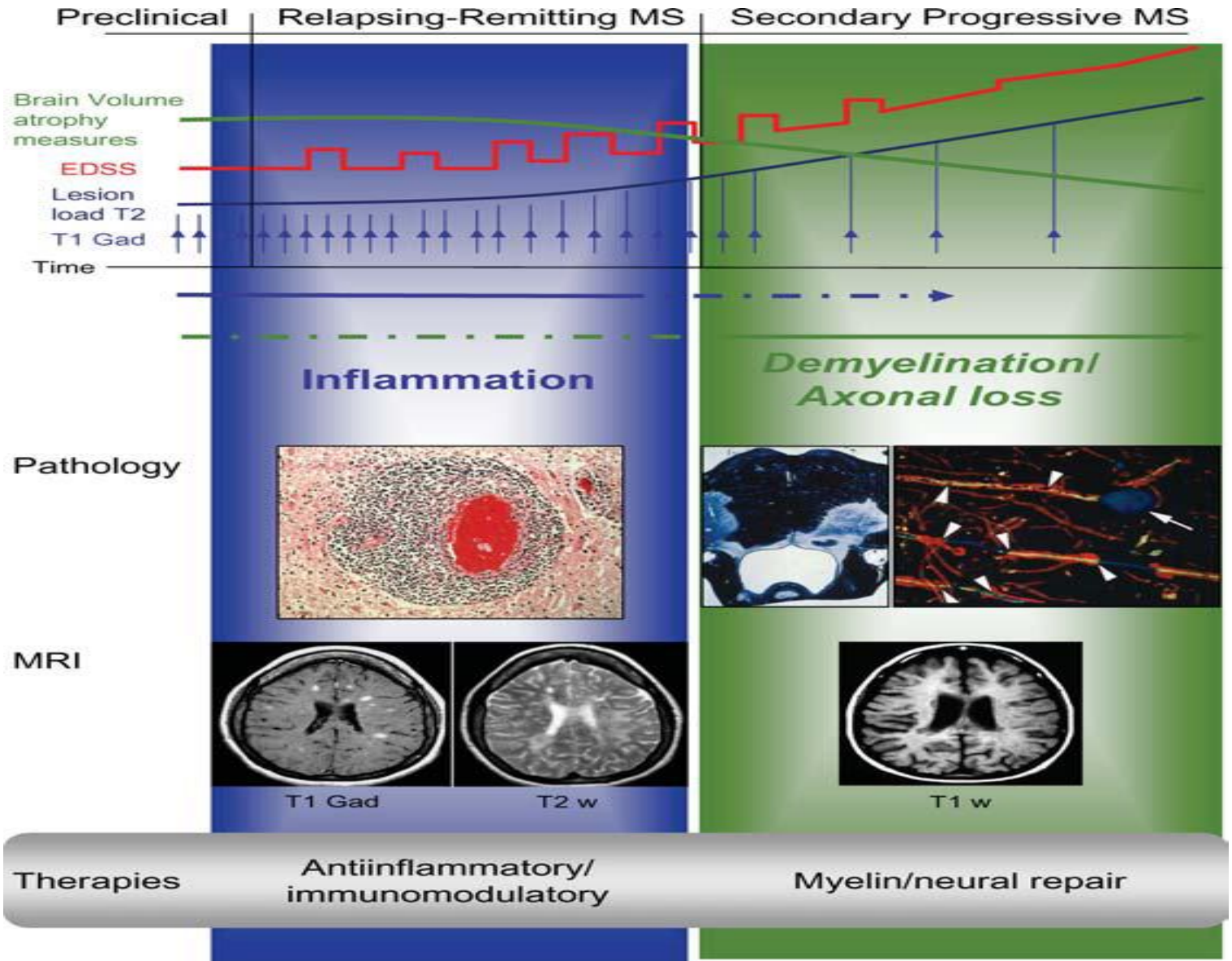
Avonex effect seems to be greater in patients with more MRI disease activity



*High-risk patients had ≥9 T2 lesions and ≥1 Gd+ lesion.

O'Connor et al. *Clin Ther*. 2003;25:2865.

MULTIPLE SCLEROSIS
overview of the disease progression



MR in multiple sclerosis

In 1962 Brownwell described the distribution of plaques in MS

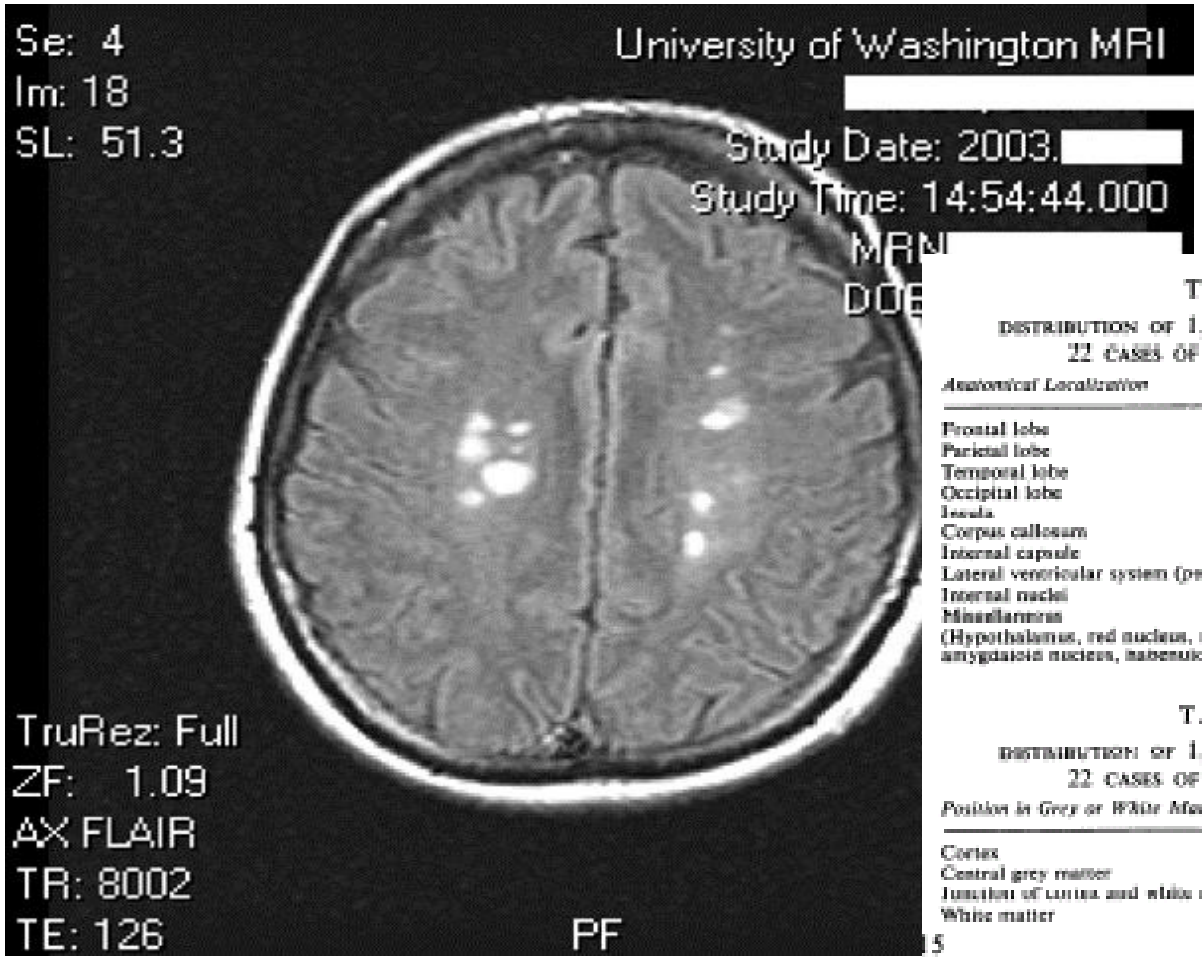


TABLE I

DISTRIBUTION OF 1,594 CEREBRAL PLAQUES IN 22 CASES OF MULTIPLE SCLEROSIS

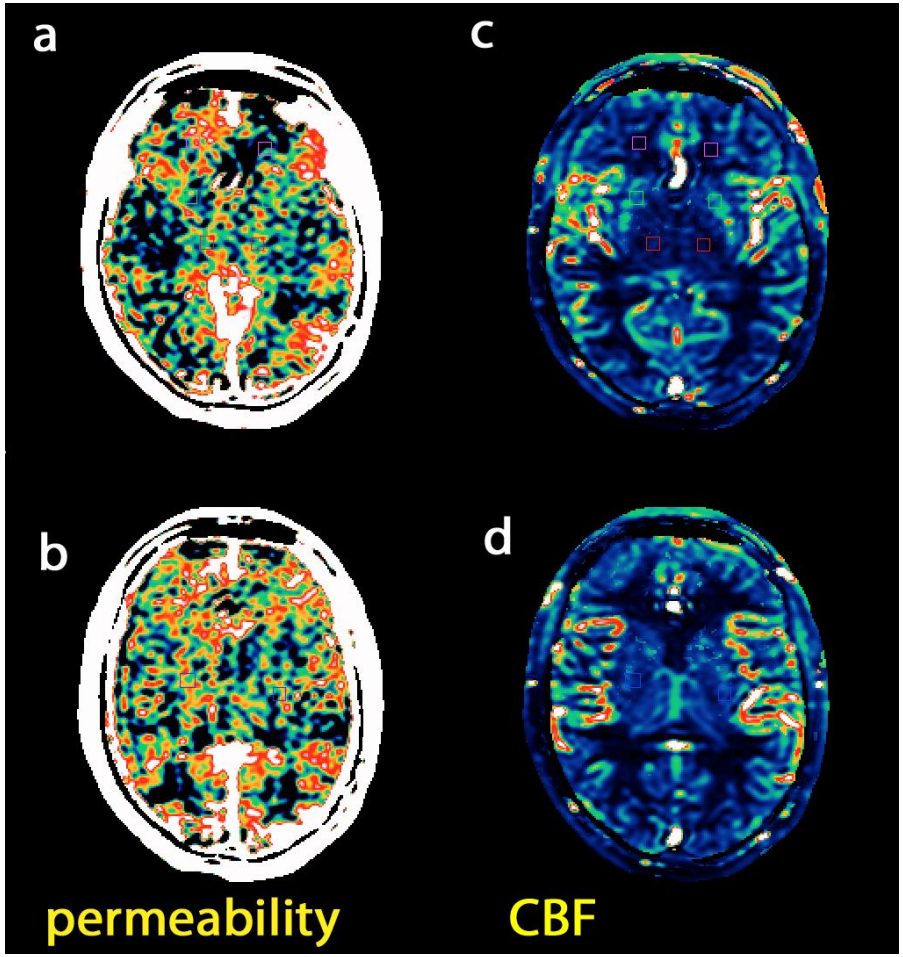
Anatomical Localization	*Number of Plaques*
Frontal lobe	348 (22%)
Parietal lobe	233 (15%)
Temporal lobe	193 (12%)
Occipital lobe	14 (1%)
Insula	24 (1%)
Corpus callosum	60 (4%)
Internal capsule	19 (1%)
Lateral ventricular system (periventricular)	637 (40%)
Internal nuclei	61 (4%)
Miscellaneous (Hypothalamus, red nucleus, subthalamic nucleus, amygdaloid nucleus, habenulopeduncular tract)	(Less than 5 (1%)

TABLE II

DISTRIBUTION OF 1,594 CEREBRAL PLAQUES IN 22 CASES OF MULTIPLE SCLEROSIS

Position in Grey or White Matter	*Number of Plaques*
Cortex	80 (5%)
Central grey matter	65 (4%)
Junction of cortex and white matter	263 (17%)
White matter	1,184 (74%)

15


a
c
b
d
permeability
CBF