Neuromyélite optique
Quels traitements fondés sur les preuves ?

Point de vue de l'ophtalmologiste

Point de vue du neurologue

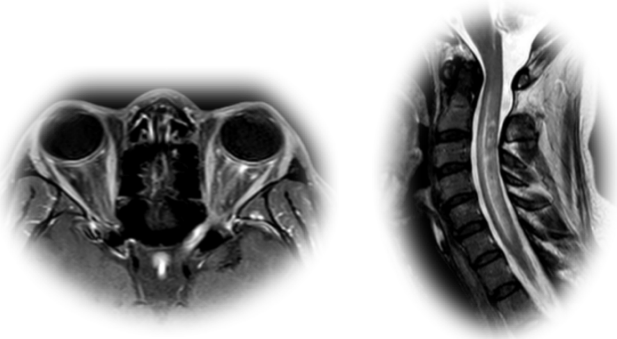
Hôpital Pitié Salpétrière

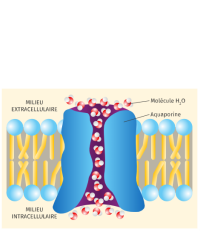
Fondation Ophtalmologique Adolphe de Rothschild

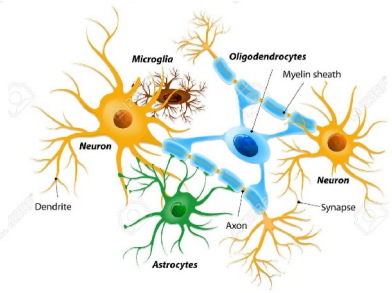
C Papeix CHU Pitié Salpêtrière
C Vignal Clermont FO Rothschild

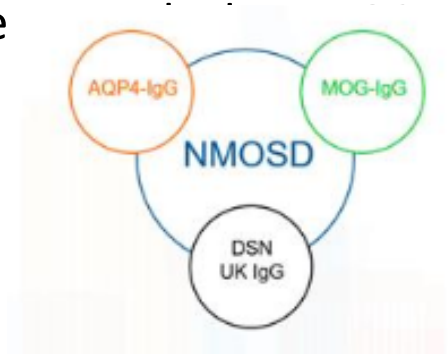
De quoi parle –t-on ?

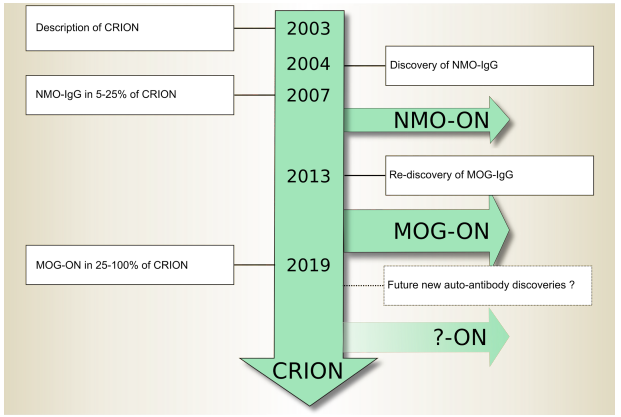
- NMO : description clinique : NO + myélite transverse
- **2004** : découverte des IgG anti-AQP4) ; cible : protéine AQP4 principalement exprimée au pied des astrocytes. *Critères de Wingerchuk en 2006*
- **2007** : introduction du spectre NMO
- **2013** : IgG anti-MOG , tableau NMO fréquent
- **2015** : critère











- *Wingerchuk et al. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006; 66 :1485-9*
- *Wingerchuk et al. The spectrum of neurmyelitis optica. Lancet Neurol 2007; 6:805-15*
- *Chen JJ, Pittock SJ, Flanagan EP, Lennon VA, Bhatti MT. Optic neuritis in the era of biomarkers. Surv Ophthalmol. 2019 Aug 16.*
- *Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177e89*

De quoi parle –t-on ?

- **2015** : critères actuels de NMO

A

NMOSD Core Clinical Characteristics
Optic neuritis
Acute myelitis
Area postrema syndrome
Acute brainstem syndrome
Symptomatic narcolepsy or acute diencephalic clinical syndrome*
Symptomatic cerebral syndrome*
** With corresponding NMOSD-typical brain lesions*

B

	AQP4-IgG Positive	AQP4-IgG Negative/Unknown
Core Clinical Characteristics Needed	≥ 1	≥ 2 unique (one must be #1-3 below)
Neuroimaging	No additional requirements needed	Must fulfill additional MRI requirements**

C

****NMOSD additional MRI requirements**
(when AQP4-IgG seronegative or unknown)

1. **Acute optic neuritis**
   - Brain MRI normal or non-specific white matter changes only
   - Extensive T2 hyperintense or T1 gadolinium enhancing optic nerve lesions
     - >50% of the optic nerve length or chiasmal involvement (Figure 1)
2. **Acute myelitis**
   - Longitudinally extensive transverse myelitis (LETM) involving >/= 3 contiguous spinal cord segments
   - >/= 3 contiguous segments of spinal cord atrophy in patients with a history of transverse myelitis
3. **Area postrema syndrome**
   - Dorsal medullary/area postrema lesions
4. **Acute brainstem syndrome**
   - Periependymal brainstem lesions

- *Wingerchuk et al. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006; 66 :1485-9*
- *Wingerchuk et al. The spectrum of neurmyelitis optica. Lancet Neurol 2007; 6:805-15*
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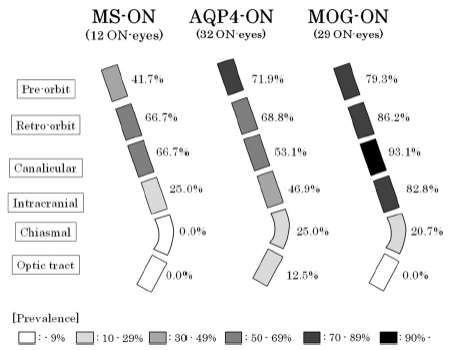
Devant une NOInfl
Rôle de l'ophtalmologiste

- **Penser à ces 2 entités**
- Lors d'une première poussée, si atypique (terrain, contexte auto immun, bilatérale, OP), sévère, mauvais récupération
- IRM atypique



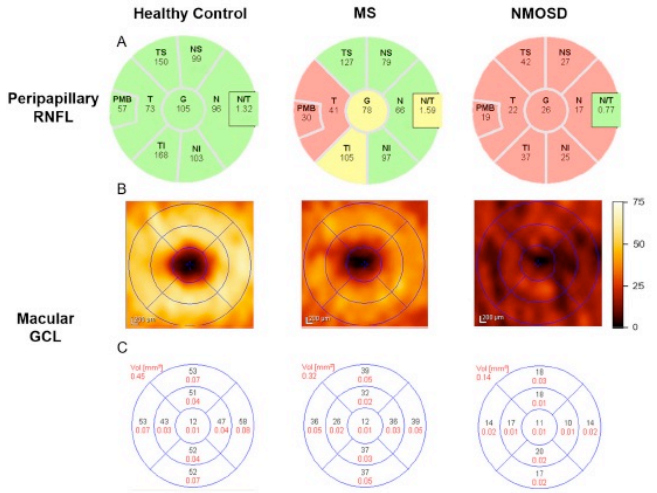
- **Lors des récidives ++++**
- **Il faudra adresser en neurologie et demander les Ac spécifiques**

MOG n = 47
Femmes 24 (51%)
Caucasiens 48 (65%)
Bilatéral simultané 19 (40,4%)
ATCD NOInfl : n=9
Douleur 89,4%
Œdème papillaire 70,2%
AV < 1/10 34 %
IRM : ZHS orbite 93,3%
NO œdémateux 44,7%
IRM cérébrale normales 66%

Biotti et al. Optic neuritis in patients with anti-MOG antibodies spectrum disorder: MRI and clinical features from a large multicentric cohort in France J Neurol (2017) 264:2173–2175
NEMOS group J Neuroinflammation. 2016 Nov 1;13(1):282.

Ophtalmologiste et Neurologue ont un point de vue identique

- Traiter les poussées pour limiter les séquelles
- Mettre en place un traitement de fond pour éviter les poussées



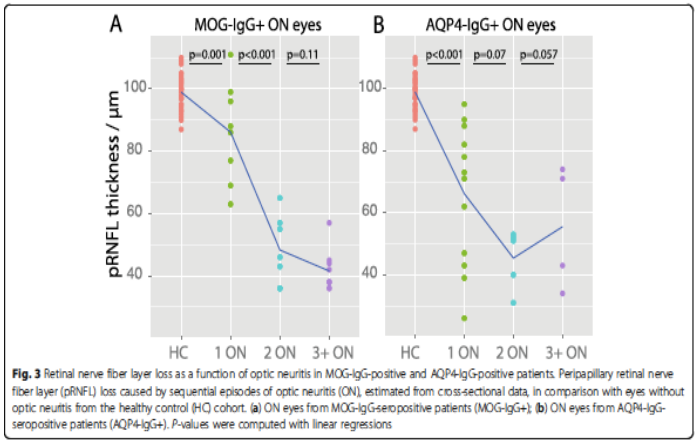


Fig. 3 Retinal nerve fiber layer loss as a function of optic neuritis in MOG-IgG-positive and AQP4-IgG-positive patients. Peripapillary retinal nerve fiber layer (pRNFL) loss caused by sequential episodes of optic neuritis (ON), estimated from cross-sectional data, in comparison with eyes without optic neuritis from the healthy control (HC) cohort. (**a**) ON eyes from MOG-IgG-seropositive patients (MOG-IgG+); (**b**) ON eyes from AQP4-IgG-seropositive patients (AQP4-IgG+). *P*-values were computed with linear regressions

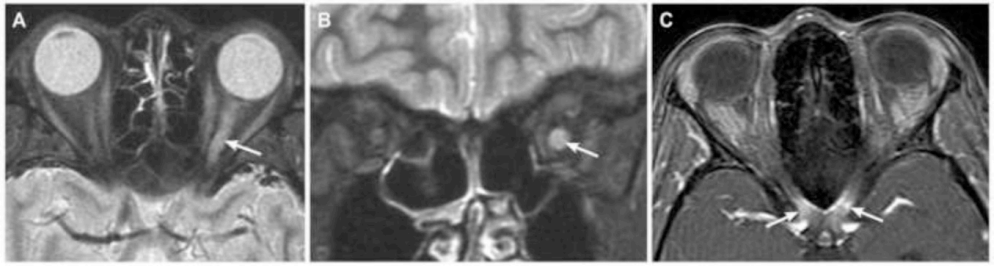
Stiebel-Kalish H, Lotan I, Brody J,Chodick G, Bialer O, Marignier R, et al. (2017)
Retinal Nerve Fiber Layer May Be Better Preserved in MOG-IgG versus AQP4-IgG Optic Neuritis: ACohort Study. PLoS ONE 12(1): e0170847.

Neuromyélite optique de devic spectrum disorder

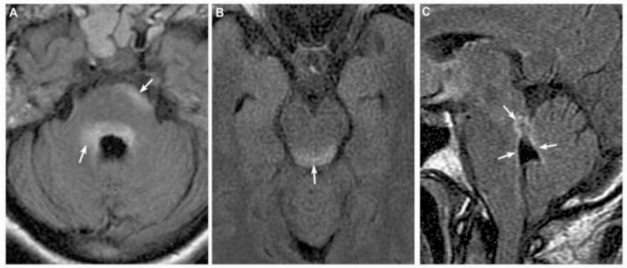
Rare : 1/100 000
Etemadifar 2015

Pronostic sévère
Wingerchuk, 1999, Neurology

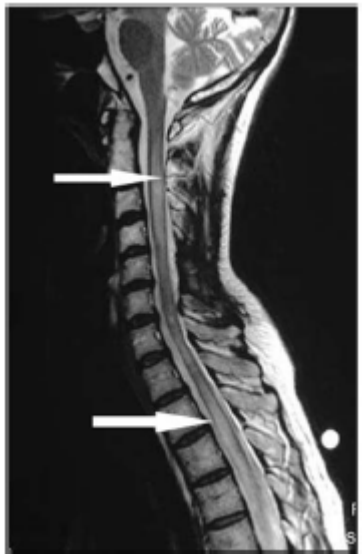
Névrite optique



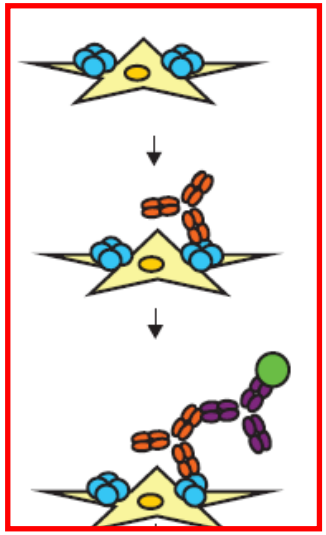
Atteinte du tronc cérébrale



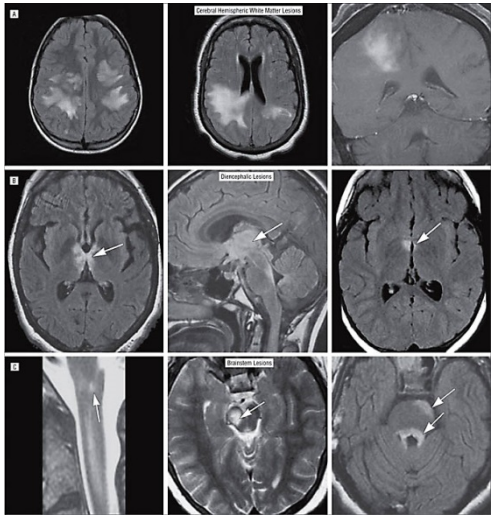
Myélite transverse étendue



AQP4



Atteinte encéphalique



Traitement de fond

- Azathioprine (Mandler, 1998)
- PLEX (Weinschenker, 1999)
- Immunosuppresseurs (Papeix, 2003)
- Rituximab (Cree, 2005)
- MFM (Jacob, 2009)
- Tocilizumab (Araki, 2014)

Comparaison du taux annualisé de poussées pré et sous traitement chez les patients NMO

Table 2. Treatment-Associated Annualized Relapse Rates (ARRs) and Hazard Risks Relative to Rituximab

Medication	Pretreatment ARR	Posttreatment ARR	Change From Pretreatment to Posttreatment, %	Hazard Risk Relative to Rituximab (95% CI)	*P* Value
Azathioprine	2.26	0.63	72.1	2.12 (1.12- 4.01)	.02
Mycophenolate mofetil					
Total	2.61	0.33	87.4	1.48 (0.75-2.93)	.26
Optimal dosing	2.55	0.25	90.2		
Rituximab					
Total	2.89	0.33	88.6	1 [Reference]	
Optimal dosing	3.25	0.20	93.9		
Switch treatments	1.03	0.14	86.4		.054

JAMA Neurol. 2014;71(3):324-330.

Perspectives thérapeutiques

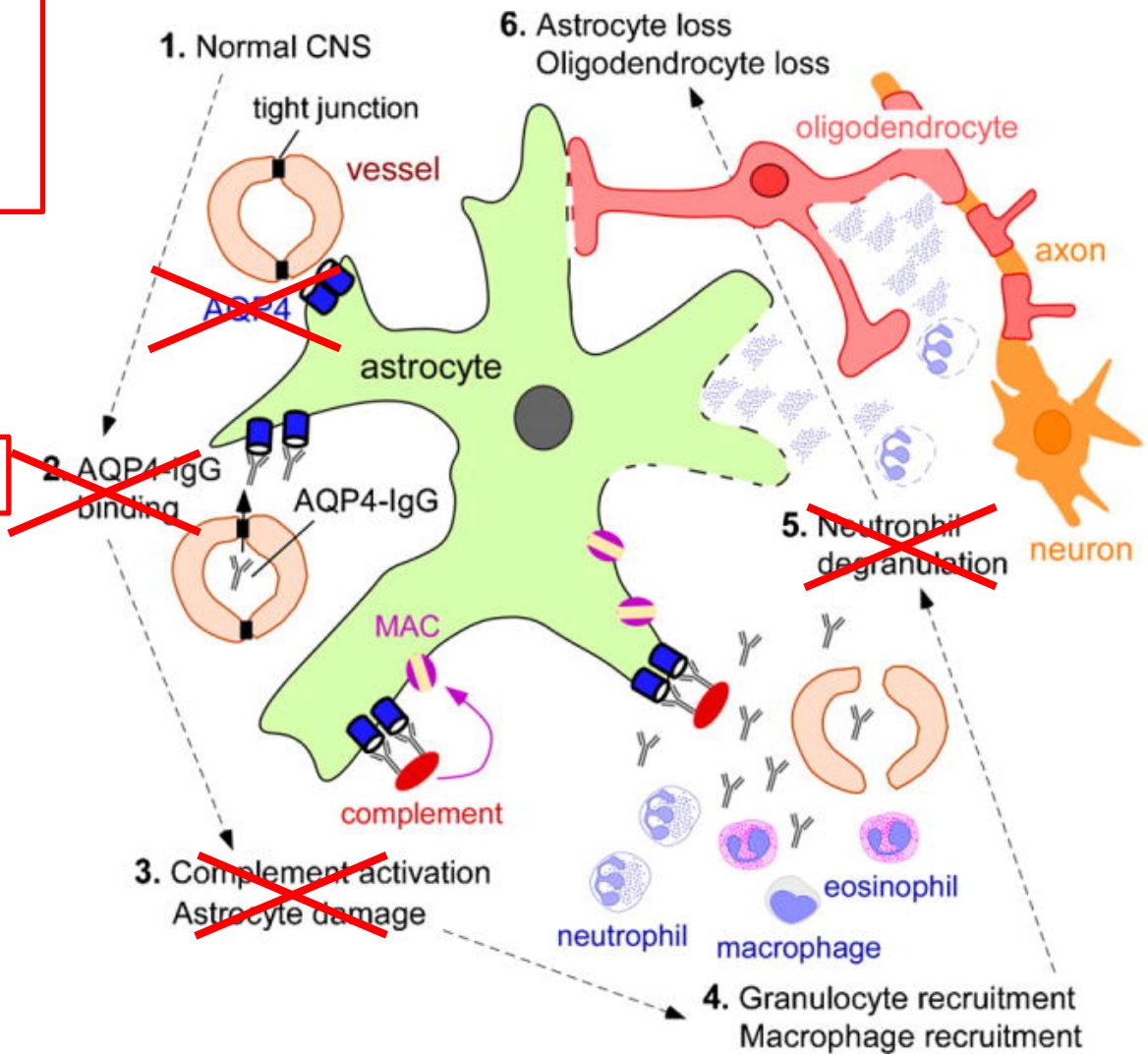
Anti Bcell
- ✓ Anti CD20
- ✓ **Anti CD19 (inebilizumab)**

Anti IL6
- ✓ Tocilizumab
- ✓ **satralizumab**

Aquaporumab

Eculizumab

Sivelestat



Ratelade, verkman, 2012 Int J Biochem Cell Biol.

RéSumé des principaux résultats

	PREVENT Eculizumab Anti- C5	N-MOmentum Inebilizumab Anti-CD19	Sakura- Sky Sartralizumab Anti –IL6R	Sakura-star Sartralizumab Anti –IL6R
Sujets	AQP4+ 143	AQP4 + et - (212+18)=230	AQP4 + et - (55+28)=83	AQP4 + et - (64+31)=95
Bras placebo	Déjà sous IS	PBo seul	Déjà sous IS	PBo seul

Ce que nous disent les résultats de ces 4 essais

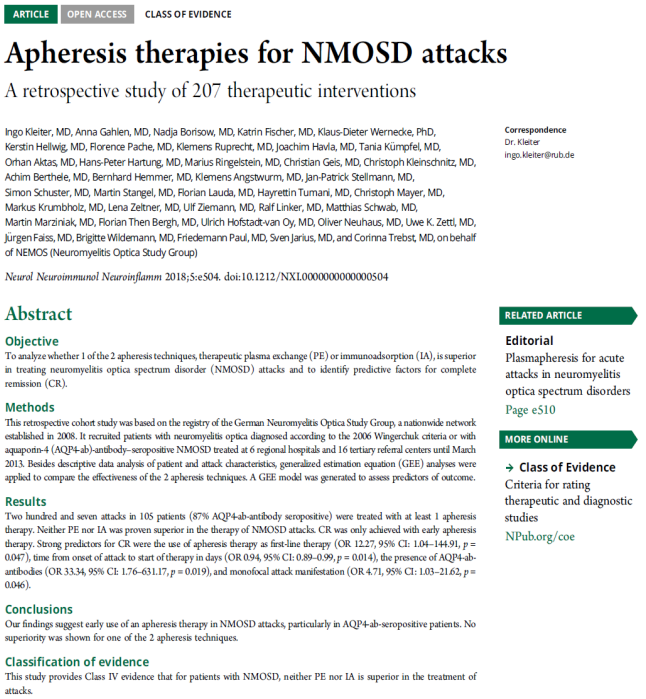
- Les trois traitements sont très efficaces sur la prévention des poussées
- Meilleure efficacité chez AQP4 +
- Analyses de sous groupes Eculizumab et inebilizumab
  - Efficacité sur la sévérité des poussées et une meilleure récupération

Traitement des poussées

O'Riordan *et al.* 1996. JNNP.

Mandler *et al*, 1998, Ann Neurol..

- **Corticoïdes : 5 à 10 g en IVL pas de relais PO**
- **Plasmaphérèse : 7 EP**
  - Possibilité de mixer Solumédrol et EP
  - Ac monoclonal 24 h après EP
  - Facteur de recupération complète :
    - Utilisation en 1ère ligne
    - Délai de traitement court
    - AQP4 +
    - Atteinte mono focale



ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Apheresis therapies for NMOSD attacks

A retrospective study of 207 therapeutic interventions

Ingo Kleiter, MD, Anna Gahlen, MD, Nadja Borisow, MD, Katrin Fischer, MD, Klaus-Dieter Wernecke, PhD, Kerstin Hellwig, MD, Florence Pache, MD, Klemens Ruprecht, MD, Joachim Havla, MD, Tania Kümpfel, MD, Orhan Aktas, MD, Hans-Peter Hartung, MD, Marius Ringelstein, MD, Christian Geis, MD, Christoph Kleinschnitz, MD, Achim Berthele, MD, Bernhard Hemmer, MD, Klemens Angstwurm, MD, Jan-Patrick Stellmann, MD, Simon Schuster, MD, Martin Stangel, MD, Florian Lauda, MD, Hayrettin Tumani, MD, Christoph Mayer, MD, Markus Krumbholz, MD, Lena Zeltner, MD, Ulf Ziemann, MD, Ralf Linker, MD, Matthias Schwab, MD, Martin Marziniak, MD, Florian Then Bergh, MD, Ulrich Hofstadt-van Oy, MD, Oliver Neuhaus, MD, Uwe K. Zettl, MD, Jürgen Faiss, MD, Brigitte Wildemann, MD, Friedemann Paul, MD, Sven Jarius, MD, and Corinna Trebst, MD, on behalf of NEMOS (Neuromyelitis Optica Study Group)

Correspondence
Dr. Kleiter
ingo.kleiter@rub.de

Neurol Neuroimmunol Neuroinflamm 2018;5:e504. doi:10.1212/NXL.0000000000000504

Abstract

Objective
To analyze whether 1 of the 2 apheresis techniques, therapeutic plasma exchange (PE) or immunoadsorption (IA), is superior in treating neuromyelitis optica spectrum disorder (NMOSD) attacks and to identify predictive factors for complete remission (CR).

Methods
This retrospective cohort study was based on the registry of the German Neuromyelitis Optica Study Group, a nationwide network established in 2008. It recruited patients with neuromyelitis optica diagnosed according to the 2006 Wingerchuk criteria or with aquaporin-4 (AQP4-ab)-antibody–seropositive NMOSD treated at 6 regional hospitals and 16 tertiary referral centers until March 2013. Besides descriptive data analysis of patient and attack characteristics, generalized estimation equation (GEE) analyses were applied to compare the effectiveness of the 2 apheresis techniques. A GEE model was generated to assess predictors of outcome.

Results
Two hundred and seven attacks in 105 patients (87% AQP4-ab-antibody seropositive) were treated with at least 1 apheresis therapy. Neither PE nor IA was proven superior in the therapy of NMOSD attacks. CR was only achieved with early apheresis therapy. Strong predictors for CR were the use of apheresis therapy as first-line therapy (OR 12.27, 95% CI: 1.04–144.91, $p = 0.047$), time from onset of attack to start of therapy in days (OR 0.94, 95% CI: 0.89–0.99, $p = 0.014$), the presence of AQP4-ab-antibodies (OR 33.34, 95% CI: 1.76–631.17, $p = 0.019$), and monofocal attack manifestation (OR 4.71, 95% CI: 1.03–21.62, $p = 0.046$).

Conclusions
Our findings suggest early use of an apheresis therapy in NMOSD attacks, particularly in AQP4-ab-seropositive patients. No superiority was shown for one of the 2 apheresis techniques.

Classification of evidence
This study provides Class IV evidence that for patients with NMOSD, neither PE nor IA is superior in the treatment of attacks.

RELATED ARTICLE

Editorial
Plasmapheresis for acute attacks in neuromyelitis optica spectrum disorders
Page e510

MORE ONLINE

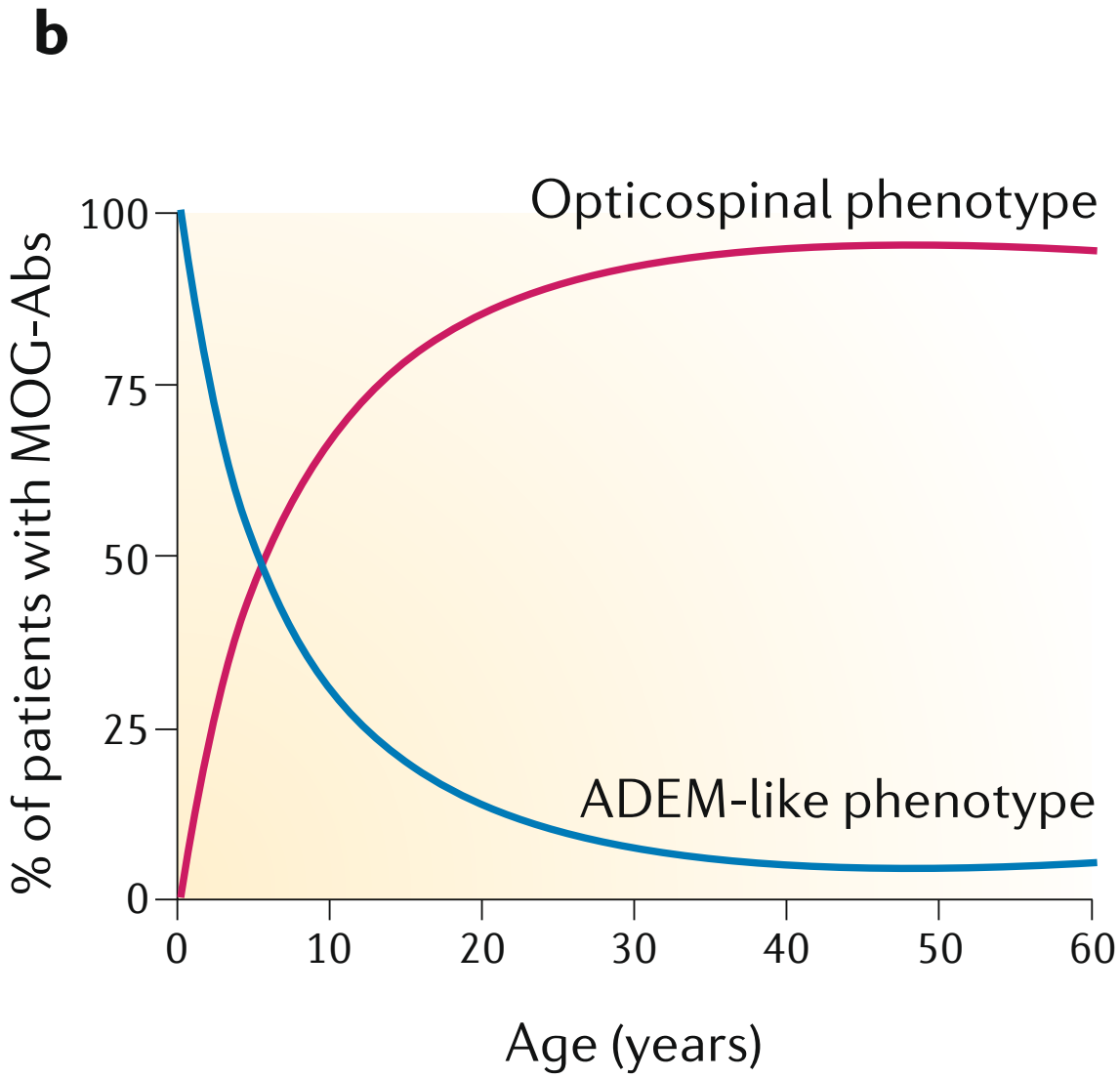
→ **Class of Evidence**
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Les interrogations qui persistent

- les effets à long terme
  - efficacité
  - Tolérance
- Durée du traitement
- Identification de facteurs prédictifs de poussée pour escalade?
  - NLF and GFAP
  - Dosage des CD19
- Doit on le proposer aux AQP4 négatifs ? Anti MOG ?

Anti MOG

Reindl, Nature Reviews Neurology 2019



Etude comparative des NMOSD AQP4+ et anti MOG +

JAMA Neurol. 2014;71(3):276-283. doi:10.1001/jamaneurol.2013.5857

Table 1. Comparison of Clinical Features in Patients With MOG-Ab–Positive and AQP4-Ab–Positive NMO/NMOSD

Feature	MOG-Ab Positive (n = 9)	AQP4-Ab Positive (n = 20)	*P* Value
Follow-up, median (range), mo	18.00 (2.2-38.5)	20.47 (5.0-36.6)	NS
Female, %	44	90	.02
White, %	78	60	NS
Age at onset, mean (SD), y	32.29 (17.1)	44.86 (14.8)	.05
Coexisting autoimmunity, No. (%)	1 (11)	9 (45)	NS
Onset episode, No. (%)			
ON only	0 (0)	6 (30)	NS
TM only	3 (33)	12 (60)	NS
ON+TM	4 (44)	0 (0)	.005
Brain/brainstem+TM	2 (22)	0 (0)	NS
Brain only	0 (0)	2 (10)	NS
Nadir EDSS score, median (range)	6.0 (4-8.5)	5.5 (1-8.5)	NS
EDSS score at best recovery, median (range)	0 (0-2.5)	4.0 (0-8)	.01
Patients with TM at onset left motor disabled, No. (%)	0 (0)	7 (58)	.007
Patients with ON at onset left visually disabled, No. (%)	0 (0)	2 (33)	NS
Subsequent relapse, No. (%)	0 (0)	8 (40)	.03

Abbreviations: Ab, antibody; AQP4, aquaporin-4; EDSS, Expanded Disability Status Scale; MOG, myelin-oligodendrocyte glycoprotein; NMO, neuromyelitis optica; NS, not significant; ON, optic neuritis; SD, spectrum disorder; TM, transverse myelitis.

Etude comparative des NMOSD AQP4+ et anti MOG +

JAMA Neurol. 2014;71(3):276-283. doi:10.1001/jamaneurol.2013.5857

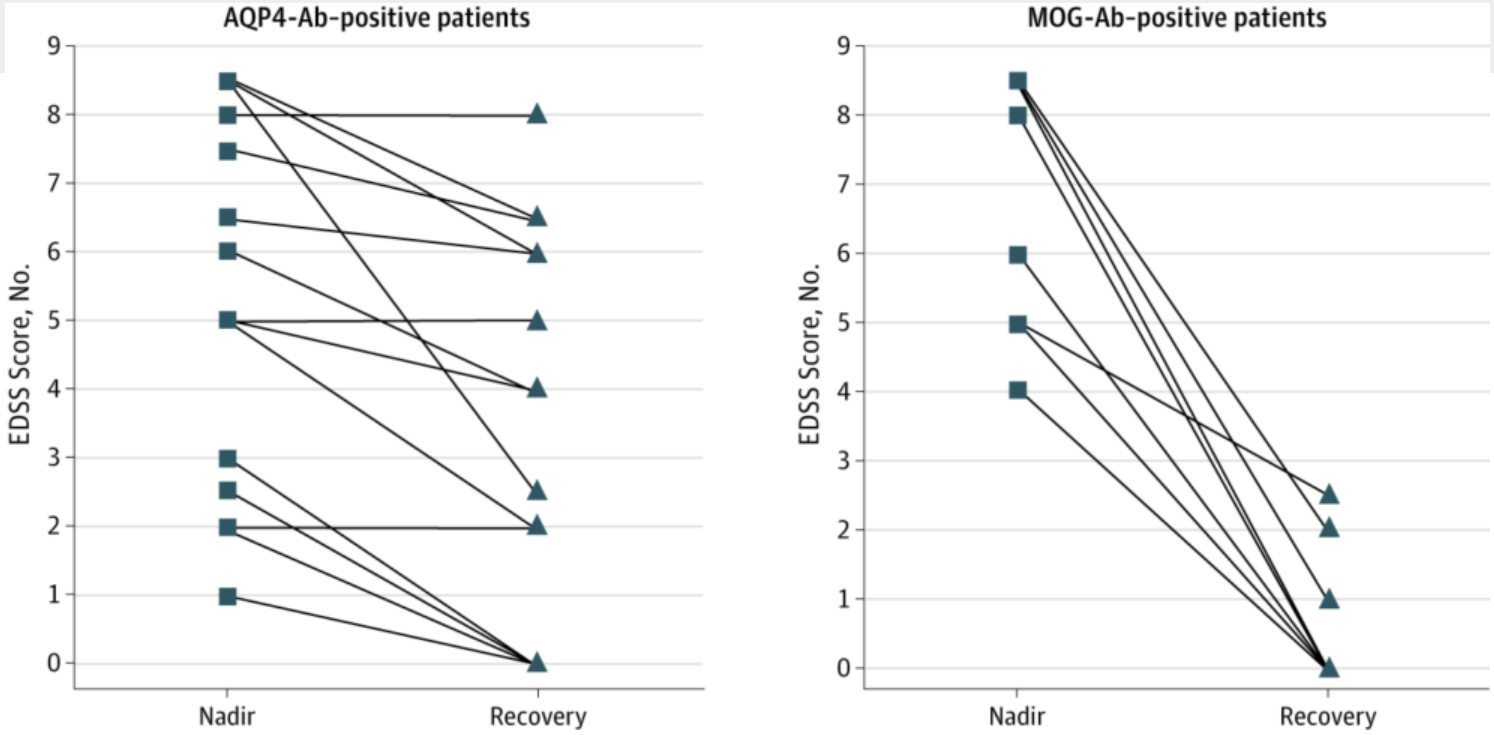


Figure Legend:

Expanded Disability Status Scale (EDSS) Scores at Nadir and Recovery of the Onset EpisodePatients with aquarorin-4 antibody (AQP4-Ab)–positive neuromyelitis optica/neuromyelitis optica spectrum disorder often showed poor recovery from the acute episode (left), with little change in EDSS scores, whereas recovery in myelin-oligodendrocyte glycoprotein antibody (MOG-Ab)–positive patients was often dramatic (right). The median change in EDSS scores between episode nadir and recovery was significantly higher in MOG-Ab–positive patients compared with AQP4-Ab–positive patients (6 vs 2; P<.001).

Histologie

	MOG	AQP4
Démyélinisation	**primaire** bien délimitée Macrophages avec débris de myéline	**secondaire**
Astrocytes	Préservation relative	Perte +++
Infiltrat inflammatoire	lymphocytes T , qq B Péri-vasculaires	PNN et PNEo
Dépôts de complément Avec complexe terminal	oui	Oui + dépôt d'IgG
Pré-OGD	Préservation des pré-OGD immature (n'exprime pas la MOG)	

RESEARCH Open Access

Evaluation of treatment response in adults with relapsing MOG-Ab-associated disease

Alvaro Cobo-Calvo[1,2,18], María Sepúlveda[3], Fabien Rollot[4,5], Thais Armangué[3,6], Anne Ruiz[2], Elisabeth Maillart[7], Caroline Papeix[7], Bertrand Audoin[8], Helene Zephir[9], Damien Biotti[10], Jonathan Ciron[10], Francoise Durand-Dubief[1], Nicolas Collongues[11], Xavier Ayrignac[12], Pierre Labauge[12], Eric Thouvenot[13], Bertrand Bourre[14], Alexis Montcuquet[15], Mikael Cohen[16], Romain Deschamps[17], Nuria Solà-Valls[3], Sara Llufriu[3], Jerome De Seze[11], Yolanda Blanco[3], Sandra Vukusic[1,18], Albert Saiz[3] and Romain Marignier[1,2,18*]

JNeuroinflammation, 2019

- 165 patients adultes MOG +
  - 59 non traités et 66 traités

Table 3 Evaluation of pre-treatment and on-treatment annualised relapse ratio and EDSS according to treatment group

Treatment group		Treated ≥ 6 months at any time, *n* (%)	Eligible for analysis, *n* (%)	FU before treatment (years), median (range)	FU under treatment (years), median (range)	ARR pre/ on-treatment, mean (SD)	Freedom of relapse on-treatment *n* (%)	*p* value ARR pre/ on-treatment	EDSS pre/ end of treatment, mean (SD)	Freedom of EDSS progression, *n* (%)	*p* value EDSS pre/end-treatment
Type I IS	AZT	19/66 (28.8)	11/19 (57.9)	2.4 (0.6–7.6)	2.1 (0.5–12.6)	1.05 (1.20)/ 0.43 (0.79)	6 (54.5)	0.041	1.86 (1.30)/ 1.68 (1.19)	11 (100)	0.157
	MMF	12/66 (18.2)	11/12 (91.7)	1.7 (0.5–46.4)	1.7 (0.5–6.8)	1.20 (1.11)/ 0.23 (0.60)	8 (72.7)	0.033	2.72 (1.69)/ 2.64 (1.76)	11 (100)	0.317
	RTX	30/66 (45.5)	26/30 (86.7)	3.3 (0.5–18.33)	1.7 (0.5–4.9)	1.08 (0.98)/ 0.43 (0.89)	19 (73.1)	0.012	3.11 (1.83)/ 2.58 (1.90)	23 (88.5)	0.096
Type II IS		6/66 (9.1)	5/6 (83.3)	5.2 (2.9–10.3)	2.0 (0.6–3.7)	0.64 (0.45)/ 0.65 (0.69)	2 (40)	0.893	3.8 (1.52)/ 4.0 (1.45)	1 (20.0)	0.317
Type III IS		8/66 (12.1)	3/8 (37.5)	–	–	–	–	–	–	–	–
[a]MS-DMD		10/66 (6.6)	9/10 (90)	1.95 (0.5–20.1)	3.7 (1.0–14.7)	1.13 (1.38)/ 0.49 (0.41)	2 (22.2)	0.374	2.5 (0.90)/ 3.17 (2.15)	7 (77.7)	0.188

*Patients treated with type III IS (corticosteroids, $n = 2$ and intravenous immunoglobulins, $n = 1$) were not eligible for analysis due to treated number ≤ 5

[a]Among the 9 patients with MS-DMD eligible for the analysis, 2 patients were treated with natalizumab, 1 with glatiramer acetate and 6 with interferon

FU follow-up, *ARR* annualised relapse ratio, *SD* standard deviation, *EDSS* Expanded Disability Status Scale, *IS* immunosuppressants, *MS-DMD* multiple sclerosis disease-modifying drugs, *AZT* azathioprine, *MMF* mycophenolate mophetil, *RTX* rituximab

Ac anti-CD20 chez les MOG ?

- Etude rétrospective de 121 patients (13 pays): 30 enfants / **91 adultes**
  - 20 traités dès P1: 30% qui rechutent (médiane 2 mois)
  - 101 traités à partir de P2 ou plus tard:

Rechute sous anti-CD20:
CD19 < 1% ds 79%

	n	Diminution du taux de poussée	Survie sans poussée à 2 ans
n	101	37% 95%CI:19-52%, p< 0.001	
En 1ere ligne	47	63% 95%CI:35-79%, p= 0.001	55%
En 2° ou 3° ligne (après AZA/MMF)	54	26% 95%CI:2-44%, p = 0,038	18%

Efficacité des IVIG chez les NMO anti –MOG

IgIV induction à 2g/KG puis 1 g/kg

		Nombre de patients	TAP avant	TAP après
Hachachen et *al*. 2018	MOG	16	2,6	0,51
Ramanathan et *al.* 2017	MOG	7	2	0
Jarius et *al.* 2016	MOG	1		0
Viwanathan et *al.* 2015	AQP4	6	0,75	1,5
Karthikeayan *P734 Ectrims 2019*	MOG	3	2,02	0,13

Cout ? Durée?

Conclusion