RIIP

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

29 et 30 SEPTEMBRE 2022

UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

IMAGE FREEPIK

Sous l'égide de :

AI2R Filière · aviesan alliance nationale pour les sciences de la vie et de la santé · CeRéMAIA · GRI · European Reference Network for rare or low prevalence complex diseases · Fédération Immunologie · Imidiate · RITA Rare Immunodeficiency AutoInflammatory AutoImmune · Société Française de Dermatologie et de Pathologie Sexuellement Transmissible · Société Française d'Immunologie · SFR société française de rhumatologie · SOFREMIP Rhumatologie & maladies inflammatoires pédiatriques · SNFEM

RIIP

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

« Comment je diagnostique ? Comment je traite ? »

Les maladies démyélinisantes auto-immunes : quelles prise en charge en 2022 ?

Professeur J. de Seze

Strasbourg

29 et 30 SEPTEMBRE 2022

UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

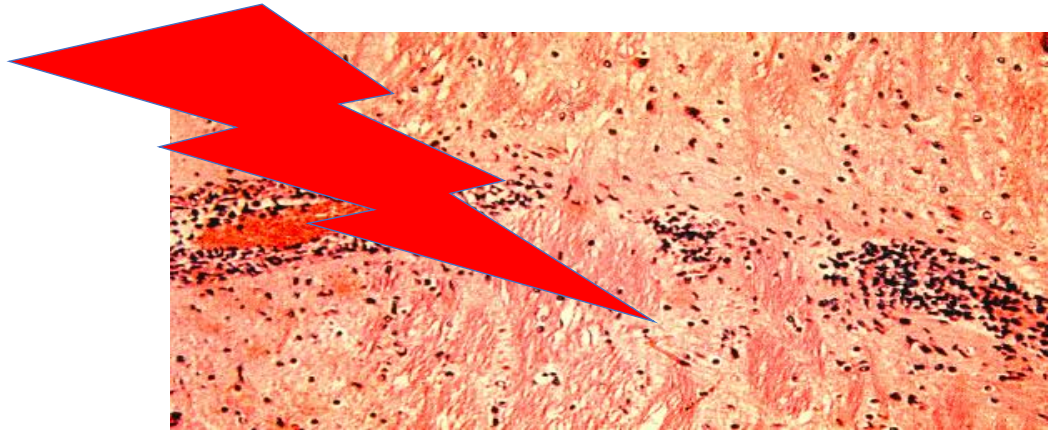
Sous l'égide de :

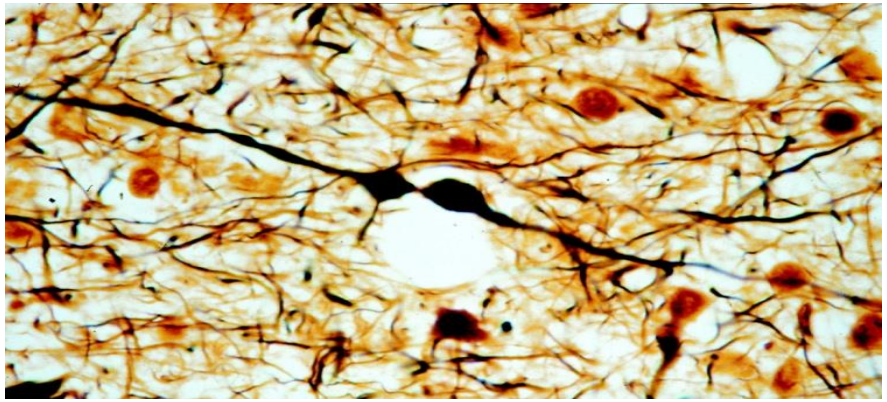
Liens d’intérêt

- **Consultant / Board / Réunions scientifiques**
  - **Novartis**
  - **Biogen**
  - **Teva**
  - **Genzyme/Sanofi**
  - **Roche**
  - **BMS Celgene**
  - **Janssen**
  - **Merck**
  - **Alexion**
  - **CSL Behring**
  - **Horizon therapeutics**

Physiopathologie

La sclérose en plaques
est une
maladie <u>inflammatoire</u>
<u>démyélinisante</u> et
<u>neurodégénérative</u>





Inflammation

Démyelinisation

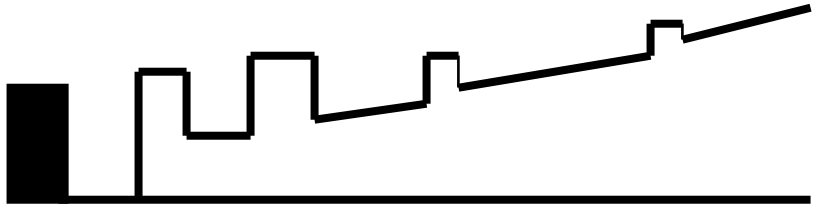
Lésions axonale

Formes clinique de la SEP

85%

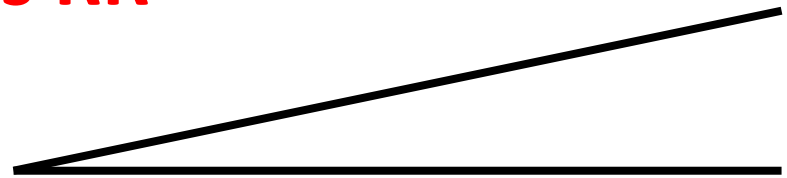
Récurrente / Rémittente

Secondairement progressive



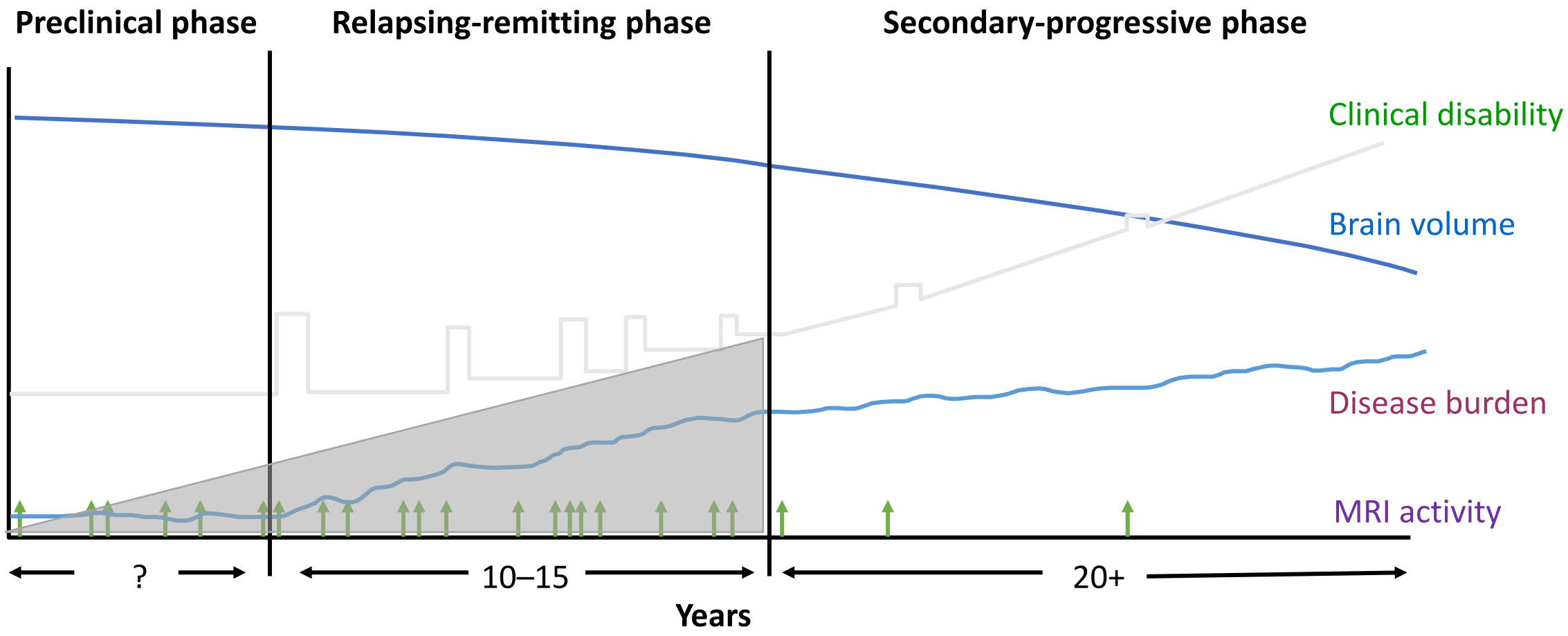
Variable env. 30-40% des formes RR

Primaire progressive



15%

Quand est-ce que la maladie débute ?



MRI, magnetic resonance imaging

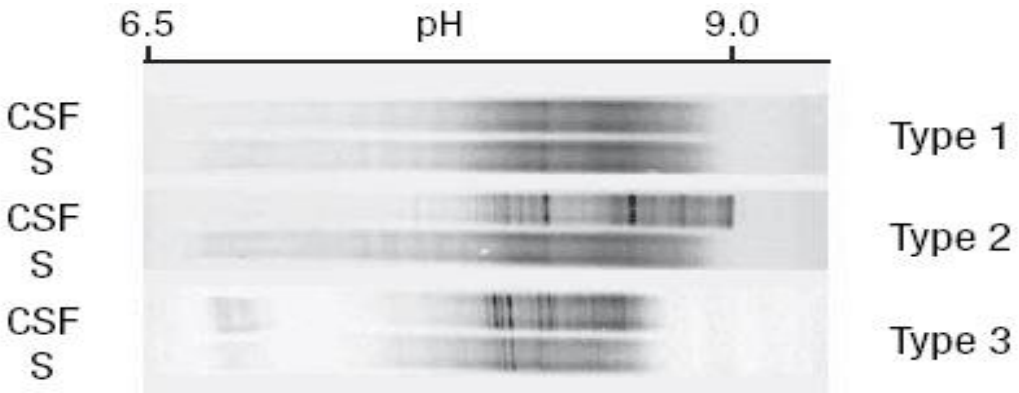
Adapted from Hersh C, Fox R. 2014. Available from: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/multiple_sclerosis

Clinique / diagnostic

Diagnostic de la SEP

3 points:
Dissémination spatiale
Dissémination temporelle
Pas d'autres causes

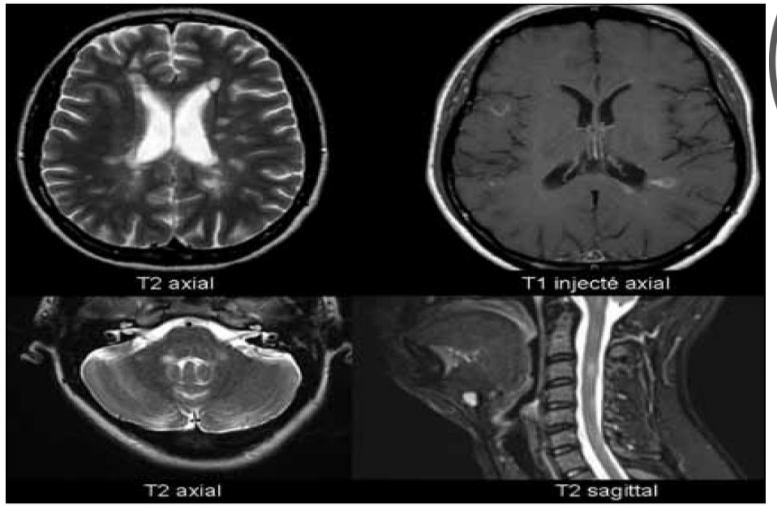
Clinique
Et/ou IRM +++
LCR

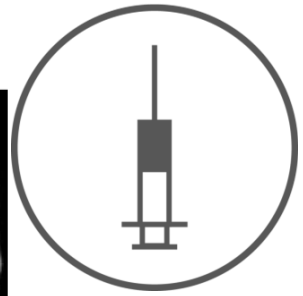


Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

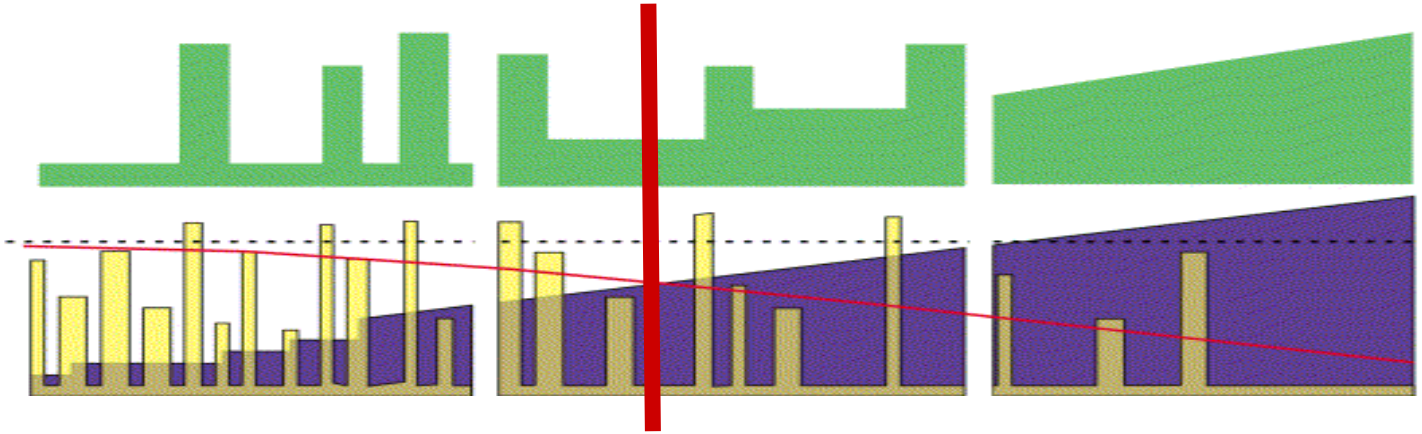
Alan J Thompson, Brenda L Banwell, Frederik Barkhof, William M Carroll, Timothy Coetzee, Giancarlo Comi, Jorge Correale, Franz Fazekas, Massimo Filippi, Mark S Freedman, Kazuo Fujihara, Steven L Galetta, Hans Peter Hartung, Ludwig Kappos, Fred D Lublin, Ruth Ann Marrie, Aaron E Miller, David H Miller, Xavier Montalban, Ellen M Mowry, Per Soelberg Sorensen, Mar Tintoré, Anthony L Traboulsee, Maria Trojano, Bernard M J Uitdehaag, Sandra Vukusic, Emmanuelle Waubant, Brian G Weinshenker, Stephen C Reingold, Jeffrey A Cohen

iag





Evolution conceptuelle

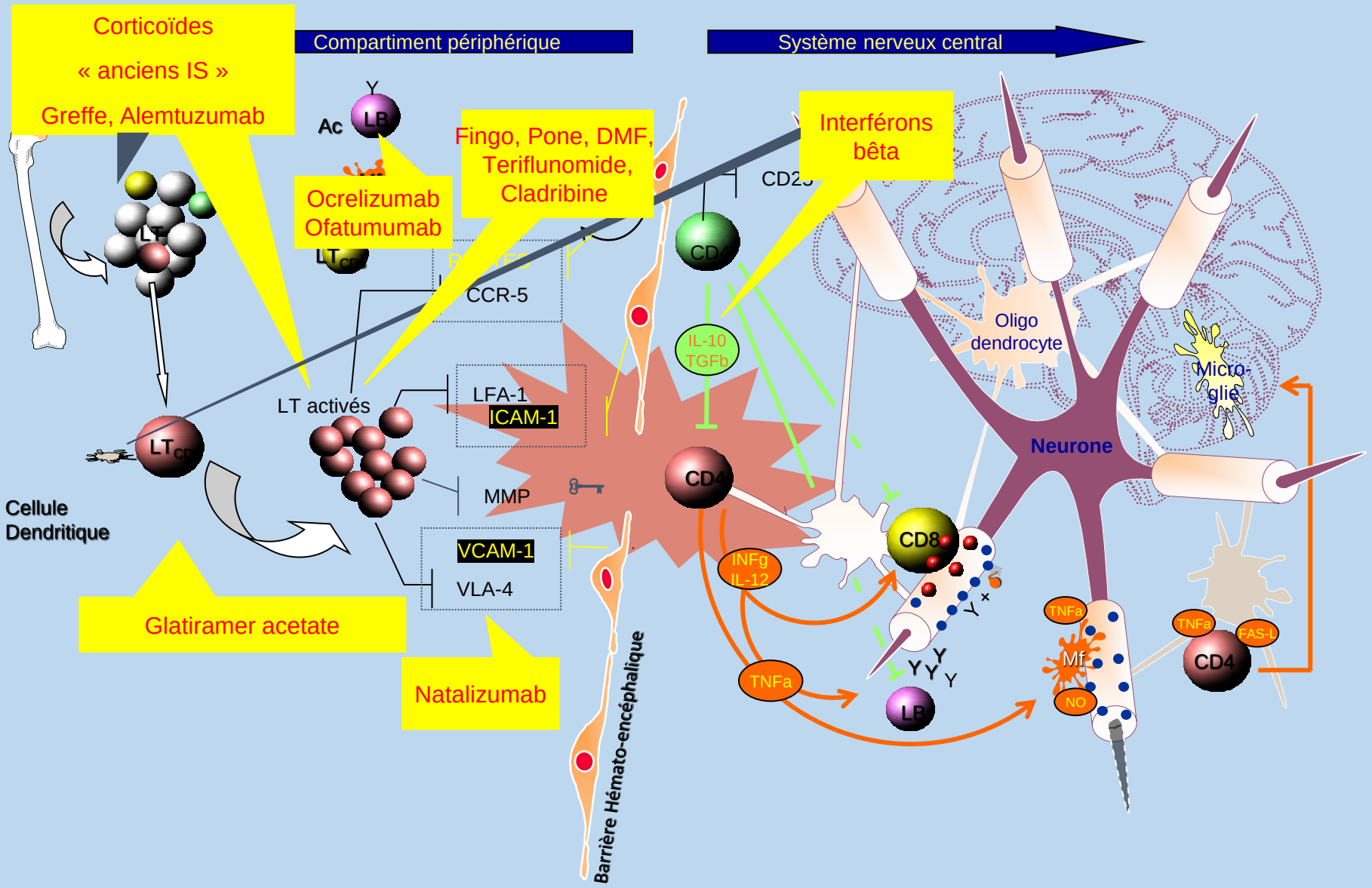


Médiane pour le diagnostic (2018) < 6 mois

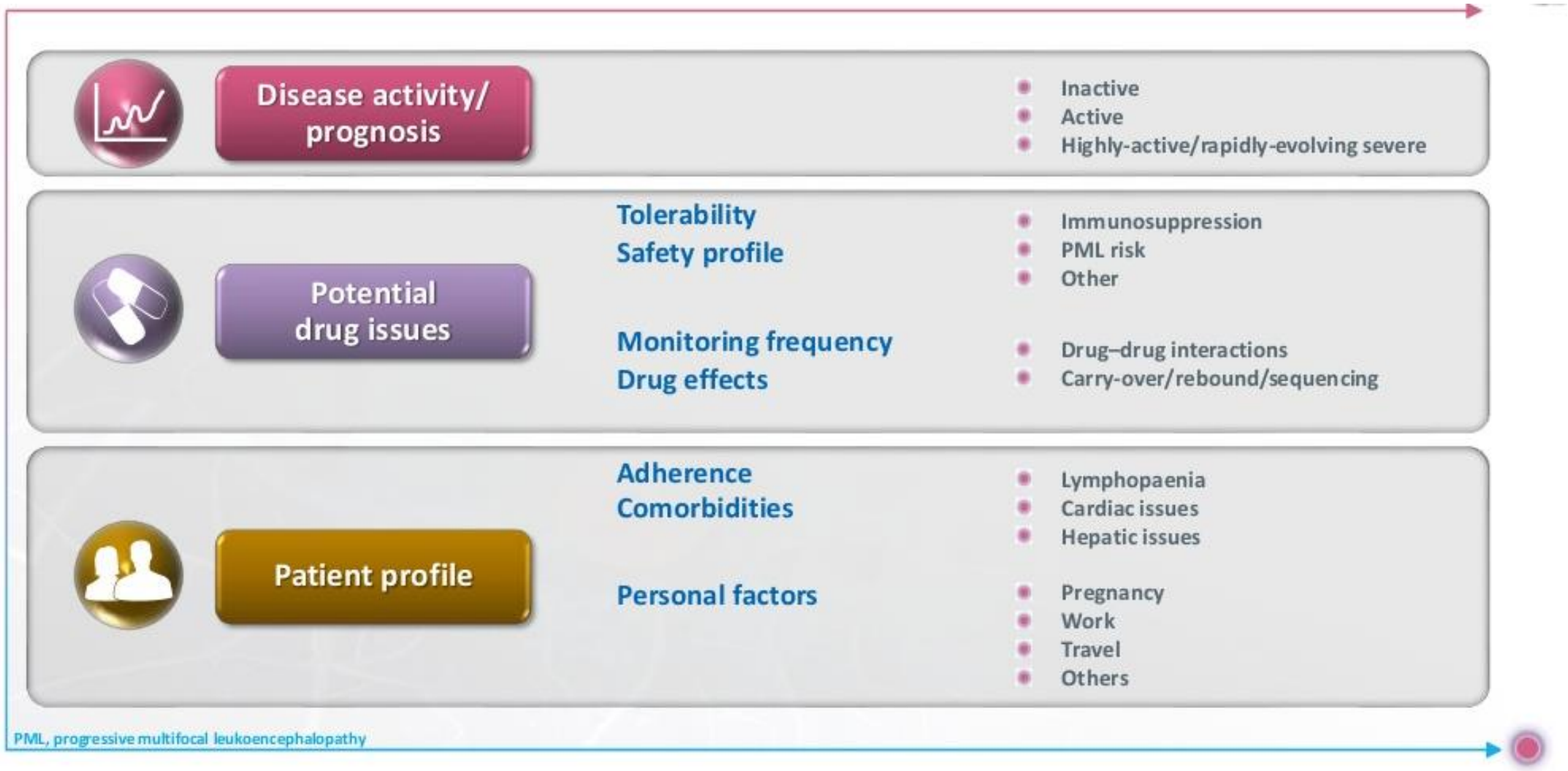
Thompson et al.,Lancet Neurol 2018; Marrie RA et al Neurology 2005;65:1066-1070

Evolution

Prise en charge thérapeutique


Corticoïdes
« anciens IS »
Greffe, Alemtuzumab
Compartiment périphérique
Système nerveux central
Ac
LB
Ocrelizumab
Ofatumumab
Fingo, Pone, DMF,
Teriflunomide,
Cladribine
Interférons
bêta
CD25
CD4
CCR-5
IL-10
TGFb
Oligo
dendrocyte
Micro-
glie
Neurone
LT activés
LFA-1
ICAM-1
MMP
VCAM-1
VLA-4
Cellule
Dendritique
CD8
INFg
IL-12
TNFa
Mf
NO
FAS-L
Glatiramer acetate
Natalizumab
Barrière Hémato-encéphalique

Deciding an appropriate treatment sequence requires a growing number of considerations



What is an appropriate treatment target and regular monitoring plan?

Is this enough?

Clinically stable

Relapses or Disability

MRI as minimum:
MRI essential for monitoring disease progression[1]

Is this achievable?

NEDA-3

Relapses

+

Disability

+

Lesions

Treat-to-Target
30-50% of patients receiving high efficacy therapies achieve NEDA[2]

Can we do better?

NEDA-5

Relapses

+

Disability

+

Lesions

+

Atrophy

+

NfL

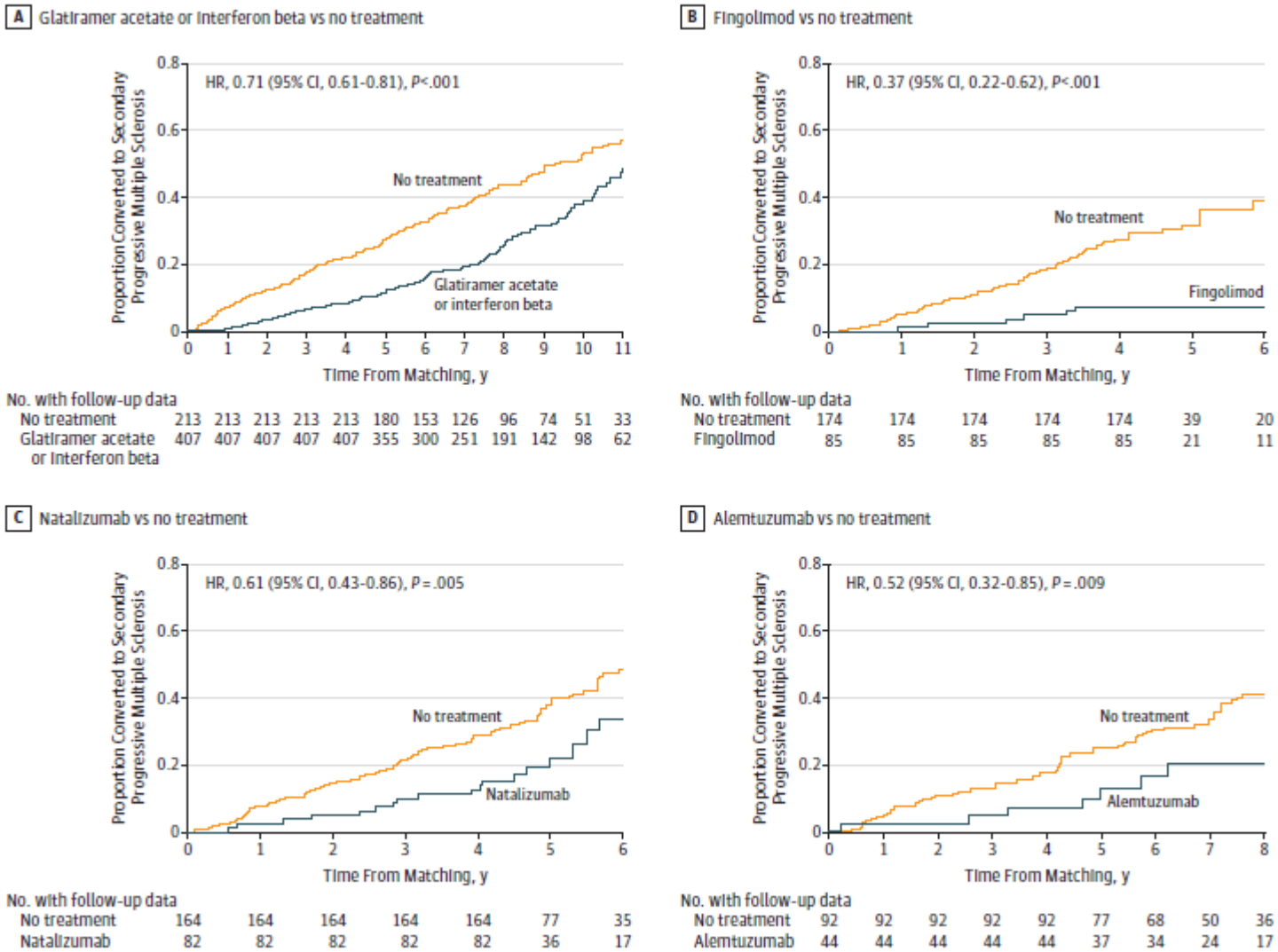
Slowing progression
Would achieving NEDA-5 slow progression?

CSF, cerebrospinal fluid; NEDA, no evidence of disease activity; NfL, neurofilament light.

1. Wattjes MP, Rovira A, & Miller D. *Nat Rev Neurol* 2015;11: 597–606; 2. Smith AL, *et al. Neurotherapeutics* 2017;14:952-960.

Traiter tôt…

Figure 2. Comparison of the Cumulative Hazard of Conversion to Secondary Progressive Multiple Sclerosis in Untreated Patients vs Matched Treated Patients Compared by Initial Treatment

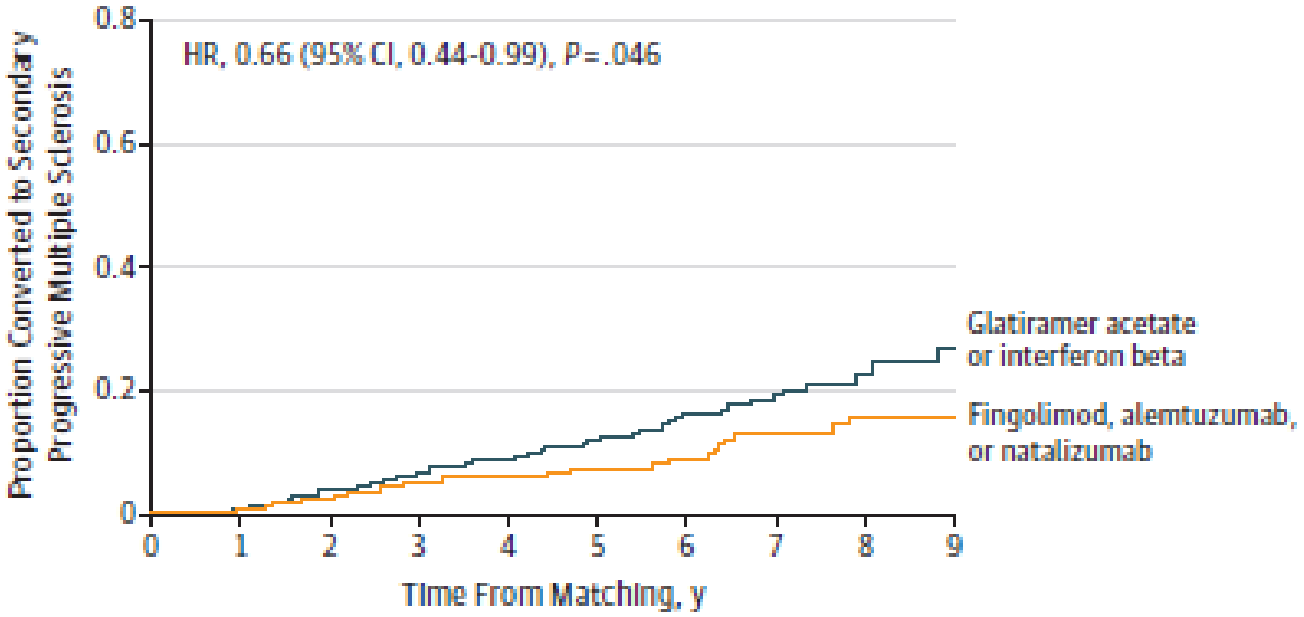


A, The median follow-up was 7.6 years (interquartile range [IQR], 5.8-9.6); B, 4.5 years (IQR, 4.3-5.1); C, 4.9 years (IQR, 4.4-5.8); and D, 7.4 years (IQR, 6-8.6) years. HR indicates hazard ratio.

Brown JWL *et al. JAMA*. 2019 Jan 15;321(2):175-187

Traiter tôt…et efficacement…

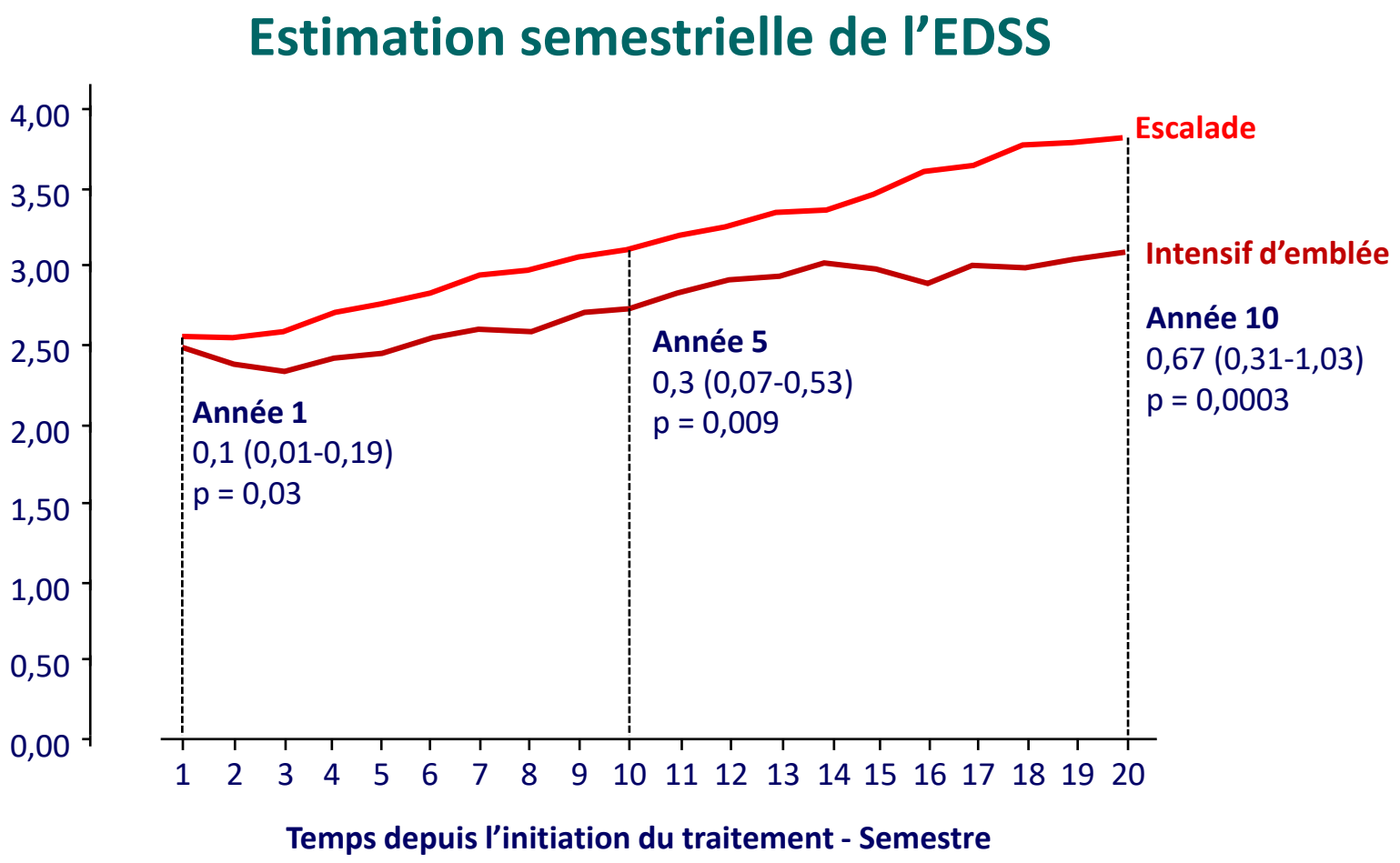
Figure 4. Comparison of Cumulative Hazard of Conversion to Secondary Progressive Multiple Sclerosis for Initial Treatment With Glatiramer Acetate or Interferon Beta vs Fingolimod, Alemtuzumab, or Natalizumab



No. with follow-up data										
Initial treatment										
Glatiramer acetate or Interferon beta	380	380	380	380	380	252	182	142	93	44
Fingolimod, alemtuzumab, or natalizumab	235	235	235	235	235	148	103	80	54	30

Brown JWL *et al. JAMA*. 2019 Jan 15;321(2):175-187

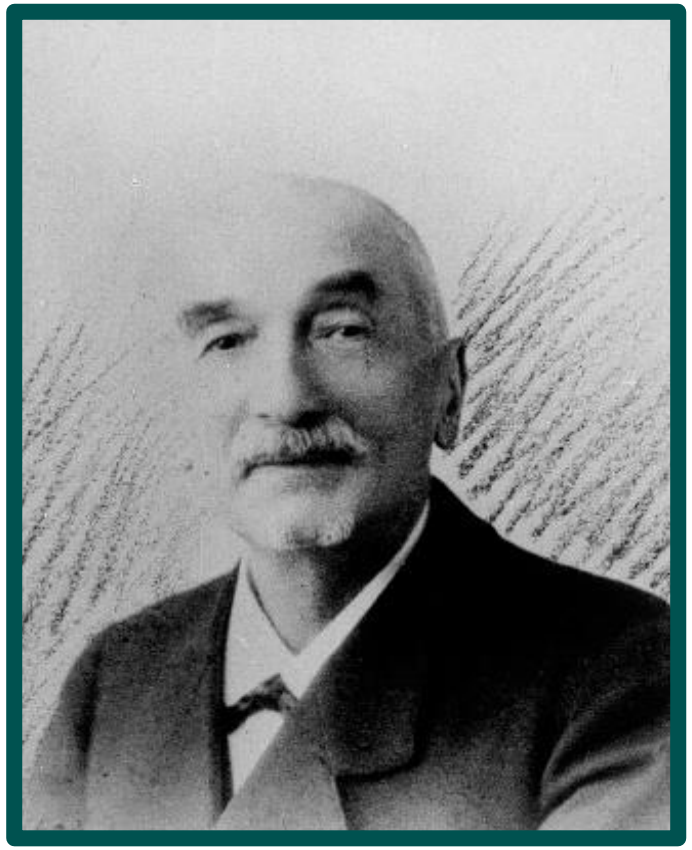
Intensification progressive vs traitement intensif d'emblée : impact sur le handicap dans la SEP-RR - Registre Italien

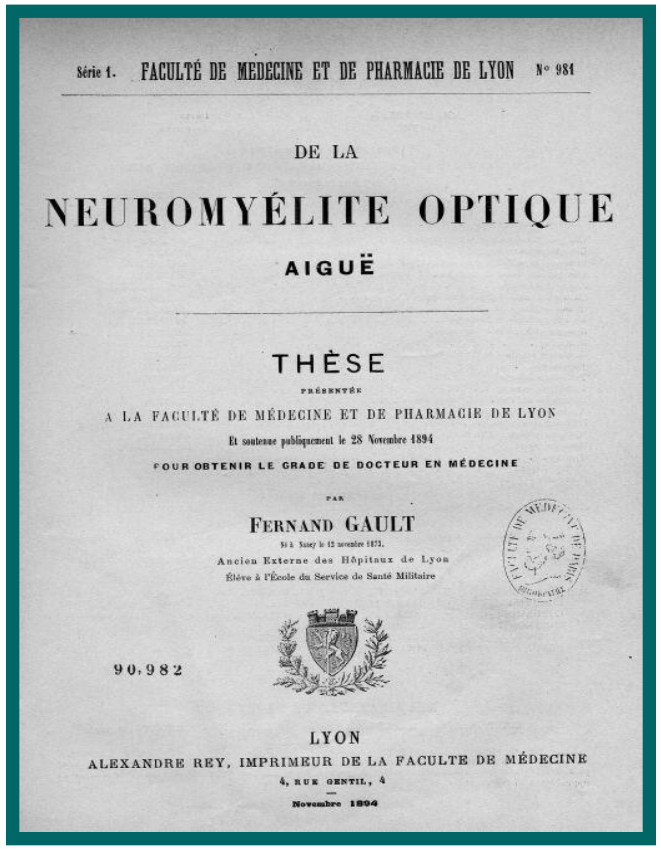


ECTRIMS-ACTRIMS 2020 - Laffaldano P, abstr. PS01.04

Autres diagnostics

Neuromyelitis optica





Série 1. FACULTÉ DE MÉDECINE ET DE PHARMACIE DE LYON N° 981

DE LA

NEUROMYÉLITE OPTIQUE

AIGUË

THÈSE

PRÉSENTÉE

A LA FACULTÉ DE MÉDECINE ET DE PHARMACIE DE LYON

Et soutenue publiquement le 28 Novembre 1894

POUR OBTENIR LE GRADE DE DOCTEUR EN MÉDECINE

PAR

FERNAND GAULT

Né à Nancy le 12 novembre 1873.

Ancien Externe des Hôpitaux de Lyon

Élève à l'École du Service de Santé Militaire

90,982

LYON

ALEXANDRE REY, IMPRIMEUR DE LA FACULTE DE MÉDECINE

4, RUE GENTIL, 4

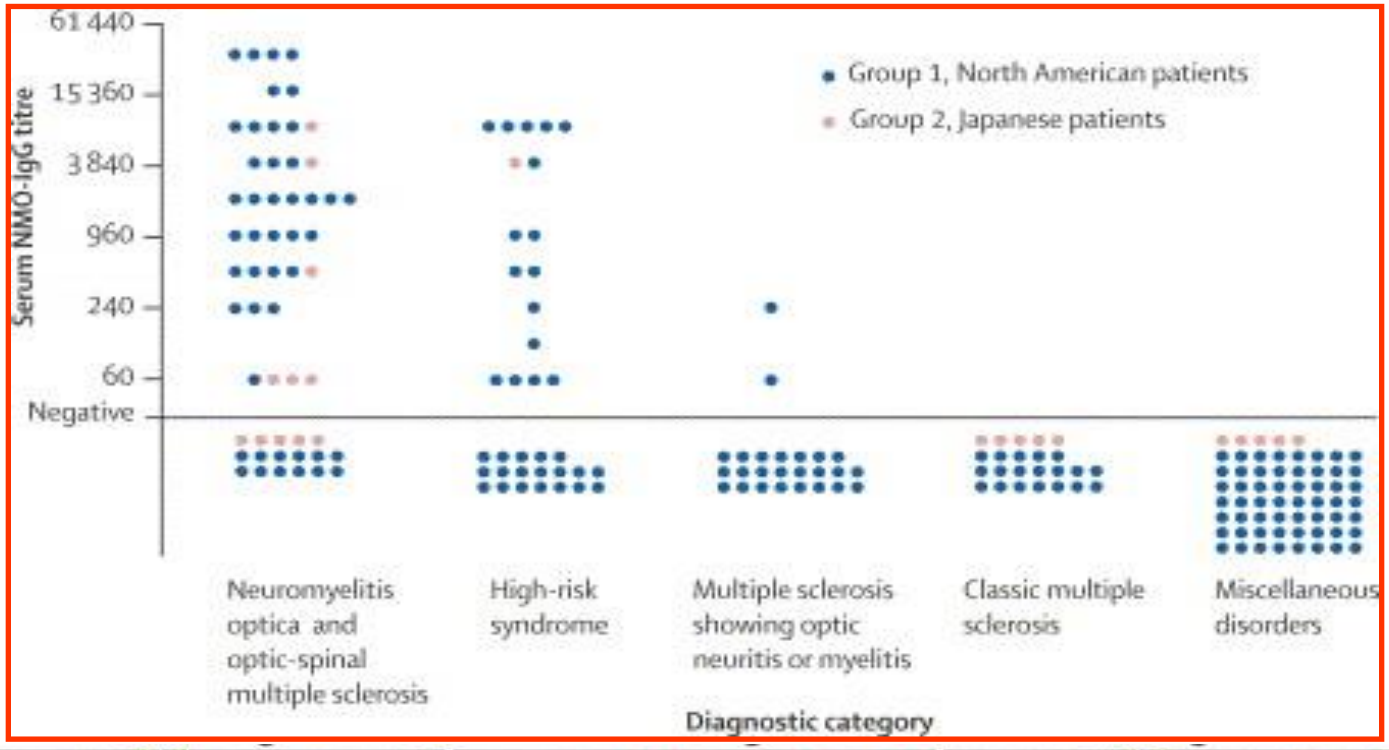
Novembre 1894

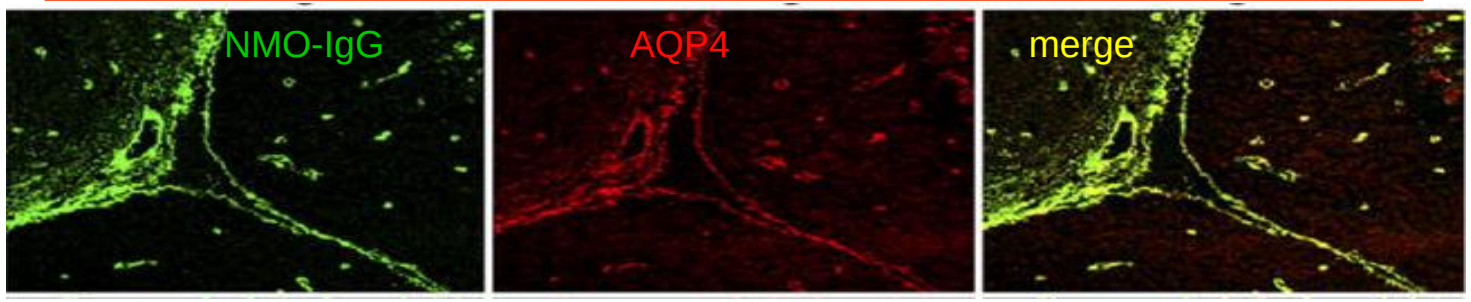
Devic E. 1894

Gault F. Thèse, Lyon, 1895

NMO-IgG /anti-Aquaporine4

Lennon et al., 2004;2005





Lennon et al, 2005

International consensus diagnostic criteria for neuromyelitis optica spectrum disorders

OPEN

Dean M. Wingerchuk, MD, FRCP(C)
Brenda Banwell, MD, FRCP(C)
Jeffrey L. Bennett, MD, PhD
Philippe Cabre, MD
William Carroll, MD
Tanuja Chitnis, MD
Jérôme de Seze, MD
Kazuo Fujihara, MD
Benjamin Greenberg, MD
Anu Jacob, MD
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Michael Levy, MD, PhD
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Brian G. Weinshenker, MD, FRCP(C)

ABSTRACT

Neuromyelitis optica (NMO) is an inflammatory CNS syndrome distinct from multiple sclerosis (MS) that is associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG). Prior NMO diagnostic criteria required optic nerve and spinal cord involvement but more restricted or more extensive CNS involvement may occur. The International Panel for NMO Diagnosis (IPND) was convened to develop revised diagnostic criteria using systematic literature reviews and electronic surveys to facilitate consensus. The new nomenclature defines the unifying term NMO spectrum disorders (NMOSD), which is stratified further by serologic testing (NMOSD with or without AQP4-IgG). The core clinical characteristics required for patients with NMOSD with AQP4-IgG include clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral presentations. More stringent clinical criteria, with additional neuroimaging findings, are required for diagnosis of NMOSD without AQP4-IgG or when serologic testing is unavailable. The IPND also proposed validation strategies and achieved consensus on pediatric NMOSD diagnosis and the concepts of monophasic NMOSD and opticospinal MS. ***Neurology*® 2015;85:1–13**

GLOSSARY

ADEM = acute disseminated encephalomyelitis; **AQP4** = aquaporin-4; **IgG** = immunoglobulin G; **IPND** = International Panel for NMO Diagnosis; **LETM** = longitudinally extensive transverse myelitis lesions; **MOG** = myelin oligodendrocyte glycoprotein; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica; **NMOSD** = neuromyelitis optica spectrum disorders; **SLE** = systemic lupus erythematosus; **SS** = Sjögren syndrome.

Neuromyelitis optica (NMO) is an inflammatory CNS disorder distinct from multiple sclerosis (MS).[1,2] It became known as Devic disease following a seminal 1894 report.[3,e1,e2] Traditionally, NMO was considered a monophasic disorder consisting of simultaneous bilateral optic neuritis and transverse myelitis but relapsing cases were described in the 20th century.[3] MRI revealed

NMOSD criteria 2015

(Wingerchuck et al., Neurology)

AQP-4 +

- **At least one symptome of the NMOSD**
  - **ON**
  - **Myelitis**
  - **Brainstem**
  - **ADEM/PRES**
  - **Narcolepsy**

AQP-4 –

- **2 symptoms with « positive » MRI**
  - **ON (normal MRI)**
  - **Myelitis (extended lesion)**
  - **Brainstem (strategic lesions)**

Figure 1 Spinal cord and optic nerve MRI patterns in neuromyelitis optica spectrum disorder

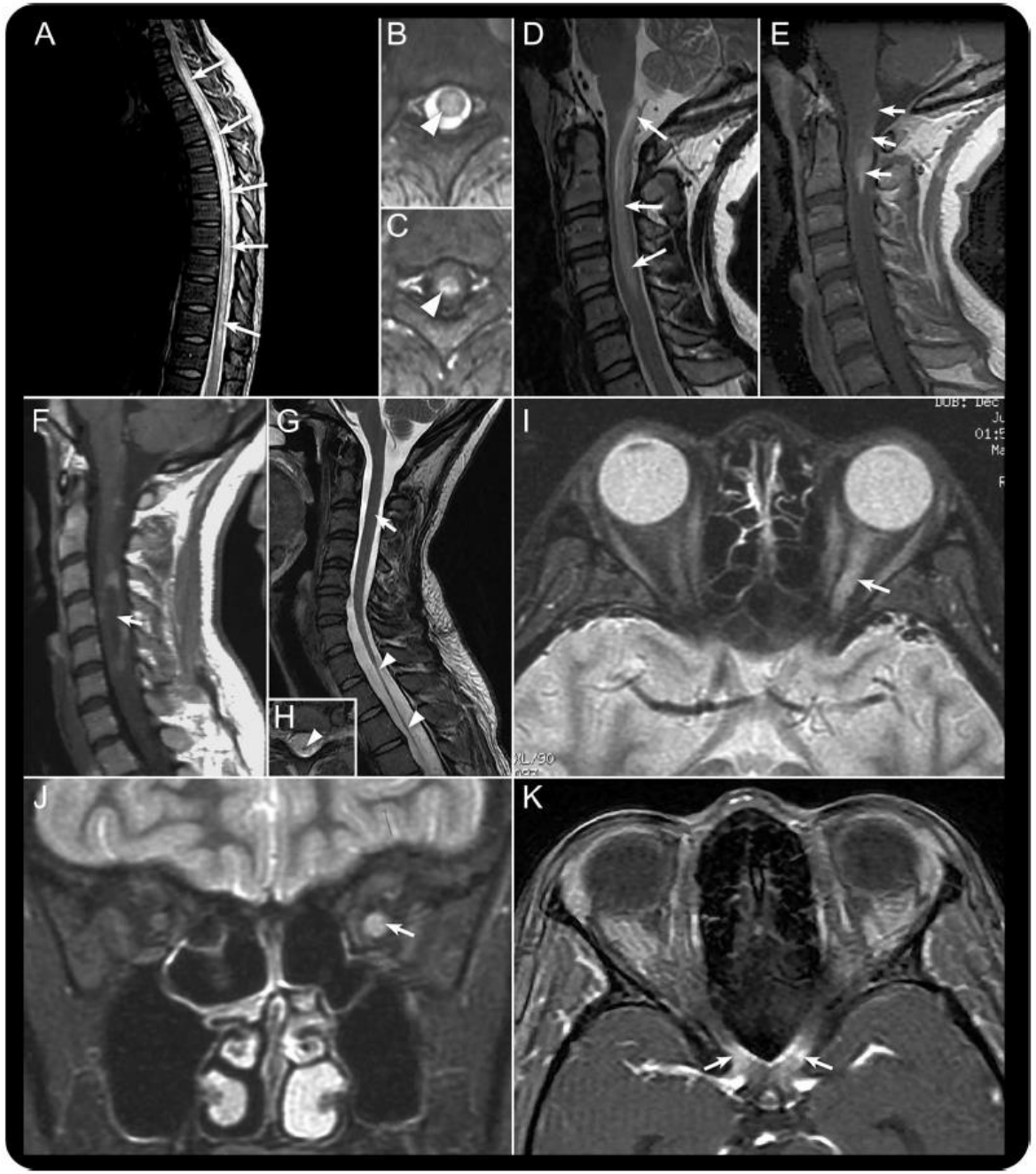


Figure 2 Dorsal medulla, area postrema, and other brainstem lesions in neuromyelitis optica spectrum disorder

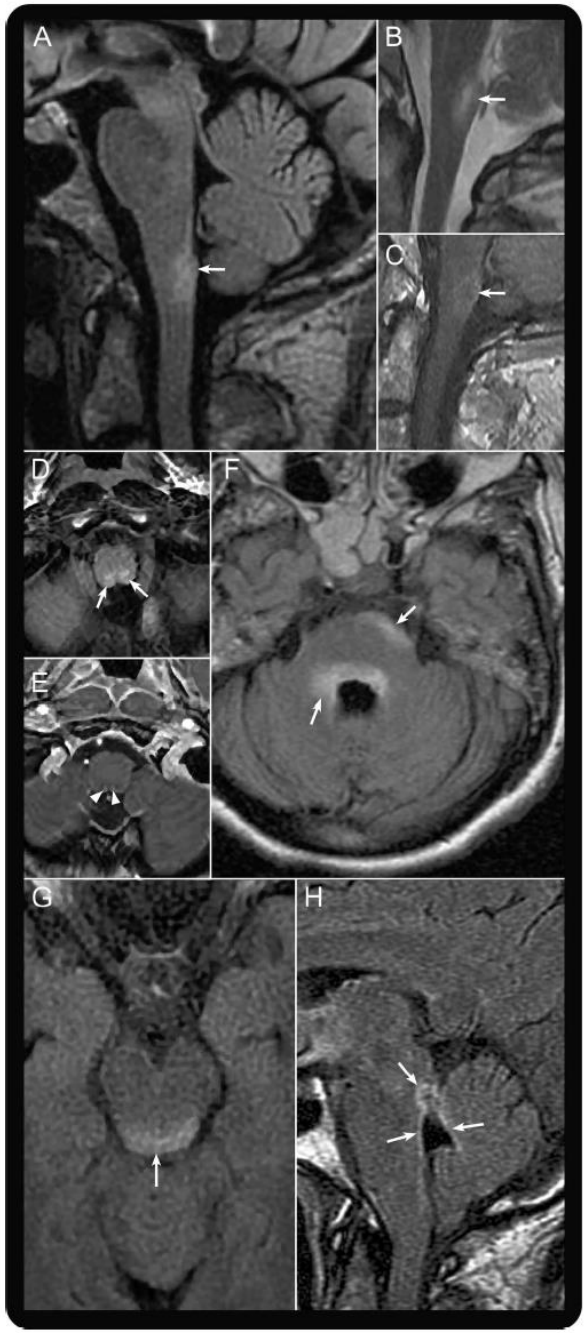
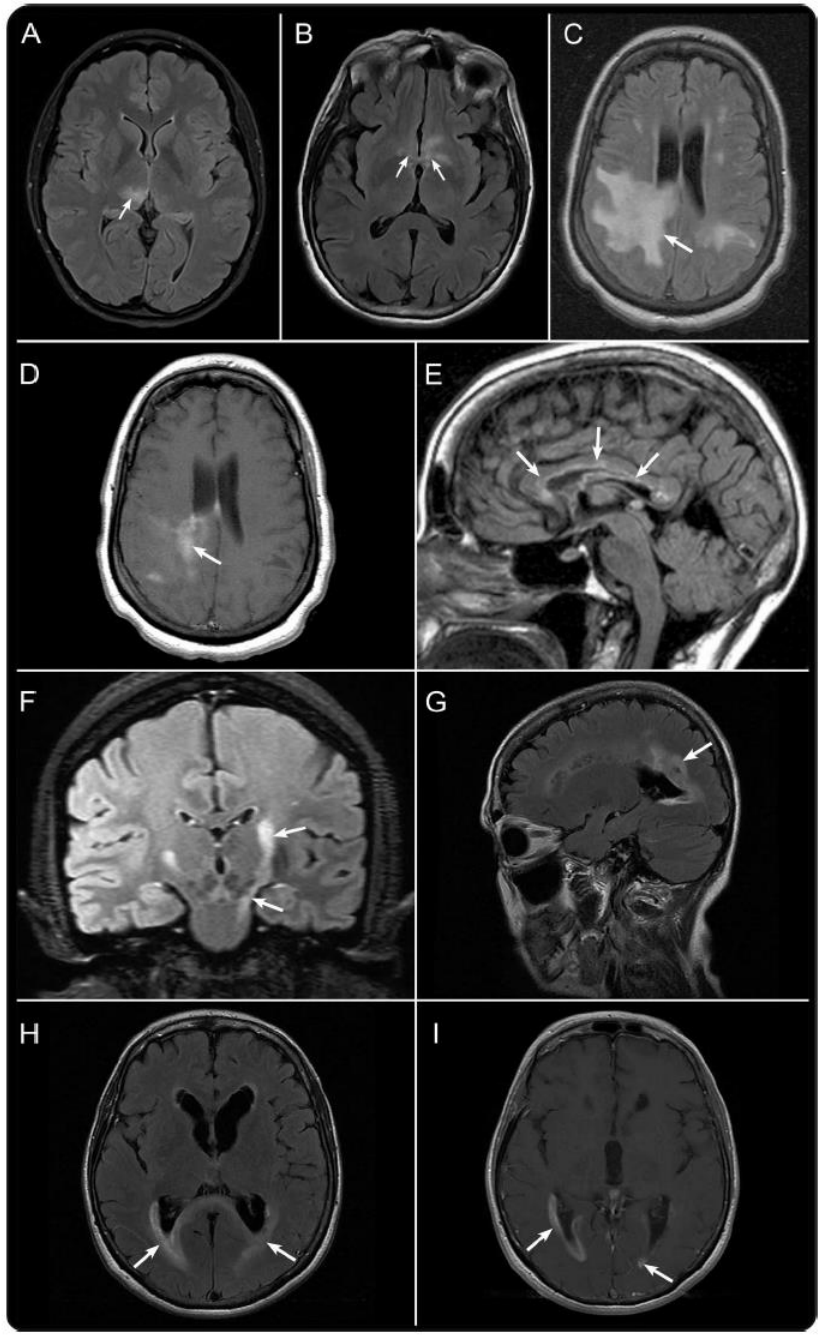
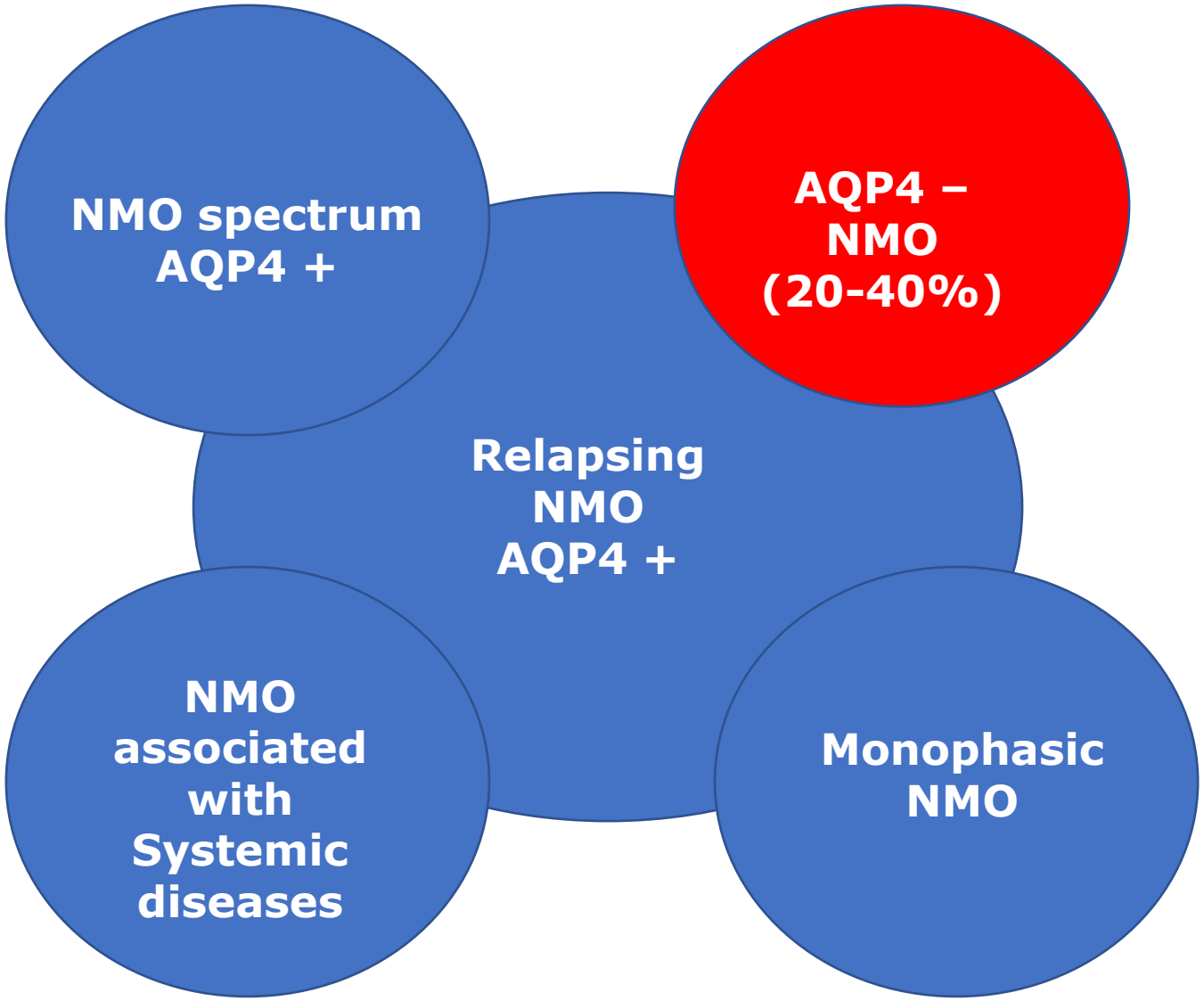


Figure 3 Diencephalic and cerebral lesions in neuromyelitis optica spectrum disorder




NMO spectrum
AQP4 +
AQP4 –
NMO
(20-40%)
Relapsing
NMO
AQP4 +
NMO
associated
with
Systemic
diseases
Monophasic
NMO

MOGAD
(pathologies associées aux anticorps anti-MOG)

Anti-MOG antibodies

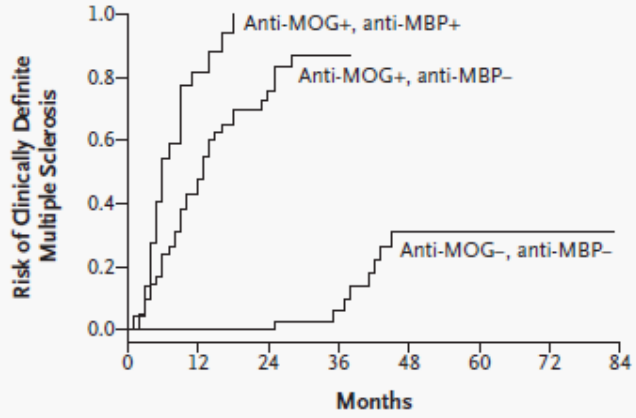


Figure 1. Kaplan–Meier Estimates of the Risk of Clinically Definite Multiple Sclerosis, According to Antibody Status.

P<0.001 for the comparison between the patients who were seronegative for antibodies against both myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) and the patients who were seropositive only for anti-MOG antibodies or for both anti-MOG and anti-MBP antibodies. Plus signs denote seropositive, and minus signs seronegative.

Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders

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ABSTRACT

Objective: To evaluate clinical features among patients with neuromyelitis optica spectrum disorders (NMOSD) who have myelin oligodendrocyte glycoprotein (MOG) antibodies, aquaporin-4 (AQP4) antibodies, or seronegativity for both antibodies.

Methods: Sera from patients diagnosed with NMOSD in 1 of 3 centers (2 sites in Brazil and 1 site in Japan) were tested for MOG and AQP4 antibodies using cell-based assays with live transfected cells.

Results: Among the 215 patients with NMOSD, 7.4% (16/215) were positive for MOG antibodies and 64.7% (139/215) were positive for AQP4 antibodies. No patients were positive for both antibodies. Patients with MOG antibodies represented 21.1% (16/76) of the patients negative for AQP4 antibodies. Compared with patients with AQP4 antibodies or patients who were seronegative, patients with MOG antibodies were more frequently male, had a more restricted phenotype (optic nerve more than spinal cord), more frequently had bilateral simultaneous optic neuritis, more often had a single attack, had spinal cord lesions distributed in the lower portion of the spinal cord, and usually demonstrated better functional recovery after an attack.

Conclusions: Patients with NMOSD with MOG antibodies have distinct clinical features, fewer attacks, and better recovery than patients with AQP4 antibodies or patients seronegative for both antibodies. ***Neurology*® 2014;82:1–8**

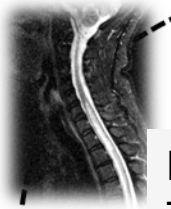
Table 2 Comparison of clinical features between patients with NMOSD with MOG antibodies, AQP4 antibodies, and seronegative patients

Characteristics	MOG Abs+ (n = 16)	AQP4 Abs+ (n = 139)	Seronegative (n = 60)	p Value
Phenotype, n (%)				
NMO	1/16 (6.3)	85/139 (61.1)	15/60 (25.0)	
NMOSD-LETM	5/16 (31.2)	43/139 (30.9)	30/60 (50.0)	<0.0001
NMOSD-ON	10/16 (62.5)	11/139 (8.0)	15/60 (25.0)	
Female, n (%)	6/16 (37.5)	122/139 (87.8)	40/60 (66.7)	<0.0001
Age, y, median (range)				
At first attack	37.5 (3-70)	37 (4-78)	32.5 (10-69)	0.0915
At sampling	42 (6-70)	49 (15-82)	38 (12-69)	0.0004
Follow-up, y, median (range)	2 (1-19)	7 (0-45)	3 (0-32)	0.0002
Patients with a single attack, n (%)	8 (50.0)	23 (16.6)	18 (30.0)	0.0031
Simultaneous ON + myelitis attacks (any time), n (%)	1 (6.25)	32 (23.0)	6 (10.0)	0.0406
No. of attacks, median (range)	1.5 (1-3)	4 (1-33)	2.5 (1-18)	<0.0001
EDSS, median (range)	1.5 (0-8)	5.8 (1-8.5)	4 (0-7)	<0.0001

Abbreviations: Abs = antibodies; AQP4 = aquaporin-4; EDSS = Expanded Disability Status Scale score; LETM = longitudinally extensive transverse myelitis; MOG = myelin oligodendrocyte glycoprotein; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis.

Sato et al., 2014

RION : Natural history (10 years)

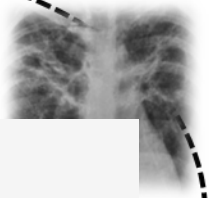


NMO

Normal brain MRI
Transverse myelitis

12%

AID



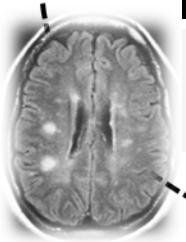
ANA +
Chest CT scan,
Salivary gland biopsy

5-10%

RION cohort before MOG
Normal work up : 50%
1/3 MOG-antibodies

29%

MS



OCB +
Few Brain MRI lesion

The Natural History of Recurrent ON

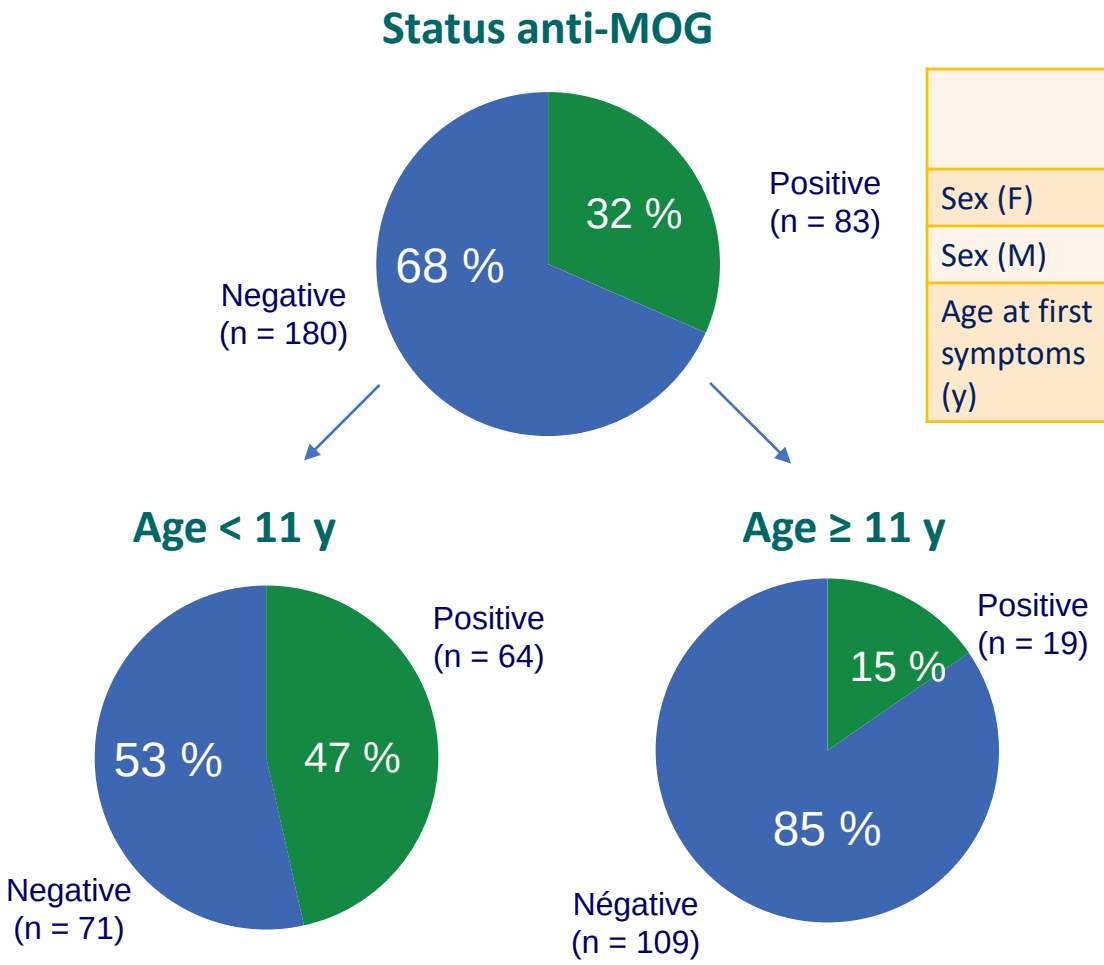
Pirko et al. Arch Neurol 2004
Benoilid et al. Mult Scl J 2013

Main cohorts on MOG-Ab

Studies	n	Age at onset	Sex ratio F/M	Initial presentation	CSF + (OCB)	Evolution
Jurynczyk et al.	252	30 y	57%	18 % : myelitis 55 % : ON 9 % : NMO	12%	> AQP-4
Kaneko et al.	259	26 y	52,1	ON > NMO > Myelitis	ND	> AQP-4
Cobo-Calvo et al.	197	36 y	49,2	22 % : myelitis 60 % : ON 15 % : NMO	5,7 %	> AQP-4

Jurynczyk et al., 2018, Kaneko et al;, 2017, Cobo-Calvo et al.2018,

Canadian cohort : 263 children



	MOG+ (n = 83)	MOG- (n = 180)	p
Sex (F)	45 (54 %)	88 (49 %)	0,43
Sex (M)	38 (46 %)	92 (51 %)	0,43
Age at first symptoms (y)	7.34 (4,91 - 10,58)	12.38 (7,92 - 14,42)	< 0,0001

ECTRIMS 2018 – Fadda G, abstr. 65

Prevalence of MOG antibodies in multiple sclerosis: a multicentre cross-sectional study

Lyon/Strasbourg cohort

Specificity = 99.7%

Features	Total MS cohort N=686
Female, n (%)	499 (72.7)
Age at MS onset, y median (range)	28.5 (3.32-77.8)
Age at sampling, y median (range)	42.3 (17-83)
Caucasian, n (%)	553 (80.6)
Magrebian	122 (17.8)
African	5 (0.7)
Asiatic	5 (0.7)
Hispanic	1 (0.2)
Type of MS, n (%)	
Clinically isolated syndrome	35 (5.1)
Relapse remitting	422 (61.5)
Secondary progressive	132 (19.2)
Primary progressive	97 (14.1)
Disease duration at sampling, y median (range)	11.4 (0-45.6)
Relapse 30 days before sampling, n (%)	50 (7.3)
I.V or oral MTP 30 days before sampling, n (%)	46 (6.7)
Long-term treatment 30 days before sampling, n (%)	441 (64.3)
[a]Immunosuppressants	29 (6.6)
[b]MS disease modifying drugs	412 (93.4)
MOG-Ab-positive patients, n (%)	2 (0.29)

Cobo-Calvo et al. Neurol Neuroimmunol Neuroinflamm. 2019 Dec 13;7(2):e649

Therapeutical approach

Acute phase

High dose of IV corticosteroids :

- 3-10 g during a week (which interval between 2 courses ?)
- Oral corticosteroids : 1mg/kg/day during one month

frequently suggested with a progressive decrease

Plasma exchange :

Weishenker et al. Ann Neurol., 1999

IVIg :

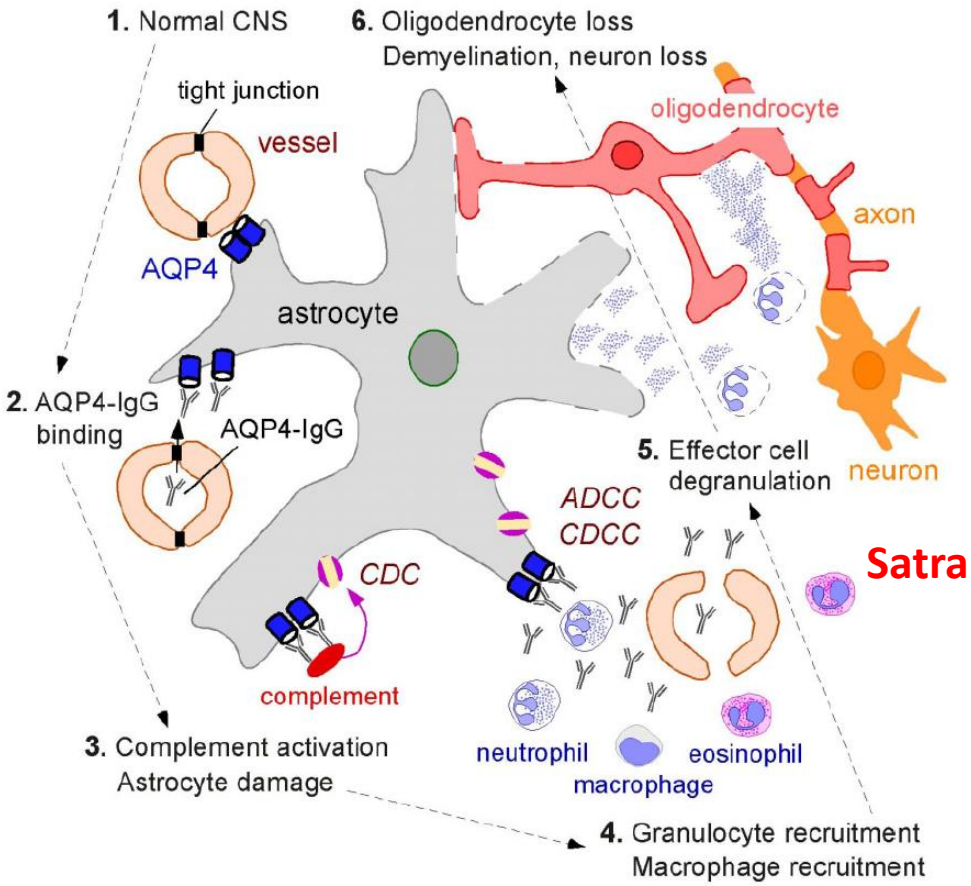
Elsone et al. Mult Sclerosis, 2013

NMOSD (AQP4+)

Traitement de fond

3 études de phase III dans les 5 dernières années !!!

OFF-LABEL	THERAPIES WITH RANDOMIZED DATA
• Rituximab • Mycophenolate mofetil • Azathioprine • Corticosteroids	• Eculizumab • Inebilizumab • Satralizumab



Eculizumab

Satralizumab*

Inebilizumab*

D'après Verkman et al. Brain Pathology, 2013;23:684

*Hors AMM

		PREVENT Eculizumab (Anti-C5)	N-MOmentum Inebilizumab (Anti-CD19)	SAkuraSky Satralizumab (Anti-IL6R)	SAkuraStar Satralizumab (Anti-IL6R)
Subjects (n)		143	230	83	95
Serostatus		AQP4+ only	AQP4+/-	AQP4+/-	AQP4+/-
Placebo arm		Background IST allowed	Placebo only	Background IST allowed	Placebo Only
Relapse reduction	Overall	NA	73%	62%	55%
	AQP4+	94.2%	77.3%	79%	74%
Relapse free (48 weeks, AQP4+)	Overall	97.9%	NA	91.5%	82.9%
	Placebo only	63.2%		59.9%	55.4%
Relapse free (96 weeks, AQP4+)	Overall	96.4%	NA	91.5%	76.5%
	Placebo only	51.9%		53.3%	41.1%

Pittock SJ et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381(7):614-625
Cree BAC et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet*. 2019;394(10206):1352-1363.
Traboulsee A et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol.* 2020;19(5):402-412. • 24.
Yamamura T et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med.* 2019;381(22):2114-2124.

Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial

Masayuki Tahara, Tomoko Oeda, Kazumasa Okada, Takao Kiriyama, Kazuhide Ochi, Hirofumi Maruyama, Hikoaki Fukaura, Kyoichi Nomura, Yuko Shimizu, Masahiro Mori, Ichiro Nakashima, Tatsuro Misu, Atsushi Umemura, Kenji Yamamoto, Hideyuki Sawada

Lancet Neurol 2020; 19: 298–306

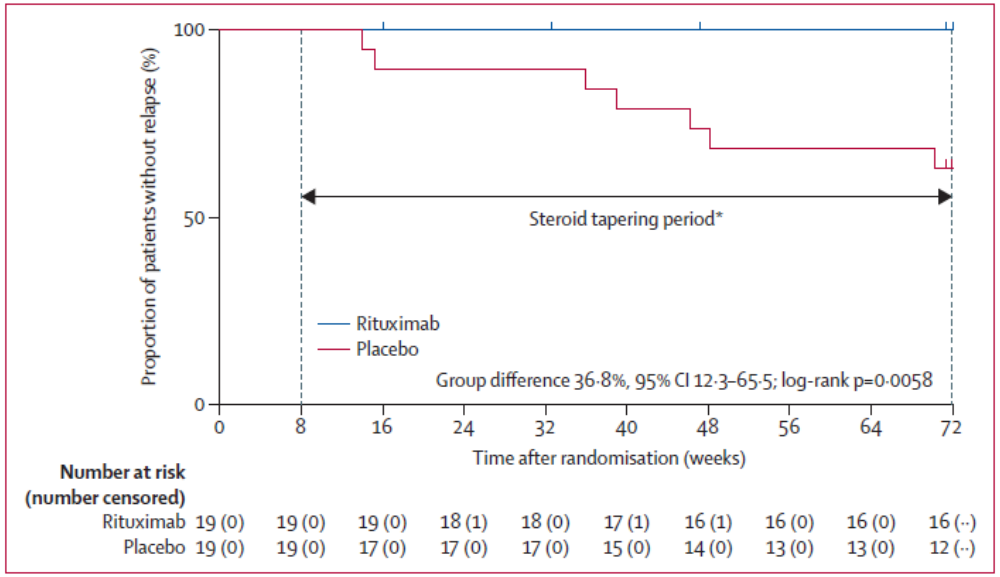


Figure 2: **Proportion of patients without relapse**
*The dose of oral steroids was tapered according to the protocol from 8 weeks after randomisation.

Hors AMM

MOGAD

Tocilizumab et MOGAD

	Cas 1	Cas 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Sexe/âge (ans) au diagnostic	Femme/11	Femme/25	Homme/46	Femme/31	Femme/20	Homme/59	Homme/20	Homme/47	Femme/24	Femme/31
Race/ethnie	Hispanique	Caucasienne	NR	NR	NR	NR	NR	Caucasienne	Caucasienne	Caucasienne
Présentation clinique initiale	Tronc cérébral +LETM, LETM, recON	Bilat ON+Tronc cérébral +LETM, recON	NR	NR	NR	Tronc cérébral +myélite courte, recON	bilatON, LETM, myélite courte, ON	NR	NR	recTM, ON
Phénotype clinique final	NMOSD	NMOSD	NMOSD	NMOSD	NMOSD	NMOSD	NMOSD	NMOSD	NMOSD	NR
Durée de la maladie (ans)	9	10	6	4	2	~ 6,5	1	7	4	11
Traitements avant le TCZ	RTX, daily PRED	AZT, RTX, IVIG, PRED	RTX	RTX	RTX	PRED, NAT, RTX, CP	RTX	PRED, RTX, MMF, BEL	AZT	IFN-b, RTX
Indication de mise sous TCZ	Activité de la maladie	Effets 2nd	Activité de la maladie, neutropénie	Activité de la maladie, neutropénie	Activité de la maladie	Activité de la maladie	Activité de la maladie	Activité de la maladie	Activité de la maladie	Activité de la maladie
Durée de suivi sous TCZ (mois)	26	8	21	29	5	54	24	65	44	12
TOC forms	IV	IV	IV puis SC	IV puis SC	IV	IV	IV	SC	SC	IV
TOC dose	8 mg/kg/mois	8 mg/kg/mois	8 mg/kg/mois, 162 mg/sem.	8 mg/kg/mois, 162 mg/sem.	8 mg/kg/mois	8 mg/kg/mois	8 mg/kg/mois	162 mg/ 1-2 sem.	162 mg/ 1-2 sem.	NR
TAP pré TCZ	1,33 (sur 6 ans)	1,56 (sur 9 ans)	1 (sur 2 ans)	1 (sur 2 ans)	1 (sur 2 ans)	~ 5 (sur 2 ans)	4 (sur 1 ans)	0,71 (sur 7 ans)	1,50 (sur 4 ans)	0,40 (sur 10 ans)
TAP sous TCZ	0	0	0	0	0	0	0	0	0	0
Effets 2nd TCZ	dyslipidémie	dyslipidémie	Infections dentaires	dyslipidémie	None	NR	None	dyslipidémie	None	NR

Hors AMM : AAN 2021 – Elsbernd P, abstr. P2.050

Autres diagnostics différentiels

- **Sd de Gougerot-Sjögren**
- **Lupus**
- **Behçet**
- **Sarcoïdose**
- **Signes différents / critères diag. / PL +++**

Merci pour votre attention