Formes frontières fulminantes des maladies démyélinisantes

Bertrand Audoin

Pôle de Neurosciences Cliniques, AP-HM, CHU Timone, Marseille

Centre de Résonance Magnétique Biologique et Médicale (CRMBM) et Centre d'Exploration du Métabolisme par Résonance Magnétique (CEMEREM), UMR AMU CNRS 7339, Marseille

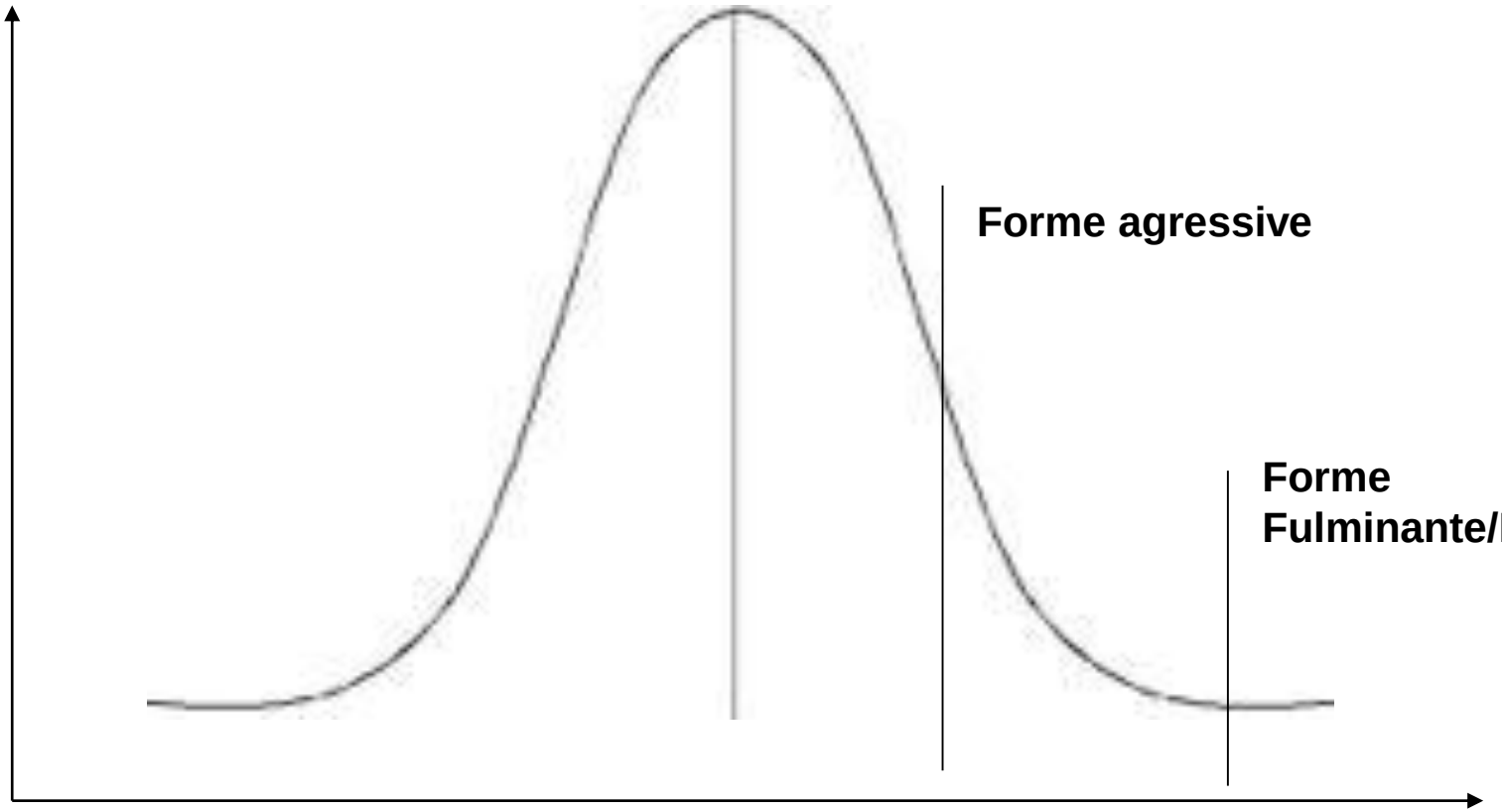
CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Aix*Marseille université

AP-HM

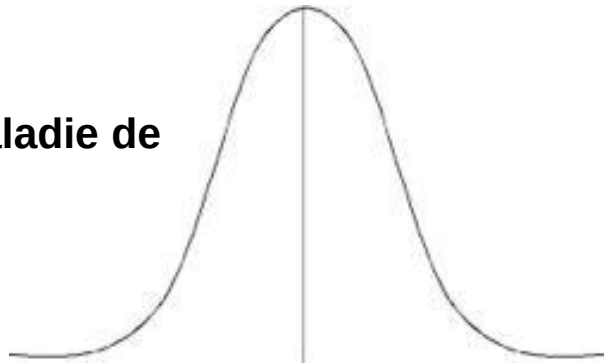
Nbre de patients

Spectre évolutif de la SEP



Activité de la maladie

Spectre de la maladie de Marburg



Forme Fulminante/Marburg

- 1ère description en 1906 par Marburg: femme de 30 ans avec un tableau aigue associant céphalées, vomissement, ataxie, hémiparésie. Décès 26 jours après le début. Démyélinisation sur l'examen pathologique
- Association le plus souvent d'une atteinte cérébrale, médullaire et du TC évoluant sur quelques semaines => troubles de la vigilance
- IRM: lésions très volumineuse, confluente, de même âge
- PL: résultats variables

Diagnostic différentiel avec EMAD complexe

Encéphalomyélite aiguë disséminée (EMAD)

- Evolution aigue et monophasique
- Très souvent signes multifocaux +/- signes encéphalopathie +/- coma
- Enfant +++ (après infection, vaccination)
- Souvent méningite lymphocytaire et hyperprotéinorachie, en général pas de synthèse
- Touche souvent les NGC

ORIGINAL CONTRIBUTION

Acute Fulminant Demyelinating Disease

A Descriptive Study of 60 Patients

Jérôme de Seze, MD; Marc Debouverie, MD; Hélène Zephir, MD; Christine Lebrun, MD; Frédéric Blanc, MD; Véronique Bourg, MD; Sandrine Wiertlewski, MD; Sophie Pittion, MD; David Laplaud, MD; Emmanuelle Le Page, MD; Romain Deschamps, MD; Philippe Cabre, MD; Jean Pelletier, MD; Irina Malikova, MD; Pierre Clavelou, MD; Valérie Jaillon, MD; Gilles Defer, MD; Pierre Labauge, MD; Olivier Gout, MD; Clotilde Boulay, MD; Gilles Edan, MD; Patrick Vermersch, MD

Background: Acute demyelinating encephalomyelitis (ADEM) is characterized by a severe inflammatory attack, frequently secondary to infectious events or vaccinations. To date, no clear criteria exist for ADEM, and the risk of subsequent evolution to multiple sclerosis (MS) remains unknown.

Objective: To evaluate the risk of evolution to MS after a first episode of ADEM.

Design: Observational, retrospective case study.

Setting: Thirteen French MS centers.

Patients: We retrospectively studied 60 patients with ADEM who were older than 15 years with no history suggestive of an inflammatory event who presented to MS centers from January 1, 1995, through December 31, 2005. We excluded 6 patients with multiphasic ADEM because this is a rare condition and somewhat difficult to classify. After a mean follow-up of 3.1 years (range, 1-10 years), the remaining 54 patients were then classified into 2 groups: monophasic ADEM (ADEM group) (n=35) and clinically definite MS (MS group) (n=19).

Main Outcome Measures: Clinical, laboratory, magnetic resonance imaging, and follow-up data were evaluated for each group.

Results: Patients in the ADEM group more frequently had atypical symptoms of MS (26 of 35 [74%]) than patients with MS (8 of 19 [42%]) ($P=.02$). Oligoclonal bands were more frequently observed in the MS group (16 of 19 [84%]) than in the ADEM group (7 of 35 [20%]) ($P<.001$). Patients in the ADEM group more frequently had gray matter involvement (21 of 35 [60%]) than those in the MS group (2 of 19 [11%]) ($P<.001$). On the basis of these results, we consider that the presence of any 2 of the following 3 criteria could be used to differentiate patients with ADEM from those with MS in our cohort: atypical clinical symptoms for MS, absence of oligoclonal bands, and gray matter involvement. On this basis, 29 of the 35 patients in the ADEM group (83%) and 18 of the 19 patients in the MS group (95%) were classified in the appropriate category.

Conclusions: Our study found some differences concerning the risk of evolution to clinically definite MS after a first demyelinating episode suggestive of ADEM. These findings led us to propose criteria that should now be tested in a larger, prospective cohort study.

Arch Neurol. 2007;64(10):1426-1432

Différentiation EMAD/SEP agressive

Table 2. Baseline Brain and Spinal Cord MRI Data[a]

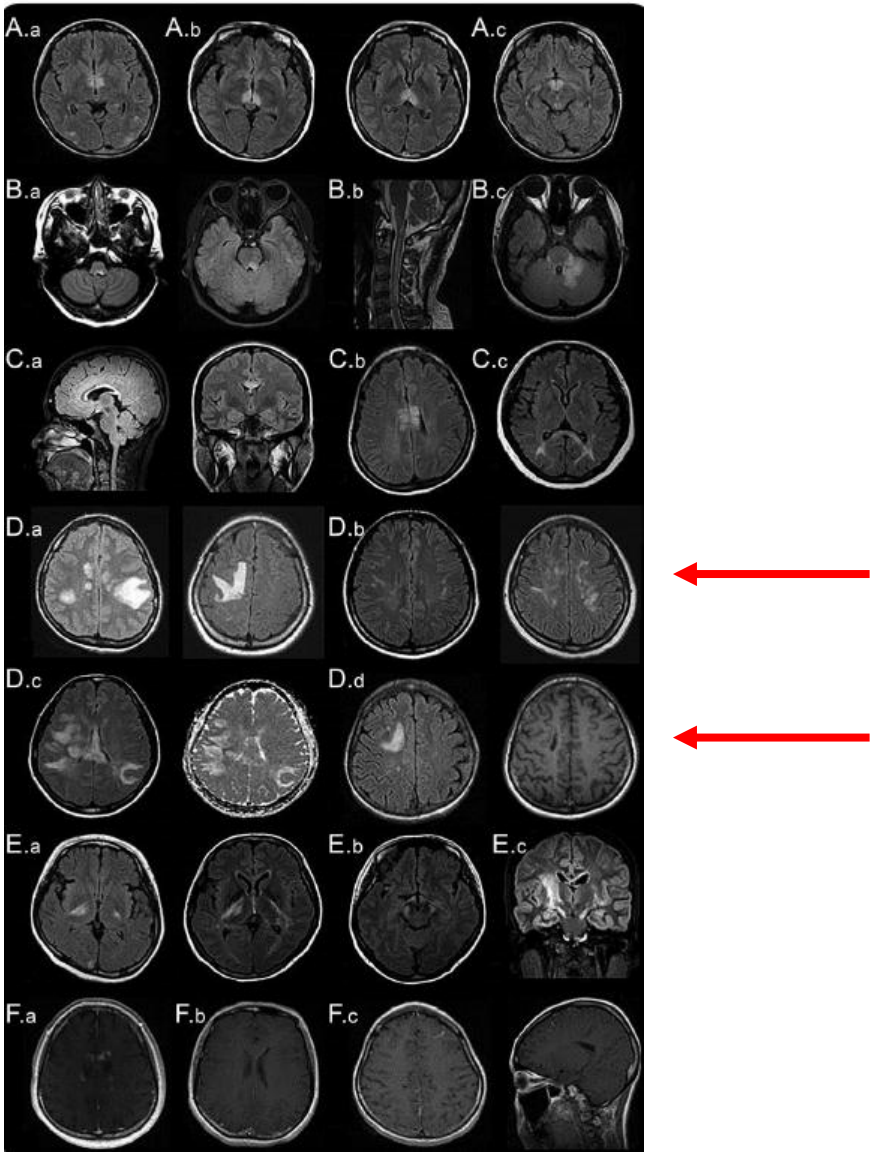
Variable	All (n = 54)	ADEM (n = 35)	MS (n = 19)	*P* Value[b]
Brain MRI				
No. of T2 lesions, mean ± SD	13.2 ± 7.8	12.2 ± 7.4	15.3 ± 8	.68
Barkhof criteria[c] met	43 (80)	26 (74)	17 (89)	.20
Edema	26 (48)	17 (49)	9 (47)	.80
Gadolinium-enhanced lesions	41 (76)	23 (66)	18 (95)	.06
Periventricular lesions	49 (91)	30 (86)	19 (100)	.24
* Corpus callosum lesions	23 (43)	8 (23)	15 (79)	<.001
Cerebellar lesions	25 (46)	15 (43)	10 (53)	.52
Brainstem lesions	27 (50)	16 (46)	11 (58)	.52
* Gray matter (basal ganglia or cortical) lesions	23 (43)	21 (60)	2 (11)	<.001
* Basal ganglia lesions	17 (31)	15 (43)	1 (5)	.004
* Cortical lesions	21 (39)	11 (31)	1 (5)	.003
Spinal cord MRI[d]				
Spinal cord lesions	25 (66)	15 (68)	10 (63)	.49
Swollen spinal cord	2 (5)	2 (6)	0	.80
Gadolinium-enhanced lesions	8 (22)	5 (23)	3 (19)	.70
Large lesion (≥2 vertebral levels)	9 (24)	7 (32)	2 (13)	.37

Abbreviations: ADEM, acute demyelinating encephalomyelitis; MRI, magnetic resonance imaging; MS, multiple sclerosis.
[a] Data are presented as number (percentage) of patients unless otherwise indicated.
[b] Comparison between the ADEM and the MS groups.
[c] Included in the criteria of McDonald et al.[10]
[d] The sample sizes for these entries are 38 for all patients, 22 for the ADEM group, and 16 for the MS group.

Table 3. Biological Data[a]

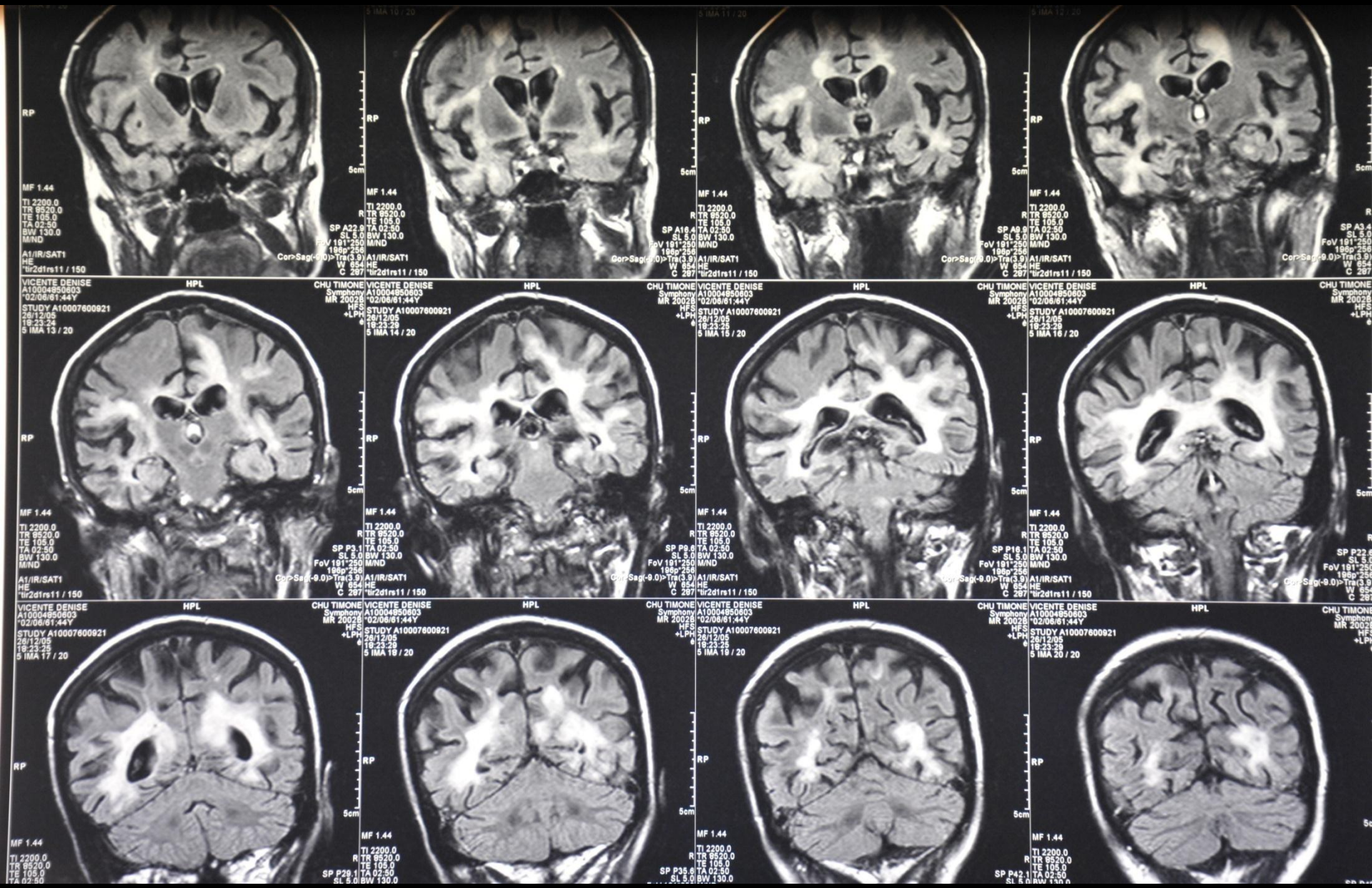
Variable	All (N = 54)	ADEM (n = 35)	MS (n = 19)	*P* Value[b]
Cerebrospinal fluid				
White blood cells/μL, mean ± SD	41.7 ± 102.5	49.2 ± 134.1	28.2 ± 35.6	.09
>30/μL	13 (24)	8 (23)	5 (26)	.80
Proteins, mean ± SD, g/dL	0.58 ± 0.3	0.63 ± 0.3	0.5 ± 0.3	.70
>1 g/dL	7 (13)	5 (14)	2 (11)	.80
* Oligoclonal bands	34 (42)	7 (20)	16 (84)	<.001
Antinuclear antibodies	3 (6)	1 (3)	2 (11)	.28

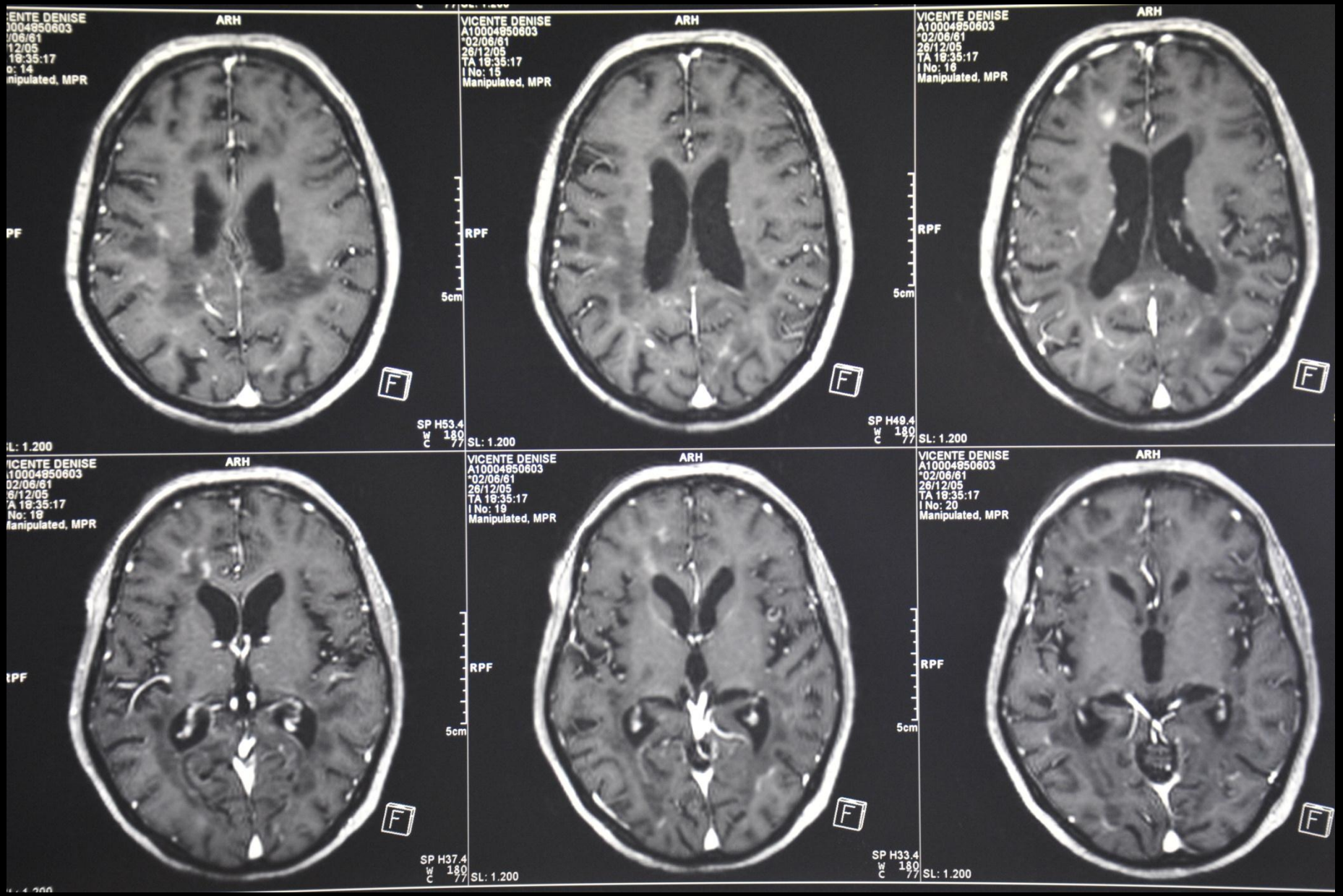
NMOSD peut s’exprimer par une atteinte inflammatoire fulminante cérébrale

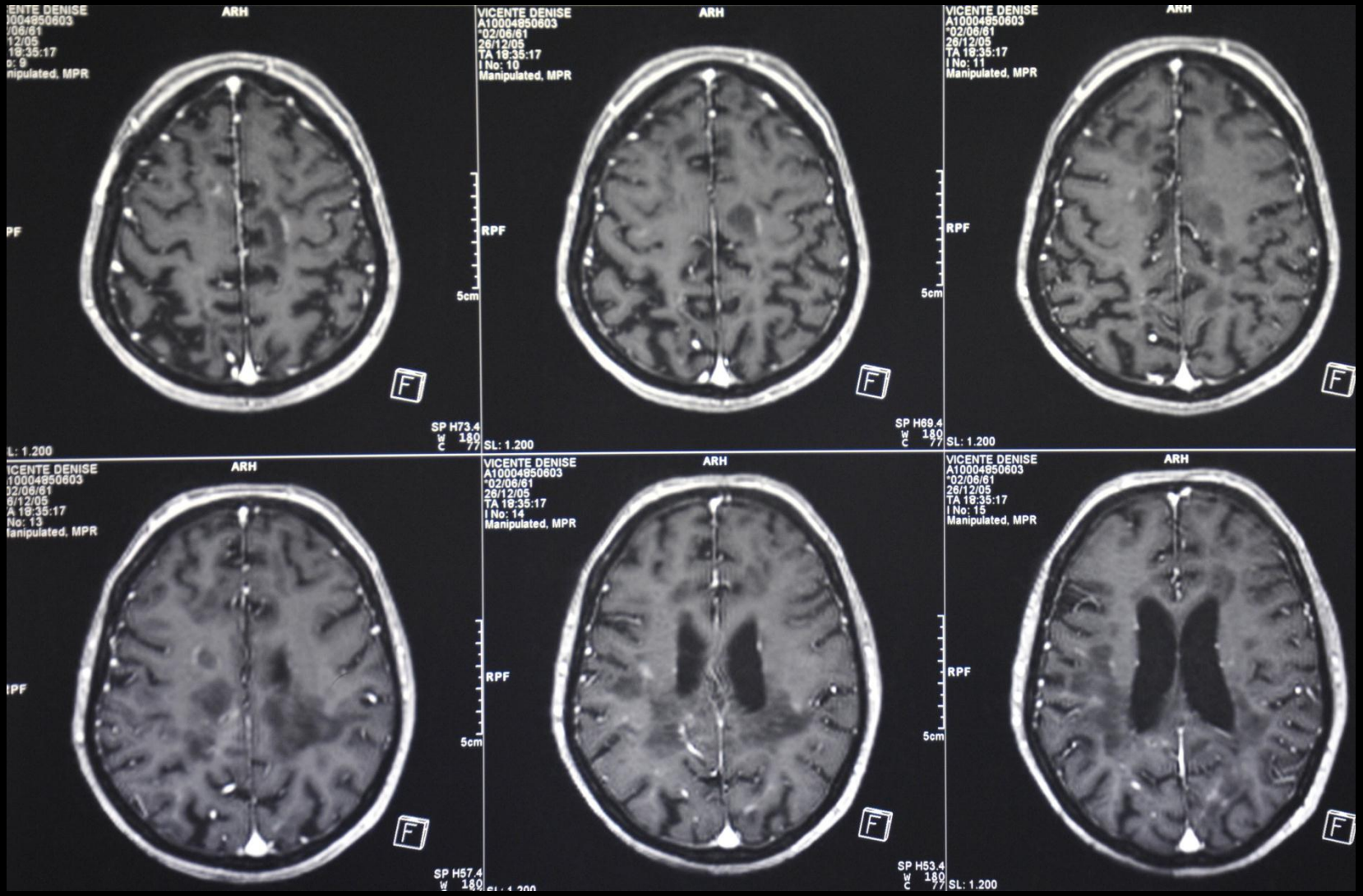


Mme VD

- Femme de 43 ans
- Apparition subaigüe d'une atteinte motrice des 4 membres, d'une ataxie mixte et d'une atteinte des fonctions supérieures (sur 3/4 semaines)
- IRM


RP
5cm
MF 1.44
TI 2200.0
TR 9520.0
TE 105.0
TA 02:50
BW 130.0
M/ND
A1/IR/SAT1
HE
*tir2d1rs11 / 150
VICENTE DENISE
A10004950603
*02/08/61:44Y
STUDY A10007600921
26/12/05
HPL
CHU TIMONE
Symphony
MR 2002B
HFS
+LPH
5 IMA 13 / 20
5 IMA 14 / 20
5 IMA 15 / 20
5 IMA 16 / 20
5 IMA 17 / 20
5 IMA 18 / 20
5 IMA 19 / 20
5 IMA 20 / 20

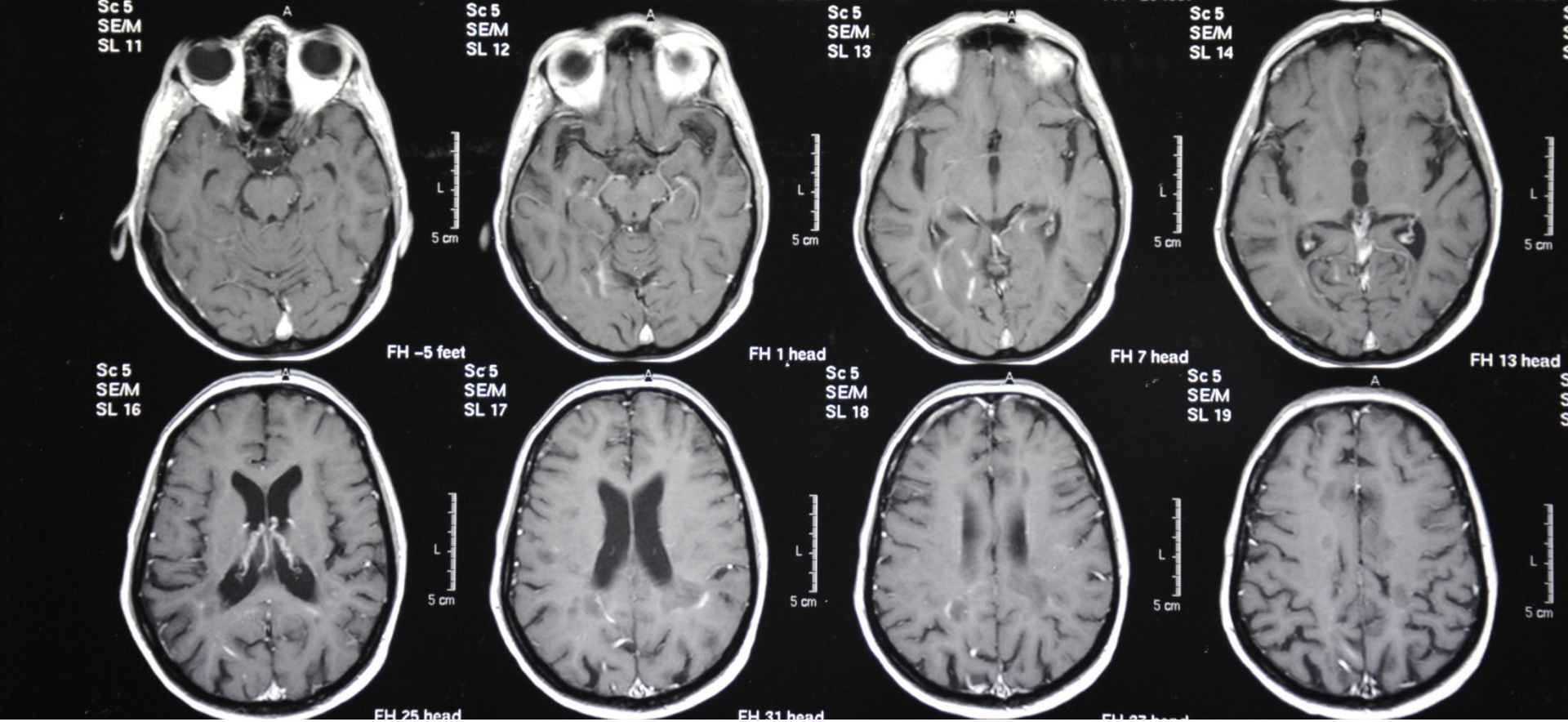

ARH
RPF
5cm
SP H53.4
W 180
C 77
SL: 1.200
VICENTE DENISE
A10004850603
*02/06/61
26/12/05
TA 18:35:17
I No: 15
Manipulated, MPR
SP H49.4
I No: 16
SP H37.4
I No: 19
SP H33.4
I No: 20


ARH
RPF
5cm
SL: 1.200
ARH
VICENTE DENISE
A10004950603
*02/06/61
26/12/05
TA 18:35:17
I No: 10
Manipulated, MPR
RPF
5cm
SP H69.4
W 180
C 77
SL: 1.200
ARH
VICENTE DENISE
A10004950603
*02/06/61
26/12/05
TA 18:35:17
I No: 11
Manipulated, MPR
RPF
5cm
SL: 1.200
ARH
RPF
5cm
SP H57.4
W 180
ARH
VICENTE DENISE
A10004950603
*02/06/61
26/12/05
TA 18:35:17
I No: 14
Manipulated, MPR
RPF
5cm
SP H53.4
W 180
C 77
ARH
VICENTE DENISE
A10004950603
*02/06/61
26/12/05
TA 18:35:17
I No: 15
Manipulated, MPR
RPF
5cm
SL: 1.200

- PL: protéinorachie=0.76G/L, absence de synthèse, absence de bande

- Amélioration partielle après plusieurs bolus de solumedrol

Un an après nouvelle majoration des troubles des fonctions supérieures puis état de mal épileptique =>IRM



Introduction ELSEP 20mg/mois pendant 6 mois début 2006

Arrêt de l’évolution de la maladie

Caractéristiques pathologiques de la maladie de Marburg

Multiple Sclerosis Journal
17(12) 1531–1538

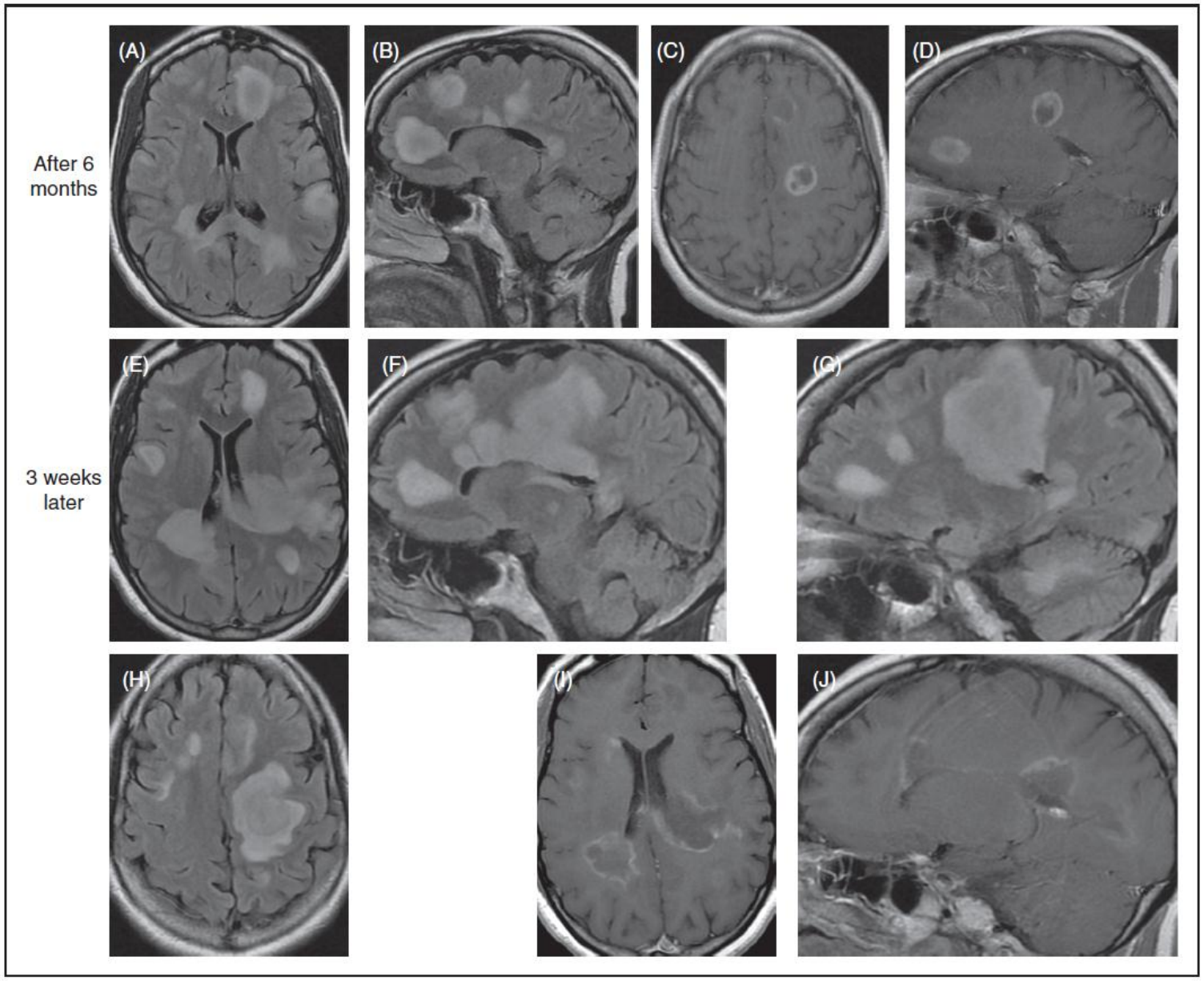
DOI: 10.1177/1352458511414042
msj.sagepub.com
SAGE

A second case of Marburg's variant of multiple sclerosis with vasculitis and extensive demyelination

Rania GA Elenein[1], Leroy R Sharer[2], Stuart D Cook[3], Andrew R Pachner[4], Jennifer Michaels[5] and Machteld E Hillen[6]

Abstract

Marburg's variant of multiple sclerosis is a rapidly progressive and malignant form of multiple sclerosis (MS) that usually leads to severe disability or death within weeks to months without remission. Few cases have been described in the literature since the original description by Marburg. The classic pathological findings usually include highly destructive zones of extensive demyelination, necrosis with dense cellular infiltrate, and giant reactive astrocytes. We report a case of a 31-year-old woman with Marburg's variant of MS who, over a period of eight months, became totally disabled, blind, and quadriplegic, with vocal cord paralysis, requiring a tracheostomy. The patient underwent diagnostic stereotactic brain biopsy. Clinical findings, magnetic resonance imaging (MRI), serologic and cerebrospinal fluid (CSF) findings, and neuropathology are discussed. MRI showed extensive white matter involvement in the brain and spinal cord that continuously progressed over time. A diagnostic stereotactic brain biopsy revealed extensive active demyelination with unexpected finding of active vasculitis and fibrinoid necrosis with a vascular inflammatory cell infiltrate, including polymorphonuclear neutrophils and rare eosinophils. Serologic work-up for vasculitis and neuromyelitis optica was unremarkable and the CSF showed only one oligoclonal band (OCB) not present in serum. This is the second case of Marburg's variant of MS that demonstrated both demyelination and vasculitis. In our case these features were demonstrated simultaneously, even though the demyelination was the predominant pathological finding. Since vasculitis is not a feature of classic MS, these findings pose the question as to whether Marburg's variant of MS is a true variant or different entity altogether.


After 6 months
3 weeks later
(A)
(B)
(C)
(D)
(E)
(F)
(G)
(H)
(I)
(J)

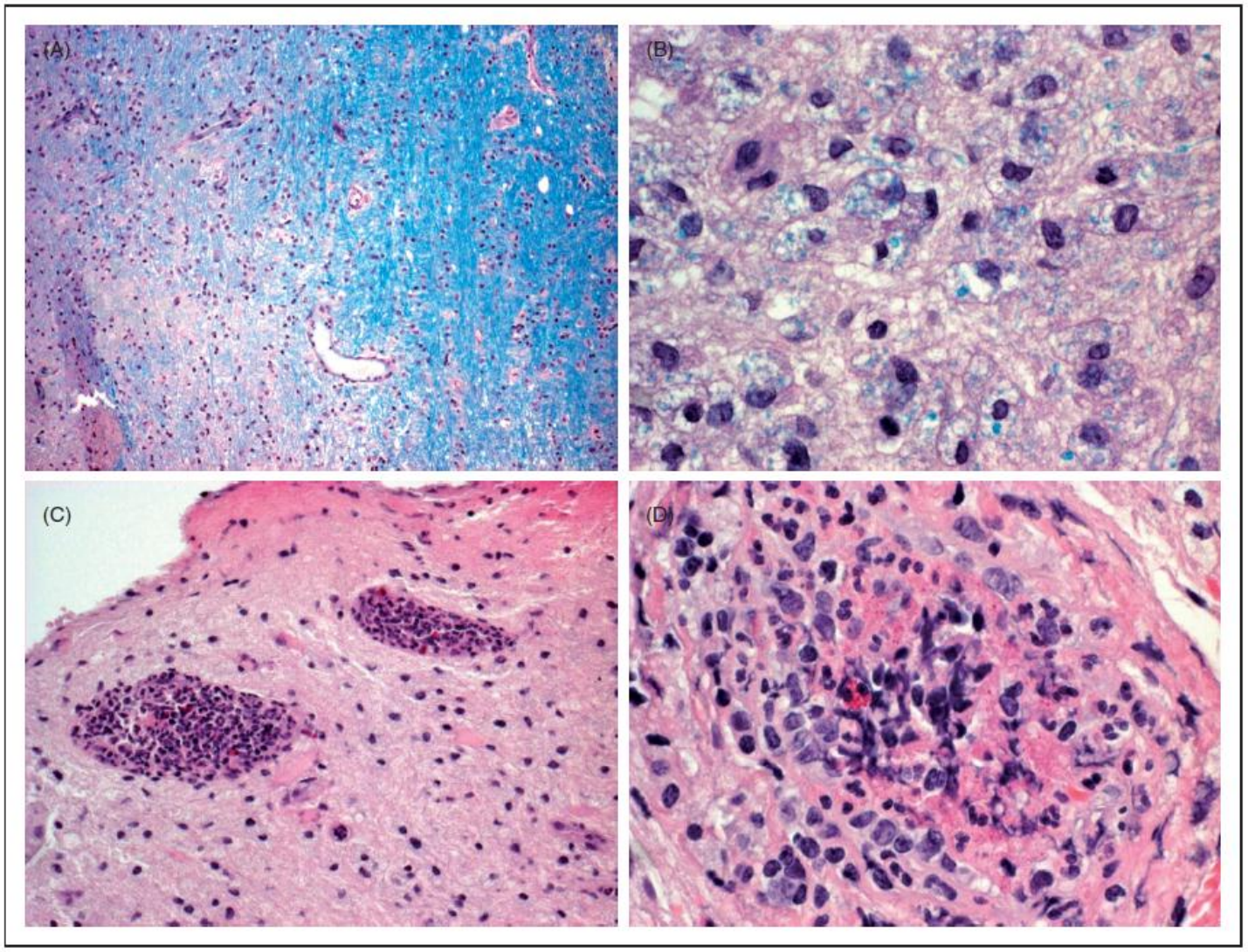
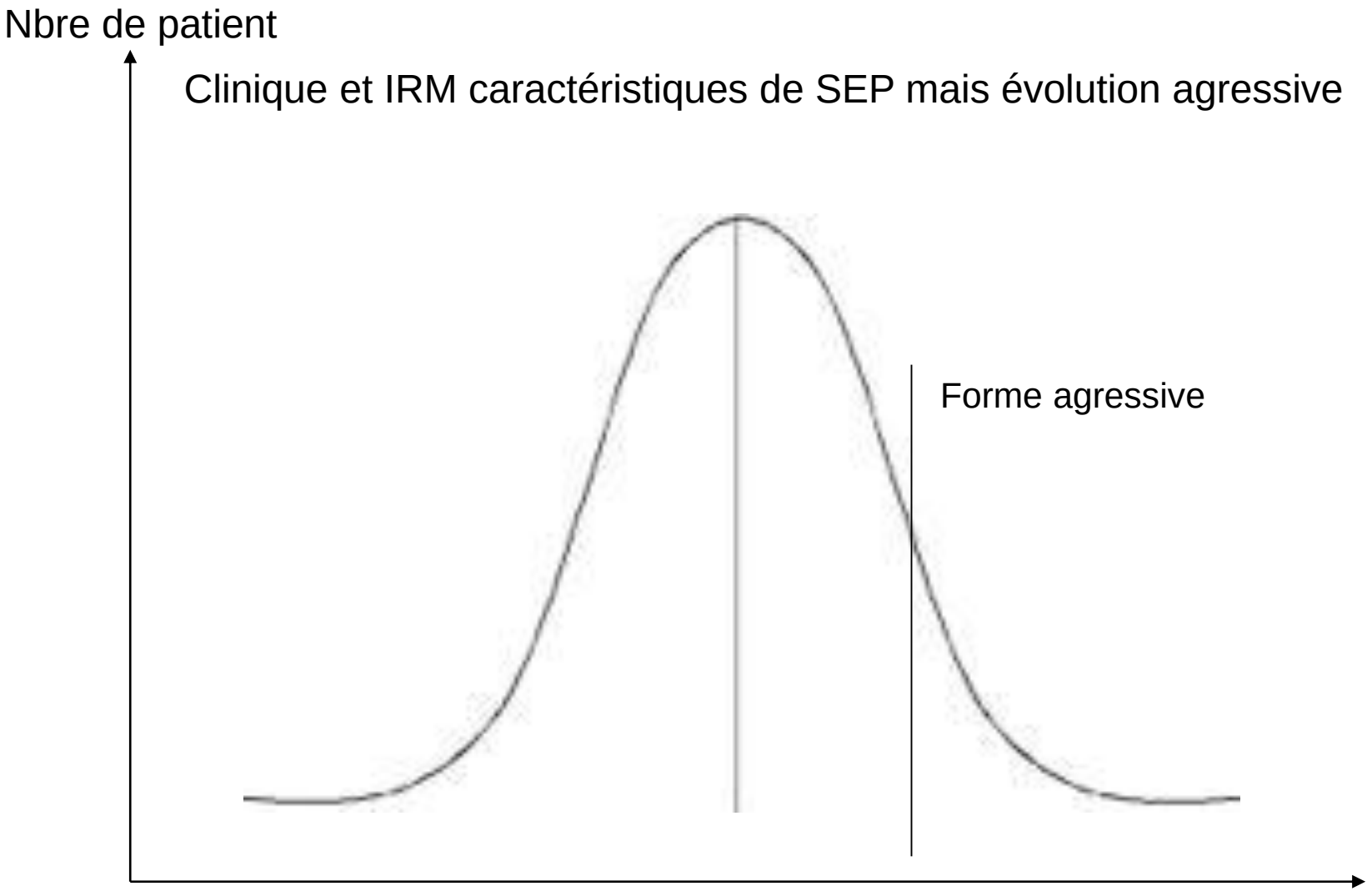


Figure 3. Unexpected findings of the brain biopsy showing vasculitis and extensive demyelination. (A) Edge of plaque, with normal myelin on right and demyelinated white matter on left. Luxol fast blue -periodic acid Schiff (LFB-PAS) stain, original magnification ×10. (B) Demyelinated region with macrophages containing LFB-positive material, indicating recent demyelination. LFB-PAS stain, original magnification ×25. (C) Vasculitis involving two vessels in demyelinated region of white matter. Eosinophils are present in the inflammatory infiltrates. Hematoxylin and eosin (H&E) stain, original magnification ×10. 3D: Vasculitis in demyelinated region, with fibrinoid necrosis. Note an eosinophil. H&E stain, original magnification ×25. (Colour online only)

SEP fulminante ou autre processus pathologique ?

Forme agressive de SEP



Forme agressive de SEP: définition?

- Proposition (Rush at al, Nature Reviews Neurology, 2015)

Au moins un des éléments suivants:

- EDSS > ou = 4 dans les 5 premières années de la SEP
- > 2 poussées avec une régression incomplète durant la dernière années
- > 2 lésions T2 et ou gado + sous traitement
- Pas de réponse à un ou plusieurs traitements de fond pris pendant au moins 1 an

Forme agressive de SEP: prévalence?

- ?

2011

Demographic and clinical characteristics of malignant multiple sclerosis

T. Gholipour, MD
B. Healy, PhD
N.F. Baruch, BSc
H.L. Weiner, MD
T. Chitnis, MD

Address correspondence and reprint requests to Dr. Tanuja Chitnis, Partners Multiple Sclerosis Center, Department of Neurology, Brigham and Women's Hospital, 1 Brookline Place, Suite 602, Brookline, MA 02445
tchitnis@partners.org

ABSTRACT

Objective: Multiple sclerosis (MS) that causes patients to require assistance for ambulation (Expanded Disability Status Scale [EDSS] ≥6) within 5 years from symptom onset is generally termed malignant. Malignant status can be transient (TM) or sustained until year 5 (SM). We studied the incidence, predictors, and demographic and clinical characteristics of malignant MS.

Methods: Patients with symptom onset in 2002–2005 and 5-year follow-up were selected from the Partners Multiple Sclerosis Center database. Patients with TM were further grouped into TM and SM. The mechanism of reaching EDSS 6 (relapse- vs progression-related) was determined.

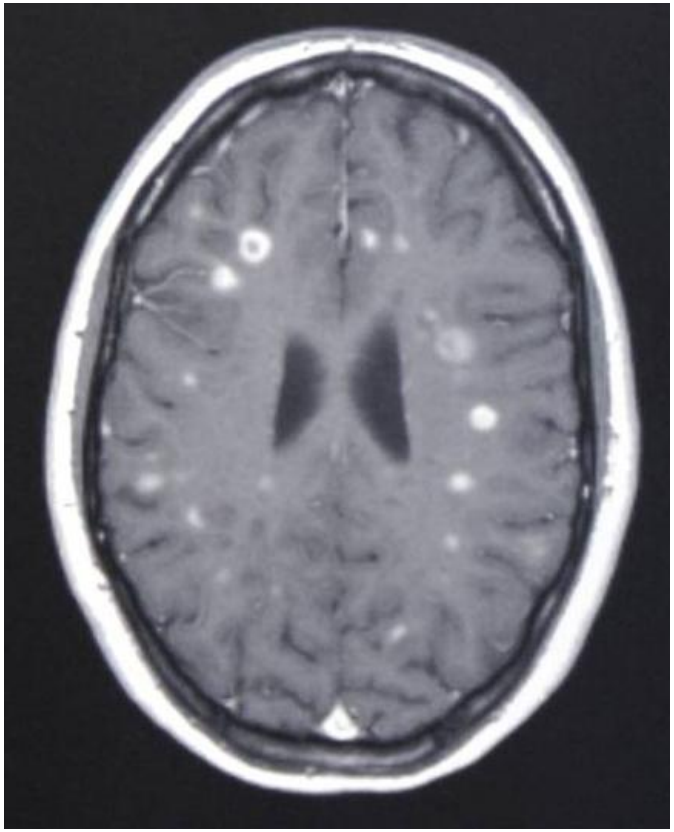
Results: A total of 487 patients were included (17 TM, 42 SM). The incidence proportion of ever malignant (EM = SM+TM) was estimated as 12.11% and SM as 8.62%. Patients with older age at onset, male gender, and positive smoking history were more likely to become SM. Compared to nonmalignant patients, the proportion of progressive-onset MS in the SM group was significantly higher, but not different in TM. Within relapsing-onset patients, most of TM, and a smaller proportion of the SM group had a relapse-related as opposed to progression-related mechanism. The final model predictors for EM vs nonmalignant were older age at onset, motor symptoms at onset, and progressive disease onset. Within the malignant patients, predictors of TM vs SM were younger age and brainstem symptoms at onset.

Conclusions: Over 10% of patients with MS experience a malignant course as defined above. Some demographic and clinical factors are found to predict a malignant outcome. MS in patients who reach a high EDSS based on disease progression is more likely to remain malignant. *Neurology*® 2011;76:1996–2001

Définition différente: patients ayant atteints l'EDSS 6 à 5 ans d'évolution

Environ 10% de l'ensemble des SEP (RRMS et PPMS)

Traitement des formes agressives de SEP



Traitement des poussée sévères

Intérêt des échanges plasmatiques en complément du Solumedrol

Weiner et al, Neurology 1989

=> effet positif chez RRMS

Weinshenker et al, Annals of Neurology 1999

=> Effet positif mais SEP/NMO/Marburg/ADEM/Myélite transverse

Magana et al, Archives of Neurology 2012

=> Effet positif associé à une durée de la maladie plus courte, des lésions cérébrales rehaussées en anneau et avec effet de masse

Mitoxantrone (Elsep®)

La mitoxantrone est un antinéoplasique cytostatique

ELSEP est un puissant agent immunosuppresseur non sélectif

Paper

Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients

JNNP, 2008

Emmanuelle Le Page,[1] Emmanuelle Leray,[2] Grégory Taurin,[1] Marc Coustans,[1] Jacques Chaperon,[2] Sean P Morrissey,[1,3] Gilles Edan[1]

Etude observationnelle sur 100 patients

Taux annualisé de poussées avant le traitement de 3.26

90% avec lésions rehaussées sur IRM

Traitement: 20 mg mitoxantrone + 1 G Solumedrol / mois pendant 6 mois

Table 2 Changes in clinical radiological parameters of multiple sclerosis activity over 5 years

	From M−12 to M0	At 1 y	At 2 y	At 3 y	At 4 y	At 5 y
No of patients	100	100	100	98	98	97
* ARR	3.29*	0.30*	0.39*	0.42*	0.38*	0.39*
* RRR of relapse frequency (%)		−91	−88	−87	−88	−88
Relapse free patients (%)	0	78	62	42.5	39	32
Time to first relapse (y)†	2.72 [1.7–5.2]					
Mean EDSS	4.1 (1) at M0	2.9 (1)	3.1 (2)	3.3 (2)	3.5 (2)	3.6 (2)
p Value**		$<10^{-5}$	$<10^{-5}$	$<10^{-5}$	$<10^{-5}$	<0.008
Patients worsened (%)	88	5	14	29	36	40
Patients not worsened (%)	12	95	86	71	64	60
Patients improved (%)		64				
Patients stable (%)		31				
RRR of worsening (%)		−94	−84	−67	−59	−54
Patients with Gd+ lesions (n (%))	65/76 (85.5)	7/76 (9)***				
* RRR of having Gd+ lesions (%)		−89.5				

ARR, annual relapse rate; EDSS, Expanded Disability Status Scale; RRR, relative risk reduction compared with M−12 to M0.
Worsening was defined as a confirmed increase in EDSS score of at least 1 point (or 0.5 points for EDSS >5.5) 3 months after the start of relapse.
Non-worsened patients did not experience any new irreversible increase in their EDSS score (by 1.0 points or more up to an EDSS score of 5.5 or by 0.5 points or more for an EDSS score >5.5, confirmed at 3 months) year after year from the end of MITOX induction.

Research paper

Mitoxantrone prior to interferon beta-1b in aggressive relapsing multiple sclerosis: a 3-year randomised trial

G Edan,[1,2,3] G Comi,[4,5] E Le Page,[1,2] E Leray,[2,3] M A Rocca,[5,6] M Filippi,[5,6] for The French—Italian Mitoxantrone Interferon-beta-1b Trial Group*

JNNP, 2011

Etude prospective randomisée

109 patients suivis sur 3 ans

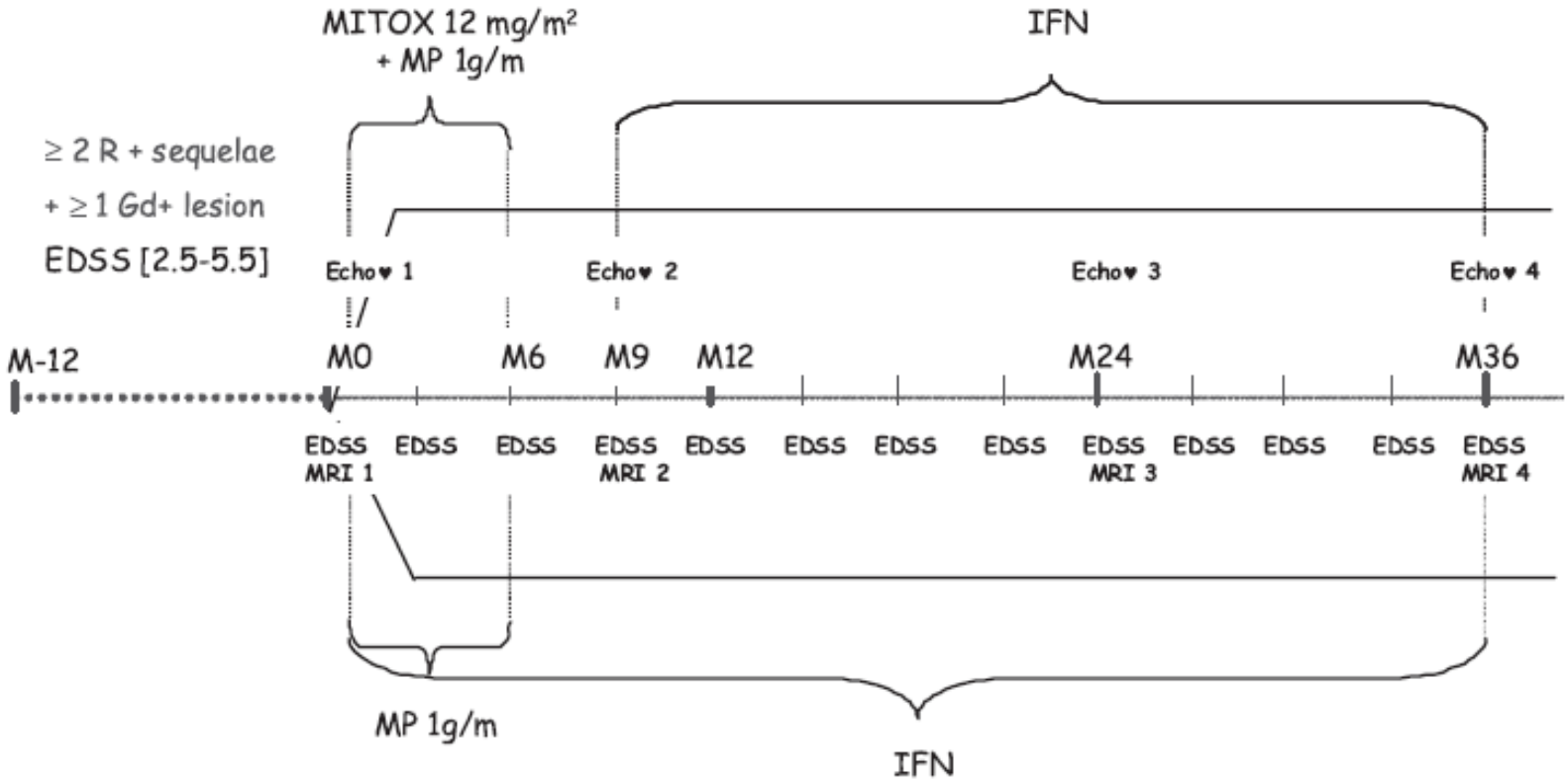

MITOX 12 mg/m²
+ MP 1g/m
IFN
≥ 2 R + sequelae
+ ≥ 1 Gd+ lesion
EDSS [2.5-5.5]
Echo♥ 1
Echo♥ 2
Echo♥ 3
Echo♥ 4
M-12
M0
M6
M9
M12
M24
M36
EDSS
MRI 1
MRI 2
MRI 3
MRI 4
MP 1g/m
IFN

Table 1 Baseline characteristics of the two study groups

Characteristic	MITOX N = 55	IFN N = 54	p Value
Demographic			
Sex ratio (female/male)	36/19	36/18	0.89
Mean age at multiple sclerosis onset (SD) (years)	26.8±7.9	27.2±7.9	0.80
Mean age at baseline (SD) (years)	33.8±7.7	32.8±8.2	0.49
Mean disease duration at baseline (SD) (years)	7.0±5.4	5.6±5.1	0.15
Previous DMT (no of patients)	21	13	0.11
Mean duration of previous DMT (SD) (months)	35±25	28±23	0.39
Clinical activity			
Previous 1-year relapse rate per patient (SD)	2.5±1.1	2.8±1.6	0.24
Previous 1-year relapse rate per group (SD)	2.5	2.6	0.90
Mean time since the last relapse (SD) (months)	3.4±2.2	3.7±2.3	0.38
Mean Expanded Disability Status Scale at baseline (SD)	4.1±1.1	3.8±0.9	0.14
MRI activity	(n =33)	(n =21)	0.96
Mean no of Gd	7.9±10.3	8.0±8.3	
Median no of Gd	5 (0–44)	6 (0–32)	
No (%) of patients with			
0 Gd-enhancing lesion	1 (3%)	1 (5%)	
1 Gd-enhancing lesion	9 (27%)	4 (19%)	
2-enhancing lesion	11 (33%)	5 (24%)	
6-enhancing lesion	5 (15%)	6 (28%)	
>10 Gd-enhancing lesion	7 (21%)	5 (24%)	

DMT, disease-modifying treatment (interferon or glatiramer acetate); Gd, gadolinium; IFN, patients receiving interferon-beta-1b for 3 years combined with 1 g of methylprednisolone monthly for the first 6 months; MITOX, patients receiving mitoxantrone monthly (12 mg/m^2; maximum 20 mg) combined with 1 g of methylprednisolone for 6 months followed by interferon-beta-1b for the last 27 months.

Table 2 Measures of disability, relapse and MRI outcomes during the trial

A. Clinical results

Outcome	MITOX N=55	IFN N=54	p Value
Disability			
Patients with sustained accumulation of disability for at least 3 months and up to the last visit			
—No (%)	5 (9.1)	14 (25.9)	
—3-year risk (%)	11.8	33.6	
Relative reduction for MITOX vs IFN	−65 %		
Mean last EDSS under study treatment (SD)	3.6±1.8	3.7±1.7	0.78
Change in mean EDSS score from baseline (SD)	−0.45±1.19	−0.06±1.39	0.12
* p Value (comparison last EDSS vs baseline)	0.007	0.771	
Relapse			
Annualised relapse rate per patient	0.44	1.15	0.03
* Relative reduction for MITOX vs IFN	−61.7 %		
Annualised relapse rate per group	0.39	0.71	0.001
Relative reduction for MITOX vs IFN	−45.1 %		
Relapse-free patients—No (%)	29 (52.7)	15 (27.8)	0.008
Relative increase for MITOX vs IFN	+93.3 %		

MRI criteria	MITOX	IFN	p Value
Mean no of new T2 lesions at each time point			
M9 (no of patients analysed)	1.48±3.31 (33)	4.81±9.10 (21)	0.028
M24 (no of patients analysed)	1.08±2.33 (26)	2.69±4.11 (16)	0.037
M36 (no of patients analysed)	2.15±4.71 (20)	3.50±4.31 (14)	0.048
* Cumulative new T2 lesions over 36 months	3.6±5.3 (18)	9.85±10.3 (13)	0.041
No of patients analysed	18	13	
No of Gd-enhancing lesions at M9	0.36±1.08	2.10±4.50	0.012
Patients without Gd-enhancing lesions, no (%)			
Baseline	1/33 (3%)	1/21 (4.8%)	1.000
M9	29/33 (88%)	12/21 (57%)	0.010
M24	18/26 (69%)	10/16 (62%)	0.653
M36	15/20 (75%)	10/14 (71%)	1.000

EDSS, Expanded Disability Status Scale; Gd, gadolinium; IFN, patients receiving Interferon-beta-1b for 3 years combined with 1 g of methylprednisolone monthly for the first 6 months; MITOX, patients receiving mitoxantrone monthly (12 mg/m^2; maximum 20 mg) combined with 1 g of methylprednisolone for 6 months followed by interferon-beta-1b for the last 27 months.

Effets indésirables de la mitoxantrone

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

Evidence Report: The efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

James J. Marriott, MD
Janis M. Miyasaki, MD, MEd, FAAN
Gary Gronseth, MD, FAAN
Paul W. O'Connor, MD, MSc

Address correspondence and reprint requests to American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN 55116
guidelines@aan.com

ABSTRACT

Objective: The chemotherapeutic agent mitoxantrone was approved for use in multiple sclerosis (MS) in 2000. After a review of all the available evidence, the original report of the Therapeutics and Technology Assessment Subcommittee in 2003 concluded that mitoxantrone probably reduced clinical attack rates, MRI activity, and disease progression. Subsequent reports of decreased systolic function, heart failure, and leukemia prompted the US Food and Drug Administration to institute a "black box" warning in 2005. This review was undertaken to examine the available literature on the efficacy and safety of mitoxantrone use in patients with MS since the initial report.

Methods: Relevant articles were obtained through a review of the medical literature and the strength of the available evidence was graded according to the American Academy of Neurology evidence classification scheme.

Results: The accumulated Class III and IV evidence suggests an increased incidence of systolic dysfunction and therapy-related acute leukemia (TRAL) with mitoxantrone therapy. Systolic dys-

Neurology 2010

Diminution de la fonction systolique (12%)
Insuffisance cardiaque congestive (0.4%)
Leucémie (0.8%)

Alemtuzumab

Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial

Alasdair J Coles, Cary L Twyman, Douglas L Arnold, Jeffrey A Cohen, Christian Confavreux, Edward J Fox, Hans-Peter Hartung, Eva Havrdova, Krzysztof W Selmaj, Howard L Weiner, Tamara Miller, Elizabeth Fisher, Rupert Sandbrink, Stephen L Lake, David H Margolin, Pedro Oyuela, Michael A Panzara, D Alastair S Compston, for the CARE-MS II investigators*

Summary

Background The anti-CD52 monoclonal antibody alemtuzumab reduces disease activity in previously untreated patients with relapsing-remitting multiple sclerosis. We aimed to assess efficacy and safety of alemtuzumab compared with interferon beta 1a in patients who have relapsed despite first-line treatment.

Methods In our 2 year, rater-masked, randomised controlled phase 3 trial, we enrolled adults aged 18–55 years with relapsing-remitting multiple sclerosis and at least one relapse on interferon beta or glatiramer. Eligible participants were randomly allocated in a 1:2:2 ratio by an interactive voice response system, stratified by site, to receive subcutaneous interferon beta 1a 44 µg, intravenous alemtuzumab 12 mg per day, or intravenous alemtuzumab 24 mg per day. Interferon beta 1a was given three-times per week and alemtuzumab was given once per day for 5 days at baseline and for 3 days at 12 months. The 24 mg per day group was discontinued to aid recruitment, but data are included for safety assessments. Coprimary endpoints were relapse rate and time to 6 month sustained accumulation of disability, comparing alemtuzumab 12 mg and interferon beta 1a in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00548405.

Findings 202 (87%) of 231 patients randomly allocated interferon beta 1a and 426 (98%) of 436 patients randomly allocated alemtuzumab 12 mg were included in the primary analyses. 104 (51%) patients in the interferon beta 1a group relapsed (201 events) compared with 147 (35%) patients in the alemtuzumab group (236 events; rate ratio 0·51 [95% CI 0·39–0·65]; p<0·0001), corresponding to a 49·4% improvement with alemtuzumab. 94 (47%) patients in the interferon beta 1a group were relapse-free at 2 years compared with 278 (65%) patients in the alemtuzumab group (p<0·0001). 40 (20%) patients in the interferon beta 1a group had sustained accumulation of disability compared with 54 (13%) in the alemtuzumab group (hazard ratio 0·58 [95% CI 0·38–0·87]; p=0·008), corresponding to a 42% improvement in the alemtuzumab group. For 435 patients allocated alemtuzumab 12 mg, 393 (90%) had infusion-associated reactions, 334 (77%) had infections (compared with 134 [66%] of 202 patients in the interferon beta 1a group) that were mostly mild-moderate with none fatal, 69 (16%) had thyroid disorders, and three (1%) had immune thrombocytopenia.

Interpretation For patients with first-line treatment-refractory relapsing-remitting multiple sclerosis, alemtuzumab could be used to reduce relapse rates and sustained accumulation of disability. Suitable risk management strategies allow for early identification of alemtuzumab's main adverse effect of secondary autoimmunity.

Phase III Alemtuzumab vs INF1a chez des patients **SEP évolutifs sous traitement de fond**

Anticorps monoclonal humanisé anti-CD52
12mg/J pendant 5 J puis 12mg/J pendant 3J un an après

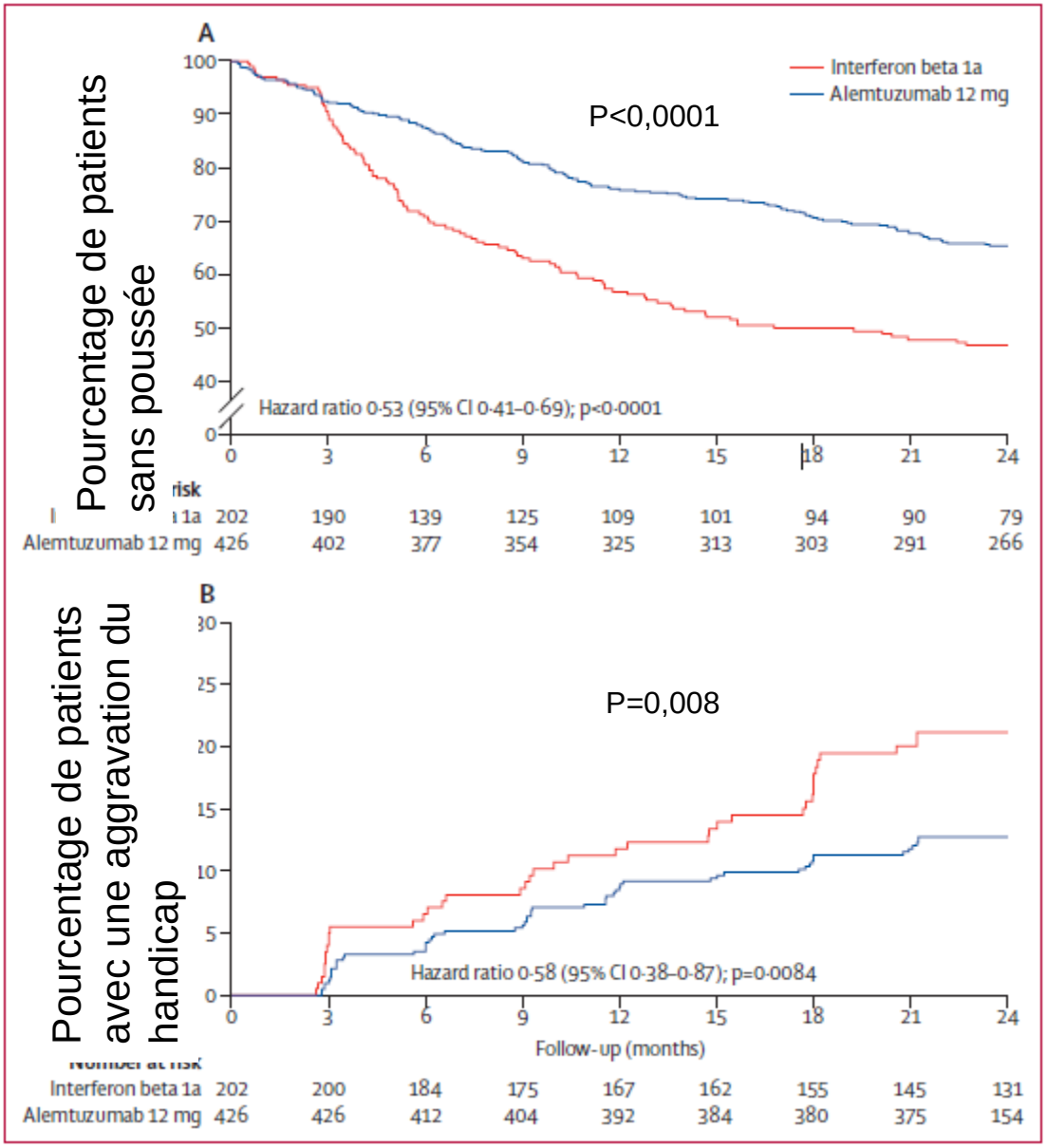
Entraîne une baisse rapide des lymphocytes suivie d'une restauration rapide des LB et plus lente des LT (avec une augmentation de la proportion des lymphocytes régulateurs et mémoire)

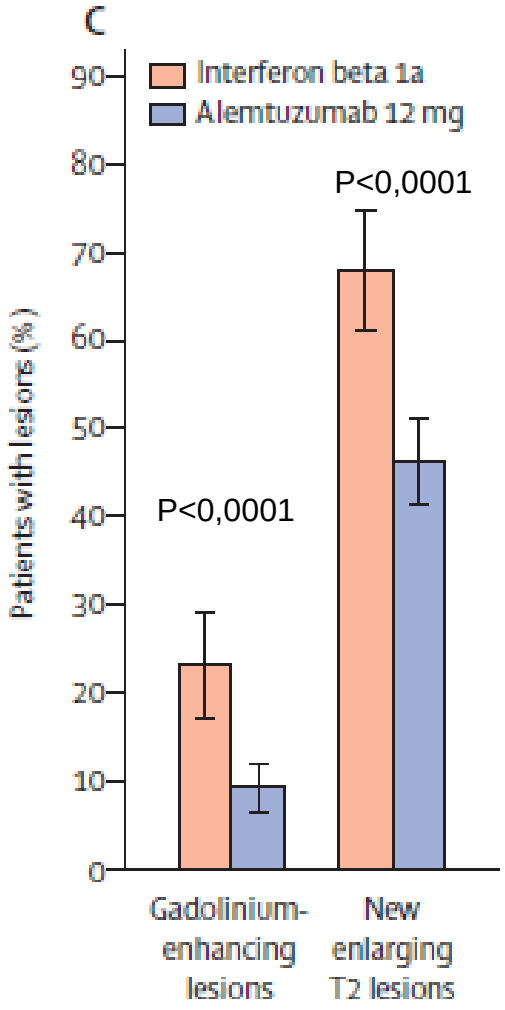
	Interferon beta 1a (n=202)	Alemtuzumab 12 mg (n=426)	Alemtuzumab 24 mg (n=170)
Age, years	35·8 (8·77)	34·8 (8·36)	35·1 (8·40)
Sex, female	131 (65%)	281 (66%)	120 (71%)
Race, white	187 (93%)	385 (90%)	142 (84%)
EDSS score			
Mean	2·7 (1·21)	2·7 (1·26)	2·7 (1·17)
Median	2·5 (0·0–6·0)	2·5 (0·0–6·5)	2·5 (0·0–6·0)
EDSS score subgroup			
0	5 (2%)	16 (4%)	4 (2%)
1·1·5	44 (22%)	89 (21%)	31 (18%)
2·0	34 (17%)	63 (15%)	29 (17%)
2·5–3·0	48 (24%)	112 (26%)	52 (31%)
3·5–4·0	50 (25%)	98 (23%)	38 (22%)
4·5–5·0	19 (9%)	42 (10%)	14 (8%)
5·5–6·5*	2 (1%)	6 (1%)	2 (1%)
Time since first clinical event, years			
Mean	4·7 (2·86)	4·5 (2·68)	4·3 (2·77)
Median	4·1 (0·4–10·1)	3·8 (0·2–14·4)	3·7 (0·2–16·9)
Relapses in previous year			
0*	5 (2%)	6 (1%)	3 (2%)
1	107 (53%)	211 (50%)	84 (49%)
2	68 (34%)	151 (35%)	64 (38%)
≥3	22 (11%)	58 (14%)	19 (11%)
Mean	1·5 (0·75)	1·7 (0·86)	1·6 (0·86)
Median	1·0 (0·0–4·0)	1·0 (0·0–5·0)	1·0 (0·0–6·0)
Number of gadolinium-enhancing lesions (T1-weighted images)			
Mean	2·10 (4·95)	2·28 (6·02)	2·88 (8·47)
Median	0·0 (0·0–41·0)	0·0 (0·0–72·0)	0·0 (0·0–90·0)
Patients with baseline lesions	87/199 (44%)	178/420 (42%)	74/165 (45%)
T2-hyperintense lesion volume, cm³			
Mean	9·04 (10·42)	9·94 (12·25)	9·47 (9·66)
Median	5·6 (0·0–70·3)	6·0 (0·0–77·6)	6·2 (0·1–52·2)
Brain parenchymal fraction			
Mean	0·817 (0·022)	0·813 (0·023)	0·816 (0·024)
Median	0·817 (0·738–0·862)	0·816 (0·730–0·863)	0·816 (0·729–0·866)
Duration of previous multiple sclerosis drug use, months			
Mean	36 (23·7)	35 (25·0)	37 (23·9)
Median	29 (6–115)	28 (4–131)	33 (6–121)
Number of previous multiple sclerosis drugs			
1	151 (75%)	299 (70%)	120 (71%)
2	41 (20%)	92 (22%)	39 (23%)
3	9 (4%)	24 (6%)	11 (6%)
≥4	1 (<1%)	11 (3%)	0
Mean	1 (0·6)	1 (0·7)	1 (0·6)
Median	1 (1–4)	1 (1–4)	1 (1–3)

(Continues on next page)

Patients inclus avaient présenté au moins une poussée sous IFN ou copaxone

	IFN1a	Alemtuzumab 12	Alemtuzumab 24
Time since first clinical event, years			
Mean	4·7 (2·86)	4·5 (2·68)	4·3 (2·77)
Median	4·1 (0·4–10·1)	3·8 (0·2–14·4)	3·7 (0·2–16·9)
Relapses in previous year			
0*	5 (2%)	6 (1%)	3 (2%)
1	107 (53%)	211 (50%)	84 (49%)
2	68 (34%)	151 (35%)	64 (38%)
≥3	22 (11%)	58 (14%)	19 (11%)
Mean	1·5 (0·75)	1·7 (0·86)	1·6 (0·86)
Median	1·0 (0·0–4·0)	1·0 (0·0–5·0)	1·0 (0·0–6·0)
Number of gadolinium-enhancing lesions (T1-weighted images)			
Mean	2·10 (4·95)	2·28 (6·02)	2·88 (8·47)
Median	0·0 (0·0–41·0)	0·0 (0·0–72·0)	0·0 (0·0–90·0)
Patients with baseline lesions	87/199 (44%)	178/420 (42%)	74/165 (45%)


A
Pourcentage de patients sans poussée
Interferon beta 1a
Alemtuzumab 12 mg
P<0,0001
Hazard ratio 0·53 (95% CI 0·41–0·69); p<0·0001
risk
Alemtuzumab 12 mg 426 402 377 354 325 313 303 291 266
B
Pourcentage de patients avec une aggravation du handicap
P=0,008
Hazard ratio 0·58 (95% CI 0·38–0·87); p=0·0084
Follow-up (months)
Interferon beta 1a 202 200 184 175 167 162 155 145 131
Alemtuzumab 12 mg 426 426 412 404 392 384 380 375 154


C
Interferon beta 1a
Alemtuzumab 12 mg
Patients with lesions (%)
P<0,0001
P<0,0001
Gadolinium-enhancing lesions
New enlarging T2 lesions

A 24 mois

Effets indésirables Alemtuzumab

Réactions précoces: faibles à modérées chez la majorité des patients, importantes chez 3% => céphalées, nausées, rash cutané, fièvre, tachycardie, bradycardie (prémédication nécessaire par corticoide, antipyrétique et antihistaminique)

Infection: Herpes buccal, zona, pharyngite, infection urinaire, infection respiratoire haute, infection oesophagienne à candida, tuberculose (prophylaxie par aciclovir pendant un mois après perfusion)

Pathologies auto-immunes (quelques fois tardives > 4 ans) : thyroidite auto-immune (34% !), purpura thrombopénique (1%), néphropathie (0.3%)

J Neurol (2015) 262:1024–1034
DOI 10.1007/s00415-015-7653-3

ORIGINAL COMMUNICATION

Alemtuzumab as rescue therapy in a cohort of 16 aggressive multiple sclerosis patients previously treated by Mitoxantrone: an observational study

Emmanuelle Le Page · Véronique Deburghgraeve · Marie-Antoinette Lester · Isabelle Cardiet · Emmanuelle Leray · Gilles Edan

8 SPMS et 8 RRMS
De 2 à 30 nouvelles lésions Gado + l'année précédente

Après Alemtuzumab:

SPMS

⇒ 2/8 étaient « disease free» (4.7 et 8 ans de recul)
⇒ 5/8 amélioration transitoire
⇒ 1/8 aggravation

RRMS

⇒ 1/8 est resté stable (9 ans de recul)
⇒ **7/8 se sont améliorés** (1-4 points EDSS) (recul de au moins 1 an, moyenne 34 mois)

3 thyroïdites

Natalizumab (Tysabri ®)

Le natalizumab est un inhibiteur sélectif des molécules d'adhésion (sous-unité alpha4 des intégrines), fortement exprimées à la surface de tous les leucocytes

Original Paper

European Neurology

Eur Neurol 2010;63:101–106
DOI: 10.1159/000276400

Received: September 18, 2009
Accepted after revision: October 18, 2009
Published online: January 16, 2010

Natalizumab Reduces Clinical and MRI Activity in Multiple Sclerosis Patients with High Disease Activity: Results from a Multicenter Study in Switzerland

Norman Putzki[a] Özgür Yaldizli[a] Robert Bühler[b] Guido Schwegler[c]
Daniela Curtius[d] Barbara Tettenborn[a]

Departments of Neurology at [a]Cantonal Hospital St. Gallen, St. Gallen, [b]Bürgerspital Solothurn, Solothurn, and [c]Cantonal Hospital Aarau, Aarau, and [d]Biogen-Dompé, Zug, Switzerland

Etude rétrospective multicentrique sur 85 patients

Taux annualisé de poussées avant inclusion de 2 +/-0.6

Période étudiée de 2 ans environ

	AFFIRM natalizumab 300 mg i.v.	AFFIRM placebo	Present trial
Baseline characteristics			
Subjects, n	627	315	85
Median age, years (range)	36 (18-50)	37 (19–50)	37 (19–62)
Duration of disease, years (range)[1]	5 (0-34)	6 (0-33)	7.4 (1.1–34.8)
Relapses in previous 12 months (mean ± SD)	1.53 ± 0.91	1.5 ± 0.77	2.0 ± 0.6
EDSS baseline (range)	2 (0–6)	2 (0–6)	3 (0–7.5)
Results			
ARR	0.26	0.81	0.27
Relapse-free	80%[2]	60%[2]	79%[3]

EDSS = Expanded Disability Status Scale score; ARR = annualized relapse rate.
[1] At entry of the study. [2] 12 months after natalizumab initiation. [3] During 17.2 months (median).

European Journal of Neurology 2010, **17:** 31–37 doi:10.1111/j.1468-1331.2009.02728.x

Efficacy of natalizumab in second line therapy of relapsing–remitting multiple sclerosis: results from a multi-center study in German speaking countries

N. Putzki[a,b], O. Yaldizli[b], M. Mäurer[c], S. Cursiefen[c], S. Kuckert[d], C. Klawe[e], M. Maschke[e], B. Tettenborn[b] and V. Limmroth[d]

[a]*Department of Neurology, University Clinic Essen, University of Duisburg-Essen, Germany;* [b]*Department of Neurology, Cantonal Hospital St. Gallen, St Gallen, Switzerland;* [c]*Department of Neurology, University Clinic Erlangen, Erlangen, Germany;* [d]*Department of Neurology, Cologne City Hospitals, Cologne-Merheim, Germany; and* [e]*Department of Neurology, Barmherzige Brueder Hospital, Trier, Germany*

Etude rétrospective multicentrique sur 97 patients

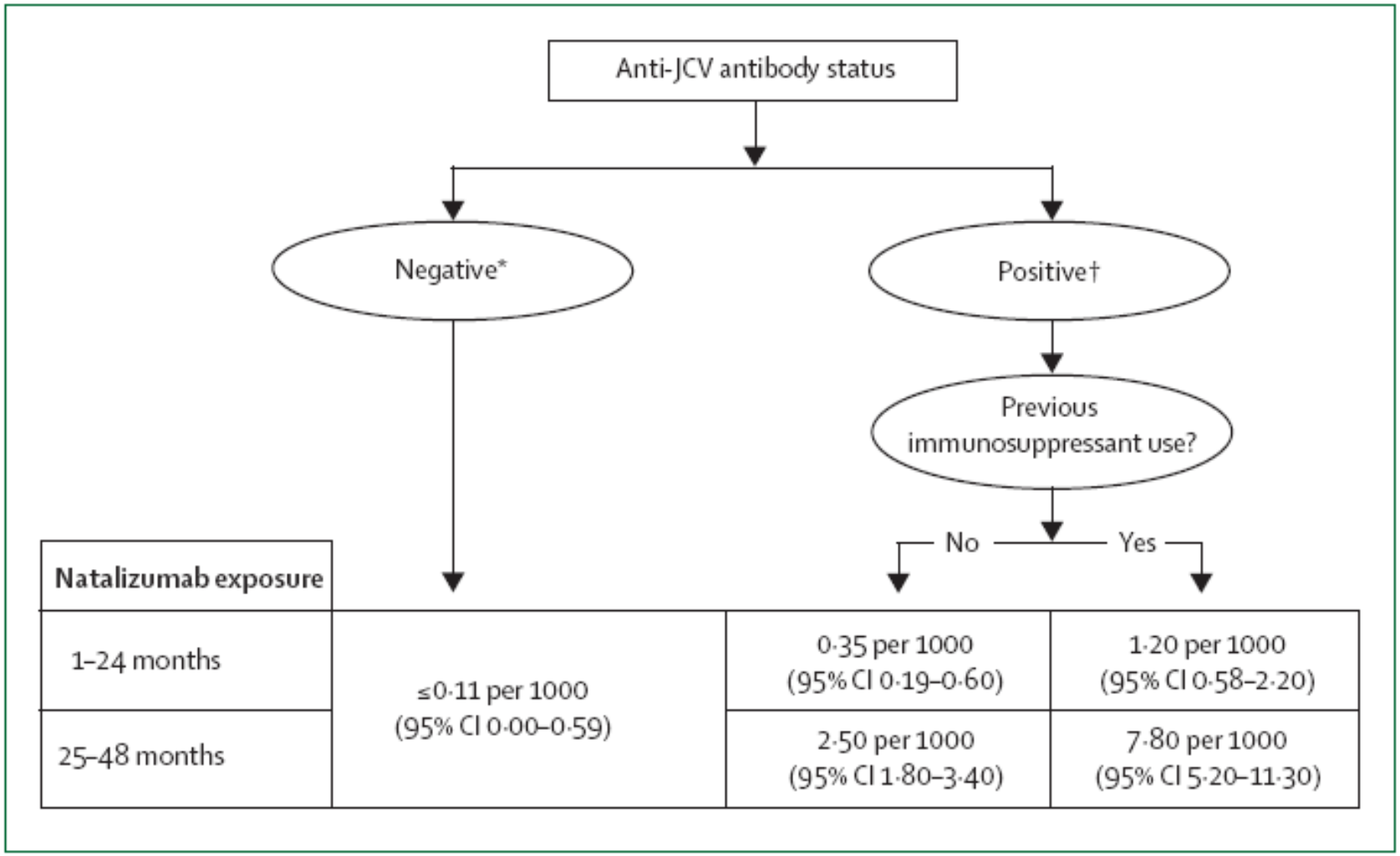
Taux annualisé de poussées avant inclusion de 2,3

Période étudiée de 2 ans environ

	AFFIRM natalizumab 300 mg i.v.	AFFIRM placebo	This trial (n = 97)
Patients			
Age, years, median (range)	36 (18–50)	37 (19–50)	36 (19–59)
Duration of MS[a], years, median (range)	5 (0–34)	6 (0–33)	6.9 (0–23)
Relapses in previous year, mean, SD	1.53 ± 0.91	1.5 ± 0.77	2.3 ± 0.6
EDSS baseline, median (range)	2 (0–6)	2 (0–6)	3.5 (0–6.5)
Results			
Annual relapse rate	0.26	0.81	0.17
Relapse free[b]	80%	60%	80%

Effets indésirables du Natalizumab

LEMP ++++



Natalizumab exposure			
1–24 months	≤0·11 per 1000 (95% CI 0·00–0·59)	0·35 per 1000 (95% CI 0·19–0·60)	1·20 per 1000 (95% CI 0·58–2·20)
25–48 months		2·50 per 1000 (95% CI 1·80–3·40)	7·80 per 1000 (95% CI 5·20–11·30)

Figure 3: **Estimated risk of PML based on anti-JCV antibody status, previous immunosuppressant use, and duration of natalizumab treatment**

Valeur de l'index de la sérologie anti-JC

RESEARCH ARTICLE

Annals of Neurology, 2015

Anti–JC Virus Antibody Levels in Serum or Plasma Further Define Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy

Tatiana Plavina, PhD, Meena Subramanyam, PhD, Gary Bloomgren, MD, Sandra Richman, MD, MPH, Amy Pace, ScD, Sophia Lee, PhD, Brian Schlain, MS, Denise Campagnolo, MD, Shibeshih Belachew, PhD, MD, and Barry Ticho. PhD. MD

Objective: The increased risk of progressive multifoc associated with the presence of anti–JC virus (JCV) ant ured as index, may further define PML risk in seropositi
Methods: The association between serum or plasma ar antibody–positive multiple sclerosis (MS) patients from PML and non-PML patients, the probabilities of having thresholds were calculated using all available data and stability of anti-JCV antibody index was also evaluated.
Results: Anti-JCV antibody index data were available diagnosis from 71 natalizumab-treated PML patients patients with no prior immunosuppressant use, anti-JC patients than in non-PML patients ($p < 0.0001$). Among the AFFIRM and STRATIFY-1 trials, 97% remained con months. Retrospective analyses of pre-PML samples c higher anti-JCV antibody index over time.
Interpretation: Anti-JCV antibody levels in serum/plasi antibody–positive MS patients with no prior immuno index and PML risk is warranted.

→ **<1.5**

Deux populations étudiées:

Population test: 1039 non-LEMP et 45 LEMP

Population pour vérification: 1483 non-LEMP et 26 LEMP

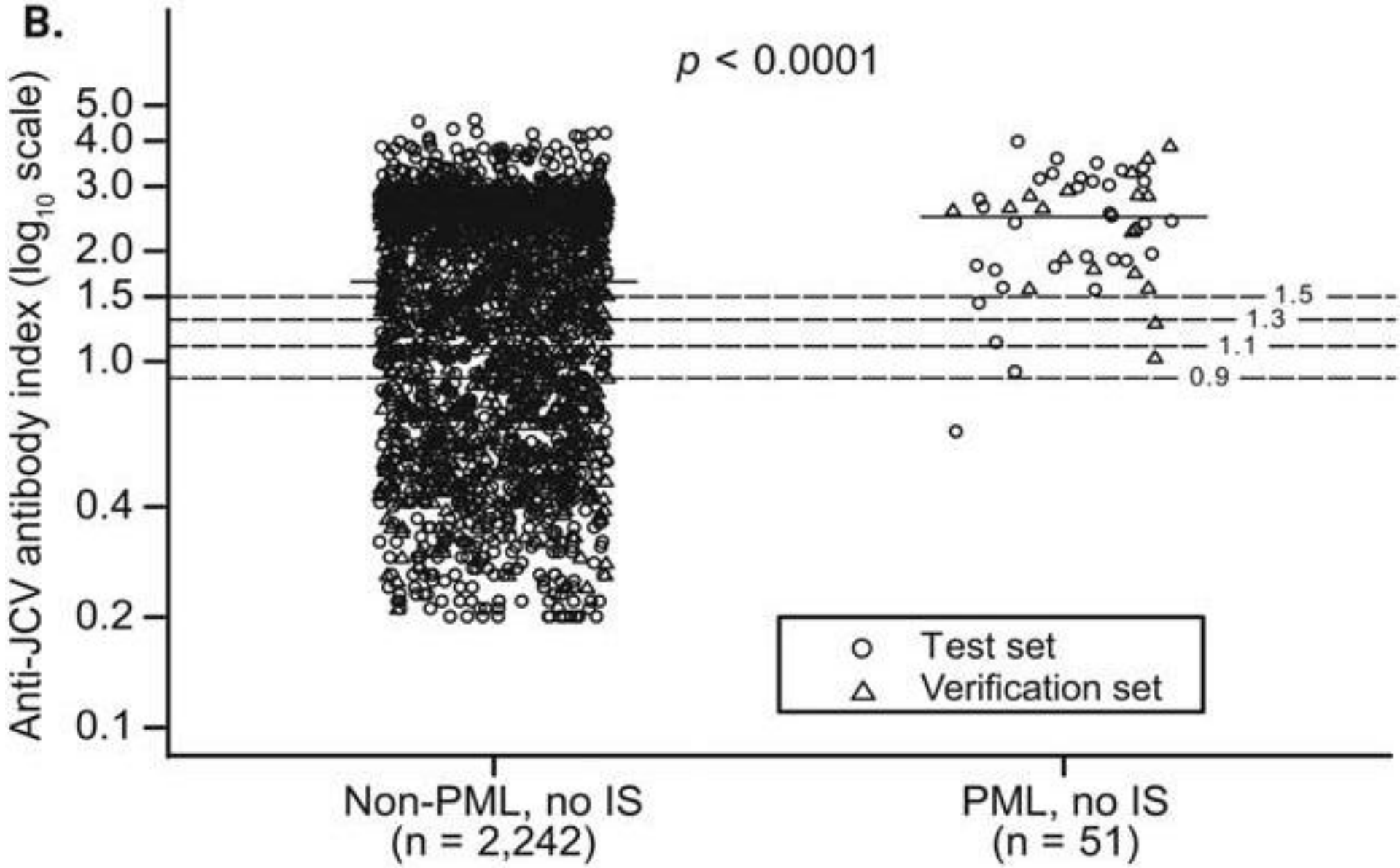
TABLE 2. PML Risk Estimates by Index Threshold in Anti-JCV Antibody–Positive Patients with No Prior IS Use

Anti-JCV Antibody Index	PML Risk Estimates per 1,000 Anti-JCV Antibody–Positive Patients by Natalizumab Treatment Duration, No Prior IS Use		
	1–24 Months (99% CI)	25–48 Months (99% CI)	49–72 Months (99% CI)
≤0.9	0.1 (0–0.15)	0.3 (0–1.28)	0.4 (0–1.25)
≤1.1	0.1 (0–0.23)	0.7 (0–1.85)	0.7 (0–1.98)
≤1.3	0.1 (0–0.28)	1.0 (0–2.38)	1.2 (0–2.56)
≤1.5	0.1 (0–0.30)	1.2 (0.20–2.61)	1.3 (0.24–2.78)
>1.5	1.0 (0.84–1.07)	8.1 (7.06–8.98)	8.5 (7.41–9.46)
No index[a]	0.6 (0.42–0.88)	5.2 (4.28–6.19)	5.4 (4.03–7.14)

PML risk estimates across anti-JCV antibody index thresholds were calculated based on the PML risk stratification algorithm (from September 2012) and predicted probabilities shown in Table 1 for the anti-JCV antibody–positive population at or below respective index thresholds from 0.9 to 1.5. For index thresholds at or below 0.7, PML patient numbers were insufficient to allow for calculation of risk estimates.
[a]Based on existing PML risk stratification algorithm using September 2012 data for the anti-JCV antibody positive group with no prior IS use.
CI = confidence interval; IS = immunosuppressant; JCV = JC virus; PML = progressive multifocal leukoencephalopathy.

Valable uniquement chez les patients naïfs de traitements immunosuppresseurs antérieurs

Valeur de l'index de la sérologie anti-JC



Rituximab

Uniquement phase II

Arrêt développement => Ocrelizumab (Phase III présenté à l'ECTRIMS 2015)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

Stephen L. Hauser, M.D., Emmanuelle Waubant, M.D., Ph.D., Douglas L. Arnold, M.D., Timothy Vollmer, M.D., Jack Antel, M.D., Robert J. Fox, M.D., Amit Bar-Or, M.D., Michael Panzara, M.D., Neena Sarkar, Ph.D., Sunil Agarwal, M.D., Annette Langer-Gould, M.D., Ph.D., and Craig H. Smith, M.D., for the HERMES Trial Group*

Rituximab in Relapsing-Remitting Multiple Sclerosis: A 72-Week, Open-Label, Phase I Trial

Amit Bar-Or, MD,[1] Peter A. J. Calabresi, MD,[2] Douglas Arnold, MD,[1,3] Clyde Markowitz, MD,[4] Stuart Shafer, MD,[5] Lloyd H. Kasper, MD[6] Emmanuelle Waubant, MD[7] Suzanne Gazda, MD,[8] Robert J. Fox, MD,[9] Michael Panzara, MD,[10] Neena Sarkar, PhD,[11] Sunil Agarwal, MD,[11] and Craig H. Smith, MD[11]

Ann Neurol 2008;63:395–400

Phase II publiée en 2008

Vs Placebo

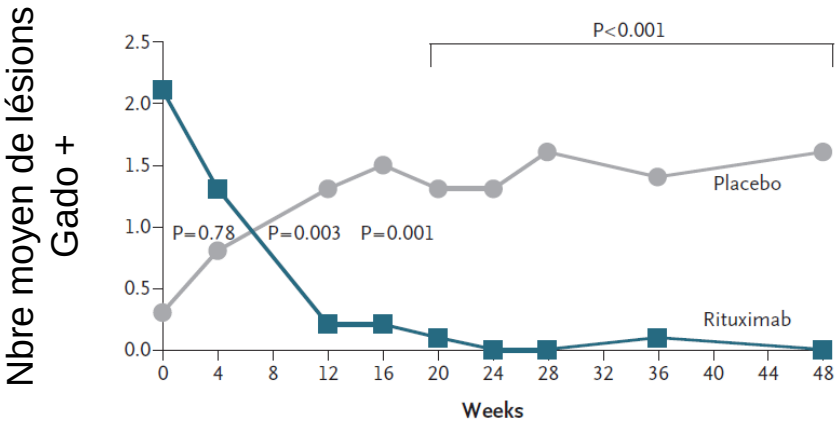
74 patients rémittents

Durée maladie 10 ans

Médiane nbre de poussée l'année précédente = 1

Médiane EDSS = 2,5

24% de patients avec au moins une lésion Gado +



Phase I publiée en 2008

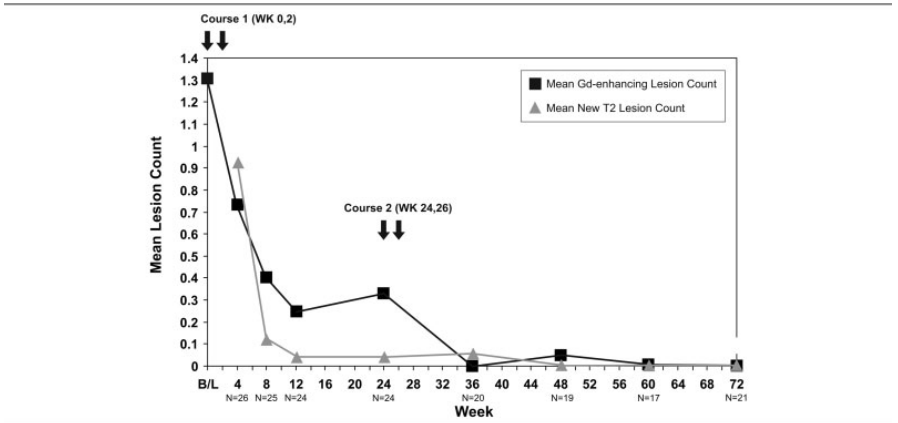
26 patients rémittents

Durée maladie 7 ans

Médiane nbre de poussée l'année précédente = 1

Médiane EDSS = 2

Nbe moyen de lésion Gado + à l'entrée de 1,31



Etude réalisée entre 2002 et 2009 (patients sous immunomodulateur injectable avec réponse partielle (au moins une poussée et 1 gado + dans les mois précédents)

Rituximab add-on therapy for breakthrough relapsing multiple sclerosis

A 52-week phase II trial

R.T. Naismith, MD
L. Piccio, MD, PhD
J.A. Lyons, PhD
J. Lauber, RN
N.T. Tutlam, MPH
B.J. Parks, MD
K. Trinkaus, PhD
S.K. Song, PhD
A.H. Cross, MD

Address correspondence and reprint requests to Dr. Robert T. Naismith, Neurology, Box 8111, 660 S. Euclid Ave., St. Louis, MO 63110
naismithr@neuro.wustl.edu

ABSTRACT

Objective: B cells and the humoral immune system have been implicated in the pathogenesis of multiple sclerosis (MS). This study sought to evaluate the efficacy, safety, and tolerability of add-on therapy with rituximab, a monoclonal antibody that depletes circulating B cells, in subjects with relapsing MS with breakthrough disease defined by clinical and MRI activity (Class III evidence).

Methods: Thirty subjects with a relapse within the past 18 months despite use of an injectable disease-modifying agent, and with at least 1 gadolinium-enhancing (GdE) lesion on any of 3 pretreatment MRIs, received rituximab administered at 375 mg/m^2 weekly × 4 doses. Three monthly posttreatment brain MRI scan
ple Sclerosis Functional Comp
obtained at baseline and throu

Results: GdE lesions were red
MRI scans being free of GdE
0.0001). Median GdE lesions
2.81 per month to 0.33 after
EDSS remained stable.

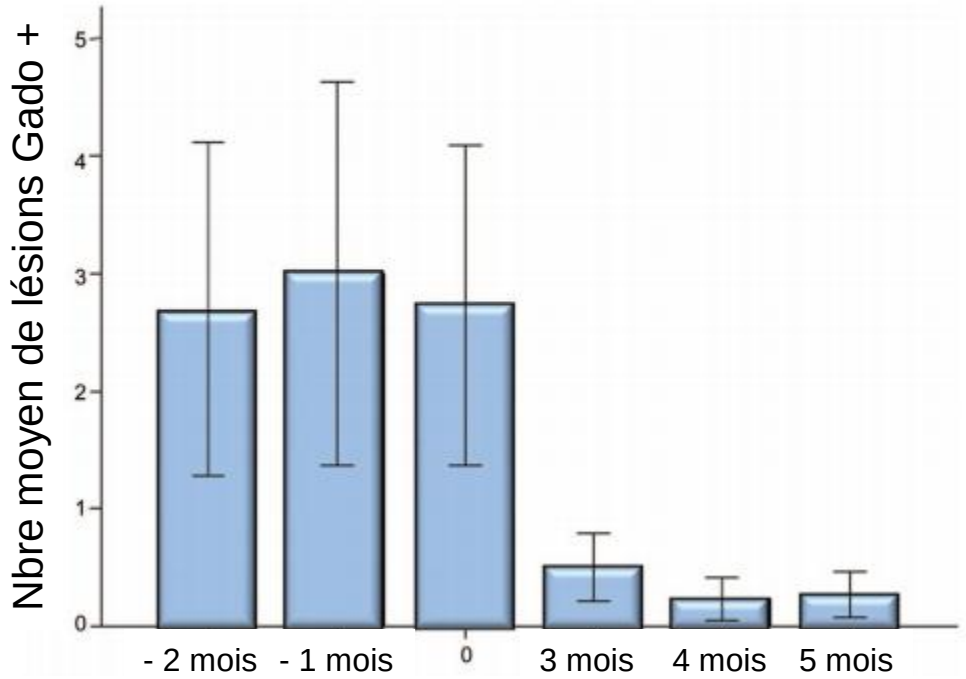
Conclusion: Rituximab add-on
phase II study. In combination w
serious adverse events. B-cell-
tients with relapsing MS with ar

Classification of evidence: This
gadolinium-enhancing brain le

30 patients rémittents
Durée maladie (médiane): 7,5 ans
Nbre de poussées durant les 18 derniers mois (médiane): 2
Nbre de lésions gado + à l'inclusion: 1 (médiane), 2,8 (moyenne)

88% de réduction des lésions Gado +

Figure 3 Reduction in mean number of enhancing lesions after rituximab



Cyclophosphamide (Endoxan®)

Le cyclophosphamide agit par interaction directe sur l'ADN => inhibition de la transcription et de la réplication de l'ADN aboutissant à la destruction cellulaire

ORIGINAL CONTRIBUTION

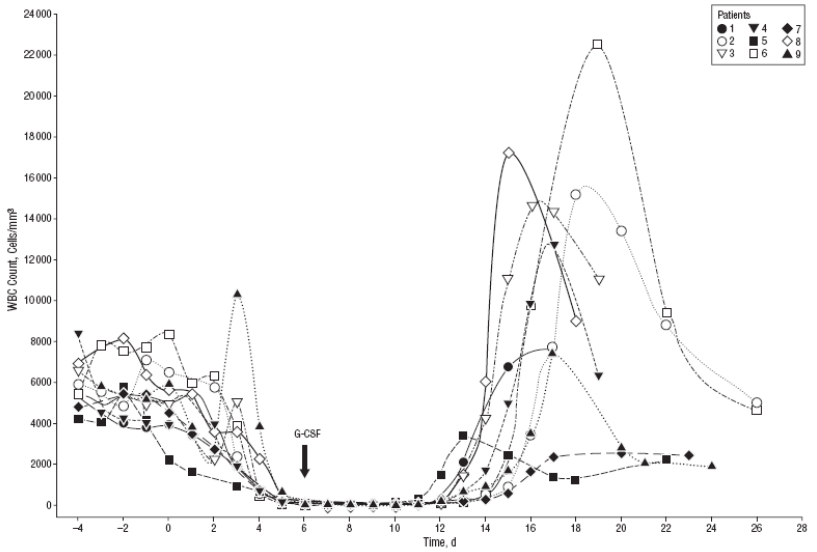
Reduction of Disease Activity and Disability With High-Dose Cyclophosphamide in Patients With Aggressive Multiple Sclerosis

ARCHIVES EXPRESS

Chitra Krishnan, MHS; Adam I. Kaplin, MD, PhD; Robert A. Brodsky, MD; Daniel B. Drachman, MD; Richard J. Jones, MD; Dzung L. Pham, PhD; Nancy D. Richert, MD, PhD; Carlos A. Pardo, MD; David M. Yousem, MD, MBA; Edward Hammond, MD, MPH; Megan Quigg, BA; Carrilin Trecker, BA; Justin C. McArthur, MBBS, MPH; Avindra Nath, MD; Benjamin M. Greenberg, MD, MHS; Peter A. Calabresi, MD; Douglas A. Kerr, MD, PhD

9 patients suivis pendant 2 ans
Au moins 2 lésions gado + sur deux IRM faites durant l'année précédente
Au moins une poussée et/ou aggravation EDSS de 1 point durant l'année précédente
Endoxan 50mg/kg/J pendant 5 jours

Suivi de facteur de croissance des granulocytes



igure 1. White blood cell (WBC) response to high-dose cyclophosphamide (HiCy). Patients were assessed for peripheral WBC counts, with administration of iCy beginning on day −4. On day 6 (6 days after completion of HiCy treatment) all patients received the myeloid growth factor, filgrastim (granulocyte

Suivi de 2 ans

81% de diminution des lésions gado + au dernier suivi (6,5 avant traitement =>1,2 après)

Table 2. Change in Disability (EDSS Score) at 12-Month Follow-up and Last Follow-up

Patient No.	Follow-up, mo	Pretreatment	12-Month Follow-up	Last Follow-up[a]	Change at Last Follow-up[a]	Change at Last Follow-up, %[a]
1	24	7.0	8.0	6.5	−0.5	−7.14
2	24	7.0	8.0	7.0	0.0	0.0
3	24	5.0	1.0	3.0	−2.0	−40.0
4	24	5.0	0.0	0.0	−5.0	−100.0
5	24	6.5	3.0	3.5	−3.0	−46.2
6	24	3.5	3.0	3.0	−0.5	−14.3
7	24	1.5	1.5	1.5	0.0	0.0
8	24	4.5	1.0	1.0	−3.5	−77.8
9	15	6.5	1.0	2.0	−4.5	−69.2
Mean (SD)	23	5.17 (1.84)[b]	2.94 (3.03)	3.06 (2.36)[b]	−2.11 (1.97)	−39.4

Abbreviation: EDSS, Expanded Disability Status Scale.
[a] Patient 9 has completed 15-month follow-up.
[b] $P = .02$ (Wilcoxon rank sum test).

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
XX(X) 1–8

DOI: 10.1177/1352458511419701
msj.sagepub.com
SAGE

Treatment of relapsing–remitting multiple sclerosis with high-dose cyclophosphamide induction followed by glatiramer acetate maintenance

Daniel M Harrison[1], Douglas E Gladstone[2], Edward Hammond[3], Jeffrey Cheng[4], Richard J Jones[2], Robert A Brodsky[2], Douglas Kerr[5], Justin C McArth Contents Frame **Adam Kaplin[1,4]**

32 patients
Etude rétrospective
Nombre de poussées l'année précédente (médiane): 2
Nombre de lésions gado + (moyenne) : 0.86

Endoxan 50mg/Kg/J pendant 4 jours suivi de Copaxone

Suivi moyen de 14.0 mois (0.5–33.8)

Table 4. Clinical outcomes.

	Pre-treatment Status	Post-treatment Status	Percentage without event	Probability of event-free survival at 2 years
Relapses	*Annualized relapse rate:** 1.37	*Annualized relapse rate:†* 0.27	75% relapse-free	0.64 (95% CI 0.37–0.82)
Disability progression	*Median EDSS at baseline:* 3.75 (range 1.5–6.5)	*Median EDSS at 1 year:* 3.5 (range 1.0–6.5)	80% without sustained disability progression	0.77 (95% CI 0.43–0.92)

Event-free survival calculated by survival analysis, with 'event' being a documented clinical relapse in the relapse analysis or sustained disability progression in the disability progression analysis.

*Annualized relapse rate in the 2 years prior to HiCy therapy.

†Annualized relapse rate during the study period.

EDSS, Expanded Disability Status Scale; HiCy, high-dose cyclophosphamide.

Greffe de moelle

RESEARCH PAPER

Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience

Joachim Burman,[1,2] Ellen Iacobaeus,[3] Anders Svenningsson,[4] Jan Lycke,[5] Martin Gunnarsson,[6,7] Petra Nilsson,[8] Magnus Vrethem,[9,10] Sten Fredrikson,[11] Claes Martin,[12] Anna Sandstedt,[13] Bertil Uggla,[7,14] Stig Lenhoff,[15] Jan-Erik Johansson,[16] Cecilia Isaksson,[17] Hans Hägglund,[18] Kristina Carlson,[18] Jan Fagius[1,2]

JNNP, 2014

48 patients inclus (83%RR) (32 avec gado +)
48 mois de suivie moyen (12-108)

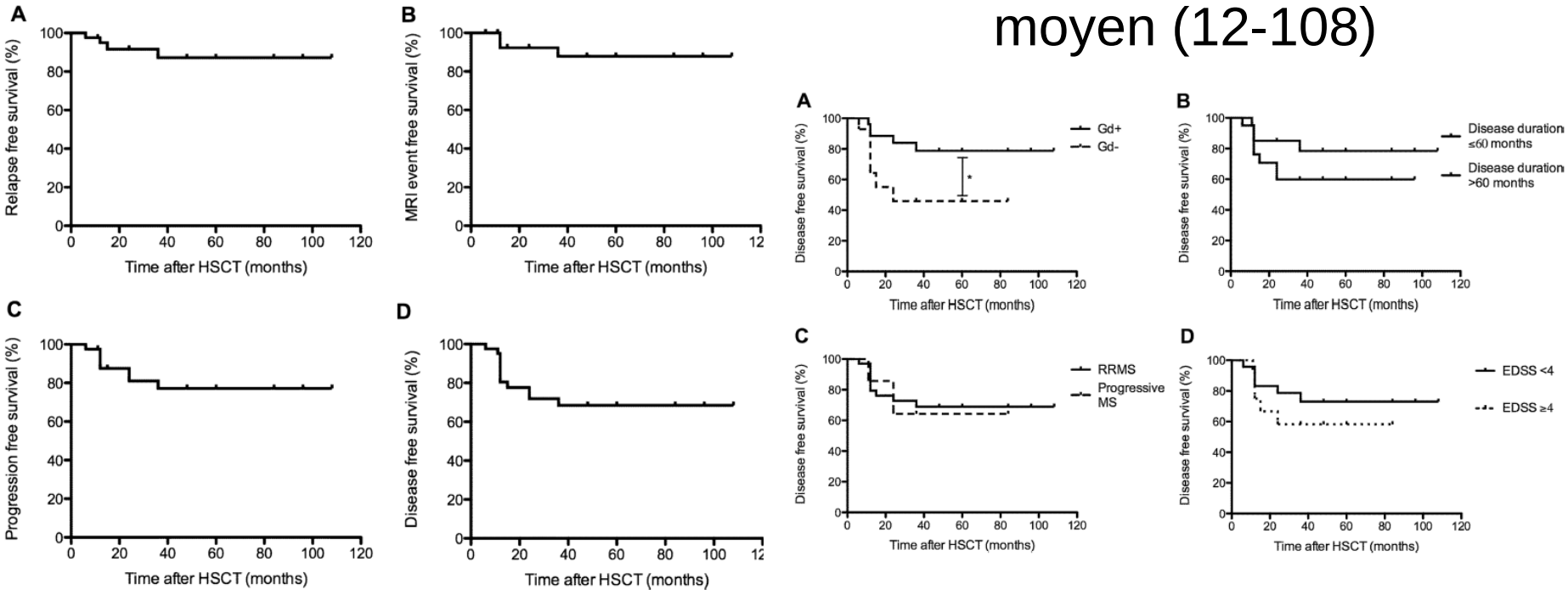


Table 2 Events related to acute toxicity

	During hospitalisation		After discharge	
	n	Per cent	n	Per cent
Bacteraemia	22	46		
α-haemolytic streptococci	5	23		
Other streptococci	6	27		
Coagulase-negative staphylococci	4	18		
Neutropenic fever	17	35		
Typhlitis	5	10		
Mucositis	4	8.3		
Clostridium difficile infection	2	4.2	1	2.1
ATG reaction (serum sickness)	2	4.2		
Herpes simplex reactivation			2	4.2
Invasive candida albicans infection	1	2.1		
Deep vein thrombosis			1	2.1
Pyelonephritis			1	2.1
Norovirus infection			1	2.1
Varicella zoster reactivation			1	2.1

The table lists events related to acute toxicity (side affects appearing within 100 days after haematopoietic stem cell transplantation). In the table, the three most common bacteria present in blood cultures are listed. The percentages of these are proportions of bacteraemic patients.

Pas de mortalité
Principaux effets secondaires à moyen terme: reactivation VZV (15%), pathologie thyroidienne (8,4%)

Autologous hematopoietic stem cell transplantation in multiple sclerosis

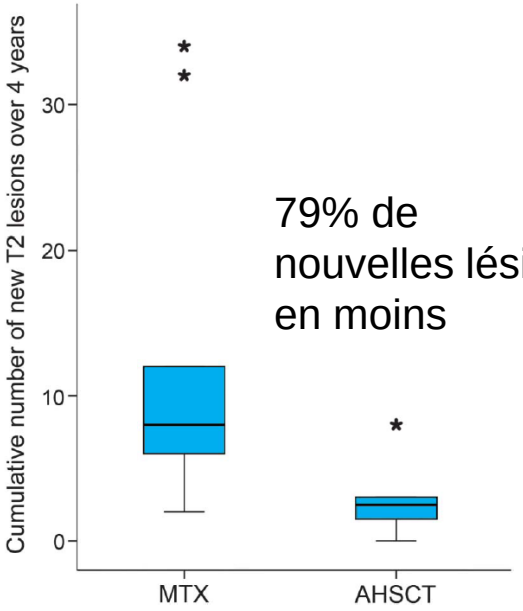
A phase II trial

Mancardi et al, Neurology 2015

Patients ayant une augmentation de l'EDSS l'année précédente avec au moins une lésion gado + sous traitement

Comparaison greffe vs Mitoxantrone, suivi de 4 ans

	AHSCT, n = 9	MTX, n = 12	Overall, n = 21
Mean (range) age, y	36 (22-46)	35 (19-43)	35.5 (19-46)
Women, n (%)	5 (24)	9 (43)	14 (67)
Median (range) EDSS	6.5 (5.5-6.5)	6 (5.5-6.5)	6 (5.5-6.5)
Median (range) EDSS 1 year before	5 (3-6)	4 (2-6)	4.5 (2-6)
Disease course, n (%)			
RR	2 (22)	5 (42)	7 (33)
SP	3 (33)	3 (25)	6 (29)
SP with relapses	4 (45)	3 (25)	7 (33)
RP	0	1 (8)	1 (5)
Disease duration (range), y	10.5 (5-20)	9.8 (2-23)	10.2 (2-23)

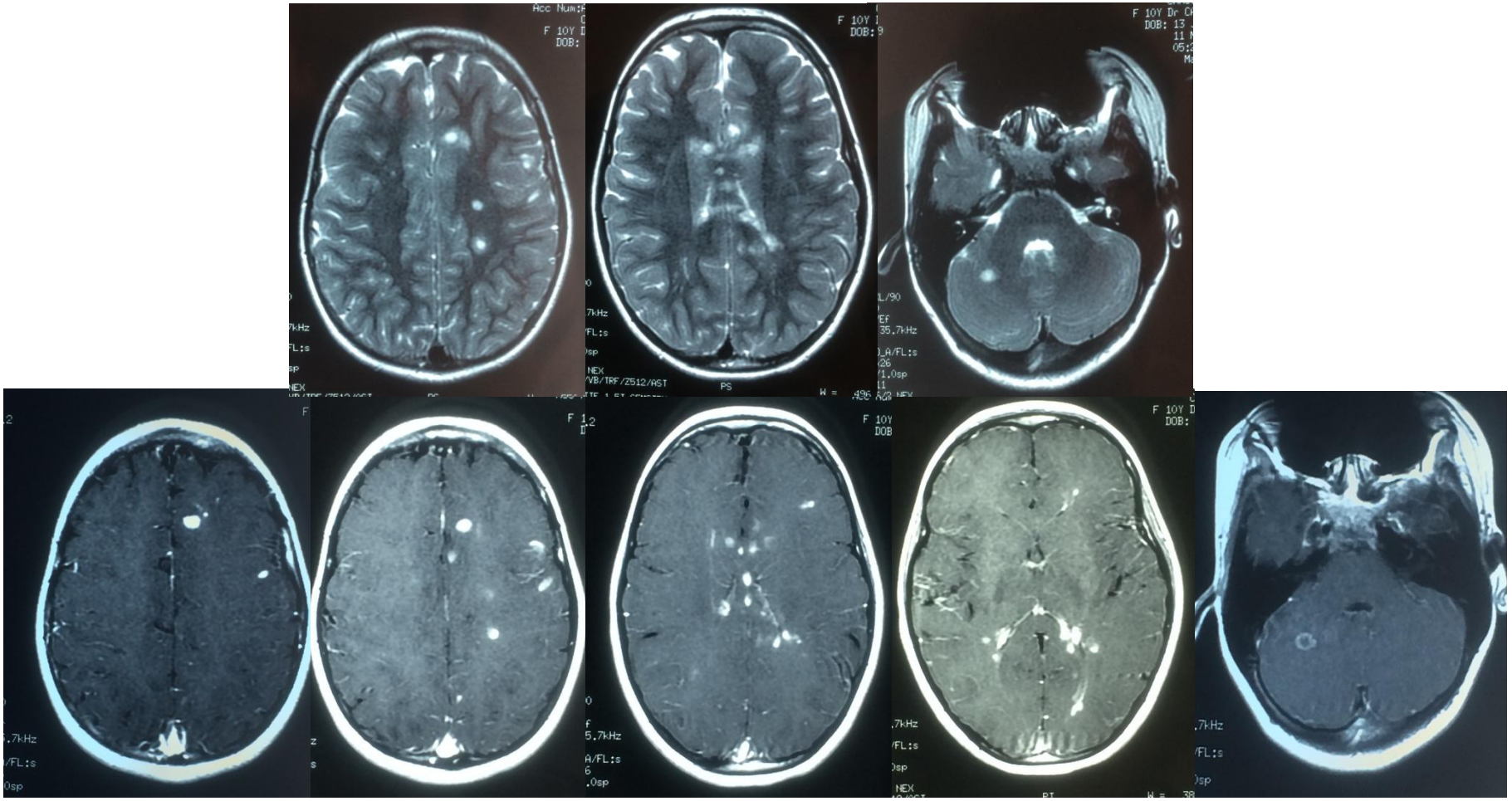


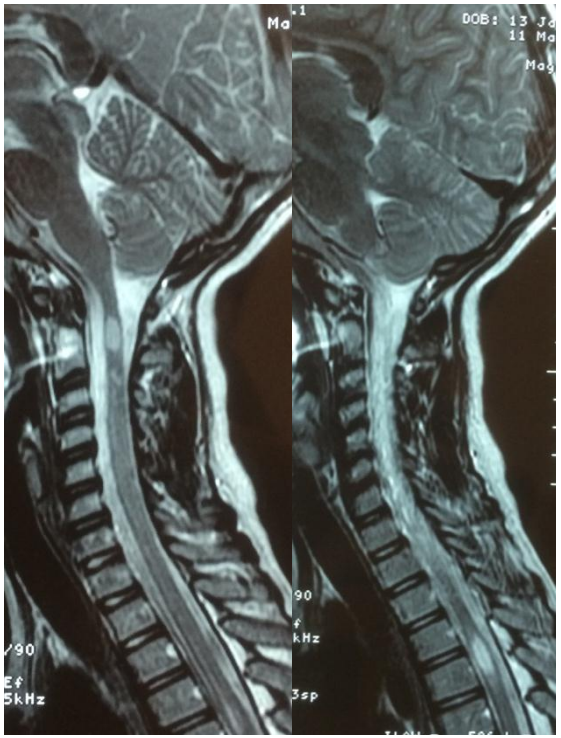
79% de nouvelles lésions en moins

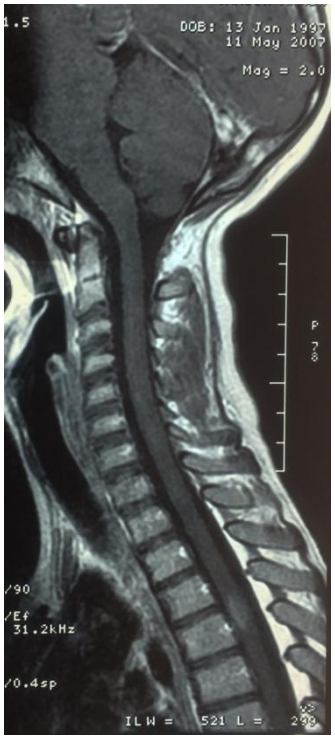
Effets secondaires précoces comparables à la littérature
Pas de mortalité, pas d'effet secondaire sévère tardif

Melle M, née en janvier 1997

- Mai 2007 (10 ans) :
  - Névrite optique rétrobulbaire droite (AV : 3/10)
  - Absence de contexte infectieux
  - Absence de vaccination récente



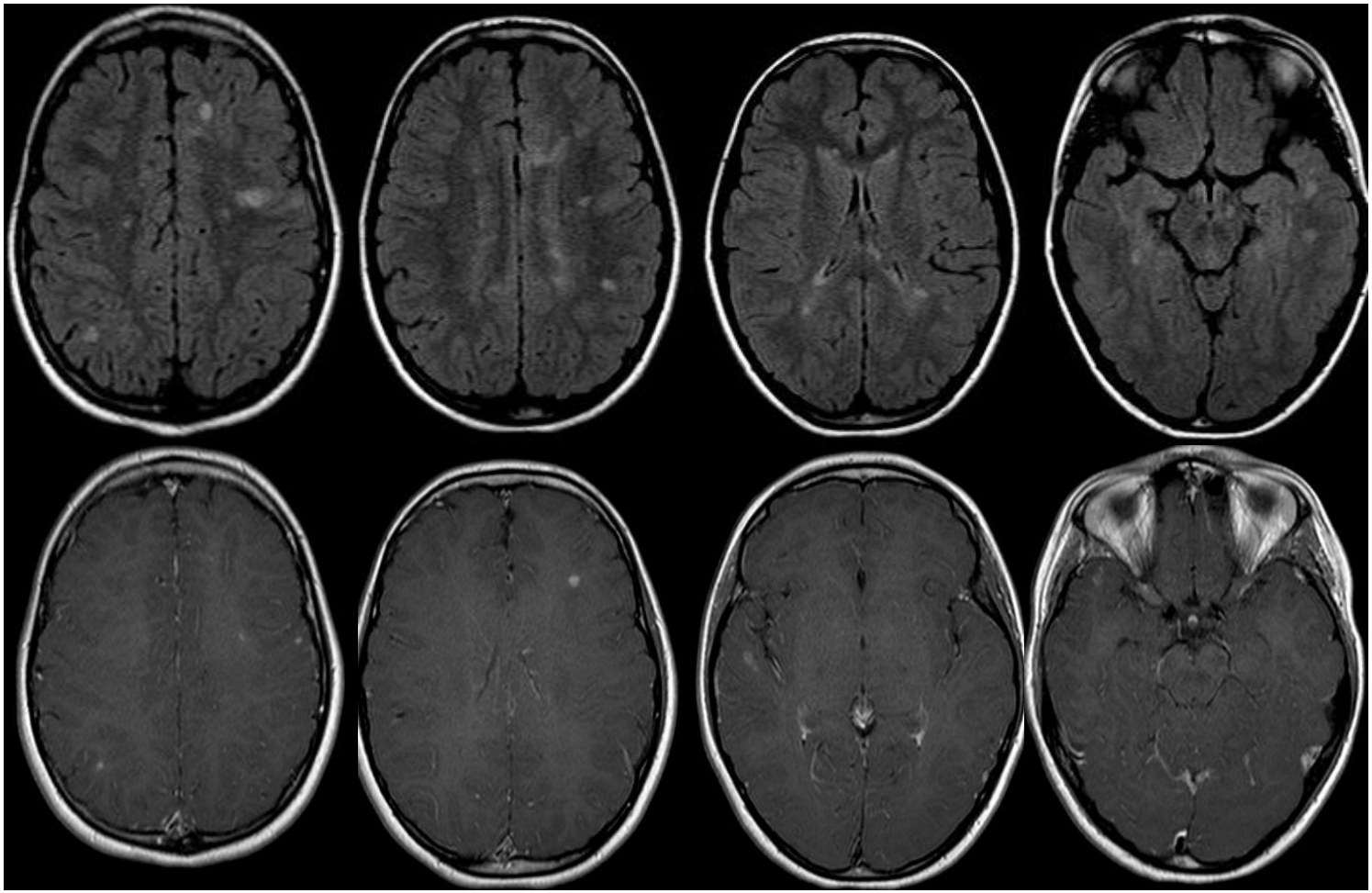

/90
Ef
5kHz
90
f
kHz
3sp


1.5
DOB: 13 Jan 1997
11 May 2007
Mag = 2.0
/90
/Ef
31.2kHz
/0.4sp
ILW = 521 L = 293

- LCR :
  - 11 Gb/mm3
  - Oligoclonalité des IgG en immunofixation
  - Protéinorachie : 0.40 g/L
- Absence de syndrome inflammatoire biologique
- Corticothérapie IV : 25 mg/kg pendant 3 jours, relais oral pendant deux mois
- Récupération visuelle complète, rapide
- Asymptomatique pendant 3 ans

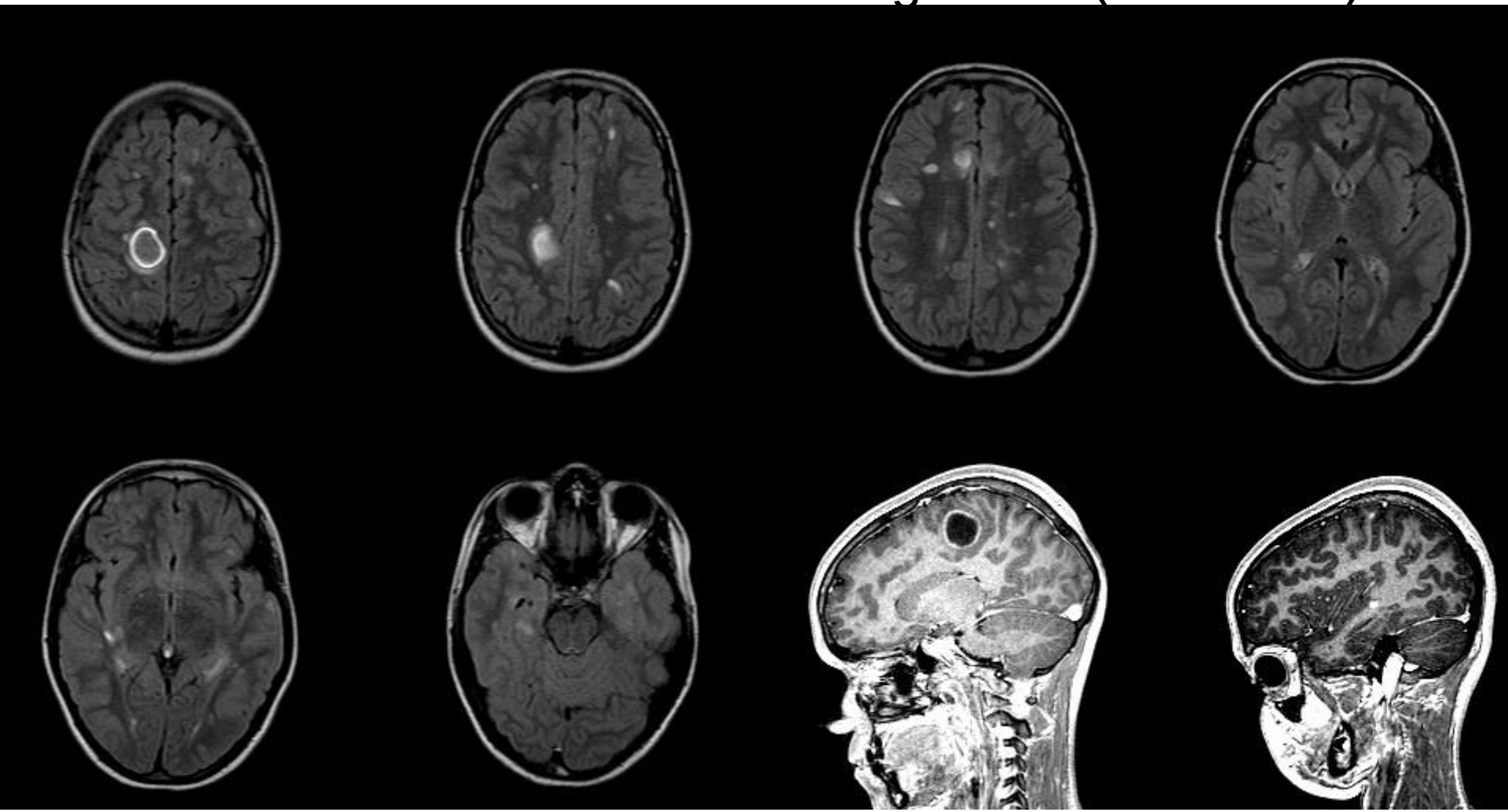
Surveillance IRM : janvier 2010 : (12 ans)

Asymptomatique (EDSS : 0)



Novembre 2010 (13 ans) :

Parésie du membre inférieur gauche (EDSS : 2)

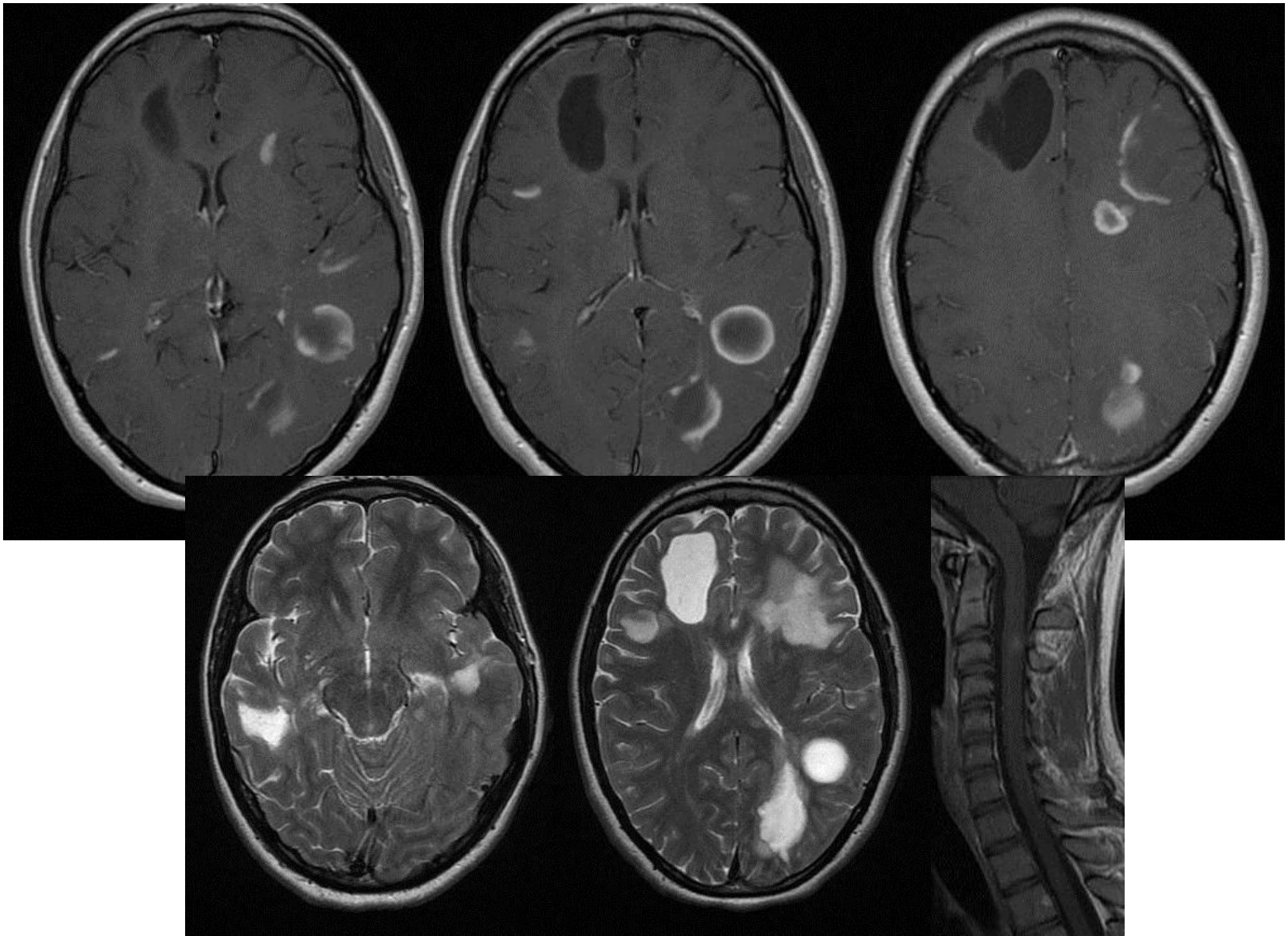


- Corticothérapie IV 800mg/ jour pendant 5 jours

$\Rightarrow$ Récupération clinique rapide

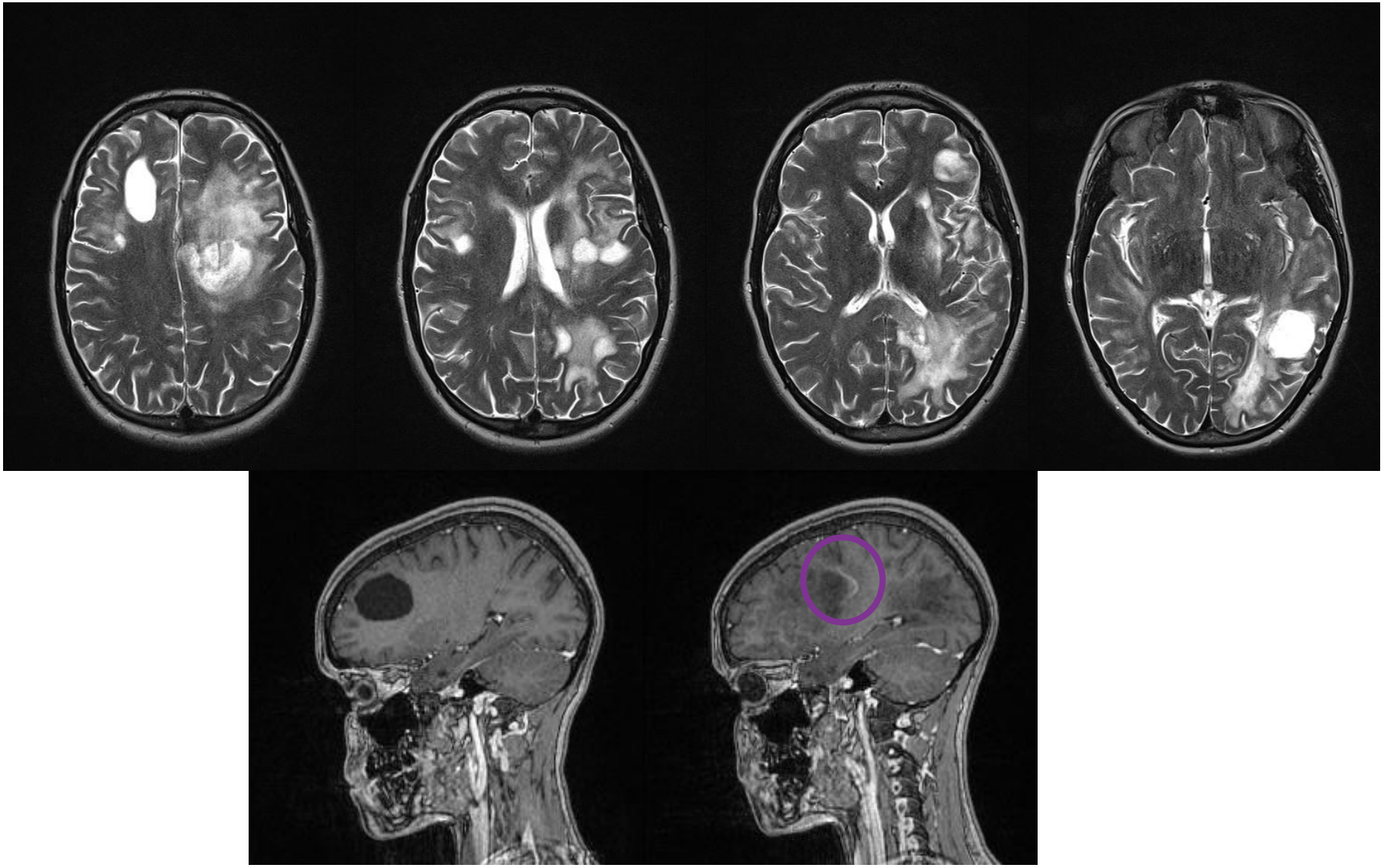
- Interferon beta-1a IM bien toléré pendant 3 ans
- Absence de surveillance IRM
- EDSS : 0 jusqu'en mai 2013

Juin 2013 (16 ans) :
Aphasie, alexie



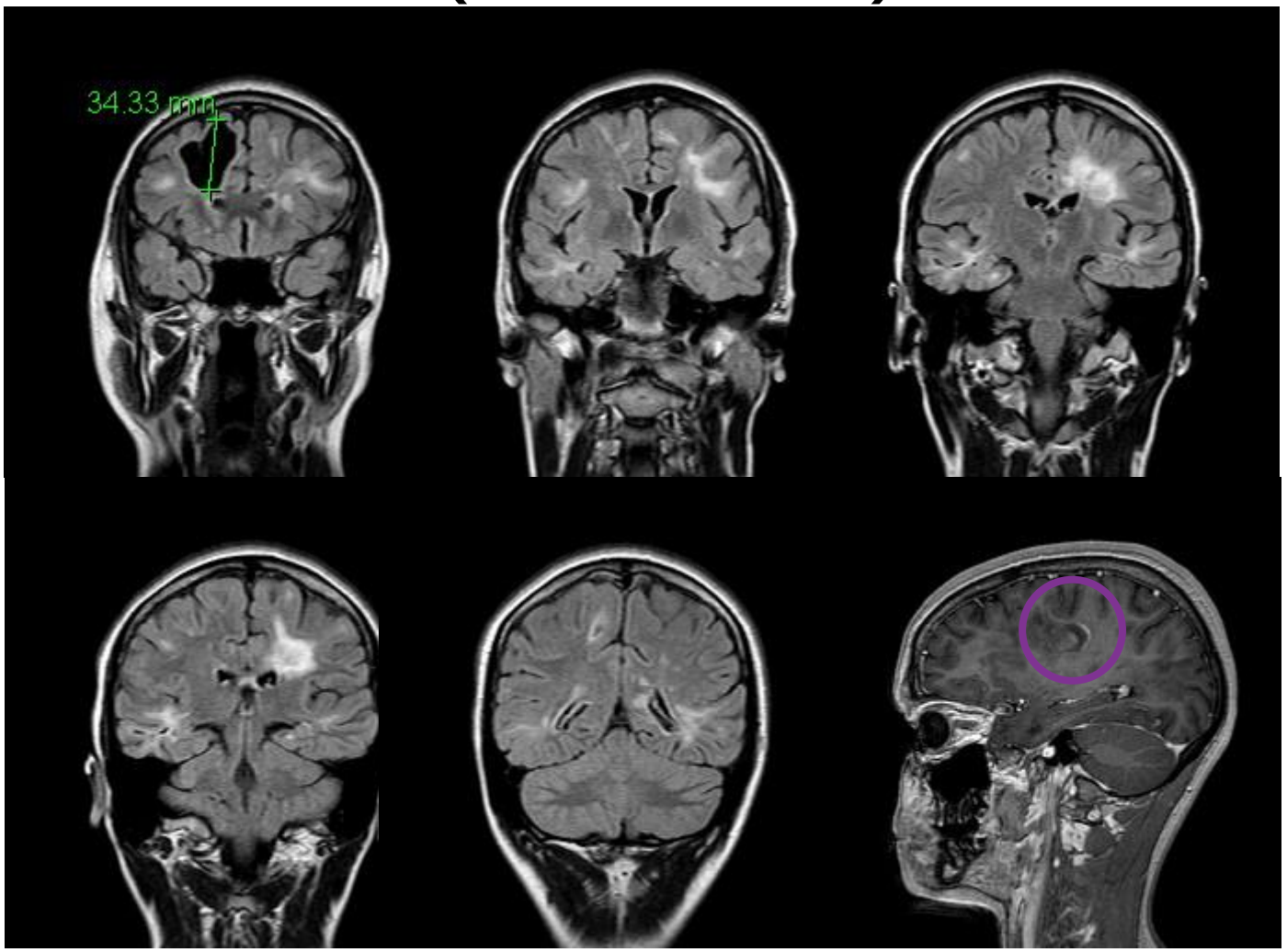
- Traitement de fond par Natalizumab (08/2013)
- Récupération visuelle en quelques semaines
- Troubles cognitifs persistants :
  - Aphasie fluente, manque du mot massif
  - Syndrome dysexecutif sévère, ralentissement idéatoire important
  - Syndrome dépressif réactionnel

Décembre 2013 :
discrète hémiparésie droite (EDSS : 4)

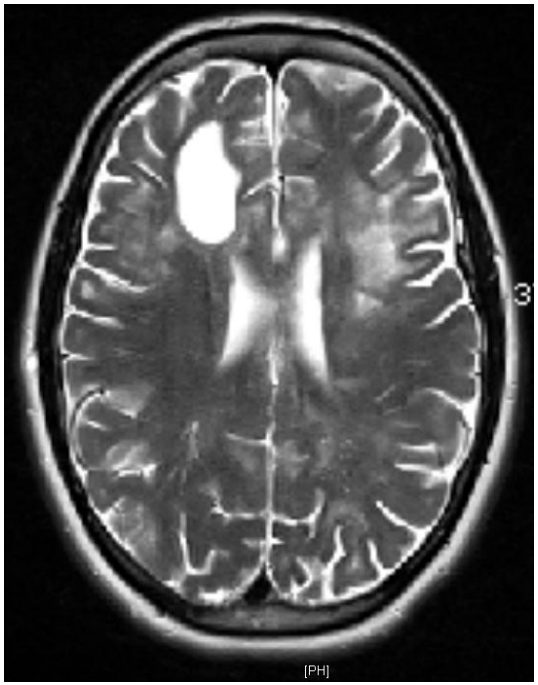


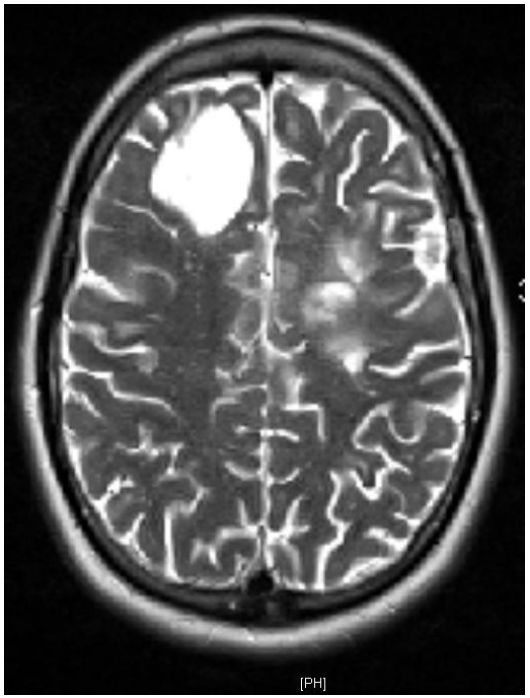
- Arrêt du natalizumab (AC négatifs)
- AC anti aquaporine 4 : négatifs
- 8 séances de plasmaphérèse
- ELSEP © (5 cures, 60 mg)
- Amélioration clinique et radiologique, troubles cognitifs persistants

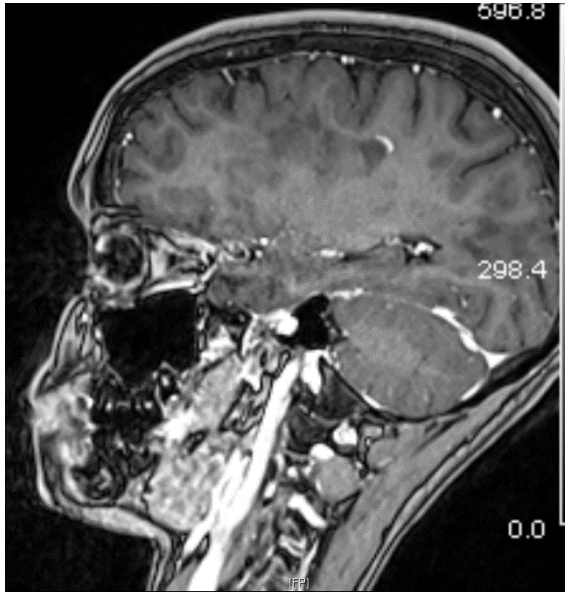
Mai 2014 (17 ans)
(EDSS : 3)



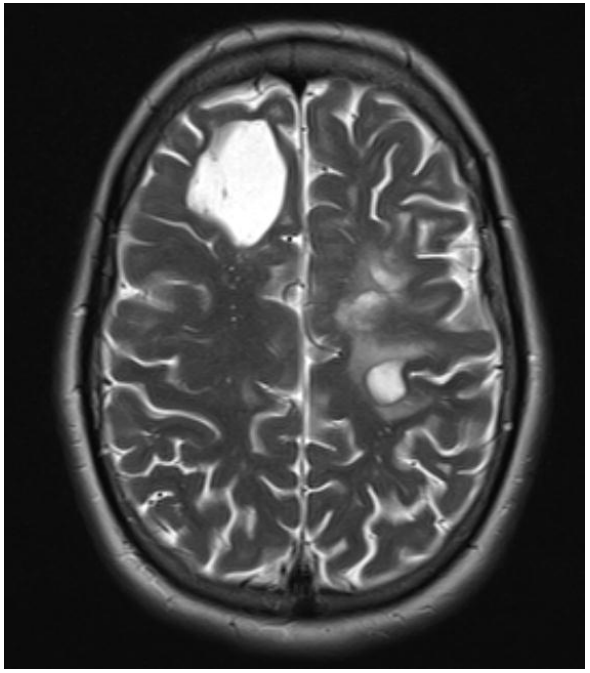
Aout 2014 (EDSS : 3)

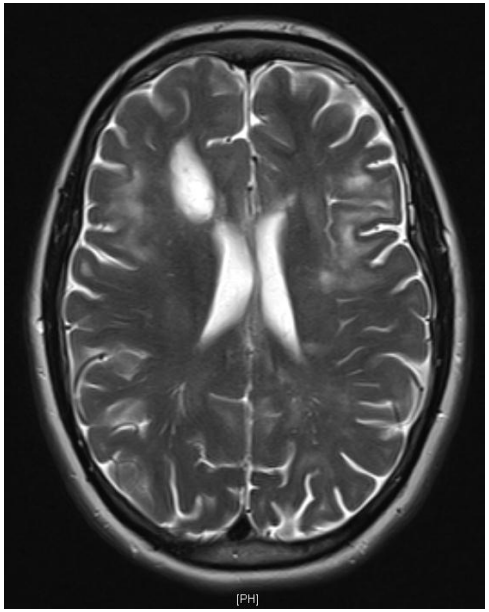


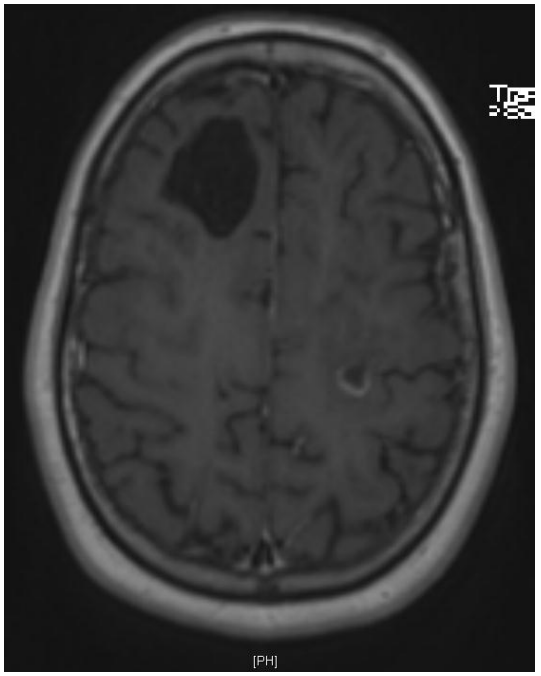




Décembre 2014 (EDSS : 3)

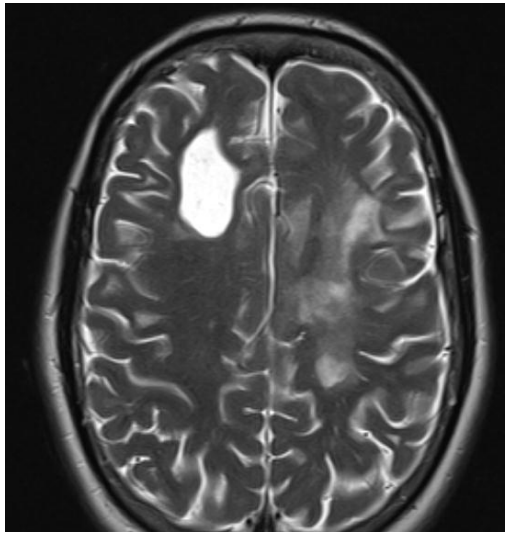


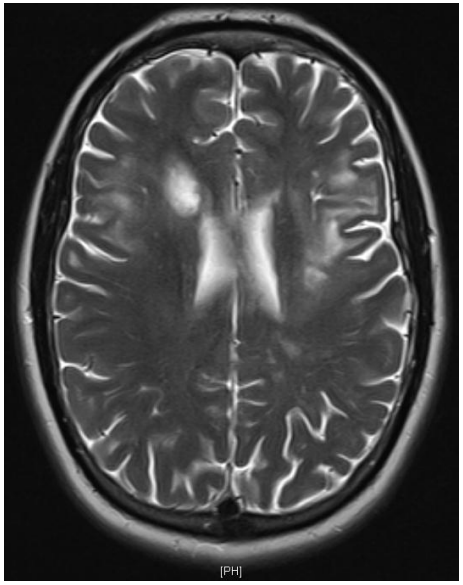


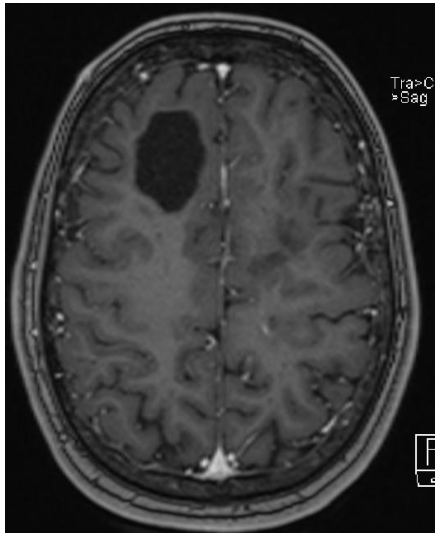


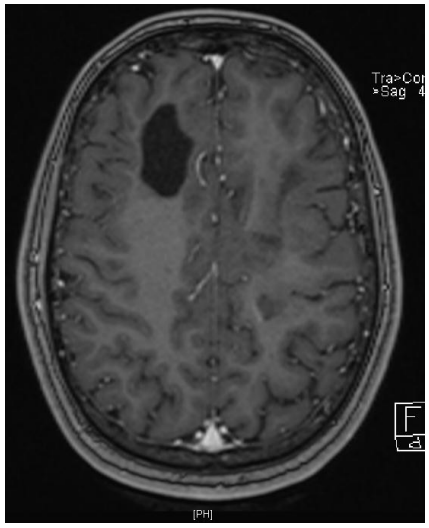
- **Dernière cure d'ELSEP en avril 2015**

Juin 2015 (EDSS : 3)

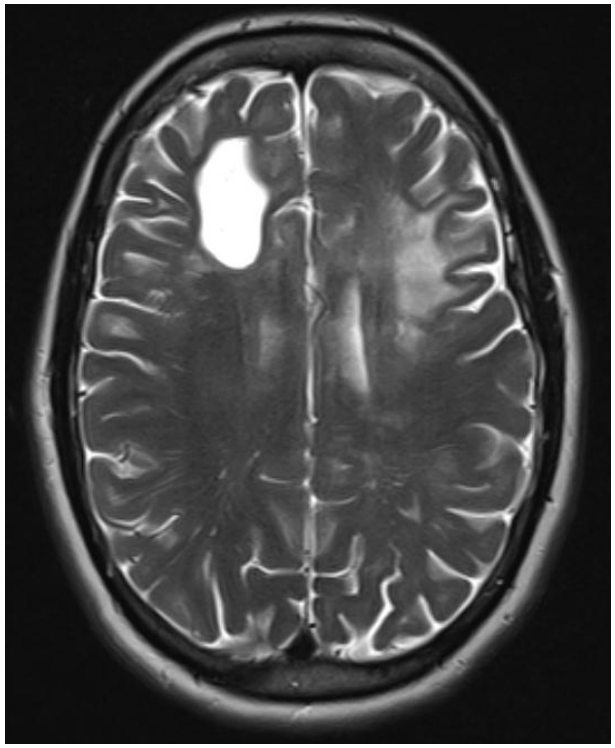


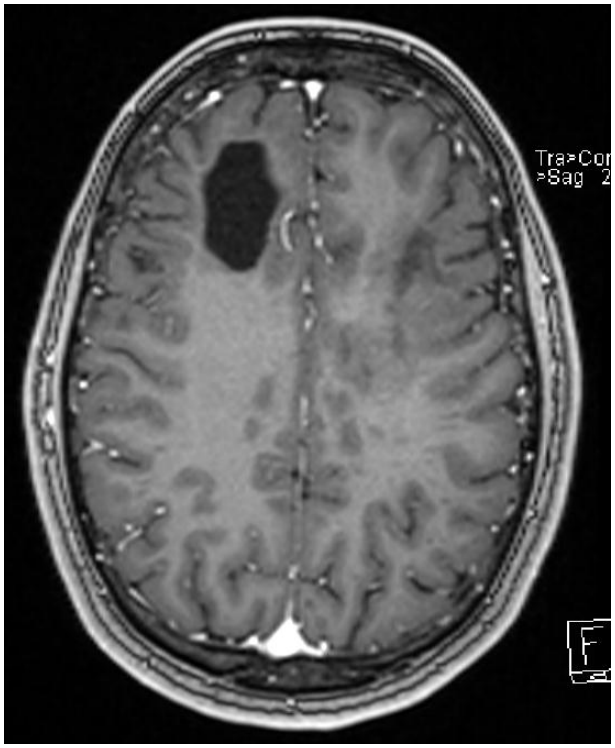






- **Induction MABTHERA en septembre 2015**





Novembre 2015 (EDSS : 3)

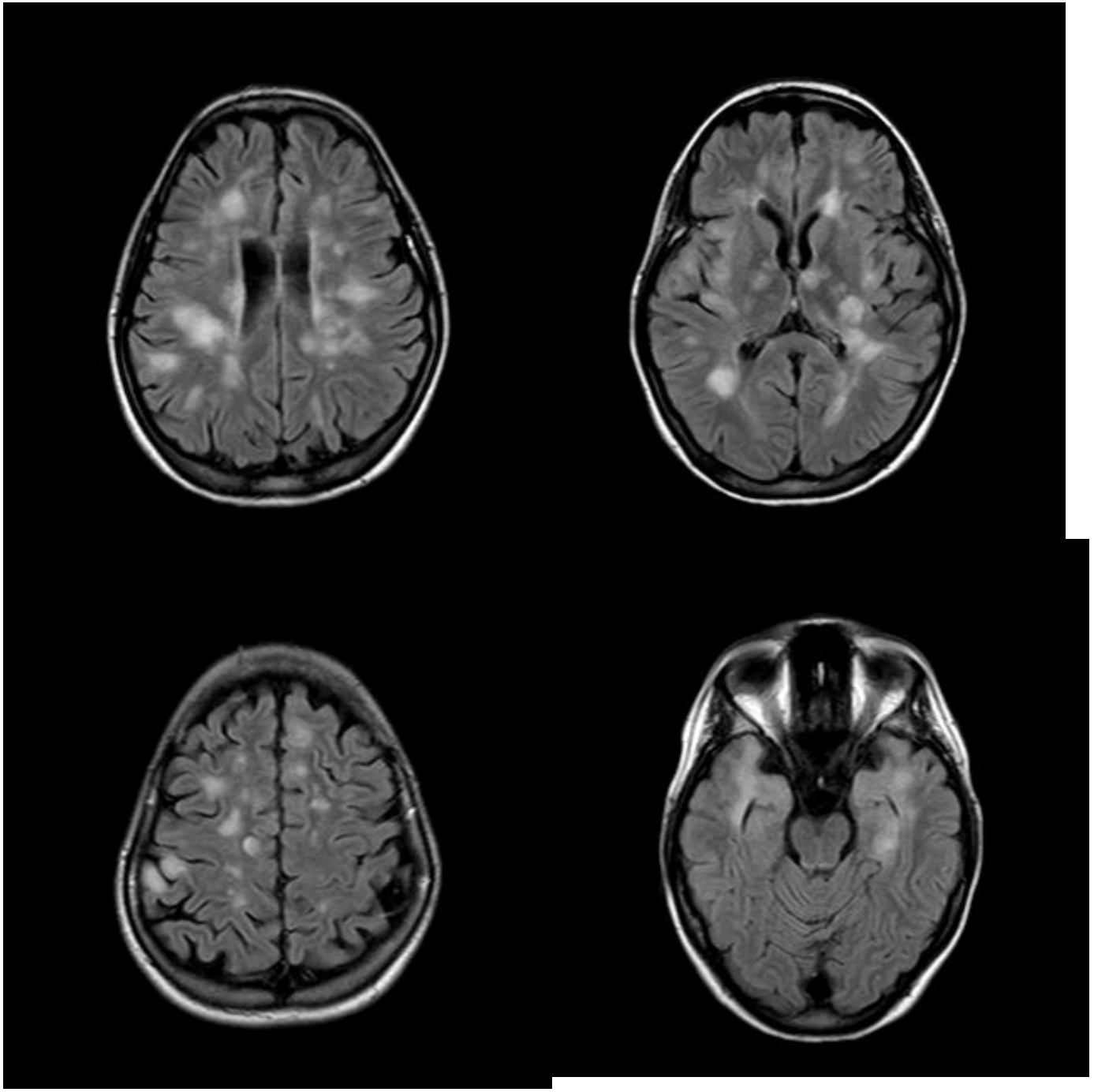
Hauser et al , Annals of Neurology 2013

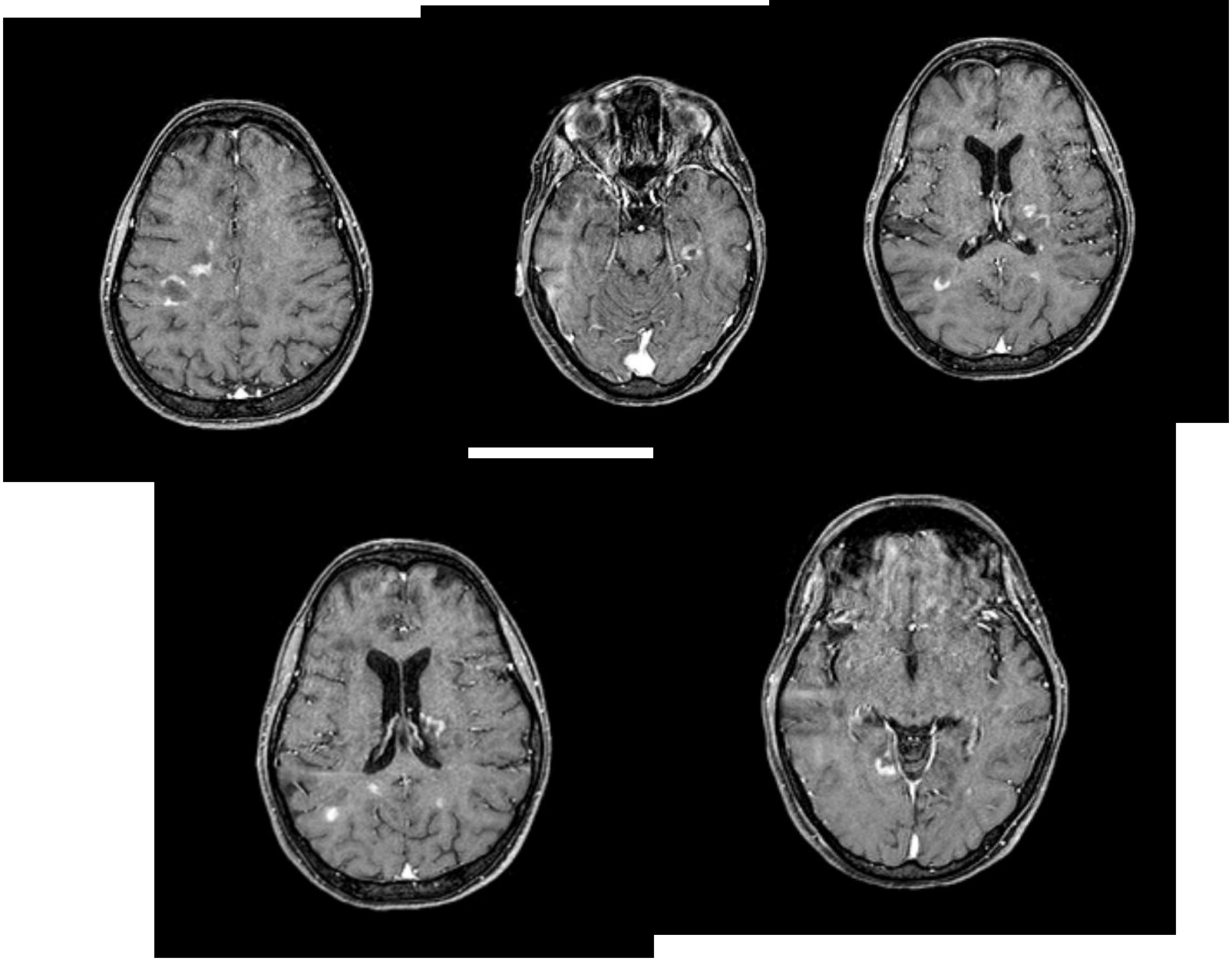
Conclusion

- Entité nosologique mal définie
- Diagnostic différentiel avec EMAD
- Clinique en général très différente entre maladie de Marburg et SEP agressive (mécanismes physiopathologiques probablement différents)
- Plusieurs traitements proposés mais rares études randomisées

Melle A

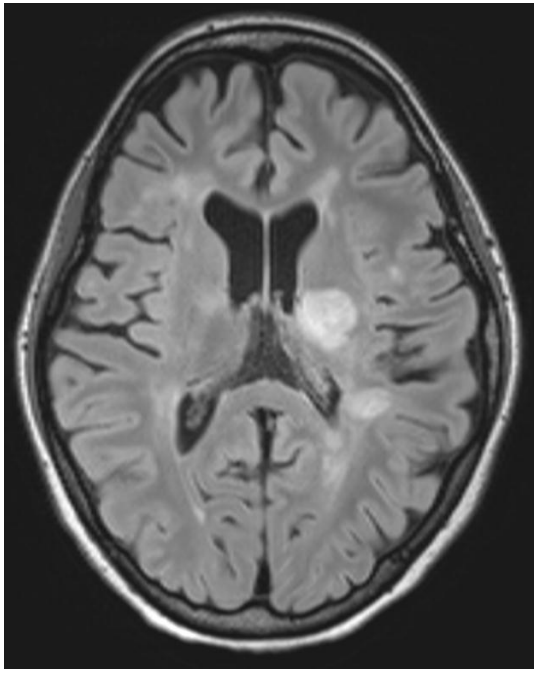
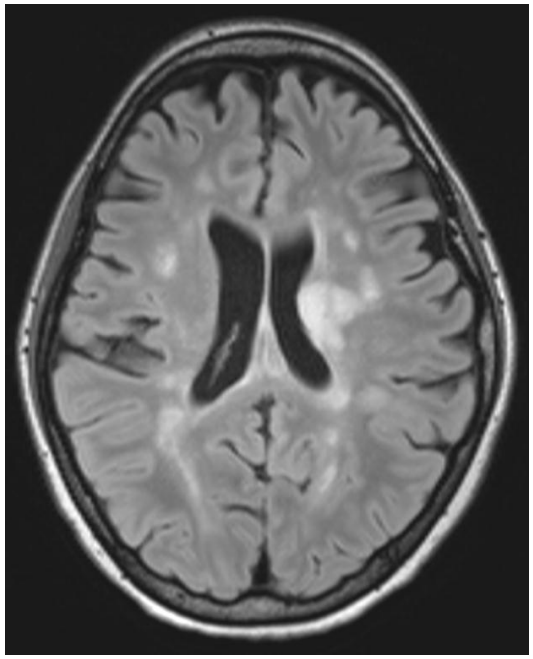
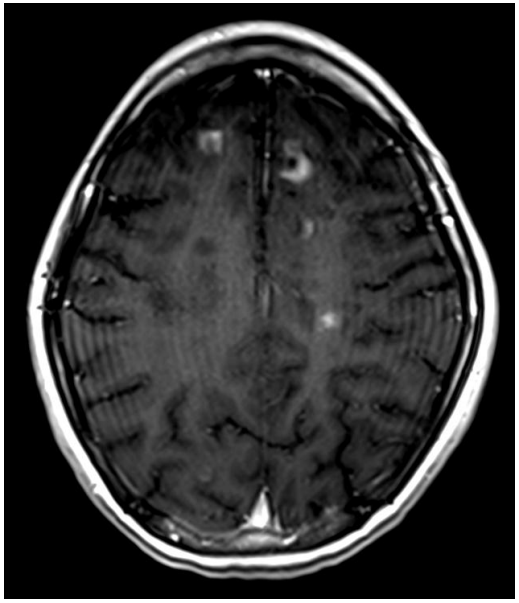
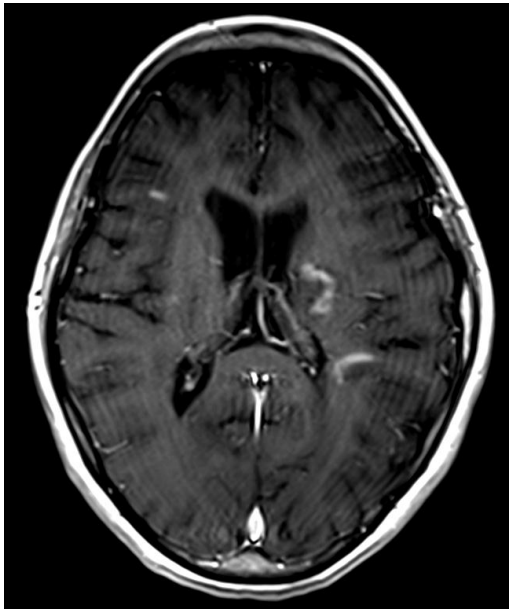
- 21 ans, étudiante école ingénieur, sort de classe prépa
- Avril 2010: paresthésies main et jambe droite résolutives en 3 semaines
- Aout 2010: asthénie majeure, troubles du comportement avec irritabilité, hallucinations visuelles, amnésie antérograde





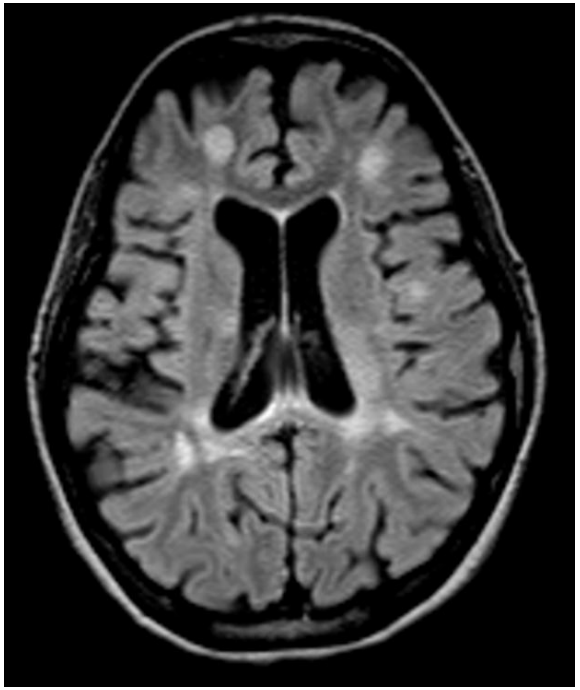
- LCR: protéinorache normale, absence d'élément, synthèse intrathécale avec bandes

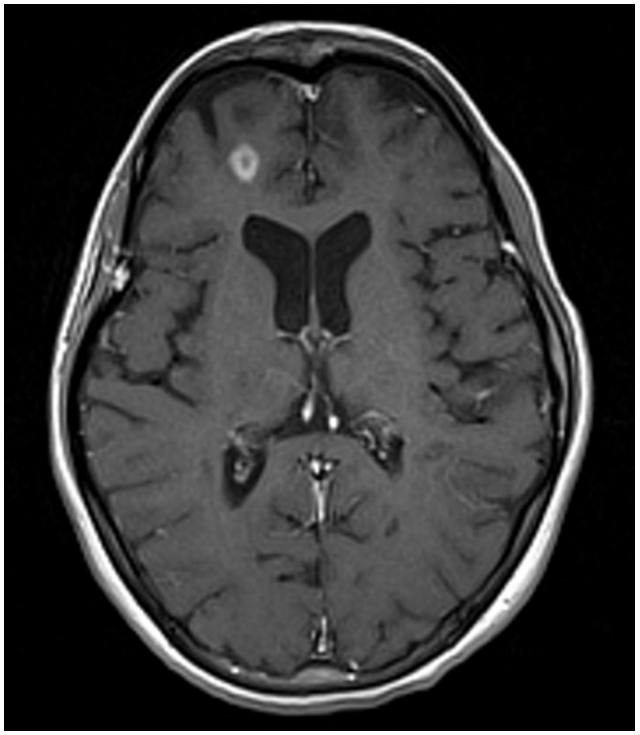
- Après 3 cures d'ELSEP, poursuite de l'aggravation: troubles cognitifs, apparition d'un déficit du membre inférieur droit

- Après 6 cures d’ELSEP récupération quasi-totale des troubles cognitifs, périmètre de marche illimité

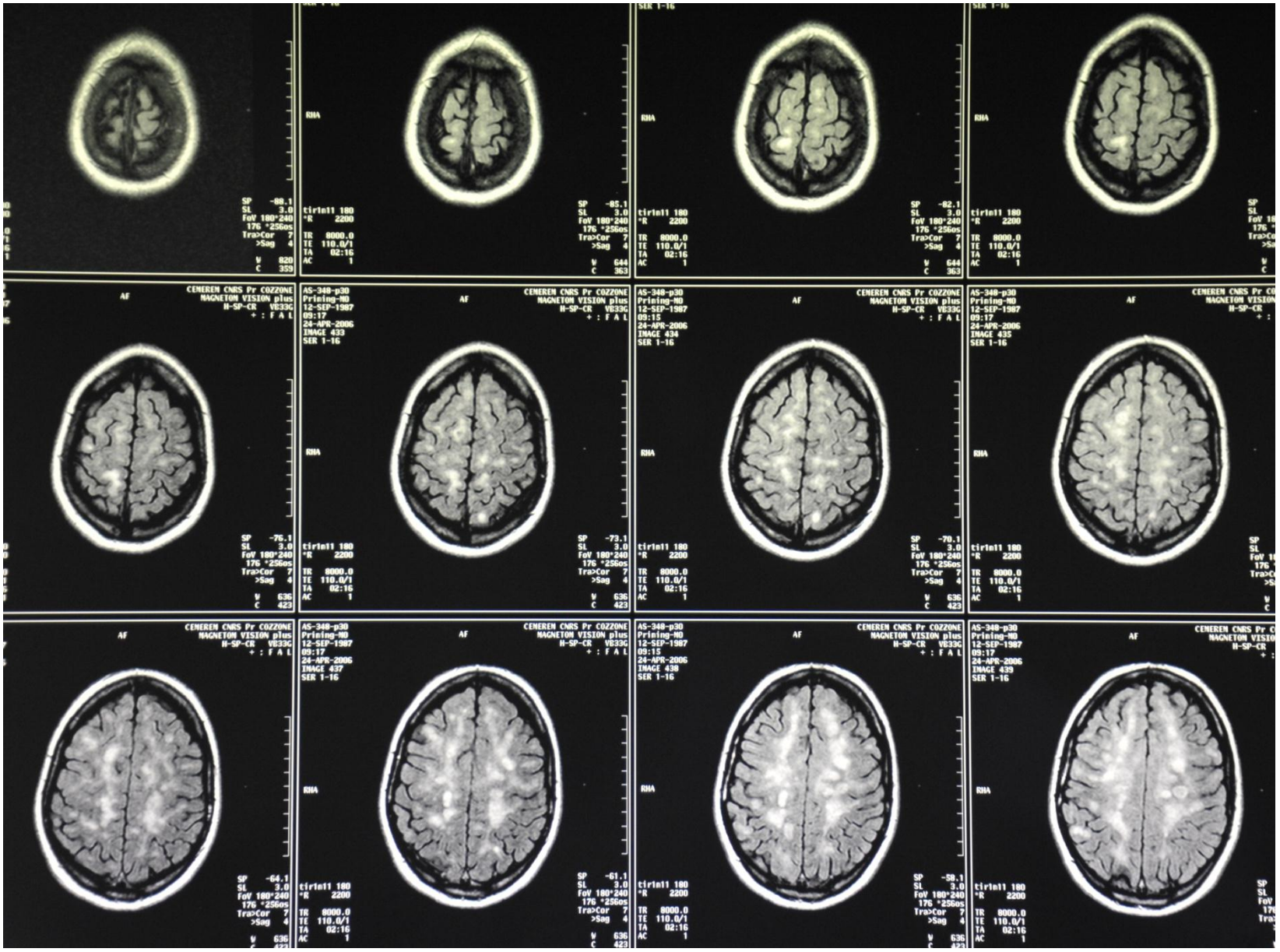
- 3 mois après la dernière perfusion (dose cumulée 120 mg atteinte), nouvelle modification du comportement avec irritabilité

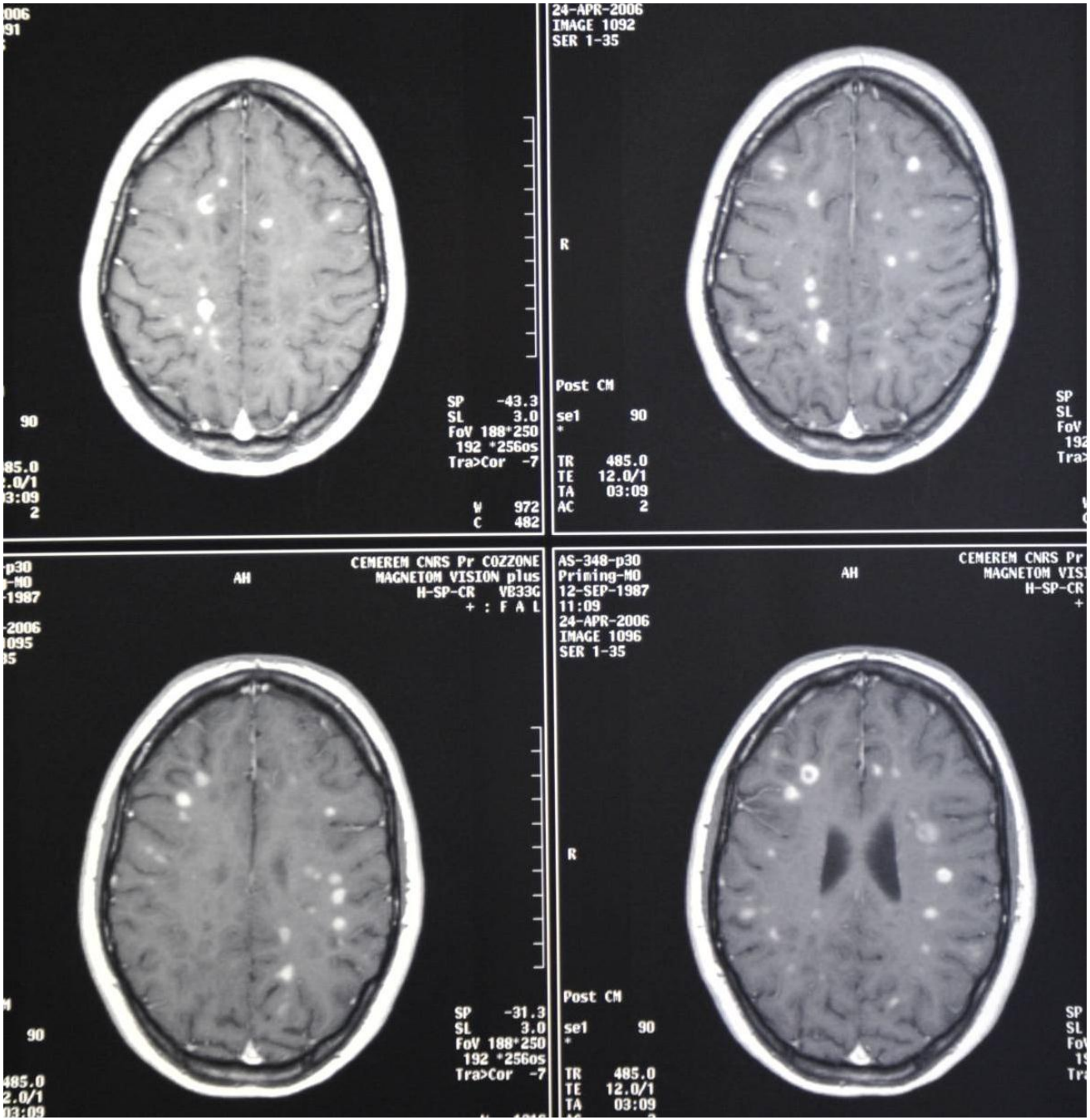




Melle S

- Femme de 17 ans
- 2005: Apparition subaigüe de difficultés majeures à la marche (ataxie et déficit moteur) associées à un ralentissement idéomoteur
- IRM


CENEREN CNRS Pr COZZONE
MAGNETON VISION plus
H-SP-CR VE33G
AS-348-p30
Priming-MD
12-SEP-1987
24-APR-2006
IMAGE 433
IMAGE 434
IMAGE 435
IMAGE 437
IMAGE 438
IMAGE 439
SER 1-16
RHA
tir1n11 180
*R 2200
TR 8000.0
TE 110.0/1
TA 02:16
AC 1
FoV 180*240
176 *256os
Tra>Cor 7
>Sag 4


24-APR-2006
IMAGE 1092
SER 1-35
R
Post CM
se1 90
TR 485.0
TE 12.0/1
TA 03:09
AC 2
SP -43.3
SL 3.0
FoV 188*250
192 *256os
Tra>Cor -7
W 972
C 482
CEMEREM CNRS Pr COZZONE
MAGNETOM VISION plus
H-SP-CR VB33G
AS-348-p30
Priming-MO
12-SEP-1987
11:09
24-APR-2006
IMAGE 1096
SER 1-35
SP -31.3
SL 3.0
FoV 188*250
192 *256os
Tra>Cor -7

- Evolution favorable sous Solumedrol

- Absence de récidive sous ELSEP puis Tysabri. EDSS 2011 = 2