

# Le diagnostic de Sclérose En Plaques

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DES Neurologie Rhône Alpes Auvergne, Lyon, 28 novembre 2014

# Bases du diagnostic

- Clinique:
  - Épisodes inauguraux typiques
  - Début progressif
- Biologie
  - LCR
  - Sang
- Imagerie

Dissémination dans l'espace  
Dissémination dans le temps

# Modes de révélation de la SEP

- Forme rémittente:
  - Âge moyen de début 25 ans (15-35)
  - Sex ratio: prédominance féminine 3/1
- Forme progressive:
  - Âge moyen de début 40 ans (35-55)
  - Sex ratio: 1/1

# Nosologie

- Syndromes radiologiquement isolés (RIS)
- Syndrome cliniquement isolé (CIS)
- CIS à haut risque (CIS+DIS ou CIS+autres facteurs de risque)
- CIS à très haut risque (critères 2010)
- SEP RR définie
- SEP PP



# Episodic

CIS in  
pract  
patie  
inflar  
The t  
20-40  
onset  
week  
at lea  
infect

- Optic nerve**  
*Typical features*
  - Optic neuritis in one eye
  - Mild pain on eye movement
  - Reduced visual acuity and reduced colour vision
  - Normal disc or mild disc swelling
  - Improvement begins within 3 weeks from onset
  - Afferent pupil defect
- Atypical features*
  - Optic neuritis in both eyes at the same time
  - Painless or very severe pain
  - No perception of light
  - Severe haemorrhages and exudates
  - Extended loss of vision
  - Vitritis and neuroretinitis
  - Photophobia
- Brainstem or cerebellum**  
*Typical features*
  - Bilateral internuclear ophthalmoplegia
  - Ataxia and gaze-evoked nystagmus
  - Sixth nerve palsy (in patients aged 20-40 years)
  - Paroxysmal phenomena (occurring for at least 24 h)
  - Multifocal signs (eg. facial sensory loss and vertigo)
- Atypical features*
  - Complete external ophthalmoplegia
  - Vascular territory signs
  - Isolated trigeminal neuralgia
  - Progressive trigeminal sensory neuropathy
  - Movement disorders
  - Fluctuating ocular or bulbar weakness, or both

- Spinal cord**  
*Typical features*
    - Incomplete transverse myelitis
    - Lhermitte's syndrome
    - Sphincter symptoms
    - Asymmetric limb weakness
    - Deafferented hand
    - Progression to nadir between 4 h and 21 days<sup>21</sup>
  - Atypical features*
    - Complete transverse myelitis
    - Complete Brown-Séquard syndrome
    - Cauda equina syndrome
    - Anterior spinal artery territory lesion
    - Localised or radicular spinal pain
    - Progressive and symmetrical spastic paraparesis or progressive sensory ataxia (from involvement of posterior columns)
    - Sharp level to all sensory modalities
    - Areflexia
  - Cerebral hemispheres**  
*Typical features*
    - Hemiparesis
    - Hemisensory disturbance
  - Atypical features*
    - Encephalopathy
    - Epilepsy
    - Cortical blindness
- Absence of recovery is an atypical feature for all clinically isolated syndromes. Adapted from Miller and colleagues.<sup>5</sup>

# Phénotype au début

**Table 1** Demographic characteristics of patients in the whole multiple sclerosis population and according to the disease phenotype at onset of multiple sclerosis

	All multiple sclerosis patients	Disease phenotype at onset of multiple sclerosis		P-value <sup>a</sup>
		Relapsing onset	Progressive onset	
Number of patients	2054	1609	445	–
Female: male sex ratio	2.30 (1431:623)	2.67 (1171:438)	1.41 (260:185)	<0.001
Mean age at onset of multiple sclerosis (years) ± SD	31.4 ± 9.8	29.5 ± 8.8	38.5 ± 10.1	<0.001
Age group at onset of multiple sclerosis				0.0001
<20 years	236 (11.5%)	223 (13.9%)	13 (2.9%)	
20 to <30 years	771 (37.5%)	688 (42.8%)	83 (18.7%)	
30 to <40 years	630 (30.7%)	488 (30.3%)	142 (31.9%)	
40 to <50 years	337 (16.4%)	183 (11.4%)	154 (34.6%)	
≥50 years	80 (3.9%)	27 (1.7%)	53 (11.9%)	
Initial symptoms of multiple sclerosis (n=1876)				<0.001
Isolated long tracts	962 (51.3%)	686 (45.3%)	276 (76.0%)	
Isolated brainstem	218 (11.6%)	216 (14.3%)	2 (0.6%)	
Isolated optic neuritis	404 (21.5%)	367 (26.2%)	7 (1.9%)	
Combined symptoms	292 (15.6%)	214 (14.1%)	78 (21.5%)	
Mean follow-up duration from onset (years) ± SD	12.8 ± 9.4	13.1 ± 9.8	11.4 ± 7.9	<0.001

a Comparison relapsing onset versus progressive onset.

Cohorte de Rennes

Leray et al., Brain, 2010



# Myélites aiguës partielles : clinique

- Asymptomatique
  - Monosymptomatique
  - Transitoire
  - Surtout chez les femmes
  - Traitement : corticoïdes
- Un seul segment médullaire  
Atteinte partielle en axial
- CIS sans DIT : myélites isolées +++
  - SEP ++
  - Plus rarement : Lupus, Gougerot, Infection (Lyme, virales...)



Coupes fines : 3 mm d'épaisseur

T2 TSE

T1 SE avant et après injection intraveineuse de gadolinium

+/- STIR : T2 avec saturation du signal de la graisse

# Moelle : Aspects classiques SEP

- Cervical ++ (50-60%) > thoracique
- Hauteur < hauteur de 2 segments vertébraux
- Ovale verticalement
- Axial < 1/2 moelle , triangulaire ou nodulaire
- Cordons postérieurs et latéraux de la moelle
- Pas de respect substance grise
- Unique, souvent multiples
- Moelle normale, élargie ou atrophique
- Hypersignal T2, STIR; Isosignal T1
- +/- Prise de contraste transitoire



Sag T2 TSE



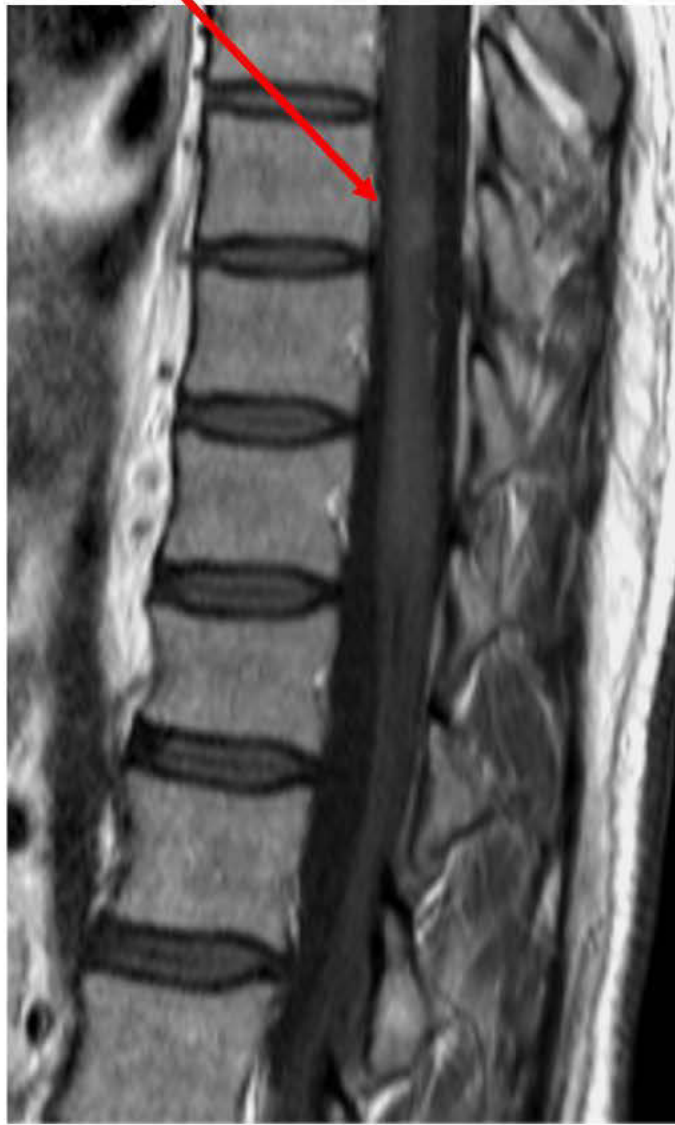
Sag T2 TSE

Axial T2 EG





Sag T2 TSE



Sag T1 gado



Axial T1 gado

## STIR

Meilleure détection des lésions intramédullaires  
Risque de faux positifs



Sag T2 TSE



Sag STIR

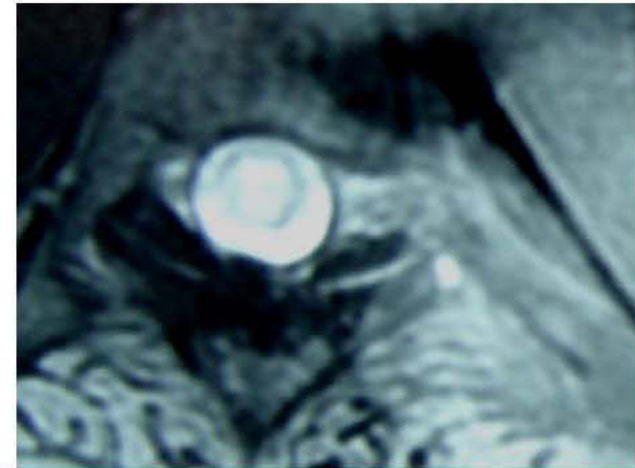


Axial T2

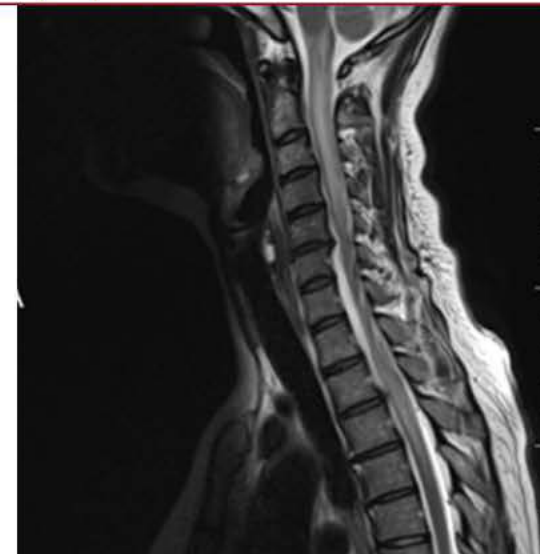


## Diagnostic différentiel: myélites aiguës transverses

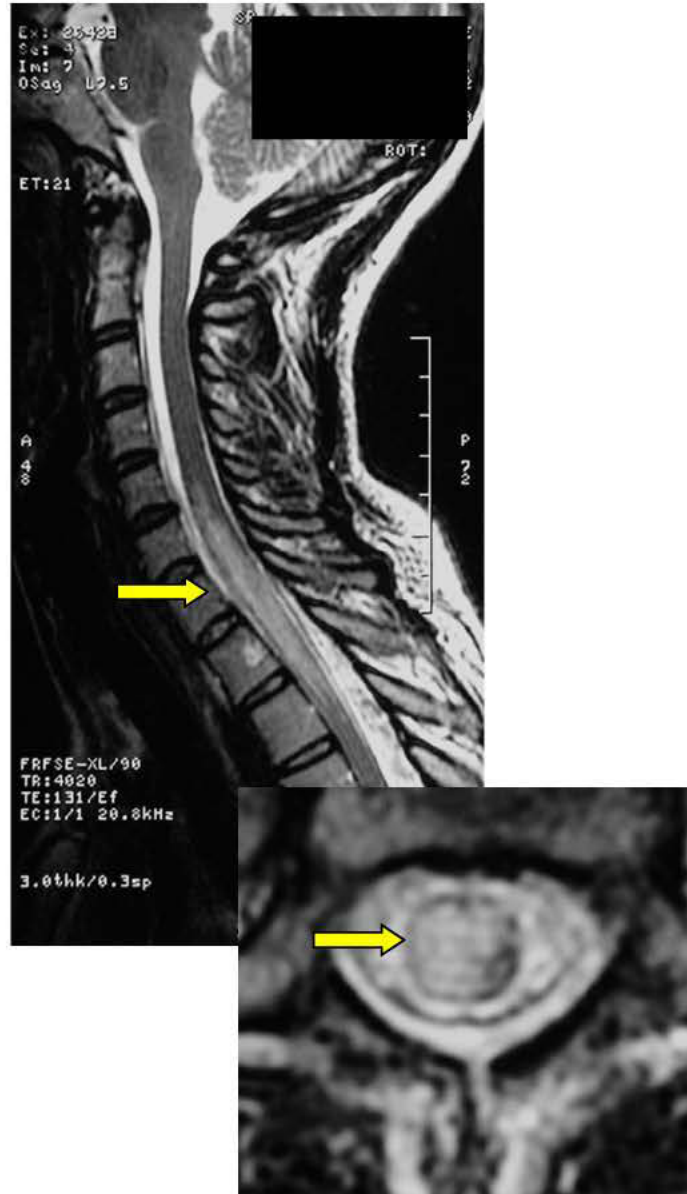
- Atteinte sensitive, motrice et sphinctérienne sévère, bilatérale,
- Sur plusieurs niveaux médullaires,
- Atteinte étendue en axial
- Autres étiologies le + svf:
  - Myélites infectieuses (Virus...)
  - Lupus; Goujerot
  - Devic NMO
  - Myélites transverses idiopathiques



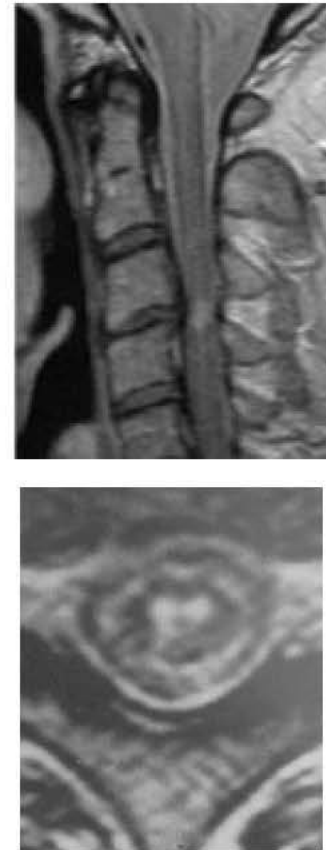
Beaucoup plus rarement SEP



# Maladie de Devic



# Pathologie Vasculaire



Infarctus Médullaire



Fistule durale

# Myélites Transverses

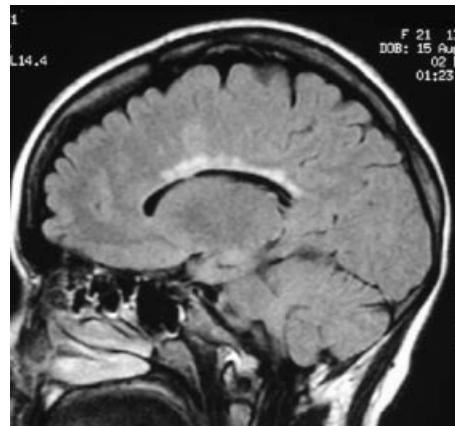
SEP



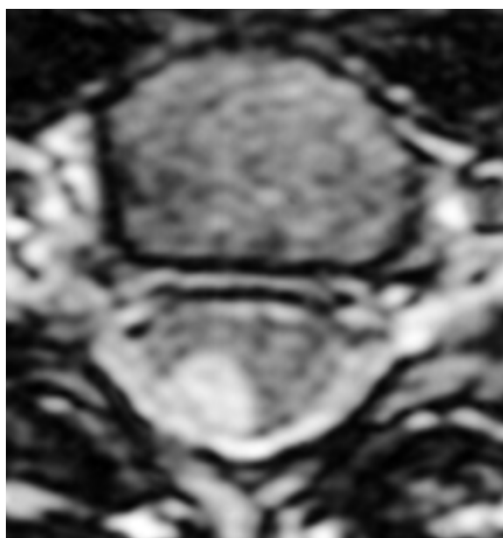
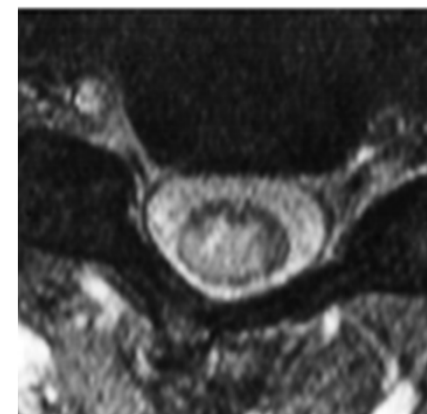
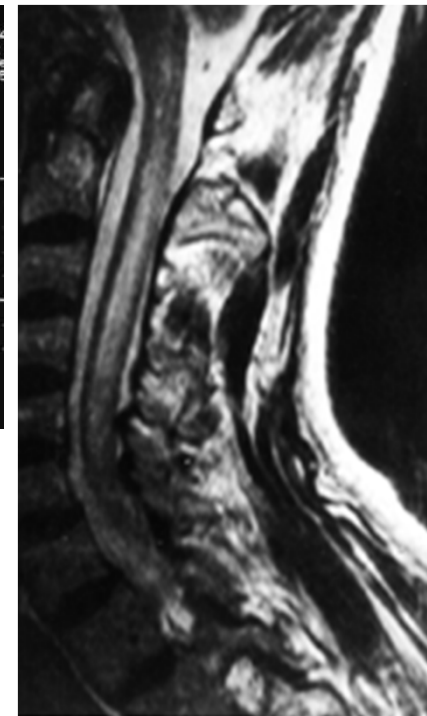
EBV



Lupus



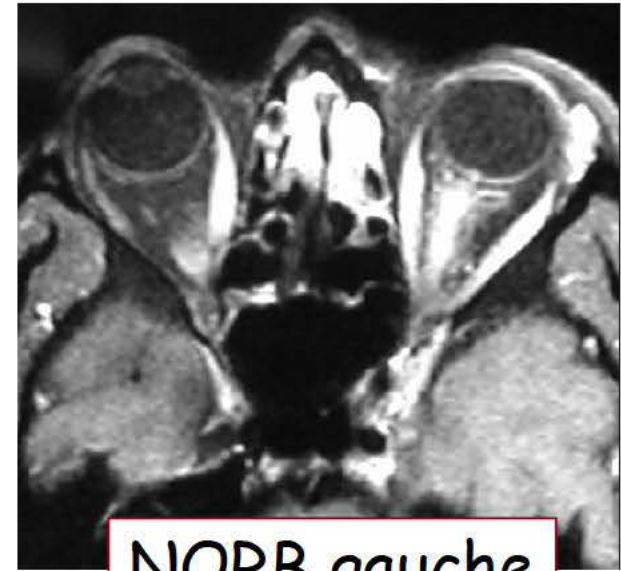
Sjogren





# NORB

- Femme jeune
- Baisse d'acuité visuelle
- unilatérale,
- rapidement progressive
- intensité variable : rarement très sévère dans SEP (absence de perception lumineuse = 2% des cas)
- douleurs péri- ou rétro-oculaires (90% des cas)
- parfois trouble des couleurs, photophobie, photopsies majorées par les mouvements (30% des cas)
- Scotome



NORB gauche

# Nerf optique

- Névrite Optique Rétro-bulbaire



Coro T2 TSE FAT-SAT

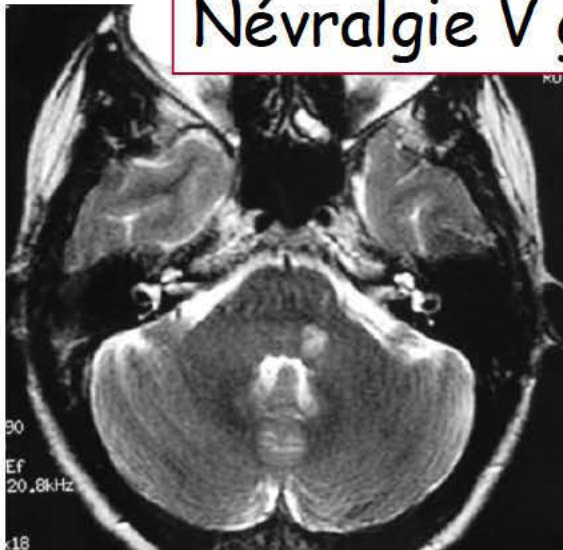


Coro T1 Gado FAT-SAT

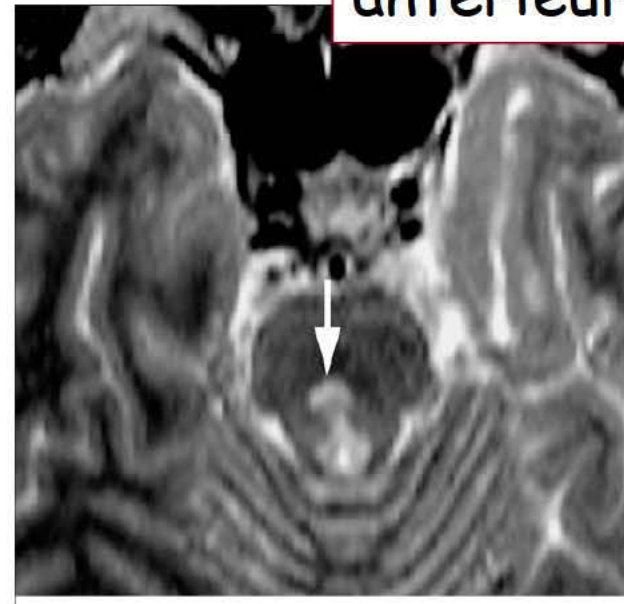
# Atteinte tronc cérébral et cervelet

- Diplopie (VI)
- Syndrome vestibulaire
- Ophthalmoplégie Internucléaire (rarement révélateur)
- Syndrome cérébelleux

Névralgie V gauche



Ophthalmoplégie internucléaire antérieure



# IRM encéphale

- Recherche de lésions évocatrices d'une atteinte inflammatoire:
  - lésions à haut-risque,
  - critères de dissémination dans l'espace
- Séquences indispensables
  - FLAIR Axial ± Sagittal
  - (T2 TSE Axial: premier écho pour fosse post)
  - T1 SE (3DT1?) avant injection
  - T1 SE après injection IV de gadolinium

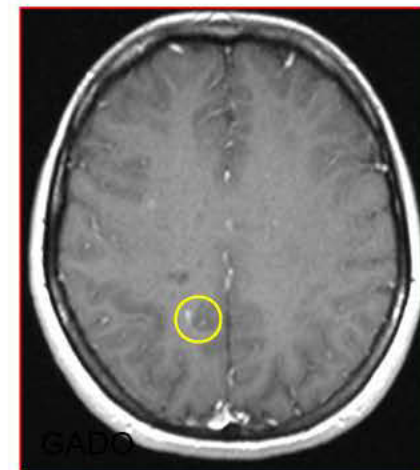
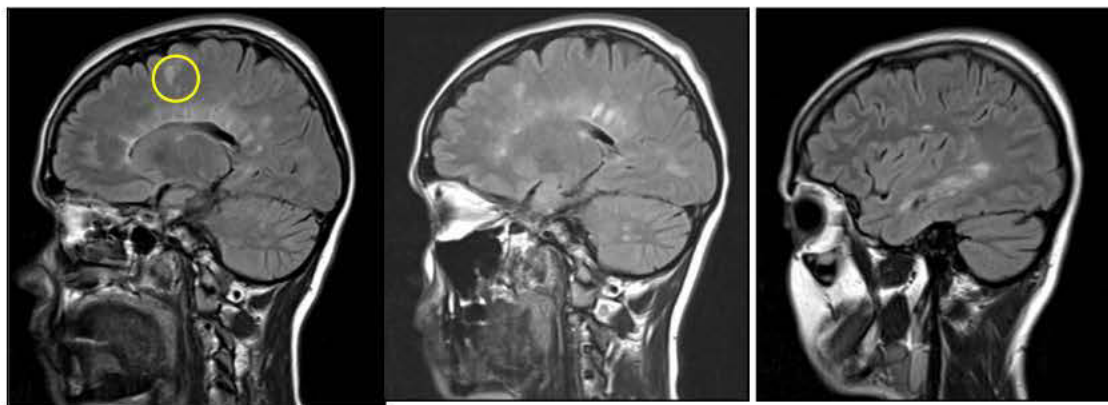
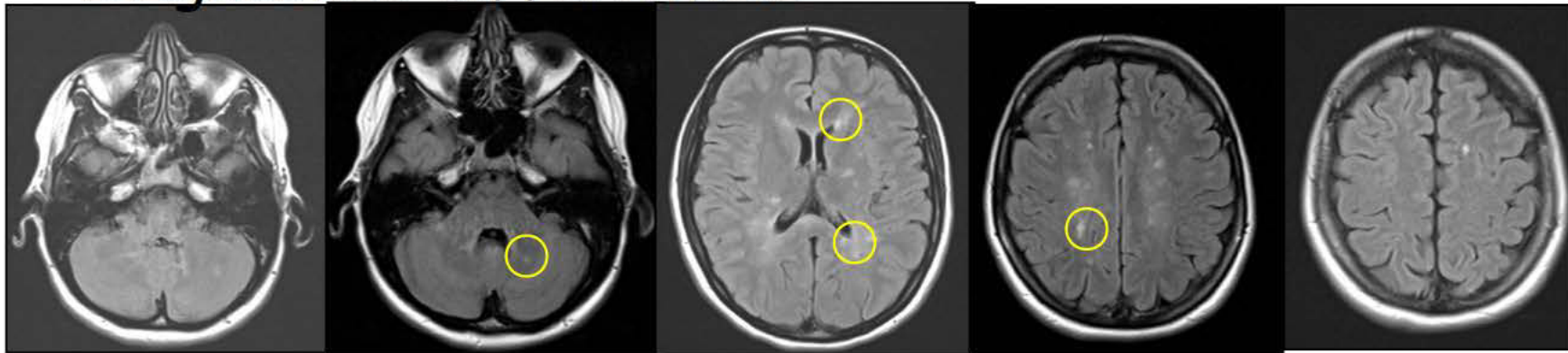


# Aspects classiques des lésions démýélinisantes de SEP

- Lésions focales multiples de la SB
  - destruction de la myéline
  - ↑ de l'eau libre
- Hypersignal FLAIR, T2 (Iso ou HYPO T1)
- Gde sensibilité
- Pas spécifiques de SEP (démýélinisation infectieuse, toxique, ischémique...)
- Critères fortement évocateurs:
  - Forme
  - Localisations

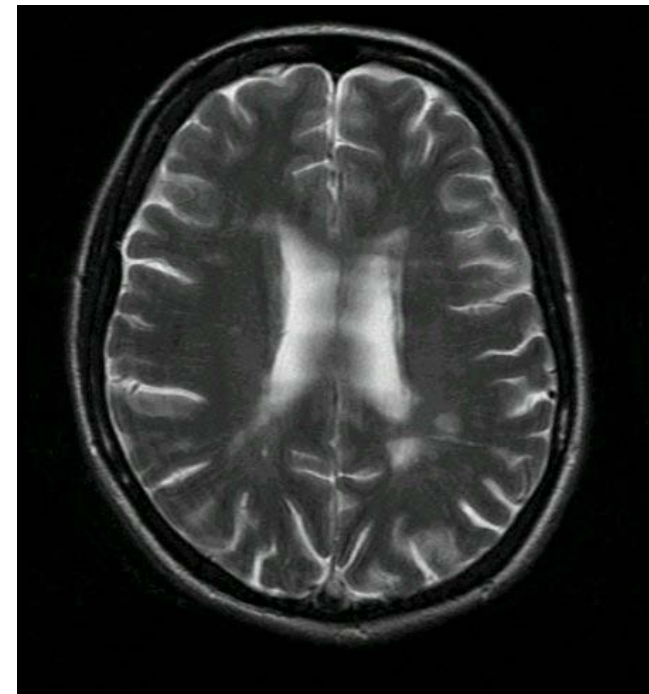
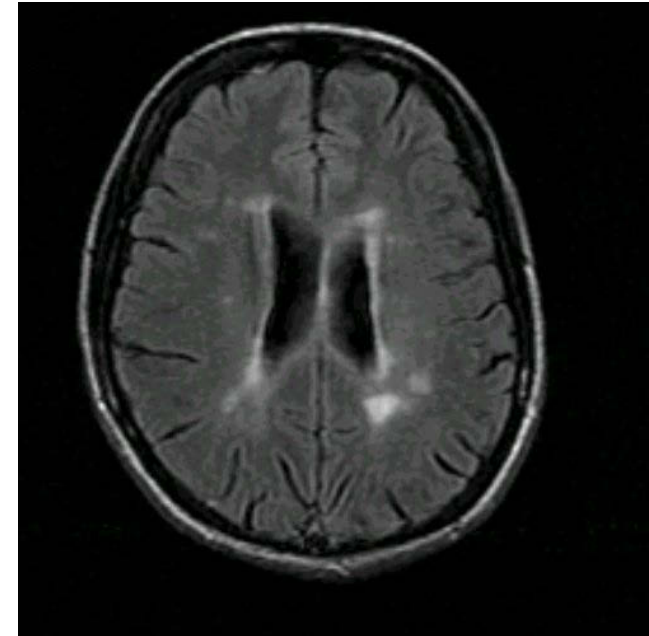
# Qu'apporte l'IRM ?

- Arguments positifs pour une atteinte démyélinisante inflammatoire du SNC
- Dissémination dans l'espace et dans le temps
- Diagnostics différentiels

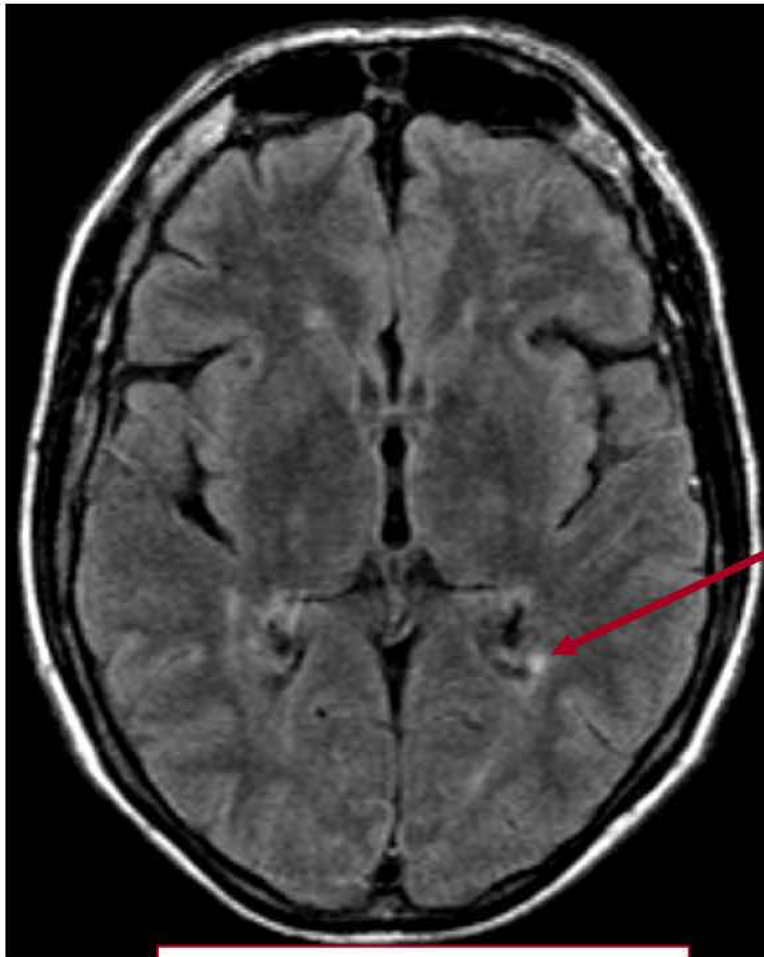


# FLAIR

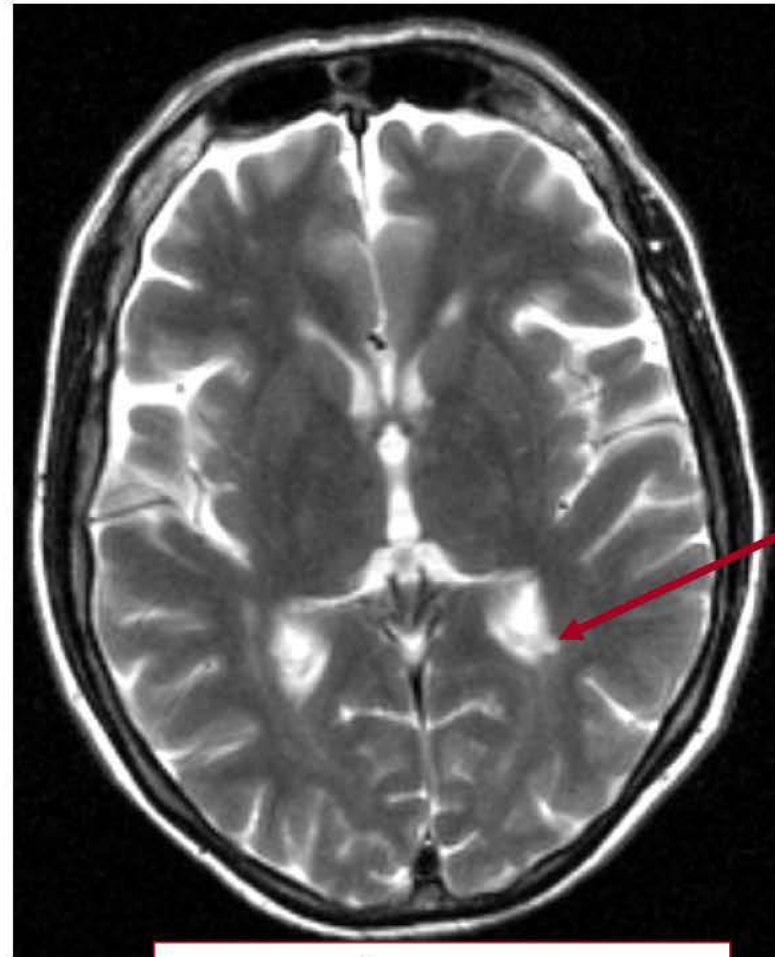
- T2 pour le parenchyme
- + suppression de l'hypersignal physiologique du LCS en T2
- Augmente la détection des lésions au contact de structures liquidiennes:
  - Juxta-ventriculaires
  - Juxta-corticales
- Problème de sensibilité en fosse postérieure: dépend de la qualité



# FLAIR / T2 pour lésions juxtaventriculaires



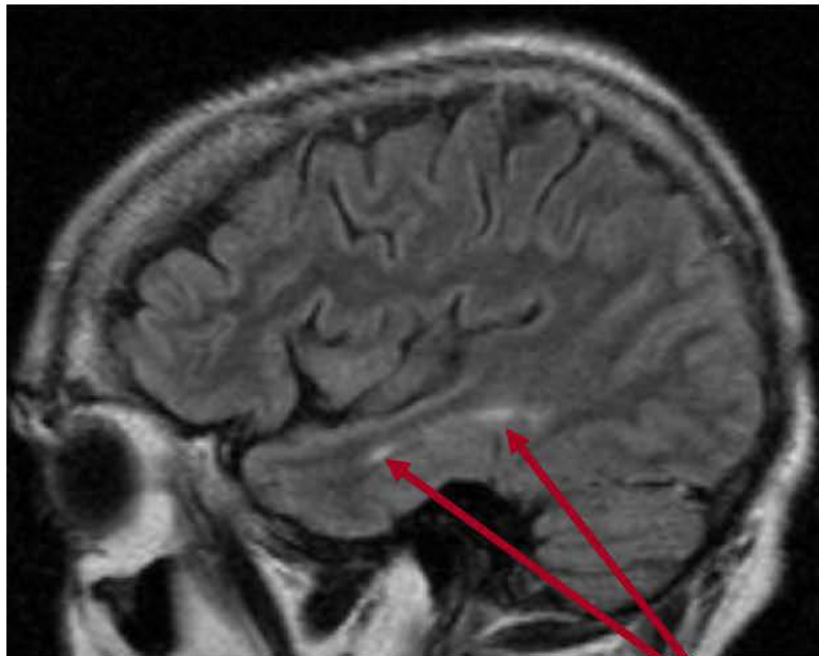
Axial FLAIR



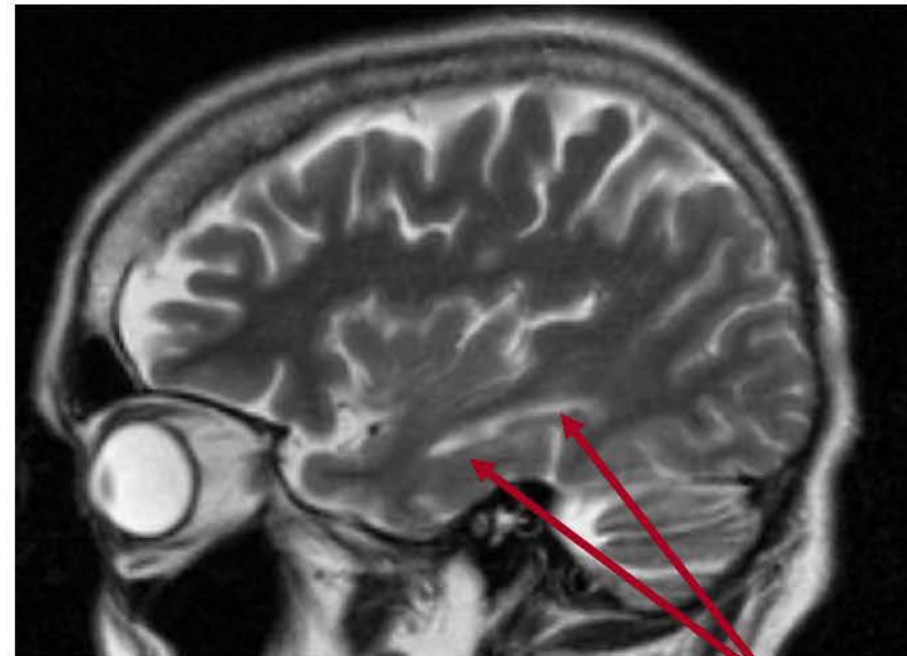
Axial T2 TSE



# FLAIR / T2 pour lésions juxtaventriculaires



Sag FLAIR

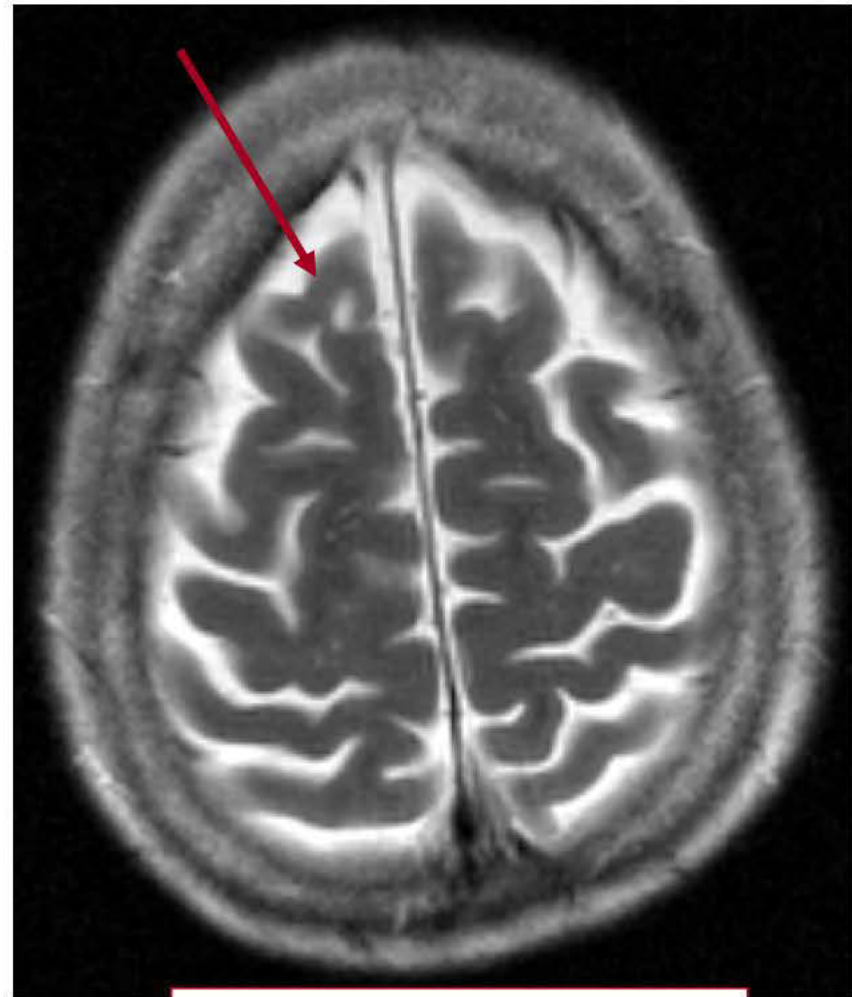


Sag T2 TSE

FLAIR / T2  
pour lésions juxtacorticales



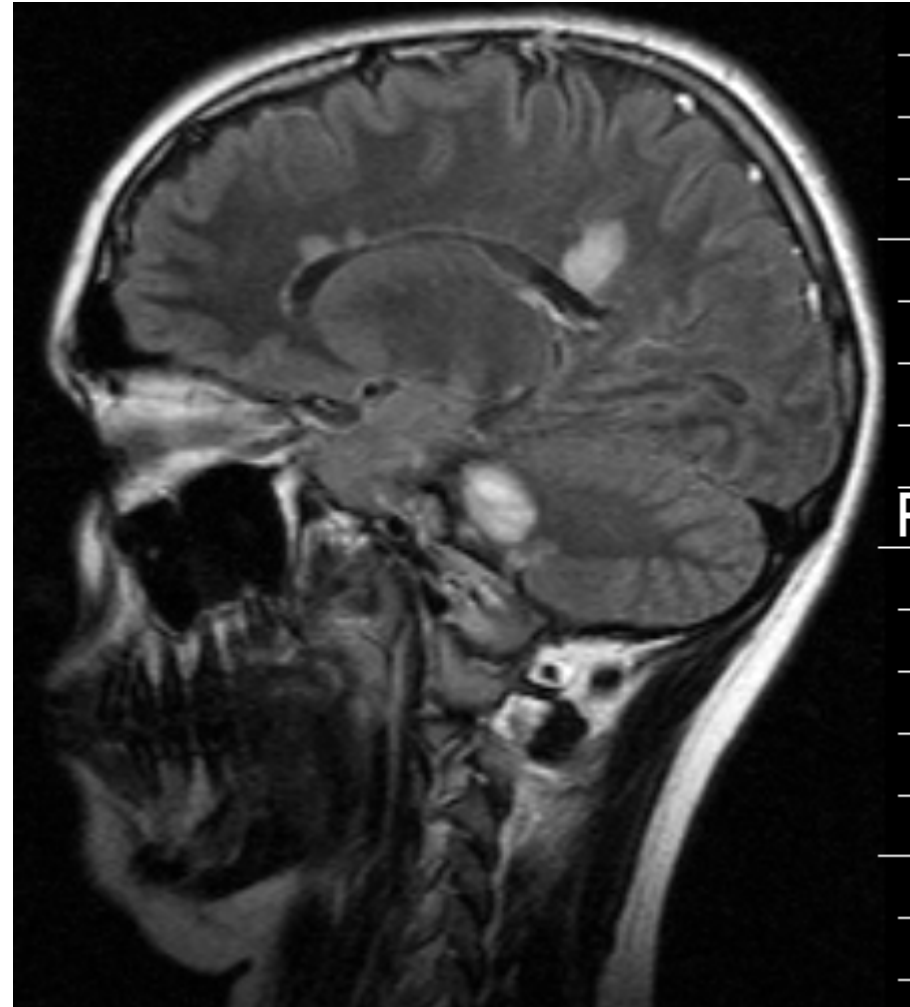
Axial FLAIR



Axial T2 TSE

## Sagittal

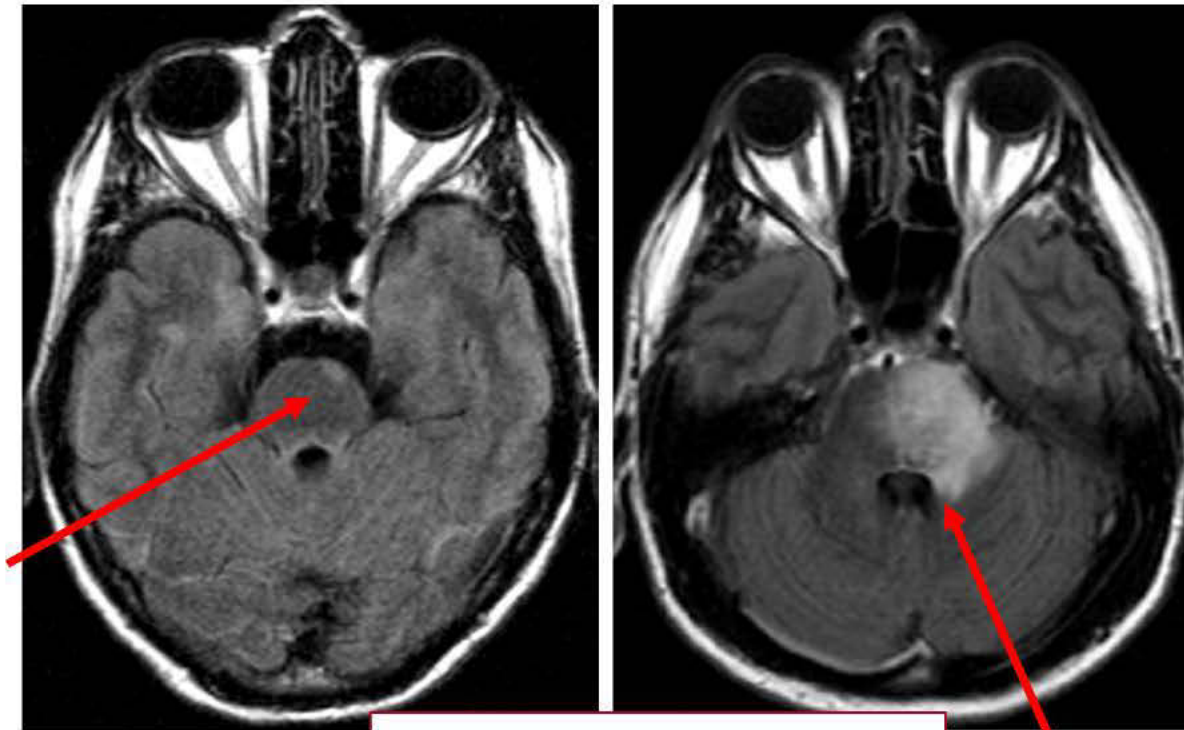
- FLAIR +++
- Meilleure analyse des HS
  - Corps calleux
  - Jonction calloso-marginale: aspect en «crête de coq»
- Evaluation atrophie
  - Corps calleux
  - Fosse postérieure





# Fosse postérieure

- Périphérie du tronc cérébral
- Contact du quatrième ventricule
- Pédoncules cérébelleux



Axial FLAIR

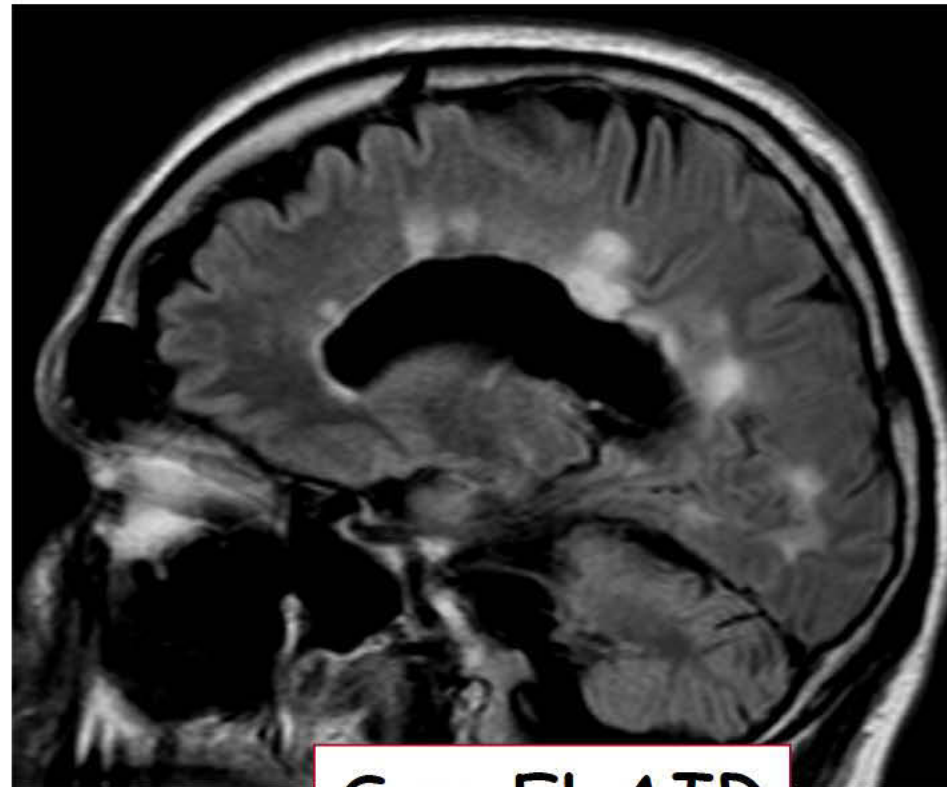
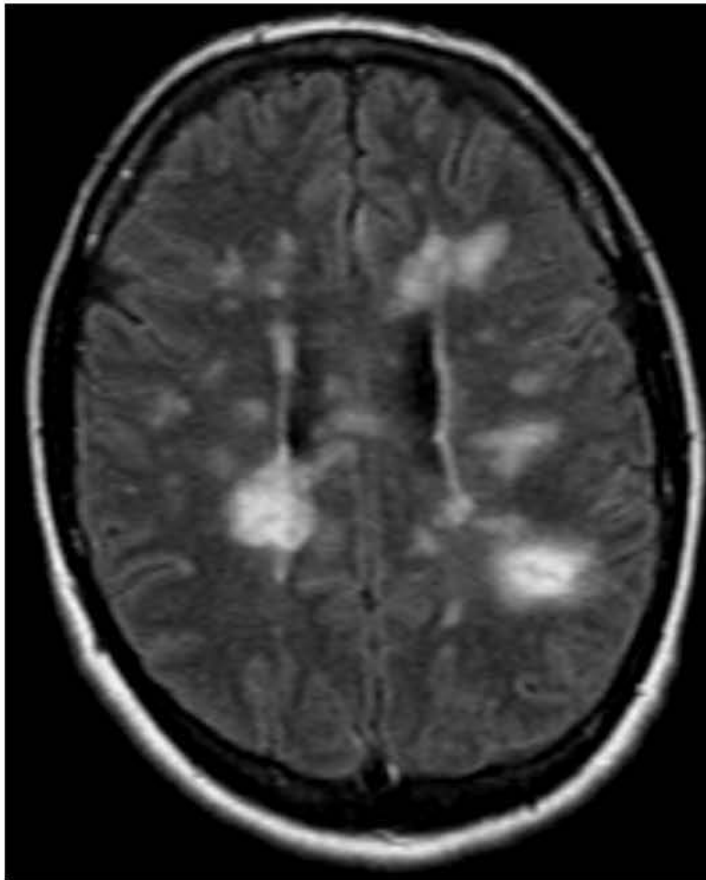


Axial T2 TSE

# Forme classique des lésions

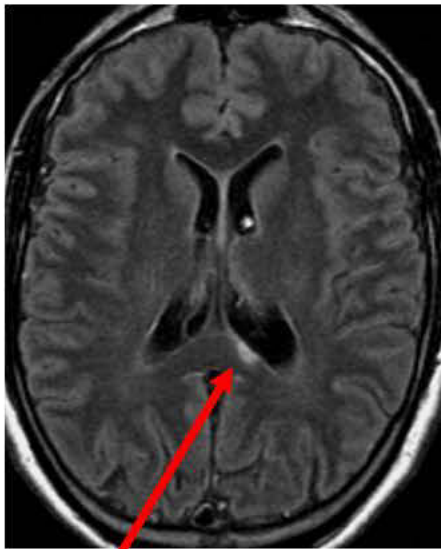
Axial FLAIR

- Forme ovoïde
- Taille > 3 mm pour être significative
- Dispositions radiaires

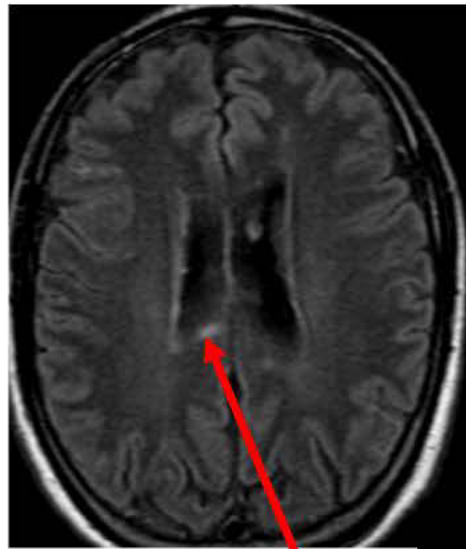


Sag FLAIR

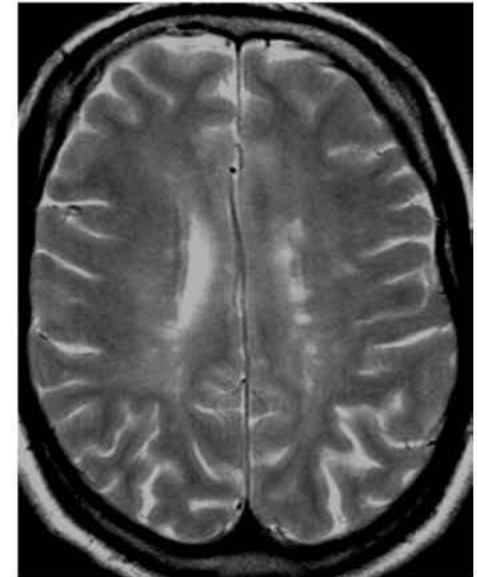
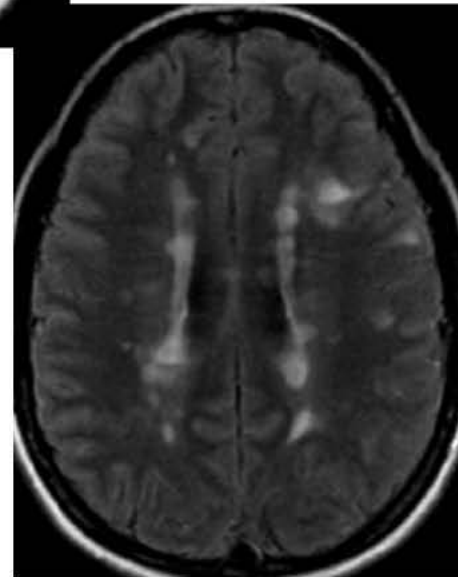
# Substance blanche périventriculaire



Axial FLAIR

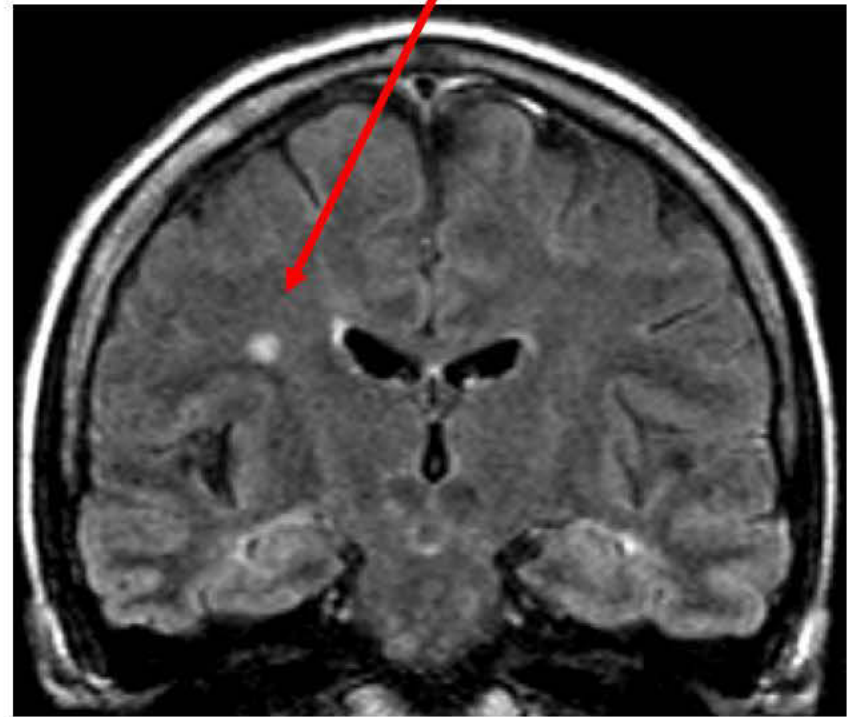
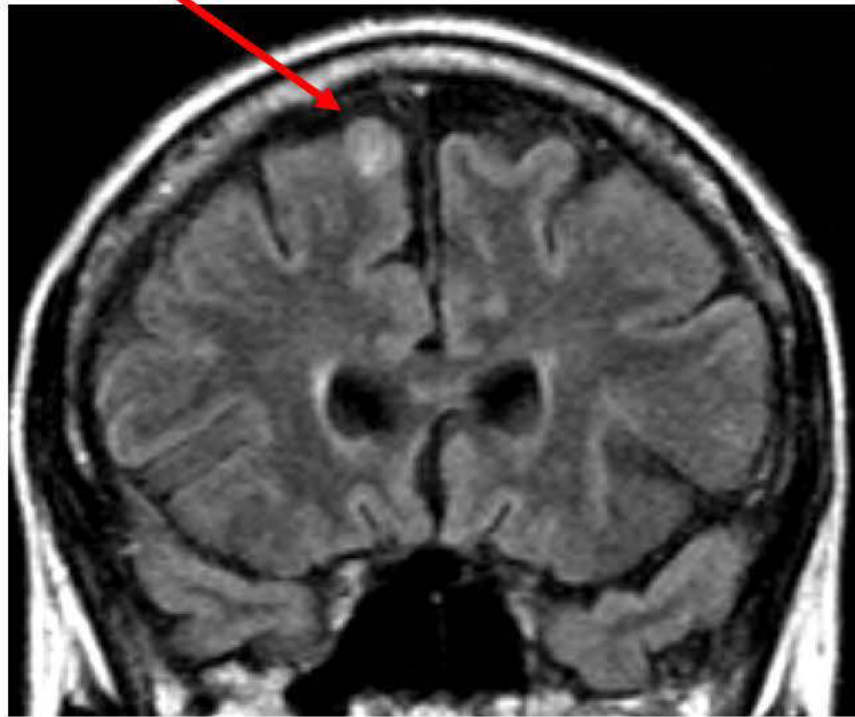


Axial T2 TSE



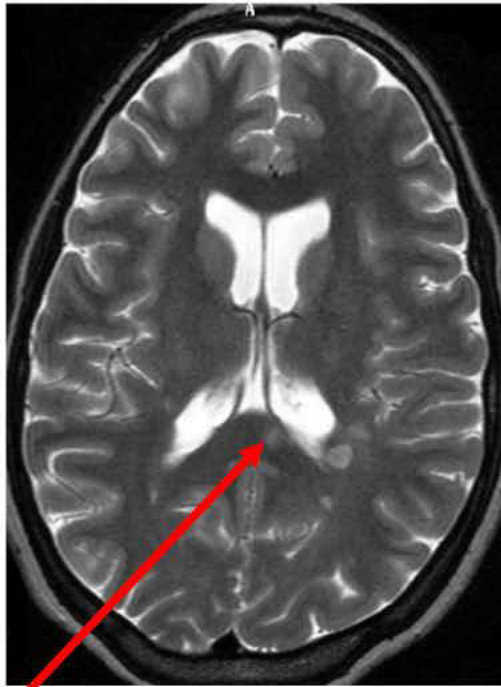


# Fibres en U juxta-corticales (+/- cortex) et substance blanche profonde

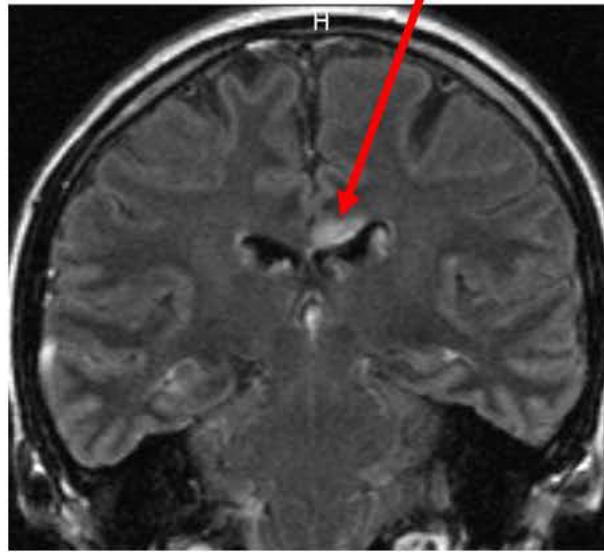


Coro FLAIR

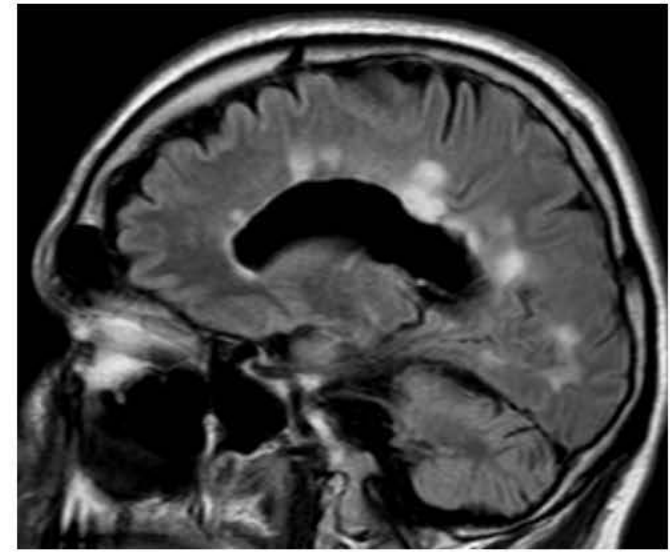
# Corps calleux et Jonction calloso-marginale en "crête de coq"



Axial T2 TSE

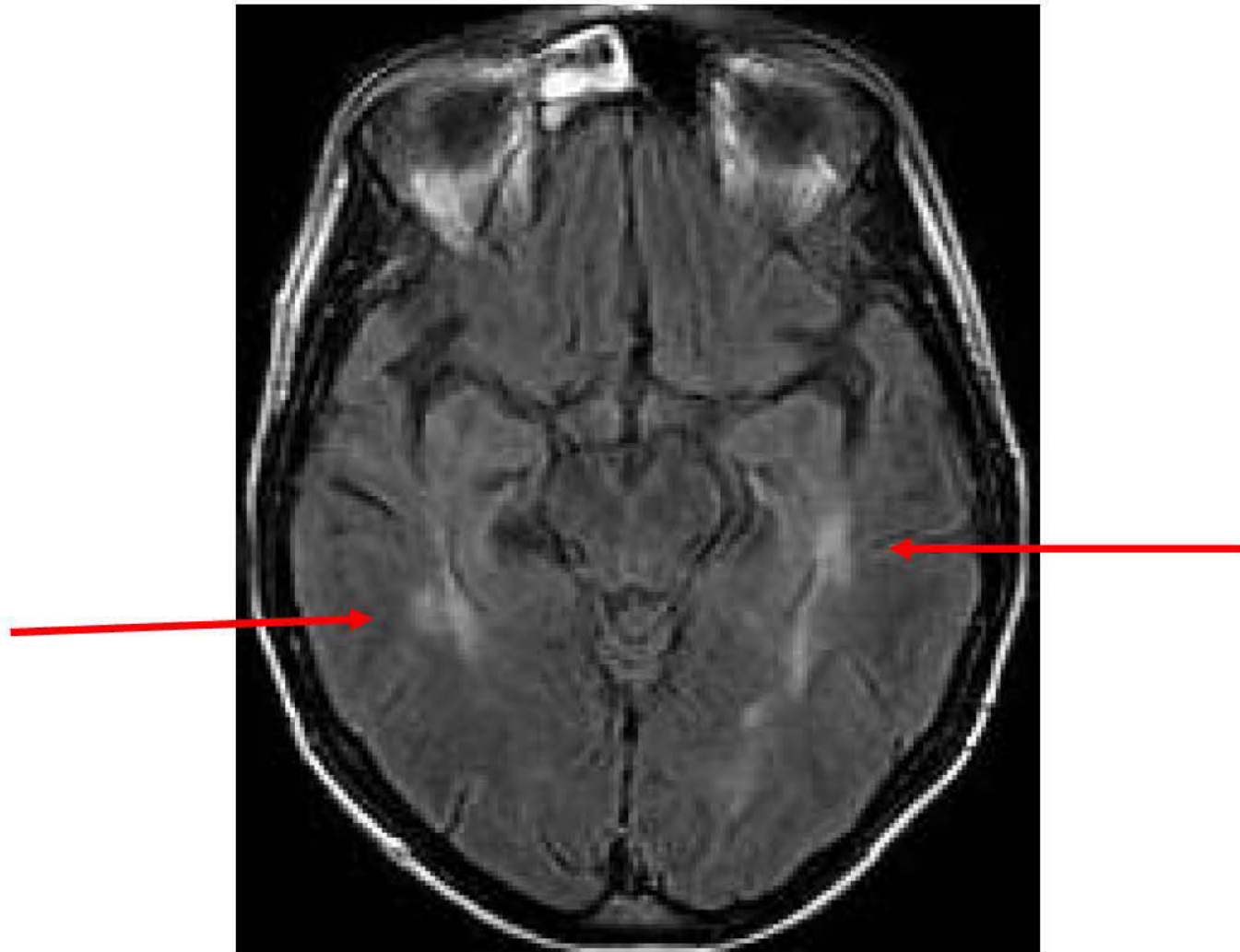


Coro FLAIR



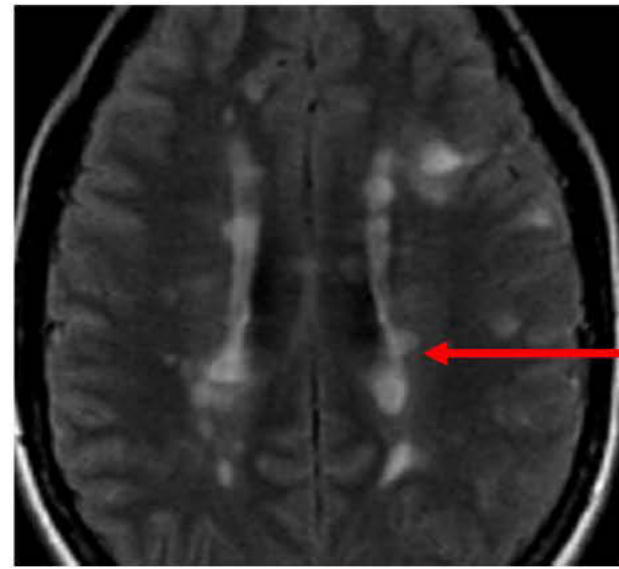
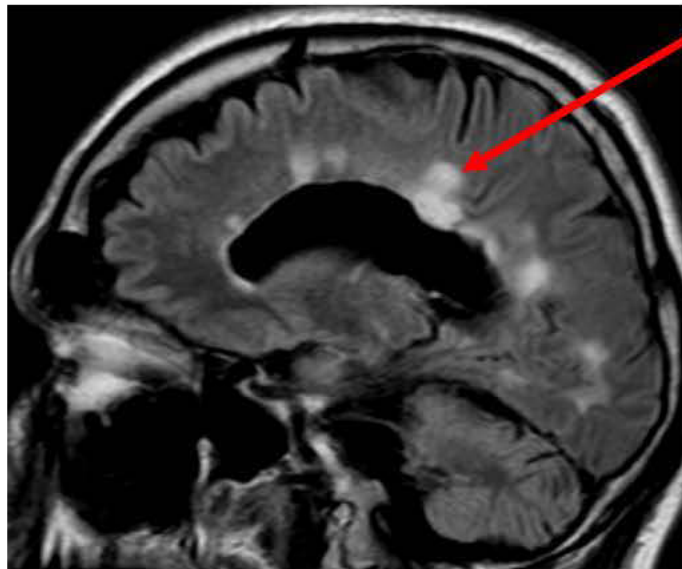
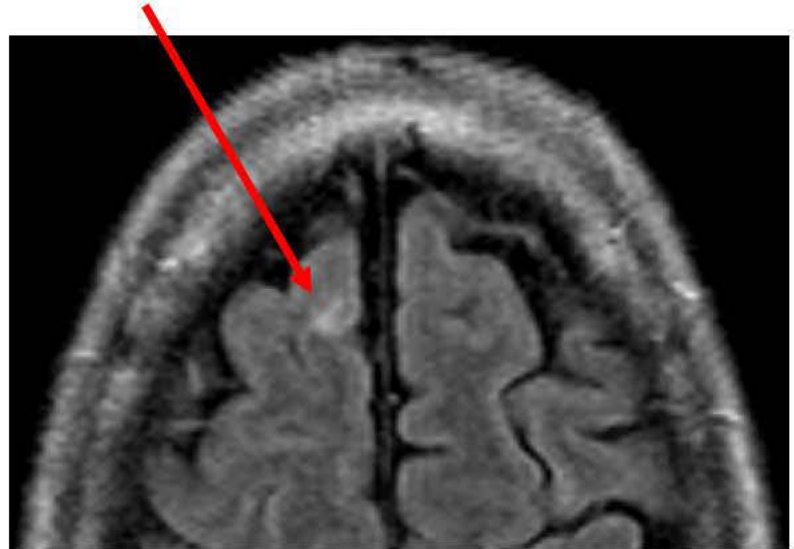
Sag FLAIR

## SB en dehors des cornes temporales





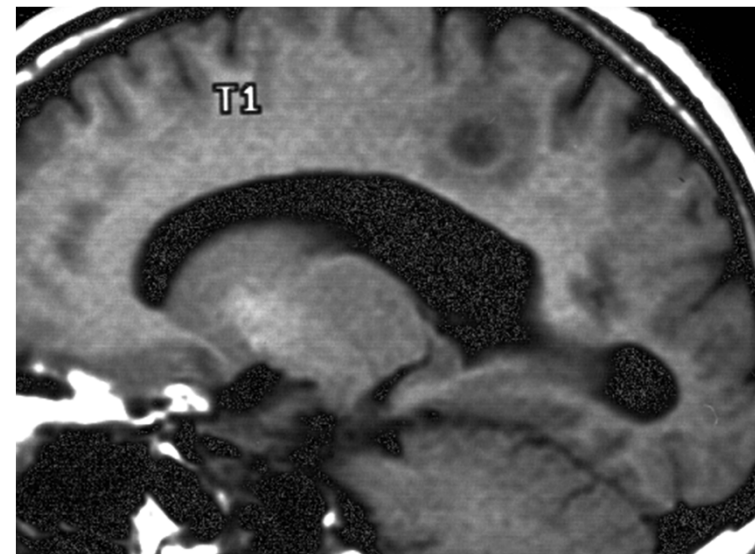
# Localisations les plus spécifiques





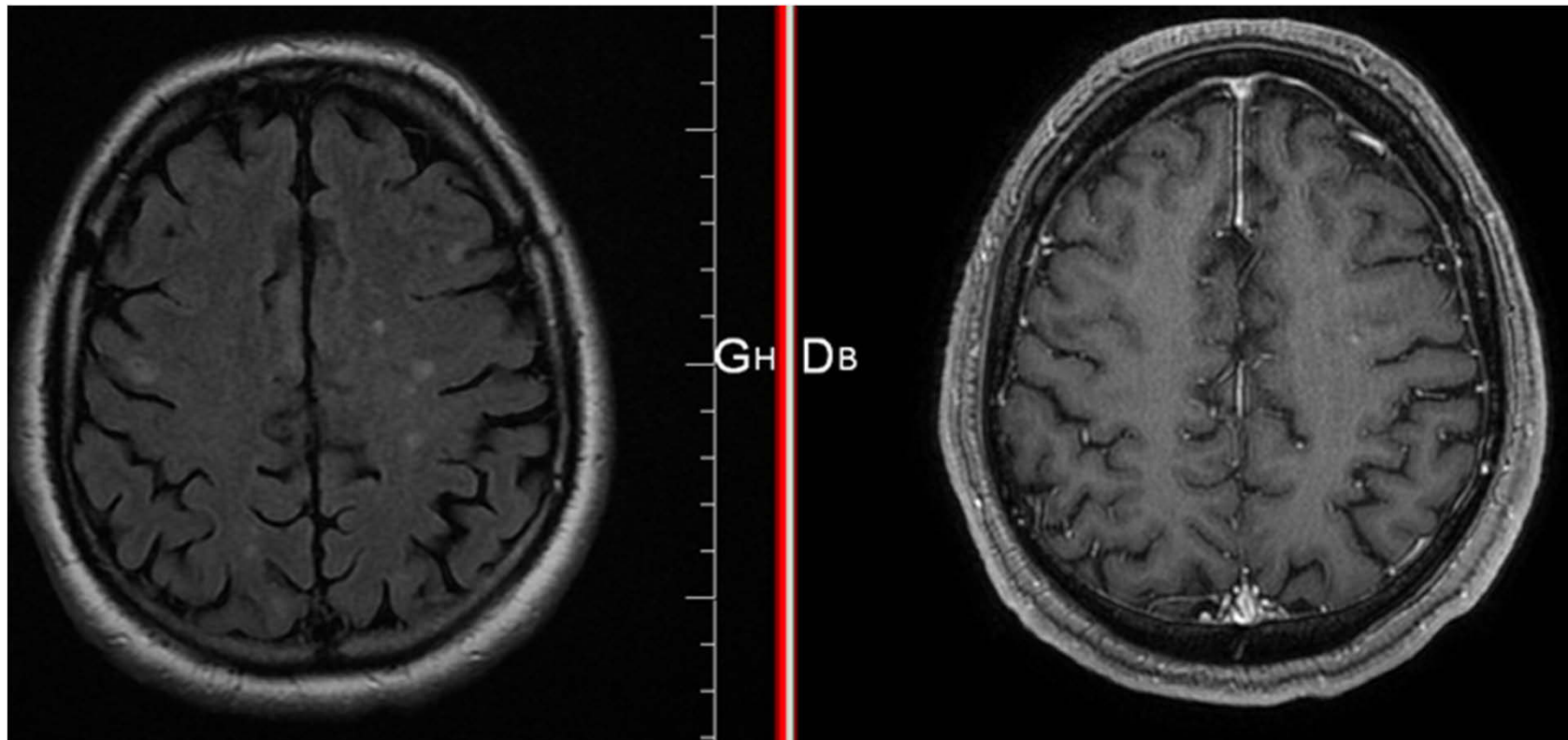
# T1 SE SANS INJECTION

- SYSTÉMATIQUE +++
- T1 de référence pour connaître le contraste spontané des lésions  
(liseré périphérique spontanément en hypersignal = macrophages chargés de corps cellulo-graisseux)
- Recherche de lésions anciennes en hyposignal

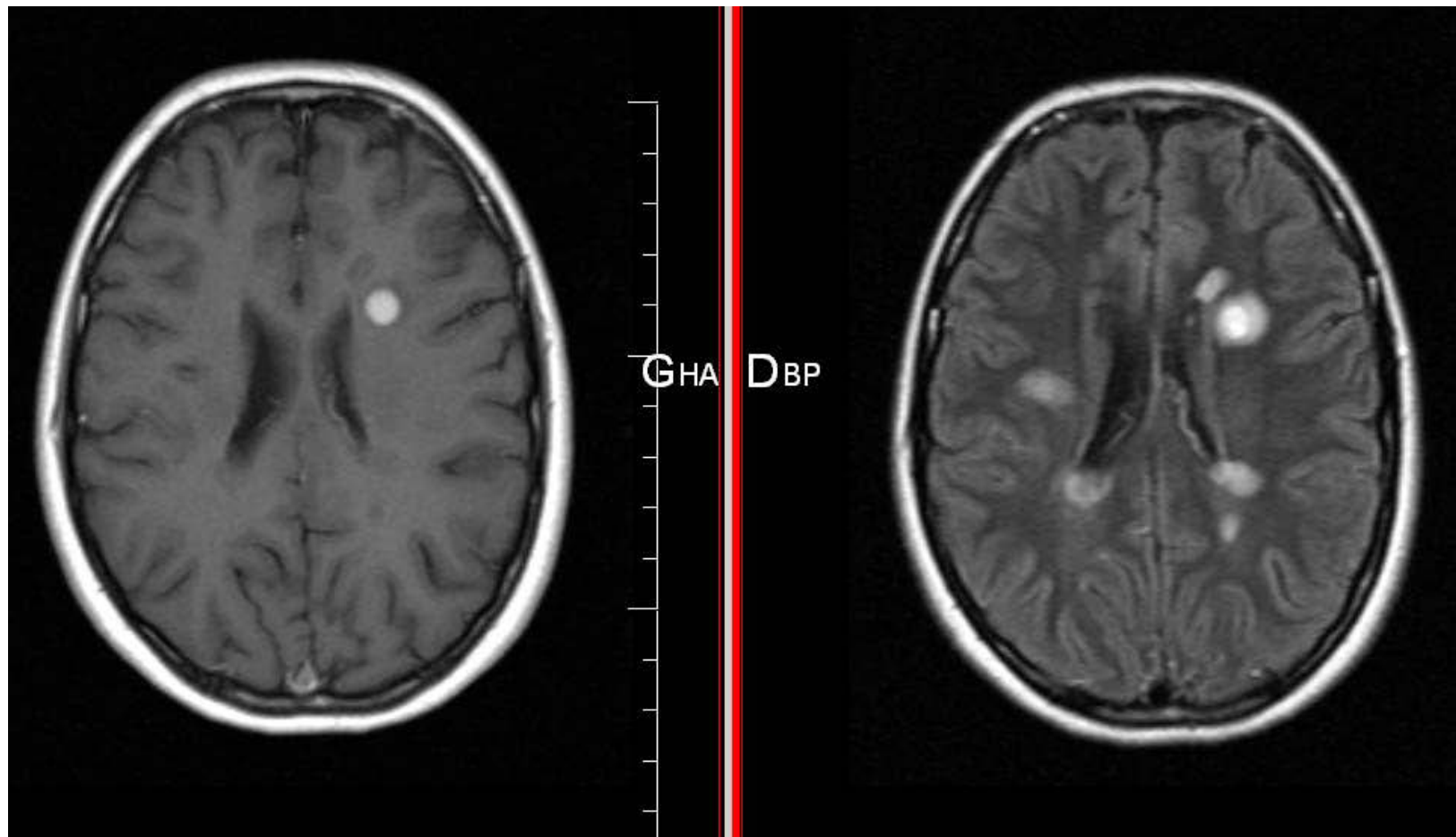


## T1 SE après Gadolinium

- Prise de contraste = "plaque active"
  - Rupture BHE (Gadolinium)
  - Phase aigue de l'inflammation: 2-6 sem <...< 3 mois
  - Rarement rupture chronique de la BHE
- Délai séquence / injection IV > 5 min



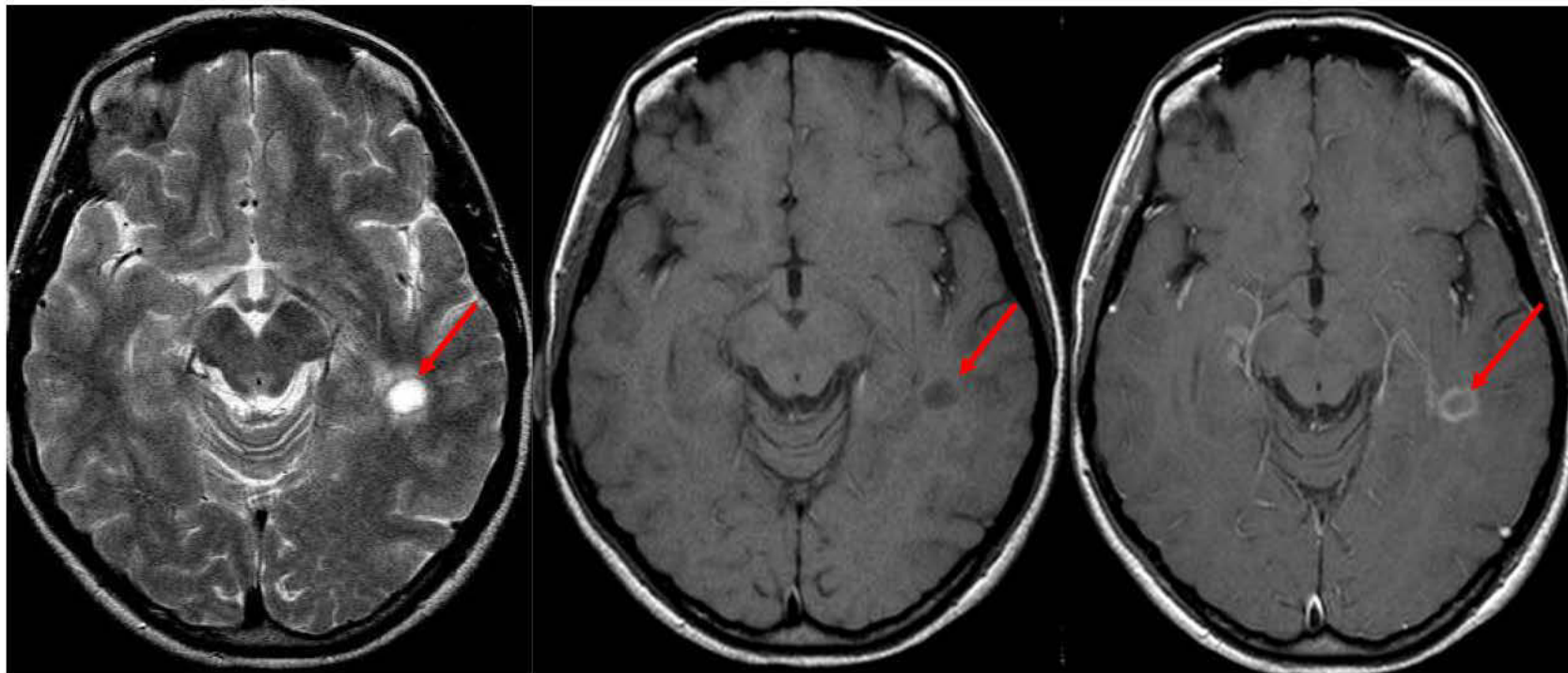
# Lésion récente





# Lésion récente

- aspect en "cocarde", en "cible" en T2
- oedème périphérique inflammatoire
- prise de contraste annulaire
- $\pm$  effet de masse ( $\neq$  tumeur, ischémie)

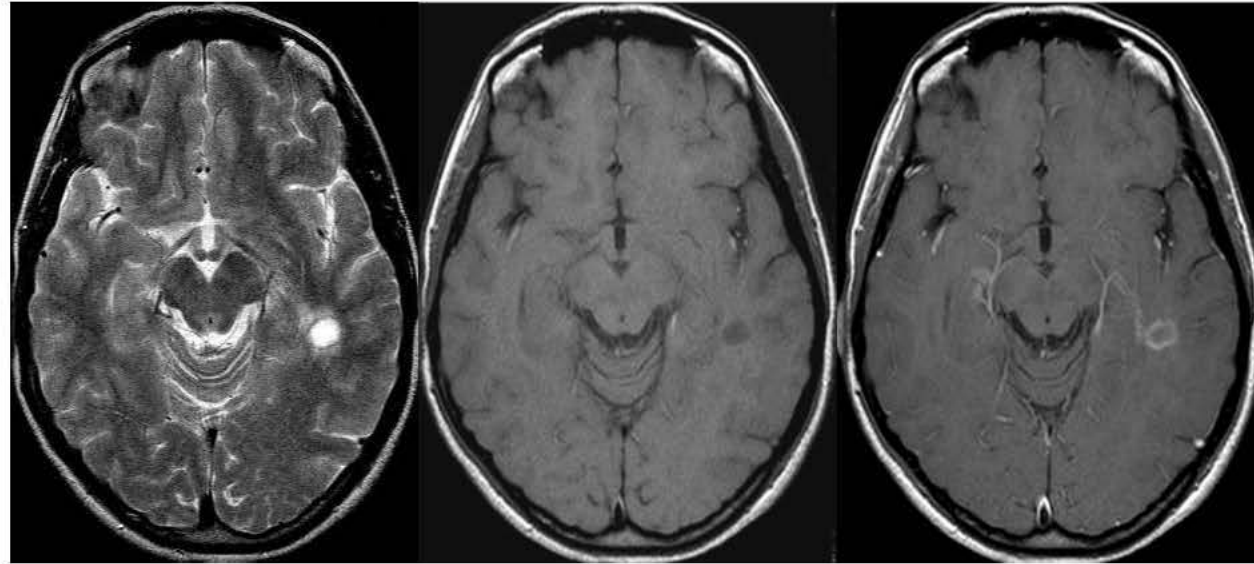


Axial T2 TSE

Axial T1 avant et après Gado

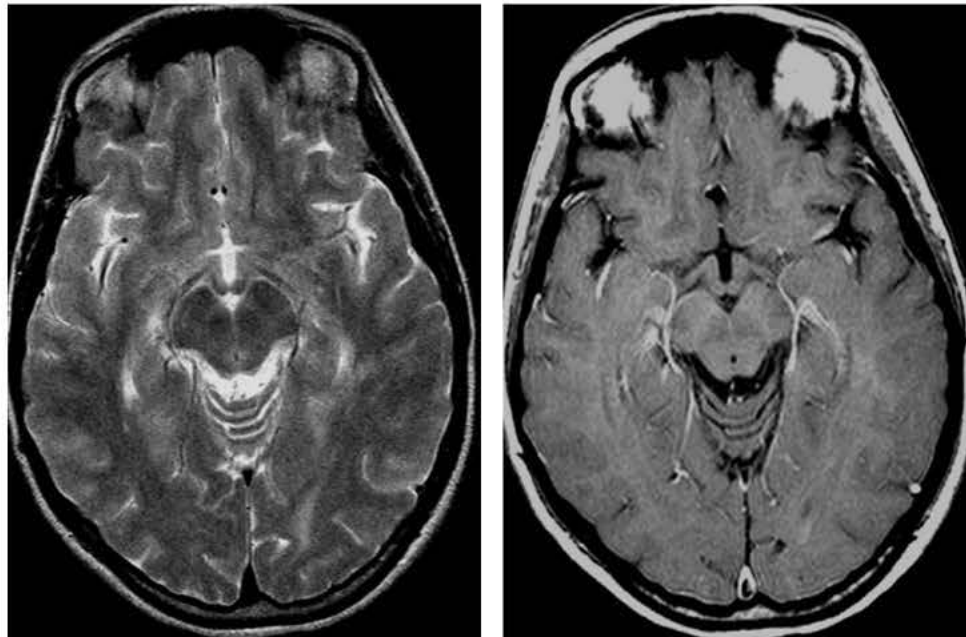
# Régression de l'œdème

Avril 04



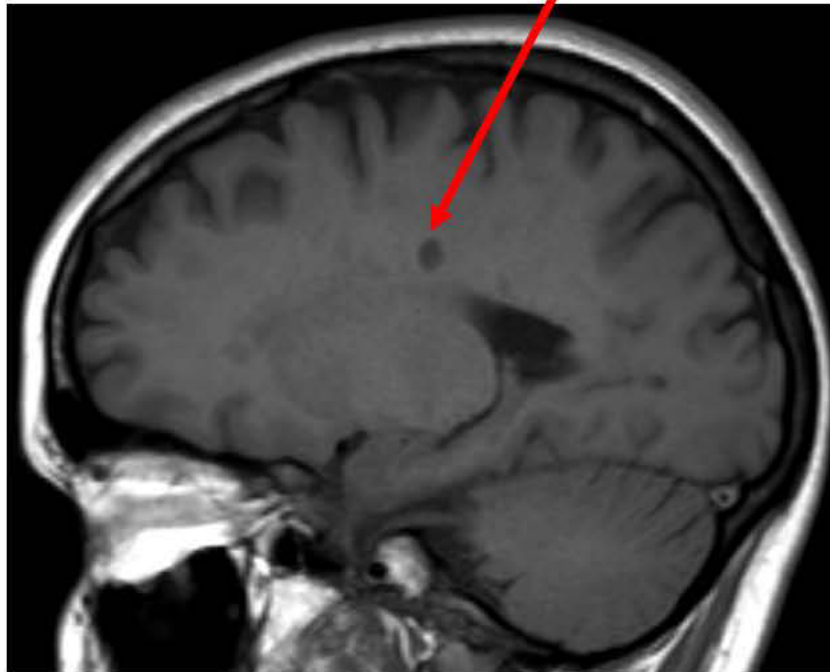
Juin 04

26 ans

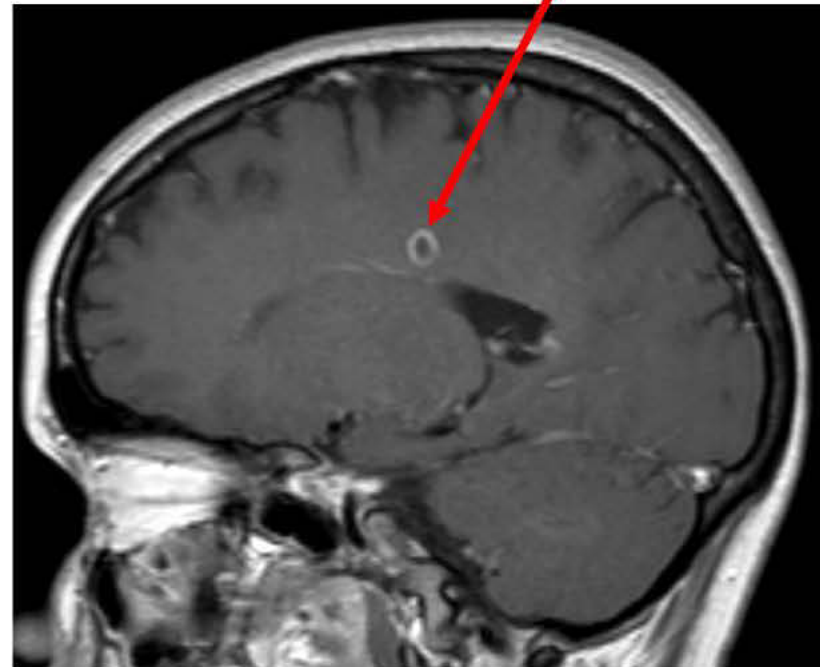


## +/- Prise de contraste

- Lésion récente, aspect variable
  - annulaire: complet ou incomplet



Sag T1

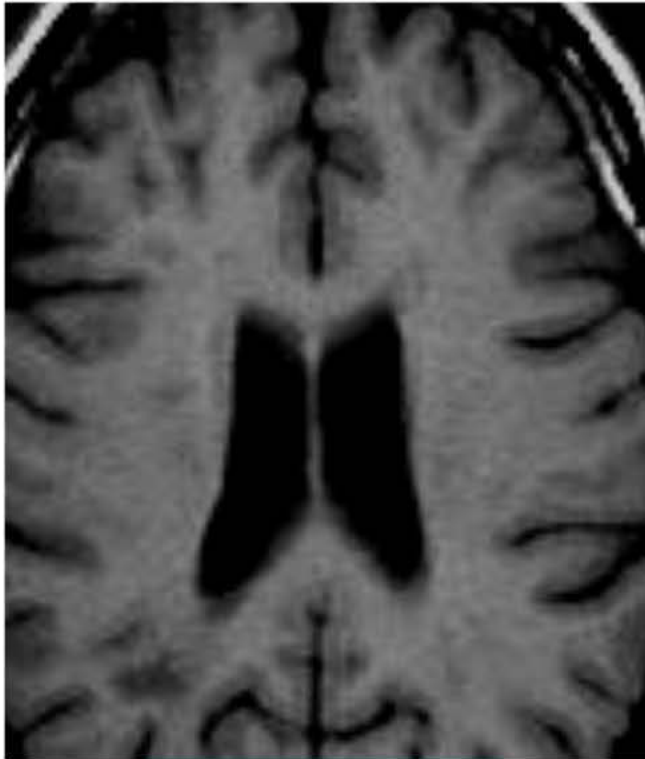


Sag T1 Gado



## +/- Prise de contraste

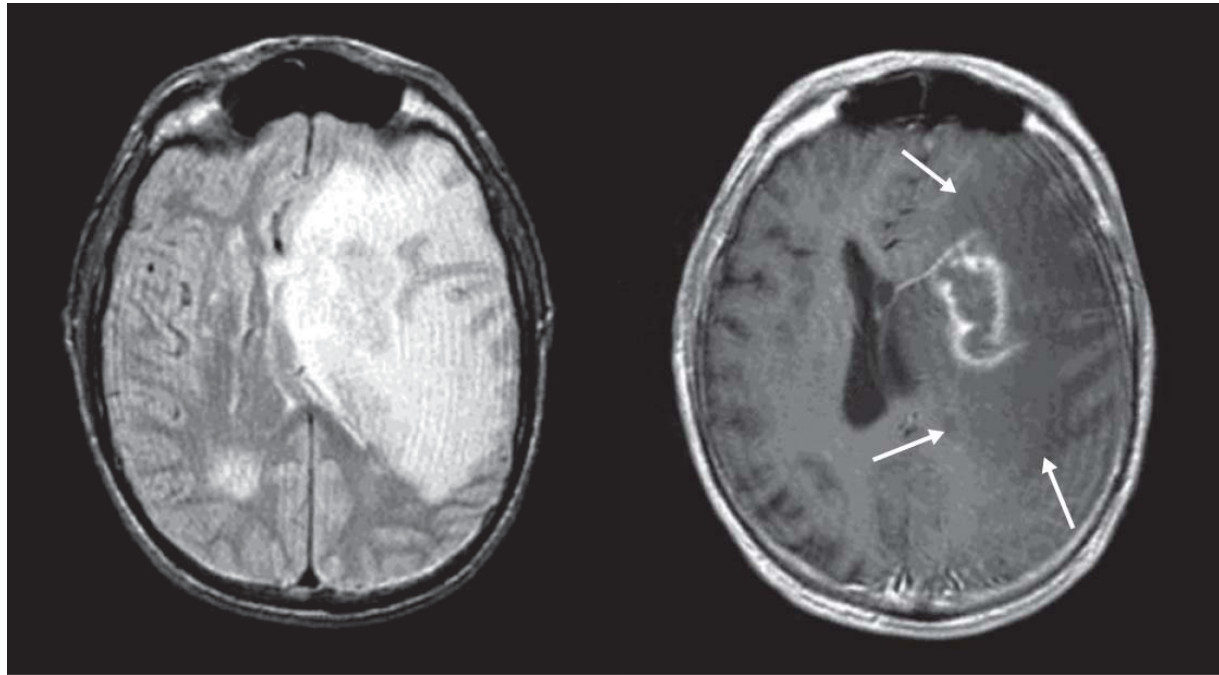
- annulaire: complet ou incomplet
- nodulaire



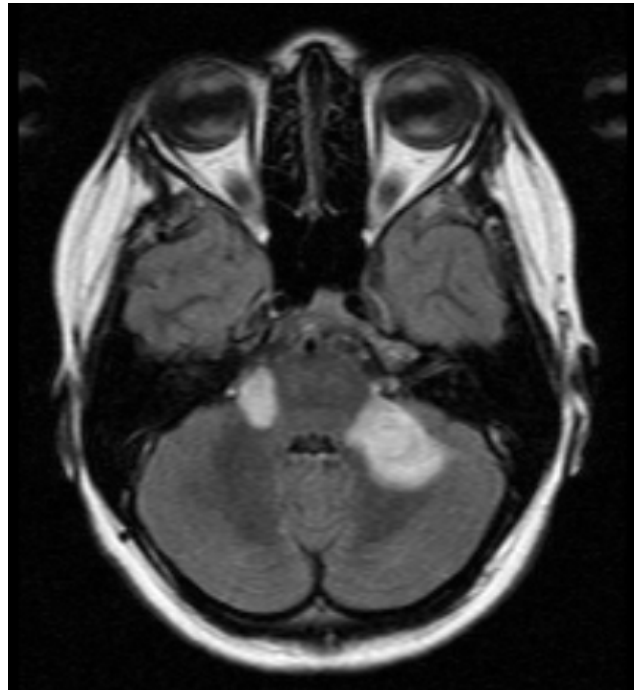
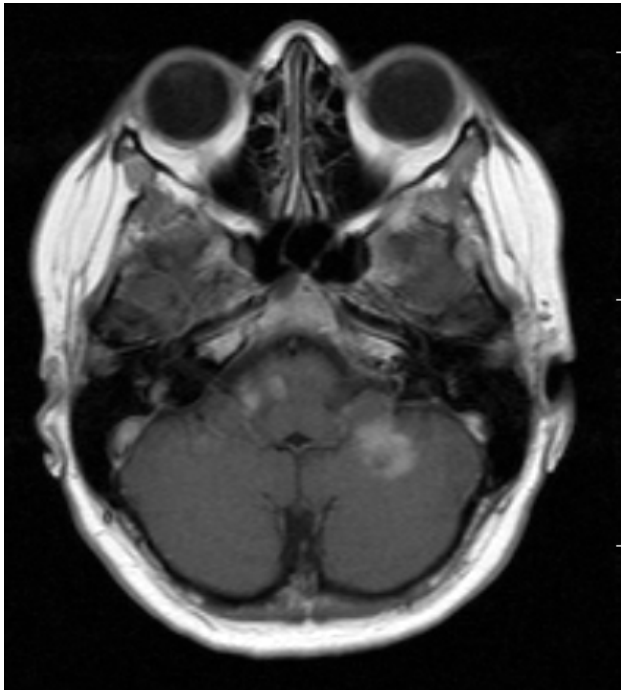
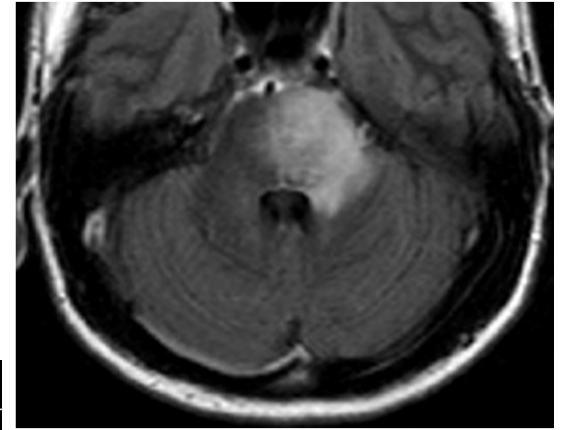
Axial T1



Axial T1 Gado



Formes  
pseudo-  
tumoraes



# Formes pseudo-tumorales

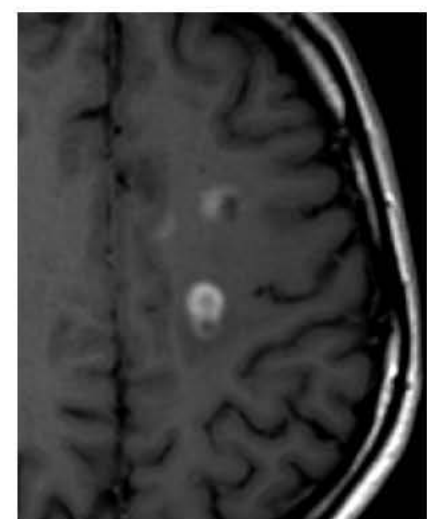
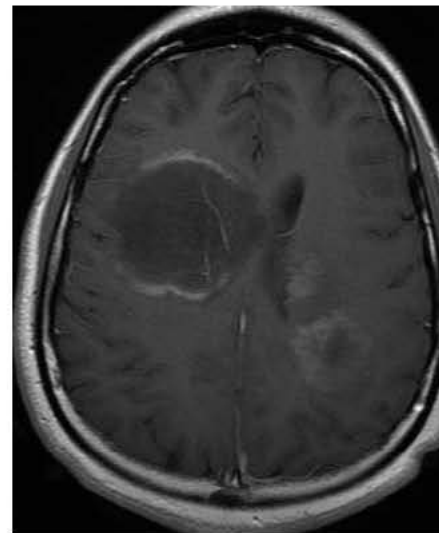
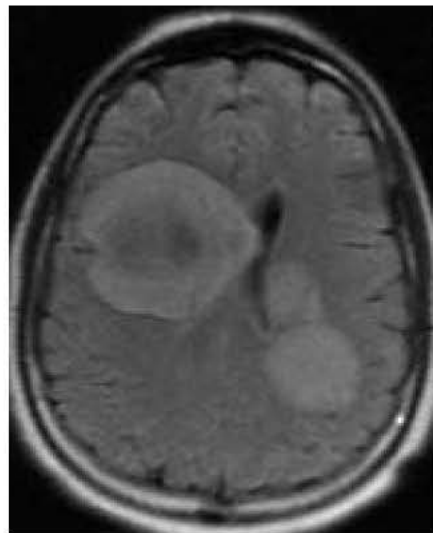
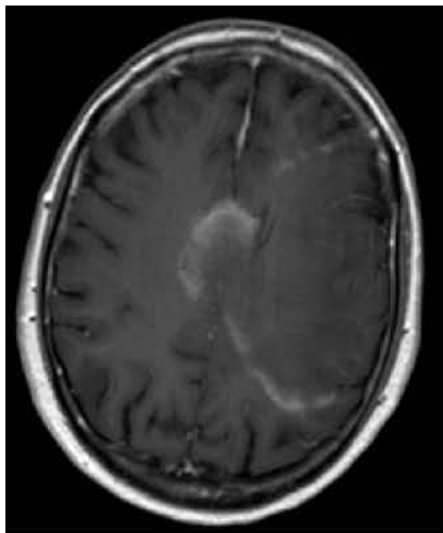
*Rehaussement en anneau incomplet: open ring imaging sign*

Fortement évocateur d'atteinte inflammatoire

- SEP
- ADEM

Spécificité 84% à 93%

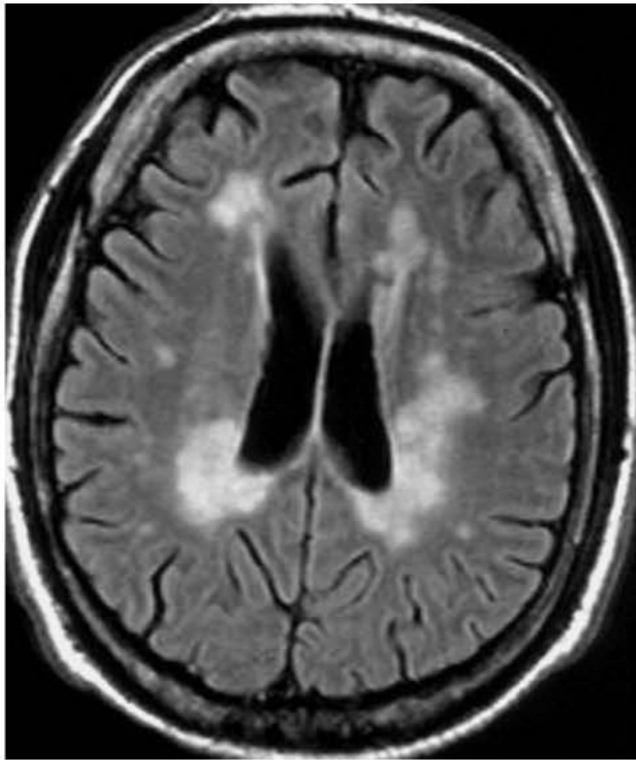
Ouvert vers la SG



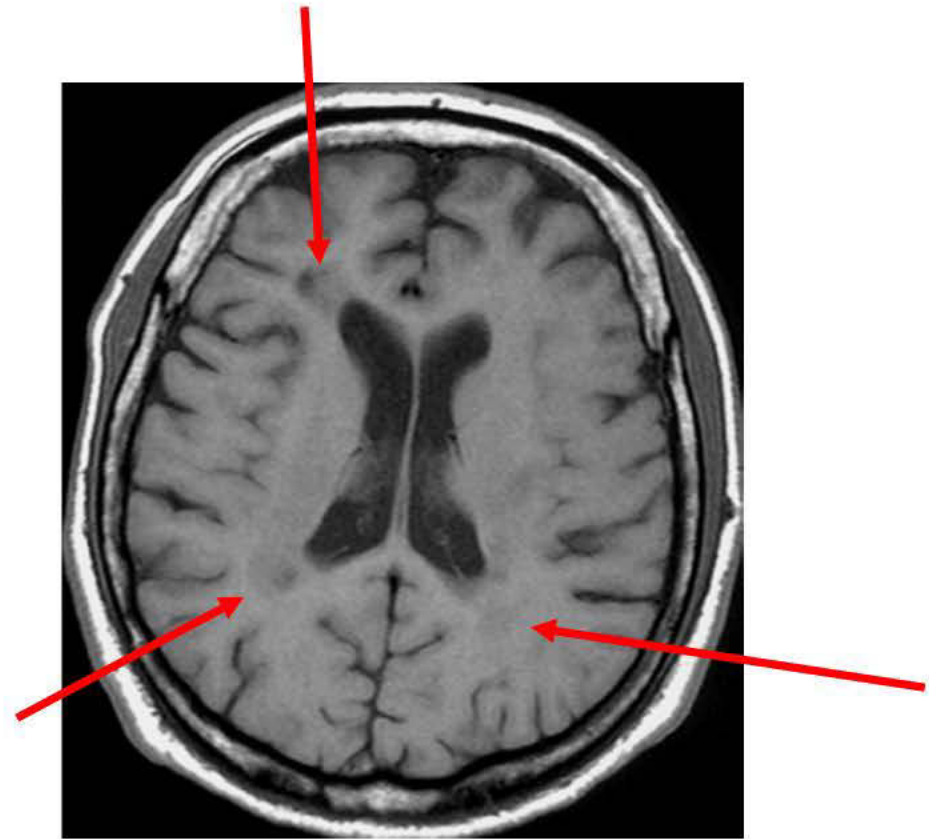


## SEP: Evolution des lésions

- Lésions en Hyposignal T1: « trous noirs »
- Confluence des lésions



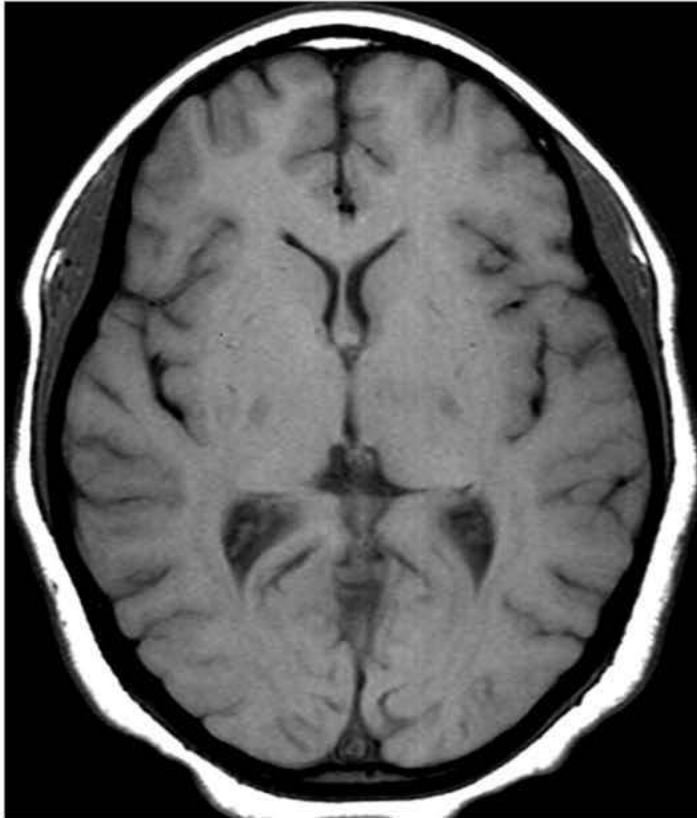
Axial FLAIR



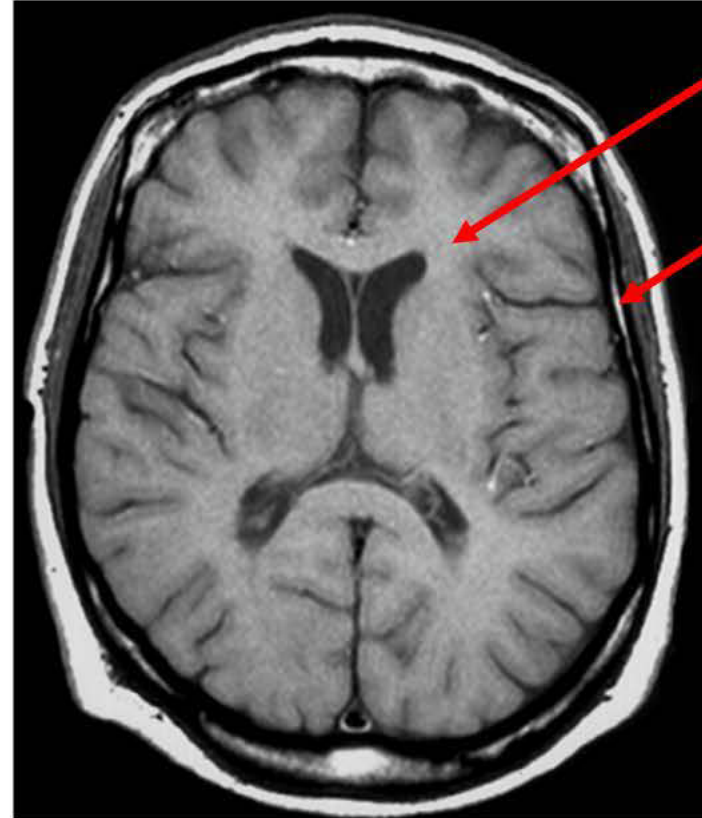
Axial T1 SE

## SEP: Evolution

- Atrophie (cérébrale ou médullaire)



Patient témoin

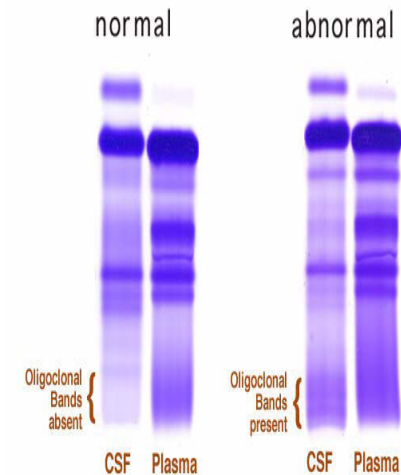


SEP

# Ponction Lominaire

- Elimine des diagnostics différentiels (infectieux: forte réaction cellulaire >50)
- Synthèse intrathécale des Ig :
  - Élément positif en faveur d'une inflammation du SNC et du risque de SEP
  - Bandes oligoclonales
  - Index IgG

Oligoclonal Bands in CSF



Greenfield et Carmichael (1925) Courbe à l'or colloïdal et sérologie syphilis négative

Kabat (1942) « Increase in gamma globulin (that) was not a reflection in the blood picture »

Lowenthal (1959) Aspect oligoclonal des gamma-globulines

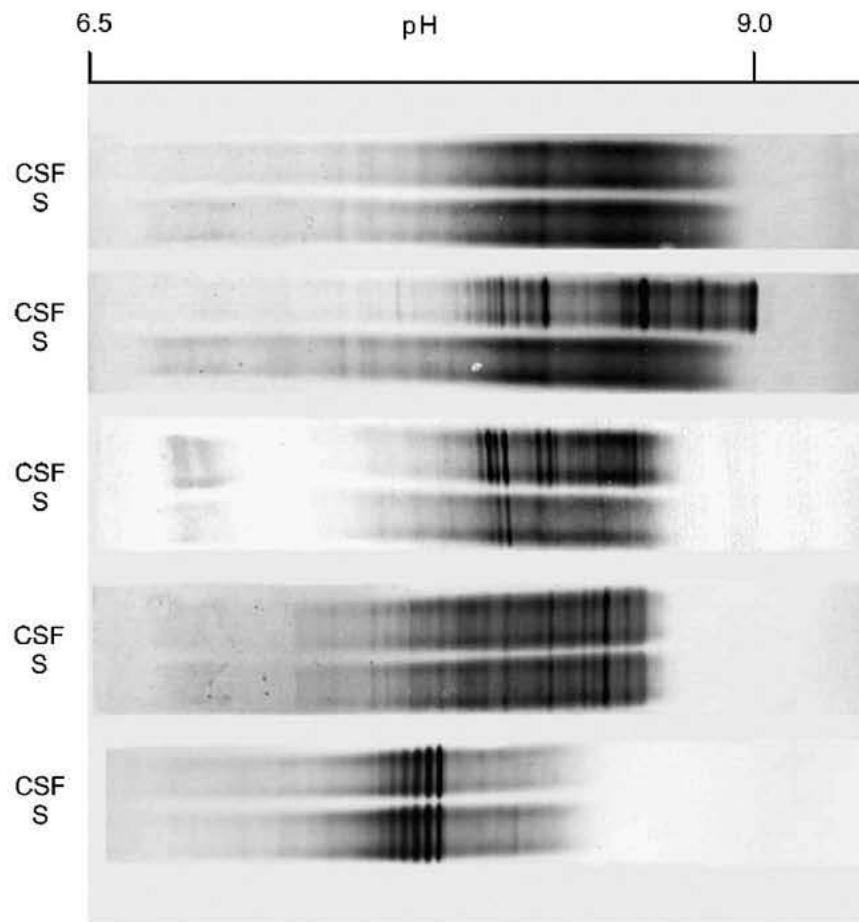
Link (1967) IgG

Link et Kostulas (1983) Iso-électrofocalisation



# Les bandes oligoclonales (BOC)

- Technique
  - Focalisation isoélectrique suivie d'une immunofixation avec anti-IgG
  - Analyse concomitante LCR/sérum
- Signification
  - Présentes dans ~95% des SEP cliniquement certaines
  - Peu de spécificité
  - Présentes tout au long de l'évolution (mais - au stade CIS ?)



Type 1 : normal, type 2 : synthèse intrathécale (SEP), type 3 : synthèse intrathécale et hyperimmunisation systémique (SEP, infections, maladies de système), type 4 : hyperimmunisation systémique sans synthèse intrathécale (Guillain-Barré, maladies de système...), type 5 : myélome, gammopathie monoclonale.

**Tableau I.** – Maladies neurologiques associées à la présence de bandes oligoclonales d'IgG spécifiques du LCR (type 2 et type 3) d'après Sindic, (1999).

*Neurological diseases associated with the presence of specific bands of IgG (IgG index); increased IgG oligoclonal in the cerebrospinal fluid (type 2 and type 3) (after Sindic, 1993).*

---

<b>Type 1</b>	Pathologies inflammatoires du SNC <ul style="list-style-type: none"> <li>• Sclérose en plaques</li> <li>• Neuromyérite optique de Devic</li> <li>• Encéphalomyélite aiguë disséminée</li> </ul>
<b>Type 2</b>	<ul style="list-style-type: none"> <li>• Neurosarcoïdose</li> <li>• Maladie de Behçet</li> <li>• Neurolupus</li> <li>• Angéite granulomateuse</li> </ul>
<b>Type 3</b>	Pathologies paranéoplasiques (encéphalite limbique, dégénérescence cérébelleuse)
<b>Type 4</b>	Pathologies infectieuses et post-infectieuses du SNC <ul style="list-style-type: none"> <li>• Neurosyphilis</li> <li>• Maladie de Lyme</li> <li>• Méningite tuberculeuse</li> </ul>
<b>Type 5</b>	<ul style="list-style-type: none"> <li>• Maladie de Whipple</li> <li>• Phase tardive des méningites à pyogènes</li> <li>• Encéphalites virales (herpès, HIV...)</li> <li>• Méningites virales (herpès, oreillons, HIV... mais non les picornavirus)</li> <li>• Paraparésie spastique tropicale (HTLV1)</li> <li>• Panencéphalite sclérosante subaiguë</li> <li>• Méningites fongiques (<i>Candida</i>, <i>Cryptococcus</i>, <i>Aspergillus</i>...)</li> <li>• Infections parasitaires du SNC (toxoplasmose, neurocysticercose, schistosomiase...)</li> <li>• Infections <i>in utero</i> avec atteinte du SNC (CMV, rubéole, toxoplasmose)</li> </ul>
	Tumeurs <ul style="list-style-type: none"> <li>• Méningites carcinomateuses et lymphomateuses</li> <li>• Lymphomes primitifs du SNC</li> </ul>

---

# Résultats en isoélectrofocalisation

- Pas de bande oligoclonale IgG dans le LCR ni dans le sérum = négatif
- Bandes oligoclonales IgG à la fois dans le LCR et le sérum = négatif (réaction inflammatoire systémique = pas de valeur)
- Bande monoclonale dans le LCR non retrouvée dans le sérum = douteux
- Au moins 2 bandes oligoclonales dans le LCR non retrouvées dans le sérum = évocateur d'une inflammation du SNC (ex. SEP)
- Plus de bandes dans le LCR que dans le sérum = évocateur d'une inflammation du SNC (ex. SEP)

# Profil ?

## Oligoclonal

- Asiatiques : fréquence PO inférieure (environ 33 %) <sup>1</sup>
- Parfois PO absent au début (si diagnostic douteux, répéter la PL peut être discuté). Problème de la technique plus ou moins sensible.
- Disparition secondaire avec la même technique :
  - en faveur encéphalomyélite aiguë disséminée (EMAD)
  - ne disparaît pas dans la SEP <sup>2</sup>

## Bande unique dans le LCR

- Moins fréquente en isoélectrofocalisation
- Si index IgG élevé : considérer comme un profil oligoclonal
- Étude de 27 patients <sup>3</sup> après 2 ans en moyenne :  
conversion à PO dans 1/3 des cas / persistance d'une bande dans 1/2 / normalisation pour les autres
- Ne pas négliger risque exceptionnel de lymphome B



# L'index IgG

- Rapport entre quotient IgG LCR/IgG sérum et quotient albumine LCR/albumine sérum
- $N < 0.7$
- Index augmenté chez 70-80% des SEP

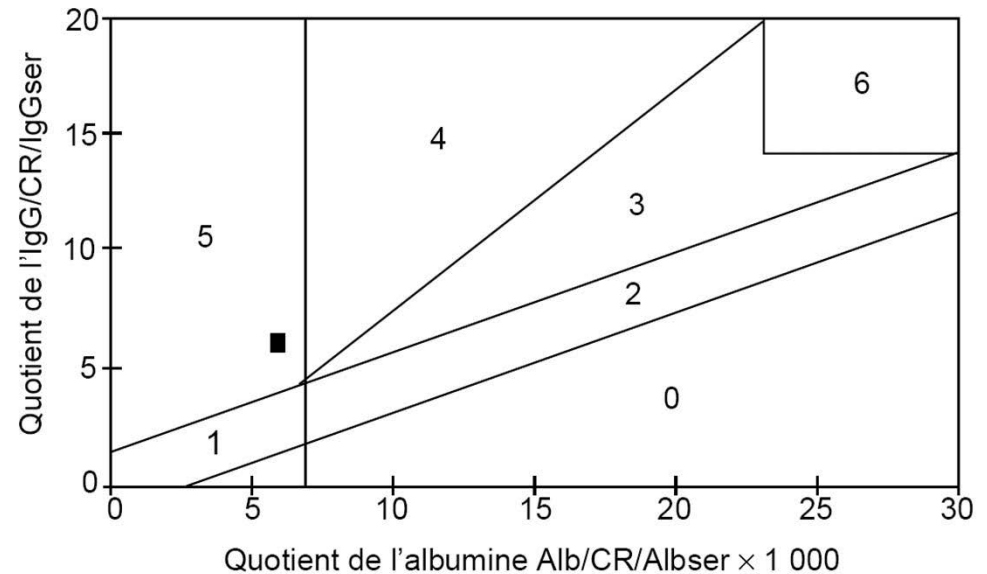


Fig. 2. – Diagramme montrant la synthèse intrathécale d'IgG (index IgG) : quotient IgG augmenté ; quotient albumine normale.  
*Graphic representation of intrathecal synthesis of IgG (IgG index); increased IgG quotient, normal albumin quotient.*

# Cellularité du LCR

- > 4/mm<sup>3</sup> chez 30-50% des patients
  - Rarement > 35 (1%)
  - Remettre en cause le diagnostic si > 50
- > 80% lymphocytes T
  - Prédominance CD4 activés
- Lymphocytes "normaux"

# Biologie sanguine

- NFS, Plaquettes, VS , CRP, HE, TP/INR, TCA
- Sérologies VIH (après accord patient) et TPHA-VDRL
- Sérologie de Lyme (ELISA),
- Ac anti-noyaux (+ ac anti-ENA) , Ac anti-phospholipides IgG,
- (Ac anti TPO ; Ac anti-thyroglobuline)

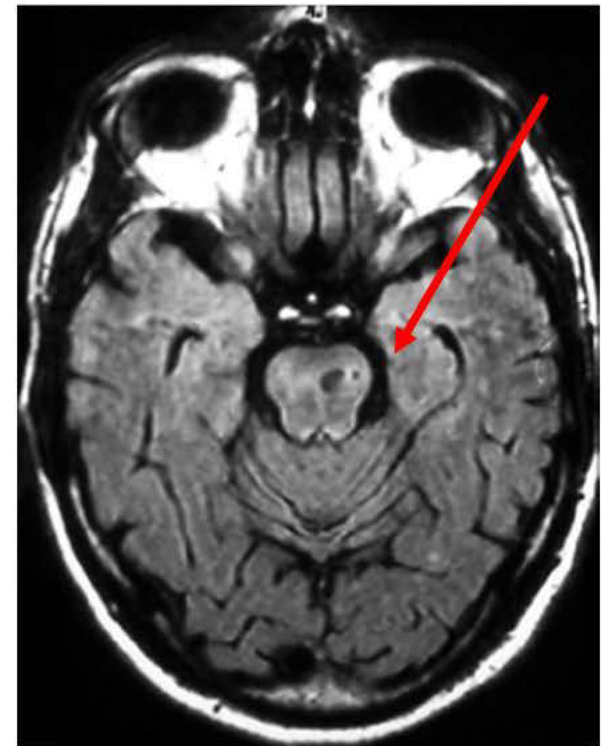
# SEP: Diagnostics différentiels

- Dilatation des espaces de Virchow-Robin
- Lésions démyélinisantes vasculaires
  - (fréquence +++)
- Autres lésions démyélinisantes inflammatoires
  - Maladies de système
  - Infections



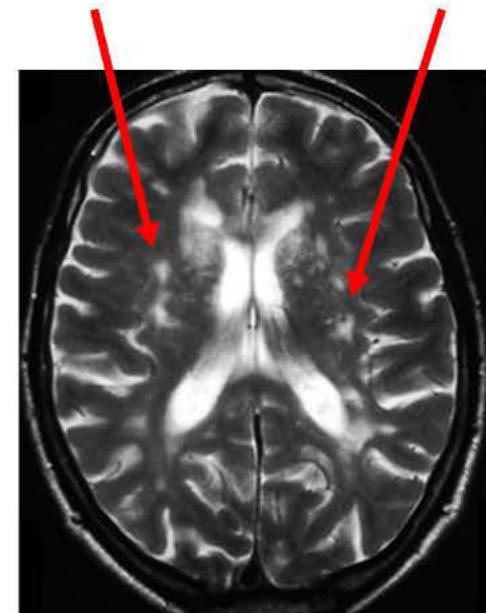
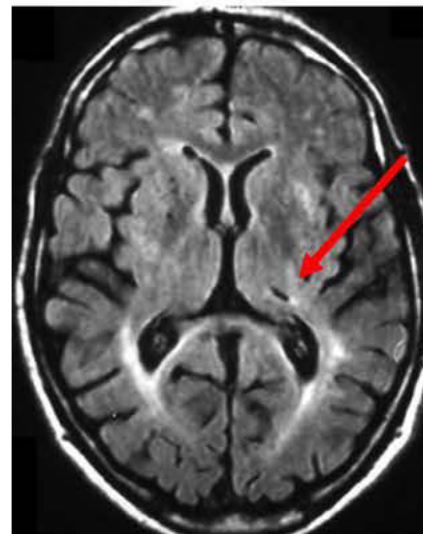
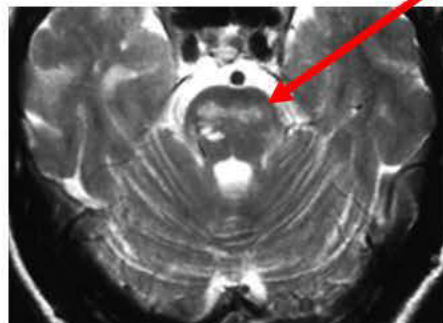
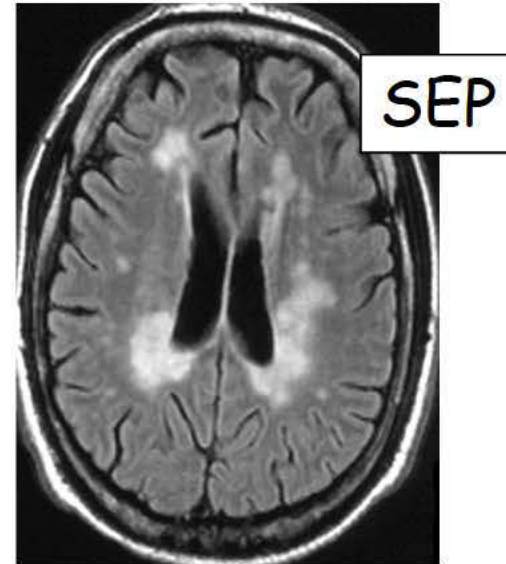
# Dilatation des espaces de Virchow-Robin

- Dilatation des gaines arachnoïdiennes périvasculaires
- Extrémités de la vie : enfant, sujet âgé
- IRM: signal liquidien = LCR
  - Hypo T1, hyper T2
  - S'efface en FLAIR +++
- Localisations + difficiles
  - SB profonde (sous-corticale)
  - Tronc cérébral
  - Pédoncules cérébraux



# Lésions démyélinisantes vasculaires

- Non ovalaires ou radiaires
- Sous-corticale (profonde) > juxta-ventriculaire
- Respect
  - régions temporales
  - corps calleux
- Atteinte centrale
  - tronc cérébral
  - NGC



# Hypersignaux de découverte fortuite :

## 2 situations cliniques

- **Patient âgé**
  - +/- troubles cognitifs
  - +/- facteurs de risque vasculaires
- **Patient jeune**
  - Problème difficile: migraine ?
  - SEP « pré-clinique » ?

# Maladie des petites artères cérébrales ?

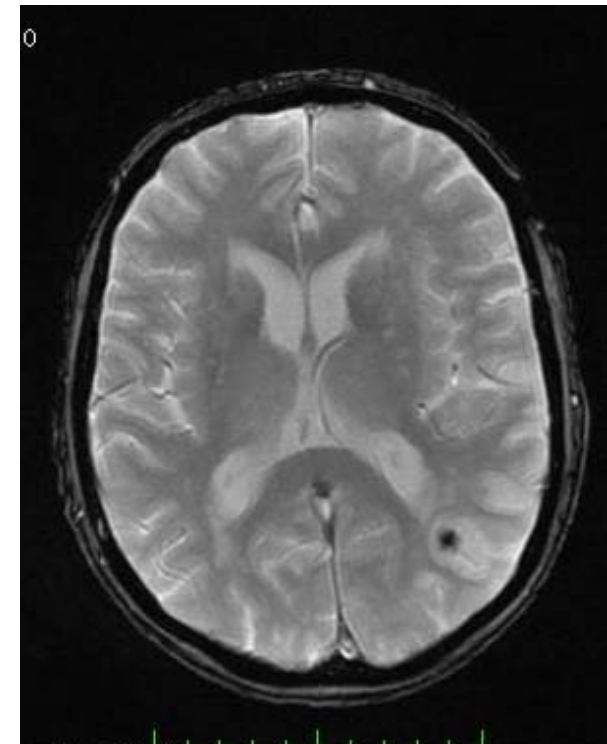
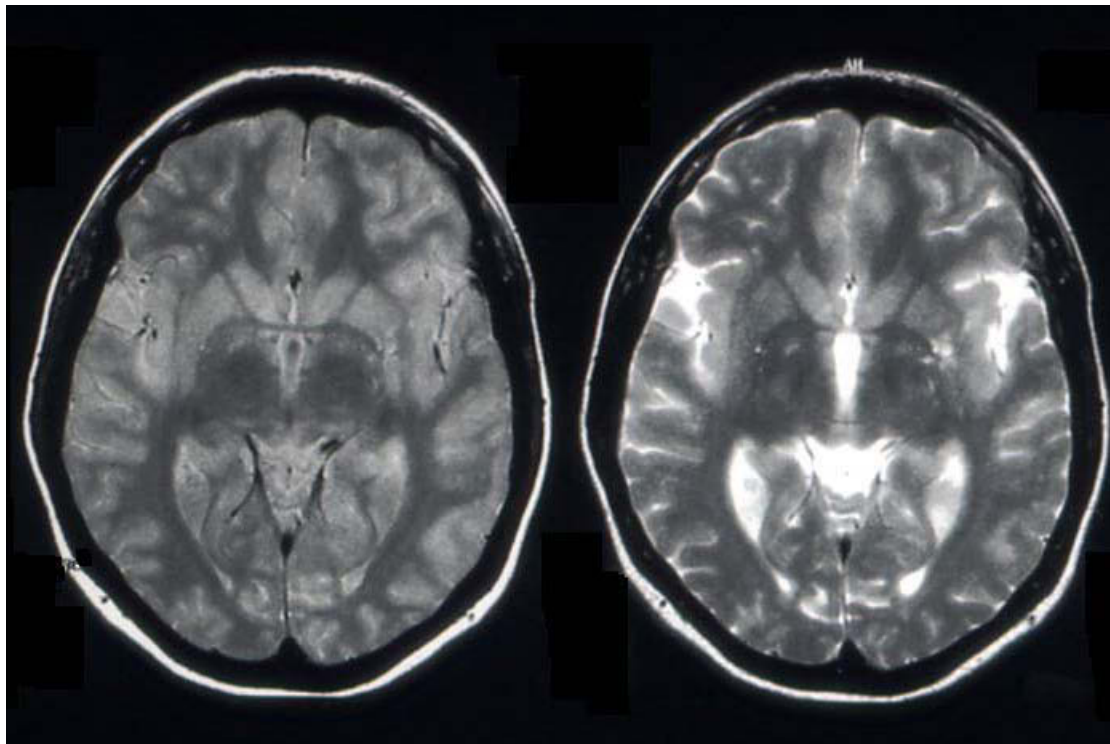
Prévalence

5 à 10 % chez les 20-40 ans

100 % ? âgé

Prévalence SEP 1/1000

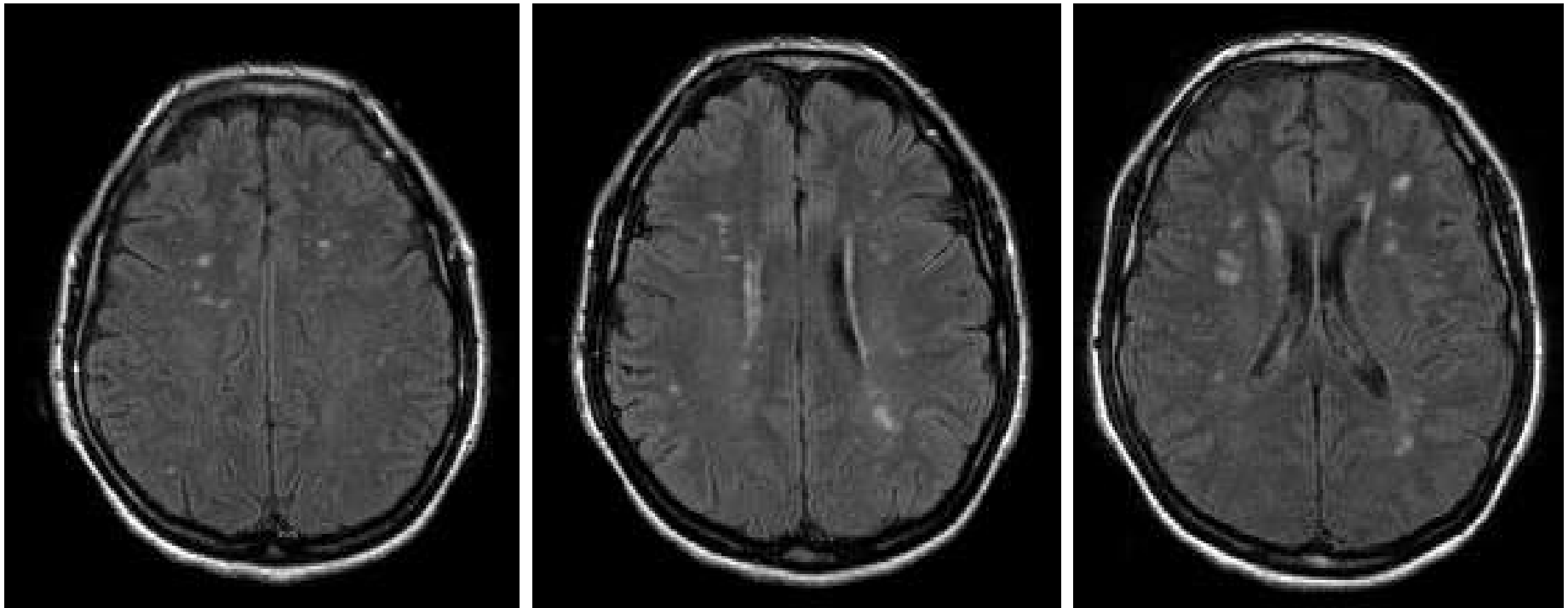
T2\*





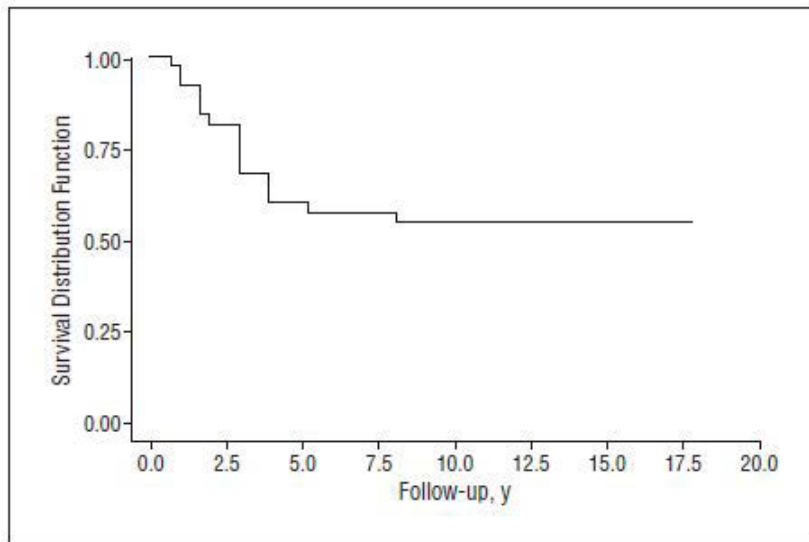
## « Incidentalome ? »

- Patiente de 24 ans, terrain allergique, consulte pour céphalées atypiques
- Examen neurologique normal
- FO normal



# RIS syndromes radiologiquement isolés

- Découverte fortuite de lésions de la substance blanche évocatrices de SEP sur une IRM réalisée pour autre motif: céphalées, crises ...
- Plusieurs séries: Lebrun et al., 2008; 2010; 2011; Okuda et al., 2009;2011; Siva et al., 2009
- Critères différents: critères de dissémination dans l'espace (Barkhof/Tintoré)



**Figure 1.** Kaplan-Meier survival curve showing the risk of developing a clinically isolated syndrome (CIS). At 1 year, 92% of patients have not had a CIS. At 2 years, 82% of patients have not had a CIS. At 3 years, 59% of patients have not had a CIS.

**Table 2. Initial Symptoms Leading to Brain Magnetic Resonance Imaging**

Characteristic	No. of Patients by Likelihood of Symptom Representing a Demyelinating Event		P Value
	Unlikely <sup>a</sup> (n=46)	Possible <sup>b</sup> (n=24)	
≥9 T2-hyperintense signals	37	21	.10
Gadolinium enhancement	16	1	.005
Infratentorial lesions	31	14	.45
Oligoclonal band	21	9	.5
Visual evoked potential	31	14	.45
Clinically isolated syndrome	15	8	.95

<sup>a</sup>Cranial trauma, research scan, headaches, and endocrinology.

<sup>b</sup>Depression, dystonia, anosmia, auditory disorders, radiculargia, cognitive complain, and seizures.

Reasons for MRI, n (%)	
Headache	24 (33.8)
Trauma/fall	6 (8.5)
Vascular events	5 (7.0)
Spell	4 (5.6)
Research control	3 (4.2)
Anxiety/panic attack	3 (4.2)
Syncope	3 (4.2)
Dysmenorrhea/amenorrhea	2 (2.8)
MS family history or twin with MS	2 (2.8)
Orthostasis	2 (2.8)
Back pain	2 (2.8)
Galactorrhea	2 (2.8)
Medical screen	2 (2.8)
Abdominal pain	1 (1.4)
Cervical rib evaluation	1 (1.4)
Curiosity	1 (1.4)
Dizziness (1 min)	1 (1.4)
Ear popping with air travel	1 (1.4)
Hypersomnolence	1 (1.4)
Hypertension	1 (1.4)
Loss of smell	1 (1.4)
Aneurysm screen (polycystic kidney)	1 (1.4)
Tumor screen	1 (1.4)
Dry eyes	1 (1.4)

Lebrun et al., 2010

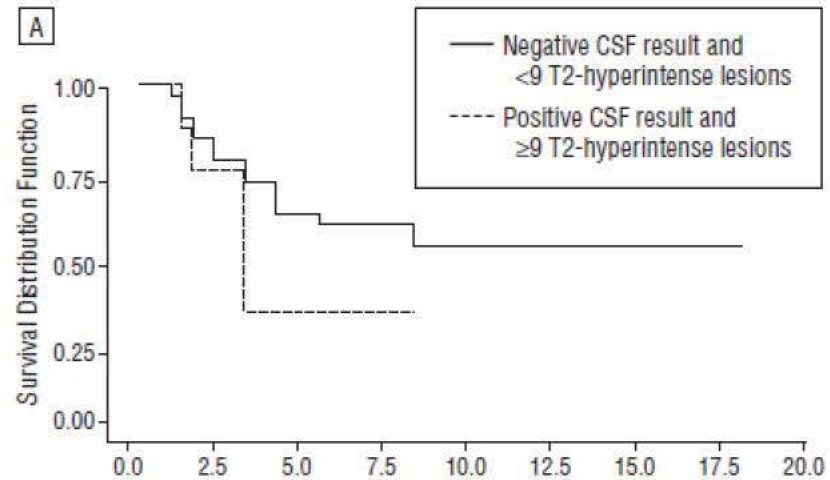
Okuda et al., 2011

**Table 3. Prognostic Factors for Developing a Clinically Isolated Syndrome**

Prognostic Factor	No. of Patients by Presence or Absence of Prognostic Factor		P Value
	Present	Absent	
<b>First MRI</b>			
Gadolinium enhancement	17	53	.46
≥9 T2-hyperintense signals	58	12	.50
Infratentorial lesions	45	25	.47
Barkhof/Tintoré criteria	56	14	.08
<b>Second MRI</b>			
Gadolinium enhancement	20	50	.01
≥9 T2-hyperintense signals	63	7	.18
Infratentorial lesions	45	25	.57
Dissemination	64	6	.07
<b>CSF</b>			
>4 Cells/mm <sup>3</sup>	28	42	.61
Oligoclonal bands	30	40	.69
Increased IgG index	28	42	.26
1 Abnormal result in CSF	51	19	.66
<b>VEP</b>			
Abnormal	45	25	.04
1 Abnormal result in CSF and ≥9 T2-hyperintense lesions on first MRI	48	22	.02
Abnormal VEP and ≥9 T2-hyperintense lesions on first MRI	38	32	.12

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; VEP, visual evoked potential.

**Lebrun et al., 2010**



**Okuda et al., 2011**

**Table 4** Multivariate logistic regression model evaluating the impact of significant covariates on clinical conversion to CIS or PPMS

Outcome: clinical progression (conversion to CIS or PPMS)	Odds ratio	95% CI (min-max)	p Value
Presence of cervical spine lesion	128.0	13.0-1,256.5	<0.0001
Presence of a brainstem/posterior fossa lesion	9.18	1.12-75.10	0.038
Age at RIS presentation (per 10-y age increase)	0.38	0.15-0.97	0.043
Brain contrast enhancement ever	1.37	0.20-9.34	0.763
Brain MRI lesion load (5-10 lesions)	2.14	0.18-25.13	0.547
Brain MRI lesion load (>10 lesions)	1.12	0.11-11.82	0.915

Abbreviations: CI = confidence interval; CIS = clinically isolated syndrome; PPMS = primary progressive MS; RIS = radiologically isolated syndrome.

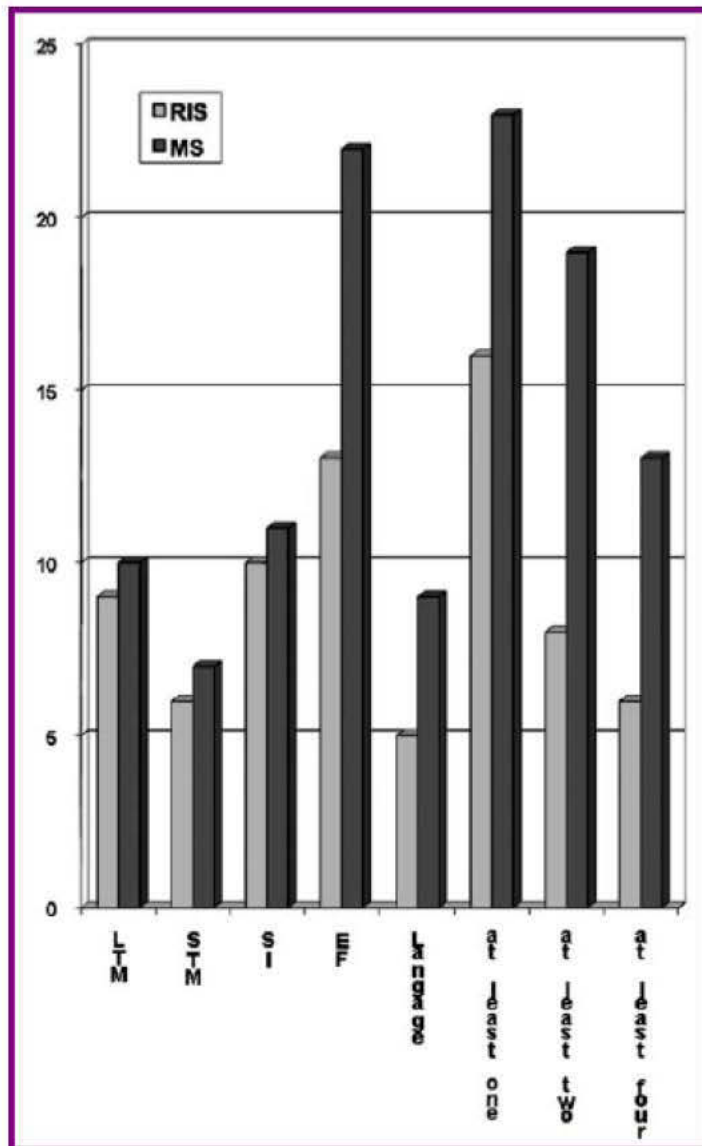


## Concept de syndrome radiologiquement isolé

### Proposed diagnostic criteria for the radiologically isolated syndrome

- A. The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria:
  - 1. Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum
  - 2. T2 hyperintensities measuring >3 mm and fulfilling Barkhof<sup>7</sup> criteria (at least 3 out of 4) for dissemination in space
  - 3. CNS white matter anomalies not consistent with a vascular pattern
- B. No historical accounts of remitting clinical symptoms consistent with neurologic dysfunction
- C. The MRI anomalies do not account for clinically apparent impairments in social, occupational, or generalized areas of functioning
- D. The MRI anomalies are not due to the direct physiologic effects of substances (recreational drug abuse, toxic exposure) or a medical condition
- E. Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter pathology lacking involvement of the corpus callosum
- F. The CNS MRI anomalies are not better accounted for by another disease process

## RIS et Cognition



	RIS patients N = 26	MS patients N = 26	p-value	Normal subjects N = 26	p-value
<b>SRT</b>					
Mean number	9	10	0.07	0	0.08
Learning	8	11	0.06	0	0.06
Differed recall	1	11	0.08	0	0.19
<b>10/36</b>					
Immediate recall	6	6	0.5	0	0.3
Delayed recall	1	4	0.07	0	0.09
<b>Digit span</b>					
Direct	4	10	0.003	0	0.002
Indirect	6	7	0.06	0	0.007
Code (WAIS)	10	12	0.63	0	0.05
<b>PASAT</b>					
3 sec	13	14	0.28	0	0.02
Cross tapping	6	9	0.05	0	0.019
Go-No-Go	2	4	0.07	0	0.001
<b>Fluencies</b>					
Phonemic	5	9	0.06	0	0.002
Semantic	3	4	0.19	0	0.3

RIS, radiologically isolated syndrome; MS, multiple sclerosis; SRT, selective reminding test; WAIS, Wechler Adult Intelligence Scale; PASAT, Paced Auditory Serial Addition Test; NS, not significant.

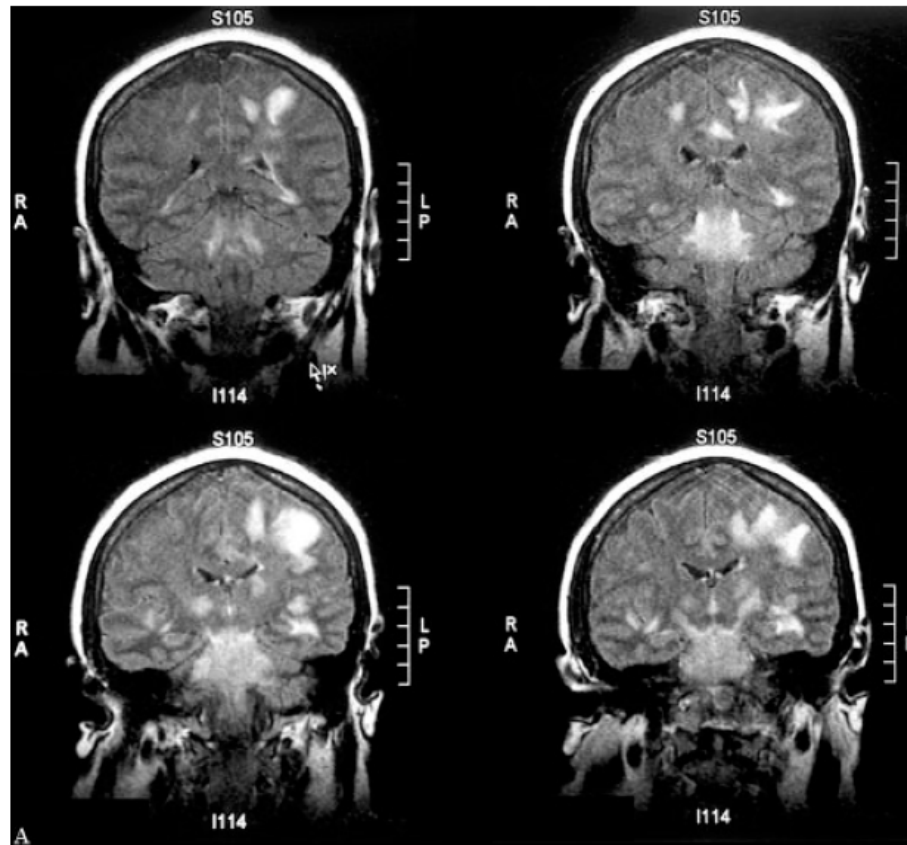
Lebrun et al, 2010

# EMAD

– Diagnostic difficile si :

- manquent : contexte infectieux, tableau médullaire
- évolution secondaire vers une SEP

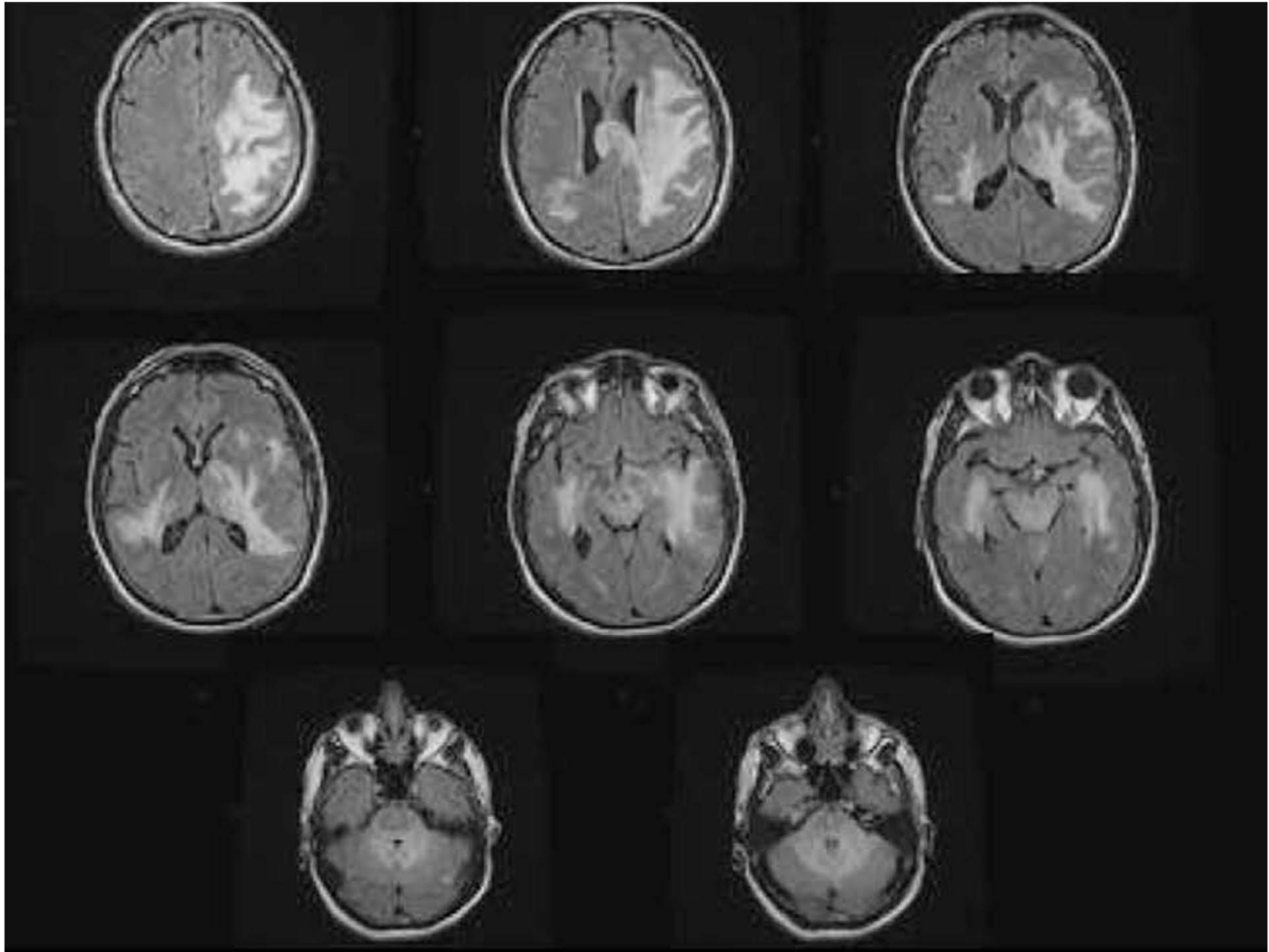
*(Schwarz, Neurology 2001 : 1257-60)*

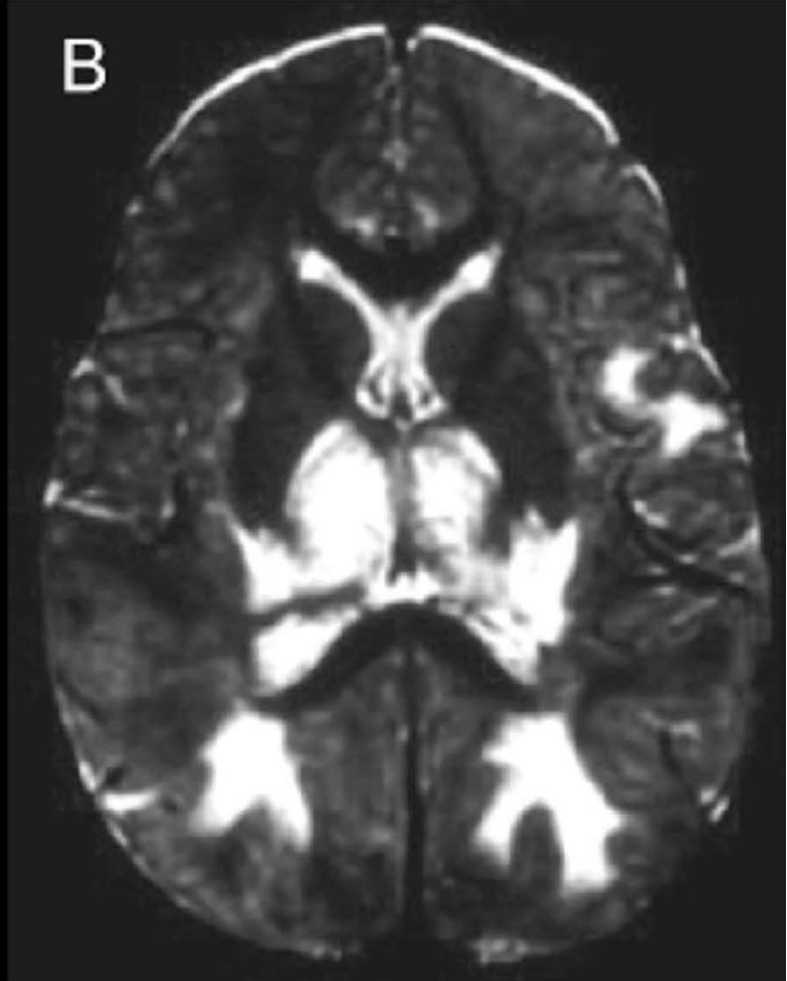
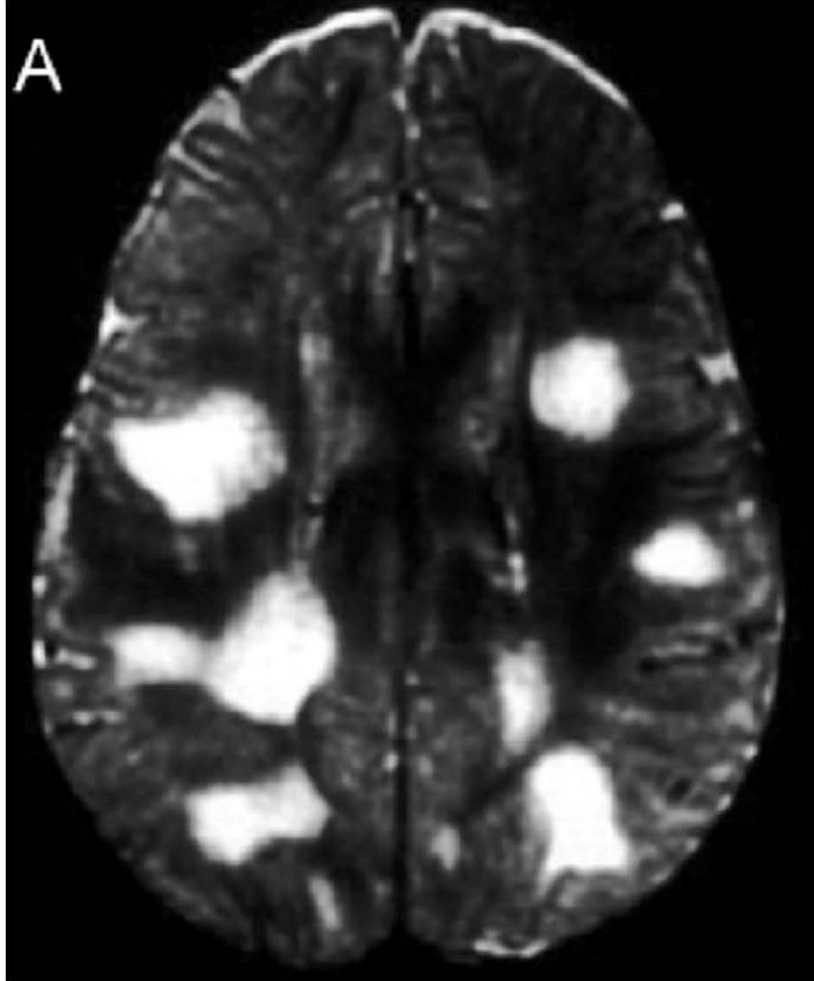


## 1er épisode démyélinisant de l'enfant : ADEM ? 1ère poussée de SEP ?

	<b>ADEM</b>	<b>SEP</b>
<b>Démographie</b>	< 10ans sexe ratio : 1	> 10ans F>M
<b>ATCD familiaux</b>	non	oui
<b>Infection récente</b>	Fréquente	Variable
<b>Encéphalopathie</b>	Requise	Rare
<b>Névrite optique</b>	Rare	Fréquente
<b>Myélite</b>	Variable	Peu fréquente
<b>Crises comitiales</b>	Variables	Rares
<b>Récupération clinique</b>	Longue ou/et incomplète	En 1 mois/sans séquelles
<b>IRM : lésions étendues mal définies avec atteinte des NGC</b>	Fréquente	Rare
<b>IRM : critères de Barkhof</b>	Rare	Oui (>10 ans)
<b>ou au moins une lésion bien définie,/perpendiculaire grand axe</b>	Rare	Fréquente
<b>IRM : nouvelles lésions &gt; 3 mois</b>	Variable	Rare
<b>LCR : pléiocytose</b>	Variable	Fréquente
<b>LCR : bandes oligoclonales</b>	Favorable	Favorable
<b>Réponse aux stéroïdes</b>		

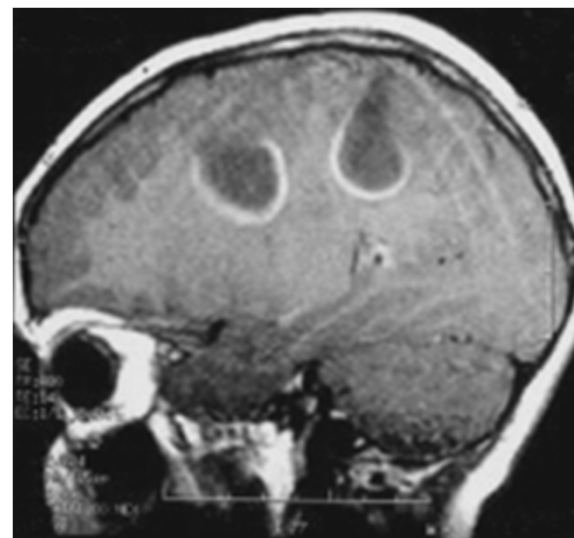








# IRM EMAD



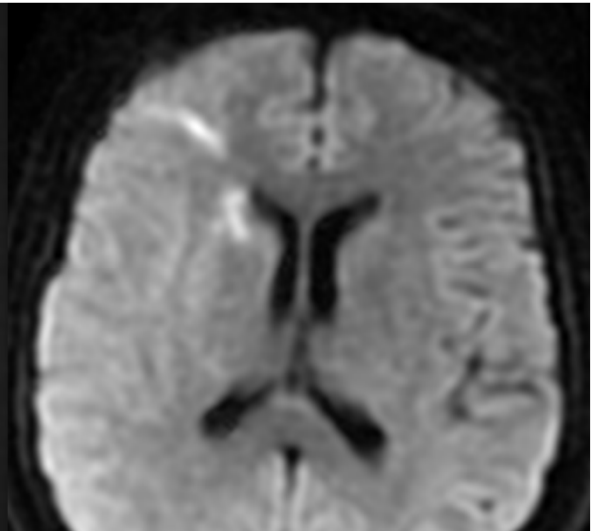
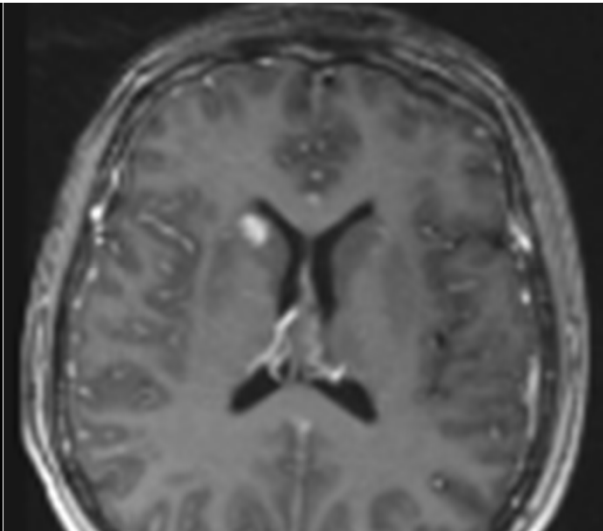
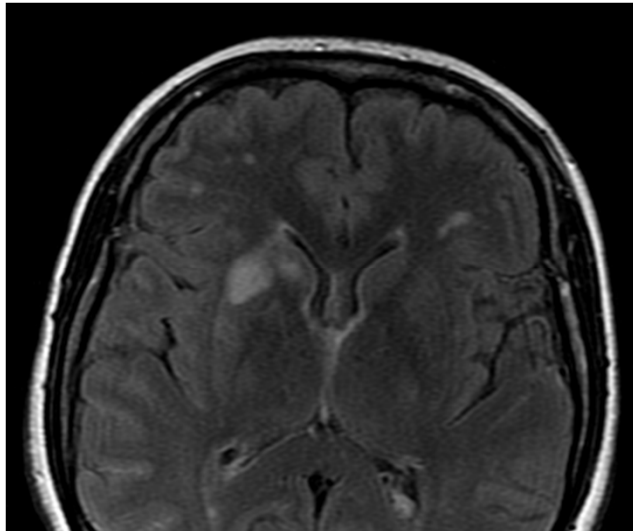
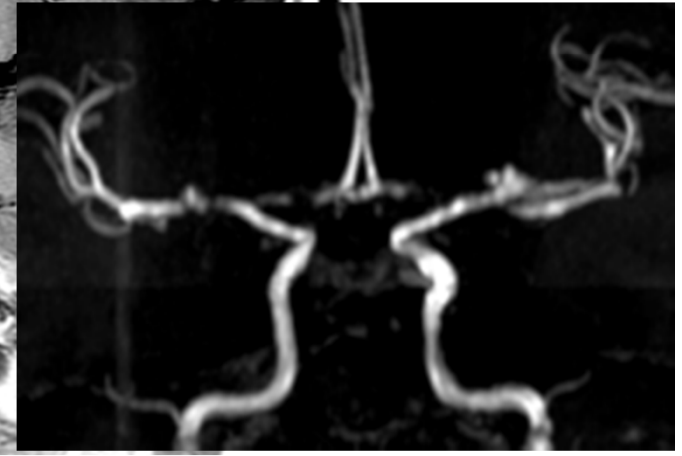
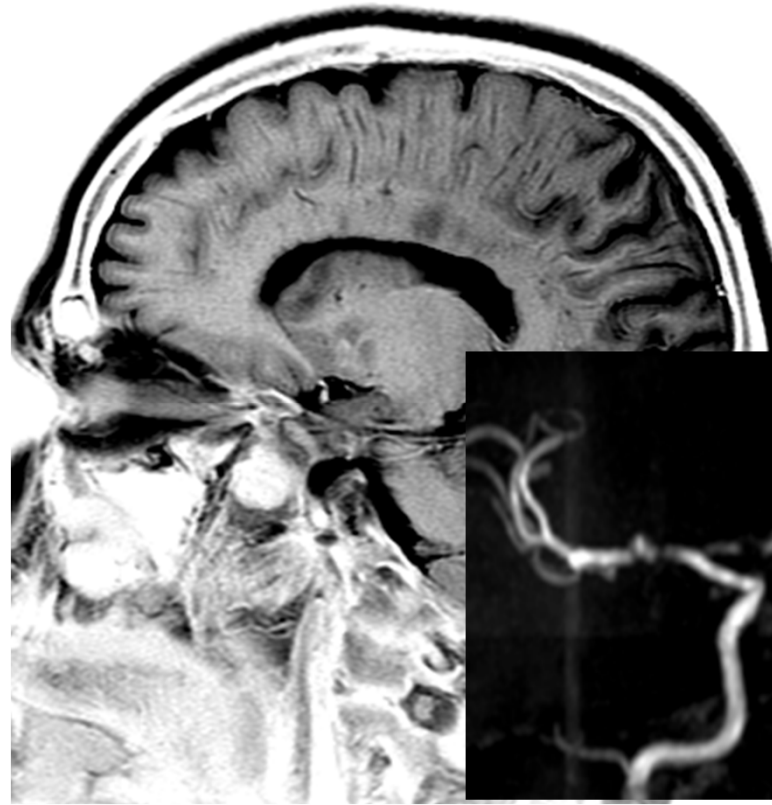
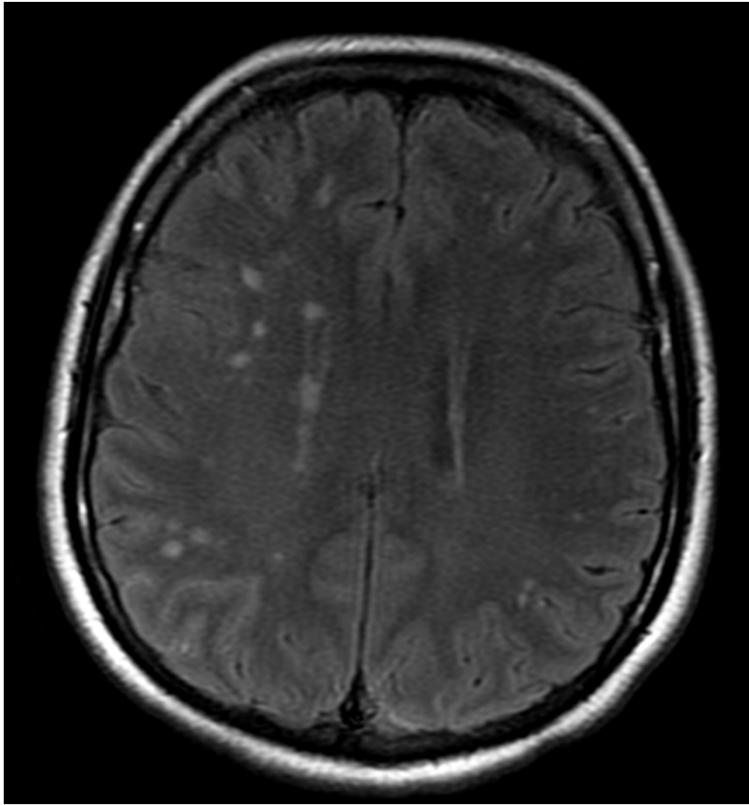
- Séquence T1 avec gadolinium :
  - Prise de contraste variable
    - Selon le stade de l'inflammation
    - 30 à 100% des lésions gado+
  - Prise de contraste complète, en cocarde, nodulaire...
- Lésions hyperintenses (en T2 et FLAIR), larges, multiples, plutôt asymétriques
  - SB encéphalique, sous corticale et profonde, cervelet, tronc cérébral,
  - atteinte fréquente du **thalamus** et des **noyaux gris** centraux (≠ SEP)
  - médullaire



	SEP n=16	EMAD n=33	
Signes cliniques atypiques	6 (37,5%)	24 (72,7%)	P=0,02
IRM Noyaux gris	1 (6,2%)	21 (63,6%)	P<0,001
BOC	14 (87,5%)	7 (21,2%)	P<0,001

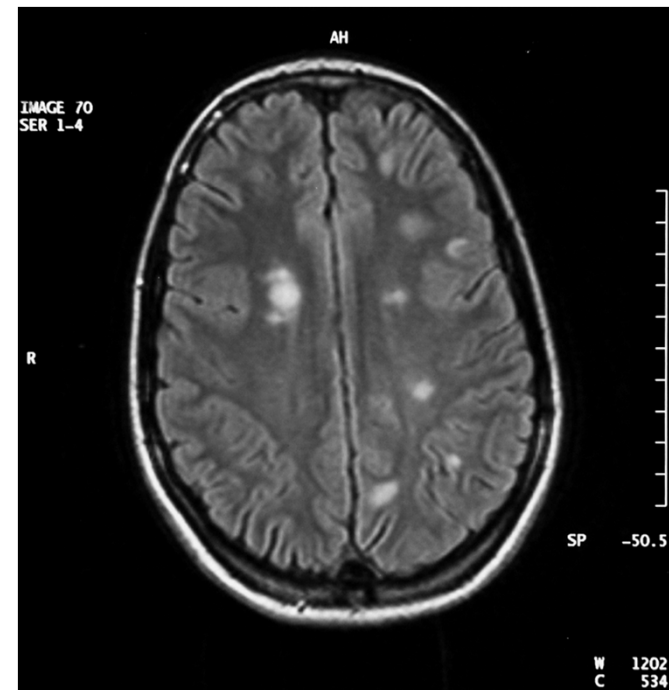
- Au moins 2 des 3 critères suivants = EMAD
    - Symptômes cliniques atypiques : épilepsie, tr. Vigilance (conscience), tr. cognitif, hémiplégie, tétraplégie, aphasie, NORB bilatérale
    - Absence de profil oligoclonal
    - Atteinte de la substance grise
  - 81,8% des EMAD (27/33) après 4 ans de suivi moyen
  - 100% des SEP ont 0 ou 1 des 3 critères
- = Classées dans la catégorie adéquate

Lupus



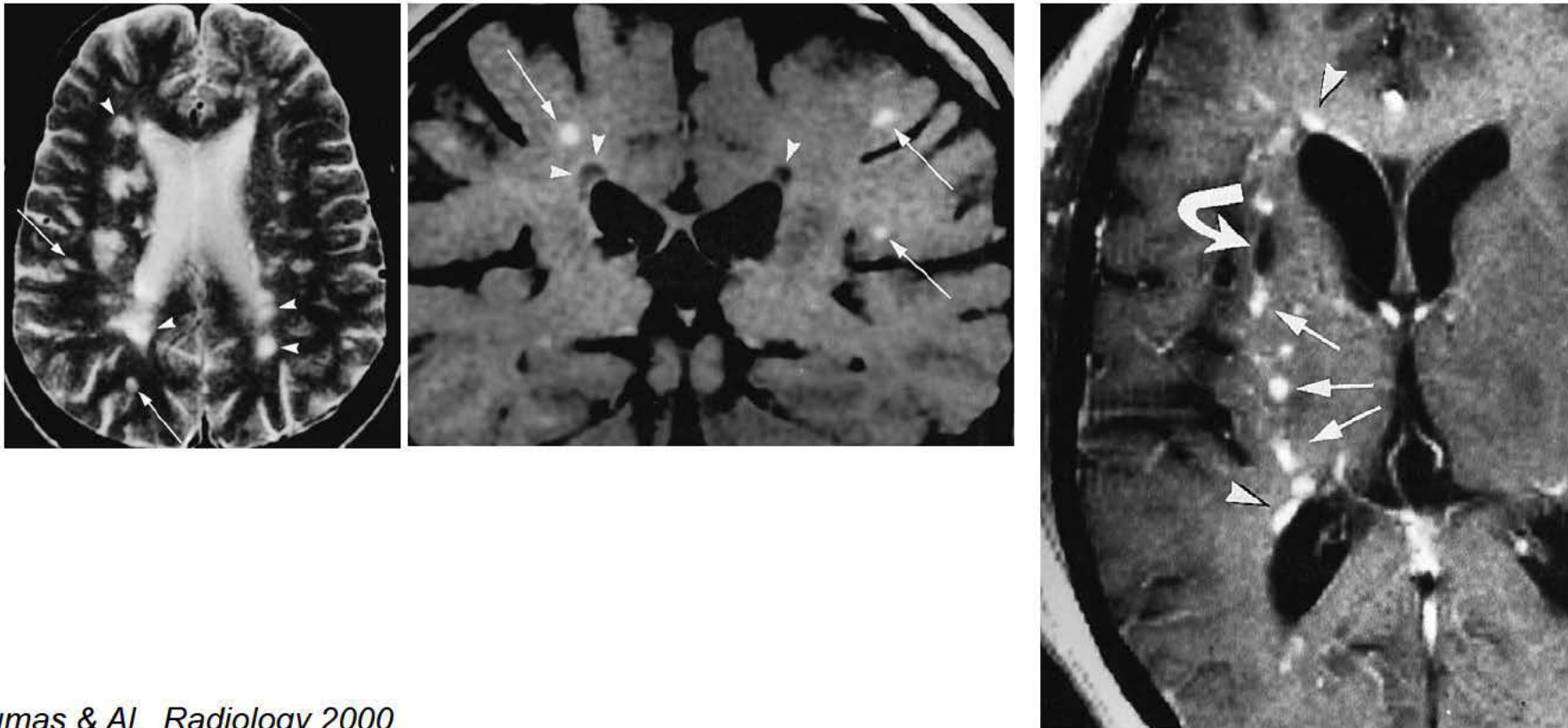
# Syndrome des antiphospholipides

- Séméiologie plutôt de type vasculaire :  
déficit moteur, HLH ;  
mouvements anormaux
- Anomalies IRM :  
répartition différente  
de SEP



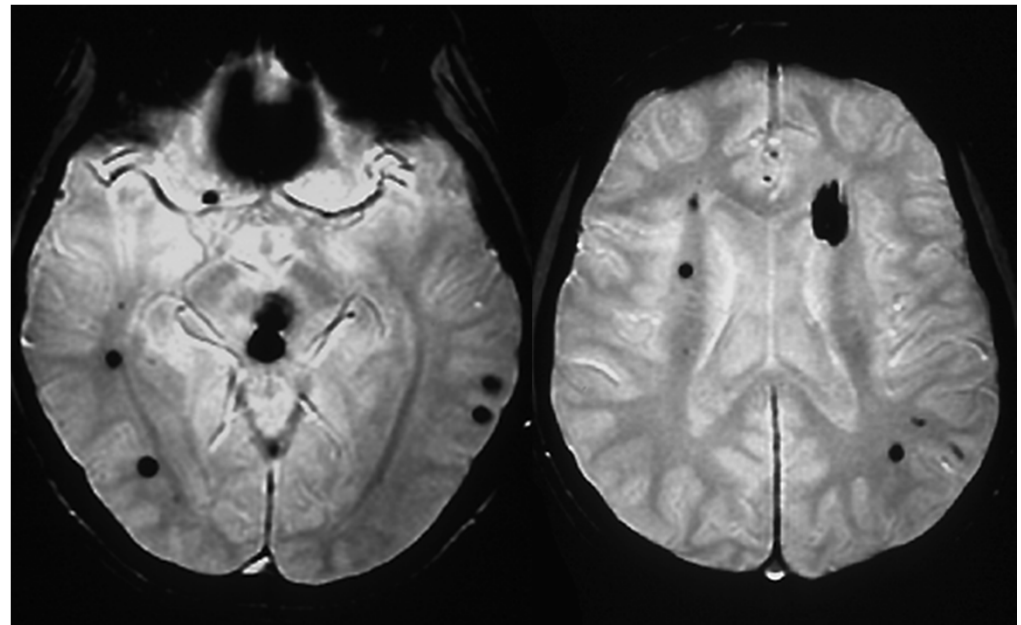
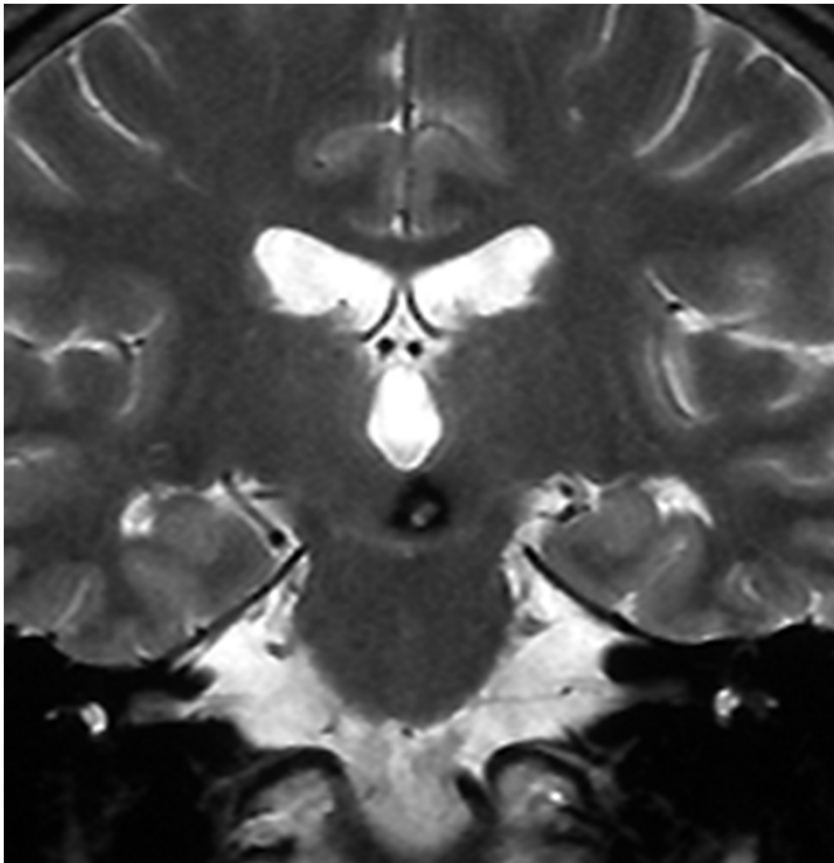
# Sarcoïdose

- Si atteinte optique et médullaire (Hoitsma *Lancet Neurol* 2004 ; 3 : 397-407)
- Critères diagnostiques (Baughman RP. *Lancet* 2003 ; 361 : 1111)

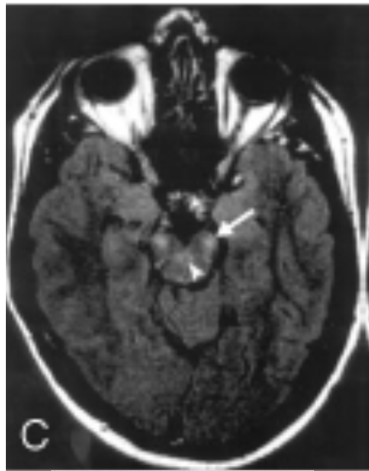
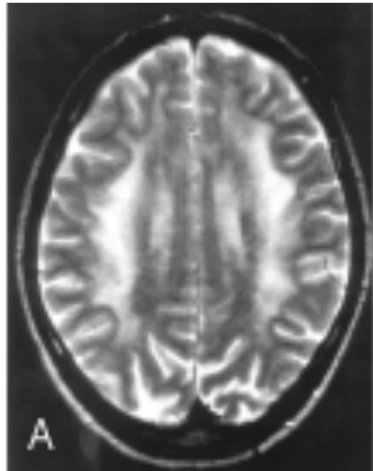
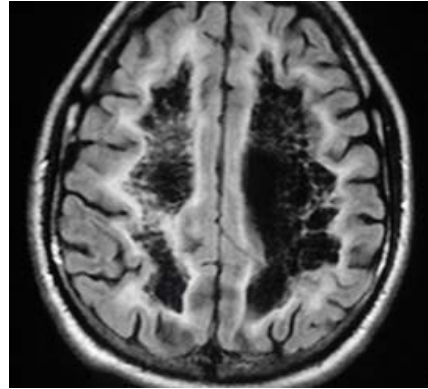
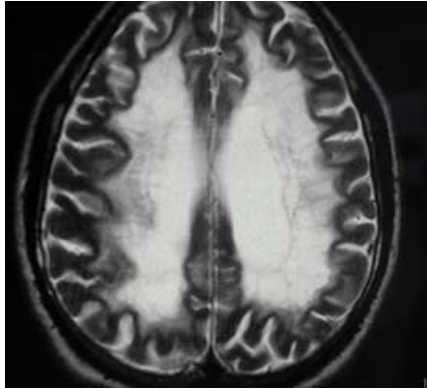




## Cavernomes multiples



....Et bien d'autres ...



Report

# CACH

Ann. J. Hum. Genet. 72:1544-1550, 2003

## Ovarian Failure Related to Eukaryotic Initiation Factor 2B Mutations

Anne Fogli,<sup>1</sup> Diana Rodriguez,<sup>2</sup> Eléonore Eymard-Pierre,<sup>1</sup> Françoise Bouhour,<sup>3</sup> Pierre Labauge,<sup>4</sup> Brandon F. Meaney,<sup>5</sup> Susan Zeesman,<sup>5,6</sup> Christine R. Kaneski,<sup>7</sup> Raphael Schiffmann,<sup>7</sup> and Odile Boespflug-Tanguy<sup>1</sup>

<sup>1</sup>INSERM Unité Mâle de Recherche 384, Faculté de Médecine, Clermont-Ferrand, France; <sup>2</sup>Service de Neuropédiatrie, Hôpital A. Troussier, INSERM U546, Paris; <sup>3</sup>Neurologie A, Hôpital Pierre Wertheimer, Lyon, France; <sup>4</sup>Département de Neurologie, Centre Hospitalier Universitaire, Nîmes, France; <sup>5</sup>Department of Pediatrics, McMaster University, and <sup>6</sup>Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences, Hamilton, Canada; and <sup>7</sup>Developmental and Metabolic Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda

## ARTICLES

nature  
genetics

# Laminopathie B1

## Lamin B1 duplications cause autosomal dominant leukodystrophy

Quasar S Padiath<sup>1</sup>, Kazumasa Saigoh<sup>1,8</sup>, Raphael Schiffmann<sup>2</sup>, Hideaki Asahara<sup>3</sup>, Takeshi Yamada<sup>4</sup>, Anulf Koeppen<sup>5</sup>, Kirk Hogan<sup>6</sup>, Louis J Ptáček<sup>1,7</sup> & Ying-Hui Fu<sup>1</sup>

Adult-onset autosomal dominant leukodystrophy (ADLD) is a slowly progressive neurological disorder characterized by symmetrical widespread myelin loss in the central nervous system, with a phenotype similar to chronic progressive multiple sclerosis. In this study, we identify a genomic duplication that causes ADLD. Affected individuals carry an extra copy of the gene for the nuclear laminar protein lamin B1, resulting in increased gene dosage in brain tissue from individuals with ADLD. Increased expression of lamin B1 in *Drosophila melanogaster* resulted in a degenerative phenotype. In addition, an abnormal nuclear morphology was apparent when cultured cells overexpressed this protein. This is the first human disease attributable to mutations in the gene encoding lamin B1. Antibodies to lamin B are found in individuals with autoimmune diseases, and it is also an antigen recognized by a monoclonal antibody raised against plaques from brains of individuals with multiple sclerosis. This raises the possibility that lamin B may be a link to the autoimmune attack that occurs in multiple sclerosis.

ing Group <http://www.nature.com/naturegenetics>

nature  
genetics

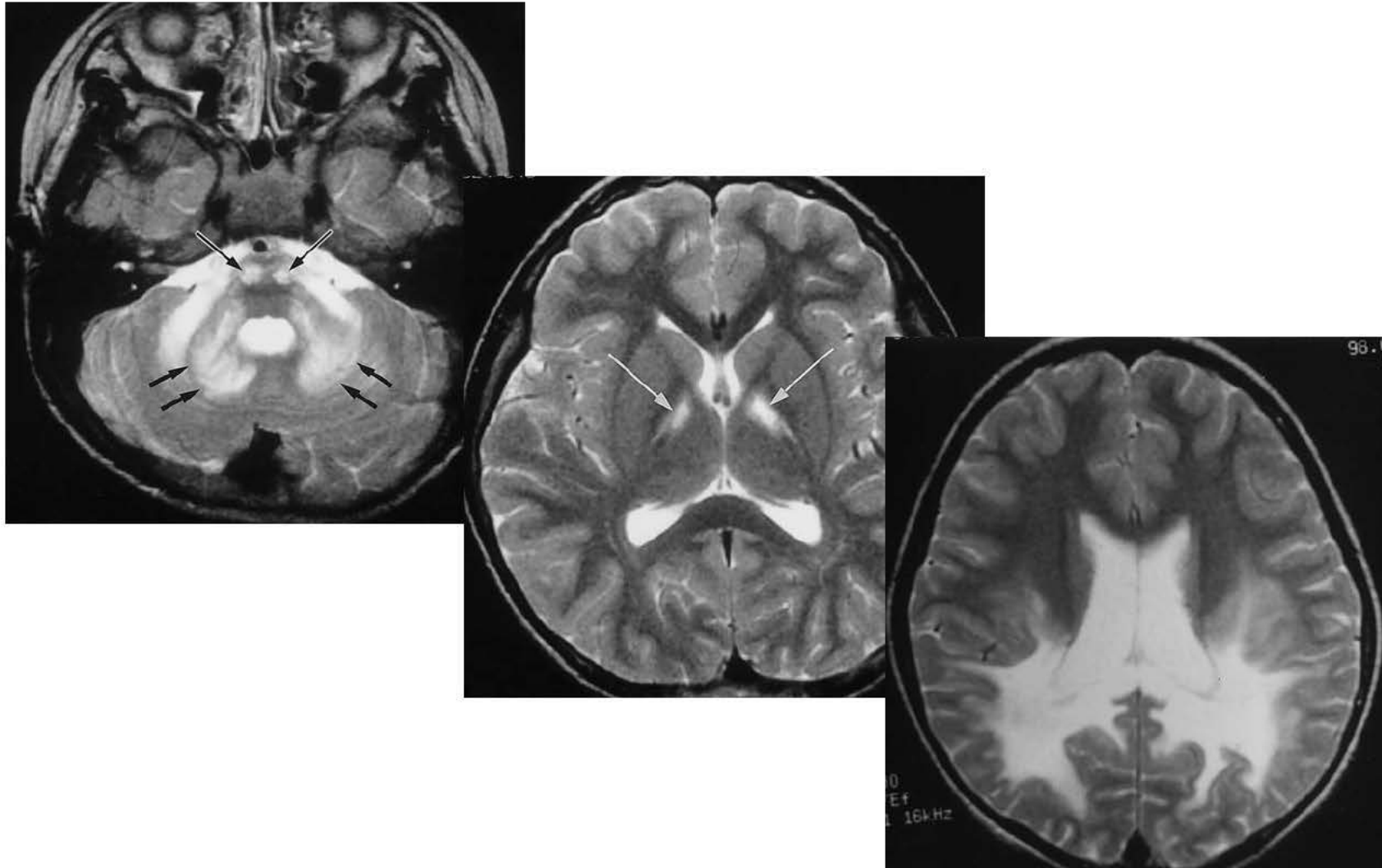
# LSBL

## Mitochondrial aspartyl-tRNA synthetase deficiency causes leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation

Gert C Schepel<sup>1</sup>, Thom van der Kloek<sup>1</sup>, Rob J van Andel<sup>1</sup>, Carola G M van Berkel<sup>1</sup>, Marie Sissler<sup>2</sup>, Joël Smet<sup>3</sup>, Tatjana I Muravina<sup>4</sup>, Sergey V Serkov<sup>5</sup>, Graziella Uziel<sup>6</sup>, Marianna Bugian<sup>6</sup>, Raphael Schiffmann<sup>7</sup>, Ingeborg Krägeloh-Mann<sup>8</sup>, Jan A M Smeitink<sup>9</sup>, Catherine Florentz<sup>2</sup>, Rudy Van Coster<sup>3</sup>, Jan C Pronk<sup>10</sup> & Marjo S van der Knaap<sup>1</sup>

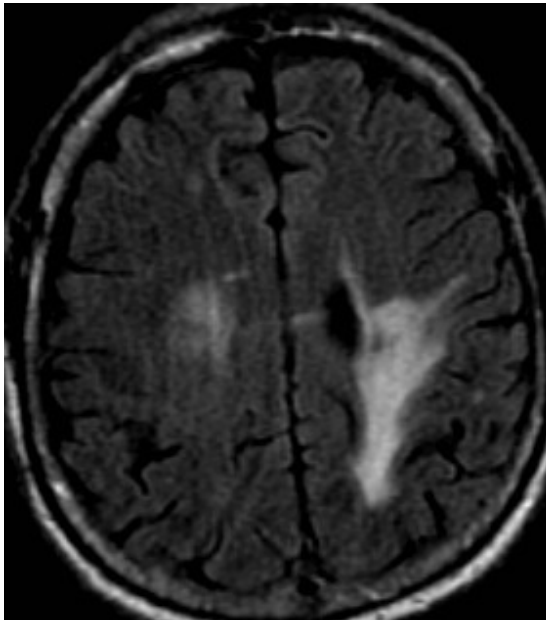
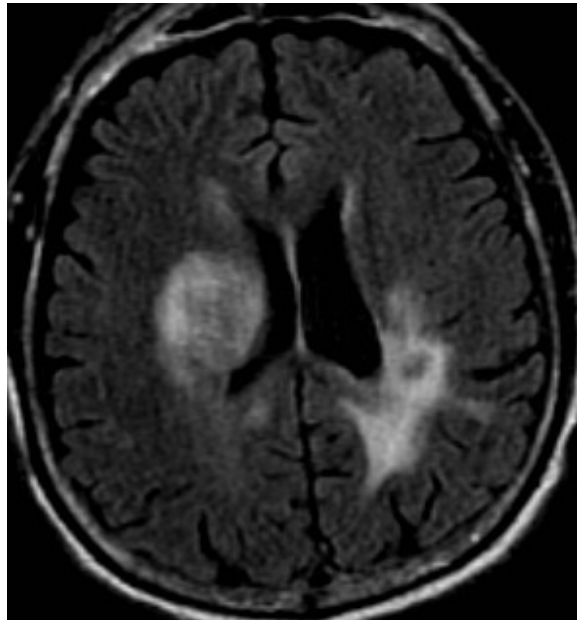
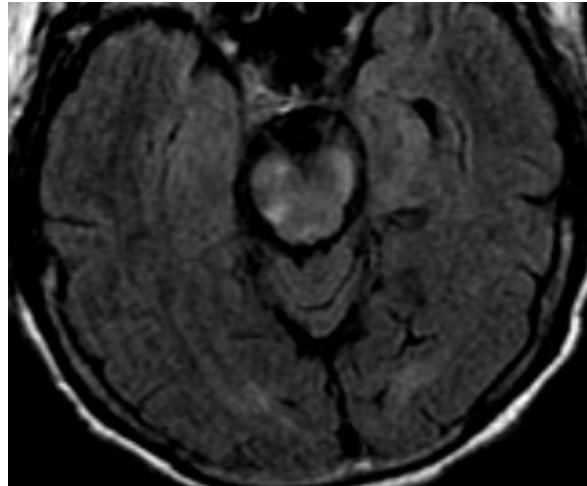
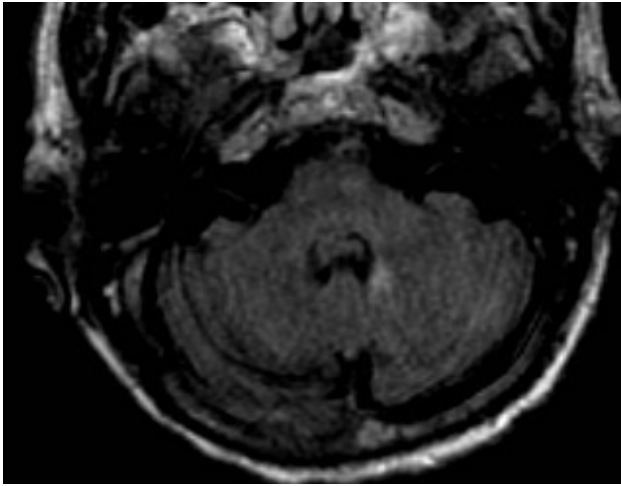
<http://www.nature.com/naturegenetics>

# Adrénoleucodystrophie



*Cheon, J.-E. et al. Radiographics 2002;22:461-476*

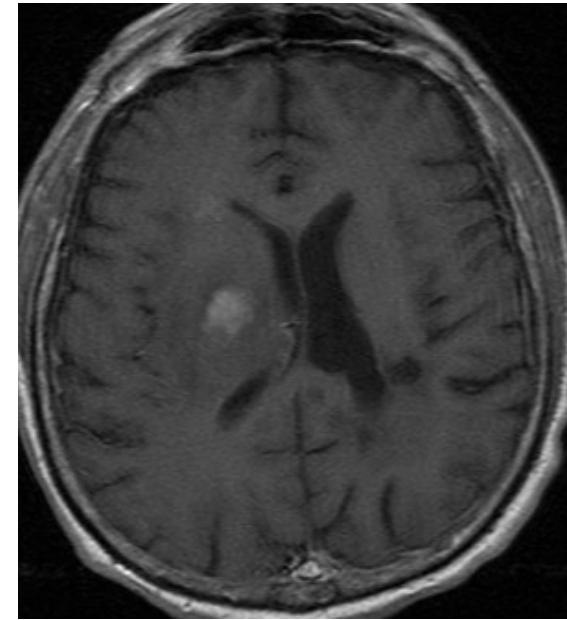
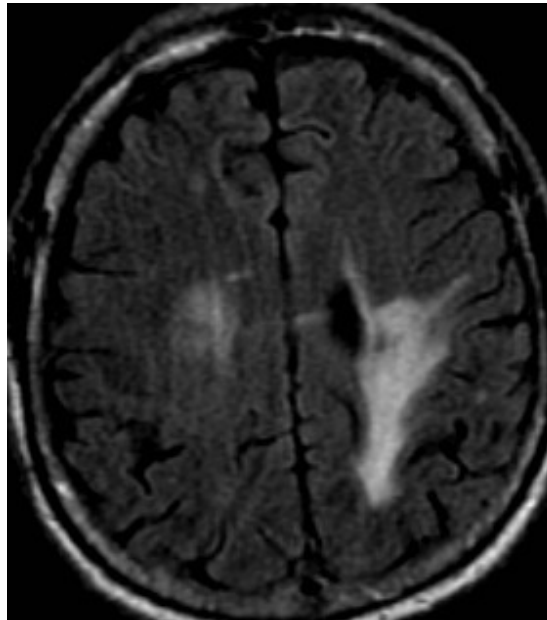
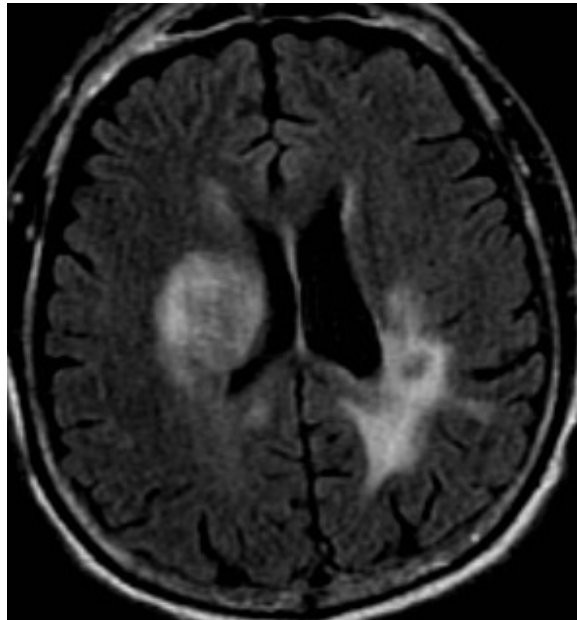
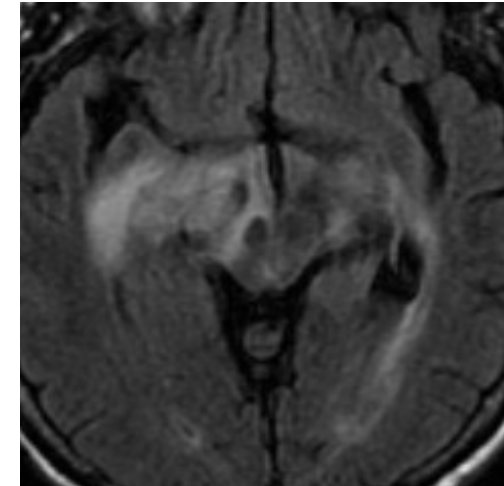
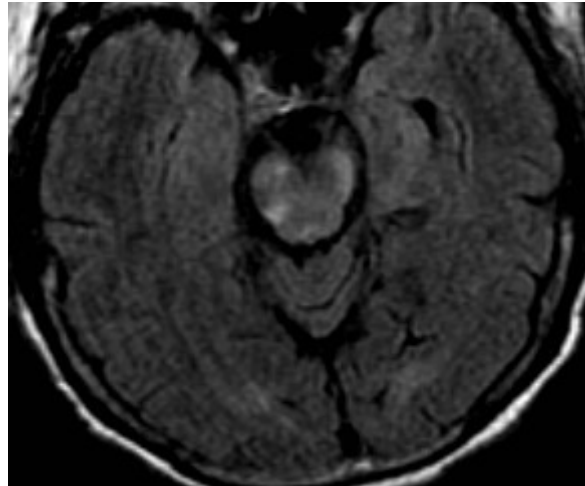
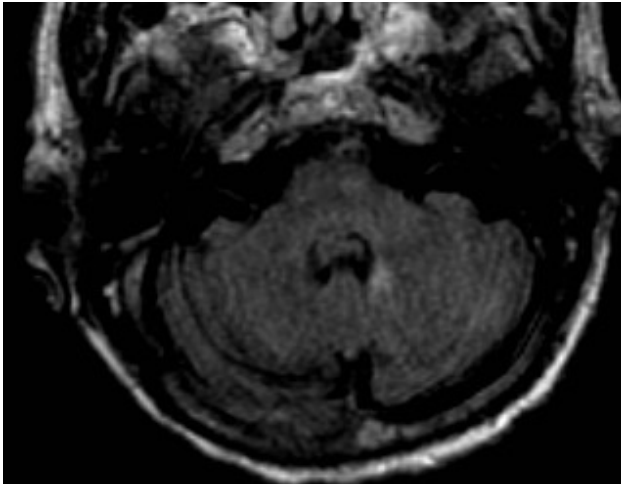
Homme, 60 ans  
Déficit moteur G, BAV

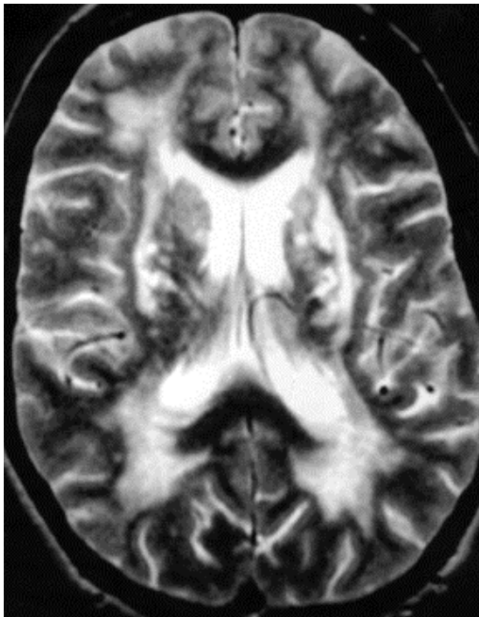




Homme, 60 ans  
Déficit moteur G, BAV

Lymphome



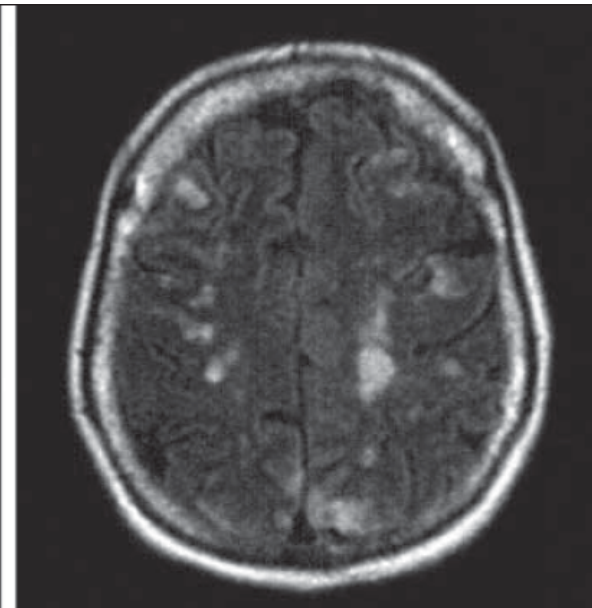
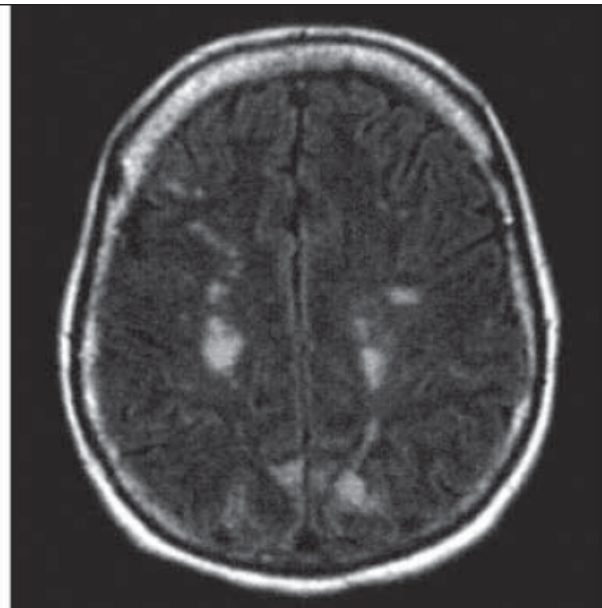
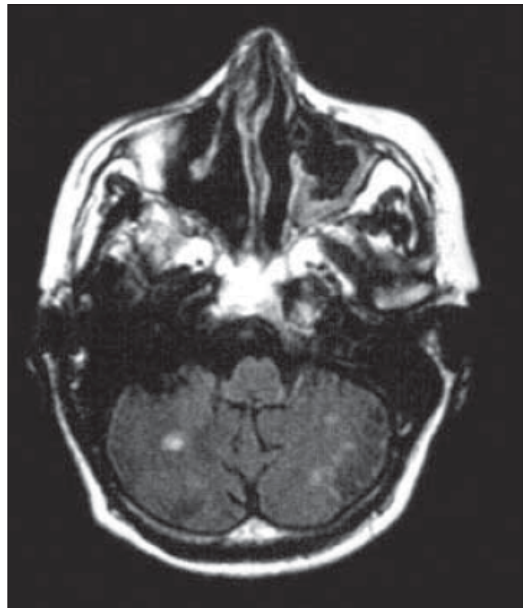
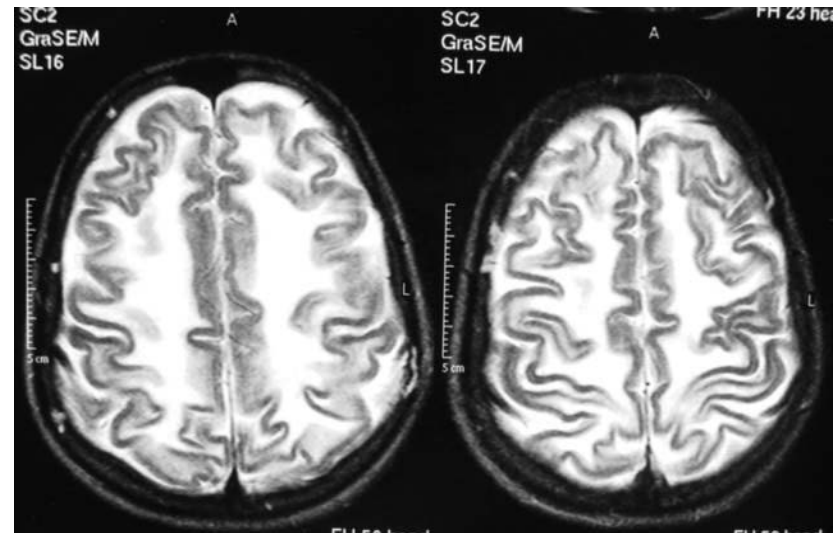


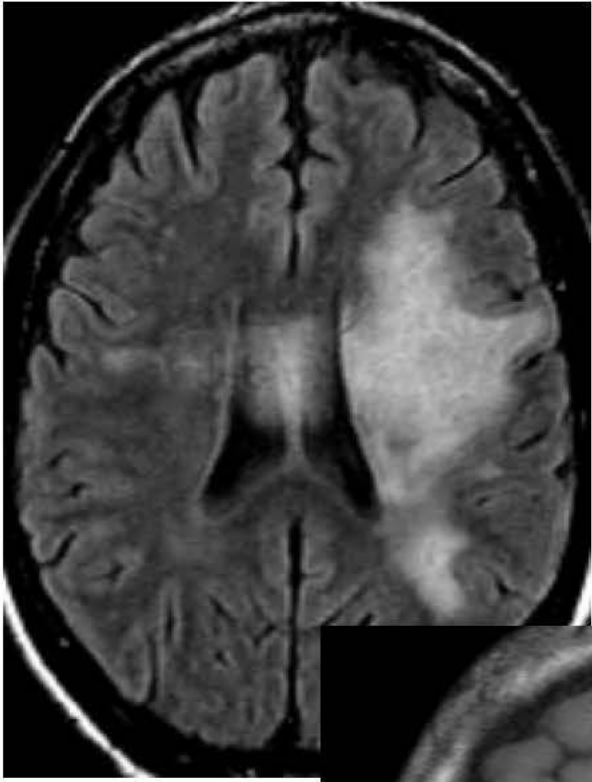
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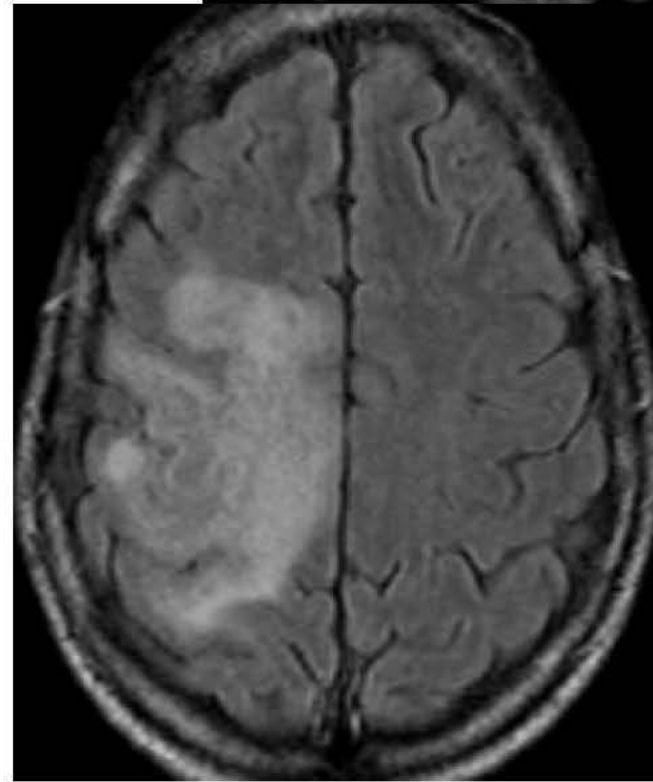
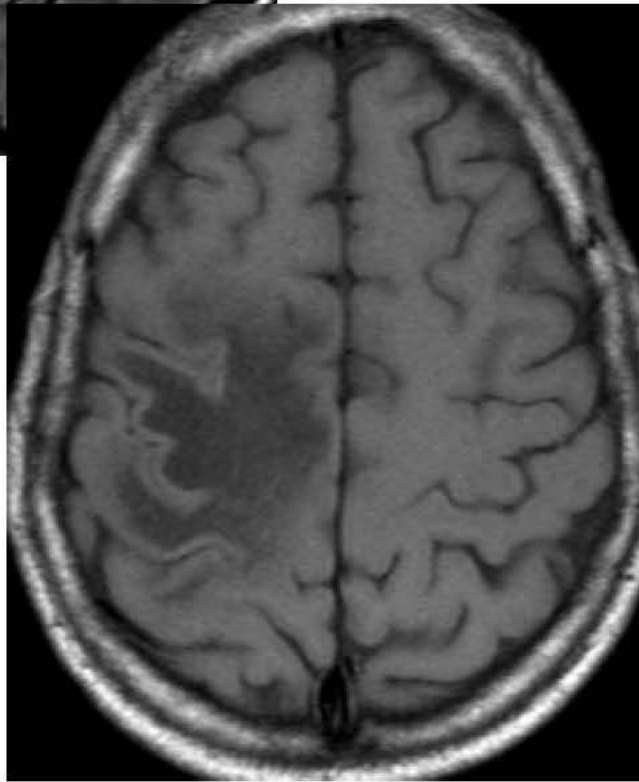
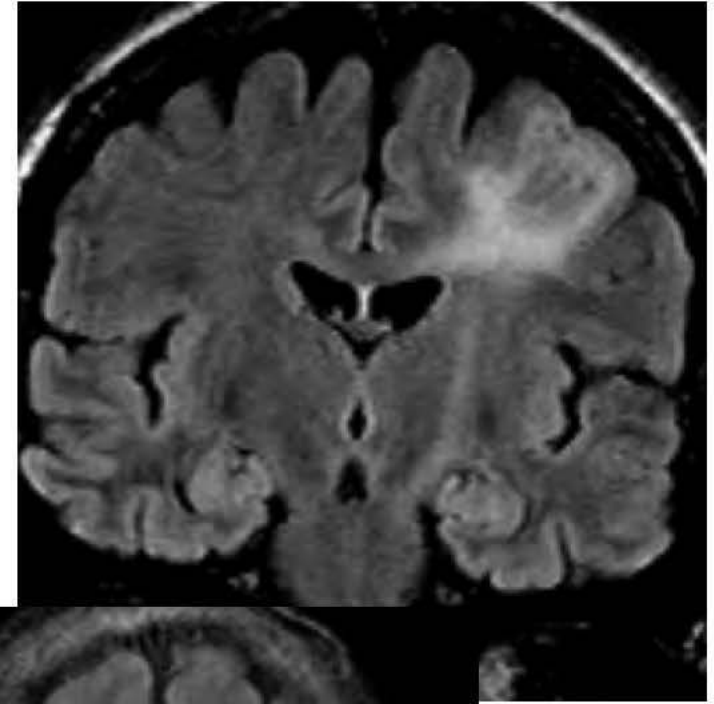
MELAS

CASH



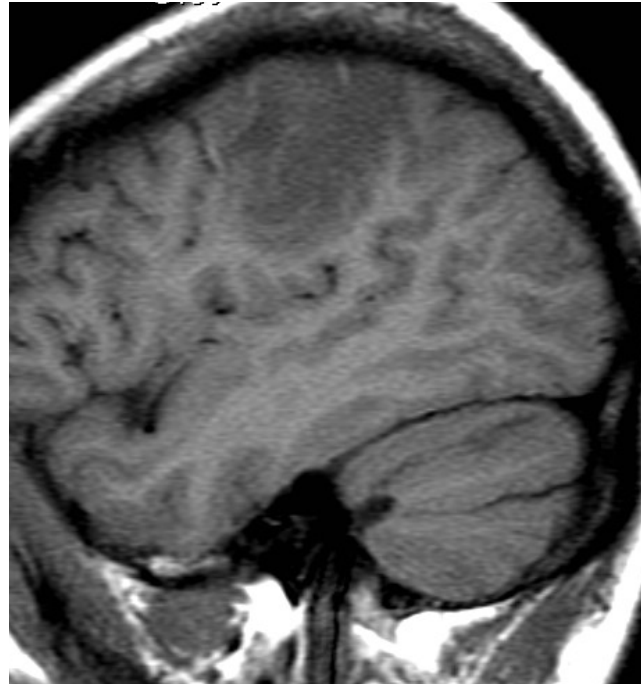
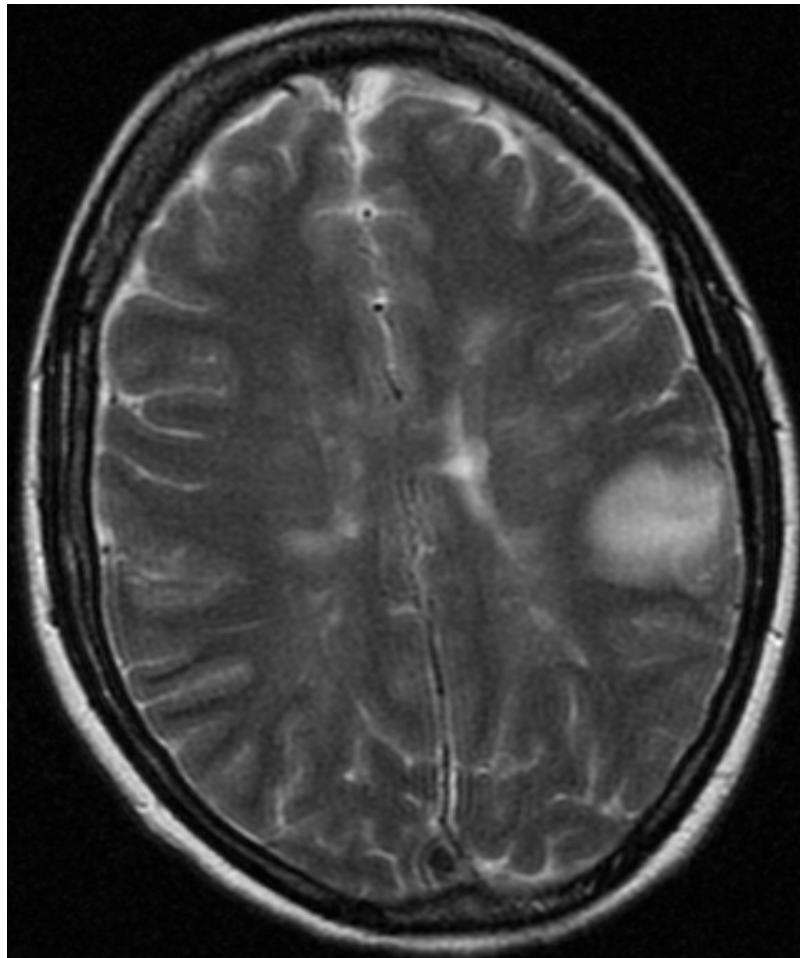


**LEMP**



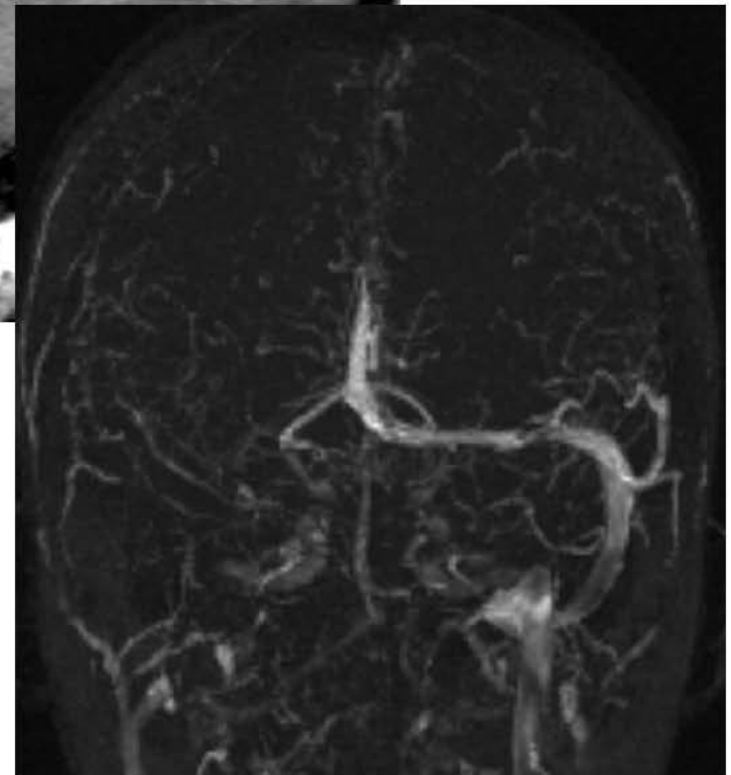
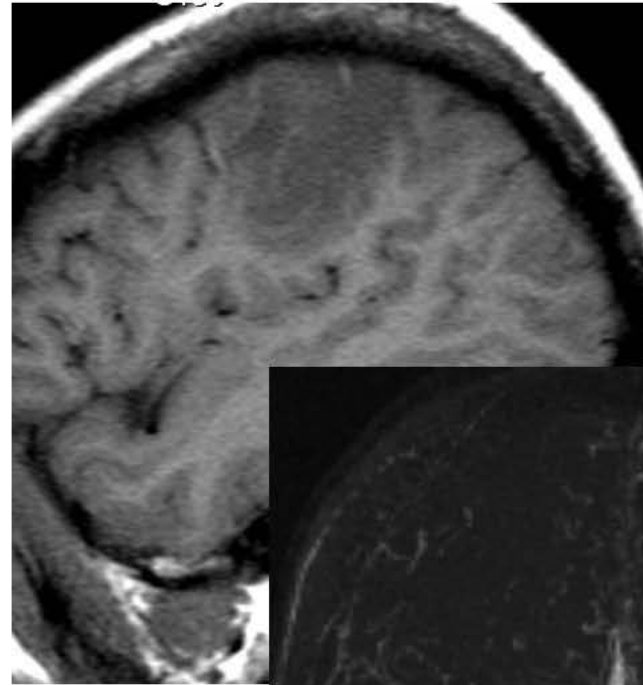
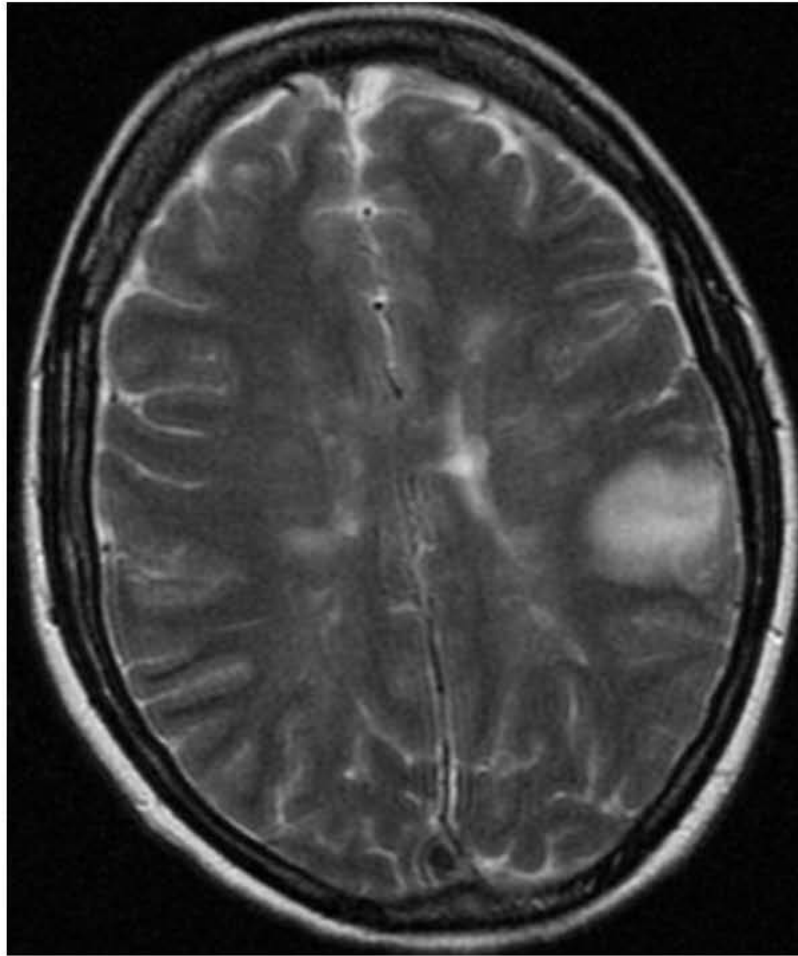


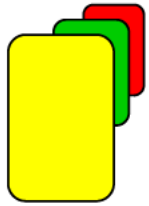
Femme, 36 ans nouvelle poussée de SEP ?





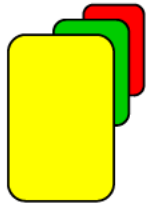
Femme, 36 ans : SEP + thrombophlébite





# Les cartons jaunes cliniques

- Age de début
  - < 10 ans et > 60 ans (5 % des SEP)
- Signes inauguraux inhabituels :
  - installation subite en quelques minutes
  - séméiologie corticale : crise d'épilepsie, aphasie, apraxie
- Evolution
  - progressive et continue (sauf > 50 ans)
  - rigidité, dystonie



## « Anomalies » devant faire reconsidérer le diagnostic après plusieurs années d'évolution de la SEP

- Absence d'anomalies ophtalmologiques (visuelles/oculomotrices)
- Absence de rémission clinique (en particulier chez le sujet jeune)
- Existence d'anomalies localisées (tronc cérébral, jonction crânio-cervicale, moelle épinière)
- Absence d'atteinte sensitive
- Absence de troubles urinaires
- Absence d'anomalies du liquide céphalorachidien
- Absence d'anomalies sur l'IRM encéphalique

# CRITERES de dissémination spatiale (Barkhof/Tintoré) version Polman 2005

## ❖ 3 des 4 critères :

– ≥ 1 lésion Gd+

• ou ≥ 9 lésions T2 (si Gd-)

– ≥ 1 lésion sous-tentorielle

 Haut risque

– ≥ 1 juxta corticale

– ≥ 3 lésions périventriculaires

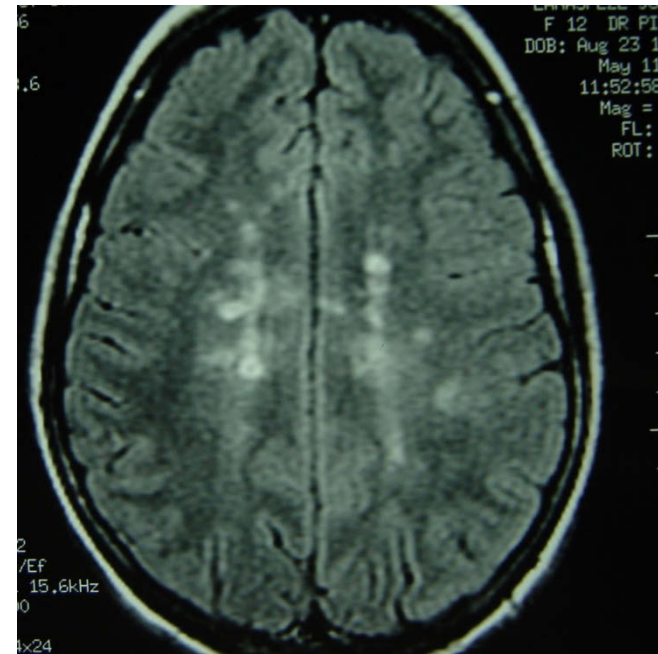
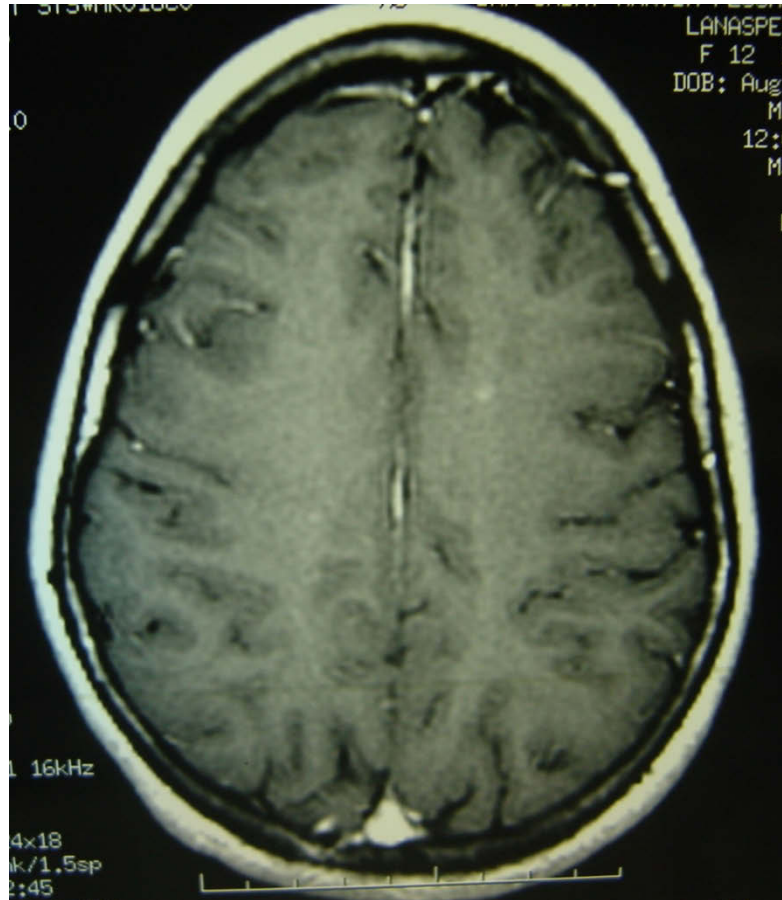
(1 lésion moelle peut remplacer 1 lésion cérébrale)

## ❖ 2 lésions + LCR

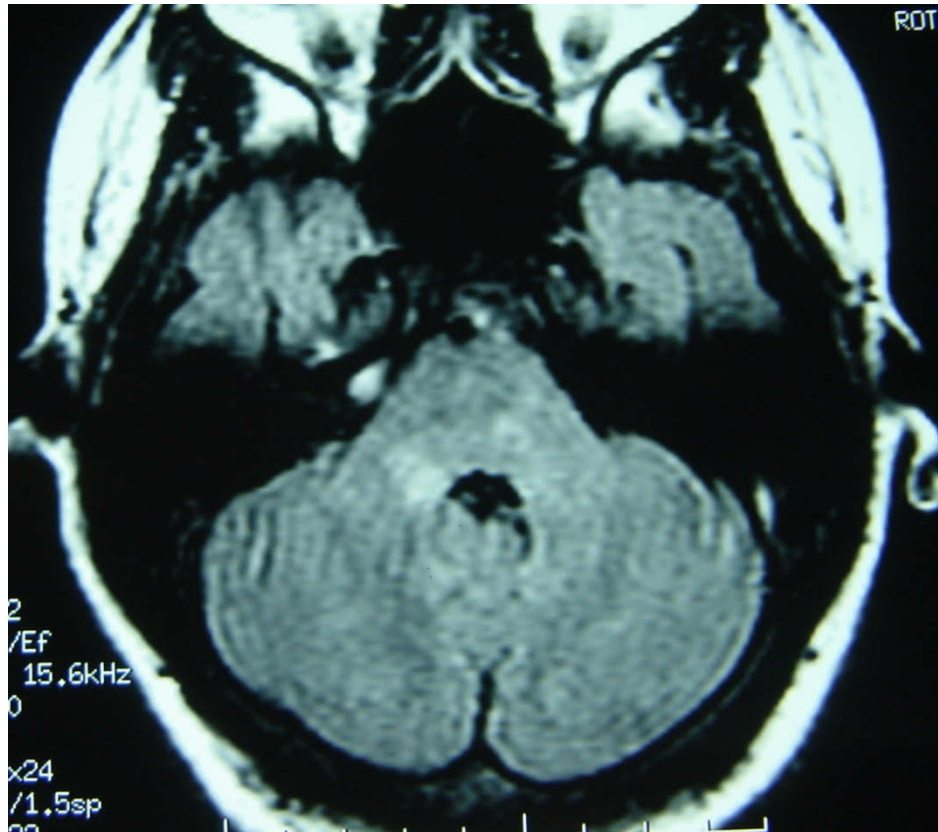
*LESIONS > 3mm*



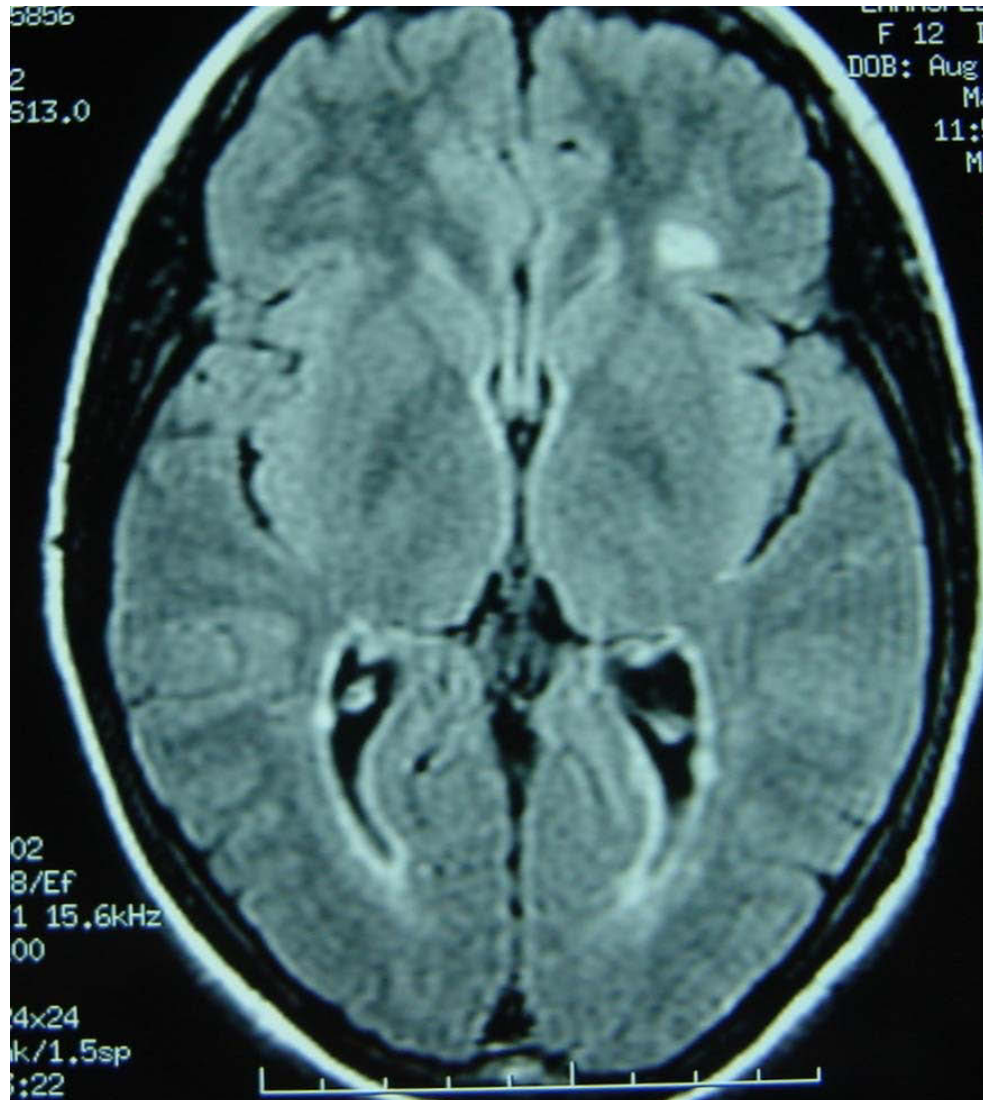
Critère 1: prise de contraste ou 9 lésions (>3mm; tout le SNC)



## Critère 2: 1 lésion fosse postérieure ou médullaire



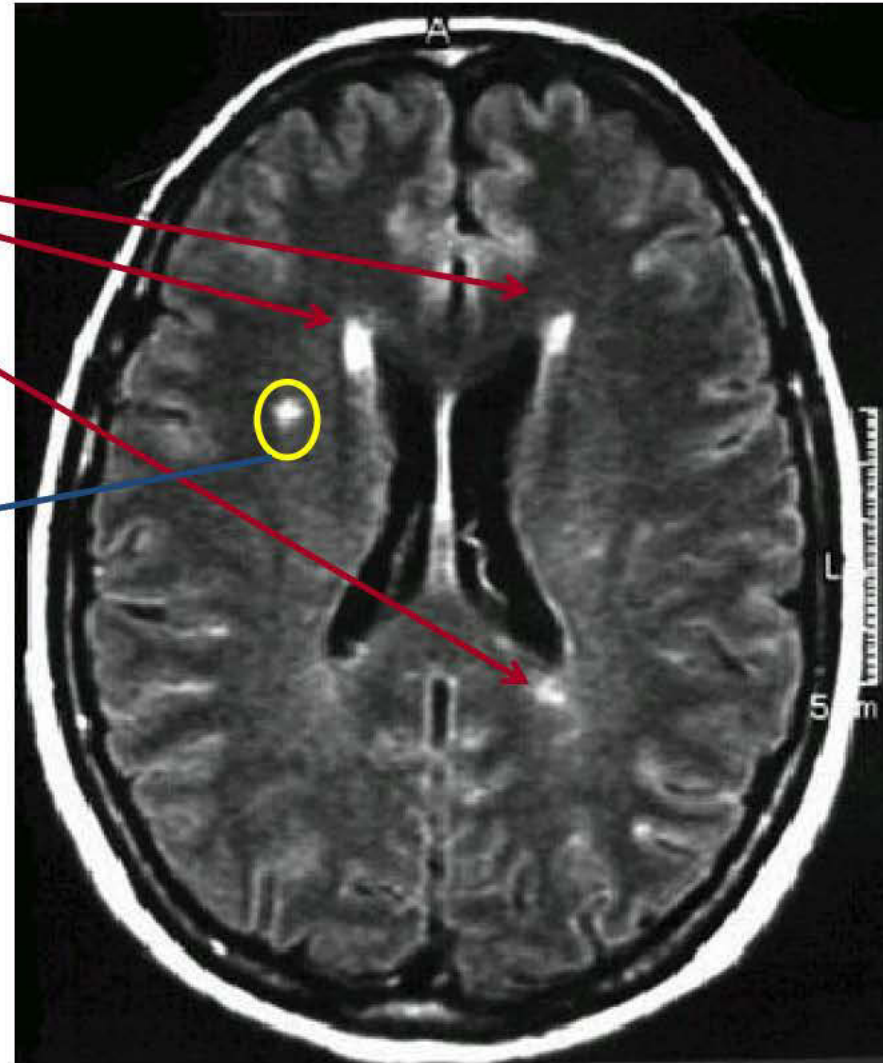
## Critère 3: 1 lésion juxta-corticale





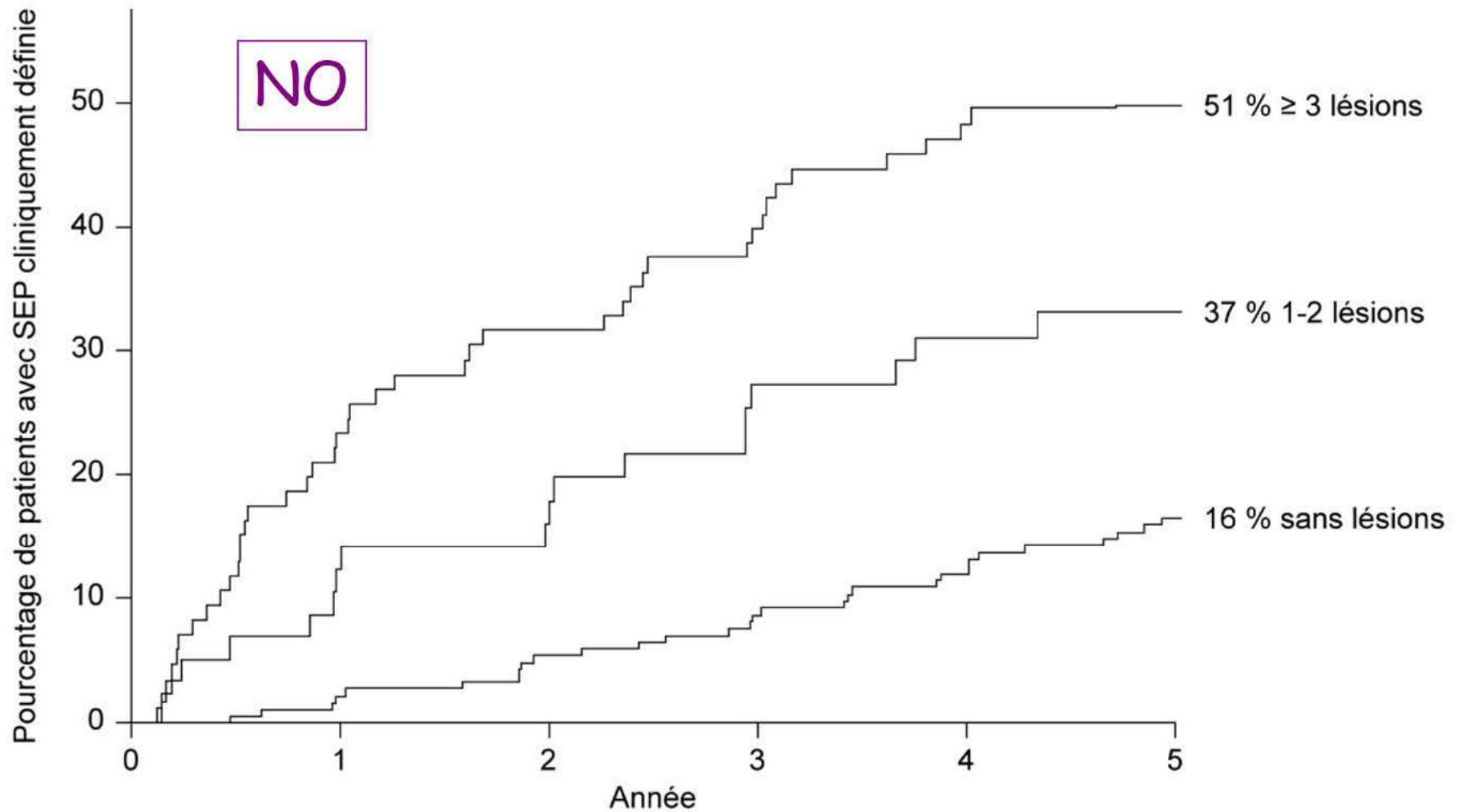
## Critère 4 : 3 lésions périventriculaires

paraventriculaire





# IRM et risque de SEP (1)



ONTT 1997

## IRM et risque de SEP (2)

Études	IRM	SEP-CD 5 ans	SEP-CD 10 ans	SEP-CD 14 ans
<b>ONTT</b> 457 NO initialement	IRM- (n = 191) IRM+ (n = 160)	30 % 16 % 51 %	38 % 22 % 56 %	
<b>Brex</b> 110 SMS initialement, 71 à 14 ans, dont la moitié de NO	IRM- (n = 21) IRM+ (n = 50)	43 % 3 % 65 %	59 % 11 % 83 %	68 % 19 % 88 %

Évolution vers la SEP après une NO

SEP-CD : SEP cliniquement définie selon les critères de Poser et al.

SMS : syndrome monosymptomatique

IRM+ : 1 lésion ou plus évocatrice de SEP

ONTT 1997, 2003 ; Brex et al. 2002

# Exploration médullaire

- Activité lésionnelle :
  - seulement 10% / cerveau
  - traduction clinique +++
- Pour dissémination spatiale
  - Une lésion médullaire est équivalente et peut se substituer à une lésion infra-tentorielle (pas à une lésion sous-corticale ou périventriculaire)
  - Une lésion médullaire Gd+ compte double : pour lésion Gd+ et pour lésion infra-tentorielle
  - Les lésions médullaires sont aussi prises en compte dans le critère « 9 lésions »
- La répétition des IRM médullaires est peu efficace pour la dissémination temporelle

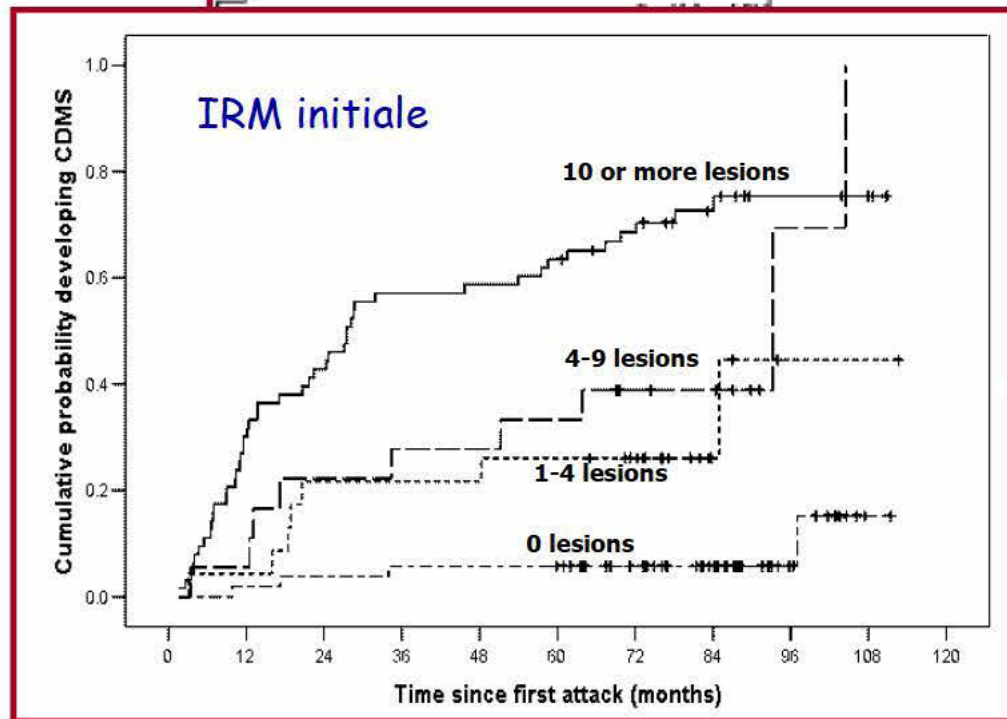
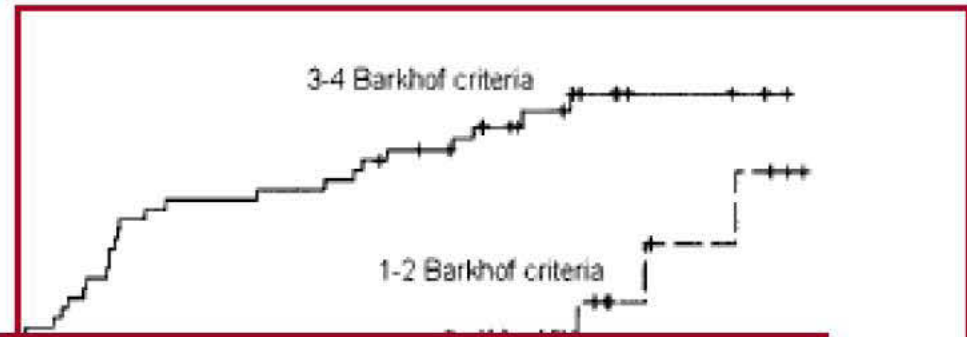


# Critères de Barkhof - Tintore

Plus le nombre de critères de Barkhof positifs est élevé, plus le risque de SEP est élevé

Deux critères : risque augmente déjà

Mais aussi le nombre



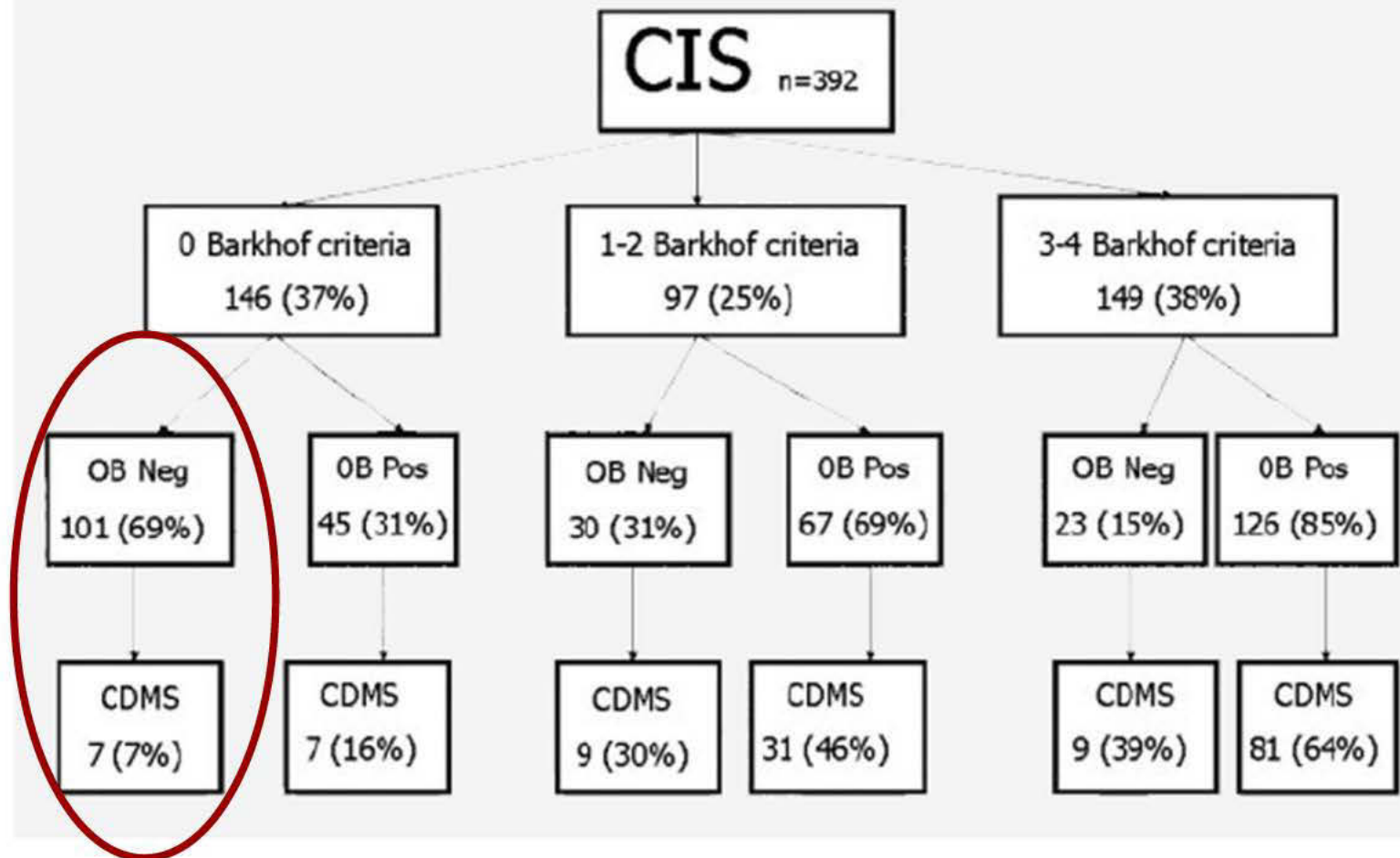
175 CIS, suivi 5 ans

Tintore et al., 2006



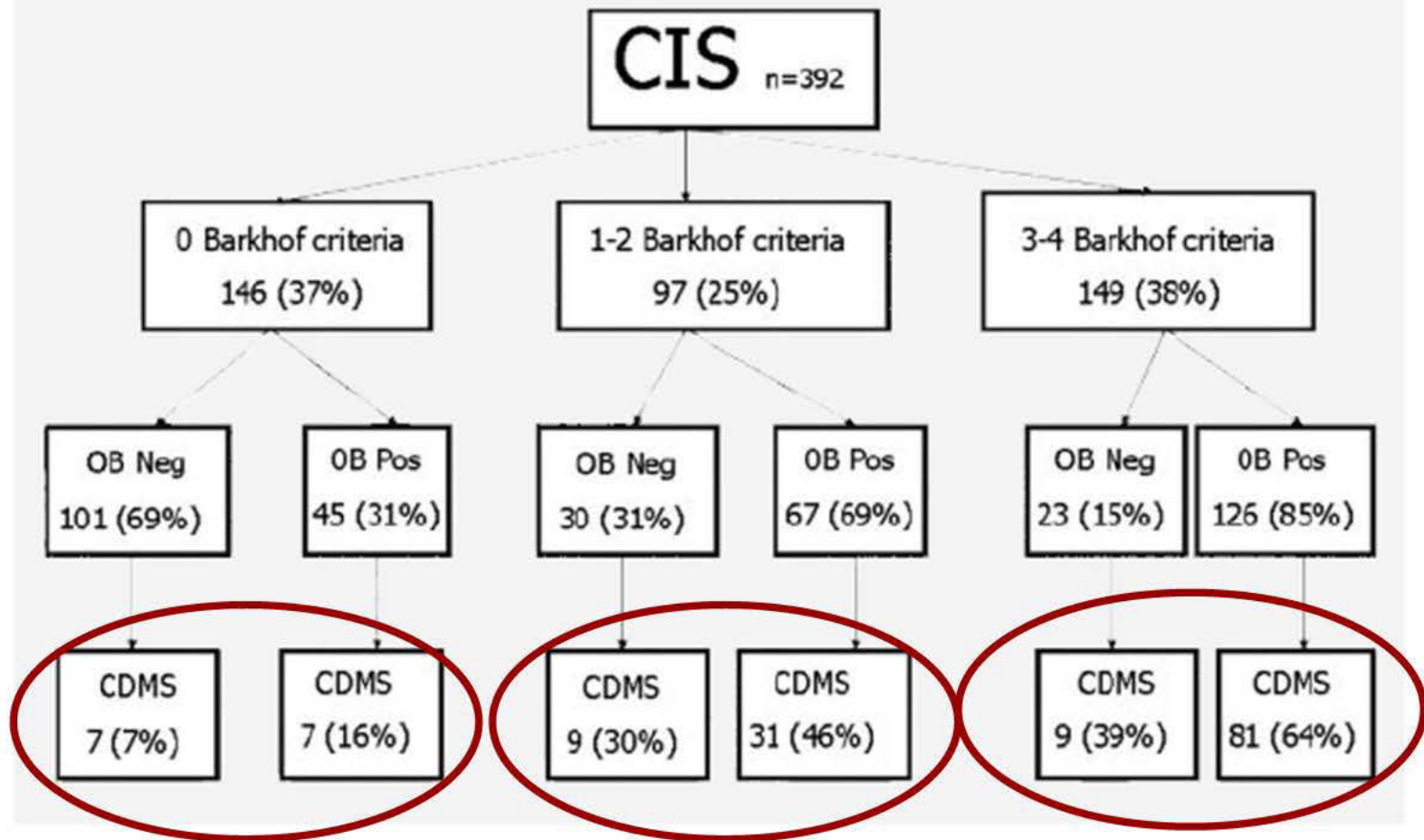
M. Tintoré, MD  
A. Rovira, MD  
J. Río, MD  
C. Tur, MD  
R. Pelayo, MD  
C. Nos, MD  
N. Téllez, MD  
H. Perkal  
M. Comabella, MD  
J. Sastre-Garriga, MD  
X. Montalban, MD

# Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis?



M. Tintoré, MD  
A. Rovira, MD  
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X. Montalban, MD

# Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis?



# Gout et al., 2011

## Prognostic value of cerebrospinal fluid analysis at the time of a first demyelinating event

0(00) 1–9

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DOI: 10.1177/1352458510385506

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Olivier Gout<sup>1</sup>, Annie Bouchareine<sup>1</sup>, Antoine Moulignier<sup>1</sup>,

and more than 4 WBC/mm<sup>3</sup> in CSF (HR: 1.44 [95% CI 1.03–2.02]) were independently associated with CDMS.

### Abstract

**Background and Objective:** This study aimed to assess the value of cerebrospinal fluid (CSF) findings for predicting conversion to clinically definite multiple sclerosis (CDMS).

**Methods:** From a database of 447 patients with a first demyelinating event, the records of 208 patients less than 51 years old who had baseline magnetic resonance imaging (MRI) and CSF examinations and a follow-up of at least 1 year were included. A multivariable Cox model was used to assess the short-term risk of CDMS according to baseline CSF findings after adjustment for prognostic factors (including brain MRI) and to provide a simple classification for predicting CDMS.

**Results:** During a median follow-up of 3.5 years, 141 (67.8%) patients converted to CDMS. In multivariate analysis, younger age (hazard ratio [HR]: 1.44 [95% CI 1.02–2.01]), spatial dissemination on brain MRI (HR: 2.07 [95% CI 1.47–2.91]) and more than 4 WBC/mm<sup>3</sup> in CSF (HR: 1.44 [95% CI 1.03–2.02]) were independently associated with CDMS. The Cox score obtained from these three predictors enabled patients to be divided into three groups with significant increased risks of CDMS at 1, 2 and 3 years; groups were classified as high-risk (64.7%, 77.4%, 96.1%), intermediate-risk (33.3%, 51.5%, 61.5%), and low-risk (11.1%, 18.3%, 40.3%).

**Conclusions:** Age at onset, spatial dissemination on brain MRI and CSF white blood cell count are independently associated with short-term conversion to CDMS. The three proposed risk group classifications could be a useful tool to select patients for early therapeutic intervention.

# LCR : Controverses

## Arguments « Oui »

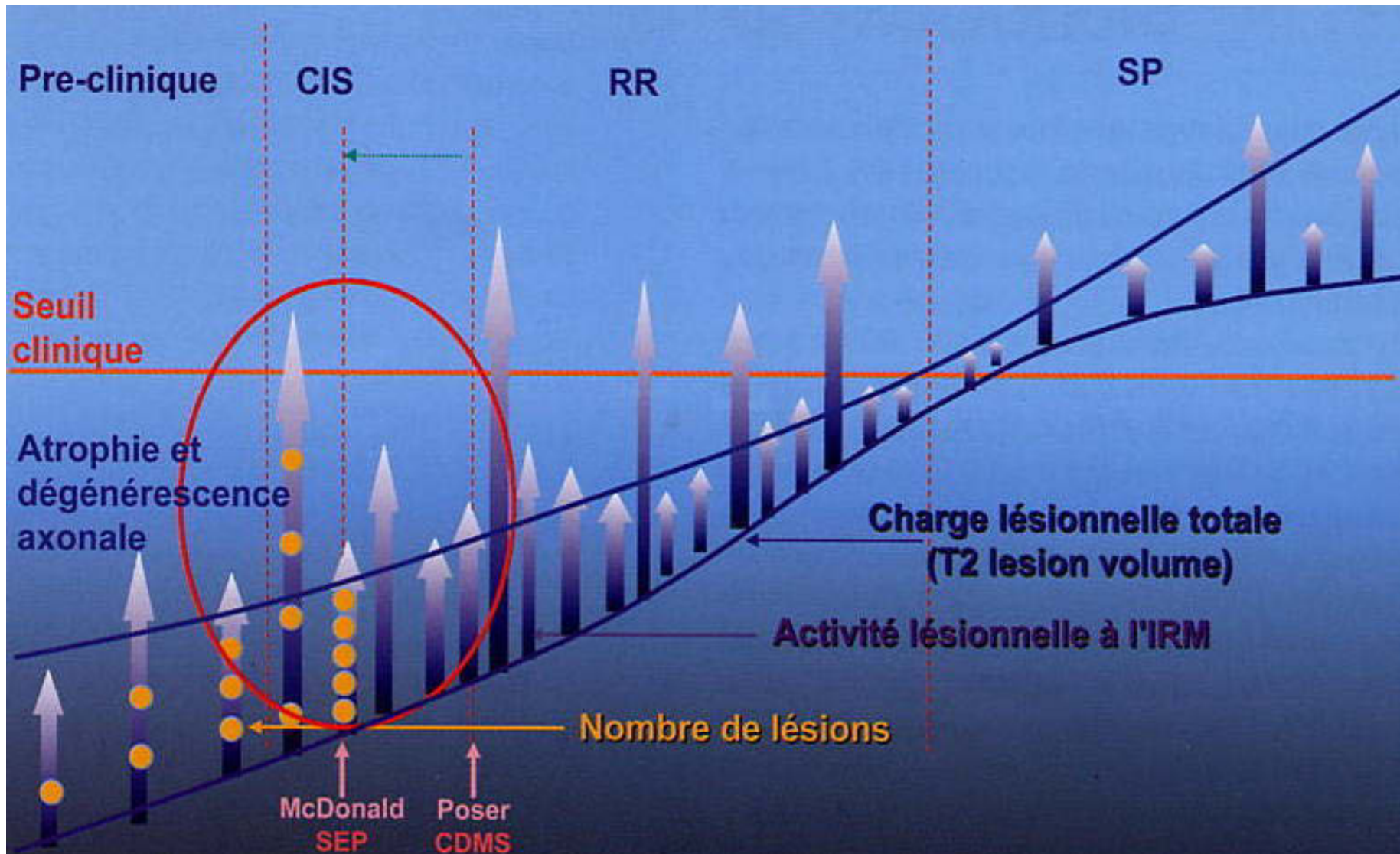
- Dans l'élimination d'un diagnostic différentiel
- Dans la démonstration d'un aspect oligoclonal qui apporte un argument complémentaire important au diagnostic positif
- Dans la logique actuelle du diagnostic précoce qui ne doit pas se faire au détriment de la spécificité
- Dans le renseignement des bio-banques

## Arguments « Non »

- Nécessité de réaliser une ponction lombaire qui reste un geste invasif
- N'apporte pas de renseignements complémentaires si la présentation clinique et radiologique est typique
- Ne change pas la prise en charge thérapeutique
- L'existence d'un OGC a une spécificité insuffisante (nombreux diagnostics différentiels)



# Profil évolutif de la SEP



# IRM et SEP : Intérêt diagnostique

- Les bases du diagnostic de la SEP
  - Dissémination spatiale lésions de la substance blanche non explicables par un autre mécanisme lésionnel
  - Dissémination temporelle des lésions
- Intégration de critères IRM aux critères cliniques : Mc Donald et al, 2001/2005
  - Permettre un diagnostic plus précoce
  - Permettre un traitement plus précoce
  - Préciser les critères de la forme primaire progressive

# Diagnostic précoce : les critères de Mc Donald

## Présentation clinique

1 poussée

1 lésion objective

- Au moins 9 lésions hyperintenses en T2 ou une lésion rehaussée au gadolinium
- Au moins une lésion sous-tentorielle
- Au moins une lésion juxtacorticale
- Au moins trois lésions périventriculaires

*Barkhof*

## Données additionnelles

Dissémination dans  
l'espace

**IRM**

*ou* LCR + et 2 lésions

IRM

ET Dissémination dans le  
temps

**IRM**

*ou* second épisode  
clinique

# IRM : dissémination temporelle





# Critères McDonald 2005


## Critères McDonald 2001

 **Modifiés en 2005**

### Critères IRM de dissémination temporelle:

Présence d'une nouvelle lésion gado + sur IRM à 3 mois de l'épisode clinique initial.


Si cette IRM de contrôle est -, une nouvelle IRM est réalisée 3 mois après: une nouvelle lésion T2 ou gado + confirme la DT

 **Idem ou toute nouvelle lésion T2 apparue par rapport à l'IRM initiale faite + 30 jours après l'épisode**

### Critères IRM de dissémination spatiale:

au moins 3 des 4 critères suivants

- une lésion prenant le Gadolinium ou 9 lésions hyperintenses en T2
- au moins 3 lésions périventriculaires
- au moins 1 lésion infratentorielle
- au moins 1 lésion juxta-corticale.

 Une lésion médullaire T2 compte une lésion sous-tentorielle  
Une lésion gado+ médullaire remplace une lésion gado + encéphalique

Présentation clinique	Examens complémentaires ou profil évolutif requis pour le diagnostic de SEP
Au moins 2 poussées Au moins 2 lésions cliniques	Aucun
Au moins 2 poussées 1 lésion clinique	Dissémination spatiale démontrée par : <ul style="list-style-type: none"> <li>• IRM</li> <li>• Au moins 2 lésions IRM évocatrices et PL positive</li> <li>• Ou poussée ultérieure dans un site différent</li> </ul>
1 poussée Au moins 2 lésions cliniques	Dissémination temporelle démontrée par : <ul style="list-style-type: none"> <li>• IRM</li> <li>• Ou survenue d'une 2<sup>e</sup> poussée</li> </ul>
1 poussée 1 lésion clinique (présentation monosymptomatique, SCI)	Dissémination spatiale démontrée par : <ul style="list-style-type: none"> <li>• IRM</li> <li>• Au moins 2 lésions IRM évocatrices et LCR positif</li> </ul> <b>ET</b> Dissémination temporelle démontrée par : <ul style="list-style-type: none"> <li>• IRM</li> <li>• Ou survenue d'une 2<sup>e</sup> poussée</li> </ul>
Progression insidieuse évocatrice de SEP	LCR positif <b>ET</b> Dissémination spatiale démontrée par : <ul style="list-style-type: none"> <li>• IRM [au moins 9 lésions T2 à l'IRM encéphalique ou au moins 2 lésions à l'IRM médullaire ou 4 à 8 lésions encéphaliques et 1 médullaire]</li> <li>• Ou PEV anormaux associés à 4 à 8 lésions encéphaliques et 1 médullaire</li> </ul> <b>ET</b> Dissémination temporelle démontrée par : <ul style="list-style-type: none"> <li>• IRM</li> <li>• Ou progression continue sur un an</li> </ul>

# MRI criteria for multiple sclerosis in patients presenting with clinically isolated syndromes: a multicentre retrospective study



Josephine K Swanton, Alex Rovira, Mar Tintore, Daniel R Altmann, Frederik Barkhof, Massimo Filippi, Elena Huerga, Katherine A Miszkiel, Gordon T Plant, Chris Polman, Marco Rovaris, Alan J Thompson, Xavier Montalban, David H Miller

Lancet Neurol 2007; 6: 677-86

	DIS*	DIT	Ref
McDonald 2001	<p>≥3 of the following:                      9 T2 lesions or 1 Gd-enhancing lesion; ≥3 periventricular lesions; ≥1 juxtacortical lesion; ≥1 posterior fossa lesion                      1 spinal-cord lesion can replace 1 brain lesion</p>	<p>A Gd-enhancing lesion ≥3 months after CIS onset                      A new T2 lesion with reference to a previous scan ≥3 months after CIS onset</p>	11
McDonald 2005	<p>≥3 of the following:                      9 T2 lesions or 1 Gd-enhancing lesion; ≥3 periventricular lesions; ≥1 juxtacortical lesion; ≥1 posterior fossa lesion or spinal-cord lesion                      A spinal-cord lesion can replace an infratentorial lesion                      Any number of spinal-cord lesions can be included in total lesion count</p>	<p>A Gd-enhancing lesion ≥3 months after CIS onset                      A new T2 lesion with reference to a baseline scan obtained ≥30 days after CIS onset</p>	15
New criteria	<p>≥1 lesion in each of ≥2 characteristic locations: periventricular, juxtacortical, posterior fossa, spinal cord                      All lesions in symptomatic region excluded in brainstem and spinal-cord syndromes</p>	<p>A new T2 lesion on follow-up MRI irrespective of timing of baseline scan</p>	16

CIS=clinically isolated syndrome. Gd=gadolinium. \*On baseline or follow-up MRI. The McDonald 2001 and 2005 DIS criteria also include the presence of two or more T2 lesions plus cerebrospinal fluid oligoclonal bands. Because cerebrospinal fluid was not examined systematically in the Magnims cohort, only the MRI criteria for DIS were used in this study.

**Table 1:** Three MRI criteria for dissemination in space (DIS) and dissemination in time (DIT) for multiple sclerosis



# MRI criteria for multiple sclerosis in patients presenting with clinically isolated syndromes: a multicentre retrospective study



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Lancet Neurol 2007; 6: 677-86

	Test positive (n)	Estimate (95% CI)				Likelihood ratio (95% CI)	
		Sensitivity	Specificity	Accuracy	Positive predictive value	Positive	Negative
<b>Overall criteria (DIS and DIT)</b>							
McDonald 2001	51	47.1% (36.1-58.2)	91.1% (84.6-95.5)	73.1% (66.5-79.0)	78.4% (64.7-88.7)	5.3 (2.9-9.7)	0.6 (0.5-0.7)
McDonald 2005	66	60.0% (48.8-70.5)	87.8% (80.7-93.0)	76.4% (70.1-82.0)	77.3% (65.3-86.7)	4.9 (3.0-8.2)	0.5 (0.3-0.6)
<b>New criteria</b>	<b>77</b>	<b>71.8% (61.0-81.0)</b>	<b>87.0% (79.7-94.2)</b>	<b>80.8% (74.8-85.9)</b>	<b>79.2% (68.5-87.6)</b>	<b>5.5 (3.4-8.9)</b>	<b>0.3 (0.2-0.5)</b>
<b>DIS criteria</b>							
McDonald 2001	104	76.5% (66.0-85.0)	68.3% (59.3-76.4)	71.6% (65.0-77.7)	62.5% (52.5-71.8)	2.4 (1.8-3.2)	0.4 (0.2-0.5)
McDonald 2005	102	75.3% (64.8-84.0)	69.1% (60.1-77.1)	71.6% (65.0-77.7)	62.8% (52.6-72.1)	2.4 (1.8-3.3)	0.4 (0.2-0.5)
<b>New criteria</b>	<b>123</b>	<b>85.9% (76.6-92.5)</b>	<b>59.4% (50.1-68.1)</b>	<b>70.2% (63.5-76.3)</b>	<b>59.4% (50.1-68.1)</b>	<b>2.1 (1.7-2.7)</b>	<b>0.2 (0.1-0.4)</b>
<b>DIT criteria</b>							
McDonald 2001	55	51.8% (40.7-62.7)	88.6% (81.6-93.6)	73.6% (67.0-79.4)	75.9% (62.8-86.1)	4.6 (2.7-7.8)	0.5 (0.4-0.7)
McDonald 2005	80	68.2% (57.2-77.9)	82.1% (74.2-88.4)	76.4% (70.1-82.0)	72.5% (61.4-81.9)	3.8 (2.5-5.7)	0.4 (0.3-0.5)
<b>New criteria</b>	<b>88</b>	<b>74.1% (63.5-83.0)</b>	<b>79.7% (71.5-86.4)</b>	<b>77.4% (71.1-82.9)</b>	<b>71.6% (61.0-80.7)</b>	<b>3.7 (2.5-5.3)</b>	<b>0.3 (0.2-0.5)</b>
<b>DIT on follow-up scan</b>							
New Gd lesion	55	49.4% (38.4-60.5)	89.4% (82.6-94.3)	73.1% (66.5-79.0)	76.4% (63.0-86.8)	4.7 (2.7-8.2)	0.6 (0.5-0.7)
New T2 lesion (all cases)	88	74.1% (63.5-83.0)	79.7% (71.5-86.4)	77.4% (71.1-82.9)	71.6% (61.0-80.7)	3.7 (2.5-5.3)	0.3 (0.2-0.5)
New T2 lesion and baseline scan at least 30 days after CIS onset (n=136)	56	68.9% (55.7-80.1)	81.3% (70.7-89.4)	75.7% (67.6-82.7)	75.0% (61.6-85.6)	3.7 (2.2-6.1)	0.4 (0.3-0.6)

DIS=dissemination in space. DIT=dissemination in time. Gd=gadolinium.

**Table 3:** Performance of MRI criteria for development of clinically definite multiple sclerosis

# Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,<sup>1</sup> Stephen C. Reingold, PhD,<sup>2</sup> Brenda Banwell, MD,<sup>3</sup> Michel Clanet, MD,<sup>4</sup> Jeffrey A. Cohen, MD,<sup>5</sup> Massimo Filippi, MD,<sup>6</sup> Kazuo Fujihara, MD,<sup>7</sup>

ANN NEUROL 2011;69:292-302

**TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS**

**DIS Can Be Demonstrated by  $\geq 1$  T2 Lesion<sup>a</sup> in at Least 2 of 4 Areas of the CNS:**

Periventricular

Juxtacortical

Infratentorial

Spinal cord<sup>b</sup>

Based on Swanton et al 2006, 2007.<sup>22,27</sup>

<sup>a</sup>Gadolinium enhancement of lesions is not required for DIS.

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

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

**TABLE 2: 2010 McDonald MRI Criteria for Demonstration of DIT**

**DIT Can Be Demonstrated by:**

1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Based on Montalban et al 2010.<sup>24</sup>

MRI = magnetic resonance imaging; DIT = lesion dissemination in time.



Clinical Presentation	Additional Data Needed for MS Diagnosis
<p>≥2 attacks<sup>a</sup>; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack<sup>b</sup></p>	None <sup>c</sup>
<p>≥2 attacks<sup>a</sup>; objective clinical evidence of 1 lesion</p>	<p>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)<sup>d</sup>; or          Await a further clinical attack<sup>a</sup> implicating a different CNS site</p>
<p>1 attack<sup>a</sup>; objective clinical evidence of ≥2 lesions</p>	<p>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<sup>a</sup></p>
<p>1 attack<sup>a</sup>; objective clinical evidence of 1 lesion (clinically isolated syndrome)</p>	<p>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)<sup>d</sup>; or          Await a second clinical attack<sup>a</sup> 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<sup>a</sup></p>
<p>Insidious neurological progression suggestive of MS (PPMS)</p>	<p>1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria<sup>d</sup>:</p> <ol style="list-style-type: none"> <li>1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions</li> <li>2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord</li> <li>3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)</li> </ol>

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# MRI criteria for MS in patients with clinically isolated syndromes *Neurology*® 2010;74:427-434

	DIS and DIT	Sensitivity (95% CI) %	Specificity (95% CI) %	PPV (95% CI) %
	<b>McDonald 2001<sup>1</sup></b>		<b>McDonald 2005<sup>2</sup></b>	<b>MAGNIMS proposal</b>
<b>DIS (on either baseline or follow-up MRI)<sup>a</sup></b>	3 or more of:		3 or more of:	≥1 lesion in each of ≥2 characteristic locations:
	≥9 T2 lesions or ≥1 Gd-enhancing lesion		≥ 9 T2 lesions <sup>a</sup> or ≥1 Gd-enhancing lesion	PV
	≥3 PV lesions		≥3 PV lesions	JC
	≥1 JC lesions		≥1 JC lesions	PF
	≥1 PF lesions		≥1 PF lesions or spinal cord lesion	Spinal cord
	1 cord lesion can replace 1 brain lesion		Any number of cord lesions can be included in total lesion count <sup>a</sup>	All lesions in symptomatic regions excluded in BS and SC syndromes
<b>DIT</b>	1) ≥1 Gd-enhancing lesion at least 3 months after CIS onset (if not related to CIS)		1) ≥1 Gd-enhancing lesion at least 3 months after CIS onset (if not related to CIS)	1) Simultaneous presence of asymptomatic Gd-enhancing and nonenhancing lesions at any time
	2) A new T2 lesion with reference to a prior scan obtained at least 3 months after CIS onset		2) A new T2 lesion with reference to a baseline scan obtained at least 30 days after CIS onset	2) A new T2 and/or Gd-enhancing lesion on follow-up MRI irrespective of timing of baseline scan

Abbreviations: BS = brainstem; DIS = disseminated in space; DIT = disseminated in time; Gd = gadolinium-enhancing lesion; JC = juxtacortical; PF = posterior fossa; PV = periventricular; SC = spinal cord.

<sup>a</sup>The McDonald 2001 and 2005 DIS criteria also include the presence of 2 or more T2 lesions plus CSF oligoclonal bands. Because CSF was not examined systematically in the MAGNIMS cohort, only the MRI criteria for DIS are considered in this study.



# Evolution des critères IRM dans la SEP

## McDonald 2005

### ESPACE

- =9 lésions T2 ou =1 lésion Gd
- =3 péri-ventriculaires
- =1 juxta corticale
- =1 fosse postérieure

### TEMPS

- =1 lésion Gd à 3 mois
- =1 nouvelle lésion T2 *par rapport à* IRM de référence (>30J)



Polman *et al.* Ann Neurol 2005;58:840-46

## MAGNIMS (MAGnetic Resonance Network In Multiple Sclerosis)

### ESPACE

- =1 lésion dans =2 localisations:
  - Péri-ventriculaire
  - Juxta corticale
  - Fosse postérieure
  - Moelle

### TEMPS

- Lésions Gd- et Gd+ simultanées
- =1 nouvelle lésion T2 *par rapport à* IRM de référence (>~~30~~J)



Swanton *et al.* JNNP 2006;77:830-33

Rovira *et al.* Arch Neurol 2009;66:587-92

Montalban *et al.* Neurology 2010;74:427-34



# Dissémination dans le temps : une seule IRM ?

## Very early scans for demonstrating dissemination in time in multiple sclerosis

C Tur<sup>1</sup>, M Tintoré<sup>1</sup>, Á Rovira<sup>2</sup>, C Nos<sup>1</sup>, J Río<sup>1</sup>, N Téllez<sup>1</sup>, I Galán<sup>1</sup>, H Perkal<sup>1</sup>, M Comabella<sup>1</sup>, J Sastre-Garriga<sup>1</sup> and X Montalban<sup>1</sup>

ORIGINAL CONTRIBUTION

## A Single, Early Magnetic Resonance Imaging Study in the Diagnosis of Multiple Sclerosis

Faux + = 13%

Àlex Rovira, MD; Josephine Swanton, MD; Mar Tintoré, MD; Elena Huerga, RT; Fredrick Barkhof, MD; Massimo Filippi, MD; Jette L. Frederiksen, MD; Annika Langkilde, MD; Katherine Miszkiel, MD; Chris Polman, MD; Marco Rovaris, MD; Jaume Sastre-Garriga, MD; David Miller, MD; Xavier Montalban, MD

Table 4. Performance of Various MRI Criteria for Predicting Conversion to Clinically Definite Multiple Sclerosis<sup>a</sup>

Criteria	No. (%) of Positive MRIs <sup>b</sup>	Sensitivity	Specificity	PPV	Positive LR	Negative LR
Early MRI for all patients (N = 250)						
Barkhof-Tintoré criteria plus $\geq 1$ gadolinium-enhancing lesion	53 (21.2)	46.9 (35.2-58.9)	87.6 (82.1-91.6)	56.6 (43.3-69.0)	3.8 (2.4-6.0)	0.6 (0.5-0.8)
Swanton criteria plus $\geq 1$ gadolinium-enhancing lesion	59 (23.6)	53.1 (41.1-64.8)	86.6 (80.9-90.7)	57.6 (44.9-69.4)	3.9 (2.6-6.1)	0.5 (0.4-0.7)
Frohman criteria plus $\geq 1$ gadolinium-enhancing lesion	64 (25.6)	53.1 (41.1-64.8)	83.9 (77.9-88.5)	53.1 (41.1-64.8)	3.3 (2.2-4.9)	0.6 (0.4-0.7)



# Red flags

Table 1 Red flags

Red flag	Type	Total score	SD	Red flag <sup>a</sup>	Examples of alternative diagnosis
Bone lesions	Clinical	30	0.00	Major	Histiocytosis; Erdheim Chester disease
Lung involvement	Clinical	30	0.00	Major	Sarcoidosis; Lymphomatoid granulomatosis
Multiple cranial neuropathies or polyradiculopathy	Clinical	30	0.00	Major	Chronic meningitis, including sarcoidosis and tuberculosis; Lyme disease
Peripheral neuropathy	Clinical	30	0.00	Major	B12 deficiency; adrenoleukodystrophy; metachromatic leukodystrophy, Lyme disease
Tendon xanthomas	Clinical	30	0.00	Major	Cerebrotendinous xanthomatosis
Cerebral venous sinus thrombosis	MRI	30	0.00	Major	Behçet's disease; vasculitis; chronic meningitis, antiphospholipid or anticardiolipin antibody syndromes
Cardiac disease	Clinical	29	0.41	Major	Multiple cerebral infarcts; brain abscesses with endocarditis or right to left cardiac shunting
Myopathy	Clinical	29	0.41	Major	Mitochondrial encephalomyopathy (e.g., MELAS); Sjögren's syndrome
Renal involvement	Clinical	29	0.41	Major	Vasculitis; Fabry disease, systemic lupus erythematosus
Cortical infarcts	MRI	29	0.41	Major	Embolic disease; thrombotic thrombocytopenic purpura; vasculitis
Hemorrhages/microhemorrhages	MRI	29	0.41	Major	Amyloid angiopathy; Moya Moya disease; CADASIL; vasculitis
Meningeal enhancement	MRI	29	0.41	Major	Chronic meningitis; sarcoidosis; lymphomatosis; CNS vasculitis
Extrapyramidal features	Clinical	28	0.52	Major	Whipple's disease; multisystem atrophy; Wilson's disease
Livedo reticularis	Clinical	28	0.52	Major	Antiphospholipid antibody syndrome; systemic lupus erythematosus; Sneddon's syndrome
Retinopathy	Clinical	28	0.52	Major	Mitochondrial encephalomyopathy; Susac, and other vasculitides (retinal infarction); neuronal ceroid lipofuscinosis

Calcifications on CT scans	MRI	28	0.52	Major	neuronal ceroid lipofuscinosis Cysticercosis; toxoplasmosis, mitochondrial disorders
Diabetes insipidus	Clinical	28	0.82	Major	Sarcoidosis; histiocytosis; neuromyelitis optica
Increase serum lactate level	Clinical	27	0.55	Major	Mitochondrial disease
Selective involvement of the anterior temporal and inferior frontal lobe	MRI	27	0.55	Major	CADASIL
Hematological manifestations	Clinical	27	0.84	Major	Thrombotic thrombocytopenic purpura; vitamin B12 deficiency; Wilson's disease (hemolytic anemia); copper deficiency
Lacunar infarcts	MRI	27	0.84	Major	Hypertensive ischemic disease; CADASIL; Susac syndrome
Persistent Gd-enhancement and continued enlargement of lesions	MRI	27	0.84	Major	Lymphoma; glioma; vasculitis; sarcoidosis
Mucosal ulcers	Clinical	27	1.22	Major	Behçet's disease
Myorhythmia	Clinical	27	1.22	Major	Whipple's disease
Hypothalamic disturbance	Clinical	26	0.52	Major	Sarcoidosis; neuromyelitis optica; histiocytosis
Recurrent spontaneous abortion or thrombotic events	Clinical	26	0.52	Major	Antiphospholipid antibody syndrome; thrombotic thrombocytopenic purpura; metastatic cancer with hypercoagulable state
Simultaneous enhancement of all lesions	MRI	26	0.52	Major	Vasculitis; lymphoma; sarcoidosis
Rash	Clinical	26	0.82	Major	Systemic lupus erythematosus; T-cell lymphoma; Lyme disease, Fabry disease
T2-hyperintensity in the dentate nuclei	MRI	26	0.82	Major	Cerebrotendinous xanthomatosis

# SCI à haut risque

- Critères de Barkhof-Tintore (McDonald 2001; Polman 2005)
- Critères de Swanton (Polman 2011)
- DIS+ DIT sur première IRM (Polman 2011)
- LCR
- 2 lésions > 3mm + LCR (McDonald 2001; Polman, 2005)
- 2/3 (3PV, LCR+, âge < 40) (Ruet 2010, 2012)

# Myélites

Variables	VPP [IC 95%]	VPN [IC 95%]	Accuracy [IC 95%]
Age $\leq$ 40 years	83.5 [75.5-91.5]	55.6 [36.6-74.6]	76.4 [68.4-84.4]
$\geq$ 3 periventricular lesions	90.7 [82.1-99.3]	37.1 [25.1-49.1]	59.0 [50.0-68.0]
Inflammatory CSF	80.6 [71.6-89.6]	44.8 [26.8-62.8]	70.3 [61.3-79.3]
<b>2 out of the 3 variables</b>	<b>88.6 [81.6-95.6]</b>	<b>57.6 [35.6-79.6]</b>	<b>78.6 [70.6-86.6]</b>

Valeur prédictive dans 114 cas de myélites inauguales d'un Dg de SEP

Ruet et al. 2010



# Confirmation cohorte SCI Barcelone

	CIS patients n (%)	HR (95% CI)	aHR (95% CI)
<b>Predictive factors:</b>			
• Age ≤40	536 (82.2)	1.8 (1.2-2.8) <sup>†</sup>	1.8 (1.2-2.7) <sup>†</sup>
• + OBs	272 (55.3)	2.2 (1.6-3.1) <sup>‡</sup>	2.3 (1.6-3.2) <sup>‡</sup>
• ≥3 PV lesions	259 (51.5)	3.0 (2.2-4.2) <sup>‡</sup>	3.8 (2.6-5.5) <sup>‡</sup>
• ≥2	323 (49.5)	<b>3.9 (2.8-5.5)<sup>‡</sup></b>	<b>4.7 (3.2-6.8)<sup>‡</sup></b>
<b>DIS criteria:</b>			
• DIS <sub>1</sub>	219 (43.4)	3.1 (2.2-4.2) <sup>‡</sup>	3.9 (2.8-5.7) <sup>‡</sup>
• DIS <sub>2</sub>	49 (19.4)	2.5 (1.4-4.4) <sup>‡</sup>	2.6 (1.5-4.5) <sup>‡</sup>
• DIS <sub>3</sub>	268 (56.8)	3.8 (2.6-5.6) <sup>‡</sup>	4.5 (3.0-6.8) <sup>‡</sup>
<b>Predictive factors without DIS<sub>1</sub></b>	82 (28.7)	<b>2.8 (1.7-4.7)<sup>‡</sup></b>	<b>3.0 (1.8-5.1)<sup>‡</sup></b>

PV, periventricular lesions; + OBs, positive oligoclonal bands; DIS<sub>1</sub>: ≥ 3 Barkhof-Tintoré criteria; DIS<sub>2</sub>: 2 lesions plus oligoclonal bands in patients not fulfilling ≥ 3 Barkhof-Tintoré criteria; DIS<sub>3</sub>: DIS according to McDonald 2005 (≥ 3 Barkhof-Tintoré criteria or 2 lesions plus oligoclonal bands).

p value: \* < .01; † < .005; ‡ ≤ .001.

Ruet et al.  
Ectrims 2012

# Forme PP : critères Dg ?

- Signes progressifs suggérant SEP (paraparésie progressive)
- Depuis plus d'un an
- Diagnostics différentiels éliminés
- LCR + (BOC)
- Dissémination IRM spatiale
  - Syndrome pyramidal progressif (80%)
    - Atteinte motrice au premier plan (svt asymétrique)
    - Peu de symptômes sensitifs
    - Troubles sphinctériens ++
  - Ataxie cérébelleuse progressive (15%)
    - ± signes d'atteinte du tronc cérébral

# Quels Critères Thompson 2000

## Diagnostic Criteria for Primary Progressive Multiple Sclerosis: A Position Paper

A. J. Thompson, FRCP,\* X. Montalban, MD,† F. Barkhof, MD,‡ B. Brochet, MD,§ M. Filippi, MD,||  
D. H. Miller, FRCP,\* C. H. Polman, MD,‡ V. L. Stevenson, MRCP,\* and W. I. McDonald, FRCP\*

Ann Neurol 2000;47:831-835

*Table. Diagnostic Criteria for Primary Progressive Multiple Sclerosis*

### Definite PPMS

- 1 Clinical progression for at least one year *and*
- 2 Positive CSF evidence *and*
- 3 Positive MRI evidence *or* equivocal MRI evidence *and* a delayed VEP

### Probable PPMS

*Either:*

- 1 Clinical progression for at least one year *and*
- 2 Positive CSF evidence *and*
- 3 Equivocal MRI evidence *or* delayed VEP

*Or:*

- 1 Clinical progression for at least 1 year *and*
- 2 Positive MRI evidence *or* equivocal MRI evidence *and* a delayed VEP (but CSF evidence either unavailable or negative)

### Possible PPMS

- 1 Clinical progression for at least one year *and*
- 2 Equivocal MRI evidence *or* delayed VEP

### SEP PP définie (3 items)

• Clinique: > 1 an

• Boc +

• IRM (1/3)

9 lésions

2 lésions médullaires

4 - 8 lésions cérébrales et 1 lésion médullaire

*PEV si 4-8 lésions et IRM médullaire normale  
ou < 4 lésions et 1 lésion médullaire*

# Quels Critères *Mc Donald (2005)*

---

- 1) Atteinte progressive > 1 an
- 2) 2/ 3
- \* 9 lésions ou 4 et PEV altérés
- \* > 2 lésions IRM médullaire
- \* BOC +

1. One year of disease progression (retrospectively or prospectively determined)
2. *Plus* two of the following:
  - a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP)
  - b. Positive spinal cord MRI (two focal T2 lesions)
  - c. Positive CSF<sup>a</sup> (isoelectric focusing evidence of oligoclonal IgG bands or increased IgG index, or both).

## Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the “McDonald Criteria”

Chris H. Polman, MD, PhD,<sup>1</sup> Stephen C. Reingold, PhD,<sup>2</sup> Gilles Edan, MD,<sup>3</sup> Massimo Filippi, MD,<sup>4</sup>  
Hans-Peter Hartung, MD,<sup>5</sup> Ludwig Kappos, MD,<sup>6</sup> Fred D. Lublin, MD,<sup>7</sup> Luanne M. Metz, MD,<sup>8</sup>  
Henry F. McFarland, MD,<sup>9</sup> Paul W. O'Connor, MD,<sup>10</sup> Magnhild Sandberg-Wollheim, MD,<sup>11</sup>  
Alan J. Thompson, MD,<sup>12</sup> Brian G. Weinshenker, MD,<sup>13</sup> and Jerry S. Wolinsky, MD<sup>14</sup>



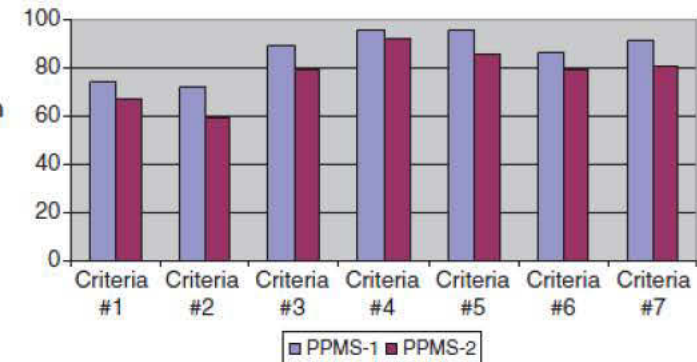
## Primary progressive multiple sclerosis diagnostic criteria: a reappraisal

X. Montalban, J. Sastre-Garriga, M. Filippi, Z. Khaleeli, N. Téllez, MM Vellinga, C. Tur, B. Brochet, F. Barkhof, M. Rovaris, DH Miller, CH Polman, A. Rovira and AJ Thompson  
*Mult Scler* 2009; 15; 1459 originally published online Dec 7, 2009;

Criterion #1 Three of the following:

1. At least one gadolinium-enhanced lesion  
or  
Nine T2 hyperintense lesions if there is no gadolinium-enhanced lesion
2. At least one infratentorial lesion
3. At least one juxtacortical lesion
4. At least three periventricular lesions

(Note: only taking into account the substitution of the infratentorial criterion by the presence of one spinal cord lesion but not incorporating spinal lesions counts into the brain lesion count)



Criterion #2 More than one T2 lesions in more than two of the following regions:

1. periventricular
2. juxtacortical
3. infratentorial<sup>1</sup>
4. spinal cord<sup>2</sup>

<sup>1</sup>Excluded in cases of brain stem syndrome; <sup>2</sup>excluded in cases of spinal cord syndrome

Criterion #3 Presence of oligoclonal bands plus two brain and/or spine lesions suggestive of MS<sup>2</sup>

Criterion #4 A combination set of criteria #1 and #3,  
 i.e. patients not fulfilling criterion #1 were then tested for fulfilment of criterion #3

Criterion #5 A combination set of criteria #2 and #3,  
 i.e. patients not fulfilling criterion #2 were then tested for fulfilment of criterion #3

Criterion #6 PPMS dissemination in space criteria defined by  
 Thompson and colleagues (definite MS versus not definite MS)<sup>1</sup>

Criterion #7 Two of the following:

1. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEPs)
2. Positive spinal cord MRI (two focal T2 lesions)
3. Positive CSF (evidence of oligoclonal IgG bands or increased IgG index, or both)

# Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,<sup>1</sup> Stephen C. Reingold, PhD,<sup>2</sup> Brenda Banwell, MD,<sup>3</sup> Michel Clanet, MD,<sup>4</sup> Jeffrey A. Cohen, MD,<sup>5</sup> Massimo Filippi, MD,<sup>6</sup> Kazuo Fujihara, MD,<sup>7</sup>

ANN NEUROL 2011;69:292-302

**TABLE 3: 2010 McDonald Criteria for Diagnosis of MS in Disease with Progression from Onset**

**PPMS May Be Diagnosed in Subjects With:**

1. One year of disease progression (retrospectively or prospectively determined)
2. Plus 2 of the 3 following criteria<sup>a</sup>:
  - A. Evidence for DIS in the brain based on  $\geq 1$  T2<sup>b</sup> lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)
  - B. Evidence for DIS in the spinal cord based on  $\geq 2$  T2<sup>b</sup> lesions in the cord
  - C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

<sup>a</sup>If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the Criteria.

<sup>b</sup>Gadolinium enhancement of lesions is not required.

MS = multiple sclerosis; PPMS = primary progressive MS; DIS = lesion dissemination in space; CSF = cerebrospinal fluid; IgG = immunoglobulin G.

## Et si ce n'était pas une SEP PP ?

- Les outils du diagnostic (positif/différentiel)
  - La clinique
    - Histoire familiale, anamnèse, examen clinique
  - Imagerie (le plus souvent cerveau ET moelle)
    - Lésions : aspect et topographie
  - Analyse du LCR
    - BOC présentes ou non, cellularité
  - Biologie sanguine
    - Vitamines, sérologies,
  - ENMG
    - Vitesses de conduction → leucodystrophies
    - Détection → motoneurone

# SEP progressive primaire

## Primary-progressive multiple sclerosis

### Cord compression

- Cervical spondylosis
- Intrinsic or extrinsic tumour

### Hereditary

- Hereditary spastic paraplegia
- Friedreich's ataxia
- Leucodystrophies (adrenomyeloneuropathy, Krabbe's disease)

### Metabolic

- B12 deficiency
- Phenylketonuria
- Copper deficiency

### Inflammatory

- Neurosarcoidosis
- CNS vasculitis

### Infection

- Human T-lymphotrophic virus 1 (HTLV-1)
- Schistosomiasis
- Syphilis
- HIV
- Brucellosis

### Degenerative

- Motorneuron disease

### Toxic

- Lathyrism
- Nitrous oxide

### Vascular

- Dural arteriovenous malformation
- CADASIL

### Paraneoplastic

## Diagnostic différentiel

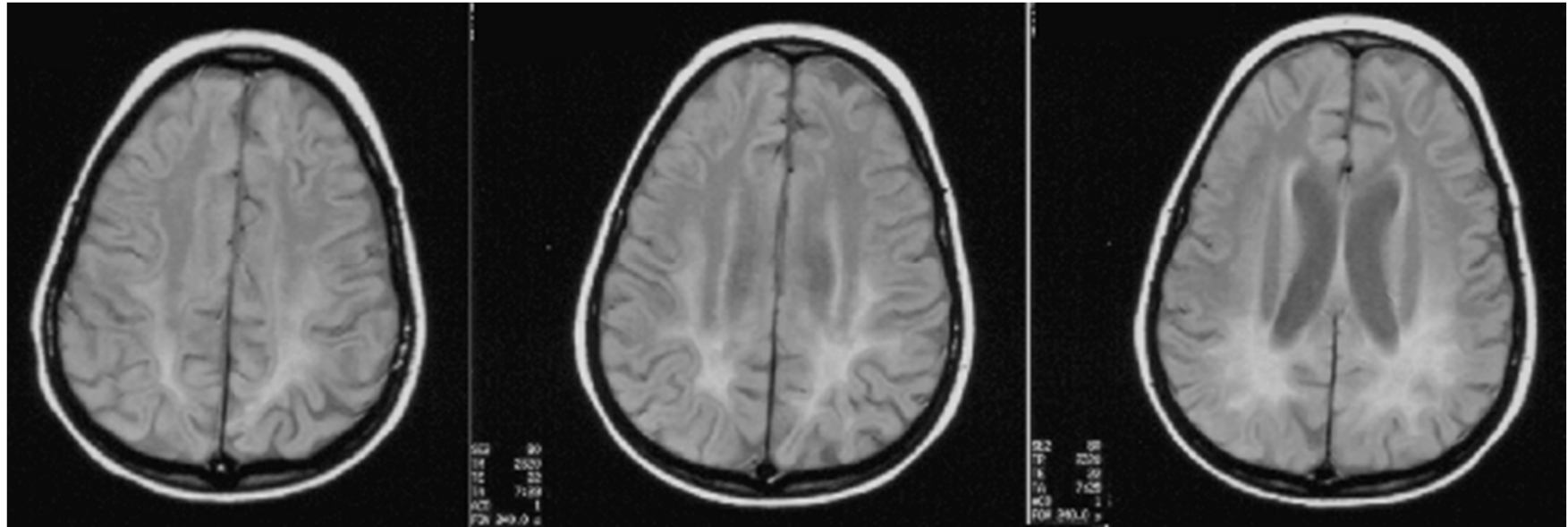
## Explorations

Myélopathie d'origine arthrosique	IRM médullaire
Néoplasie (primaire ou secondaire)	IRM médullaire (+ encéphalique)
Arnold Chiari	IRM médullaire (+ encéphalique)
Diplégie infantile	IRM, anamnèse
MAV médullaire	IRM, angiographie
SEP progressive	IRM, LCR, PEV (NB: McDonald)
SLA	EMG
SCA	IRM, génétique
ALD, AMN	IRM, AGTLC, VCN + PES
Leucodystrophie métachromatique	IRM, arylsulfatase
Maladie de Krabbe	IRM, galactocérébrosidase
Sclérose combinée	NFS, Dosage B12
Abetalipoprotéinémie	Électrophorèse des lipoprotéines
Dystonie dopasensible	Test à la L-dopa, génétique
Déficit vitamine E	IRM, Dosage vit E
Friedreich	EMG, IRM, génétique
Neurosyphilis	IRM, LCR, sérologie
HTLV-1	Sérologie
HIV	IRM, LCR, Sérologie

*Miller & Leary 2007*



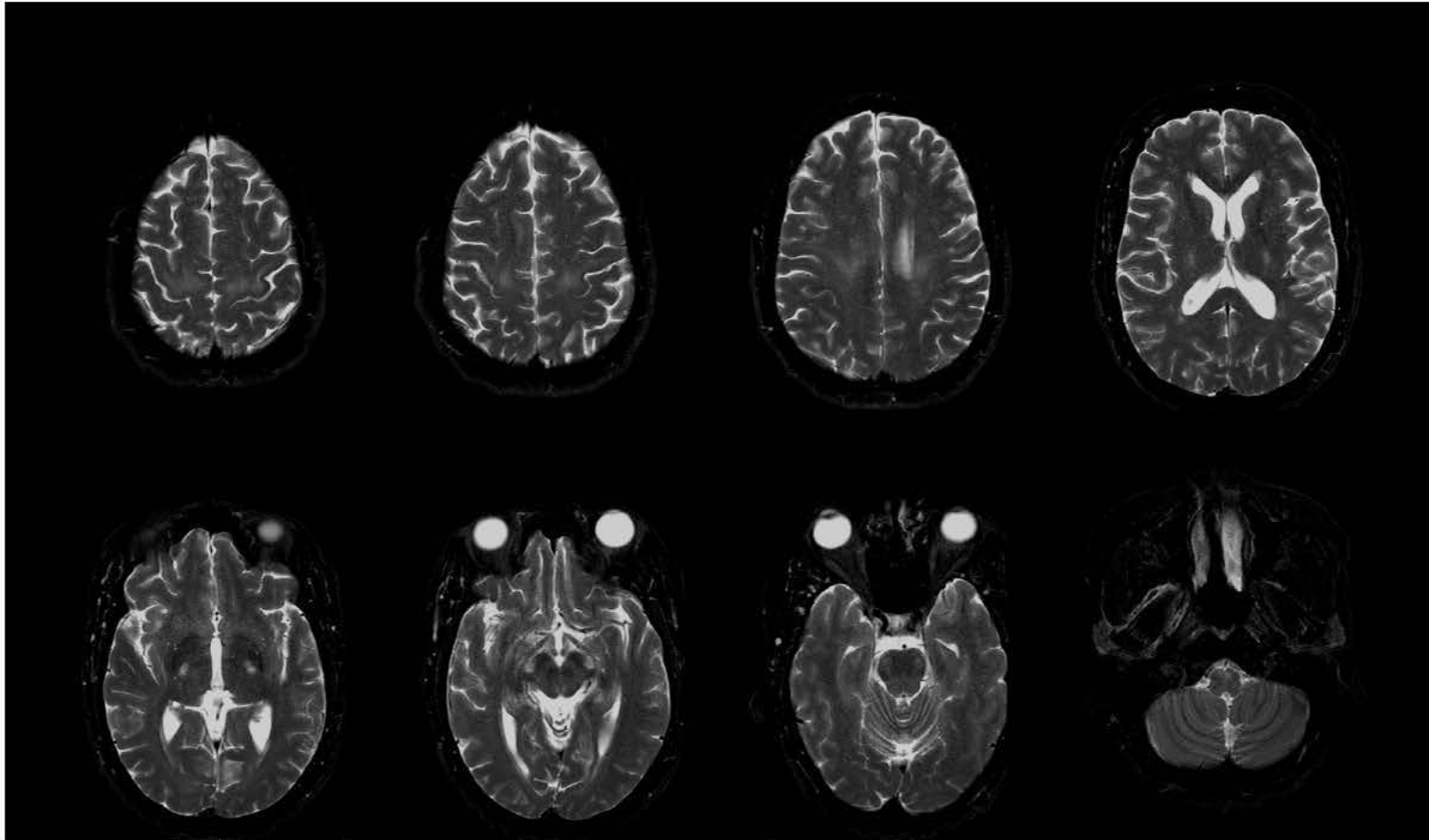
## Paraparésie progressive et troubles sphinctériens chez une femme de 35 ans



L'ENMG montre un ralentissement des VCM et VCS en faveur d'une neuropathie démyélinisante  
Diagnostic : augmentation des AGTLC

*Adrénomyélonuropathie*

## Tétraparésie progressive chez une femme de 44 ans

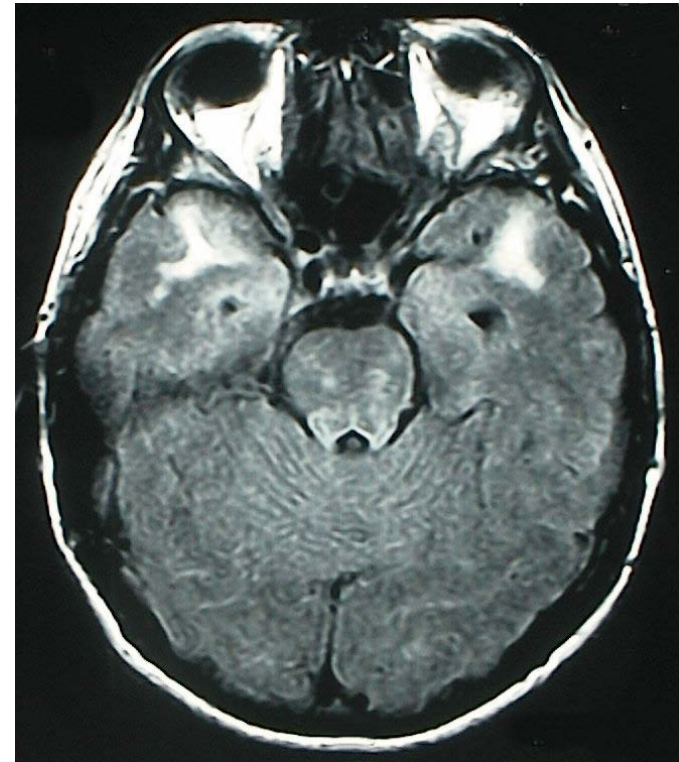


Réflexe massétérin vif, fasciculations des 2 bras

ENMG : dénervation diffuse

Diagnostic : SLA (atteinte prédominante du motoneurone central)

# Paraparésie spastique et troubles cognitifs chez une femme de 60 ans



Mutation ponctuelle du gène Notch 3  
Diagnostic : *CADASIL*