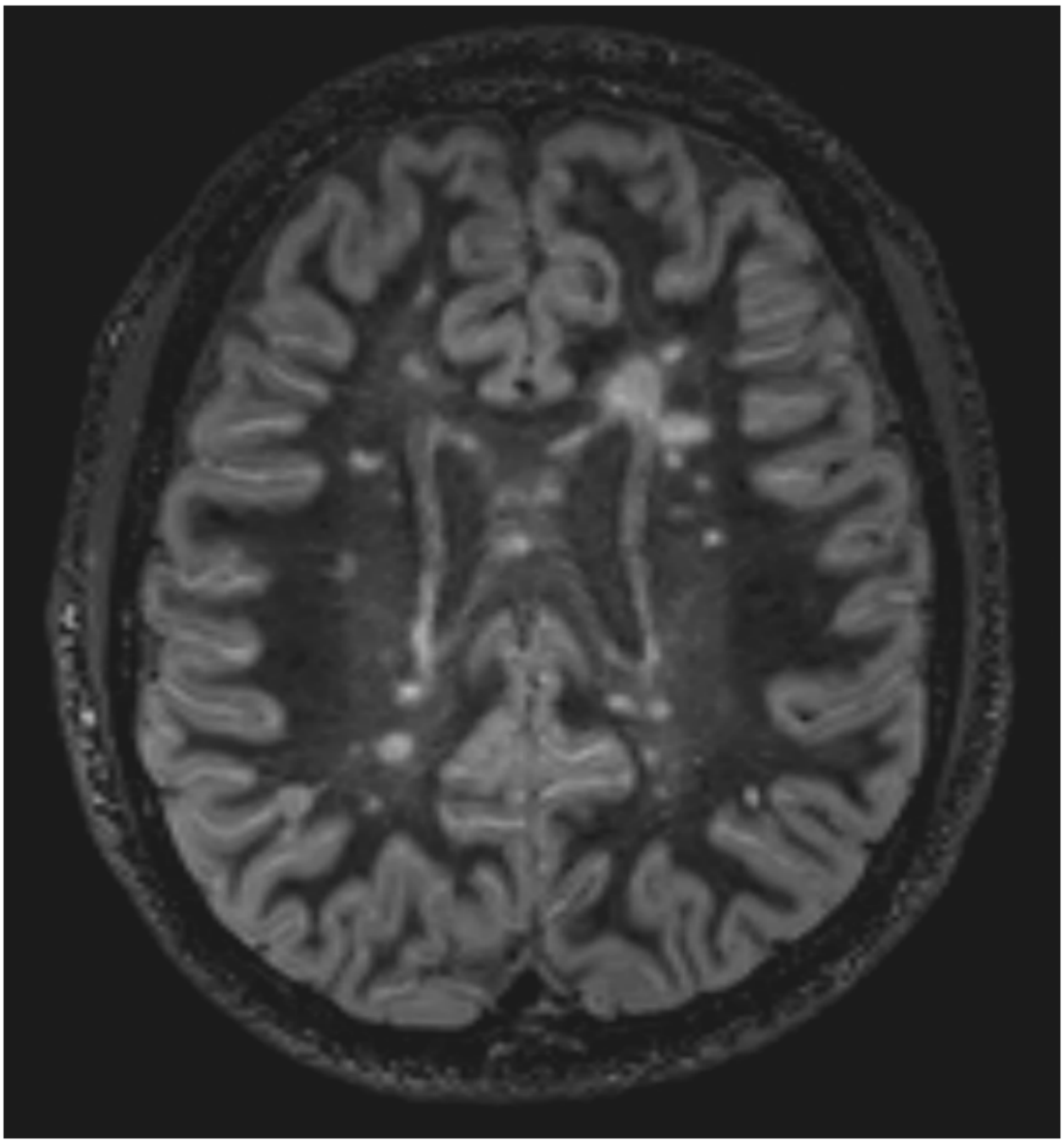
Service de radiodiagnostic
et radiologie interventionnelle
Professeur Reto Meuli, Chef de service
Rue du Bugnon 46, 1011 Lausanne, Suisse
Web.: www.chuv.ch/rad

Imagerie de la sclérose en plaques
Où en sommes-nous en 2015 ?

Samedi 21 mars 2015 09h00-13h00

Auditoire Mathias Mayor, CHUV, Lausanne

Dr Patric HAGMANN



avec le soutien de

NOVARTIS PHARMACEUTICALS

BRACCO LIFE FROM INSIDE

Guerbet Contrast for Life

SIEMENS

canton de vaud

Imagerie de la sclérose en plaques – Où en sommes-nous en 2015 ?
Samedi 21 mars 2015 – 9h00-13h00, Auditoire Mathias Mayor, CHUV, Lausanne
Dr Patric HAGMANN

Programme

08h30	Inscription, café d'accueil	
08h55	Mot d'introduction	Reto MEULI
09h00	**La sclérose en plaques : pathophysiologie et clinique** ➢ Mécanismes moléculaires de l'inflammation et de la neuro-générescence ➢ Symptomatologie, cognition et handicap	Myriam SCHLUEP
09h45	**Le rôle du radiologue dans l'établissement du diagnostic et du suivi médical** ➢ Techniques d'imagerie ➢ Critères diagnostics ➢ Critères de suivi ➢ Comment établir un rapport de qualité	Patric HAGMANN
10h30	PAUSE	
11h00	**Diagnostic différentiel des lésions de la substance blanche et des complications liées au traitement**	Philippe MAEDER
11h45	**Les techniques d'imagerie avancées pour la SEP**	Cristina GRANZIERA
12h15	Apéritif	

Sclérose en Plaques
Pathophysiologie & Clinique

PD Dr Myriam Schluep
Service de neurologie, Neurosciences Cliniques

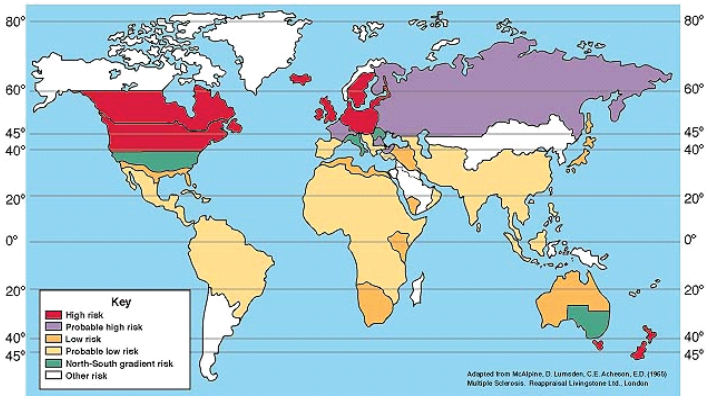
UNIL | Université de Lausanne

Imagerie de la Sclérose en Plaques 2015, 20.03.2015

SEP

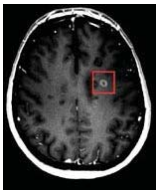
- Cause de handicap neurologique la plus fréquente du jeune adulte en Occident
- Prévalence en Suisse 110/10^5
- Prédominance féminine

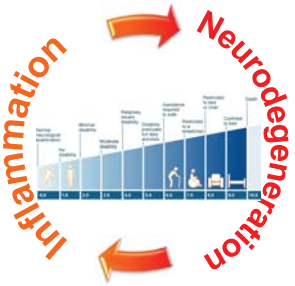
World Distribution of Multiple Sclerosis

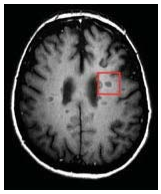


Prévalence suisse 110/10^5 - Population jeune 15-45 ans - 2.3 ♀ : 1 ♂

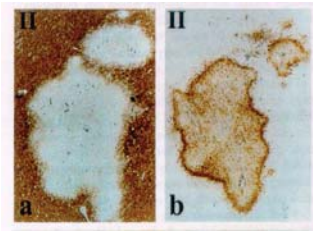
Pathophysiologie de la SEP





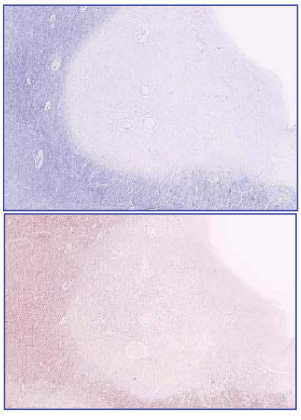


Barkhof F et al. Nat Rev Neurol 2009;5:256-266; Compston A et al. Lancet 2008;372:1502-1517
Adapted from Kurtzke JF. Neurology 1983;33:1444-1453.



MOG

Macrophages
Microglie CD68

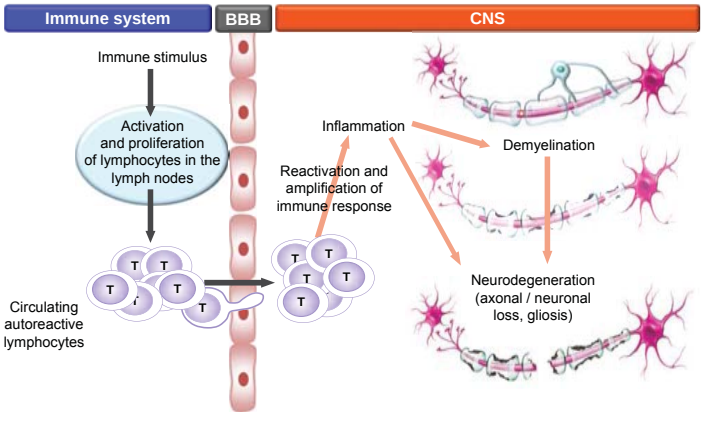


Lésion SEP

- ✓Inflammation
- ✓Démyélinisation
- ✓Perte axonale

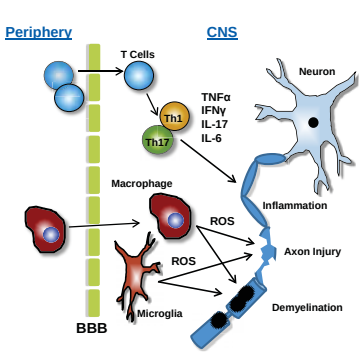
Luchinetti et al. Ann Neurol; Lassmann et al. TIMM 2001
Noseworthy JH et al. N Engl J Med 2000;343:938-952.

Pathologie de la SEP: système immunitaire et SNC



BBB, blood / brain barrier; CNS, central nervous system
Chun J, Hartung HP. *Clin Neuropharmacol* 2010; Mehling M *et al. Neurology* 2010

Activated Immune Cells in the CNS Mediate Inflammatory Damage and Oxidative Stress

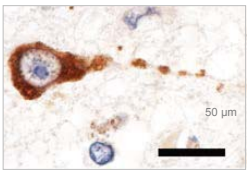


- MS is a chronic disease of the CNS, characterised by Th1-/Th17-driven inflammation, demyelination, and axonal injury
- Infiltrating macrophages and activated microglia produce large quantities of ROS, resulting in oxidative stress
- As nondividing, highly active cells, neurons are particularly vulnerable to production of ROS and damage
- Axonal degeneration is correlated with irreversible damage in MS

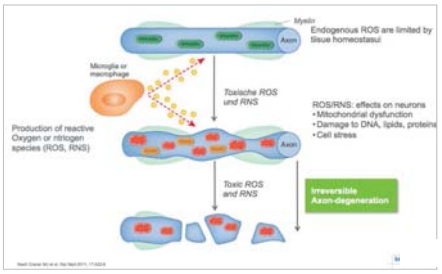
CNS=central nervous system; Th=T helper cell; TNFα=tumour necrosis factor alpha; IFNγ=interferon gamma; IL=interleukin; ROS=reactive oxygen species; BBB=blood-brain barrier.
Compston A, Coles A. Lancet 2008;372:1502-1517; van Horssen J et al. Biochem Biophys Acta 2011;1812:141-150.

Oxidative Damage in MS Lesions

Oxidised Cytoplasmic Phospholipids in a Fragmenting Neuron of an Active Cortical MS Lesion*

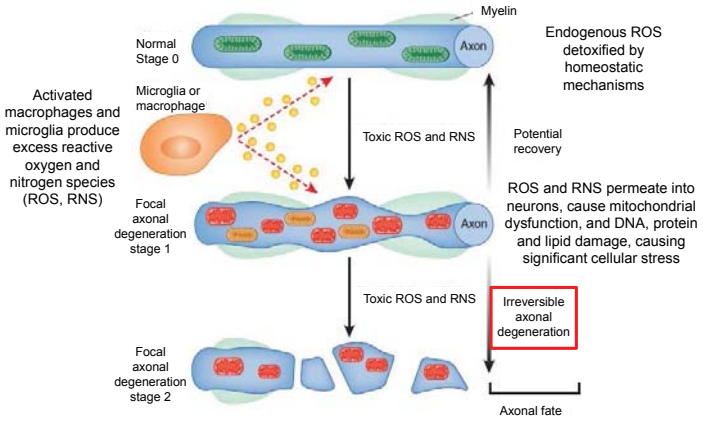


Oxidative Stress in the Pathophysiology of MS: Schematic View



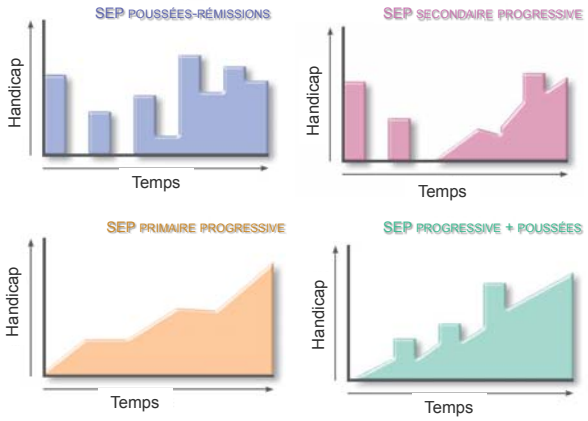
*Monoclonal antibody (mouse) against oxidized phospholipids (Palinski et al. J Clin Invest. 1996;98:800-814).
RNS=reactive nitrogen species.
Fischer MT et al. Brain. 2013;136:1799-1815.

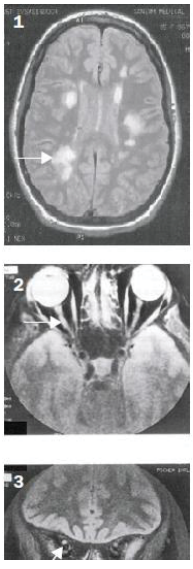
In Vivo Studies in EAE Suggest Myelinated Axons Are Susceptible to Oxidative Stress



EAE=experimental autoimmune encephalomyelitis.
Nikic I et al. *Nat Med.* 2011;17:495-500; Craner MJ, Fugger L. *Nat Med.* 2011;17:423-426.

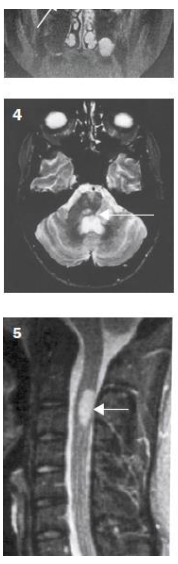
Traduction clinique des différentes formes de SEP





Site	Symptoms	Signs
Cerebrum	Cognitive impairment	Deficits in attention, reasoning, and executive function (early); dementia (late)
	Hemi-sensory and motor	Upper motor neuron signs
	Affective (mainly depression)	
	Epilepsy (rare)	
	Focal cortical deficits (rare)	
Optic nerve	Unitateral painful loss of vision	Scotoma, reduced visual acuity, colour vision, and relative afferent pupillary defect
Cerebellum and cerebellar pathways	Tremor	Postural and action tremor, dysarthria
	Clumsiness and poor balance	Limb incoordination and gait ataxia

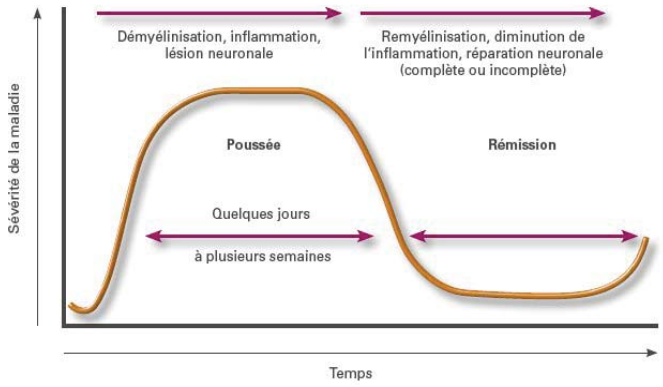
Compston and Coles, Lancet 2002



Brainstem	Diplopia, oscillopsia	Nystagmus, internuclear, and other complex ophthalmolplegias
	Vertigo	
	Impaired speech and swallowing	Dysarthia and pseudo-bullbar palsy
	Paroxysmal symptoms	
Spinal cord	Weakness	Upper motor neuron signs
	Stiffness and painful spasms	Spasticity
	Bladder dysfunction	
	Erectile impotence	
	Constipation	
Other	Pain	
	Fatigue	

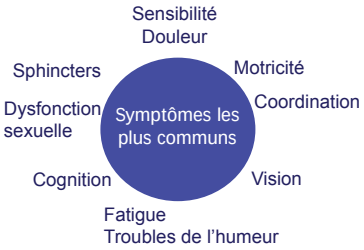
Compston and Coles, Lancet 2002

SEP Poussées et phases de rémission



Adapté de Noseworthy et al., N Engl J Med. 2000

Poussée de SEP: définition & traitement

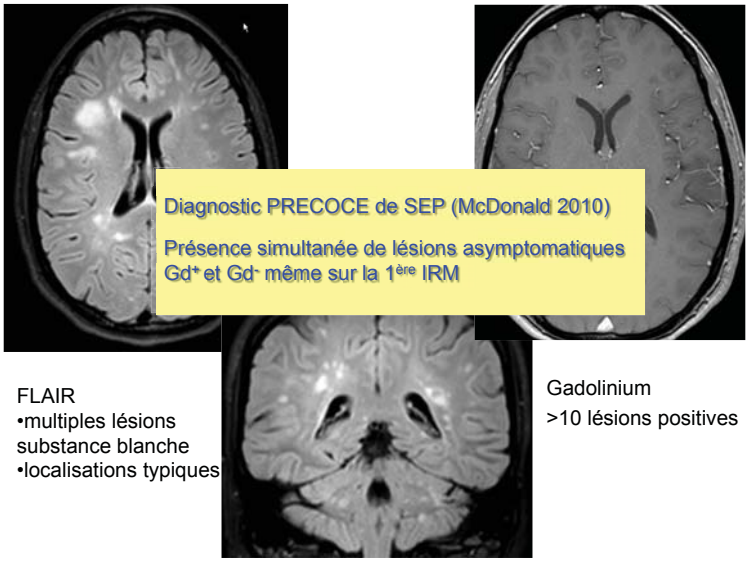


- Symptômes nouveaux
- Ou en aggravation
- Durée ≥24 h
- Déficits objectifs
- Période stable ≥1 mois

- Exclure les pseudo-poussées infection, ↑ T° ↓ pH (Uhthoff), épisodes paroxystiques

- Traitement

Méthylprednisolone iv 1 g/j sur 3-5 j
Méthylprednisolone po 500 mg/j sur 5 j

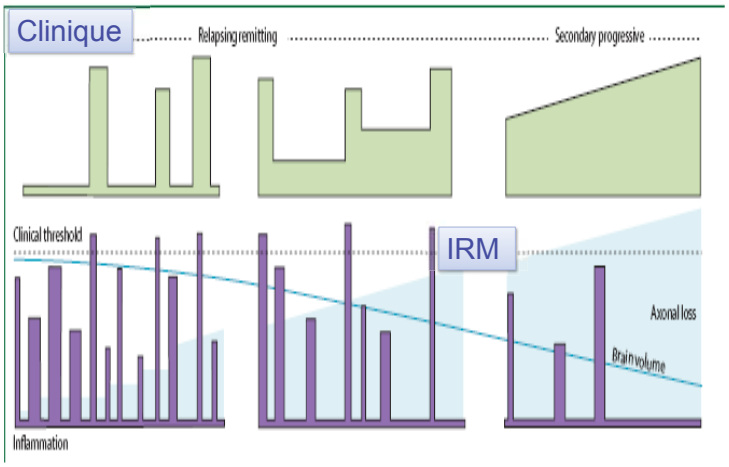


Diagnostic PRECOCE de SEP (McDonald 2010)

Présence simultanée de lésions asymptomatiques Gd⁺ et Gd⁻ même sur la 1ère IRM

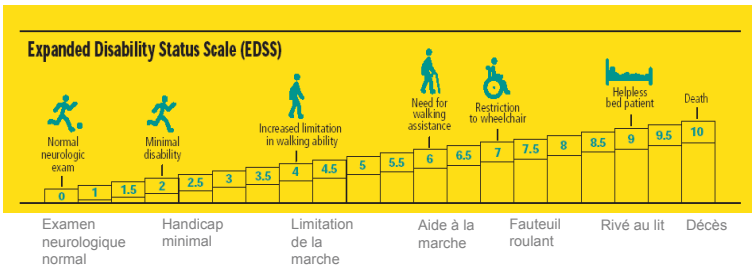
FLAIR
- multiples lésions substance blanche
- localisations typiques

Gadolinium
>10 lésions positives



Compston and Coles, Lancet 2008

Mesurer le handicap neurologique
Indicateur du type d'évolution de la SEP



Sévérité de la SEP: équilibre réparation-endommagement
Importance du diagnostic précoce

Kurtzke, Neurology 1983

Cognition et SEP

- Haute prévalence de difficultés cognitives
  - ✓ 40-65% des patients SEP selon les études
- Parfois présents dès début de la SEP
  - ✓ Pas de lien clair avec durée de la SEP
  - ✓ Possibles en l'absence de handicap neurologique
  - ✓ Peu de corrélation avec progression du handicap neurologique
- Impact sur le fonctionnement social, professionnel et sur la qualité de vie

Amato et al. 1995; Ruggieri et al. 2003; Rao et al. 1991; Defer 2001

Difficultés cognitives dans la SEP

Vitesse de traitement de l'information → Ralentissement lors de tâches cognitivement complexes

Attention soutenue

\+

Composante exécutive de la mémoire de travail →

Coordination de tâches multiples

Switching attentionnel, flexibilité

Inhibition, attention sélective

Manipulation d'information en mémoire

Nature des troubles cognitifs et IRM

Localisation des lésions (mesures T2/FLAIR, T1)

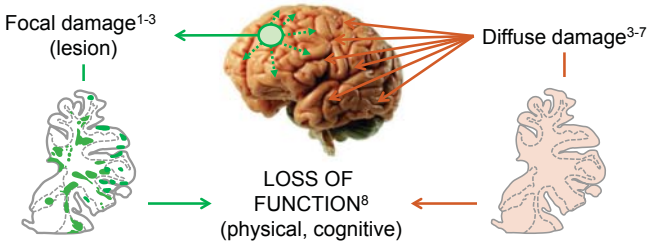
- ✓ Frontale ⟶ difficultés de résolution de problèmes, de mémoire, d'incitation
- ✓ Pariéto-occipitale ⟶ déficits de mémoire, d'aptitudes spatiales

Diminution du volume cérébral

- ✓ Atrophie substance blanche ⟶ meilleur *prédicteur* des difficultés de traitement rapide de l'information, de mémoire de travail
- ✓ Atrophie substance grise ⟶ meilleur *prédicteur* des difficultés de mémoire verbale, des comportements de type euphorie-désinhibition

Swirsky-Sacchetti Arnett et al.,1994; Rovaris et al. 1998; Swirsky-Sacchetti et al. 1992; Benedict et al. 2006

MS causes focal and diffuse damage to the brain



MRI
T_2 / Gd^+ T_1 lesions (focal damage)
T_1 black holes (severe localised tissue damage / destruction)

MRI
Brain volume loss

1. Smirniotopoulos JG *et al. Radiographics* 2007; 2. Markovic-Plese S, McFarland HF. *Curr Neurol Neurosci Rep* 2001; 3. Kutzelnigg A and Lassmann H. *Handbook Clin Neurol* 2014; 4. Kutzelnigg A *et al. Brain* 2005; 5. Frischer JM *et al. Brain* 2009; 6. Chun J and Hartung HP. *Clin Neuropharmacol* 2010; 7. Lassmann H. *Glia* 2014; 8. Barten LJ *et al. Drug Des Devel Ther* 2010. Left and right brain images adapted with permission from Kutzelnigg A *et al.*, Cortical demyelination and diffuse white matter injury in multiple sclerosis, *Brain* 2005; 128 (Pt 11); 2705-2712 by permission of Oxford University Press

Impact of cognitive dysfunction in MS

Cognitive dysfunction has a negative impact on the lives of people with MS and affects a number of factors in addition to physical impairment[1-4]

Everyday life	Disease management	Safety
Employment	Medication adherence	Driving
Leisure	Rehabilitation outcomes	Falls
Relationships	Medical decision-making	
Physical independence	Symptom management	
Mood and behaviour		
Quality of life		

1. Henry A *et al. J Int Neuropsychol Soc* 2011; 2. Hoogs M *et al. Int J MS Care* 2011; 3. Langdon DW. *Curr Opin Neurol* 2011; 4. Schultheis MT *et al. Arch Phys Med Rehabil* 2010

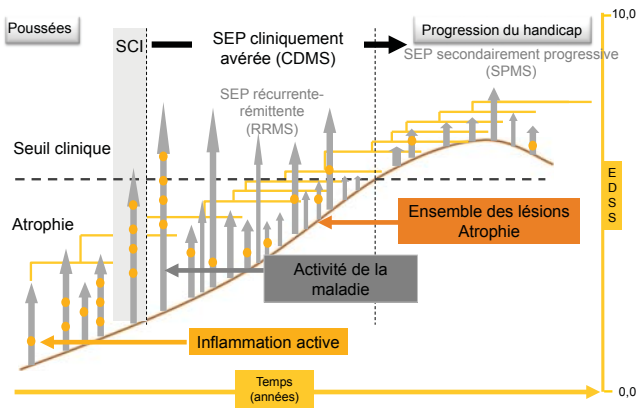
Annonce du diagnostic de SEP

Démarche médicale

- o Evolution des critères McDonald 2001, 2005, 2010
- o Diagnostic précoce
- o Après l'exclusion de tout autre diagnostic
  - ✓ L'IRM seule ne suffit pas
- o Refaire une IRM à 3 mois ou plus tardivement ?
- o Définir
  - ✓ Le type de SEP
  - ✓ Le stade de la SEP (SEP possible ou syndrome clinique isolé, CIS)

Sclérose en plaques

Caractéristiques de l'évolution de la SEP



SCI: syndrome cliniquement isolé; RRMS, relapsing-remitting multiple sclerosis, SEP récurrente-rémittente; SPMS, secondary progessive Multiple Sclerosis; EDSS, Extended Disability Status Scale, échelle étendue de l'état d'invalidité.

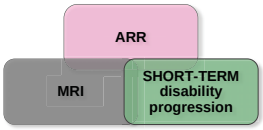
Annonce du diagnostic de SEP

Transmettre au patient

- o Importance d'un diagnostic précoce
- o Traitements prophylactiques efficaces
  - ✓ Les premiers dès 1995
  - ✓ Dynamisme thérapeutique depuis lors
- o Vaincre l'image délétère de la SEP
  - ✓ Reconnaître ce qui correspond à chacun
  - ✓ Connaître les symptômes et mécanismes
  - ✓ Eviter les idées préconçues

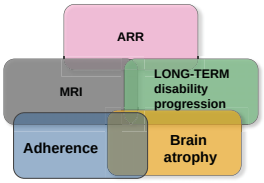
Traiter la SEP: effets à court et à long terme

Traditional clinical measures for short-term treatment response



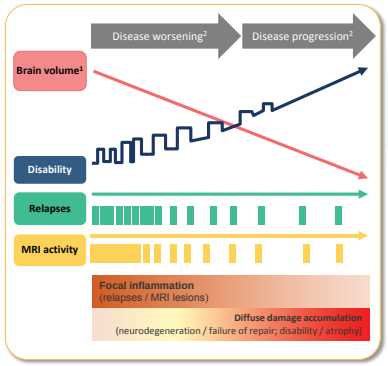
- ARR and MRI still used clinically for short-term management

Changing the paradigm is imperative with the development of new clinical measures and the understanding of their relevance



- Brain atrophy confirmed as a predictor of long-term outcomes
- Higher efficacy treatments shown to have long-term impact on disability
- Tolerability and long-term adherence are considered as drivers of treatment choice

No evidence of disease activity (NEDA-4)



NEDA-4 defined as:

- No confirmed relapses[3,4] (inflammatory disease activity)
- No MRI activity (new / enlarging T_2 lesions)[3,4]
- No confirmed EDSS progression[3,4]
- No annual brain volume loss >0.4%[5,6]

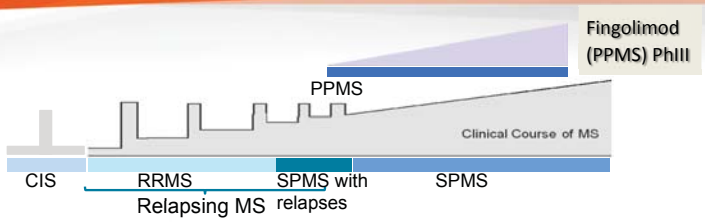
Adapted from Drug design, development and therapy 4, Barten LJ et al New approaches in the management of multiple sclerosis, pp 343-66, copyright (2010) with permission from Dove Medical Press1. Bevan CJ, Cree BA. *JAMA Neurol* 2014; 2. Lublin FD *et al. Neurology* 2014; 3. Havrdova E *et al. Lancet Neurol* 2009; 4. Giovannoni G *et al. Lancet Neurol* 2011; 5. Radü EW *et al. Swiss Med Wkly* 2013; 6. De Stefano N *et al. CNS Drugs* 2014

The NEDA-4 definition

Relapses	Clinically confirmed relapses*
Confirmed EDSS progression	Increase in EDSS score at 6 months of: • 1.5 points if baseline score is 0 • 1.0 point if baseline score is ≥1.0 • 0.5 points from a baseline score of >5.0
MRI activity	New / enlarging T_2 lesions (Gd⁺ lesion activity did not provide additional contribution beyond that of T_2 lesion counts[1])
Disease-related brain volume loss	Annual percentage brain volume change of >-0.4%

*New neurological symptoms present for at least 24 hours, in the absence of fever or infection, manifesting ≥30 days from onset of a preceding demyelinating event and confirmed by an independent evaluating physician within 7 days of onset. Gd⁺, gadolinium-enhancing
1. Kappos L *et al.* Oral FC1.5 presented at *ECTRIMS-ACTRIMS* 2014

SEP: possibilités et développements thérapeutiques



IFN-β 1a-1b, GA
Fingolimod, Teriflunomide, Natalizumab

Dimethyl fumarate
Alemtuzumab

IFN-β 1a-1b, Mitoxantrone
Siponimod PhIII

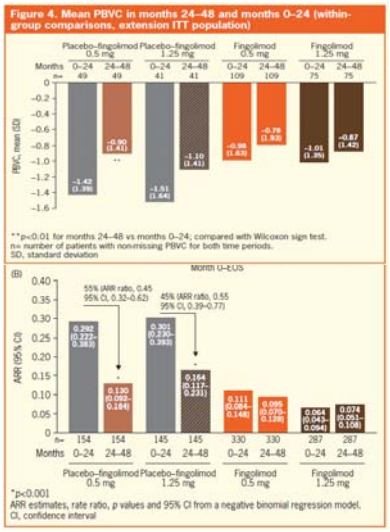
Daclizumab
Laquinimod
Ocrelizumab

Fingolimod
Gilenya® 1ère ligne

Perte de volume cérébral

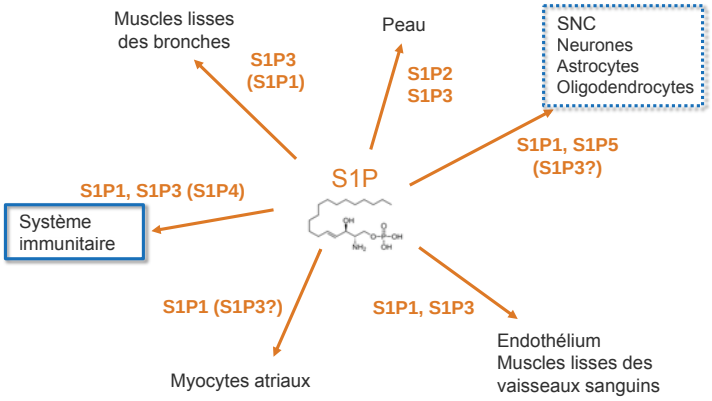
- ✓ Poussées: ↓ 54%
- ✓ Atrophie cérébrale: ↓ 31%

Taux annuel de poussées



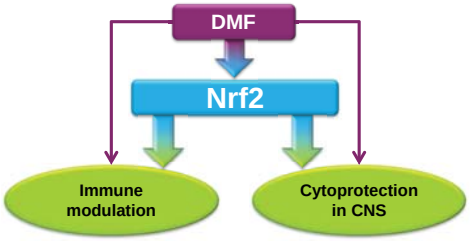
Kappos et al. Poster 979 presented at ECTRIMS 2012

Fingolimod
Cible les récepteurs sphingosine-1-phosphate (S1P)



Modifié d'après Pyne S et al. Cell Signal 2009; 21: 14-21

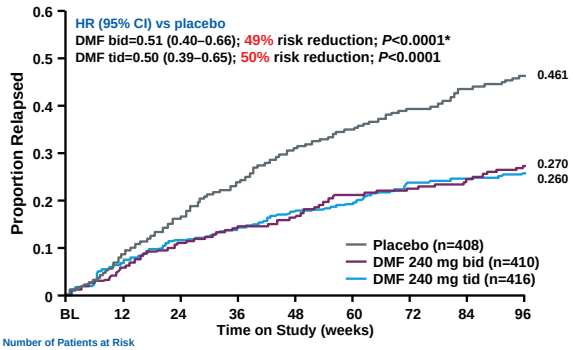
Dimethyl Fumarate: Potential Mode of Action
Tecfidera® 1ère ligne



- Reduced CNS infiltration of immune cells
- Attenuation of proinflammatory cytokine production
- Modulation of Th1/Th2 balance toward anti-inflammatory phenotype
- Tissue distribution includes CNS
- Neuroprotection in multiple animal models of neurodegeneration
  - Inflammatory
  - Toxic
  - Genetic
- Cytoprotection against oxidative stress in vitro

Linker RA et al. Brain 2011;134:678-692; Schilling S et al. Clin Exp Immunol 2006;145:101-107; Ellrichmann G et al. PLoS One 2011;6:e16172; Scannevin RH et al. J Pharmacol Exp Ther 2012;341:274-284.

DEFINE: Proportion of Patients Relapsed

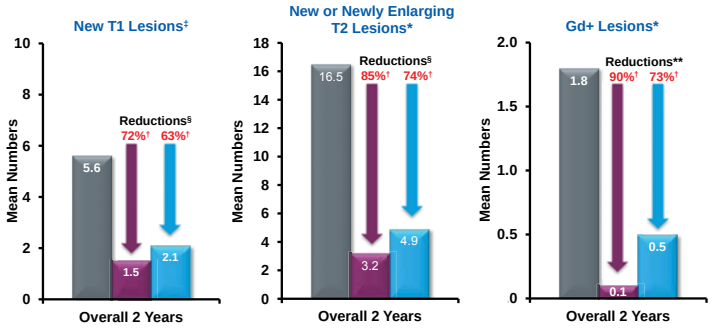


Number of Patients at Risk

Placebo	408	356	321	282	243	224	205	190	115
DMF bid	410	353	324	303	286	267	255	243	154
DMF tid	416	346	322	301	286	270	251	244	166

INEC=independent neurology evaluation committee; HR=hazard ratio; CI=confidence interval; BL=baseline.
* In CONFIRM, reduction of the estimated proportion of patients with a relapse at 2 yr with DMF bid vs. Placebo was 44% (P≤0.01).
Gold R et al. Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis. *N Engl J Med*. 2012;367:1098-1107

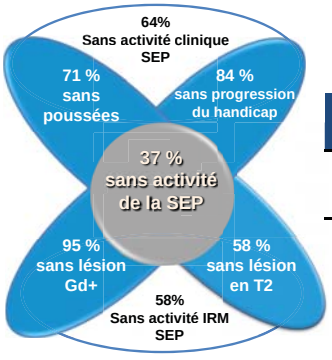
DEFINE#: MRI Results at 96 weeks



*Secondary endpoint; ‡ Tertiary endpoint; †P<0.001 vs. placebo
§Negative binomial regression, adjusted for region and baseline lesion volume; **Ordinal logistic regression analysis, adjusted for region and baseline number of Gd+ lesions.

#In CONFIRM , MRI lesions were significantly reduced in patients with DMF BID vs. Placebo: T2: 71%; T1: 57%; Gd+: 74%
Gold R et al. Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis. *N Engl J Med*. 2012;367:1098-1107
Arnold DL, Gold R, Kappos L, et al. Effects of delayed-release dimethyl fumarate on MRI measures in the Phase 3 DEFINE study, J Neurol DOI 10.1007/s00415-014-7412-x. Published online: 03 July 2014.

Natalizumab (Tysabri®)



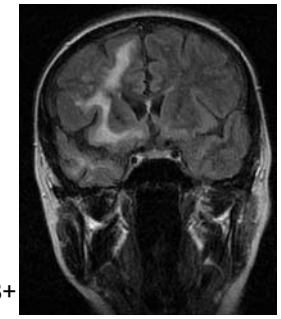
Patients sans aucune activité de la maladie sur 2 ans		
Placebo (n=304)	7%	*P*<0.0001
Natalizumab (n=600)	37%	

P<0.0001, natalizumab vs placebo, for all individual and combined disease measures. MRI=magnetic resonance imaging; Gd+=gadolinium-enhancing.
Havrdová E et al. *Lancet Neurol*. 2009;8:254-260.

Natalizumab: risque de leucoencéphalopathie multifocale progressive (LEMP)

Polyomavirus JC (JCV)

- Individus sains infectés
  - 55% des patients SEP JCV+
- Sites latents: reins, moelle osseuse cerveau ?
- Immunosuppression
  réplication active JCV dans cellules gliales, oligodendrocytes lysés
- LEMP: 7/10³ HIV négatif, 5% AIDS
- Rôle crucial des lymphocytes T CD8+
  (Du Pasquier RA et al, Brain 2004)



Polman CH et al, N Engl J Med 2006; Rudick RA et al, N Engl J Med 2006;
Yousry TA et al, N Engl J Med 2006

La LEMP est un effet secondaire rare: 2.11/1000
Définir le risque pour chaque patient SEP

Avoir été infecté par le virus JC
- 55% des patients SEP ont des anticorps positifs

Etre traité depuis plus de 24 mois par le natalizumab

Avoir reçu des traitements immunosuppresseurs auparavant

Patients avec anticorps JCV négatifs

- Test STRATIFY JCV 1x/6 mois: 2% séroconversion/an

Index result	PML risk estimates per 1000 patients (no prior IS use) 1–24 months (95% CI)	25–48 months (95% CI)	49–72 months (95% CI)
≤0.9	0.1 (0–0.41)	0.3 (0.04–1.13)	0.4 (0.01–2.15)
≤1.1	0.1 (0–0.34)	0.7 (0.21–1.53)	0.7 (0.08–2.34)
≤1.3	0.1 (0.01–0.39)	1.0 (0.48–1.98)	1.2 (0.31–2.94)
≤1.5	0.1 (0.03–0.42)	1.2 (0.64–2.15)	1.3 (0.41–2.96)
>1.5	1.0 (0.64–1.41)	8.1 (6.64–9.8)	8.5 (6.22–11.38)

PML risk estimates for anti-JCV antibody index thresholds were calculated based on the current PML risk stratification algorithm (from September 2012) and predicted probabilities shown in Table 1 for the population at or below that particular index (0.9–1.5) and for the population above an index of 1.5. For index thresholds below 0.9, patient numbers were insufficient to allow for calculation of risk estimates.

- Contrôles neurologiques réguliers
- IRM cérébrale 1x/an (JCV-), 2x/an (JCV+)

Plavina T et al., Anti-JCV antibody index further defines PML risk in natalizumab-treated MS patients. Presented at the 27th Annual Meeting of the Consortium of Multiple Sclerosis Centers May 29–June 1, 2013 Orlando, Florida.

SEP: quel suivi, quels risques ?

Risques des traitements

Maladie évolutive, potentiellement handicapante

Traitement
✓tardif
✓insuffisant

Programme

- Inflammation et neuro-dégénérescence
- Histoire naturelle des lésions
- Les types de lésions

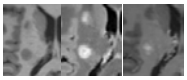
- Critères diagnostics
- Suivi: Charge lésionnelle et atrophie cérébrale
- Technique d'imagerie, protocole « Swiss MS »

Rappel patho-physiologique: inflammation et neurodégénérescence

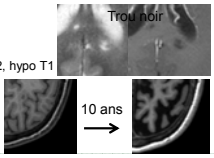
- **Inflammation**
  - Lymphocytes, Macrophages passent la BHE et attaquent la myéline, les oligodendrocytes, les axones
  - Haut degré d'inflammation:
    - Formation de plaques dans MB autour de venules
    - Œdème, rupture de la BHE
  - Bas degré d'inflammation:
    - Démyelinisation corticale (lésions corticales)
    - Dysmélynisation de la MB (Normal Appearing White Matter, plaques chroniques)
- **Neurodégénérescence**
  - Résultat de l'inflammation chronique
    - Apoptose des Oligodendrocytes, Transections d'axones, Dégénérescence wallérienne, Mort neuronale
    - Atrophie cérébrale, foyer de gliose

Imagerie de l'inflammation et de la neurodégénéresence

- **Inflammation:**
  - Oedeme, démyélinisation, rupture de la barrière HE
  - Plaque: hypointensité T1, hyperintensité T2, prise de contraste

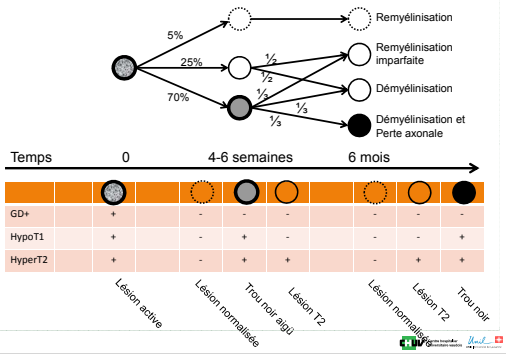


- **Neurodégénéresence:**
  - Apoptose/nécrose des oligodendrocytes, rupture axonales -> mort neuronale
  - Focalement:
    - gliose et perte de substance
    - Plaque chronique (trou noir): hyper T2, hypo T1
  - Diffusement:
    - Perte de volume = atrophie

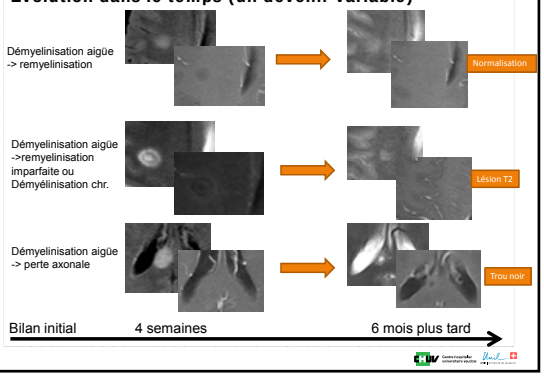


Adapté de Zivadinov, 2007

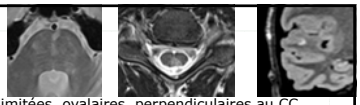
Evolution dans le temps de la plaque



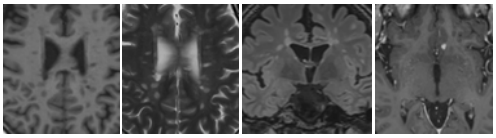
Evolution dans le temps (un devenir variable)



Types de lésions

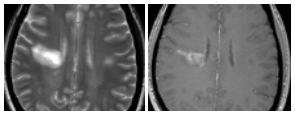


- Classique:
  - Multiples, bien délimitées, ovalaires, perpendiculaires au CC, « en doigt de gant », péri-venulaire
  - Peuvent impliquer les régions sous-corticales, le tronc cérébral, la moelle
  - Hyper T2, Iso ou hypo T1
  - Prise de contraste en phase aigue (~ 1 mois), nodulaire, arciforme
  - ADC: ↑ en général, parfois ↓ si aigues
  - MRS: ↓ NAA, Choline → ou↑

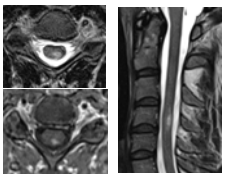


Type de lésions

- Plaque géante

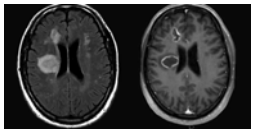


- Lésion médullaire
  - 10-20% des SEP
  - En général cervical
  - Dorso-latérale, <1/2 surface
  - < 2 segments
  - À cheval entre MB et MG

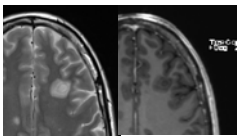


Types de lésions

- Forme pseudo-tumorale
  - CBV ↓
  - MRS: si Cho ↓ utile



- Sclérose concentrique de Balò
  - Plaque avec image en cible correspondant à des fronts de démyélinisation successive.



Diagnostique de la sclérose en plaque (SEP)

- Le diagnostique de SEP est basé sur une combinaison de signes et symptomes ainsi que de tests paracliniques (IRM, ponction lombaire) évocateur de maladie inflammatoire. Pas de clinique = Pas de SEP
- **Eléments clés:**
  - **Dissémination dans le temps (DIT) et l'espace (DIE)** de la présentation clinique ou/et radiologique
  - **Pas d'alternative** diagnostique plausible

Il faut toujours faire un bilan d'exclusion

Présentation clinique	IRM
DIT +, DIE +	-
DIT +, DIE -	DIE +
DIT -, DIE +	DIT +
DIT -, DIE –	DIT +, DIE +
DIT+: 2 attaques (>24h) DIE+: 2 déficits neurologiques distincts	DIT+, DIE+: c.f. critères de Mc Donald 2010

Syndrome Clinique Isolé (CIS)

- Signe d'atteinte focale du SNC d'une durée d'au moins 24 heures suggestif d'être une première **poussée** de SEP.
- *Exemples: dysesthésies, diminution de l'acuité visuelle, faiblesse d'un membre, diplopie, trouble de la coordination, vertiges*
- Il peut y avoir plusieurs déficits en même temps mais **un seul épisode**
- **Patient à risque** de développer une sclérose en plaque (Fisniku et al, 2008; ON Study group, 2008):
  1. IRM-: Risque de développer un SEP : 20%
     - IRM+: ≥1 lésions suggestive de SEP
  2. IRM+: Risque de développer SEP : 70%
  3. IRM avec critères de McDonald 2011: le patient a une SEP

Patient présentant un CIS: que faut-il pour en faire une SEP

- Il faut que les **critères de McDonald 2010** soient remplis (Polman et al, 2011) → IRM: DIT ± DIE

Dissémination dans le temps (DIT)	Dissémination dans l'espace (DIE)
Apparition d'une nouvelle lésion par rapport à un examen comparatif. **OU** Présence simultanée de lésions T2 Gd+ et Gd-.*	≥1 lésion T2 dans au moins 2 des 4 régions suivantes: - Périventriculaire - Juxtacortical - Infratentoriel - Moelle épinière

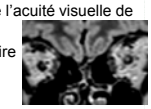
- Dans le cadre d'un CIS ces critères on une sensibilité de 77% et une spécificité de 90% (Swanton 2006).

Ne s'applique pas à une découverte radiologique fortuite (RIS)!
Manque de spécificité!

* Il faut 1 lésion Gd+ non symptomatique

Cas no 1

- Patient de 25 ans développant une diminution de l'acuité visuelle de l'œil G
- Ophalmoscopie démontre une névrite rétrobulbaire
- CIS -> SEP? Ad IRM



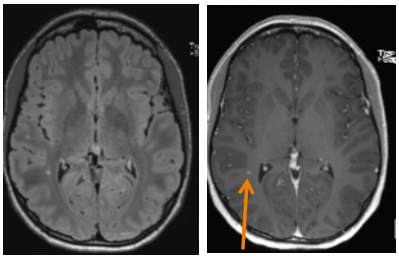
IRM montre une DIE, pas la DIT -> CIS

Pas de prise de contraste

Cas no 1

Nécessité de 2 IRM pour établir la DIT -> SEP

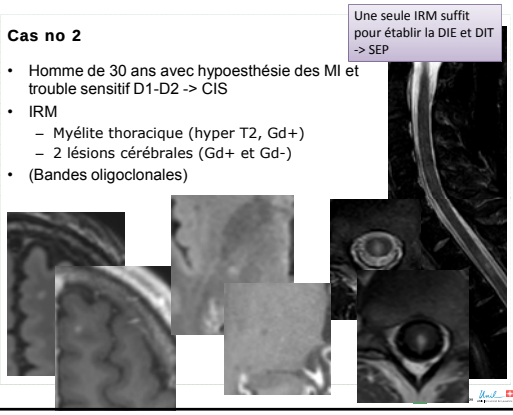
- 3 mois plus tard, contrôle
- DIT+ -> SEP



Cas no 2

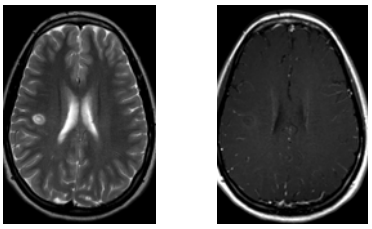
Une seule IRM suffit pour établir la DIE et DIT -> SEP

- Homme de 30 ans avec hypoesthésie des MI et trouble sensitif D1-D2 -> CIS
- IRM
  - Myélite thoracique (hyper T2, Gd+)
  - 2 lésions cérébrales (Gd+ et Gd-)
- (Bandes oligoclonales)



Cas no 3

- Fille de 16 ans ayant présenté initialement avec une dysarthrie



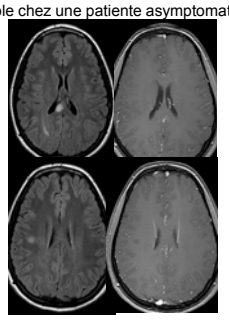
- Lésion type Balò à l'IRM, hautement suggestive de SEP

IRM ne montre pas de DIE ni de DIT -> CIS

Cas no 3

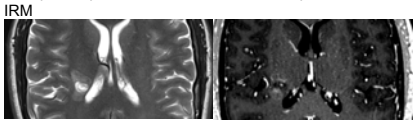
- 6 mois plus tard contrôle chez une patiente asymptomatique

La 2ème IRM établi la DIE et DIT -> SEP



Cas no 4

- Homme de 35 ans, présentant un hemisyndrome G progressif sur quelques jours.
- Clinique suspecte de SEP, DIS-, DIE- cliniquement => CIS => ad IRM



- Une seule lésion d'allure inflammatoire (SEP possible)
- DIS-, DIE- => CIS

Il faut faire un bilan d'exclusion
Il faut attendre soit une nouvelle poussée ou de nouvelles lésions à l'IRM

Syndrome Radiologique Isolé (RIS)

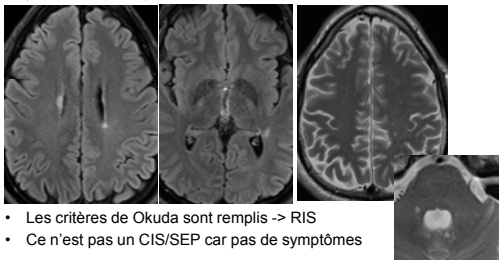
- **Définition**: Découverte fortuite à l'IRM de lésions cérébrales hautement suggestives de SEP en l'absence de symptomes.
- **Critères RIS selon Okuda**:
  - Lésions de morphologie suggestive (ovoïdes, bien délimitées, homogènes)
  - Hyperintensitiés T2 de >3 mm et remplissant au moins 3 des 4 critères (McDonald 2001):
    - ≥9 lésions ou ≥1 Gd+
    - ≥3 périventriculaires
    - ≥1 lésions juxtacorticales
    - ≥1 lésions infratentorielles/spinales
  - Les lésions de sont pas évocatrices de microangiopathie hypertensive ou en relation avec une ingestion de toxiques
  - Anamnèse négative pour des symptomes neurologiques transitoires
  - Pas d'alternative diagnostique probante

Okuda et al, 2008

Cas no 5

~~≥9 lésions ou ≥1 Gd+~~
≥3 périventriculaires
≥1 lésions juxtacorticales
≥1 lésions infratentorielles/spinales

- Bilan de céphalées
- On trouve des lésions suggestives de SEP (ovoïdes, périventriculaires)



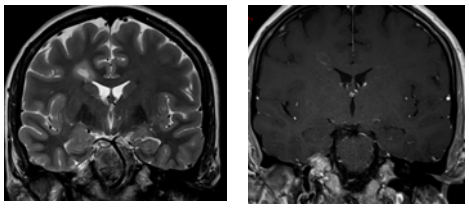
- Les critères de Okuda sont remplis -> RIS
- Ce n'est pas un CIS/SEP car pas de symptômes

Caracteristiques des patients avec présentant un RIS

- Examen neurologique normal au moment de l'examen IRM initial dans presque tous les cas
- Chez 60% de ces patients on observe une progression radiologique lors du suivit (nouvelles lésions)
- **30% développent un CIS ou une SEP**
- Si lésion médullaire asymptomatique le risque de CIS/SEP est de 80%!
- La présence de lésions Gd+ lors du bilan initial prédit une dissémination dans le temps lors du suivit HR=3.4.

Cas no 6

- Bilan d'infertilité chez une patiente de 29 ans autrement asymptomatique



- Lésion d'allure inflammatoire, non spécifique (possible SEP)

L'IRM ne remplis pas les critères de Okuda.
Ce n'est pas un RIS ni CIS ni SEP.
C'est néanmoins une lésion d'allure inflammatoire ouvrant un DD, nécessite un bilan et doit être suivie

Facteurs prognostics

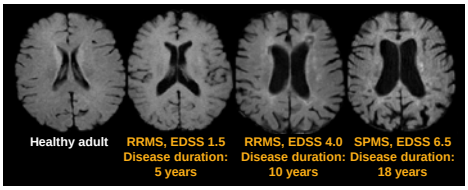
- **Charge lésionnelle (lésions T2)**
  - Le **nombre de lésions** sur la 1ère IRM diagnostique de CIS est prédictive du handicap à 10 ans (r=0.45*) (O'Riordan et al, 1998;
  - **L'évolution du volume lésionnel** dans les 5 premières années est prédicitif du handicap à 14 ans (r=0.61*) (Brex et al 2002)
- **Atrophie cérébrale** (Zivadinov et al, 2001)
  - Suivit sur 2 ans de patients avec SEP
  - Corrélation + entre diminution de performance **cognitive** et diminution de volume cérébral (r=0.51*)
  - Corrélation + entre augmentation du **EDSS** et diminution de volume cérébral (r=0.59*)

Charge lésionnelle et atrophie cérébrale sont des éléments qui intéressent le neurologue

Idéalement quantifiable

Courtesy Dr A Weidenfeller

Brain volume change is a global marker of neuronal loss in MS

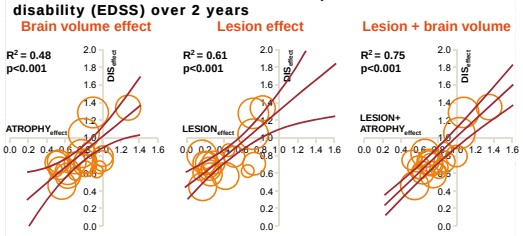


- Occurs in all clinical stages[1,2]
- **Annual rate of loss in MS 0.5-1.35%**[3-5]
- Measures of global brain volume change are
  - robust
  - sensitive
  - relatively easy to standardise[1,2]

RRMS, relapsing-remitting MS; SPMS, secondary progressive MS. 1. Filippi M, Agosta F. *J Magn Reson Imaging* 2010; 2. Giorgio A *et al. Neuroimaging Clin N Am* 2008; 3. De Stefano N *et al.* Oral presentation S13.006 at *AAN* 2014; 4. Barkhof F *et al. Nat Rev Neurol* 2009; 5. Images reproduced from *Lancet Neurol* 5(2), Bermel RA, Bakshi R. The measurement and clinical relevance of brain atrophy in multiple sclerosis, pages 158-170. Copyright (2006), with permission from Elsevier

Courtesy Dr A Weidenfeller

Treatment effect on brain volume loss predicted disability (EDSS) over 2 years



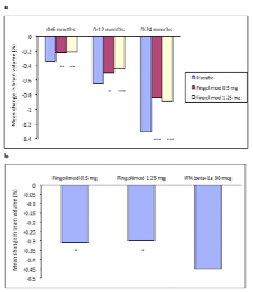
- Meta-analysis of 13 RCTs (>2 years; n > 13 500; RRMS)
- Each circle = 1 study; size of circle = effect size, adjusted for trial size / duration

Effect of brain volume loss was independent of lesion effect on disability
This suggests it relates to a different mechanism of progression

RCT, randomised clinical trial; RR, relative reduction
Sormani MP *et al. Ann Neurol* 2014, Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. 75(1):43-49. doi: 10.1002/ana.24018. http://dx.doi.org/10.1002/ana.24018

Exemple d'effet médicamenteux sur le volume cérébral

- **(a)** Perte de volume cérébral à 6 mois, 1 an et 2 ans après randomization (placébo contre fingolimod, 0.5 ou 1.25 mg (FREEDOMS Study)
- **(b)** Perte de volume cérébral à 1 an sous différents traitements: fingolimod 0.5 ou 1.25 mg ou IFNβ-1a 30 µg (TRANSFORMS Study)

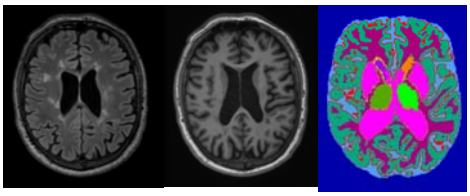


Comment évaluer le développement de l'atrophie

- Exercice très difficile pour un radiologue, plus facile pour un algorithme
- Il faut intégrer l'atrophie "physiologique" liée au vieillissement
- Pour que l'atrophie cérébrale devienne mesurable **il faut du temps**.
  - au moins un intervalle de 1 an.
  - au moins 2 ans pour objectiver l'effet bénéfique d'un médicament.
- Cavéat: **Pseudo-atrophie**
  - Lors de l'initiation d'un médicament, effet anti inflammatoire -> dégonfle le cerveau (anti œdème)
  - Pour quantifier l'atrophie il faut avoir une image baseline entre 3 et 6 mois après l'initiation du traitement.

Ségmentation automatique

- Ségmentation automatique (multiples techniques possibles: VBM, histogrammes et a priori anatomiques, matching de surfaces, etc)
- Comparaison à base de donnée normative
- Basée sur MPRAGE 1 mm



Evolution au cours de 1 an de maladie

T=1 an

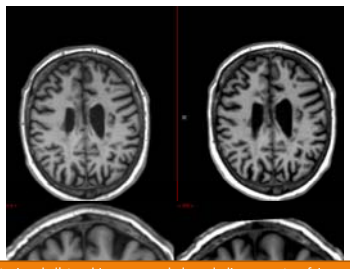
Tissue	Absolute [ml]	Normalized^ [%]	Normative Range^^ [%]
TIV	1392.8		
GM	613.3	44.0	[42.5 - 49.7]
cortical GM	475.9	34.2	[32.2 - 38.3]
WM	345.7	* 24.8	[27.3 - 33.0]
WMab	3.4	0.2	
CSF	433.9	* 31.2	[20.1 - 26.6]

T=0

Volumetric Measurement	Absolute [ml]	Normalized^ [%]	Normative Range^^ [%]
TIV	1376.2		
GM	592.6	* 43.1	[43.4 - 49.3]
cortical GM	459.2	33.4	[32.6 - 37.4]
WM	368.2	* 26.8	[28.1 - 33.9]
WMab	2.5	0.18	
CSF	415.4	* 30.2	[18.5 - 26.7]

^ Percentage of TIV (Total Intracranial Volume)
^^ 80% of healthy age-matched population
* Out-of-range volumes

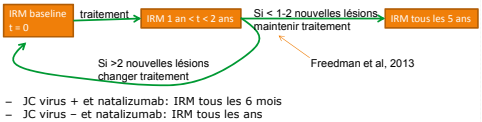
T=0 T=1 an



Le monitoring de l'atrophie au cours de la maladie ne peut se faire qu'à l'aide d'outils de ségmentation automatique
L'utilité de ce monitoring dans le cadre d'une étude thérapeutique est indéniable
Par contre dans la cadre de la pratique clinique courante reste à être démontrée

Monitoring

- Motivation:
  - Traiter tôt et efficacement
    → éviter l'accumulation de nouvelles lésions et l'atrophie
    → limiter le handicap à long terme
- Conséquences
  - Monitoring IRM pour vérifier l'efficacité thérapeutique
    - À court terme: contrôle de l'activité
    - A long terme: accumulation de la charge lésionnelle et l'atrophie
  - Monitoring IRM pour détection précoce de complications des traitements puissants
- Recommandation:
  - Protocole de base



  - JC virus + et natalizumab: IRM tous les 6 mois
  - JC virus – et natalizumab: IRM tous les ans

« Both criteria, clinical and MRI, are needed to recognize very active or aggressive relapsing MS patients, leading to decide a rapid use of second-line treatment therapy » (Edan, 2013)

Protocole d'imagerie

- Le CHUV participe à une grande étude observationnelle nationale sur la SEP (Swiss MS).
- Dans ce cadre tous les centres universitaires ainsi que d'autre participants ont élaboré un protocole d'imagerie commun.
  1. 3D GRE MPRAGE 1 mm isotropique
  2. Injection de GD (0.1 mmol/kg)
  3. 2D TSE T2/PD 46 coupes de 3 mm
  4. 3D GRE FLAIR 1mm isotropique
  5. 3D GRE MPRAGE 1mm isotropique

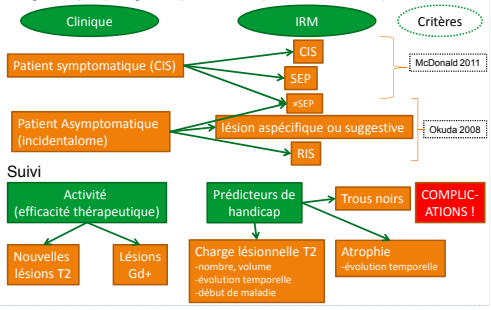
Suivre ce protocole permet une homogénéité au niveau Suisse.
Néanmoins séquences 3D peuvent être remplacées par du 2D

Reporting pour le suivi de SEP

- Prédicteurs du handicap (EDSS, cognition)
  - Charge lésionnelle T2
    - Nombre, volume
    - Baseline, évolution
    - Localisation, en particulier pour les régions éloquentes
  - Atrophie
    - État actuel, évolution
  - Trous noirs
- Activité:
  - Nombre de nouvelles lésions (T2)
  - Lésions Gd+
- Eventuelles complications
  - PML

Conclusion: rôle de l'IRM

- Diagnostique (diagnostique de SEP pas encore établi)



- Suivi

Diagnostic différentiel des lésions de la substance blanche et des complications liées au traitement de la SEP

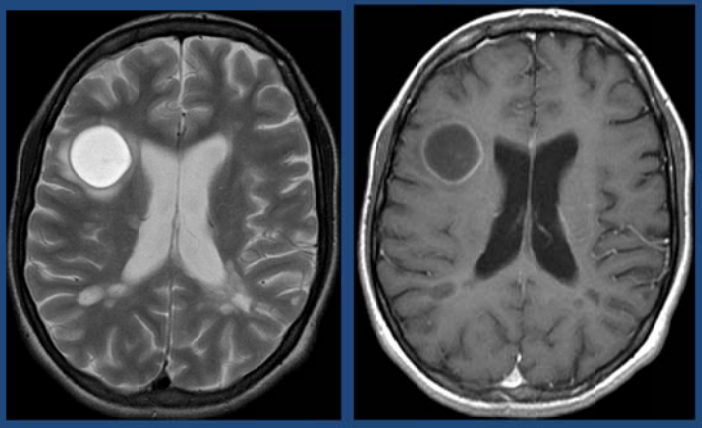
Philippe Maeder

- MS variants & MS like diseases
- Marburg
- Baló's concentric sclerosis
- Schilder's myelinoclastic diffuse sclerosis
- Neuromyelitis optica (NMO) Devic syndrome
- Monophasic post-infectious demyelination: ADEM, AHLE, SSPE
- Vasculitis
- Susac's disease
- Primary CNS vasculitis
- Behçet, PAN, lupus, Sjögren, Wegener…
- Toxic: amphetamin, cocain, methotrexate…
- Other diseases of white mater mimicking MS
- Lyme, Viral encephalitis, AIDS, PML, Sarcoïdosis, HTA leukoencephalopathy, CADASIL, late onset leukodystrophies, mitochondriopathies, Fabry, histiocytosis, primary CNS lymphoma, FRES…
- Normal zones of late myelination
- Isolated optic neuropathy
- Chronic relapsing inflamatory optic neuropathy (CRION)
- Complications of treatment
- Natalizumab-PML-IRIS

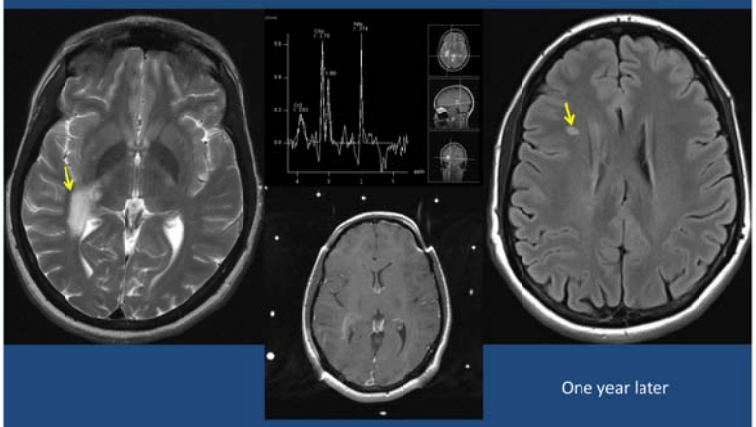
Marburg

- In 1906 Otto Marburg described three cases of a withering demyelinating disorder in young adults
- Macroscopy: large tumor like plaques in the hemispheric white matter
- Microscopy: Hypercellular demyelinating plaques, with oedema, severe axonal injury, faint astroglial reaction, and presence of hypertrophic and giant astrocytes
- CSF: increase in proteins, slightly increased or normal celullarity, oligoclonal bands less frequent than in MS
- MRS: increase of the peak of choline and a decrease of *N-acetyl-aspartate (NAA)*
- Pathogenesis: chemical modifications of the MBP may cause a structural instability of the central myelin sheath

Marburg



Tumefactive plaque as the first manifestation of MS



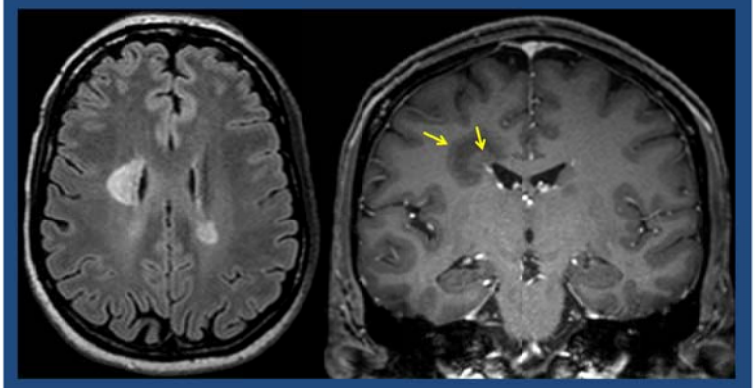
One year later

Baló

- In 1928 József Baló described the case of a young student who died rapidly after the onset of a progressive neurological illness thought to be caused by a brain tumour located in the left cerebral hemisphere
- Macroscopy: concentric target-like lesions
- Microscopy: alternating bands of partial preservation of myelin and myelin loss, with preserved axons, lipidcontaining macrophages, giant astrocytes with multiple nuclei and perivascular cuffs of lymphocytes
- Young adults and result in death within a period of weeks or months but some cases have a milder course
- Baló's type lesions are only a stage of the disease and evolve with time in a diffuse demyelinated plaque

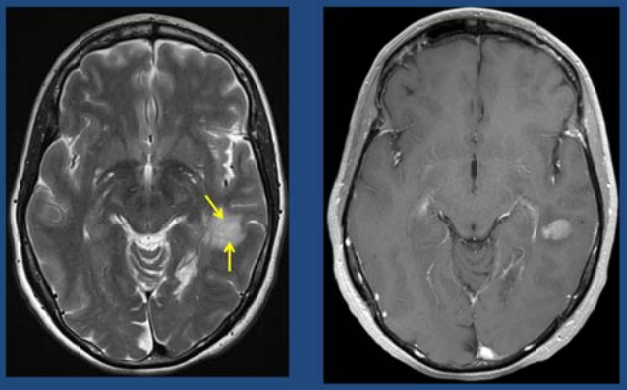
MS variants & MS like diseases

Baló



MS variants & MS like diseases

Baló



MS variants & MS like diseases

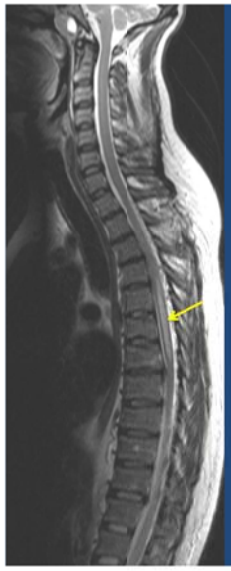
Neuromyelitis optica (NMO)

Devic syndrome

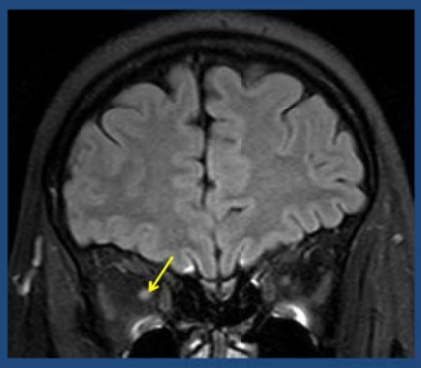
- In 1894, Eugène Devic reported the clinical course and autopsy findings of a 45-year old woman who developed bilateral optic neuropathy and transverse myelopathy within 2 weeks and died later
- Pathological examination of the case showed severe demyelination and necrotic changes in the optic nerves and spinal cord, but no brain lesion
- Microscopy: extensive loss of immunoreactivities to AQP4 and glial fibrillary acidic protein (GFAP) with relative preservation of the staining of myelin basic protein in acute NMO lesions
- Female preponderance.
- Autoantibodies to aquaporin-4 (AQP4): dominant water channel in the central nervous system densely expressed on foot processes of astrocytes.
- Predominant polymorphonuclear pleocytosis, and absence of oligoclonal IgG bands
- Limited variants (either recurrent myelitis or optic neuritis), Asian opticospinal MS, and "atypical" forms with brain involvement

Diagnosis Criteria

- ➢ The Mayo Clinic proposed a revised set of criteria for diagnosis of Devic's disease in 2006. The new guidelines require 2 absolute criteria plus at least 2 of 3 supportive criteria.
- ➢ Absolute criteria
- Optic neuritis
- Acute myelitis
- ➢ Supportive criteria
- Brain MRI not meeting criteria for MS at disease onset
- Spinal cord MRI with contiguous T2-W signal abnormality extending over 3 or more segments
- NMO-IgG seropositive status (antibodies against aquaporin 4 antigen)



Devic



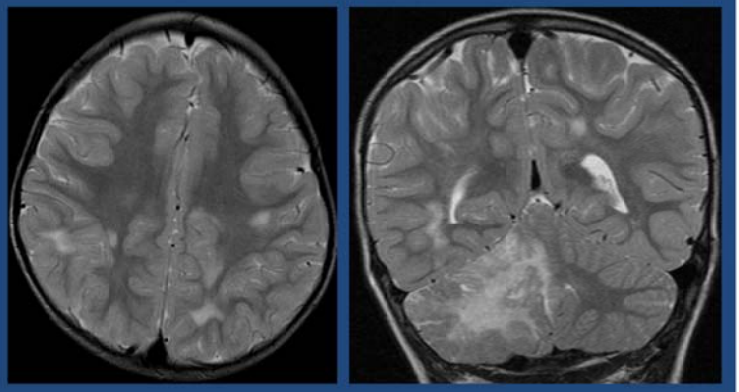
Monophasic post-infectious demyelination

Acute Disseminated Encephalo-myelitis (ADEM) and Acute Hemorrhagic Leucoencephalitis (AHLE) (Hurst)

- Immunomediated monophasic demyelination disease of the central nervous system.
- Follows an unspecific respiratory infection. Crossreactivity between human myelin antigens and viral or bacterial antigens is thought to initiate an autoimmune process causing demyelination usually sparing the subcortical U fibers.
- Typically affects children and young adults.
- AHLE: most severe variant with perivascular demyelination and hemorrhage with predominantly neutrophilic and macrophagic inflammatory infiltrates and fibrinoid necrosis of the vessels
- ADEM can relapse and some patients may ultimately convert to multiple sclerosis

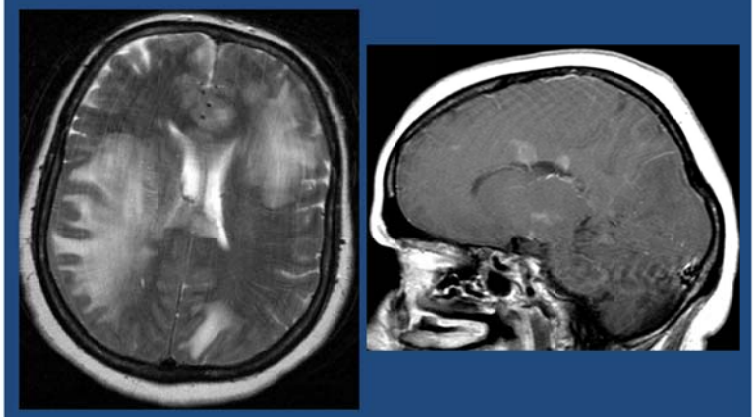
Monophasic post-infectious demyelination

ADEM



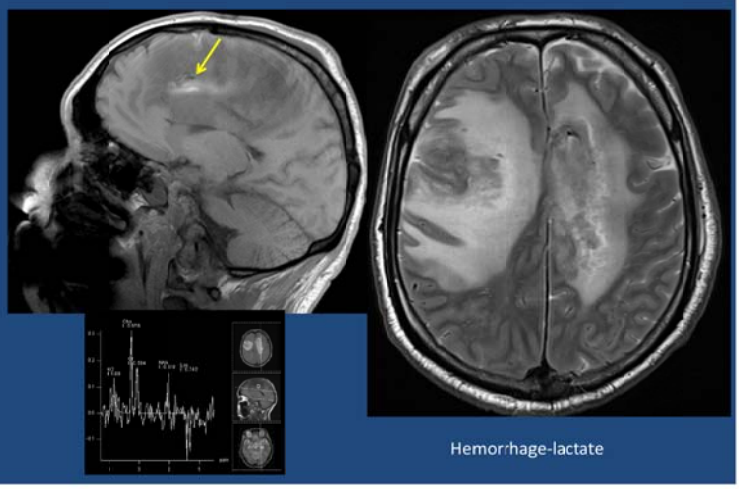
Monophasic post-infectious demyelination

ADEM



Monophasic post-infectious demyelination

AHLE

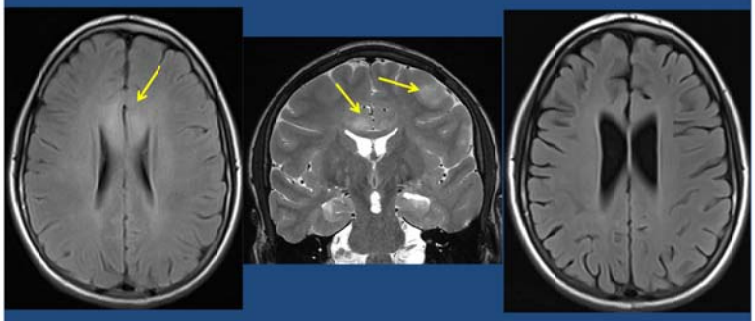


Hemorrhage-lactate

Monophasic post-infectious demyelination

Subacute sclerosing panencephalitis (SSPE)

Rare chronic, progressive encephalitis caused by a persistent infection of measles virus.
T2 hyperintensities in deep white matter and progressive cerebral atrophy.



Atrophy after 16 months

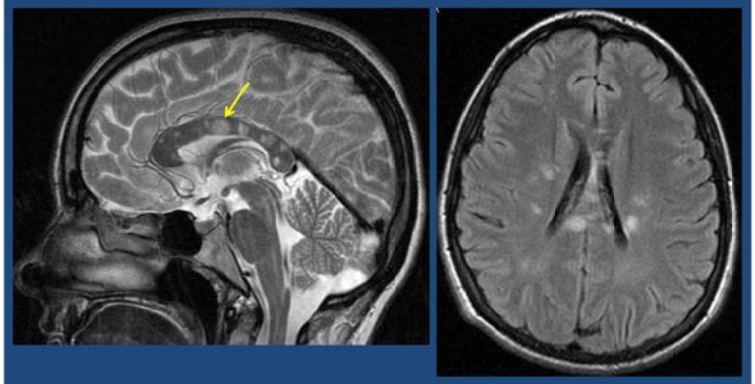
Vasculitis

Susac's disease

- In 1979 Drs. Susac, Hardman and Selhorst reported two patients with the triad of encephalopathy, branch retinal artery occlusion (BRAO), and hearing loss (HL)
- Autoimmune endotheliopathy affecting the pre-capillary arterioles of the brain, retina, and inner ear (cochlea and semicircular canals)
- Encephalopathy, with psychiatric features, confusion, memory loss and other cognitive changes
- Typically affects young women (20-40)
- Central corpus callosum, leptomeningeal involvement

Vasculitis

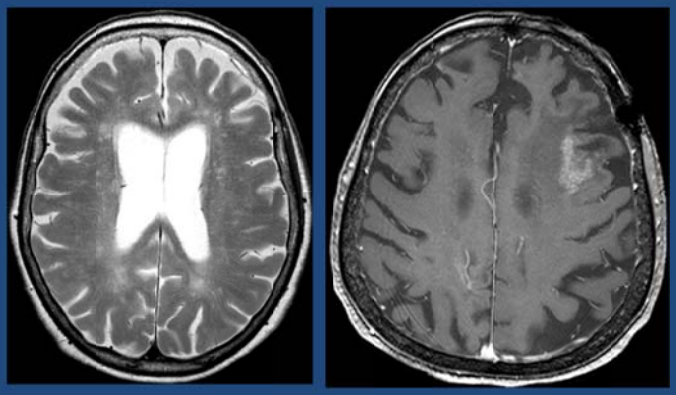
Susac's disease



Vasculitis

Primary CNS angiitis

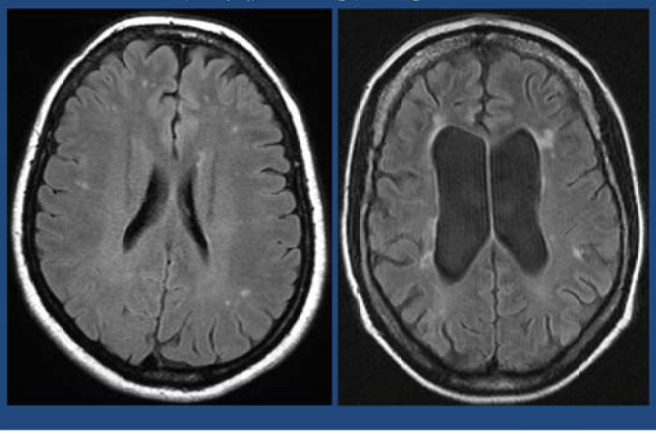
Inflammation of CNS vessels without evidence of systemic vasculitis. Irregularities of vessels (MRA DSA), multiple infarcts, hemorrhages, and patchy or confluent white matter T2 abnormalities, leptomeningeal enhancement.



Vasculitis

Lupus

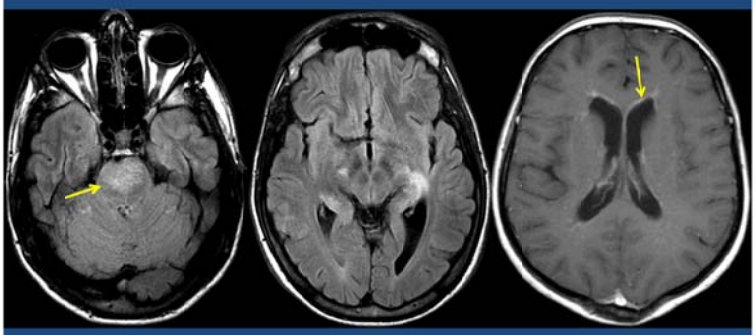
Systemic auto-immune connective tissue disease with frequent autoantibody-mediated CNS vasculitis. White mater hyperintensities in frontal and parietal lobes, infarcts, atrophy, hemorrhage, meningeal enhancement.



Vasculitis

Behçet

Sytemic vasculitis of unknown origin (genetic predisposition). Oral and genital ulcers & uveitis. Cerebral venous thromboses, meningoencephalitis and rhombencephalitis.



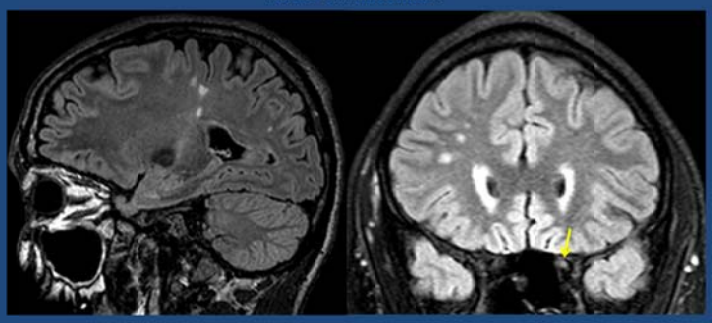
rhombencephalitis

Ventriculitis

Other diseases of white mater mimicking MS

Lyme

Neuroborreliosis is a tick-borne infection which affects the peripheral and central nervous system. MRI shows non specific white matter hyperintensities and cranial nerve enhancement.

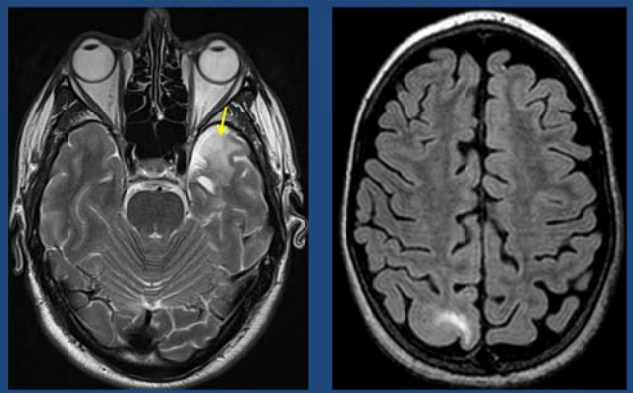


Optic neuritis

Other diseases of white mater mimicking MS

Infectious encephalitis

Involvement of white and gray matter (diffusion) necrosis and hemorrhage if untreated. Subacute and chronic variants.



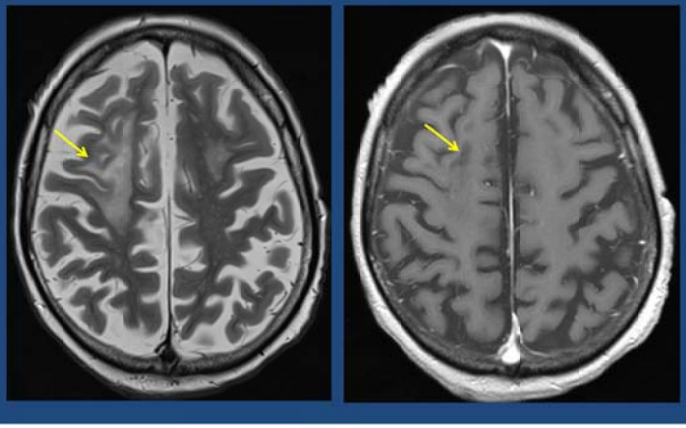
Herpes simplex (HSV1)

Herpes Zoster (VZV)

Other diseases of white mater mimicking MS

Progressive Multifocal Leukoencephalopathy (PML)

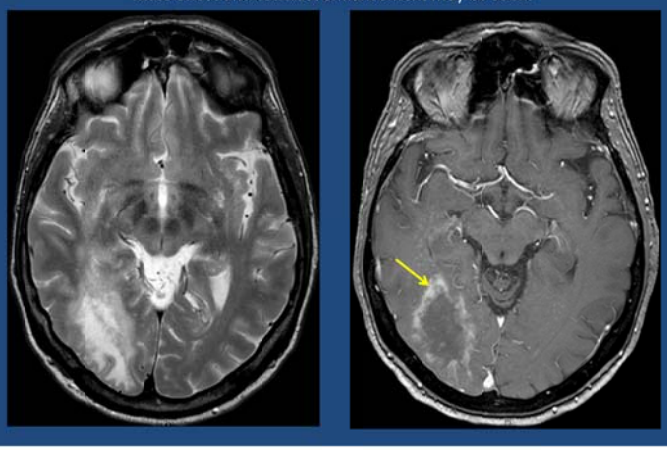
Demyelinating disease of the brain caused by the reactivation of JC virus (John Cunningham) infection. Manifests in patients with reduced cellular immunity (HIV, Hematological diseases, immunosuppressive therapies) T2 hyperintensity and T1 hypointensity of subcortical white matter, without mass effect and contrast enhancement.



Other diseases of white mater mimicking MS

PML and immune reconstitution inflammatory syndrome (IRIS)

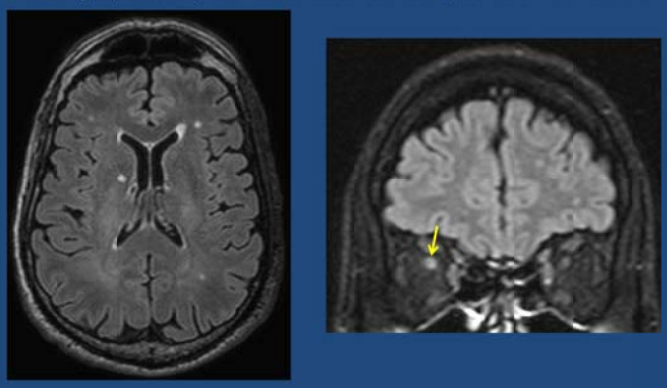
Mass effect and contrast enhancement may be seen.



Other diseases of white mater mimicking MS

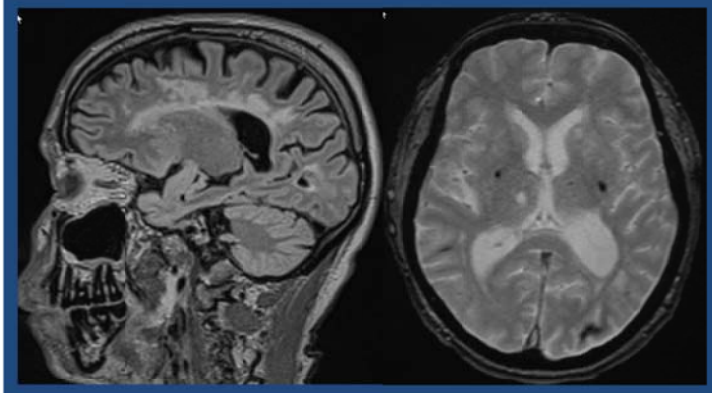
Neurosarcoidosis

Granulomatous disease of unknown origin affecting the CNS in 5-10%
Periventricular T2 hyperintensities, thickening and enhancement of the meninges particularly at the skull base. Common optic nerve involvement.



Other diseases of white mater mimicking MS

HTA leukoencephalopathy

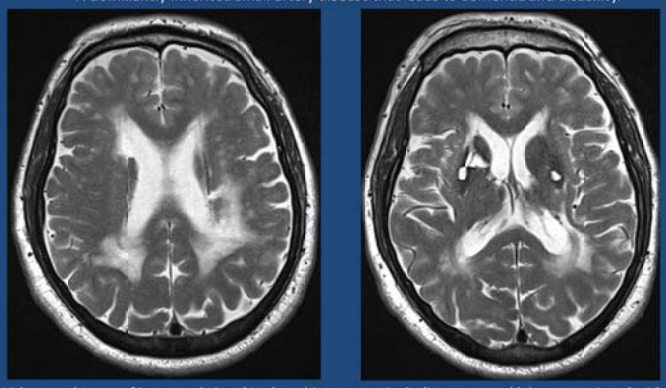


Lacunar infarcts and microbleeds.

Other diseases of white mater mimicking MS

CADASIL

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
A dominantly inherited small artery disease that leads to dementia and disability.



Widespread areas of increased signal in the white matter, including temporal lobes, associated with focal hyperintensities in basal ganglia, thalamus, and brainstem.

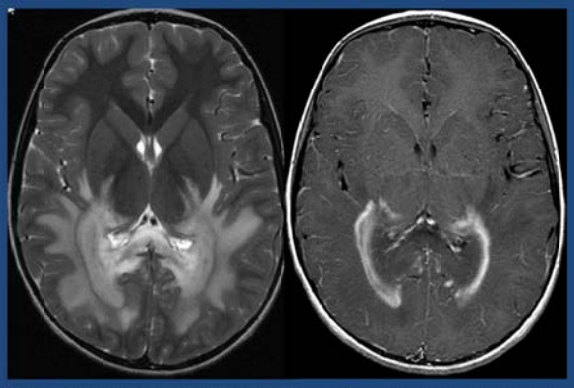
Other diseases of white mater mimicking MS

A practical approach to diagnosing adult onset leukodystrophies

Adult onset leukodystrophies

(adreno,metachromatic...)

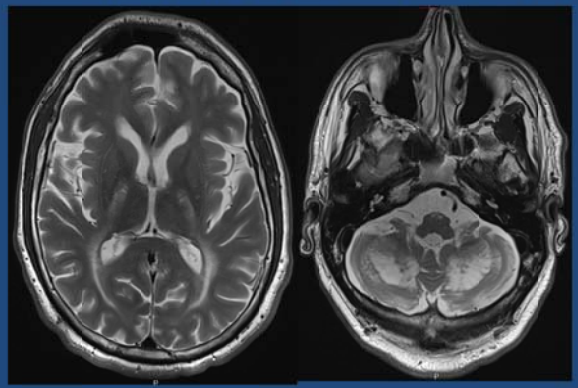
X-linked adrenoleukodystrophy (X-ALD) is a rare sex-linked recessive inherited peroxisomal disorder with accumulation of saturated very long chain fatty acid (VLCFA) in the nervous system, adrenal glands and other tissues.



Confluent posterior white matter lesions, with contrast enhancemment

Cerebrotendinous xanthomatosis

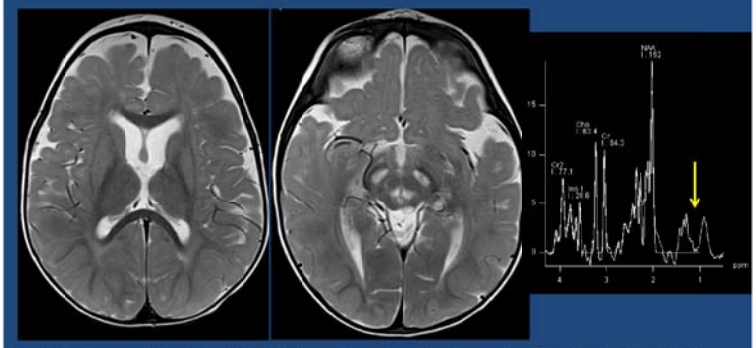
Cerebrotendinous xanthomatosis (CTX) is a rare autosomal-recessive lipid storage disease caused by mutations in the CYP27A1 gene. MRI: dentate nucleus and white matter lesions



Other diseases of white mater mimicking MS

Mitochondrial diseases (Leigh, MELAS)

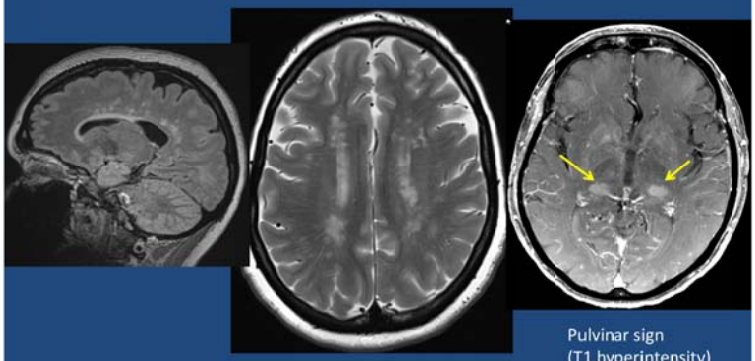
Mutations in nuclear-encoded respiratory chain complexes (Leigh) or mtDNA (MELAS)



Leigh. Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (MRS)

Fabry disease

Rare X-linked genetic lysosomial storage disease with accumulation of glycosphingolipids in blood vessels, smooth muscle, myocardium, renal epithelium, cornea, and brain. Ischemic and microhemorrhagic lesions in the brain.

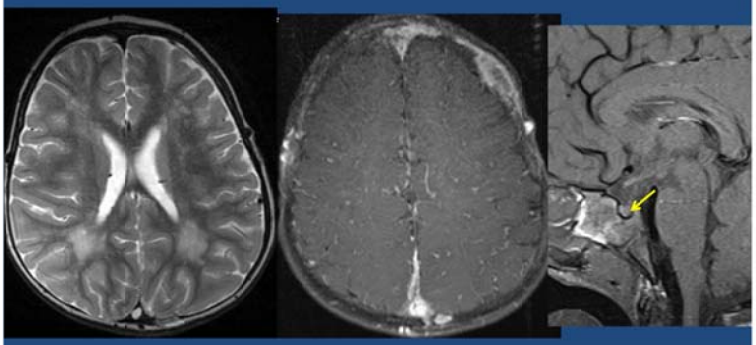


Pulvinar sign
(T1 hyperintensity)

Other diseases of white mater mimicking MS

Histiocytosis

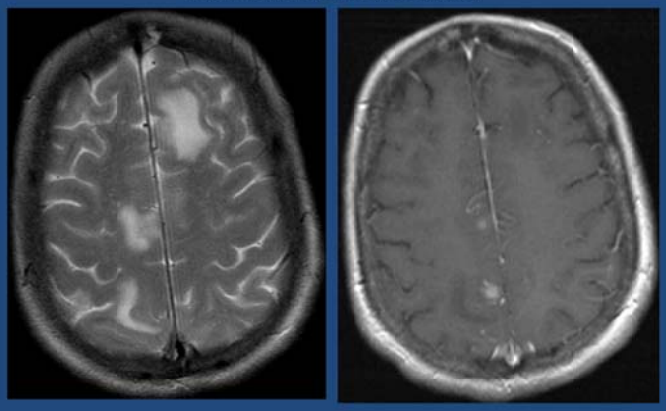
Abnormal elevation of the number of histiocytes .(Langerhans cell, non langerhans cell, malignant.) Pituitary, white matter and bone lesions



Other diseases of white mater mimicking MS

Primary CNS lymphoma

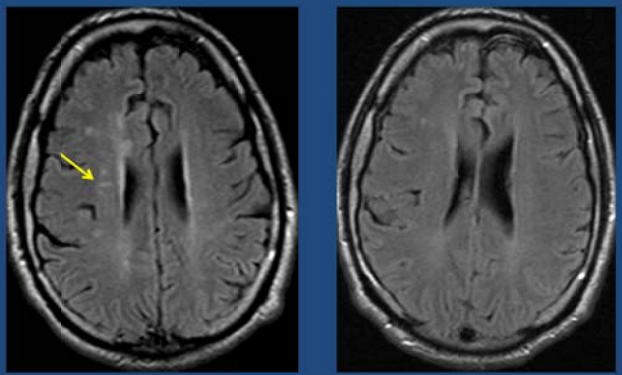
Mostly diffuse B-cell lymphoma often appearing in white matter and basal ganglia. Contrast enhancement, except in AIDS.



Other diseases of white mater mimicking MS

Posterior reversible encephalopathy syndrome (PRES)

Reversible vasogenic (cytotoxic) edema in the subcortical white matter of the parietal and occipital lobes. Common causes: eclampsia, hypertension, acute renal failure, cytotoxic drugs... Many atypical variants.

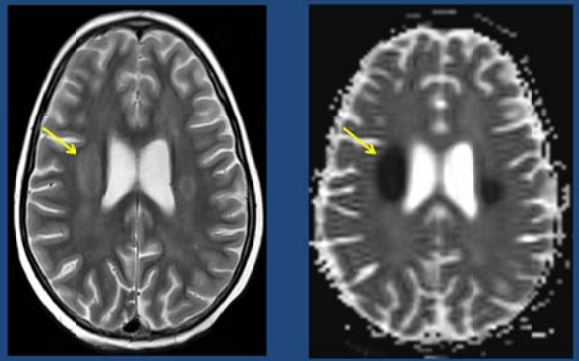


hypertension

2 weeks later

Other diseases of white mater mimicking MS

PRES induced by cytotoxic treatment



T2

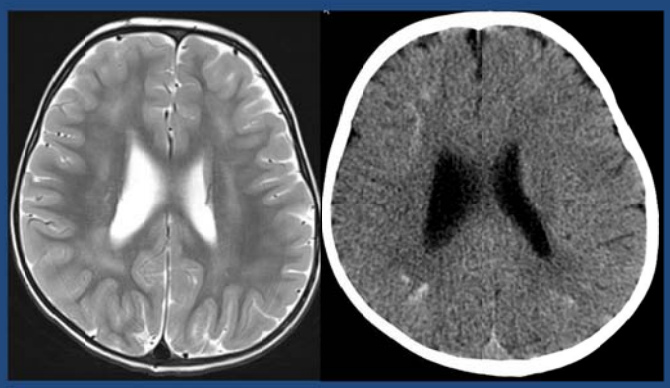
ADC

Asparaginase and cytarabine for acute lymphoblastic leukemia

Other diseases of white mater mimicking MS

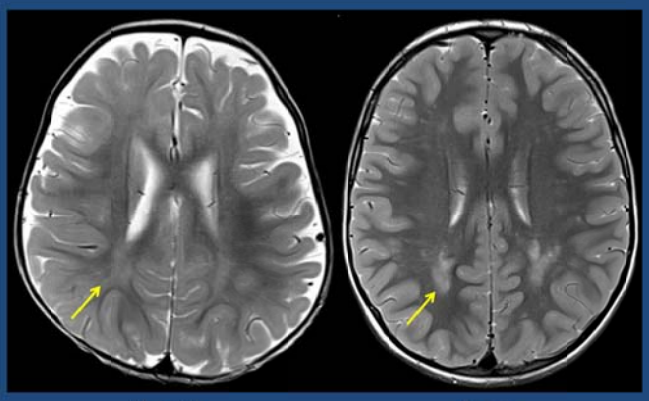
Methotrexate toxicyty

White matter, basal ganglia, calcifications on CT



Normal myelination

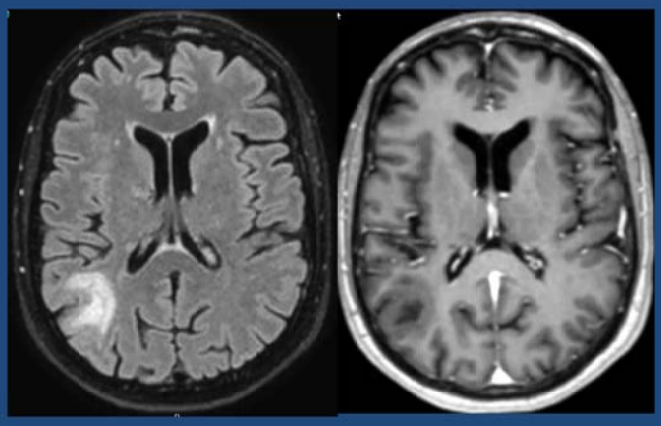
Normal zones of late myelination



11 month 5 years

Complications of treatment

Complications of treatment



Complications of treatment

Natalizumab induced PML

- PML in patients receiving Natalizumab was first reported in 2005. Risk estimated to 1.5/1000
- More than 400 cases reported (2014)
- Risk factor for Natalizumab induced PML:
- Prolonged use of the drug (more than 2 years)
- Prior immunosuppressive treatment (mitoxantrone, azathioprine, methotrexate) but not interferon beta and GA or bolus of corticosteroids.
- Anti-JCV antibodies

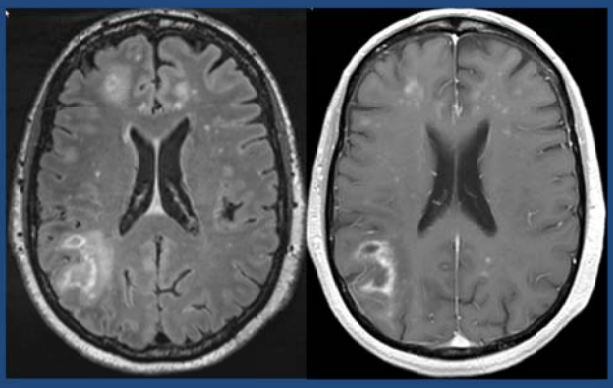
Complications of treatment

NTZ induced PML

- Outcome of PML infection is better than in HIV patients
- Routine brain MRI every 6 months is recommended in JCV positive patients receiving NTZ
- Early detection of PML by MRI and immediate cessation of NTZ ttt leading to rapid immune reconstitution but…
- Immune reconstitution inflamatory syndrome (IRIS) may result in inflamatory brain damage
- Treatment with corticosteroids

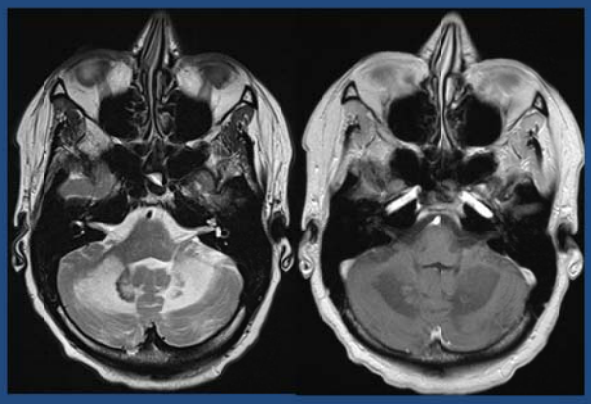
Complications of treatment

IRIS



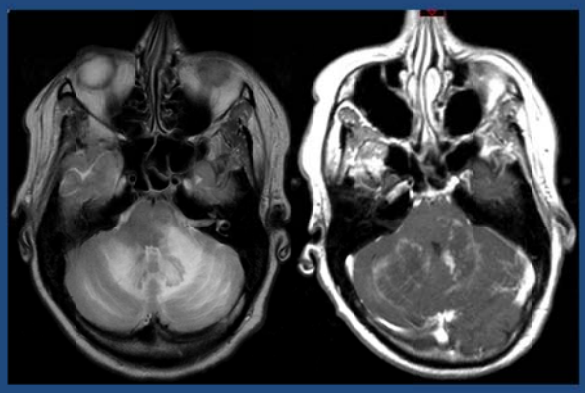
Complications of treatment

PML



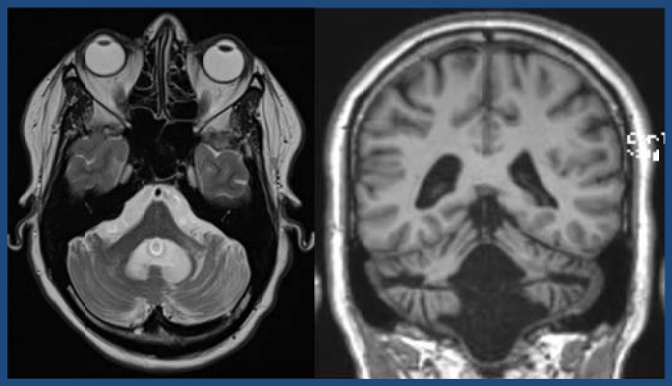
Complications of treatment

IRIS



Complications of treatment

Damage post PML and IRIS



Merci

Advanced MRI techniques in multiple sclerosis

PD Dr C. Granziera
Neuroimmunology Unit and Laboratoire de Recherche en Neuroimagerie, DNC, CHUV
Advanced Clinical Imaging Technology Group, EPFL
Laboratoire de Traitement de Signaux 5, EPFL

UNIL | Université de Lausanne

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

CHUV

Outline

- Cortical lesions
  - Double Inversion Recovery at 1.5 and 3T
  - MP2RAGE at 3T
  - T2* FLASH at 7T
- Brain microstructure
  - Multi-parametric quantitative MRI
- Brain connectivity
  - Connectomics
- Towards automatic quantitative metrics

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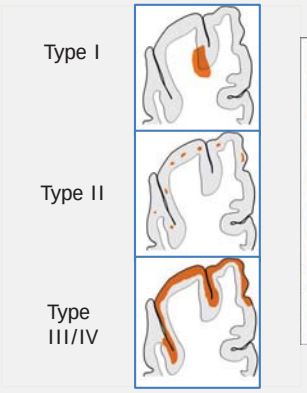
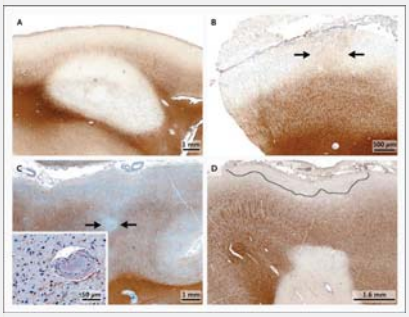
Cortical lesions in MS





Double Inversion Recovery (DIR)

- Conventional spin echo (SE) sequence preceded by a 180° inverting pulse
  - Improves cortex visualization by suppressing CSF and WM signal
  - Gray matter appears relatively hyperintense

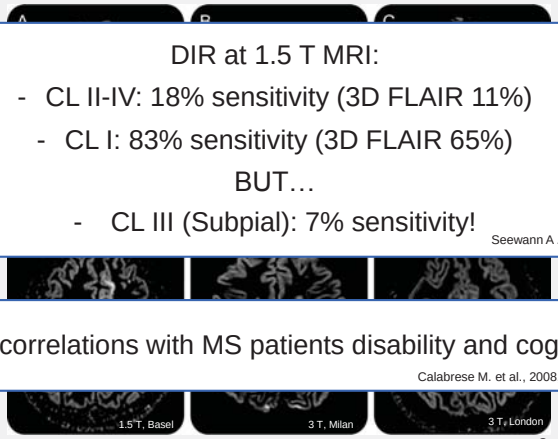
Geurts et al., 2005

DIR at 1.5 and 3T MRI

DIR at 1.5 T MRI:
- CL II-IV: 18% sensitivity (3D FLAIR 11%)
- CL I: 83% sensitivity (3D FLAIR 65%)

BUT…
- CL III (Subpial): 7% sensitivity!

Seewann A . et al., 2012

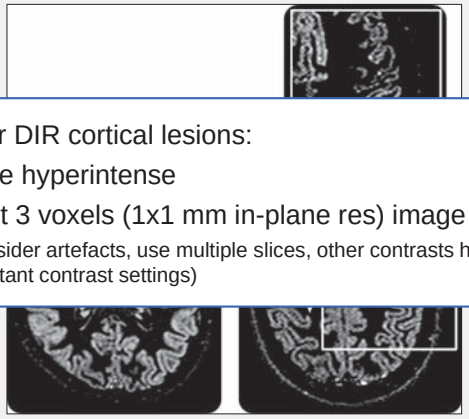


Good correlations with MS patients disability and cognition

Calabrese M. et al., 2008, 2009, 2010

Geurts et al., 2011

DIR: artefacts and criteria



Criteria for DIR cortical lesions:

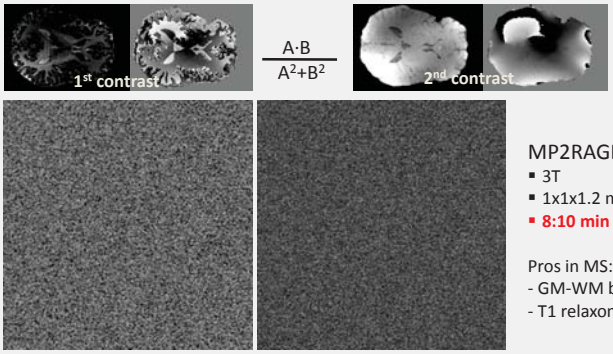
- Must be hyperintense
- At least 3 voxels (1x1 mm in-plane res) image

  (consider artefacts, use multiple slices, other contrasts help, constant contrast settings)

Geurts et al., 2011

MP2RAGE

- Combine images to compensate for B1-effects and calculate T1



MP2RAGE:
- 3T
- 1x1x1.2 mm
- **8:10 min**

Pros in MS:
- GM-WM border
- T1 relaxometry

Homogeneous T1w | T1-map

Marques, Kober et. al.: Neuroimage (2010)

MS lesions-advanced MRI at 3T

TABLE 2. Average Lesion Counts

	MP2RAGE		DIR		FLAIR-SPACE*		MP-RAGE		2D FLAIR	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cerebral WM	47.1	41.0	45.6	31.5	37.3	18.6	44.4	39.2	30	27.9
Cortical type I	4	4.1	4	3.5	3.7	3.1	3.2	2.7	2.9	2.4
Cortical type II	0.1	0.3	0.7	1.0	0.2	0.4	0.0	0.0	0.1	0.3
Cerebellar WM	1.8	2.0	2.3	2.8	1.5	1.6	1.7	2.6	1.1	1.1
Mixed cerebellar GM/WM	0.9	1.2	1.2	2.0	1.5	1.7	0.9	1.2	0.5	1.2
Cerebellar GM	0.0	0.0	0.4	1.2	0.0	0.0	0.0	0.0	0.0	0.0
Total	53.9		54.2		44.2		50.2		34.6	
MP2RAGE	–		0.72		1		0.05†		0.01‡	
DIR	–		–		0.59		0.14		0.01‡	
FLAIR-SPACE	–		–		–		1		0.03†	
MP-RAGE	–		–		–		–		0.01‡	

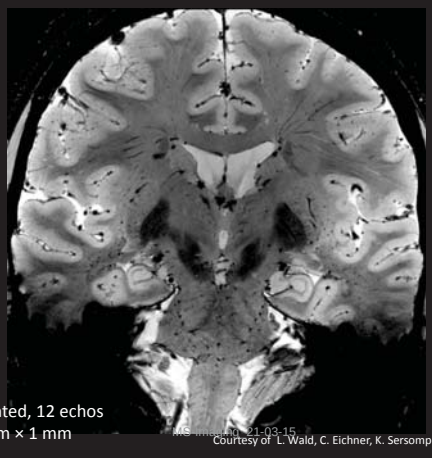
Mean lesion count and corresponding standard deviation in all brain regions across patients. Most lesions were identified with the DIR and the MP2RAGE, followed by the MP-RAGE and the FLAIR-SPACE. The fewest were seen in the 2D FLAIR.

In the bottom part, *P* values of the Wilcoxon signed-rank tests mutually comparing the 5 image contrasts with respect to TLC are given. All significance levels reported are before Bonferroni correction. After correction, no value reached significance, which is expected because of the small sample size and the high number of tests performed.

*Based on 6 patients instead of 10.
†$P \leq 0.05$.
‡$P \leq 0.01$

Kober T et al., Invest Radiol 2012

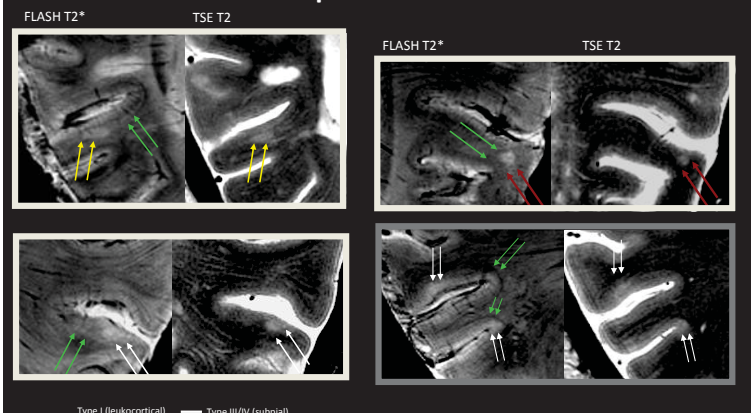
T2* at 7T MRI



7T, 2D T_2* weighted, 12 echos
330 µm × 330 µm × 1 mm

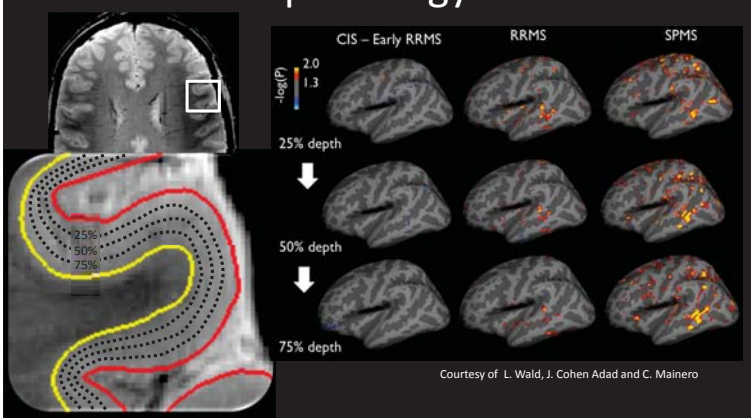
Courtesy of L. Wald, C. Eichner, K. Sersompop, C. Mainero-MGH, Boston

7T zooms into focal pathology in multiple sclerosis



Courtesy: B. Rosen, C. Mainero, MGH

7T zoom into cortical layers pathology



Courtesy of L. Wald, J. Cohen Adad and C. Mainero

0.33 × 0.33 × 1 mm³ 12-echo FLASH T2*

Mainero et al., 2015

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Multiparametric quantitative MRI

T1 relaxation time	T2 relaxation time	T2* relaxation time	Magnetisation Transfer Ratio (MTR)
high / low			
↑ T1 : ↓ structure ↓ T1 : ↑ structure	↑ T2 : ↓ structure/ ↑ H_2O ↓ T1 : ↑ structure/ ↓ H_2O	↑ T2* : ↓ Fe^{3+} ↓ T2* : ↑ Fe^{3+}	↑ MTR: ↑ macrom/ ↓ H_2O ↓ MTR: ↓ macrom/ ↑ H_2O

Interpretation of quantitative MRI

Brain tissue pathology with multiparametric MRI

T1	T2	T2*	MTR	Biological substrate
↓	↓	=	↑	Increase in structure/macromolecules (myelin/cells)
↓	↓	↓	=	Increase in Fe content
↑	↑	=/↑	=/↓	Loss of structure/ macromolecules/iron
↑	↑	=	↓	Increase in water (oedema)

CAVE: microstructural features +/- volume changes

Granziera et al., HBM 2013; Granziera et al., PLOS one 2013; Bonnier et al., Annals Clin Trasl Neurol 2014

«Advanced MRI» cohort

- 45 RRMS patients
  - 18 M/27 F, age: 34 ± 9 y; < 5 y from diagnosis.
- 20 Healthy controls
  - 10 M/10 F, age: 33 ± 10 y

– Advanced MRI protocol at 3T/7T
  - ➢ 2 time points at 3T (2 y follow-up)
  - ➢ Sub-group scanned at 7T

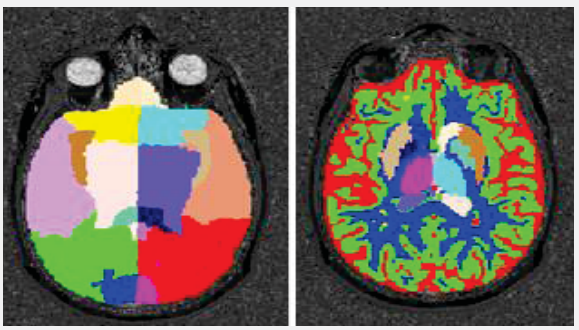
– Clinical assessment
  - ➢(motor/disability/cognition/behavior)

«Advanced» MRI protocol at 3T

Sequence	Spatial resolution/Aquisition time	Information
MPRAGE	1.0×1.0×1.2 mm³, AT = 5min12	Structural
MP2RAGE	1.0×1.0×1.2 mm³, AT = 8min22	Lesion count/T1 map
DIR	1.0×1.0×1.2 mm³, AT = 12min52	Lesion count
3DFLAIR	1.0×1.0×1.2 mm³, AT = 6min27	Lesion count
T2*_M0 T2*_MT	1.6×1.6×1.6 mm³, AT = 5min38 x2	MTR/T2* maps
T2	1.1×1.1×4.0 mm³, AT= 3.15 min	T2 map
DSI	2.2×2.2×3.0 mm³, AT = 18min57	Structural connectome GFA map
rsfMRI	3.3×3.3×4.2 mm³, AT= 2min56	Functional connectome

Automatic analysis: normal-appearing brain tissue

Lobes segmentation | Tissues segmentation

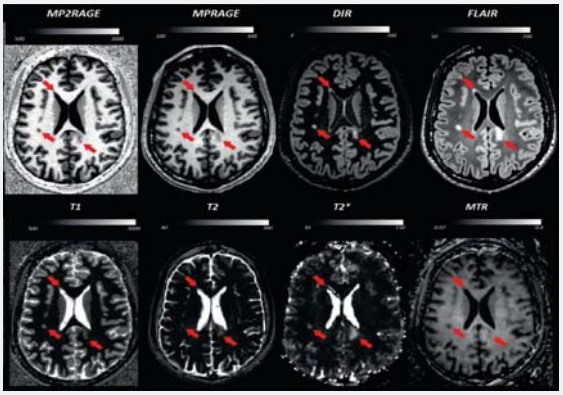


Bonnier et al., Annals Clin Trasl Neurol 2014

Quantitative MRI: lesions

WMLs/CLs Count and Delineation

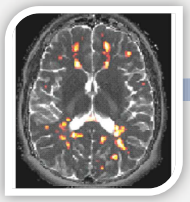
Microstructure



Bonnier et al., Annals Clin Trasl Neurol 2014

Quantitative MRI in lesions

Manual lesion detection (cortex and white matter)

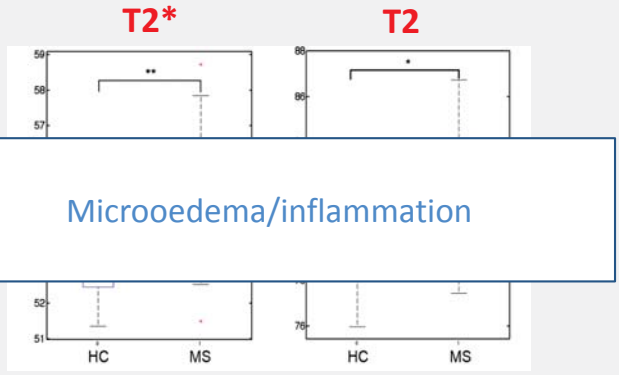


Co-registration to quantitative maps (T1, T2. T2*, MTR)

Demyelination/Tissue degeneration

Bonnier et al., Annals Clin Trasl Neurol 2014

Temporal normal-appearing white matter



Microoedema/inflammation

Bonnier et al., Annals Clin Trasl Neurol 2014

Clinico-radiological correlations

	Clinical scores	SDMT	MSFC	FSMCCog	FSMCMotor	Disease Duration	WLG	10/36	SRT
Stepwise regression	p-value	0.00006	0.00397	0.00197	0.00156	0.00589	0.01748	0.02043	0.00999
	Corrected p-value	0.00051	0.03178	0.01577	0.01250	0.04708	0.13984	0.16344	0.07995
	Adjusted-R	0.59	0.43	0.36	0.42	0.35	0.13	0.29	0.32
Cross validation	p-value	0.00001	0.00010	0.00087	0.00145	0.16720	0.09650	0.11650	0.02650
	Corrected p-value	0.00004	0.00080	0.00696	0.01160	1.33760	0.77200	0.93200	0.21200
	Adjusted-R	0.44	0.24	0.26	0.24	0.03	0.05	0.04	0.11
Predictors (p-value)									
Conventional	Lesion: Cortical Volume	0.0036		0.0434	0.0219	0.0984			
	Lesion: Cortical count	0.0022				0.0467			0.0870
	Lesion: Subcortical volume		0.1418		0.1048				
	Lesion: Subcortical count			0.0426	0.0005	0.0009		0.0166	0.0956
New & Covariates	Lesion: T1 zscore	0.0025	0.0811						0.0009
	Lesion: T2 zscore	0.0073	0.0806			0.0349		0.1706	0.0345
	Lesion: T2* zscore	0.0188			0.0857	0.0327		0.0433	
	Lesion: MTR zscore					0.2129			
	Temporal NAWM: T1 mean	0.0607		0.0024	0.0001				
	Temporal NAWM: T2 mean		0.0377	0.0068	0.0089				0.0011
	Temporal NAWM: T2* mean	0.0006	0.0245					0.0042	0.0007
	Temporal NAWM: MTR mean	0.0004	0.0201					0.0153	
	Covariates: Age								
	Covariates: Gender	0.0395	0.0010			0.0436	0.0175	0.0152	
	Covariates: Educational years		0.0986						
	Covariates: HADA (anxiety)		0.2009					0.1972	0.0609
	Covariates: HADD (Depression)		0.0330	0.0072	0.0969			0.0638	

p < 0.001
p < 0.01
p < 0.05

Bonnier et al., Annals Clin Trasl Neurol 2014

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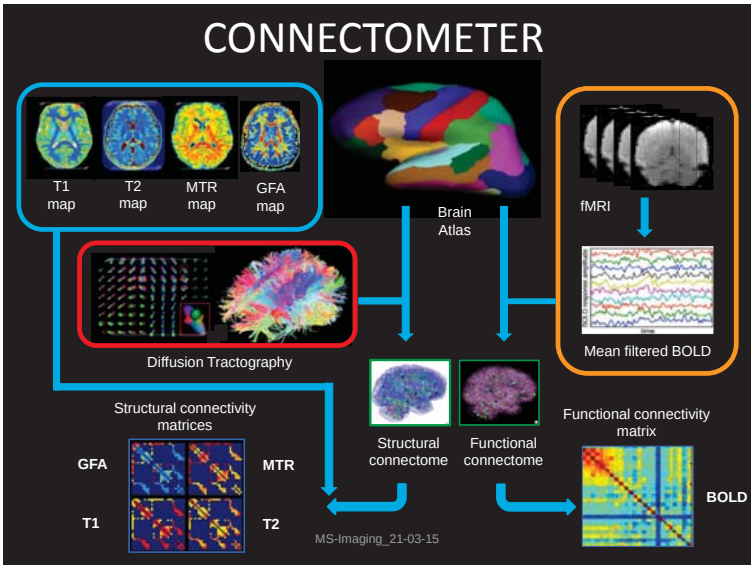
Connectomics in MS

- Connectomics:
  - production and study of *connectomes* → comprehensive maps of brain neural connections
- Few connectomic studies in MS:
  - technical limited (Shu N. et al., 2011, Li Y et al., 2012)
  - only structural or functional
  - pathological substrate unknown
  - heterogeneous patients cohorts

Brain & cerebellum connectometer

- To quantify damage/ plasticity in MS patients by:
  - performing structural/functional MS connectomics
  - applying multi-contrast MRI to investigate the nature of connectivity alterations in MS
  - studying a homogeneous cohort (“early MS with minimal deficits”)



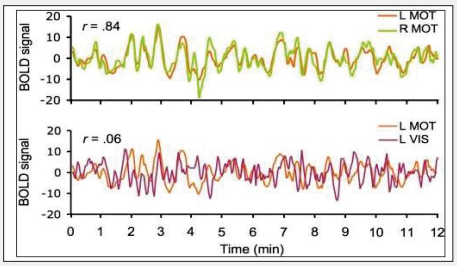
Structural tractometry

T1 relaxation time	T2 relaxation time	Magnetisation transfer ratio (MTR)	Generalized fractional Anisotropy (GFA)
high / low			
↑T1 : ↓ structure ↓T1 : ↑ structure	↑T2 : ↑ H_2O ↓T2 : ↓ H_2O	↑MTR: ↑ myelin. ↓MTR: ↓ myelin	↑GFA: ↑ axon integrity ↓GFA: ↓ axon integrity

Biological Interpretation

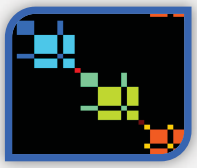
Functional tractometry

- Resting state fMRI:
  - measures BOLD (deoxy-Hb) signal at rest
  - reflects blood flow/volume/metabolism, indirectly neuronal activity



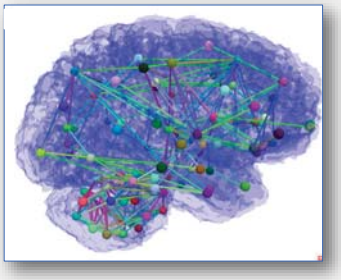
Review: Koene R. et al., 2010

Multi-contrast brain connectome analysis

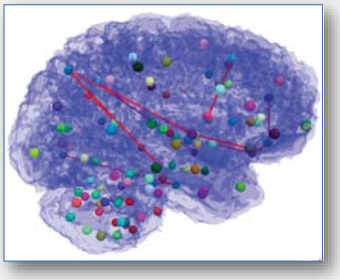


- Network analysis
  - Global
  - Subnetwork
  - Local node
- Local connection tractometry
  - Prevalent network (109 connections)
  - *Soft Thresholding Screening and Filtering* (Meskaldji et al., 2013).
    - Bonferroni correction for multiple comparison
- Correlations
  - Lesion load (number/volume/lesion on altered connections)
  - Disease duration
  - Clinical tests
    - Bonferroni correction for multiple comparison

Brain local connections alterations in MS



Structural connectome



Stuctural connections altered in MS vs HC

Romascano et al., in preparation

Inflammation or degenaration?

Altered connection
Increased T2
Right lateralorbitofrontal - Right Putamen (B_1^*)
Right superiorfrontal- Right Caudate (B_2^*)
Left lateralorbitofrontal - Left Putamen (B_3^*)
Left superiorparietal- Left superiortemporal (B_4^{***})
Left superiorparietal - Left Putamen (B_5^{***})
Left lateraloccipital - Left inferiortemporal (B_6^*)
Left fusiform - Left inferiortemporal (B_7^*)
Decreased GFA
Right lateralorbitofrontal - Right Putamen (B_1^{**})
Increased T1
Right superiorparietal - Right Putamen (B_8^{***})
Right superiorparietal - Right Hippocampus (B_9^*)
Right precuneus - Left isthmuscingulate (B_{10}^*)
Left superiorparietal - Left-Putamen (B_5^{**})
Multivariate differences
Right precuneus - Left isthmuscingulate (B_{10}^*)
Left lateralorbitofrontal - Left parsorbitalis (B_{11}^*)
Left parsorbitalis - Left rostralmiddlefrontal (B_{12}^*)

↑ T2 and ↓ GFA: microoedema

↑ T2 and ↓ T1: axonal degeneration

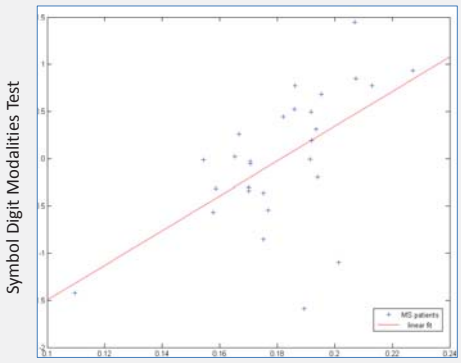
Romascano et al., in preparation

Altered connections correlate with lesion load

Connections	Correlates	Pearson R
B1	Lesions number/volume	0.7 ***, 0.7 ***
B2	Lesions volume	0.5 *
B3	Lesions volume	0.5 *
B8	Lesions volume	0.5 *
B9	Lesions number/volume/ on fiber tract	> 0.6 *
B10	Lesions number/volume/ on fiber tract	> 0.6 *
B11	Lesions volume	> 0.6 *
B12	Lesions number/volume/ on fiber tract	> 0.6 **/ >0.7***/>0.6*

Romascano et al., in preparation

Attention function correlates with B7 integrity

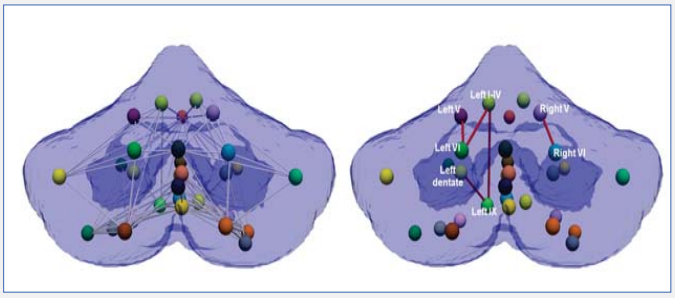


R= 0.6
p < 0.05

Mean GFA along B7 (L fusiform-L inferior temporal)

Romascano et al., in preparation

Cerebellar local connections alterations in MS



Cerebellar structural connectome

Stuctural connections altered in MS vs HC

Independent from lesion load/Duration

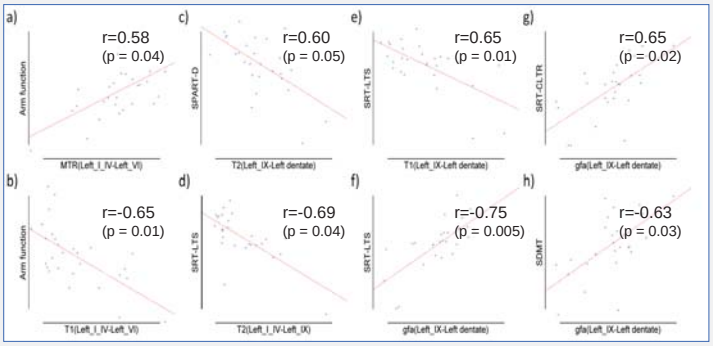
Romascano et al., HBM 2014

Structural alterations in local cerebellar connections

Altered connection	Function
Increased T1	
Right_V-Right_VI (C_1) **	Mainly motor
Decreased GFA	
Left_I_IV-Left_IX (C_2) *	Motor (Left_I_IV) and cognitive (Left_IX)
Left_IX-Left-dentate (C_3) **	Mainly cognitive
Multivariate differences	
Left_I_IV-Left_VI (C_4) *	Mainly motor
Left_V-Left_VI (C_5) *	Mainly motor
Left_IX-Left dentate (C_3) *	Mainly cognitive

Romascano et al., HBM 2014

Correlations between clinical scores and cerebellar connectivity

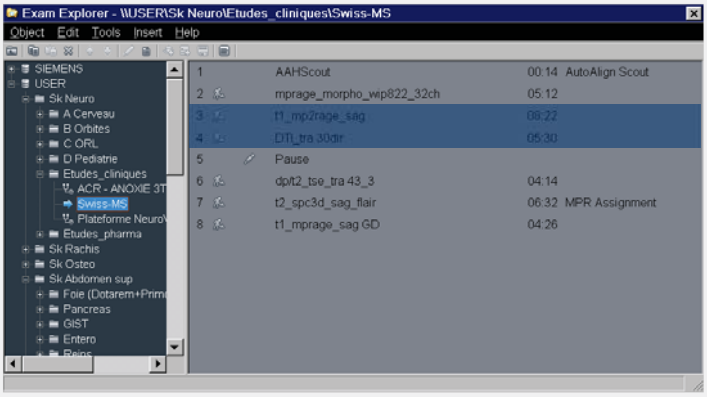


Romascano et al., HBM 2014

Outline

- Cortical lesions
  - Double Inversion Recovery at 1.5 and 3T
  - MP2RAGE at 3T
  - T2* FLASH at 7T
- Brain microstructure
  - Multi-parametric quantitative MRI
- Brain connectivity
  - Connectomics
- Towards automatic quantitative metrics

Clinical MRI in multiple sclerosis



Swiss MS cohort protocol

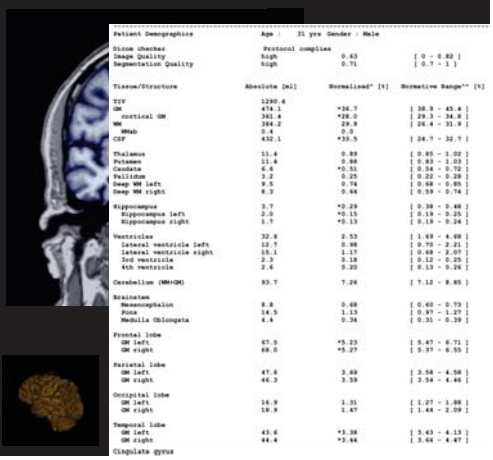
MR-based brain morphometry

SIEMENS

Automated tissue classification based on T1 weighted 3D brain MRI (MPRAGE)

Quantification of brain tissue and structure volumes

Identification of out-of-range structures based on reference and cut-off points from age-matched controls



Automatic lesion detection

Post-Processing

Type of Lesion	Manual Segmentation	Automatic Detection	Automatic Segmentation
White Matter			
Cerebellum			

Best WMLs detection on 3DFLAIR + MPRAGE CLINICAL
- 77 % (> 3.6 µL)
- 85 % (≥5 µL)

Best CLs detection on 3DFLAIR + MP2RAGE + DIR RESEARCH
- 62% (> 3.6 µL)
- 68 % (≥5 µL)

Fartaria de Oliveira M. et al., submitted

Thank you!

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