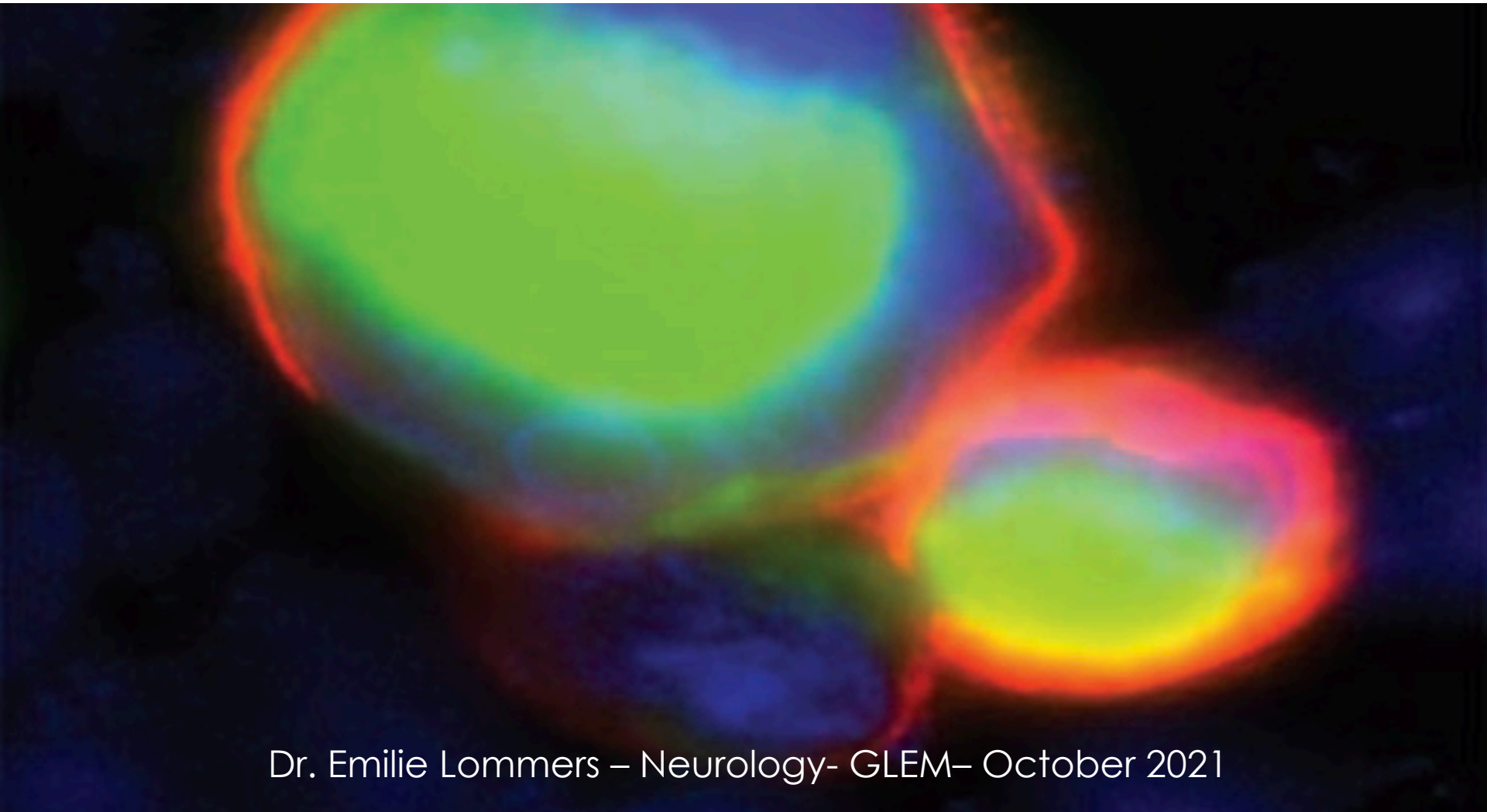
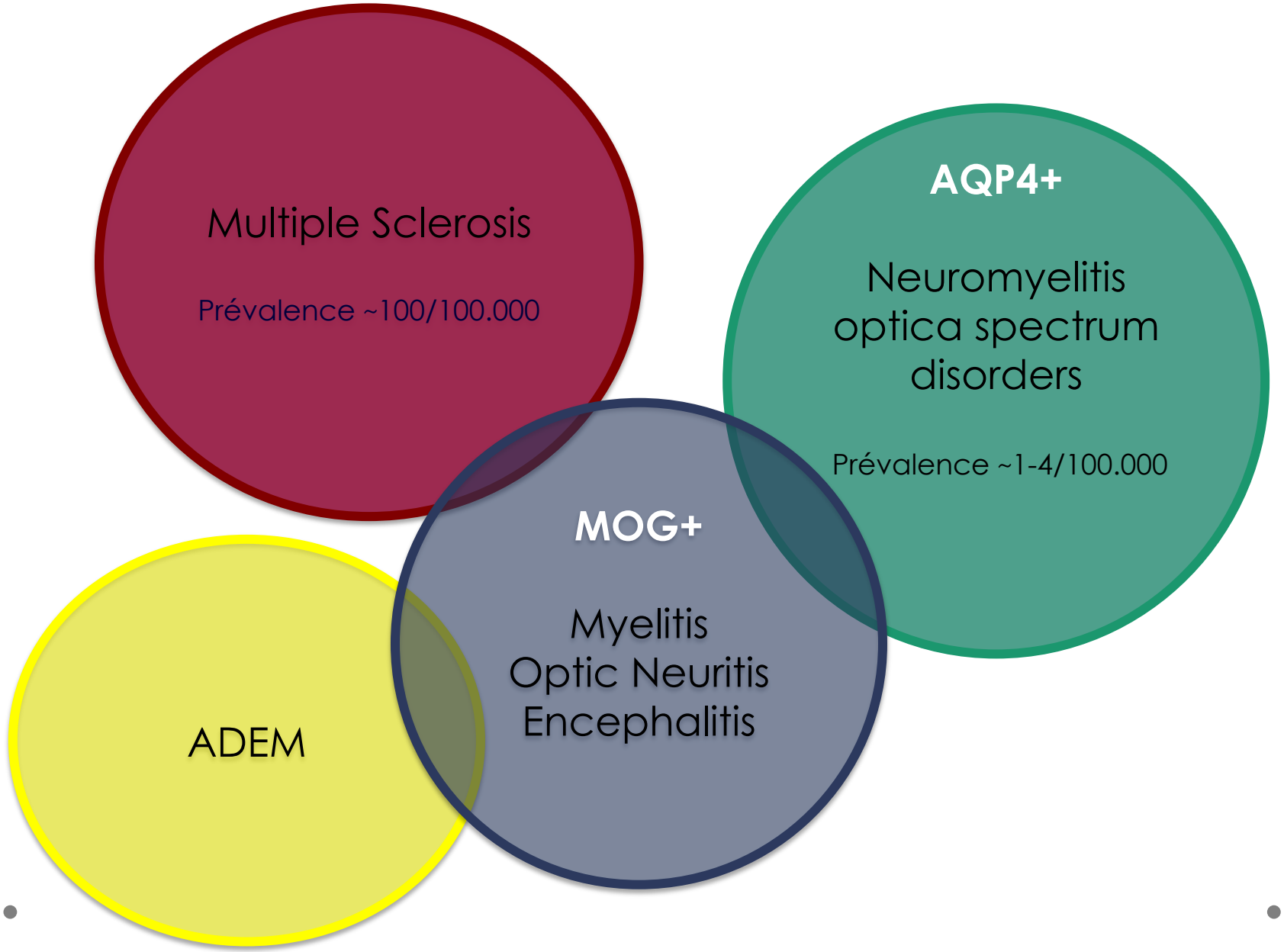
Neuromyelitis optica spectrum disorders:

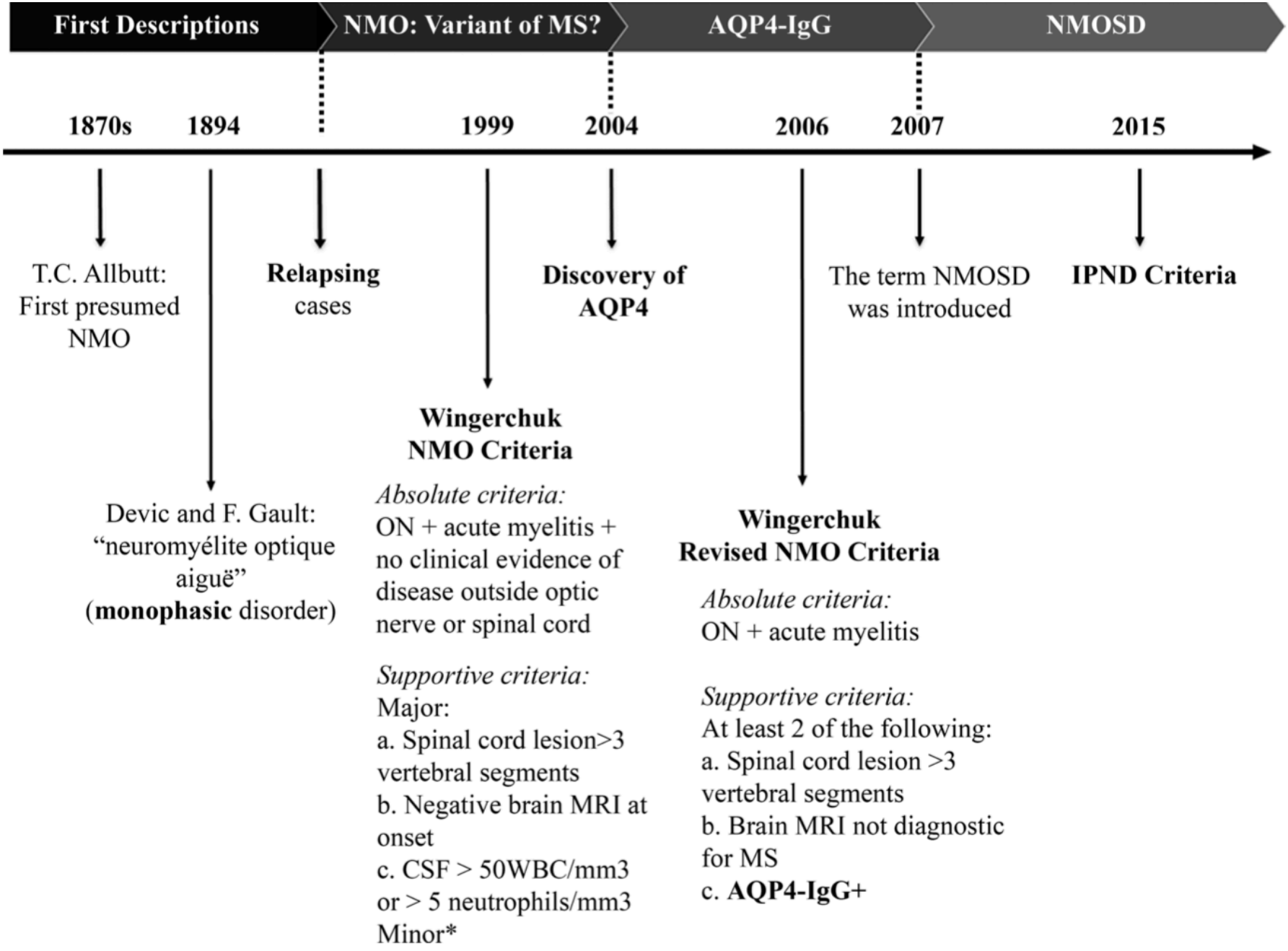
anti-AQP4 & anti-MOG associated diseases



Dr. Emilie Lommers – Neurology- GLEM– October 2021

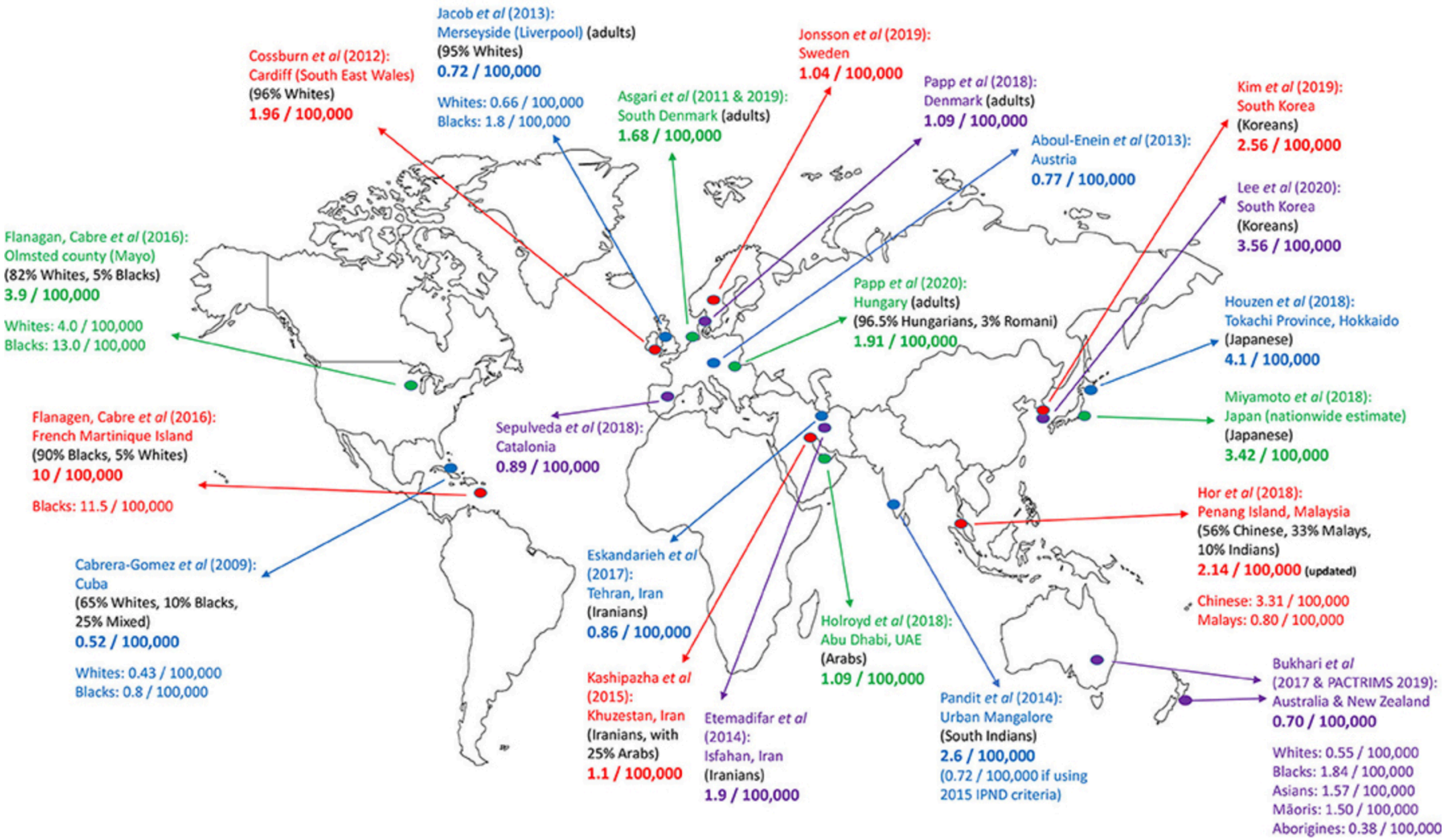
Introduction





- Dutra et al., 2018 https://doi.org/10.1148/rg.2018170141

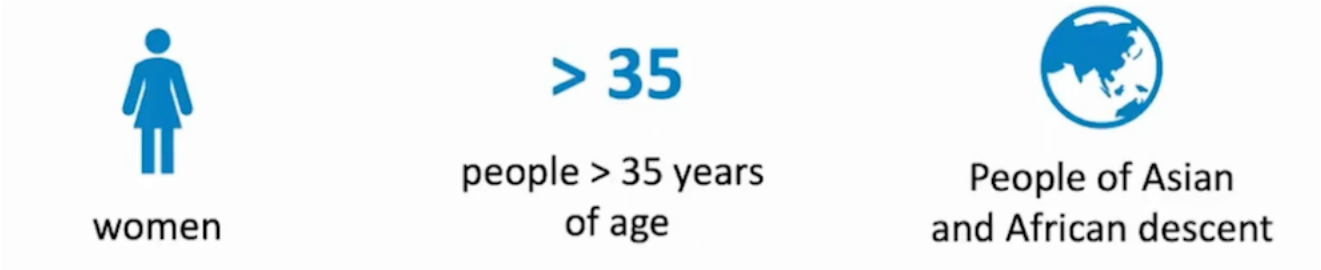
Worldwide prevalence of NMOSD



- Hor et al., 2020 https://doi.org/10.3389/fneur.2020.00501

Epidemiology of NMOSD

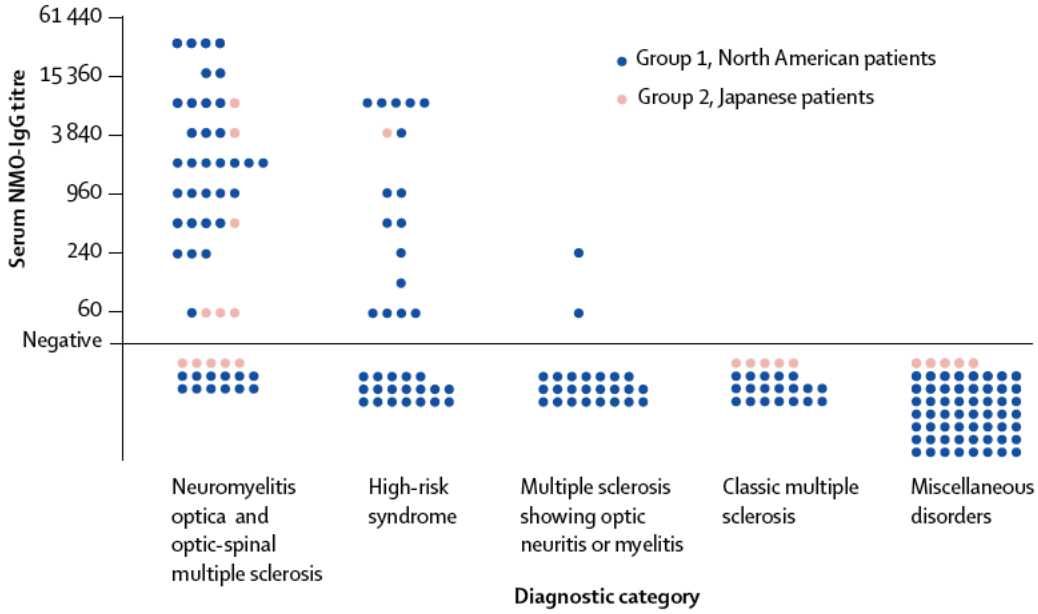
- NMOSD affects **0.52-10** people per 100 000 population worldwide
- The NMOSD risk is higher in:

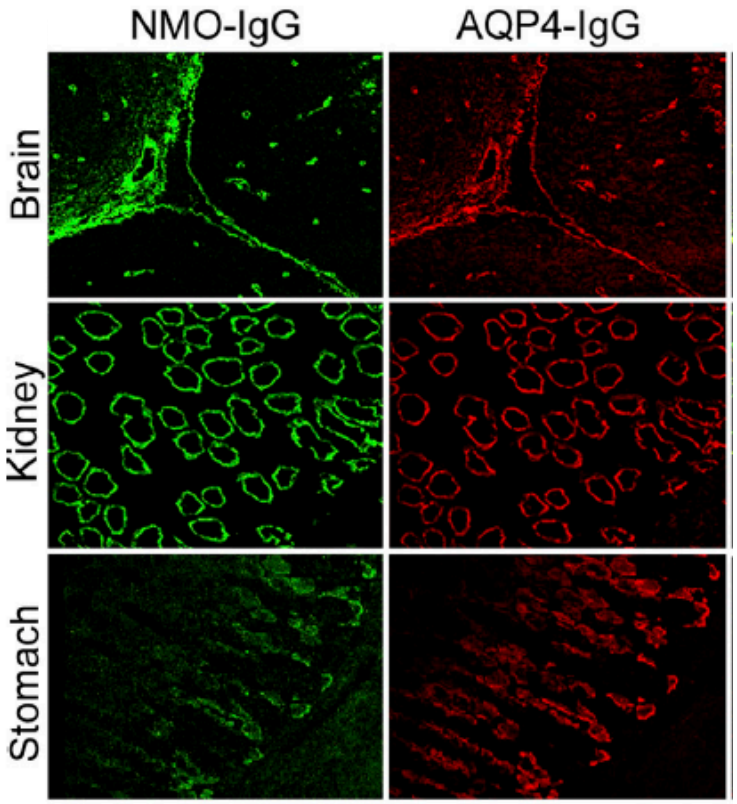


- 1/6 NMOSD patients are in the pediatric (<16 years) or elderly (>65 years) groups
- Small proportion of familial NMOSD (3%): AQP4 IgG seropositivity associated with with HLA-DRB1*03
- Associated *systemic* or *organ-specific* autoimmune disease: SLE, SS myasthenia gravis, autoimmune thyroid diseases, NMDA-R encephalitis, …

- Kunchok et al., 2020 https://doi.org/10.1177/1352458520933884

Anti-aquaporine-4 IgG



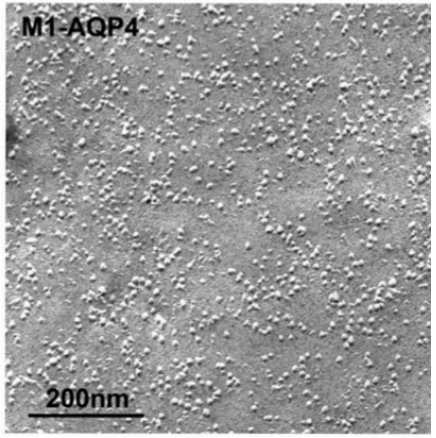


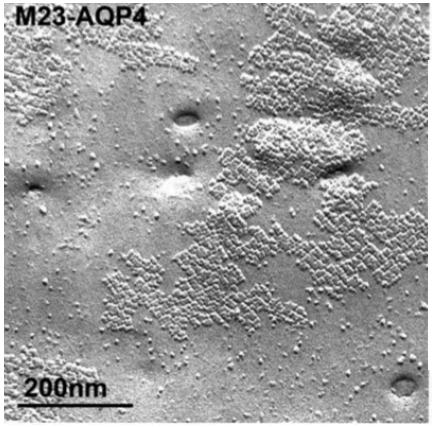
10-25% of NMOSD cases are categorized as seronegative

Specificity ~99%
Sensibility 76-95% (CBA)

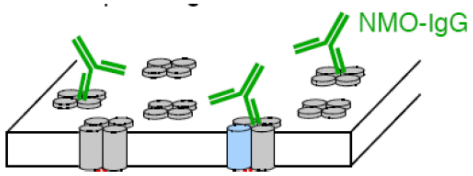
- Lennon et al., 2004 https://doi.org/10.1084/jem.20050304

Anti-aquaporine-4 IgG

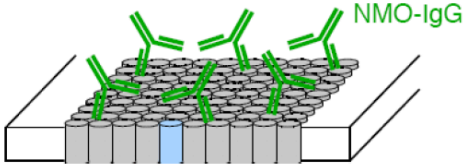


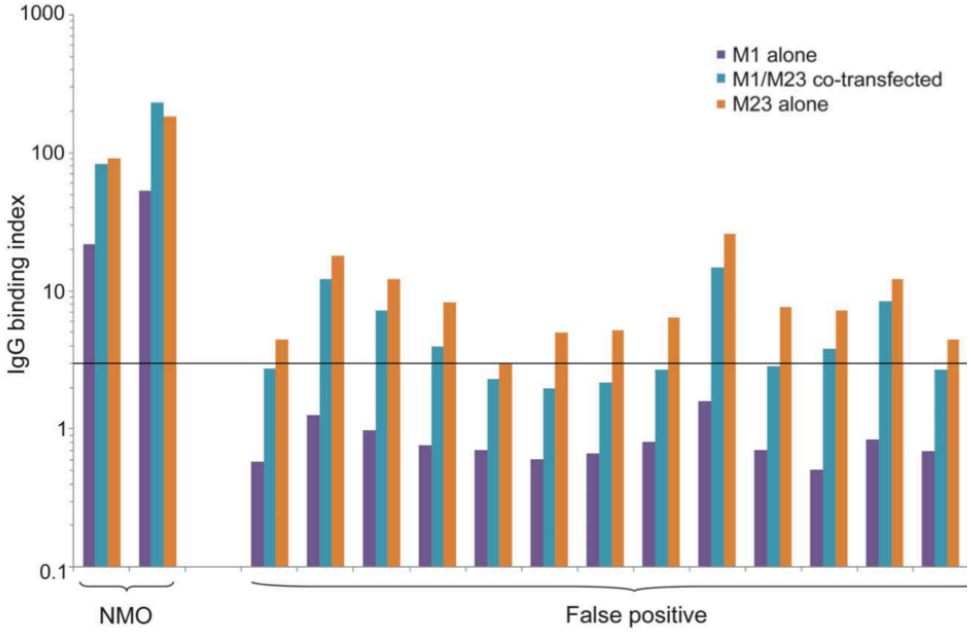


Isoforme M 1



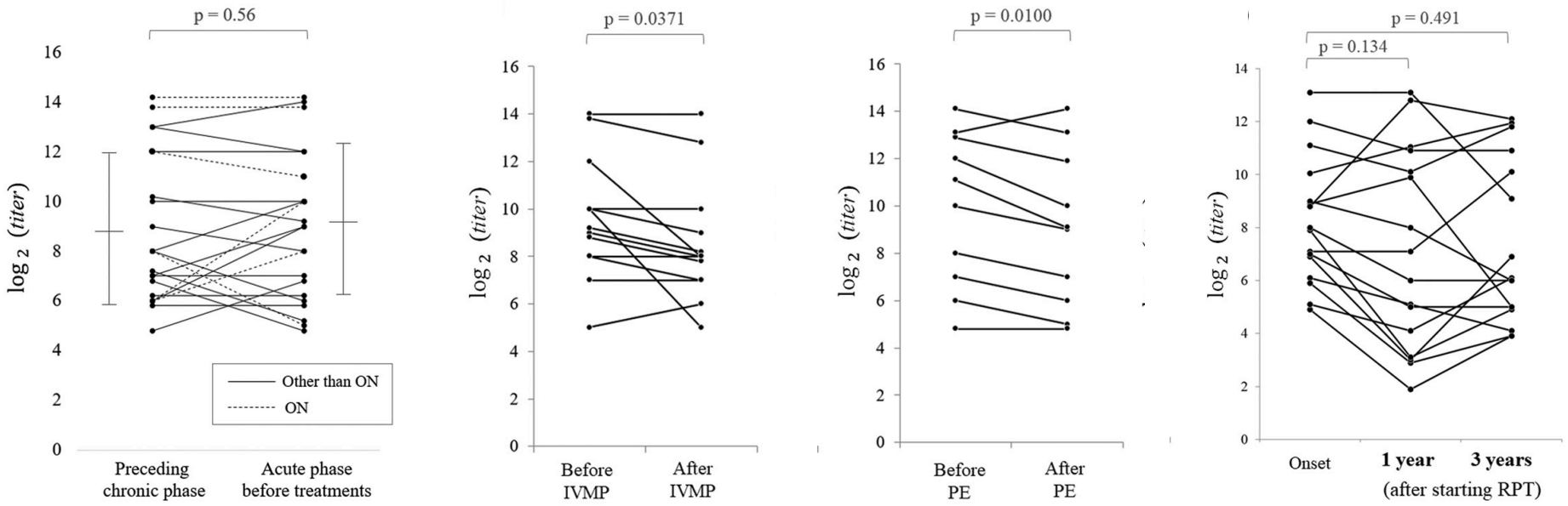
Isoforme M 23





- Fryer et al., 2014 https://doi.org/10.1212/NXI.0000000000000011

Anti-aquaporine-4 IgG

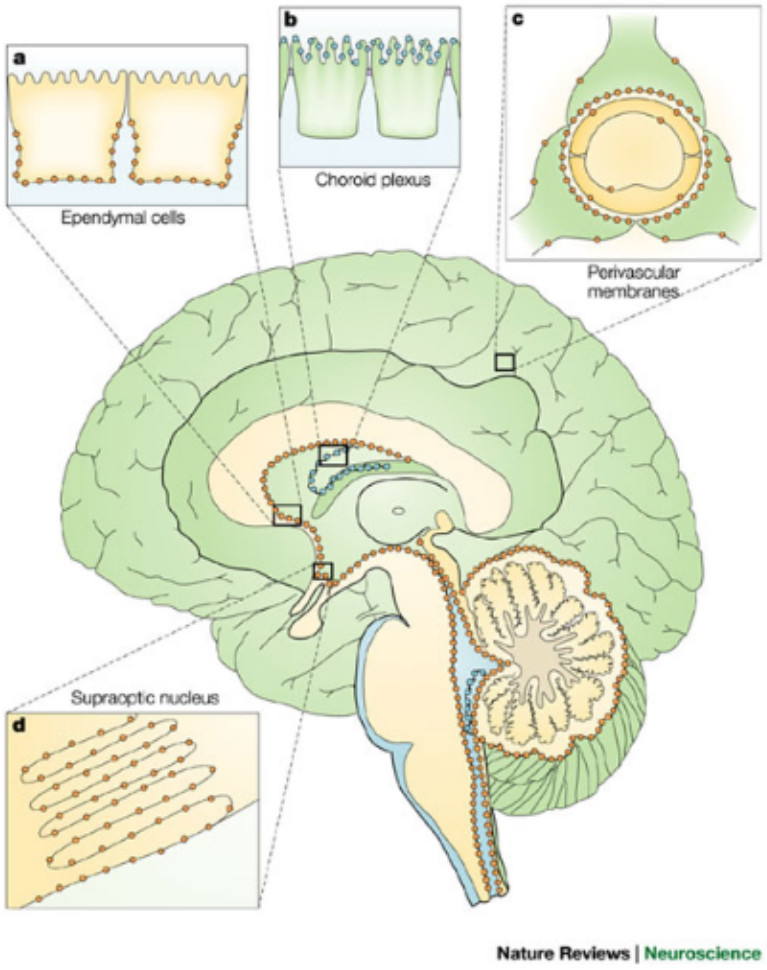


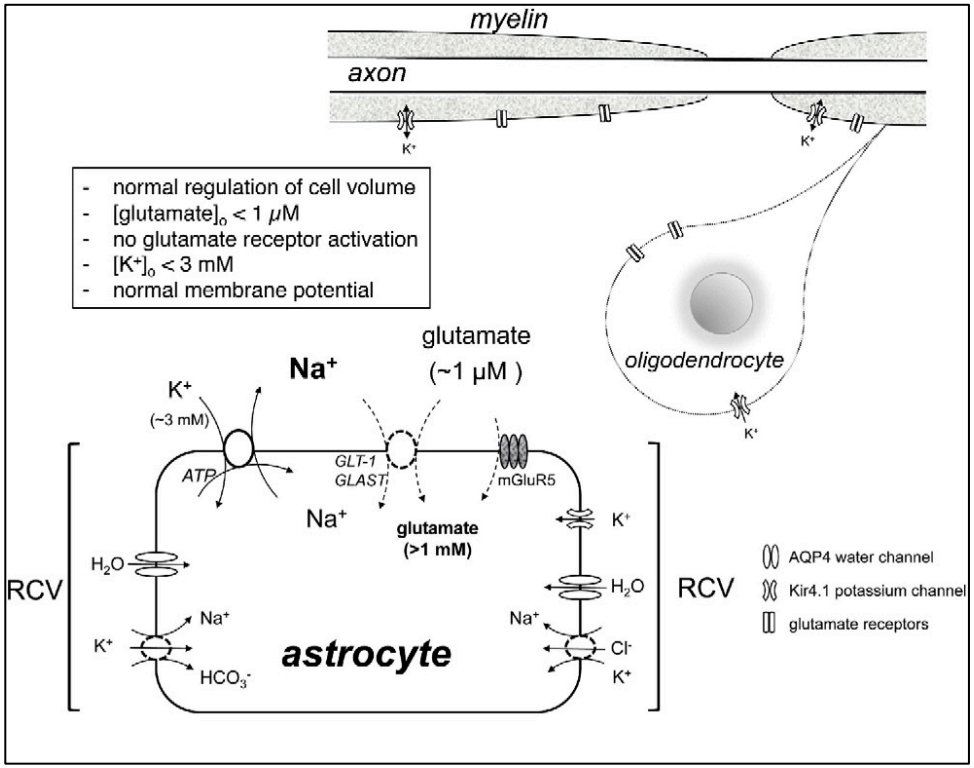
Evaluating the positivity of serum AQP4-IgG at the onset is necessary **BUT** titer level does not reflect the ongoing disease activity or the following neurological prognosis.

Repeated follow-up of titer levels may not be useful for the management of NMOSD patients.

- Akaishi et al., 2020 https://doi.org/10.1016/j.jns.2020.116671

Aquaporine-4: function & location

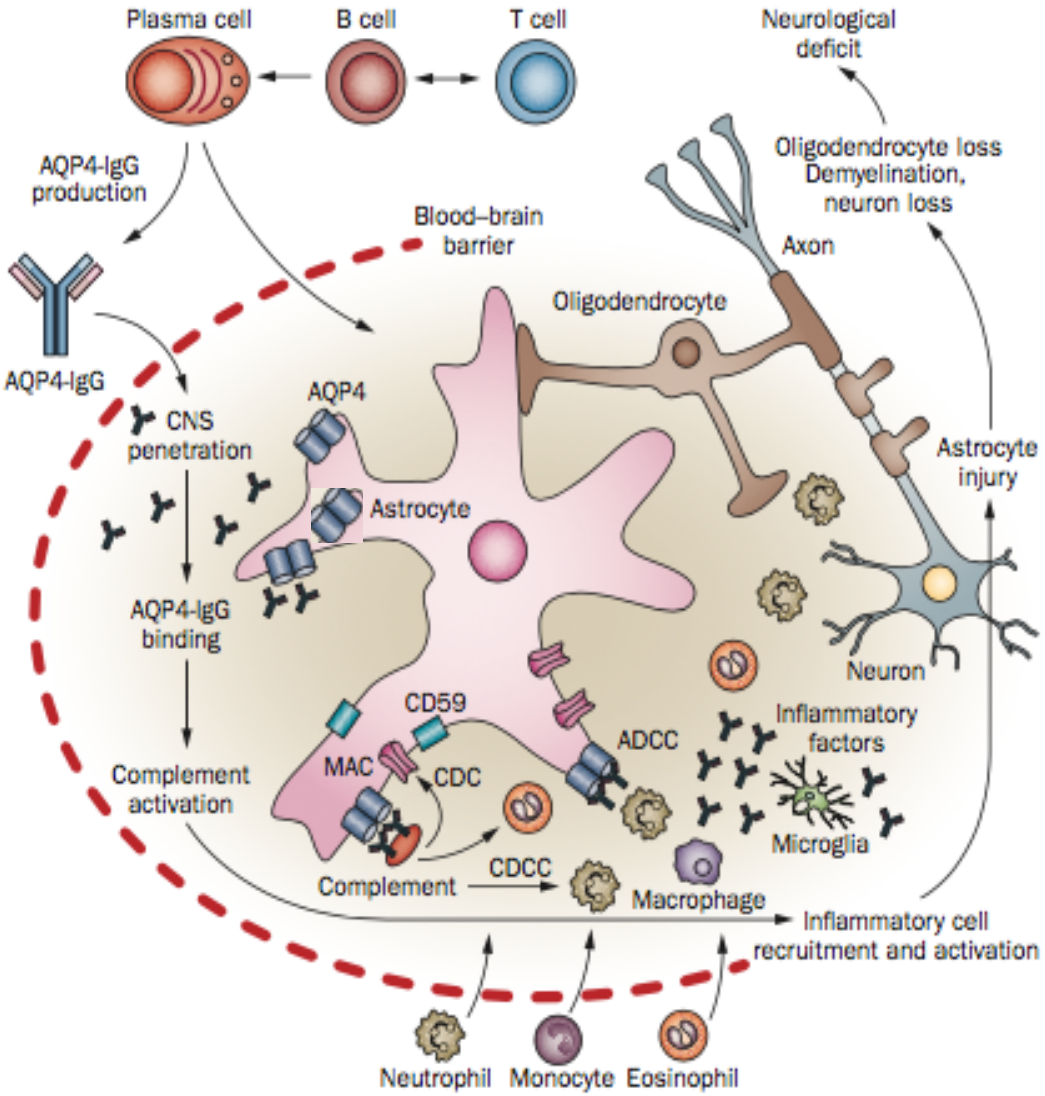


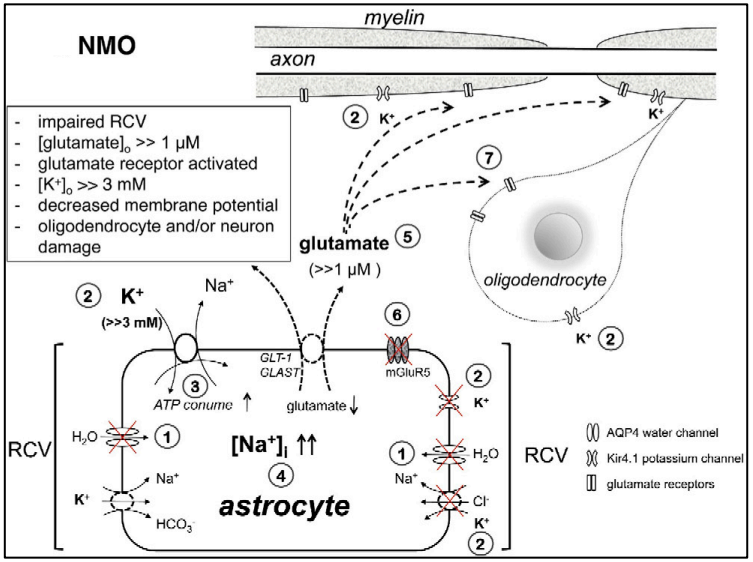


Amiry-Moghaddam et al., 2003
https://doi.org/10.1038/nrn1252

Yang et al., 2016
https://doi.org/10.1016/j.jneuroim.2016.06.002

Physiopathology

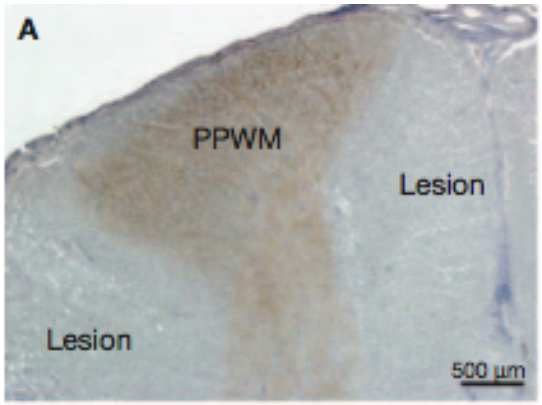


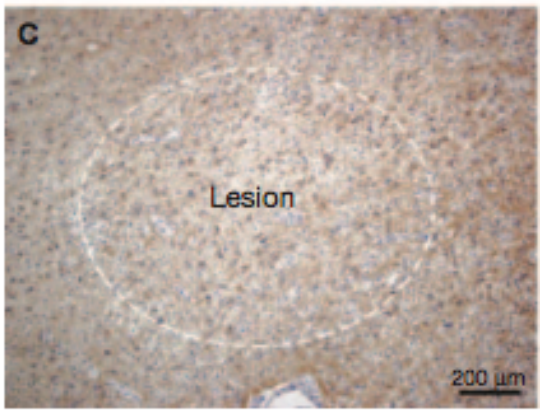


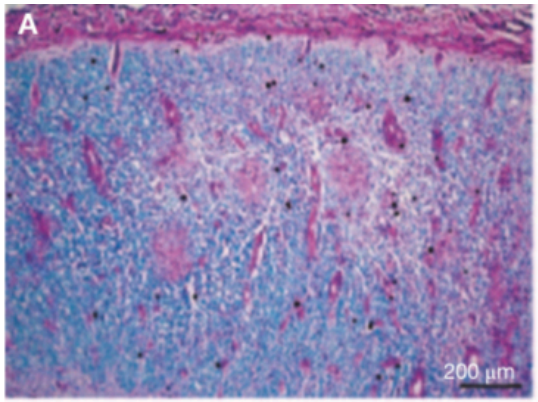
- Papadopoulos et al. 2014 https://doi.org/10.1038/nrneurol.2014.141

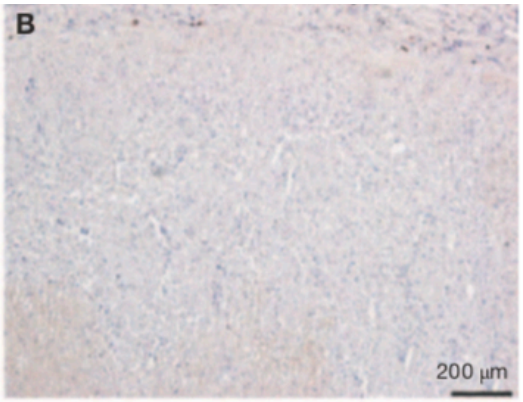
Histopathology

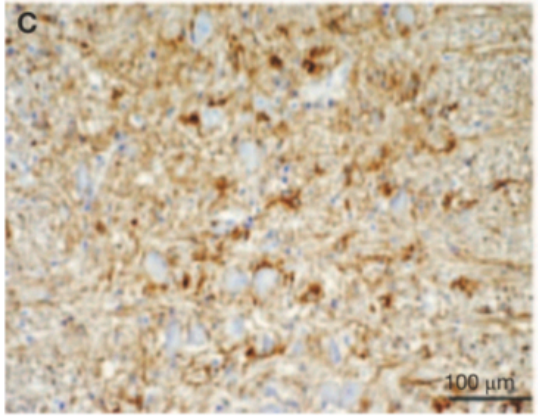
Early loss of AQP4
Astrocytopathy with or without astrocyte death
Associated or not with secondary demyelination and axonal loss
No cortical demyelination

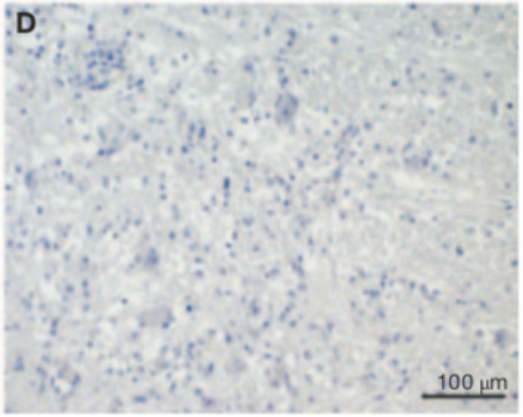






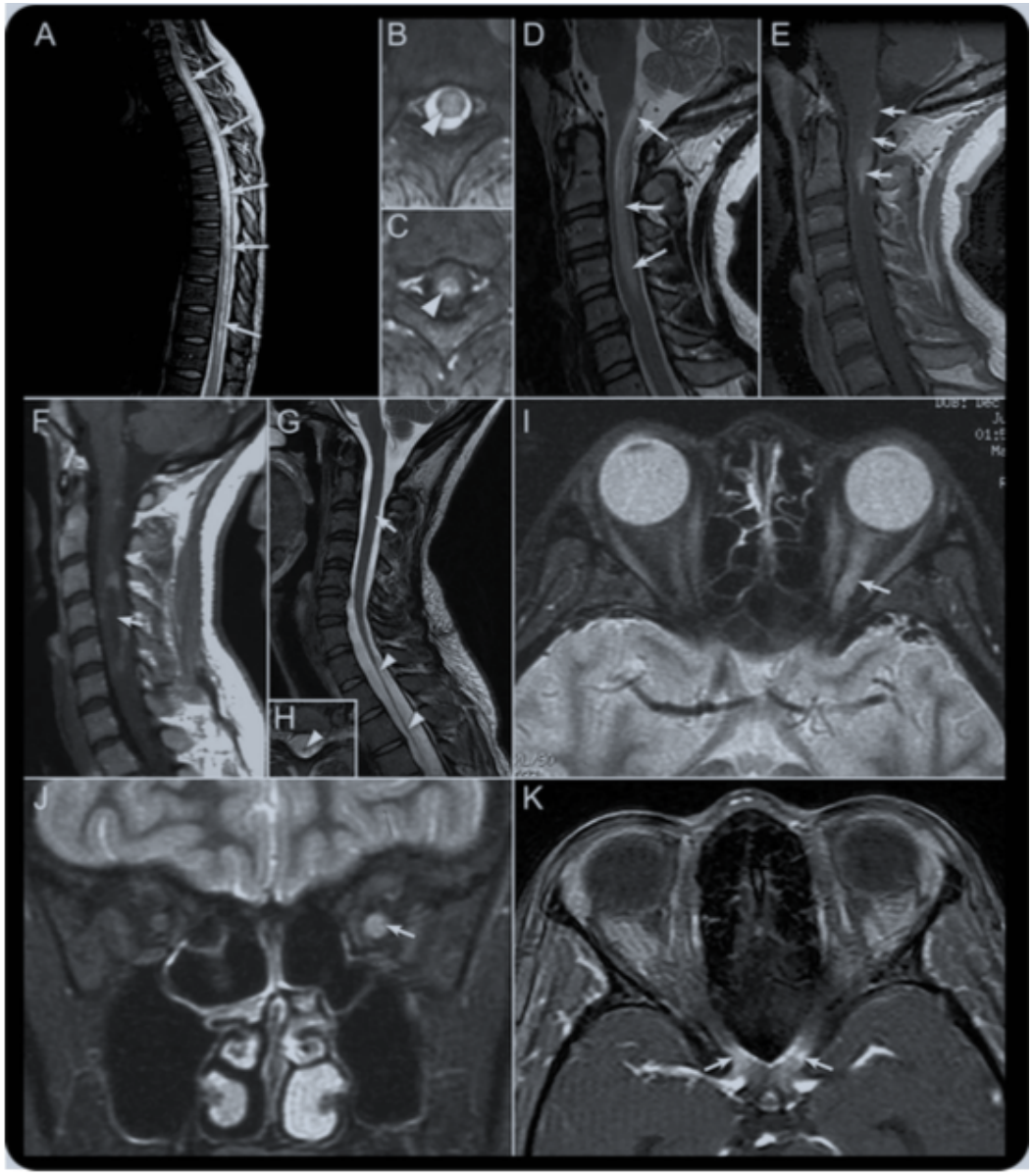






- Misu et al. 2003 https://doi.org/ 10.1007/s00401-013-1116-7

Clinical manifestations



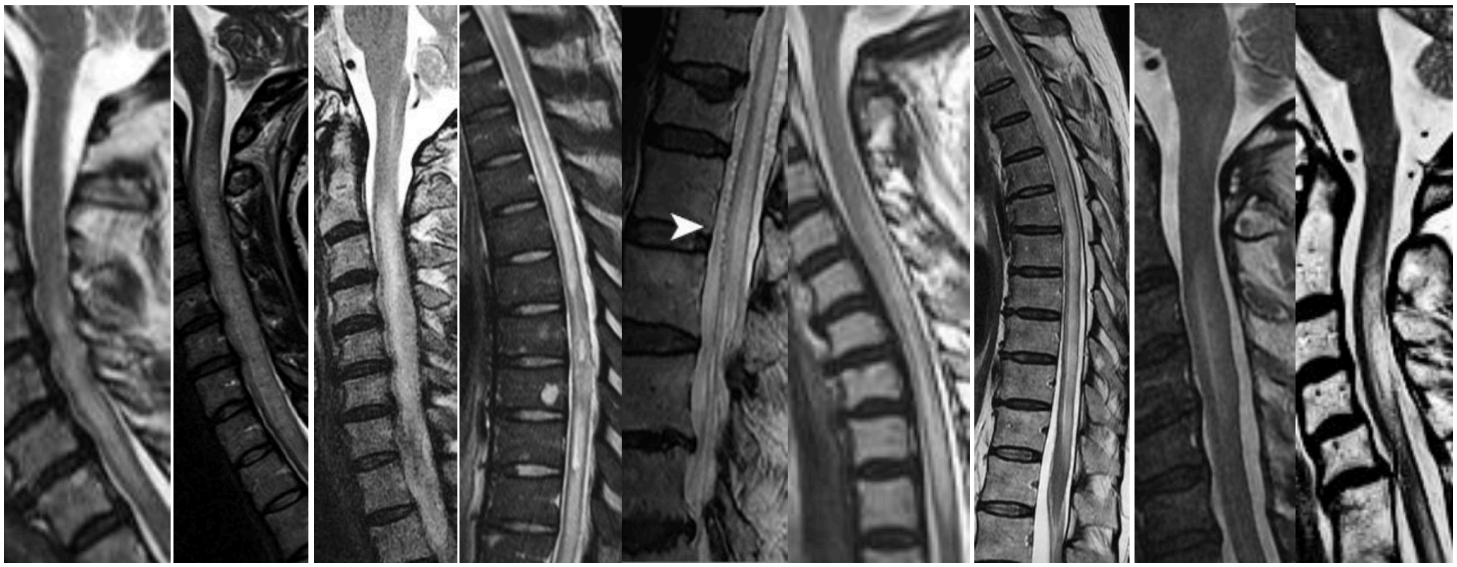
SEVERE Acute Optic Neuritis

- Bilateral, simultaneous or recurrent
- Extensive and posterior
- Severe visual impairment

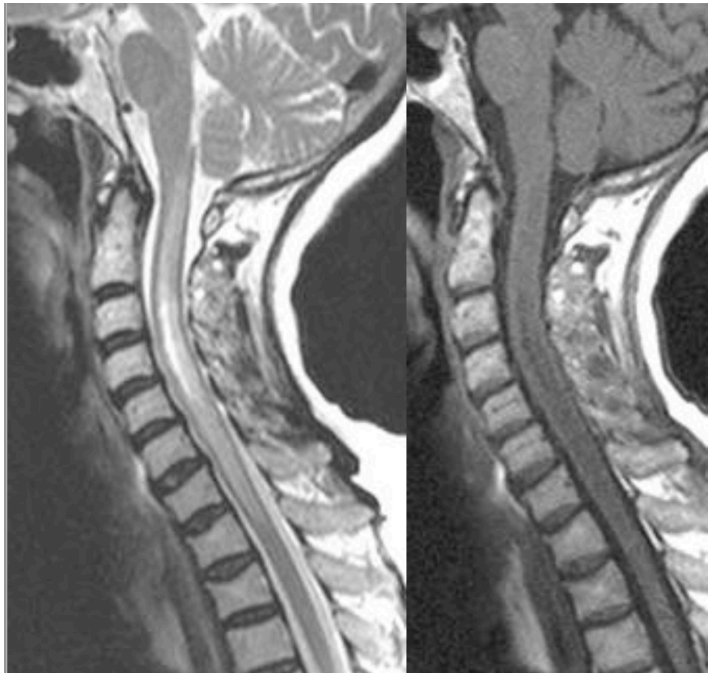
Longitudinally exensive *transverse myelitis (LETM)*

- Complete (>50% cord section)
- > 3 vertebral segments

Wingerchuk et al., 2015
https://doi.org/10.1212/WNL.0000000000001729



LETM lesions



Bright-spotty T2 and hypointense T1 lesions

- Yonezu et al. 2013 https://doi.org/10.1177/1352458513495581

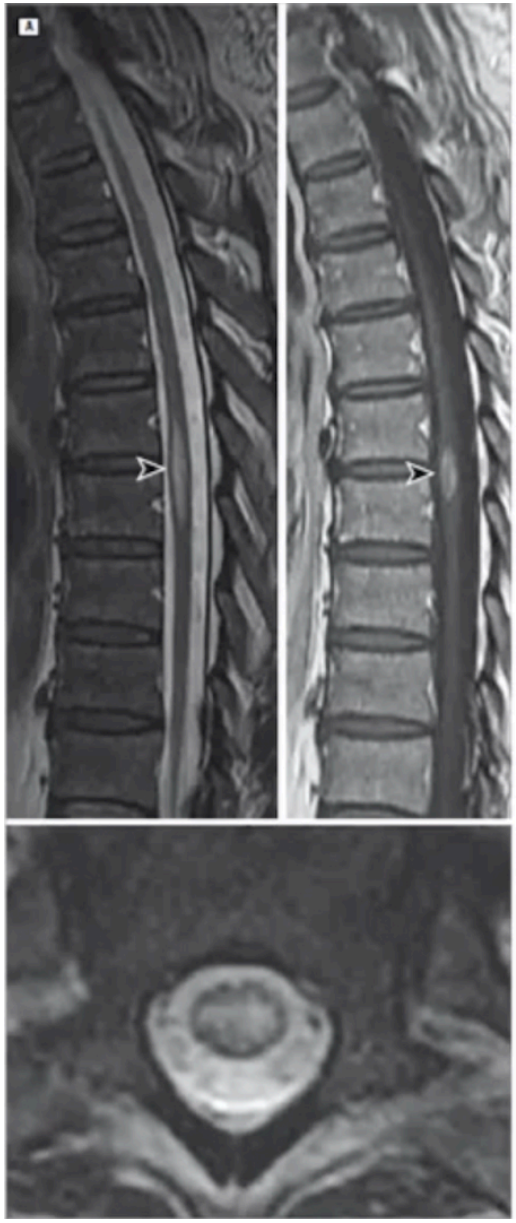
JAMA Neurology

Original Investigation

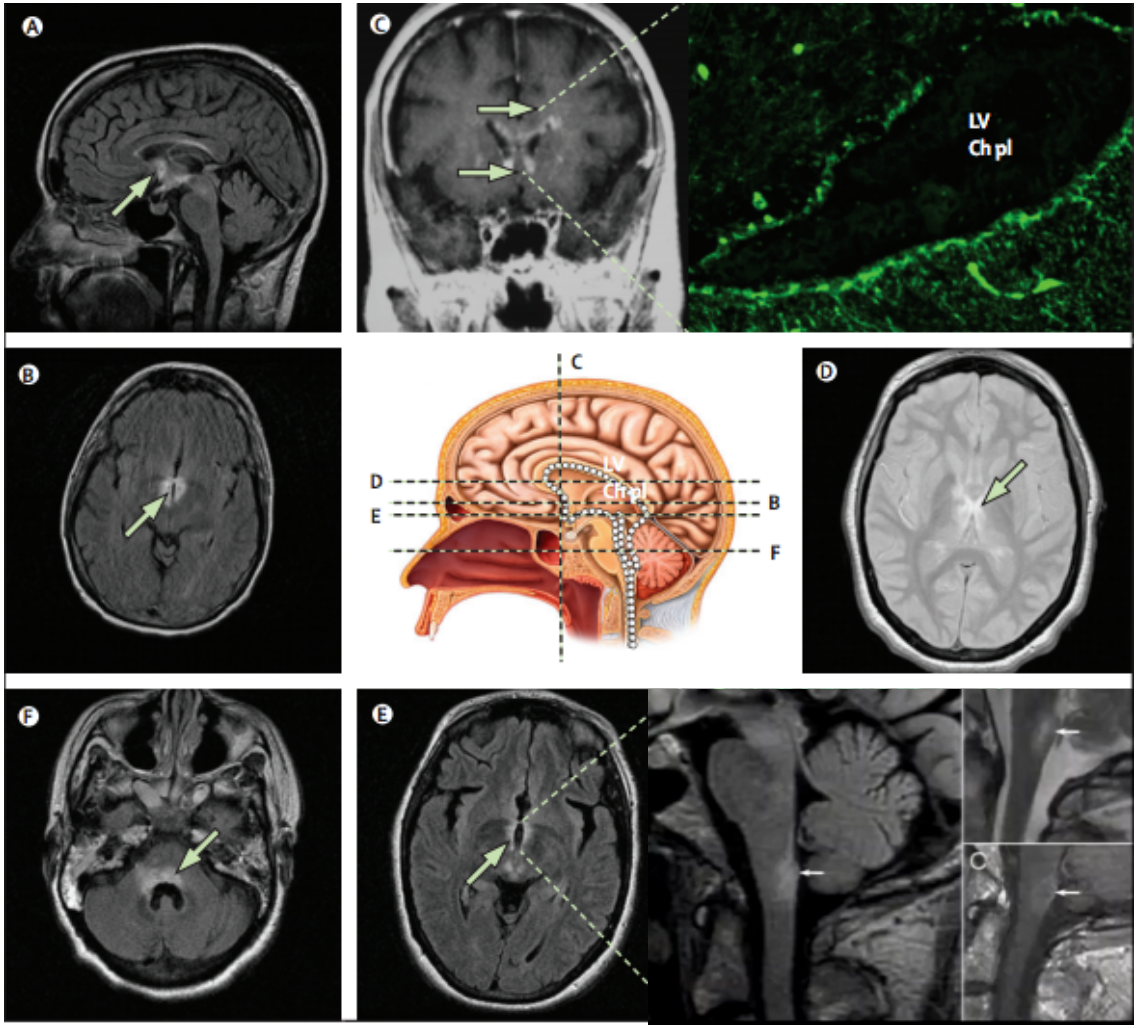
Short Myelitis Lesions in Aquaporin-4-IgG–Positive Neuromyelitis Optica Spectrum Disorders

Eoin P. Flanagan, MBBCh; Brian G. Weinshenker, MD; Karl N. Krecke, MD; Vanda A. Lennon, MD, PhD; Claudia F. Lucchinetti, MD; Andrew McKeon, MBBCh; Dean M. Wingerchuk, MD; Elizabeth A. Shuster, MD; Yujuan Jiao, MD; Erika S. Horta, MD; Sean J. Pittock, MD

- 14% of initial NMO myelitis lesions have “short transverse myelitis” (STM)
- 92% of subsequent myelitis is LETM
- ! Timing of scan ! : too early or to late to see LETM



Clinical manifestations



Brain MRI abnormalities ≃ 60%

Brainstem and diencephalic lesions > 30%

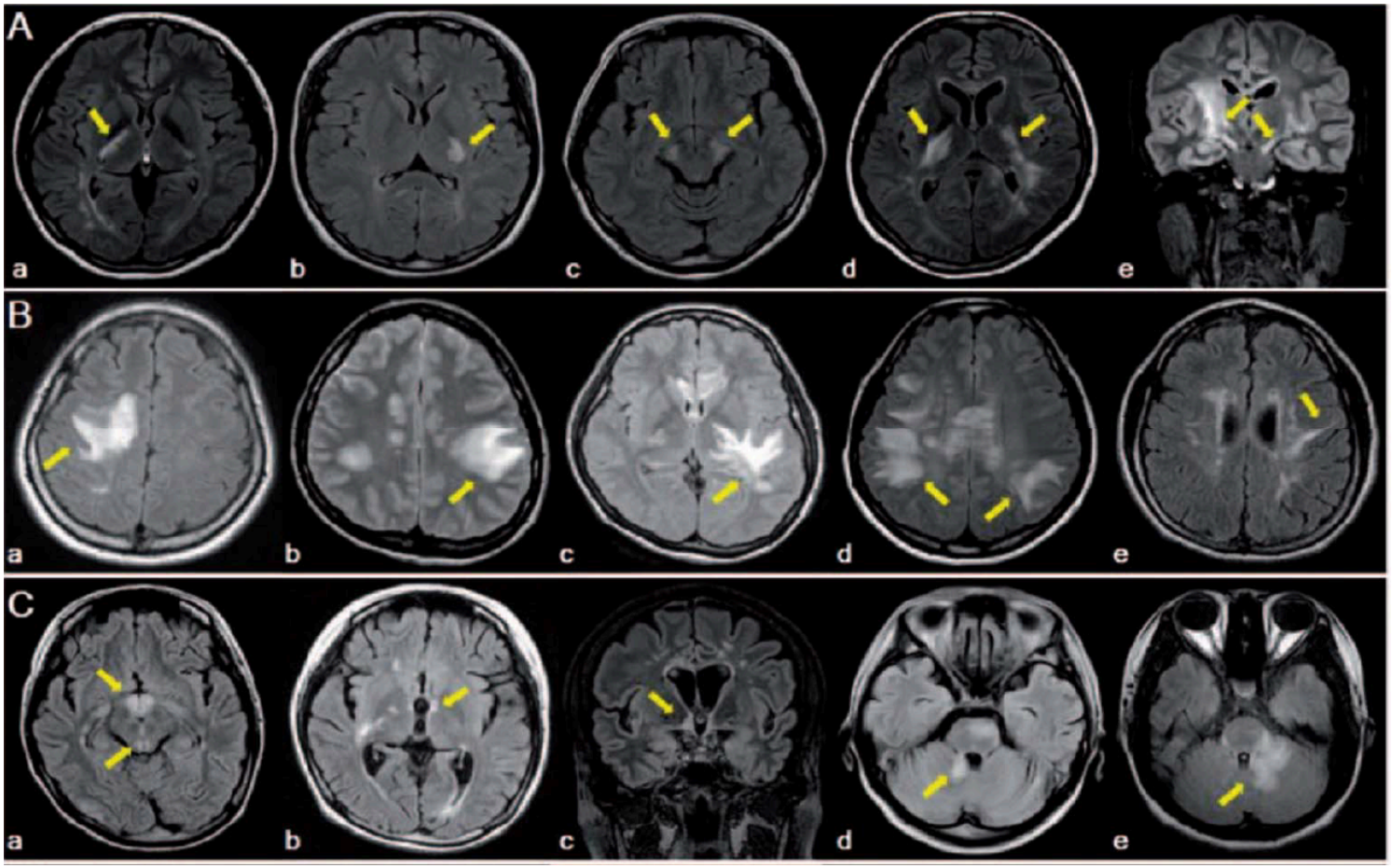
- Nausea, vomiting, hiccups (area postrema)
- Narcolepsia, hypothermia, SIADH (diencéphale)
- Impaired oculomotor function, vertigo, hypoacousia, ataxia, …

Brain MRI

Cortico-spinal tract

Pseudo T

Peri V3-V4



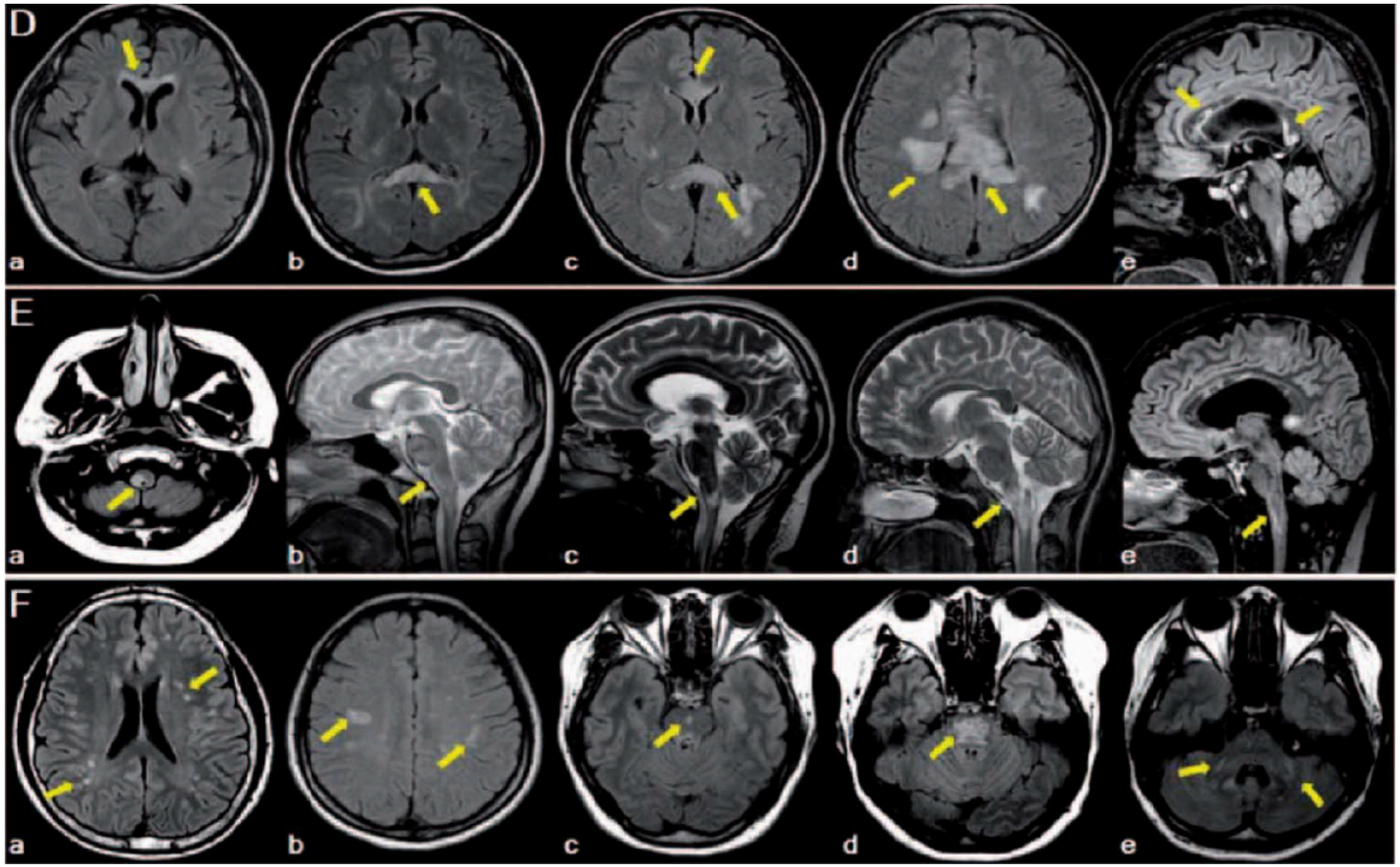
Kim et al., 2011 https://doi.org/10.1177/1352458511404917

Brain MRI

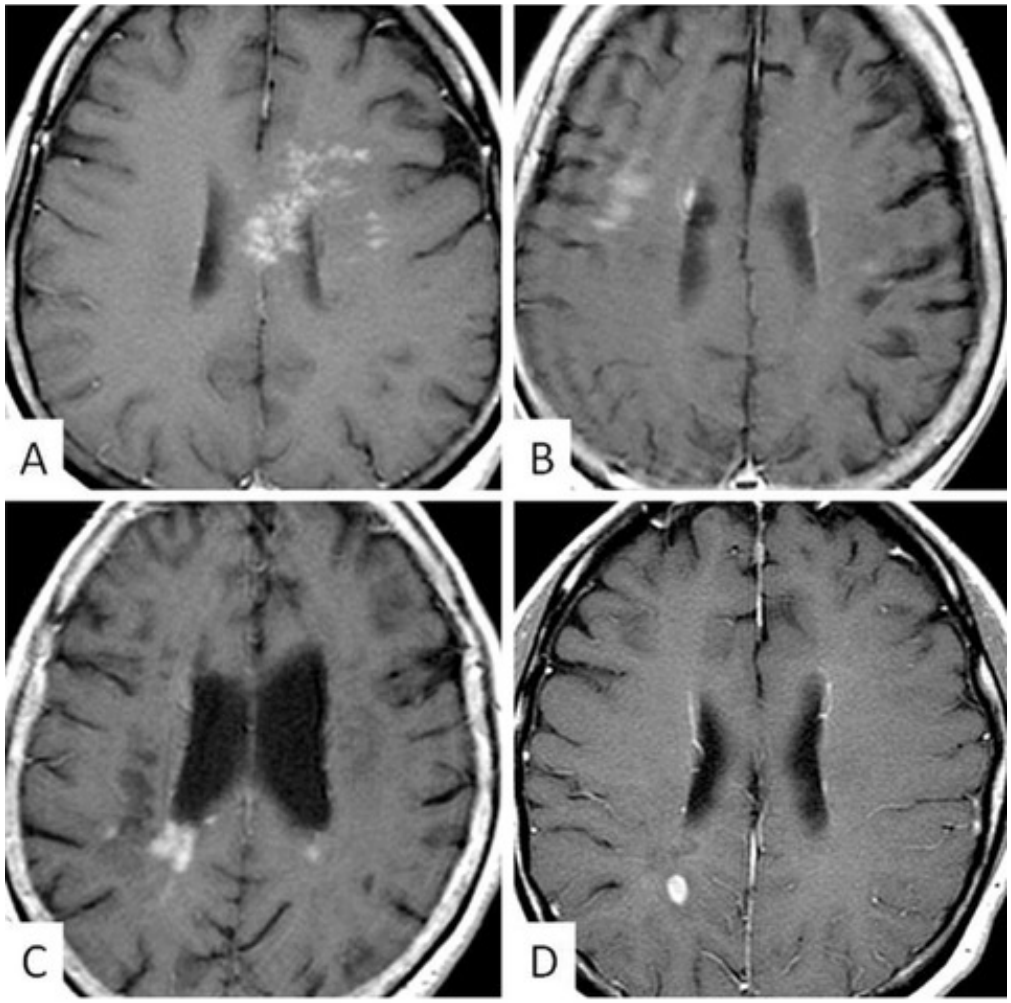
Pericallosal

Cervico-bulbar

Non-specific



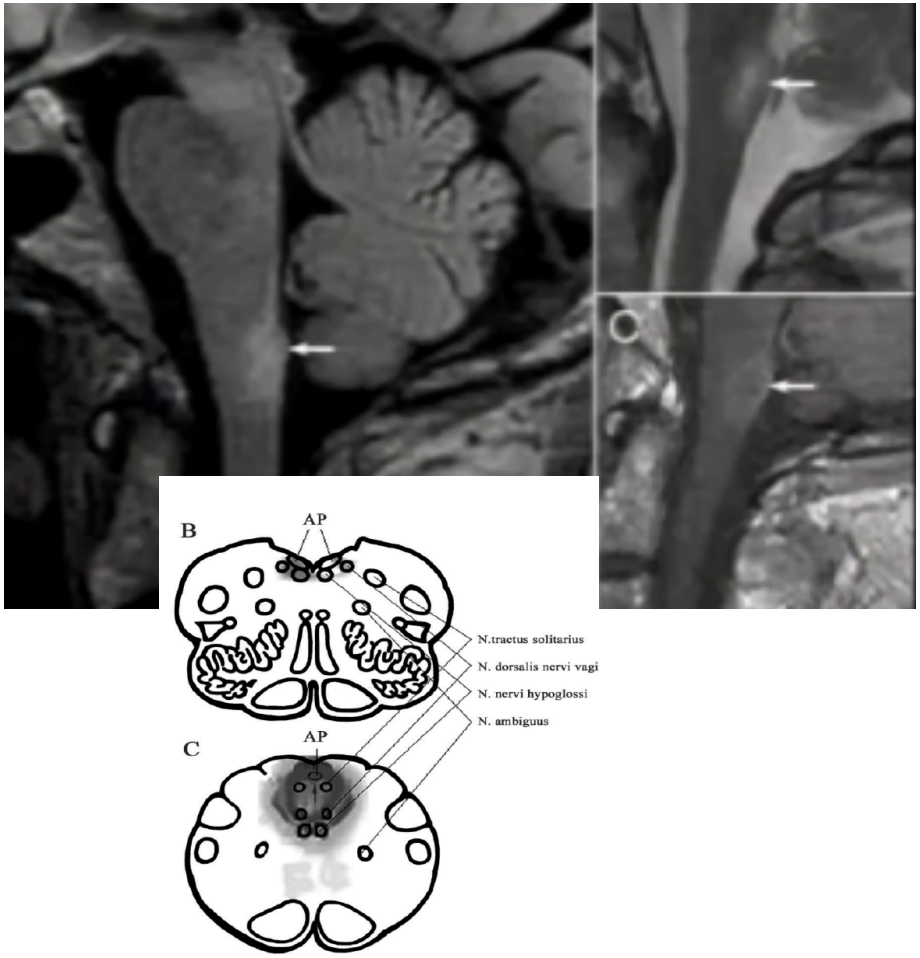
Brain MRI



Cloud-like enhancement

- Ito et al. 2009 https://doi.org/10.1002/ana.21753

Area postrema syndrome

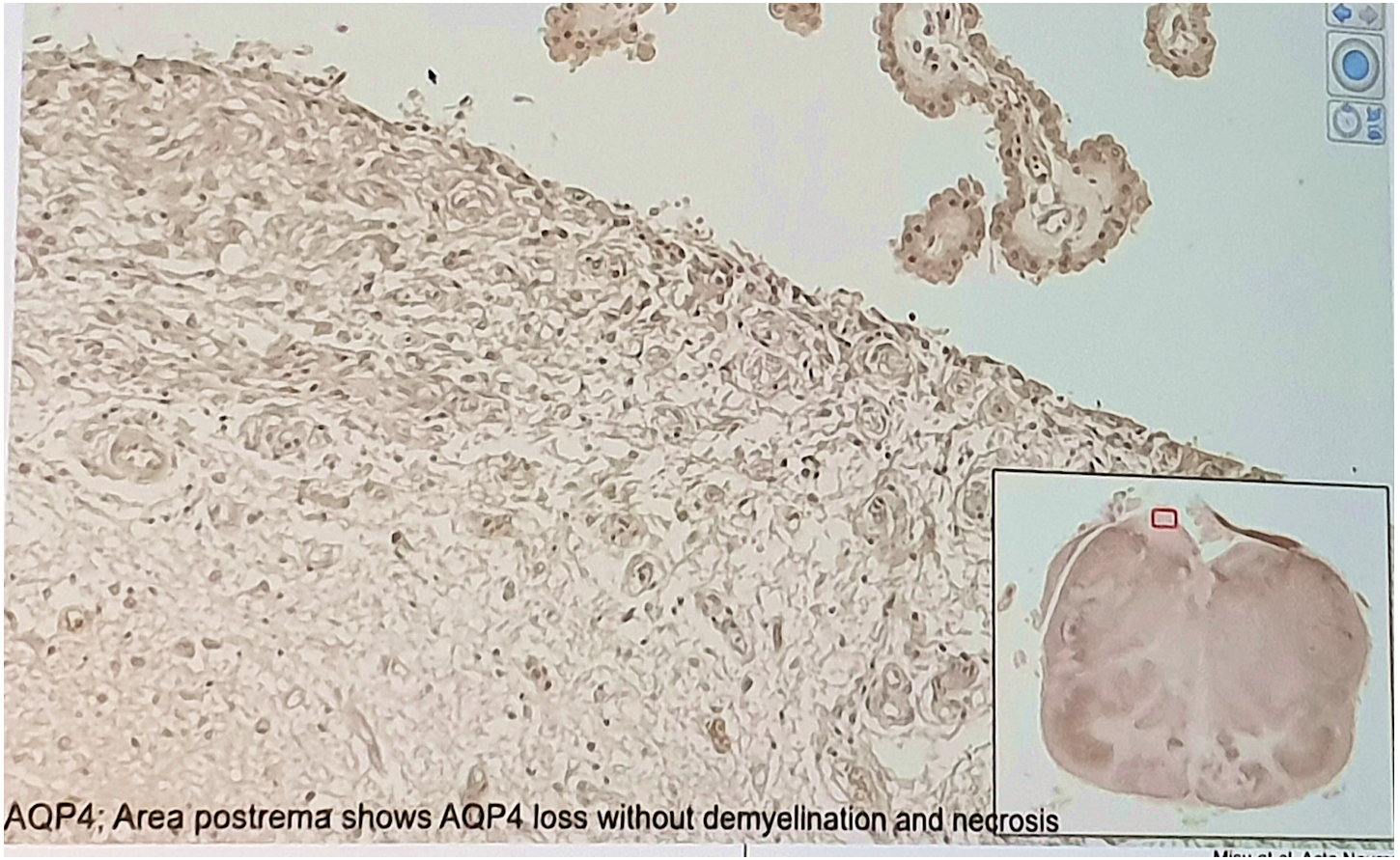


Intractable nausea, vomiting and/or hiccups **> 48h**

- Before (54%)or during an attack
- Sometimes isolated or inaugural
- Bulbar lesion (47%)

- Shosha et al., 2018 https://doi.org/10.1212/WNL.0000000000006392

Area postrema syndrome

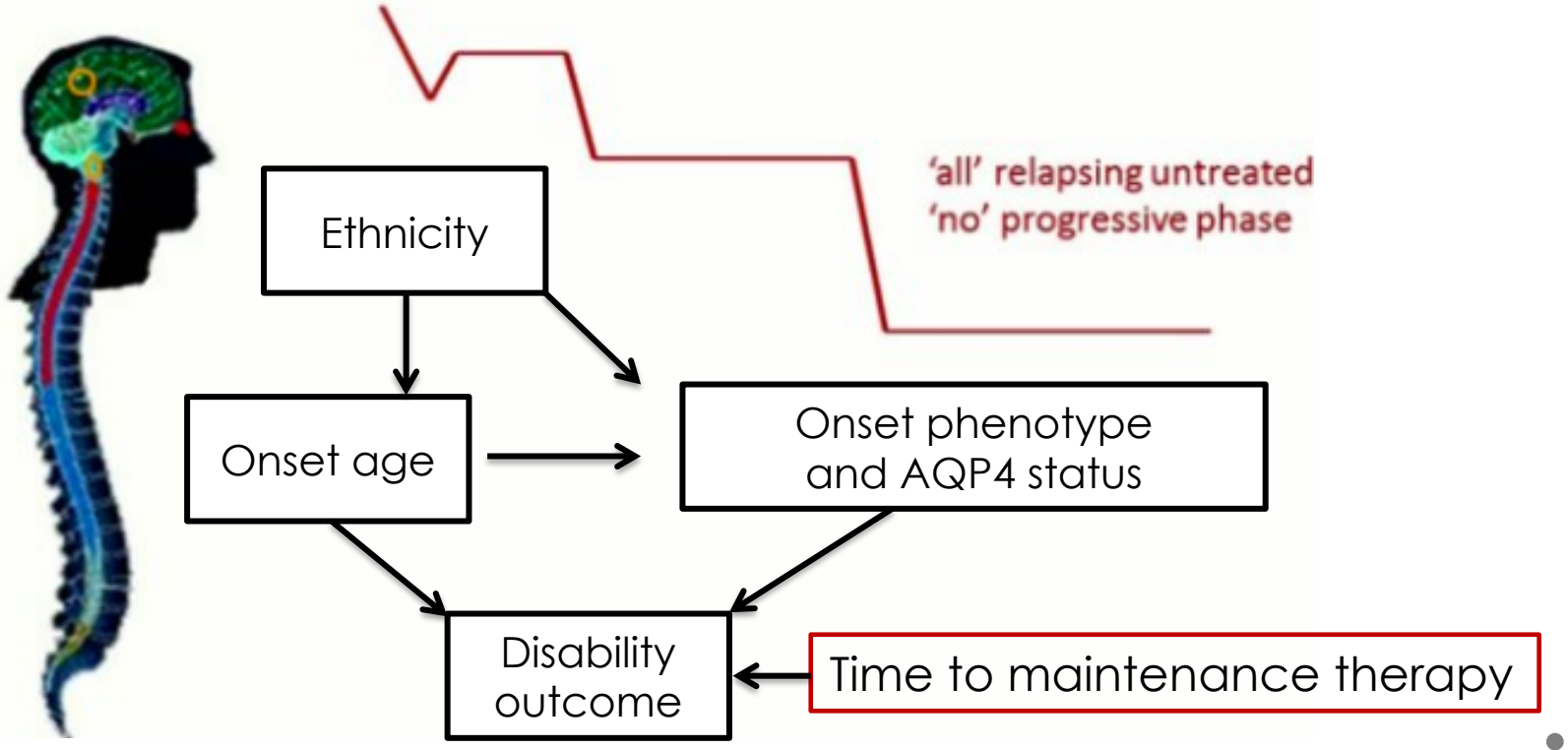


- R. Höftberger , Charcot meeting 2019, Baveno

Clinical evolution and prognosis

Initial presentation

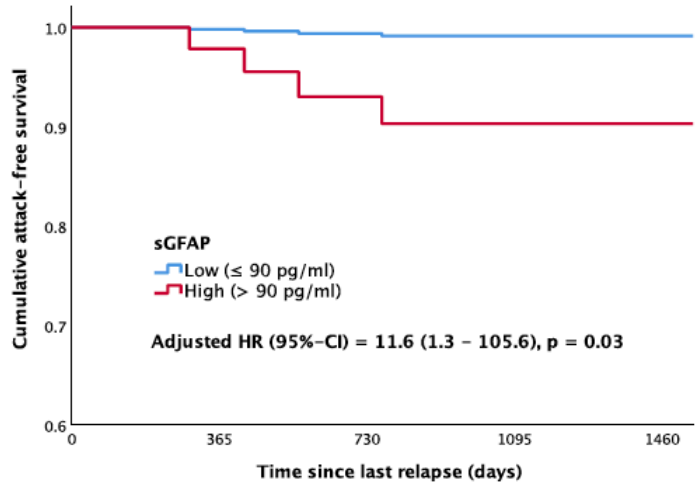
- 80% ON **or** LETM
- 4% ON **+** LETM (50% during follow-up)
- 12% area postrema syndrome



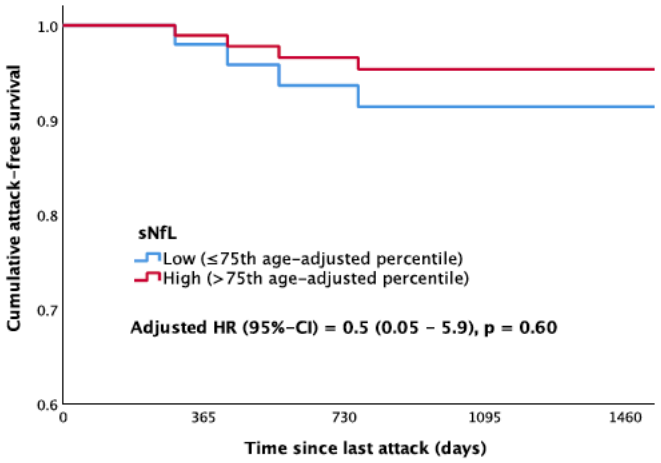
Clinical evolution and prognosis

Serum GFAP and **Neurofilament** as disease severity and prognostic biomarkers in patients with AQP4+ NMOSD

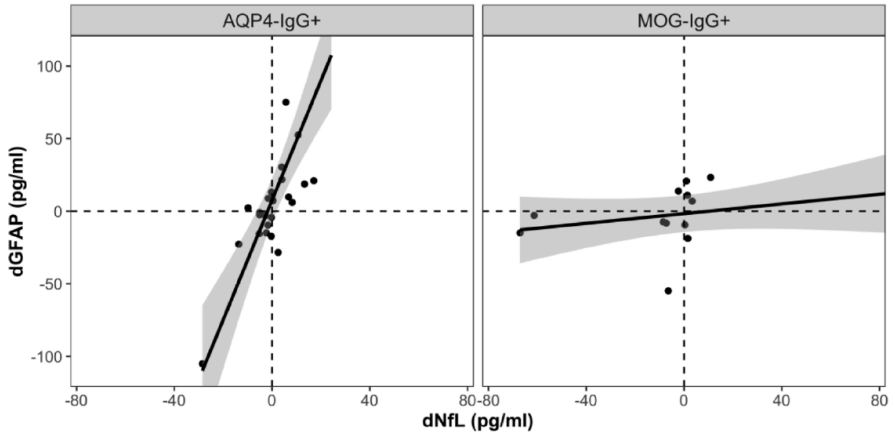
A



B



Correlation between dGFAP and dNFL



Schindler et al., 2021 https://doi.org/10.1186/s12974-021-02138-7

NMOSD Diagnostic Criteria

Table 1 – Neuromyelitis optica spectrum disorder (NMOSD): diagnosis in the presence or absence of aquaporin-4 (AQP4) antibody.

NMOSD with AQP4 antibodies	NMOSD without AQP4 antibodies
At least one clinical manifestation of NMOSD (see below)	At least two different clinical manifestations of NMOSD (at least one of #1, #2 or #3) Optic neuritis/myelitis or area postrema syndrome Magnetic resonance imaging (MRI) in accordance with clinical manifestations
Clinical manifestations	
1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome 4. Acute brainstem syndrome 5. Symptomatic narcolepsy 6. Symptomatic brain syndrome (ADEM/PRES) with MRI lesions	
New diagnostic criteria for NMOSD (Wingerchuck et al., 2015) [10]	
These criteria are applicable only in cases of no better clinical explanation. Recommendation: AQP4 should be tested with a cell-based assay	

~80% AQP4 +

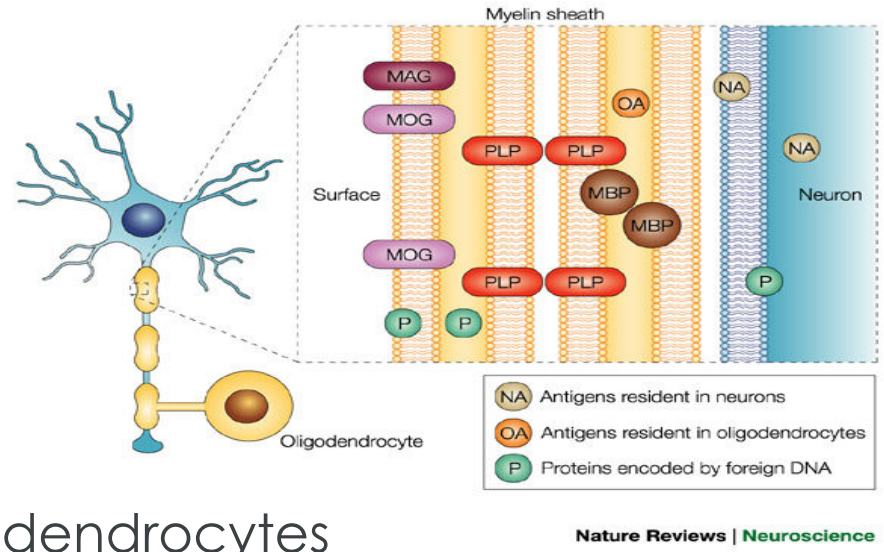
30-40% MOG +

Wingerchuk et al., 2015 https://doi.org/10.1212/WNL.0000000000001729

Li et al., 2021 https://doi.org/ 10.1016/j.msard.2021.103030

Myelin oligodendrocyte glycoprotein (MOG)

- SNC membrane protein



- Localization:

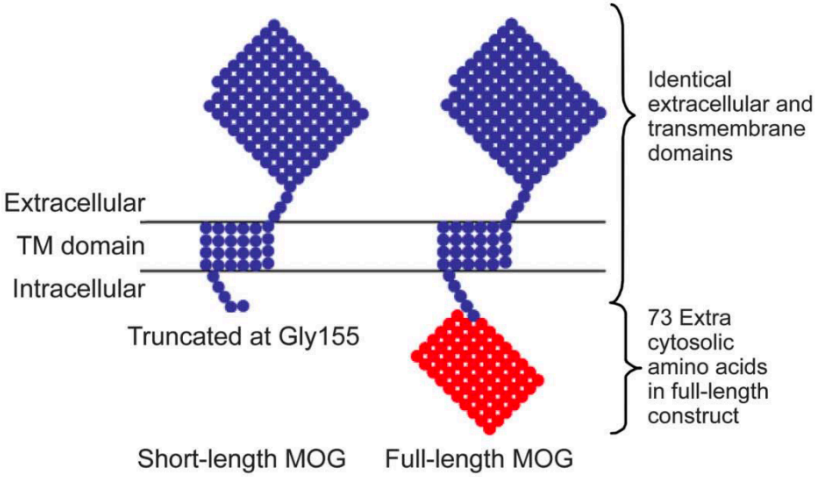
- extracellular surface of oligodendrocytes
- outermost lamellae of myelin sheat

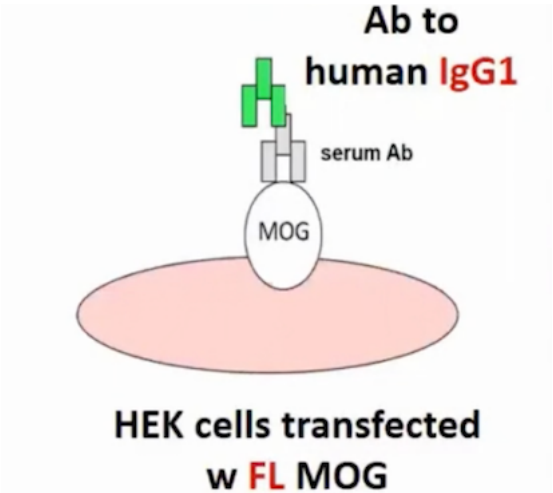
- Function:

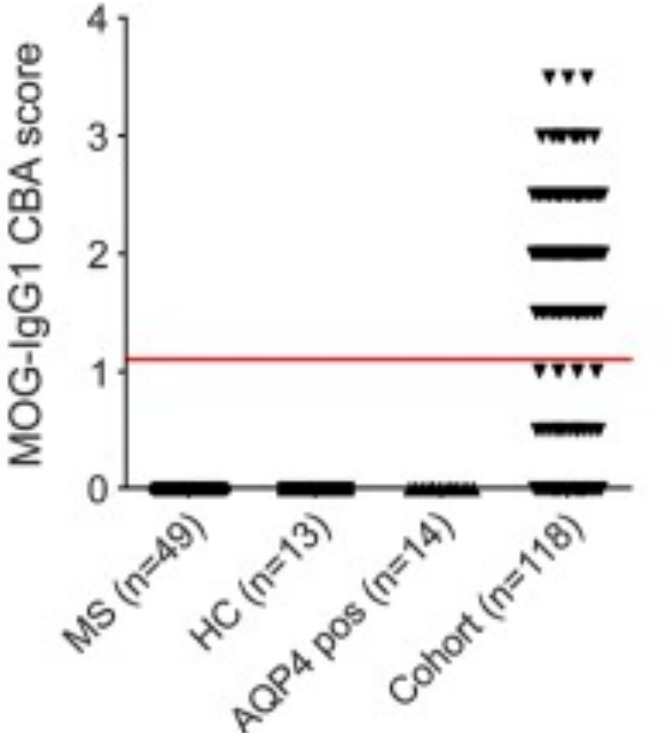
- adhesion receptor
- compaction/maintenance of myelin

- Hemmer et al., 2002 https://doi.org/10.1038/nrn784

Anti-MOG IgG detection



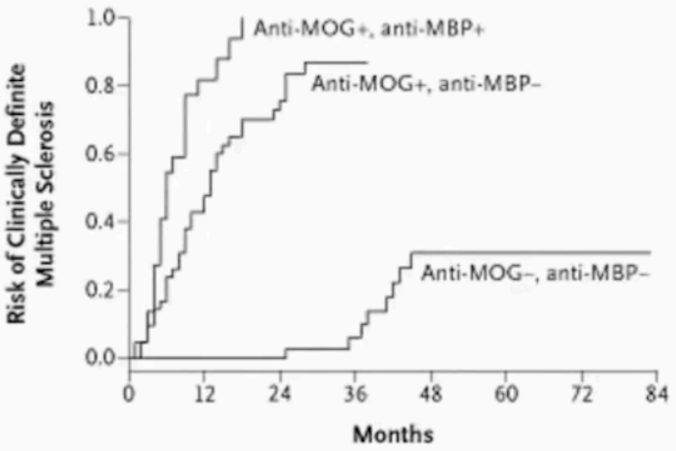




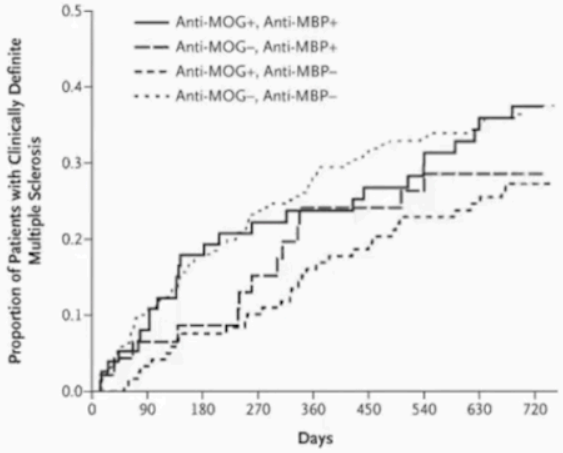
- Waters et al., 2015 https://doi.org/10.1212/NXI.0000000000000089

Anti-MOG IgG and MS

A role of anti-MOG antibodies in MS?



Berger, T. et al. *N Engl J Med* 2003; 349: 139-145



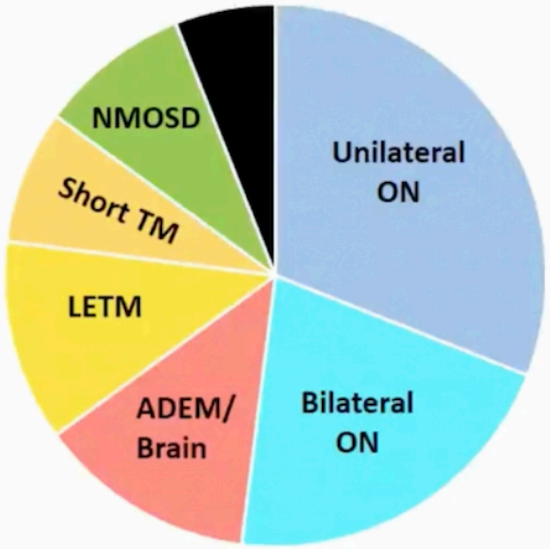
Kuhle, J. et al. *N Engl J Med* 2007; 356: 371-378

Antibodies decting linear MOG epitopes in ELISAs are probably irrelevant!

Onset phenotypes

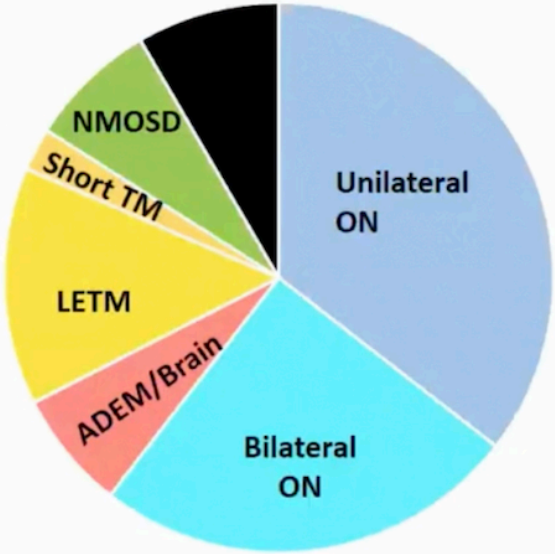
UK cohort =252

Jurynczyk et al, Brain, 2017;140(12):3128



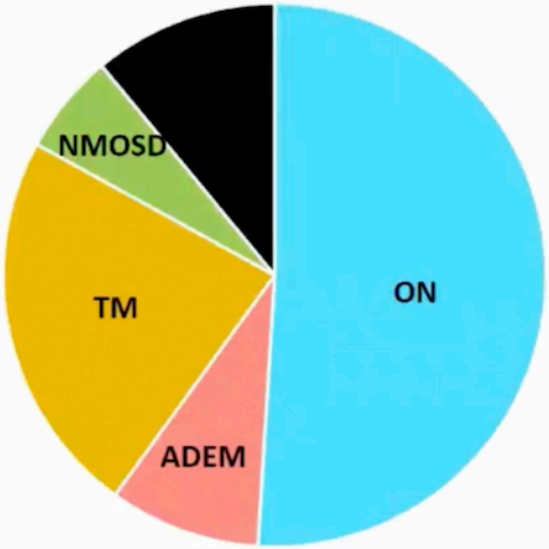
French adult cohort =197

Cobo-Calvo et al, Neurol 2018:90



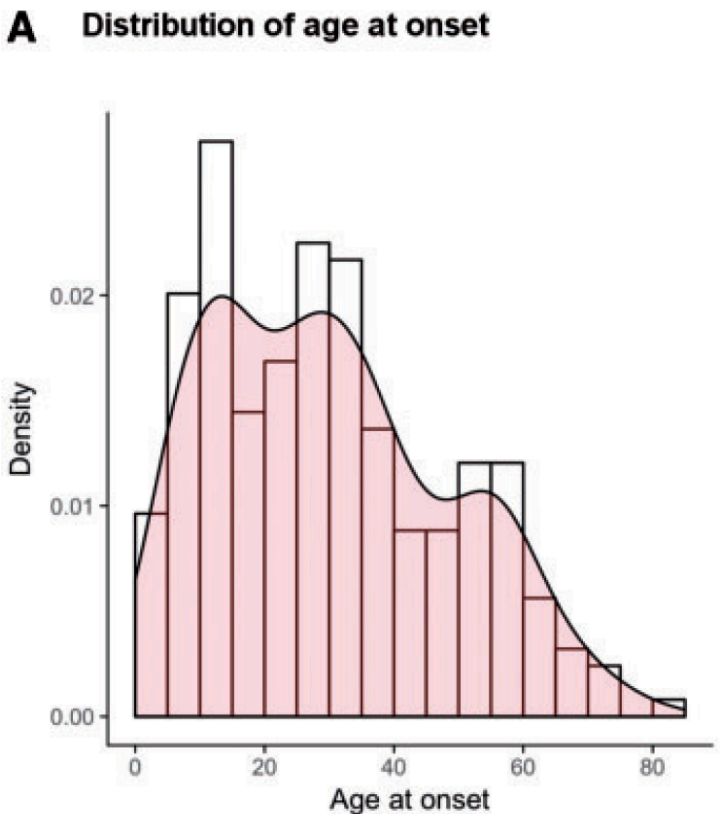
Sri Lankan cohort =126

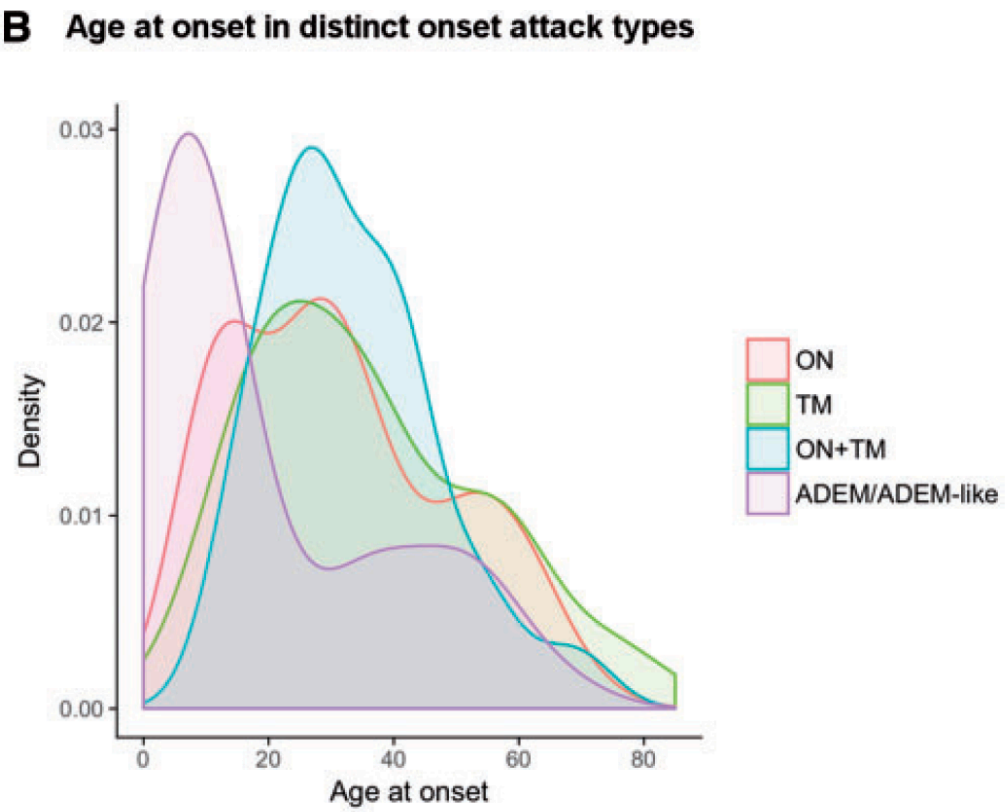
Senanayake et al, JNNP 2019;0:1-3



Female: 49-57%
Relapsing: 41-43% at 24 months in incident cohorts
Ethnicity: no racial predominance

Age at onset and phenotypes





- Jurynczk et al. 2017, https://doi.org/ 10.1093/brain/awx276

LETTER

Journal of Neurology, Neurosurgery & Psychiatry

Prevalence and incidence of neuromyelitis optica spectrum disorder, aquaporin-4 antibody-positive NMOSD and MOG antibody-positive disease in Oxfordshire, UK

	Prevalence/million	Incidence/million
AQP4-IgG +ve	12	2.0
MOG-Ab +ve	20	3.4

- O'Connell et al., 2020 http://dx.doi.org/10.1136/jnnp-2020-323158

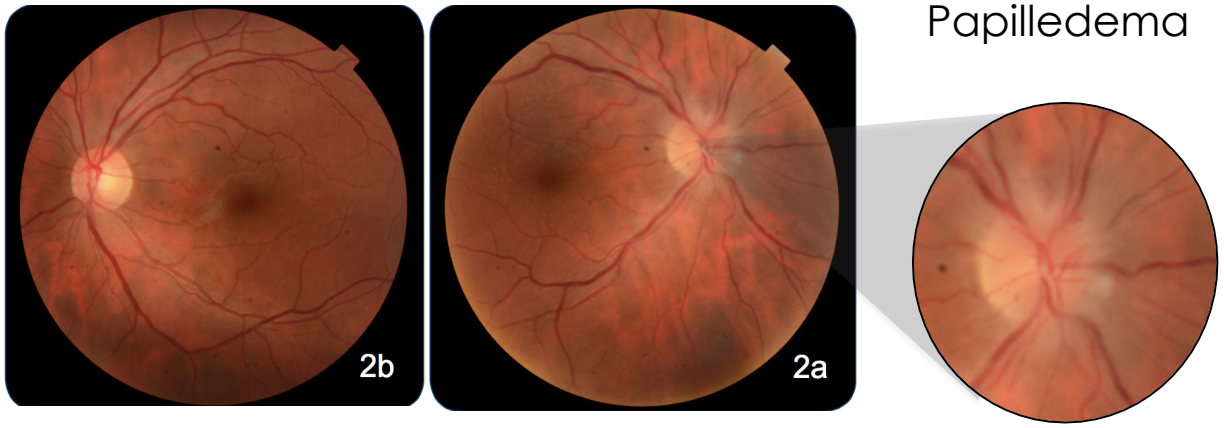
Acute Optique Neuritis

Clinical presentation

- AQP4 and MOG-IgG: severe vision loss at nadir, pain or not
- MOG-IgG: Bilateral 37-44%, high risk of recurrence, steroid dependant

Fundoscopy

- MOG-IgG: Optic disc edema (80%)
- AQP4-IgG: Mild edema if present

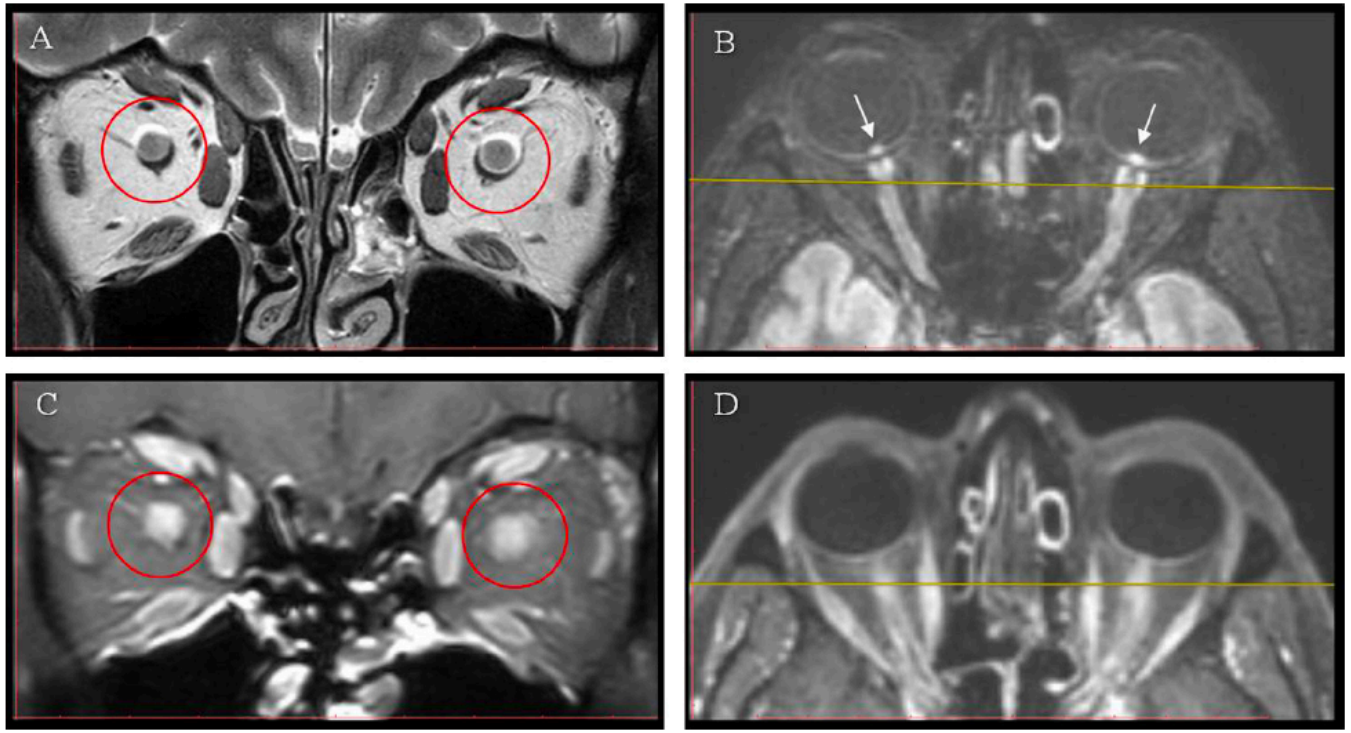


Chen et al., 2020 https://doi.org/10.1093/brain/awx276

Acute Optique Neuritis

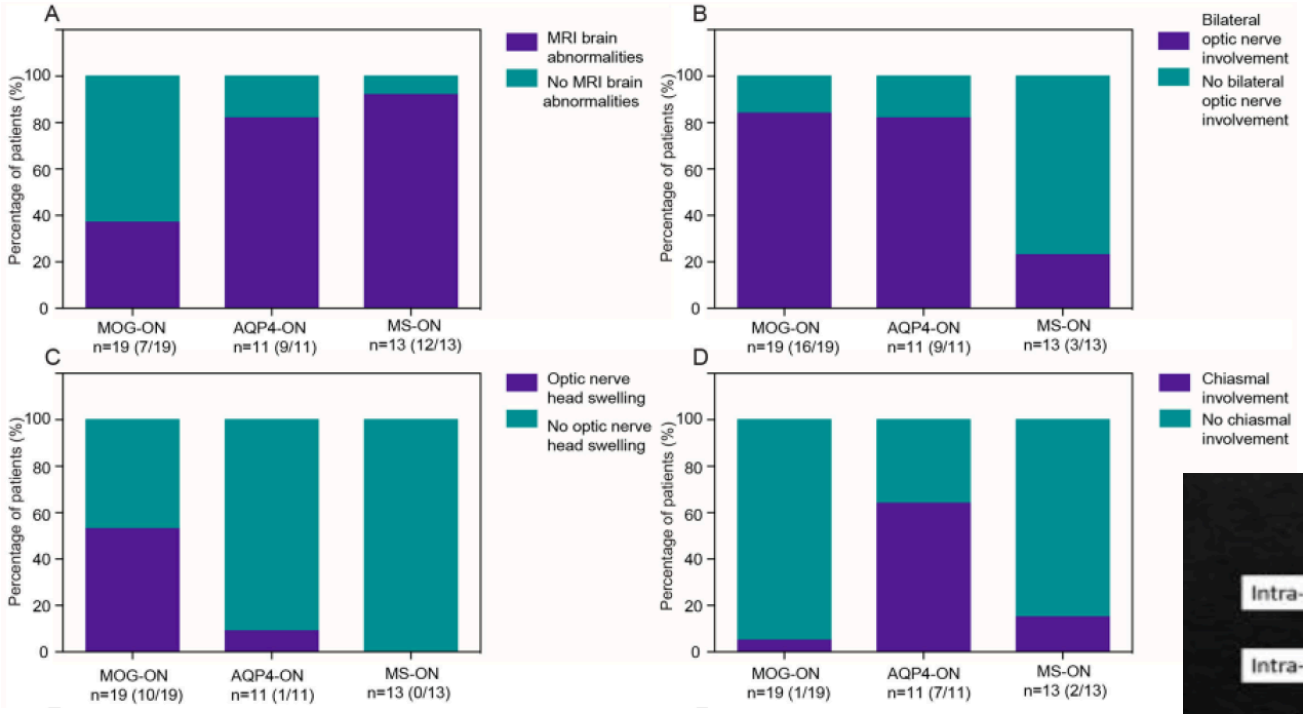
MRI

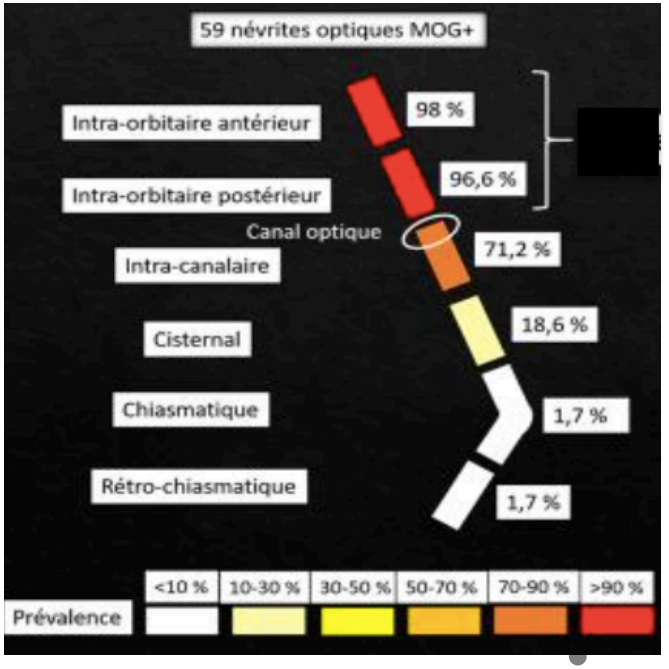
- AQP4-IgG: intracranial, chiasmal, optic tract, longitudinal extention
- MOG-IgG: intra-orbital, perineuritic/orbital inflammation, longitudinal extention



Denève et al., 2019 https://doi.org/10.1016/j.neurad.2019.06.001

Acute Optique Neuritis





50 patients
First NORB

- Ramanathan et al., 2016
  https://doi.org/10.1177/1352458515593406

Acute Transverse Myelitis

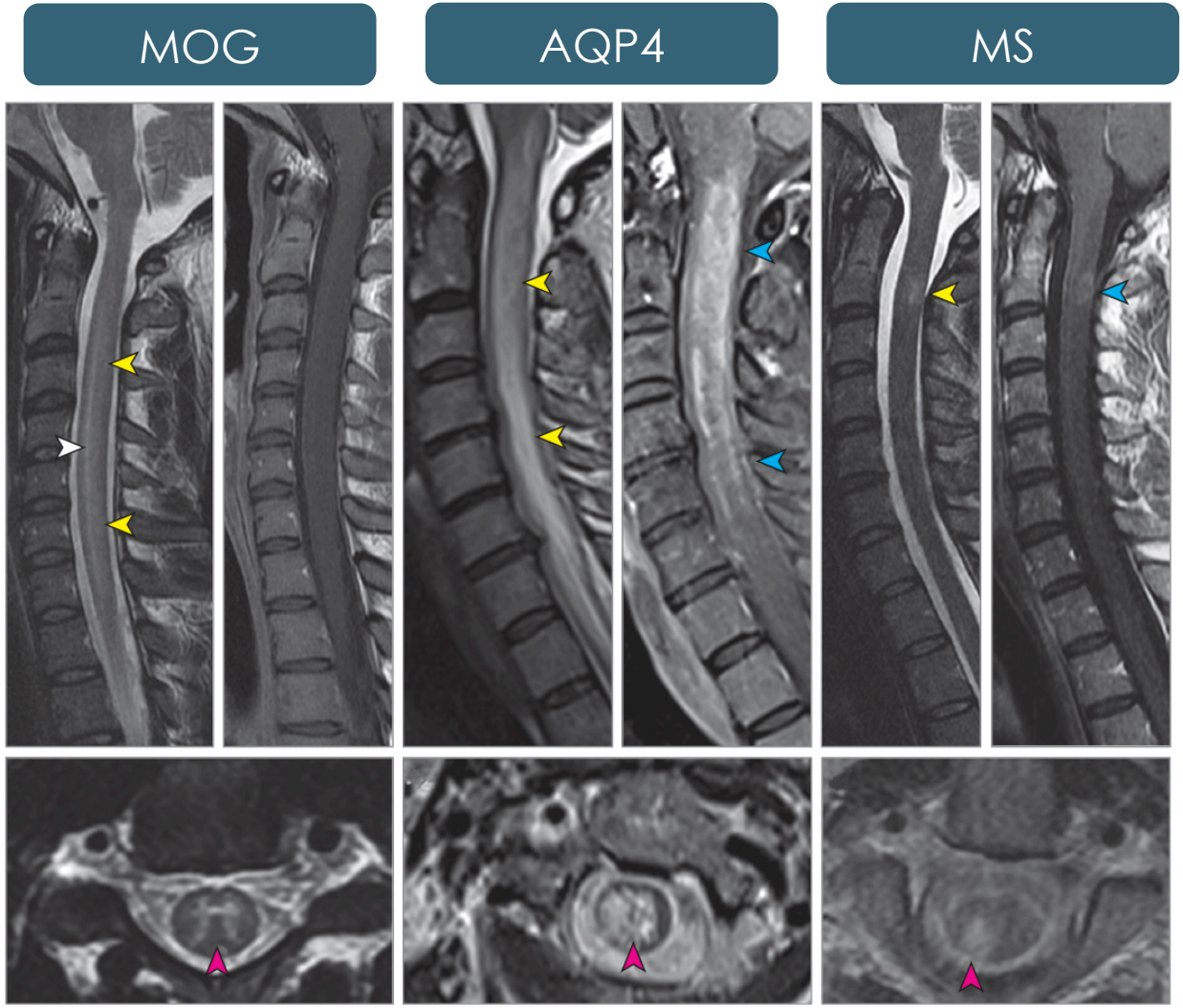
MRI

- AQP4-IgG

  85% LETM
  Cervical
  Bright spotty T2, Hypo T1

- MOG-IgG

  45% short lesions
  Conus medullaris lesion
  T2 hyperintense line
  "H" sign"



- Dubey et al., 2019 https://doi.org/10.1001/jamaneurol.2018.4053

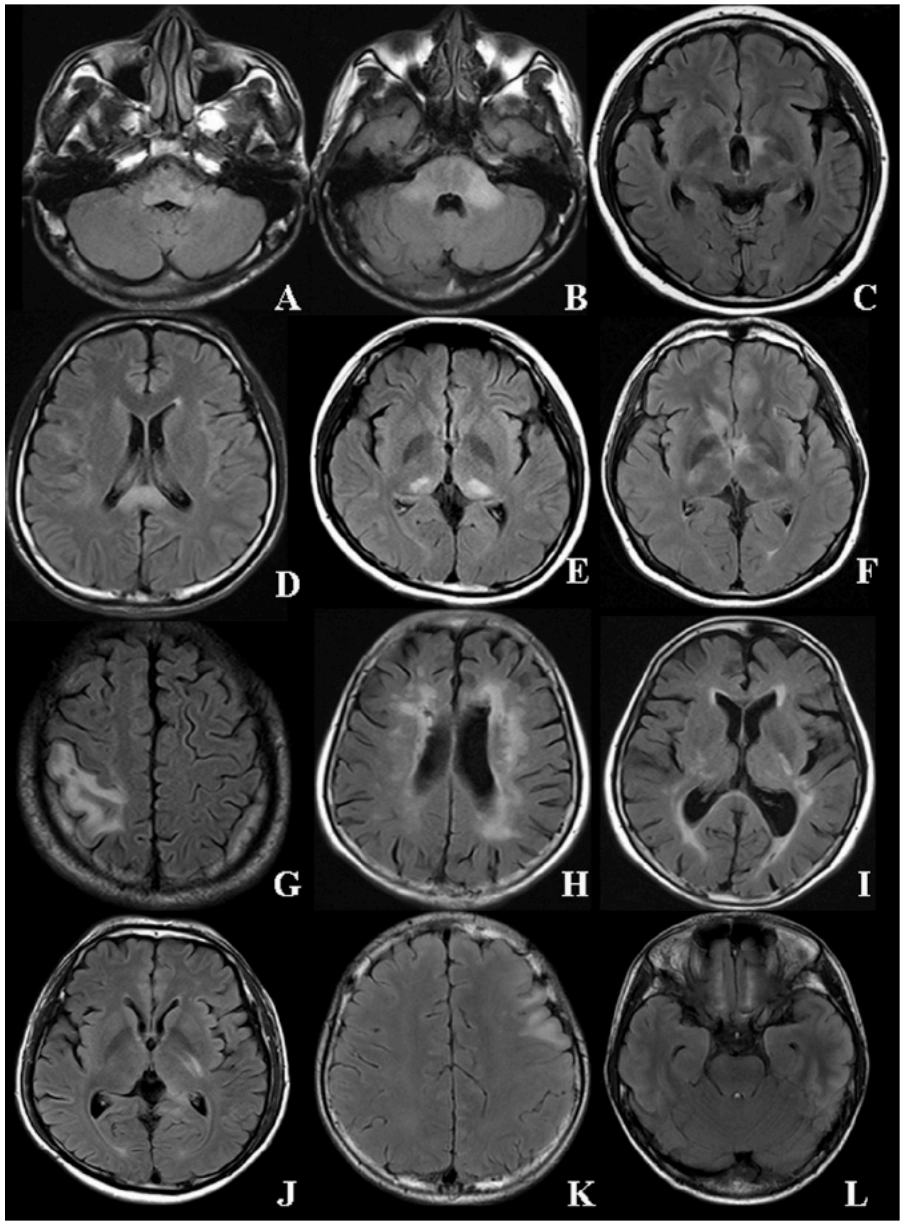
Cerebral involvement

Patterns	Example	Frequency
Lesions involving midline structures and deep grey matter	Diencephalon, pontine, medulla oblongata	31.4% (11/35)
	Corpus callosum	28.5% (10/35)
	Middle cerebral peduncles	25.7% (9/35)
	Peri-third ventricle area	25.7% (9/35)
	Thalamus	17.1% (6/35)
	Basal ganglia	11.4% (4/35)
Supratentorial white matter lesions	Juxtacortical white matter	68.5% (24/35)
	Periventricular deep white matter	48.5% (17/35)
	Juxtaventricular white matter	37.1% (13/35)
	Internal capsule	20% (7/35)
Cortical gray matter lesions	Both cortical gray matter and juxtacortical white matter	42.8% (15/35)
	Lesions confined to cortical gray matter	14.3% (5/35)

Cortical/juxta-cortical lesions

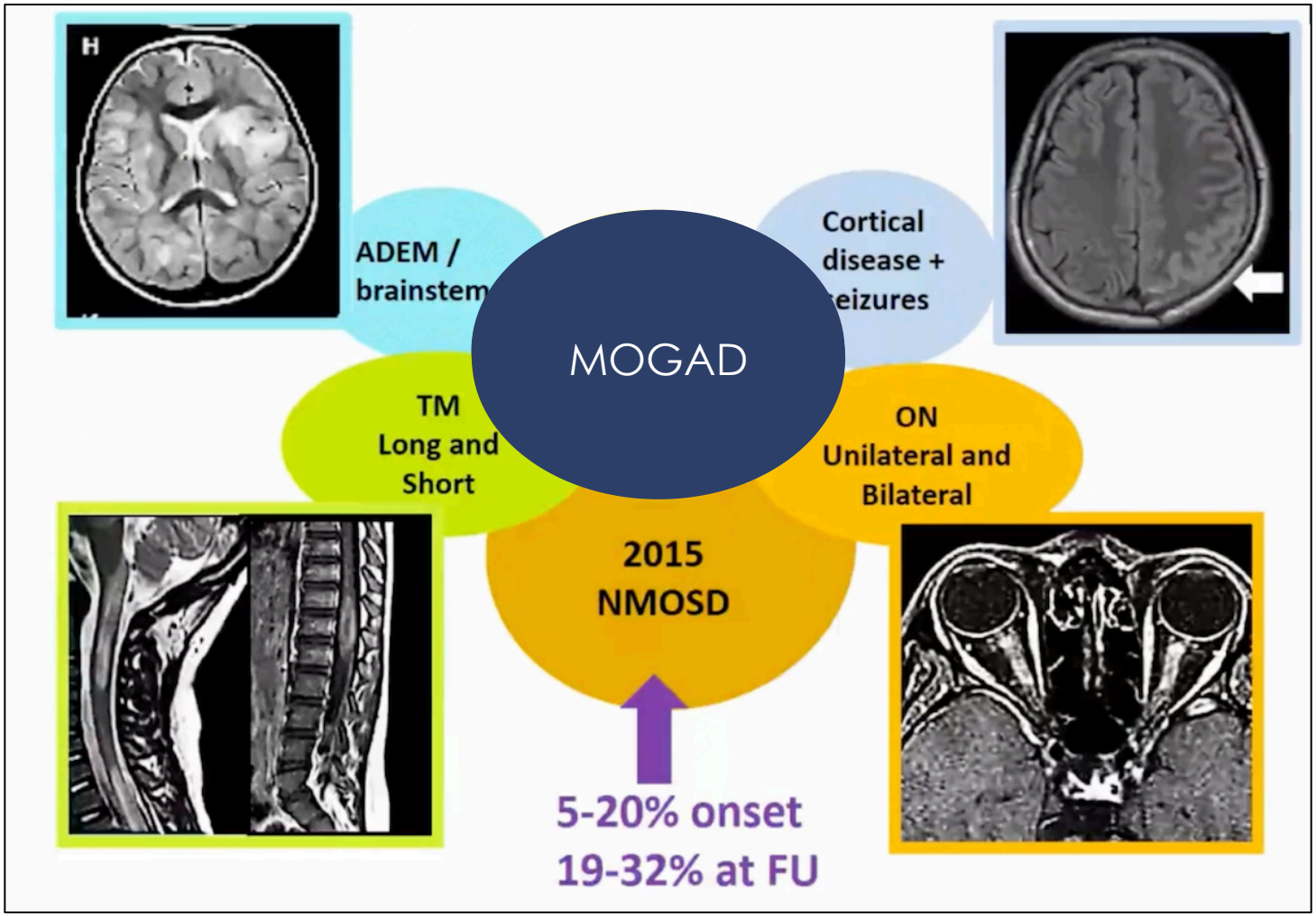
Middle cerebral peduncles lesions

Fluffy ADEM-like lesions



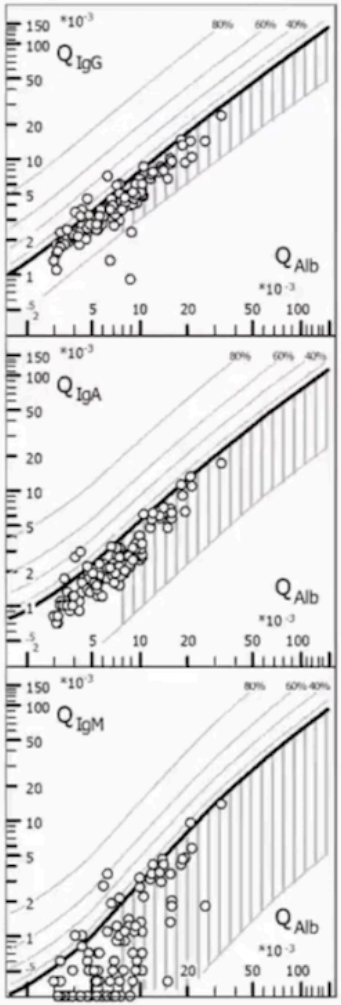
- Li et al., 2020
  https://doi.org/10.1016/j.msard.2020.102167

Minority of MOG-IgG have NMOSD



- J. Palace , Charcot meeting 2019, Baveno

Cerebrospinal fluid findings



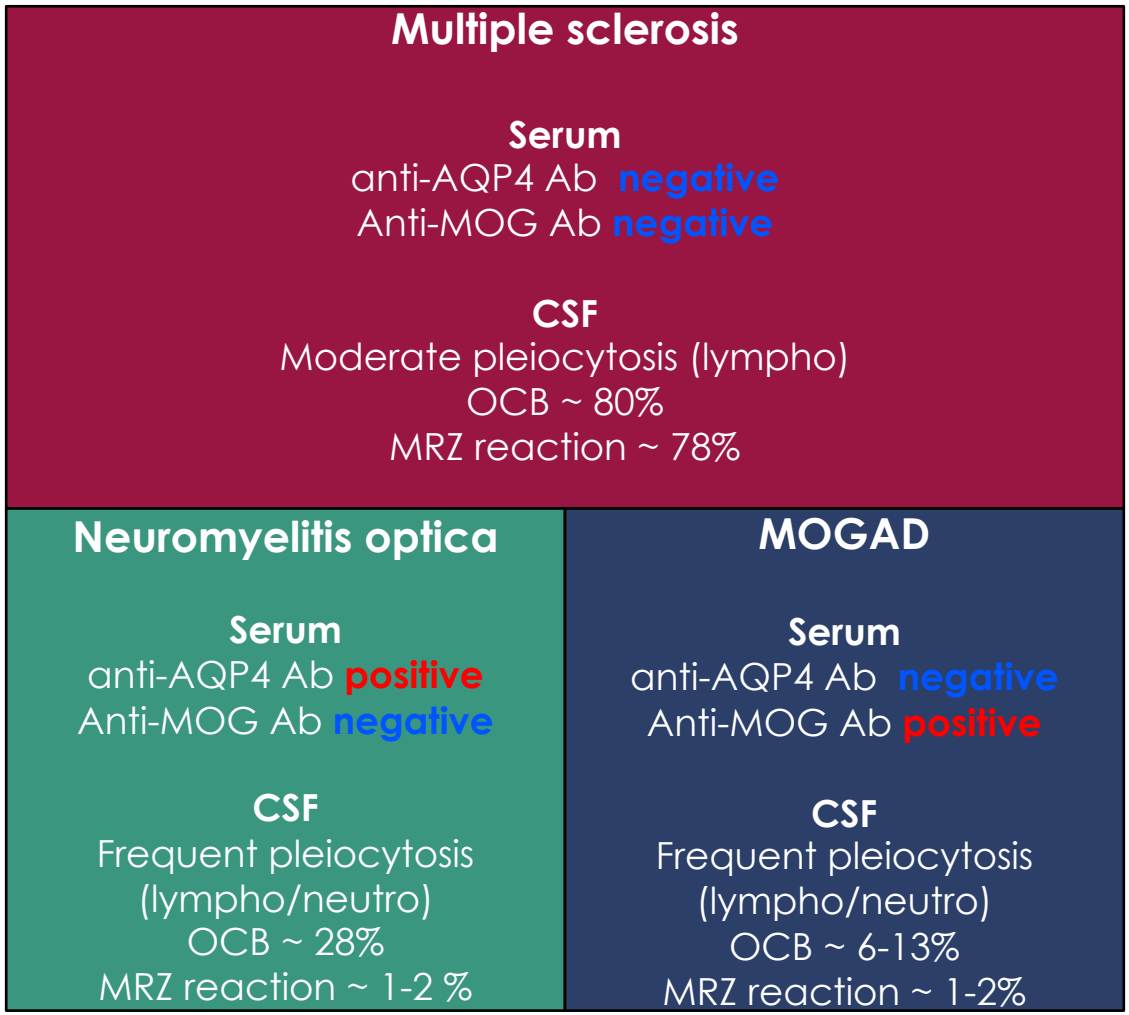
Intrathecal IgG production and CSF-restricted oligoclonal IgG bands, a hallmark of MS, were absent in almost 90% of samples (N=100).

The MRZ reaction, the most specific laboratory marker of MS known so far, was absent in 100% (N=62).

	Units	Total cohort
MRZ reaction (M+R, M+Z, R+Z or M+R+Z)	*patients*	0/48 (0%)
MRZ reaction (M+R, M+Z, R+Z or M+R+Z)	*samples*	0/62 (0%)
AI measle virus (M)	*samples*	2/61 (3.3%)
AI rubella virus (R)	*samples*	1/52 (1.9%)
AI varizella zoster virus (Z)	*samples*	3/76 (3.9%)

- Jarius et al., 2020 https://doi.org/10.1186/s12974-020-01824-2

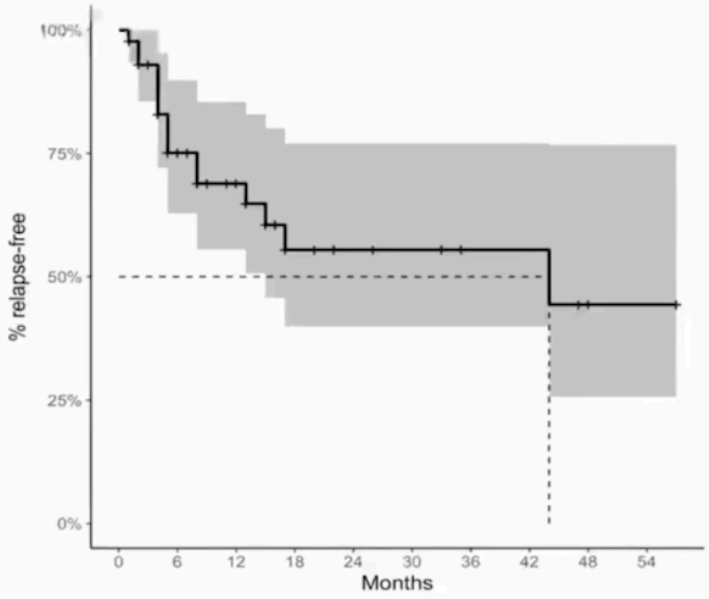
Cerebrospinal fluid findings



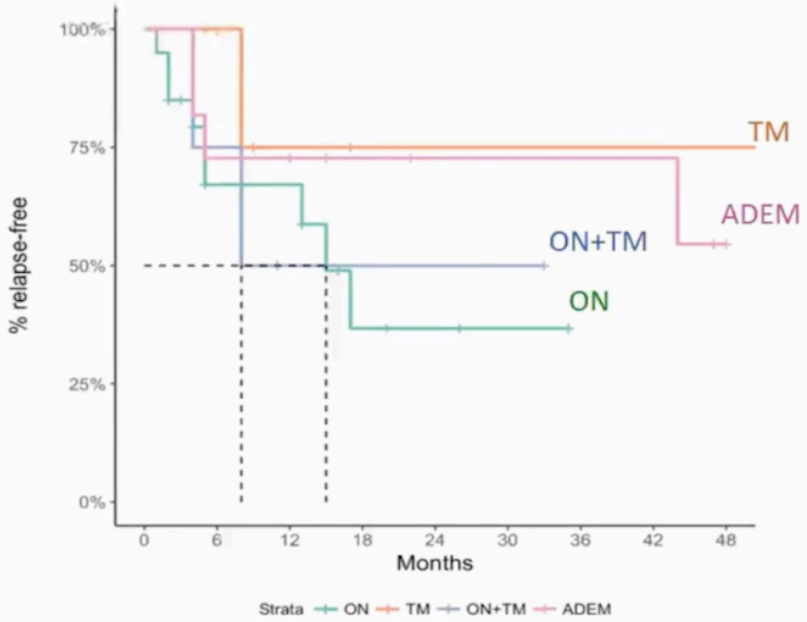
- Weber et al., 2018 https://doi.org/10.1177/1756286418762083

Clinical evolution and prognosis

Cumulative probability of remaining relapse-free in patients diagnosed after the onset attack



Cumulative probability of remaining relapse-free in patients diagnosed after different onset attack

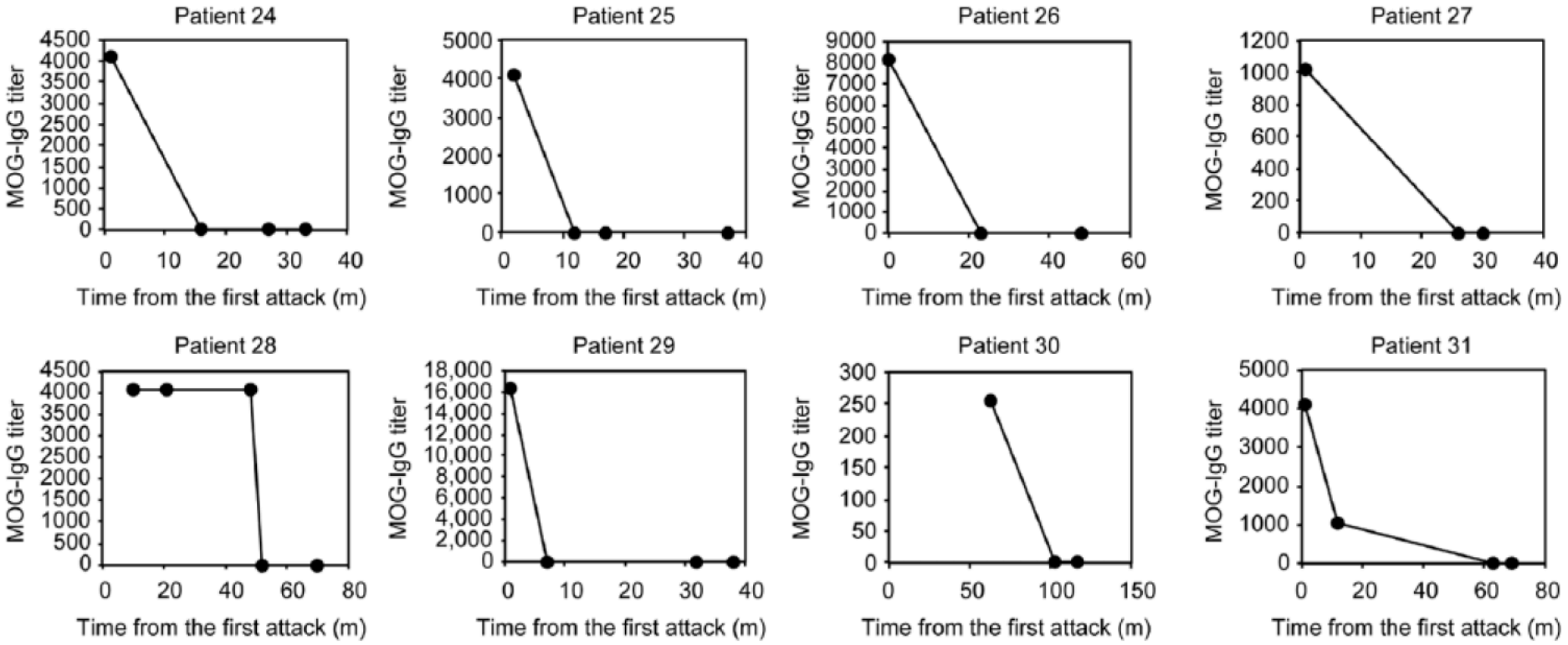


80% relapses are ON

- Jurynczk et al. 2017, https://doi.org/ 10.1093/brain/awx276

Clinical evolution and prognosis

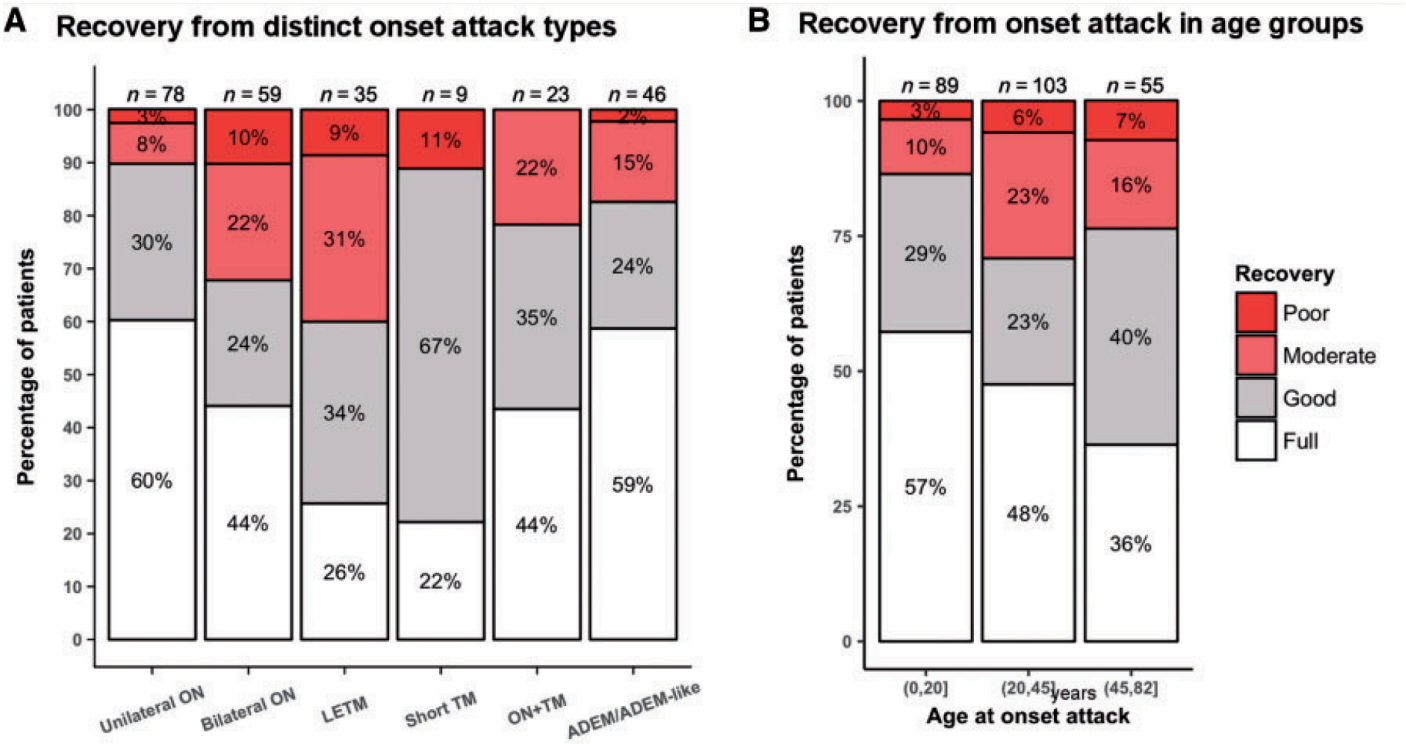
- Monophasic or relapsing (44-84%)
- The risk of relapse is associated with longitudinally persistent MOG-IgG seropositiviy



- Oliveira et al., 2019 https://doi.org/10.1177/1352458518811597

Clinical evolution and prognosis

- Severity of attack at nadir similar for both MOG- and and AQP4-IgG
- Better recovery in MOG-IgG patient



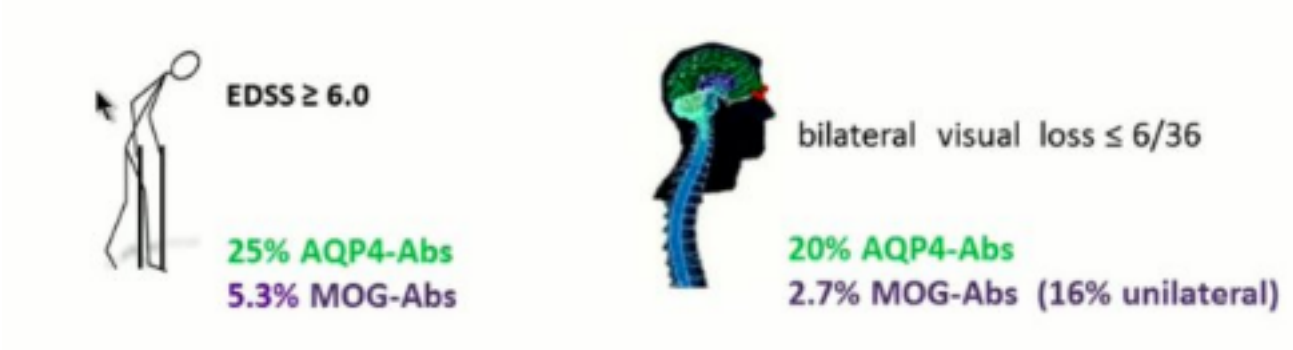
- Jurynczk et al. 2017, https://doi.org/ 10.1093/brain/awx276

Clinical evolution and prognosis

- Majority of disability is from onset attack

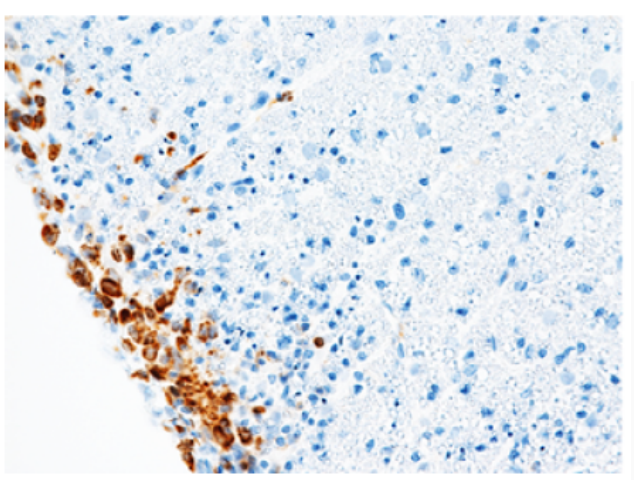
Permanent bladder dysfunction (20%)
Bowel dysfunction (20%)
Erectile dysfunction (45% of ♂ with TM at onset)

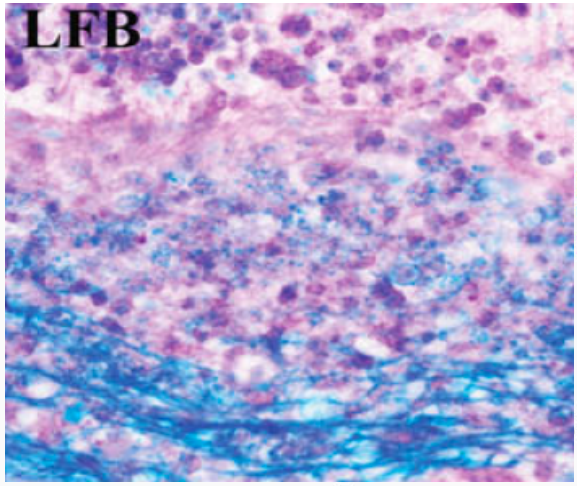
28 months

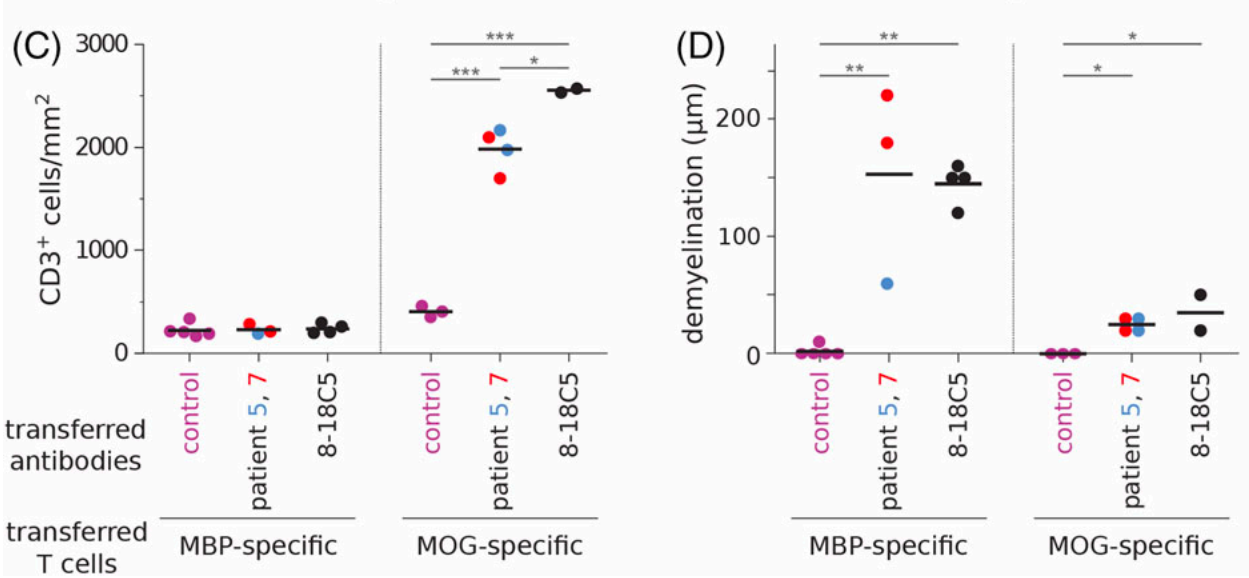


- Jurynczk et al. 2017, https://doi.org/10.1093/brain/awx276

Are anti-MOG antibodies pathogenic?

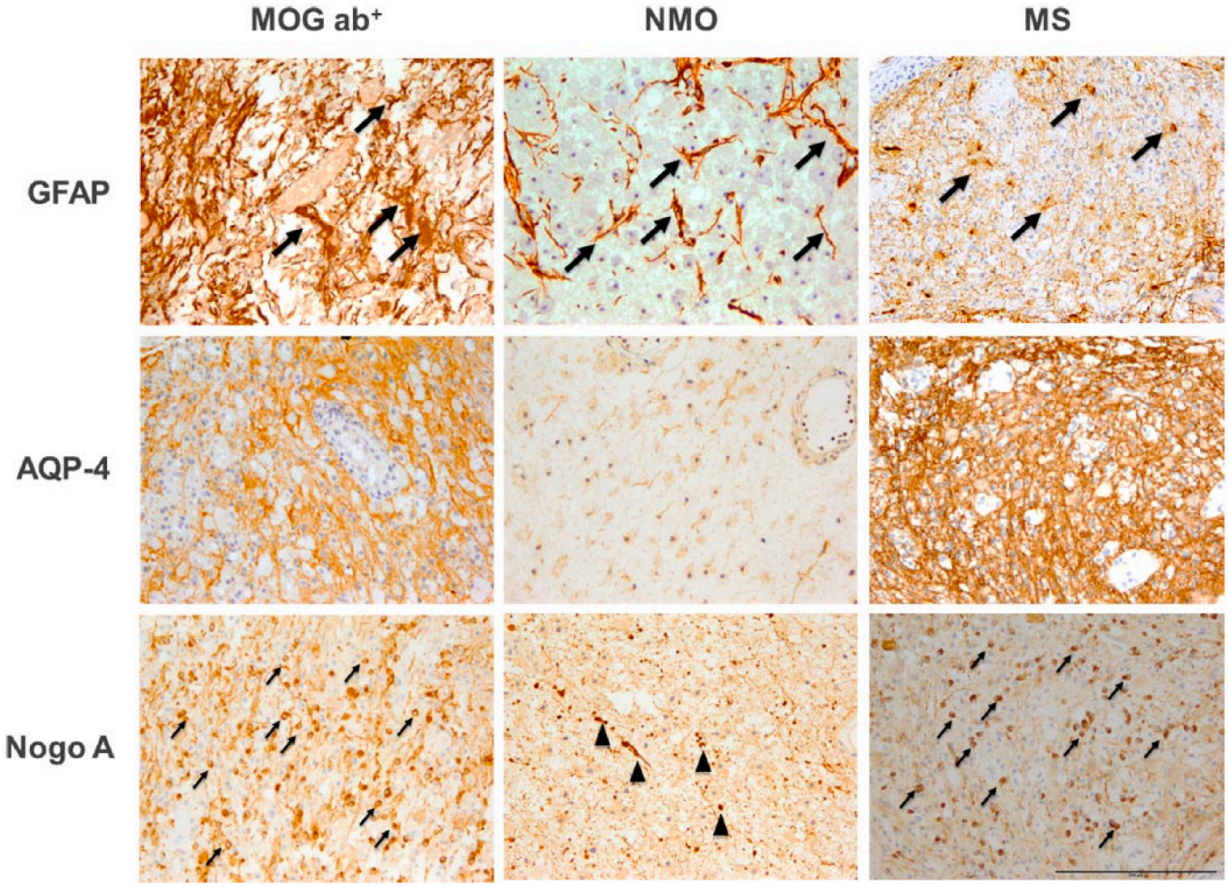






- Spadaro et al., 2018 https://doi.org/10.1002/ana.25291

Histopathology



Confluent demyelination

Complement deposits in macrophages (MS pattern II)

Cortical demyelination

No oligodencrocytes loss

No astrocytopathy

No AQP4 loss

No MOG loss

- Weber et al., 2018 https://doi.org/10.1177/1756286418762083

Histological comparison

	MOG ab+							NMO	MS
	König *et al.*[96] 1 case, 2 biopsies	Spadaro *et al.*[103] 1 case	Jarius *et al.*[97] 1 case	Wang *et al.*[98] 1 case	Körtvelyessy *et al.*[99] Case 1	Körtvelyessy *et al.*[99] Case 2	Di Pauli *et al.*[104] 1 case, MOG and AQP-4 ab+		
Confluent demyelination	+	+	+	+	+	+	+	+	+
Inflammation (T cells, macrophages)	+	+	+	+	+	+	+	+	+
Eosinophils	–	–	–	n.r.	–	–	n.r.	+	–
Complement in macrophages	+	+	+	n.r.	+	+	– Lesions were not actively demyelinating	–	+ In pattern II, not in pattern I or pattern III lesions
Perivascular complement deposition	–	–	–	n.r.	–	-	+ Optic chiasm, not cerebrum	+	–
Astrocytopathy	–	–	–	–	–	–	+ Optic chiasm, not cerebrum	+	–
AQP-4 loss	–	–	–	n.r.	–	–	+ Optic chiasm, not cerebrum	+	–
Oligodendrocyte loss	–	–	–	n.r.	+	-	–	+	–

Weber et al., 2018 https://doi.org/10.1177/1756286418762083

Controversies

Controversies in Multiple Sclerosis

MOG-antibody-associated disease is different from MS and NMOSD and should be considered as a distinct disease entity – Yes

Maria Isabel Leite and Douglas Kazutoshi Sato

Multiple Sclerosis Journal

2020, Vol. 26(3) 272–274

DOI: 10.1177/1352458519868796

MOG-antibody-associated disease is different from MS and NMO and should be considered as a distinct disease entity – No

Alvaro Cobo-Calvo and Romain Marignier

Recommandation on MOG antibody testing

Clinical syndrome suggestive of inflammatory demyelinating CNS disease **plus** radiological aspect compatible with demyelination

Monophasic or relapsing

Bilateral ON / Recurrent ON
LETM / STM
ADEM / Brainstem

And **at least one** of the following …

Clinical Findings

* Simultaneous bilateral Acute ON
* High ON frequency or disease mainly characterized by recurrent ON
* Severe visual deficit during or after acute ON
* Severe or frequent myelitis
*Permanent sphincter or erectile dysfunction after myelitis
* CS dependence

Fundoscopy

Papilledema!!
Papillitis
Optic disc swelling

CSF findings

No OCB
CSF WCC >50/ul
No MRZ reaction

CNS MRI findings

* LETM
* LE spinal cord atrophy
* LE optic nerve lesion
* Perioptic Gd enhancement
* Normal supratentorial brain MRI
* Brain MRI abnormal but no periventricular ovoid lesions and no Dawson's finger or juxtacortical U fiber lesion
* Large confluent T2 brain lesions (fluffy ADEM like)

Histopathology

Primary demyelination + intralesional complement deposits
(MS II pattern)

- Jarius et al., 2018 https://doi.org/10.1186/s12974-018-1144-2

Therapeutic approach: anti AQP4-IgG

As early as possible

Acute treatment

IV Corticosteroids (5 days, 1g/day)
± Plasma exchanges (6 to 9)

Preventive therapies

Azathioprine/Mycophenolate
Rituximab
Ciclophosphamide/Mitoxantrone

Potentially harmful

IFN
Natalizumab
Fingolimod
Alemtuzumab
Glatiramer acetate

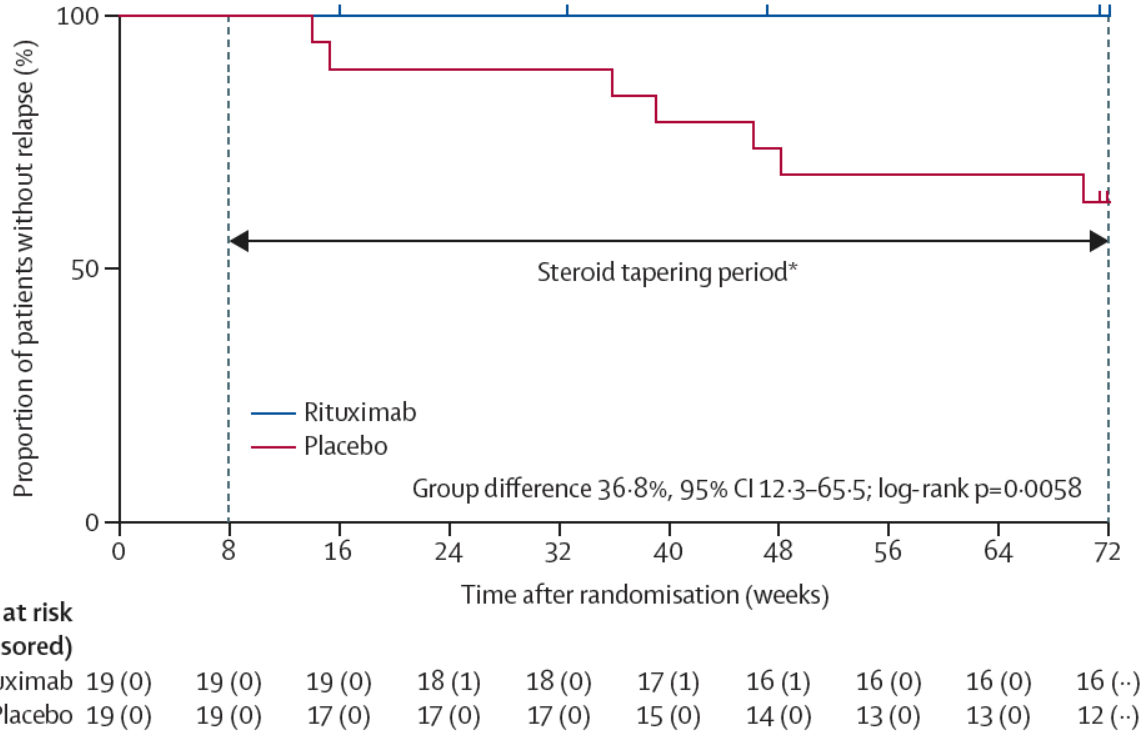
Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial

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

38 AQP4+ patients

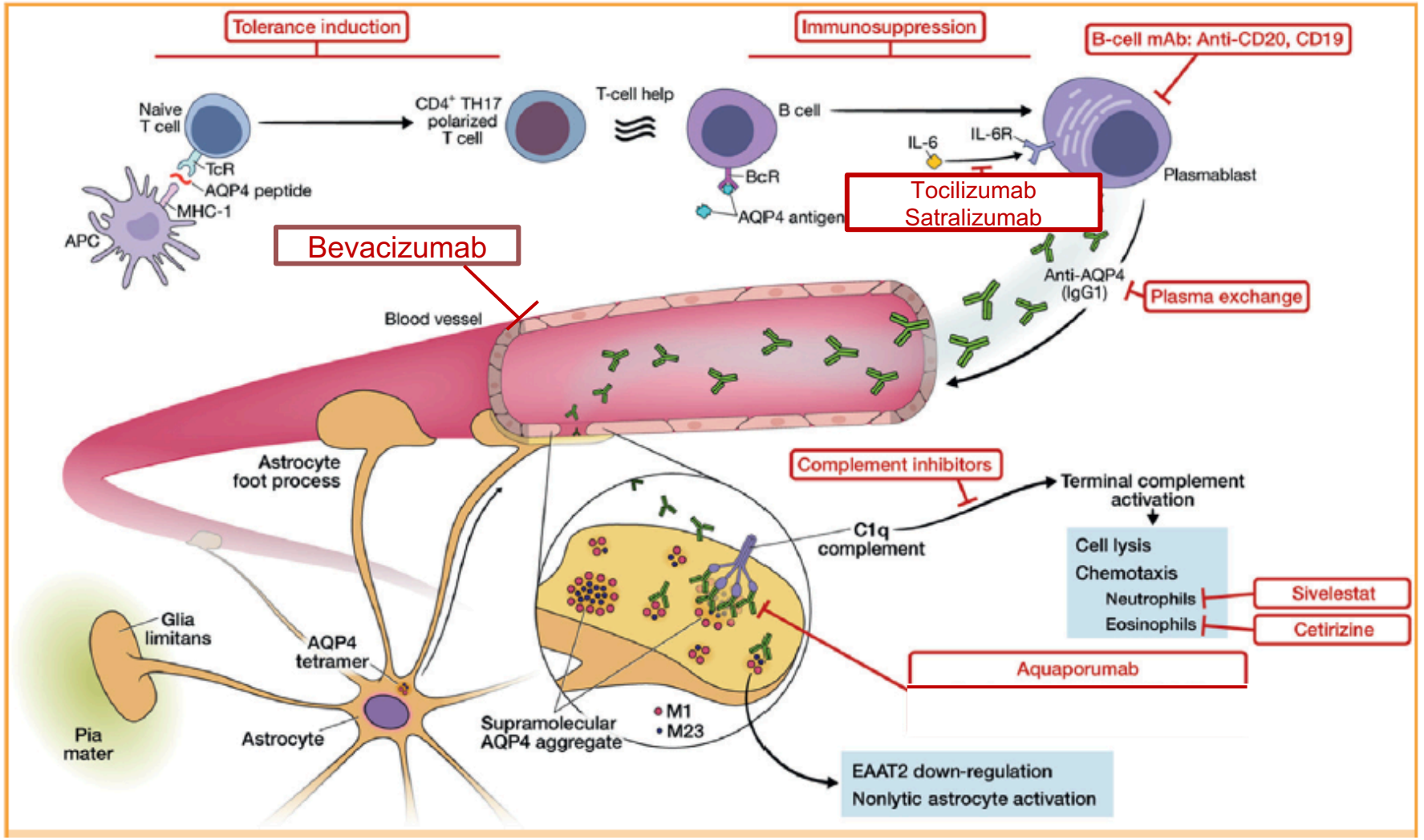
Rituximab (375 mg/m^2) IV every week for 4 weeks

then 6-month interval dosing (1000 mg every 2 weeks)



- Tahara et al., 2020 https://doi.org/10.1016/S1474-4422(20)30066

Therapeutic approach: anti AQP4-IgG



- Weinshenker et al. 2017 https://doi.org/10.1016/j.mayocp.2016.12.014

Therapeutic approach: anti AQP4-IgG

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder

Sean J. Pittock, M.D., Achim Berthele, M.D., Kazuo Fujihara, M.D., Ho Jin Kim, M.D., Ph.D., Michael Levy, M.D., Ph.D., Jacqueline Palace, D.M., Ichiro Nakashima, M.D., Murat Terzi, M.D., Natalia Totolyan, M.D., Shanthi Viswanathan, M.R.C.P., Kai-Chen Wang, M.D., Ph.D., Amy Pace, Sc.D., et al.

ORIGINAL ARTICLE

Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder

Takashi Yamamura, M.D., Ph.D., Ingo Kleiter, M.D., Kazuo Fujihara, M.D., Ph.D., Jacqueline Palace, D.M., Benjamin Greenberg, M.D., Beata Zakrzewska-Pniewska, M.D., Ph.D., Francesco Patti, M.D., Ching-Piao Tsai, M.D., Albert Saiz, M.D., Ph.D., Hayato Yamazaki, M.D., Ph.D., Yuichi Kawata, Ph.D., Padraig Wright, M.D., Ph.D., et al.

Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial

*Bruce A C Cree, Jeffrey L Bennett, Ho Jin Kim, Brian G Weinshenker, Sean J Pittock, Dean M Wingerchuk, Kazuo Fujihara, Friedemann Paul, Gary R Cutter, Romain Marignier, Ari J Green, Orhan Aktas, Hans-Peter Hartung, Fred D Lublin, Jorn Drappa, Gerard Barron, Soraya Madani, John N Ratchford, Dewei She, Daniel Cimbora, Eliezer Katz, on behalf of the N-MOmentum study investigators**

- Eculizumab: MAB against C5
- Inebilizumab: MAB against CD19
- Satralizumab: MAB against IL6

All 3 treatments are highly effective in preventing attacks

In 2/3 studies including AQP4+/AQP4- , effect primarily seen in AQP4+

Therapeutic approach: anti AQP4-IgG

As early as possible

Acute treatment

IV Corticosteroids (5 days, 1g/day)
± Plasma exchanges (6 to 9)

Preventive therapies

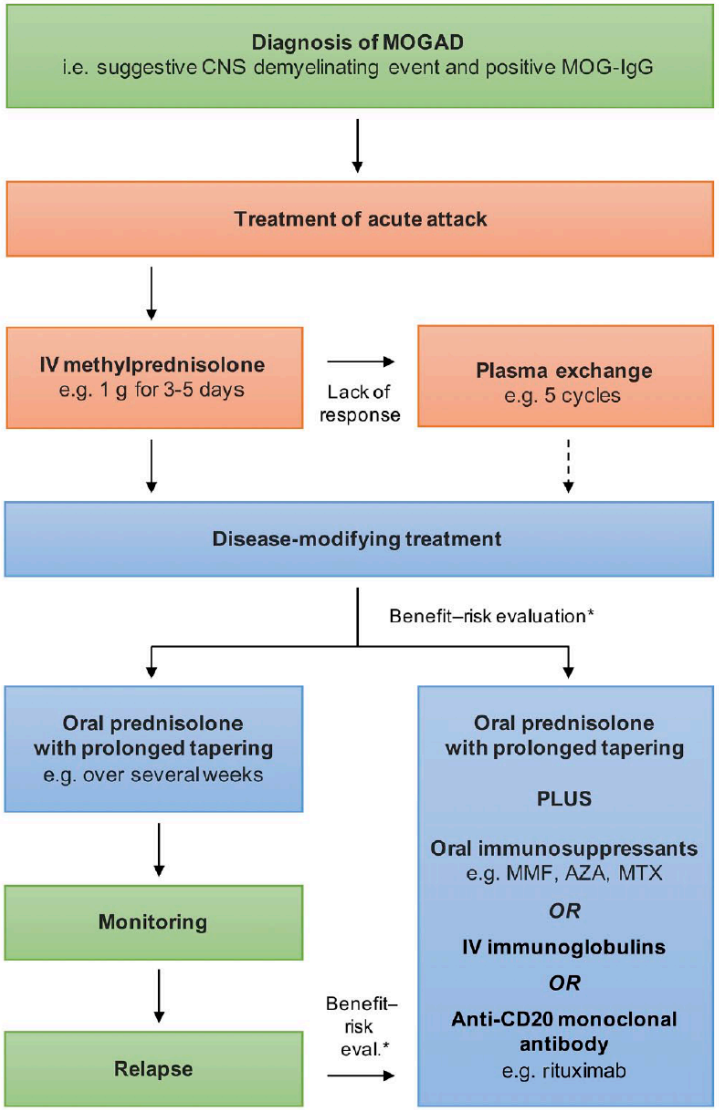
Azathioprine/Mycophenolate
Rituximab
Ciclophosphamide/Mitoxantrone

Potentially harmful

IFN
Natalizumab
Fingolimod
Alemtuzumab
Glatiramer acetate

Eculizumab
Satralizumab
Inebilizumab
Tocilizumab
Aquaporumab
Bevacizumab
C1 inhibitor
…

Therapeutic approach: anti MOG-IgG



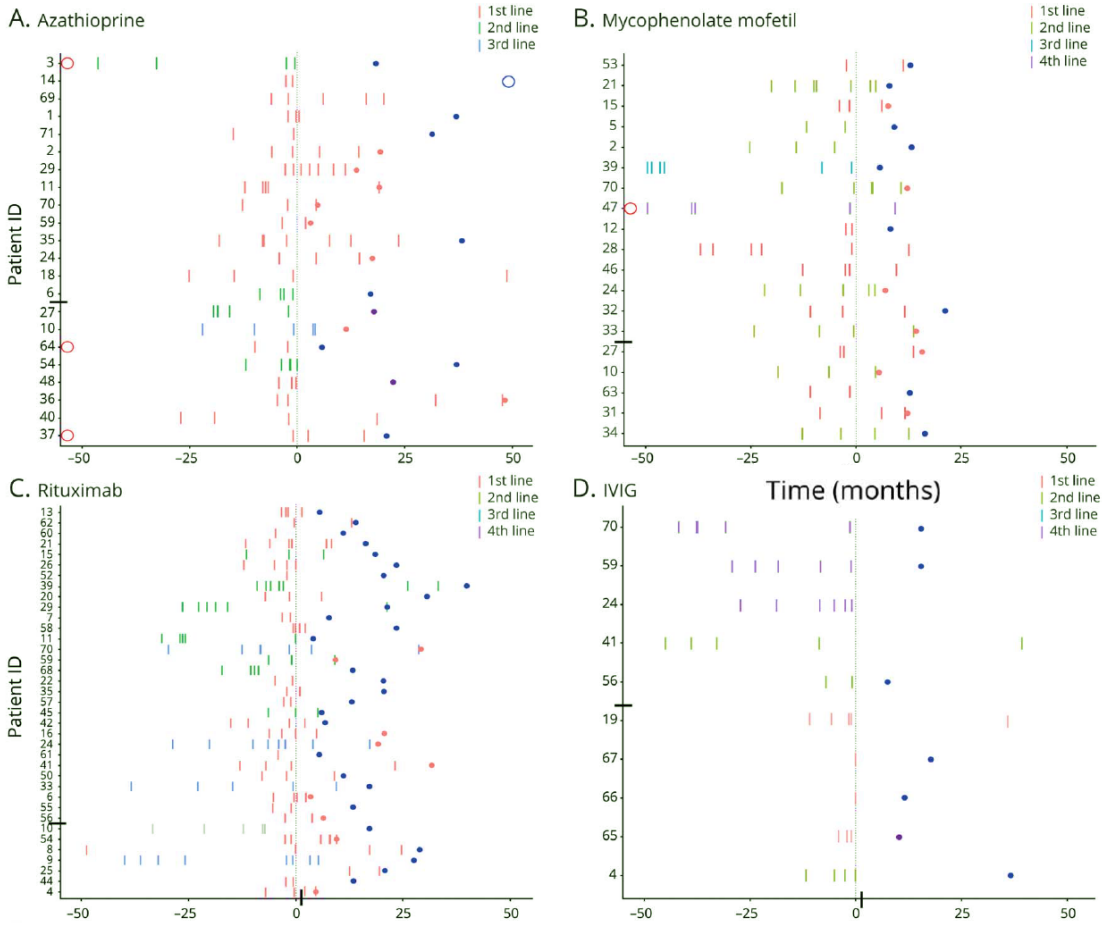
*Benefit–risk evaluation based on prognostic factors for relapse and/or disability:
patient's age, previous disease course, present clinical syndrome or MOG-IgG persistency.

Hegen et al., 2020 https://doi.org/10.1177/1756286420945135

Therapeutic approach: anti MOG-IgG

Maintenance Immunotherapy

Disease activity of patients with MOG-IgG associated disorder on maintenance immunotherapy



Treatment	% of patients with relapse, ARR
MMF	74%, 0.67
Azathioprine	59%, 0.2
Rituximab	61%, 0.2
IVIG	20%, 0

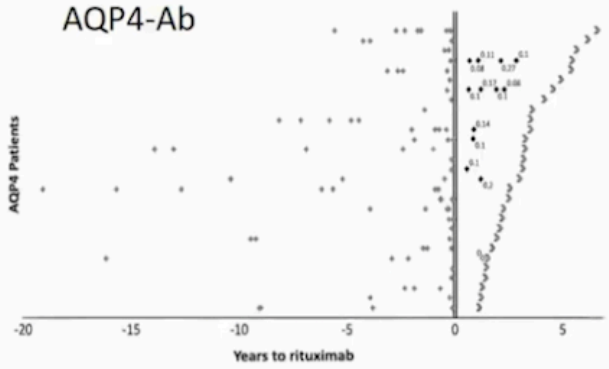
- Chen et al., 2020 https://doi.org/10.1212/WNL.0000000000009758

Therapeutic approach: anti MOG-IgG

29 AQP4-Ab 79% 1st line

24% relapsed mean FU 38 months

AQP4-Ab

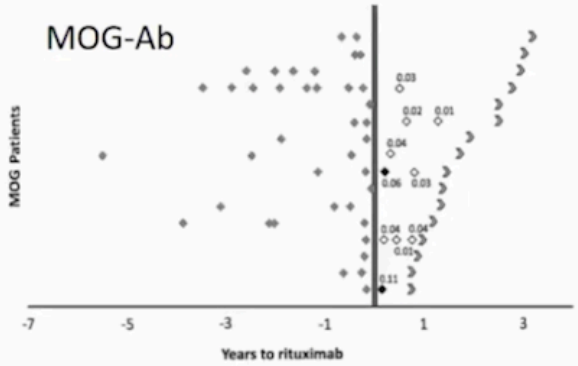


92% relapses CD27+ > 0.05% (12/13)

16 MOG-Ab (5 monophasic) 69% 1st line

38% relapsed mean FU 19 months

MOG-Ab

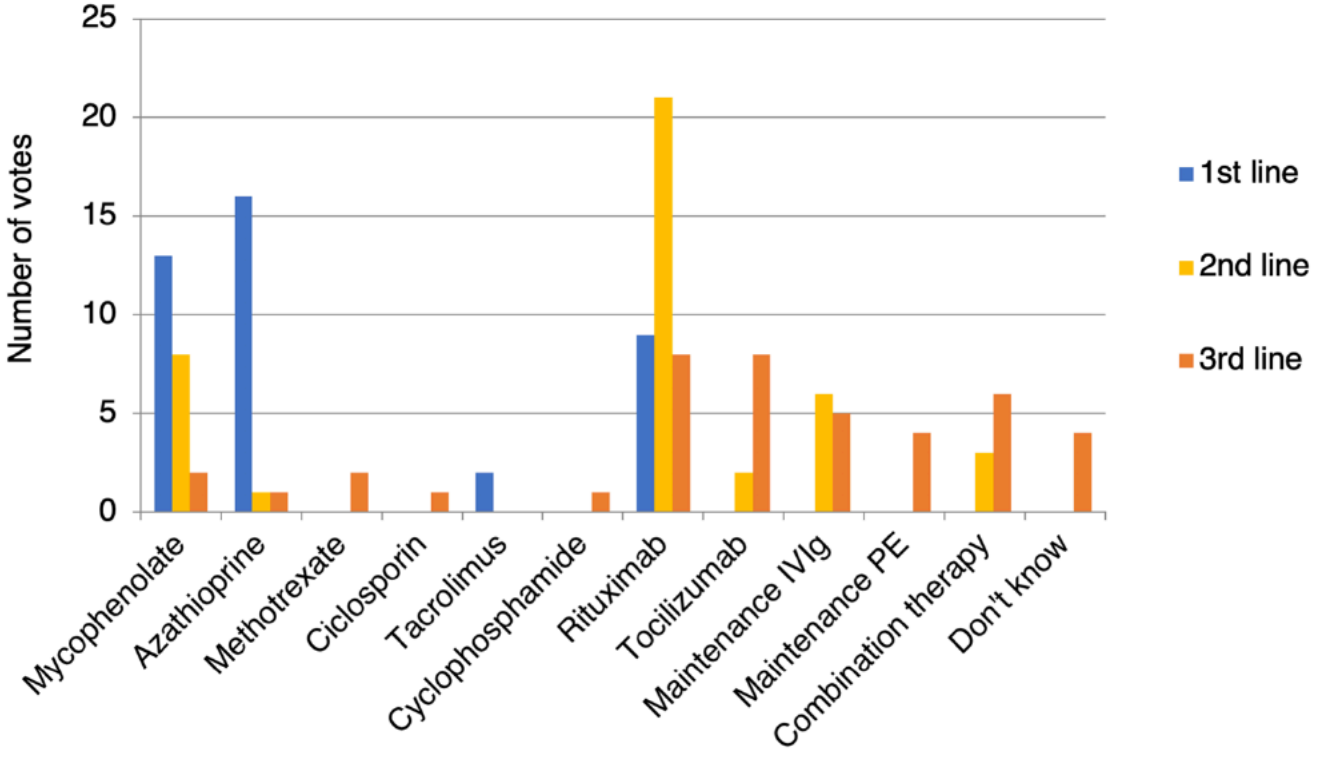


20% relapses CD27+ > 0.05% (2/10)

Durozard et al., 2020 https://doi.org/10.1002/ana.25648

Therapeutic approach: anti MOG-IgG

International survey on treatment of MOGAD by neurologist (52 experts)



Whittham et al., 2020 https://doi.org/10.1007/s00415-020-10026-y

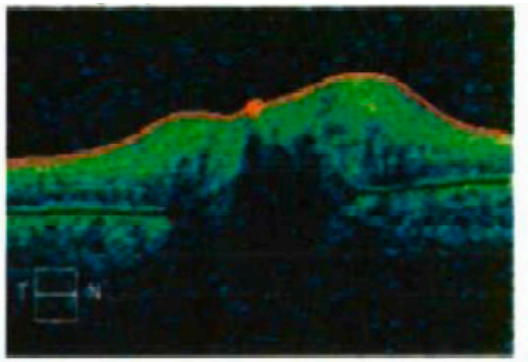
Case report 1

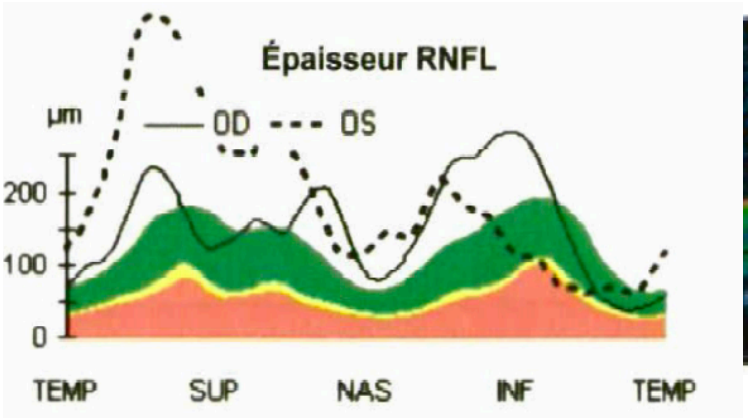
- Male, 29 year-old /Caucasian
- No particular medical or family history
- May 2017

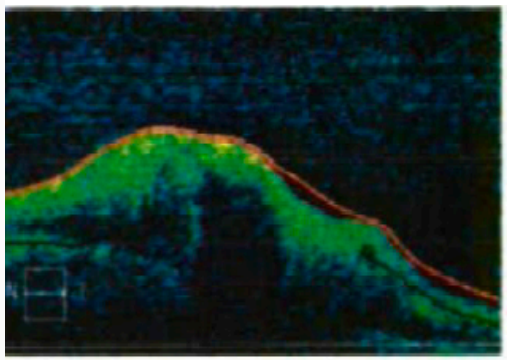
  - severe headache and bilateral periorbital pain
  - nausea and vomiting
  - rapidly followed by a severe bilateral visual loss (left eye > right eye)

- Neurological and general examination: normal

- Brain scan: normal
- Lumbar puncture with ICP measurement: **23 cmH_20**
- Ophthalmologic examination: - bilateral papillary edema (Left >> Right)
  - severe visual loss (VA: **R** 3/10 and **L** NLP)







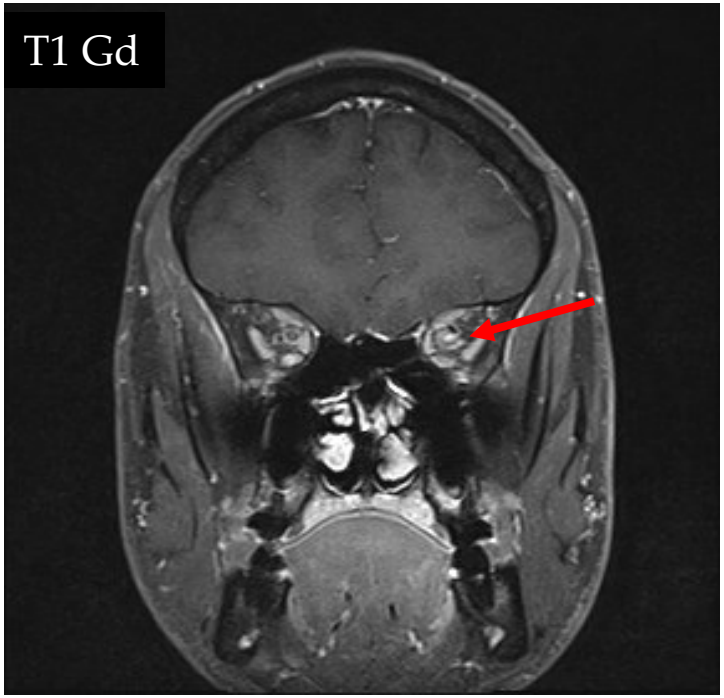
- Treatment with **acetazolamid** 500 mg t.i.d

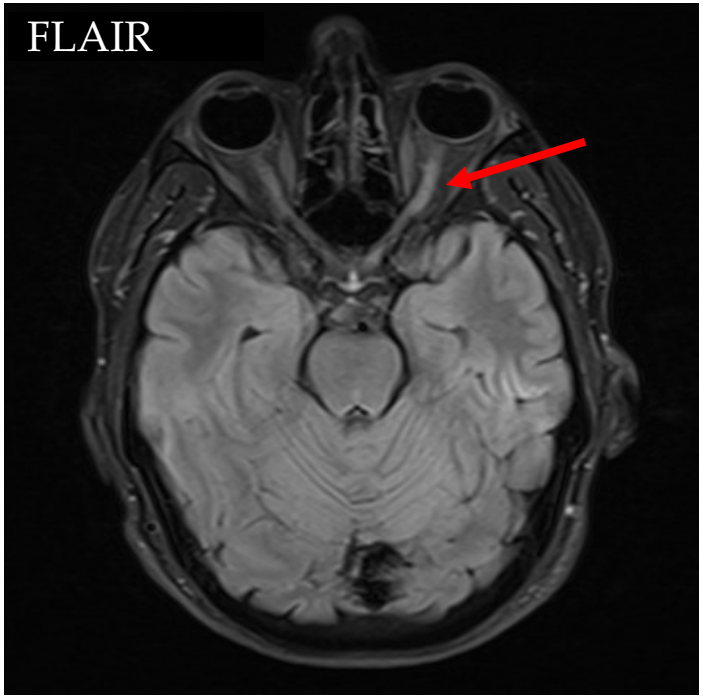
  … **but** worsening of right VA to LP within 24 hours

- Decision to start **IV steroids** despite rather high ICP (1g/d 5 days) followed by oral steroids with tapering regimen (8 mg/d)

➔ rapid improvement of right VA to 10/10 but no change in the left eye

- Brain MRI





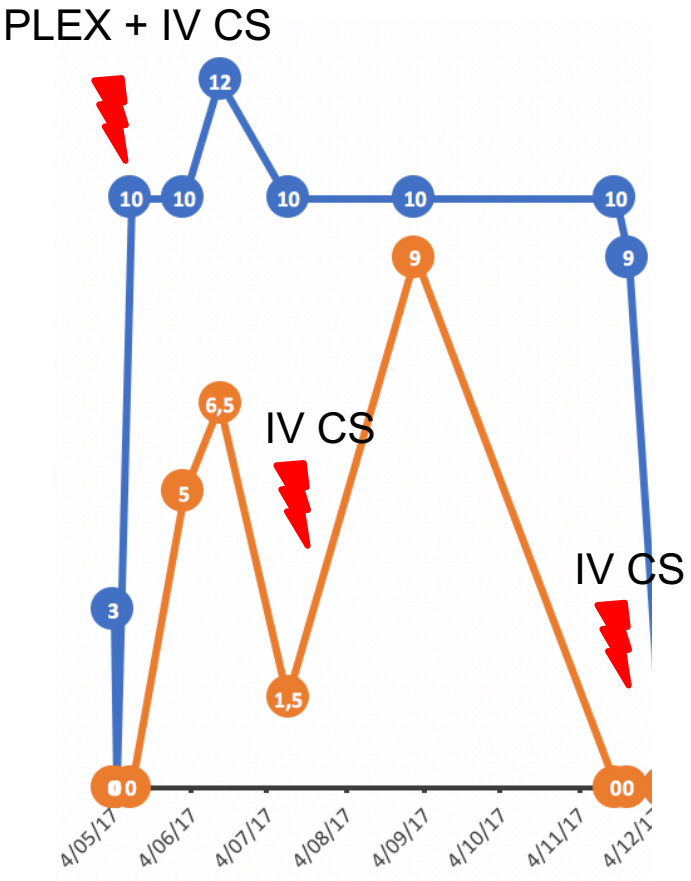
Severe bilateral optic neuritis with papillary oedema and sensibility to steroïds

- **CSF**: 3 WBC, normal protein and glucose levels, a few OCB, negative culture and common PCRs
- **Serum**: ANA 1/160 (no characterisation), RF - , ACE - , normal lymphocytic typing
- **Negative serology** for CMV, EBV, VZV, HBV, HCV, Borrelia, HIV, Syphilis, Toxoplasma and Bartonella; Negative Quantiferon°
- Spinal cord MRI: normal (including conus)
- PET CT: normal
- **MOG/AQP4 IgG testing?**

How to treat ?

- IV corticosteroids (1g/d 5 days)
- PLEX + oral prednisolone tapering + oral IS

Visual acuity



VA left eye

VA right eye

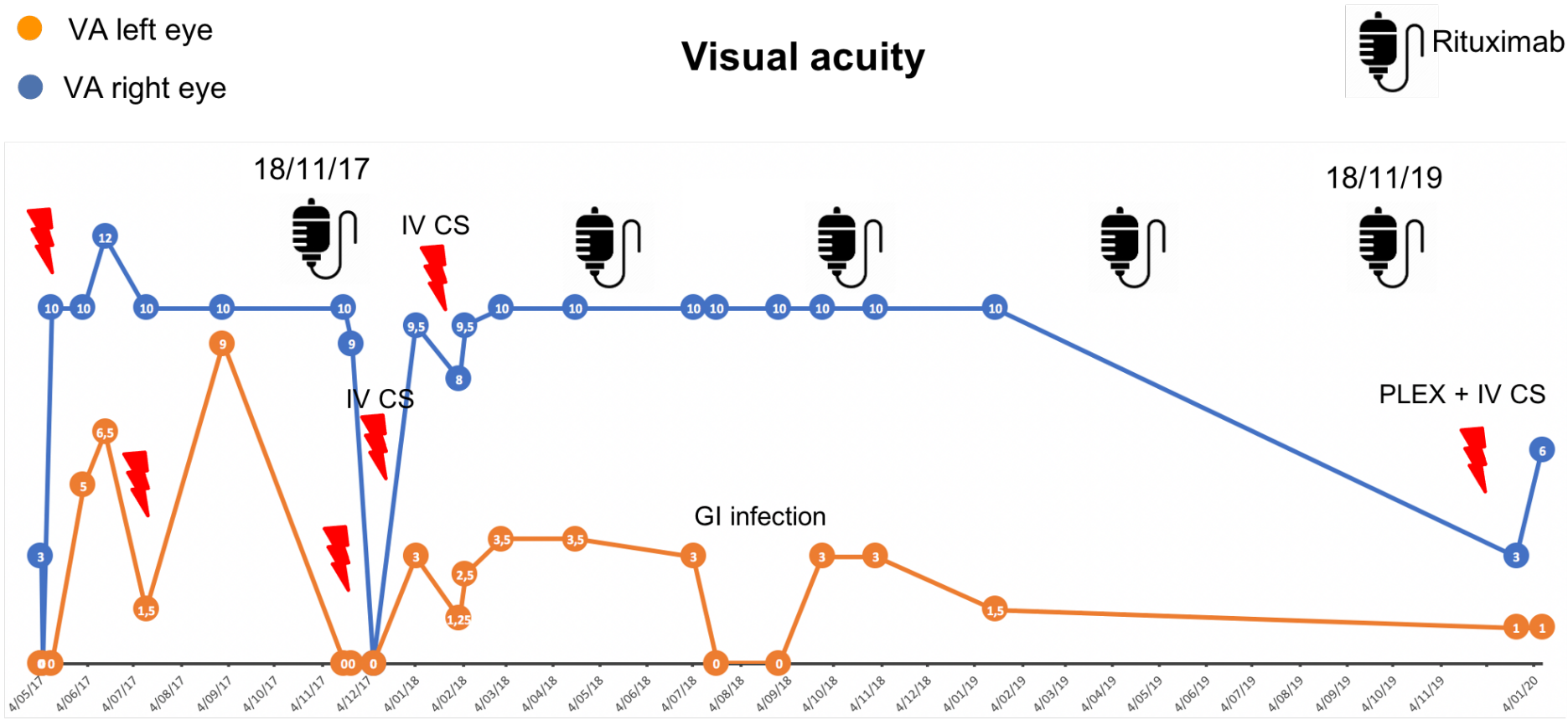
ON relapse

From May to November 2017

2 relapses of left ON despite

- Mycophenolate mofetil 1g b.i.d
- Oral prednisolone from 4 to 8 mg/d

Each relapse occurs after steroids tapering or interruption


VA left eye
VA right eye
Visual acuity
Rituximab
18/11/17
IV CS
IV CS
18/11/19
PLEX + IV CS
GI infection
4/05/17
4/06/17
4/07/17
4/08/17
4/09/17
4/10/17
4/11/17
4/12/17
4/01/18
4/02/18
4/03/18
4/04/18
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4/04/19
4/05/19
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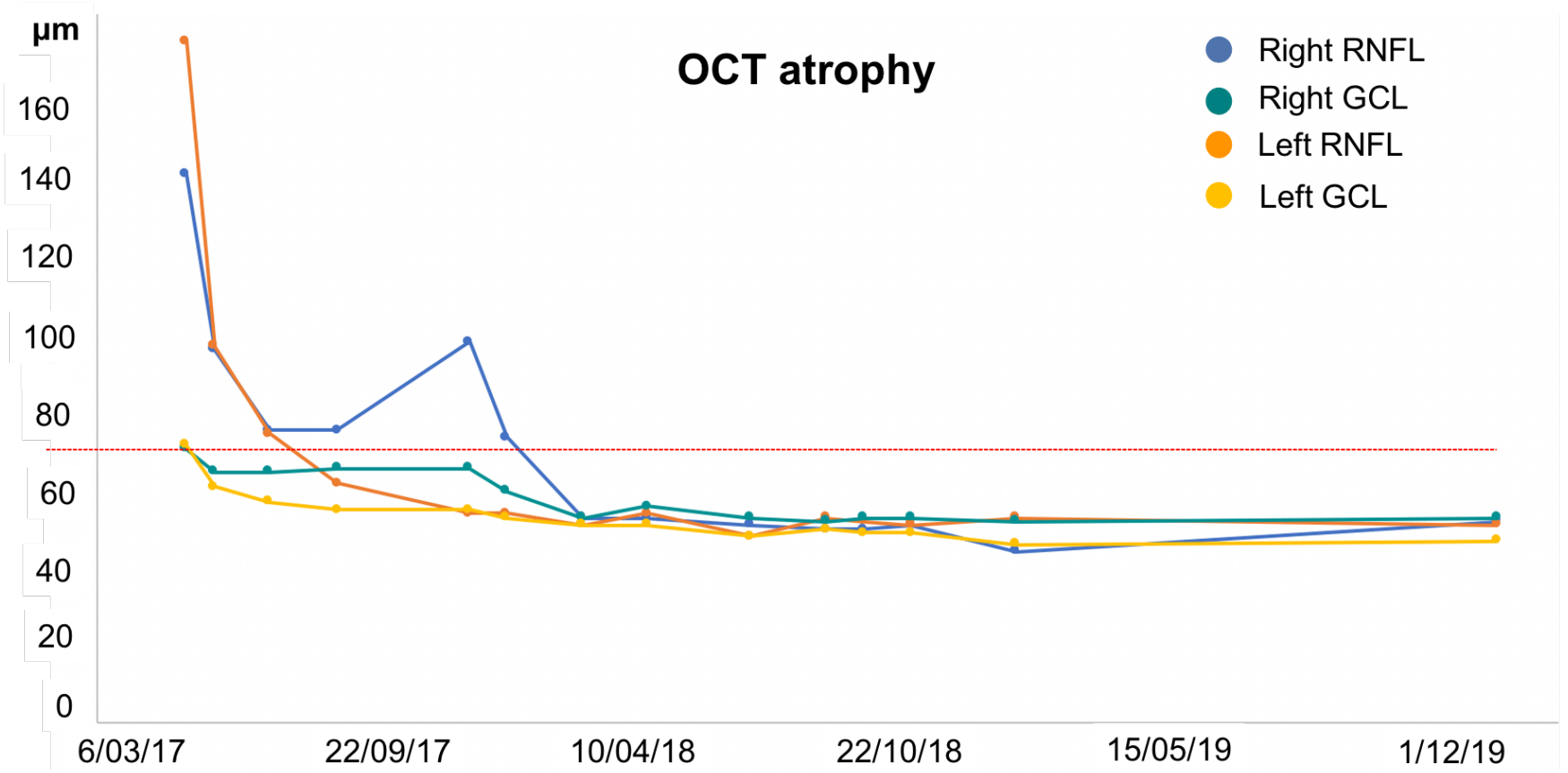
4/10/19
4/11/19
4/01/20

MOG IgG+


OCT atrophy
µm
160
140
120
100
80
60
40
20
0
6/03/17
22/09/17
10/04/18
22/10/18
15/05/19
1/12/19
Right RNFL
Right GCL
Left RNFL
Left GCL

From November 2017 to December 2019 … while treated with Rituximab

- At least 3 optic neuritis relapses : 2 in the right eye, 1 bilateral

I

  - Despite 4-8 mg prednisolone daily
  - Despite circulating B CD19+ were uncountable

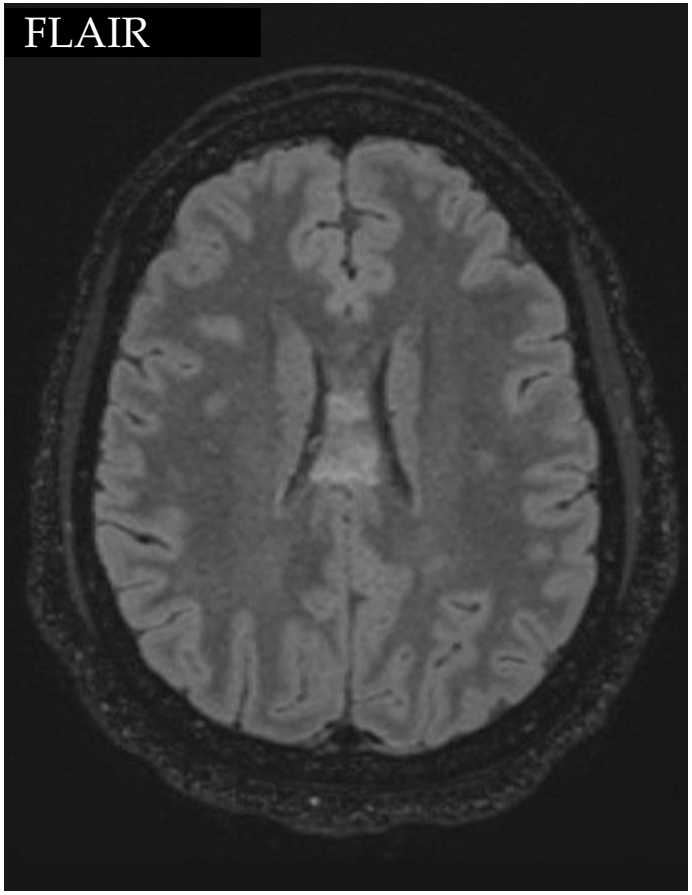
- Significant bilateral OCT atrophy (RNFL and GCL)
- Yearly brain and spinal cord MRI still unremarkable
- MOG IgG1 still positive …

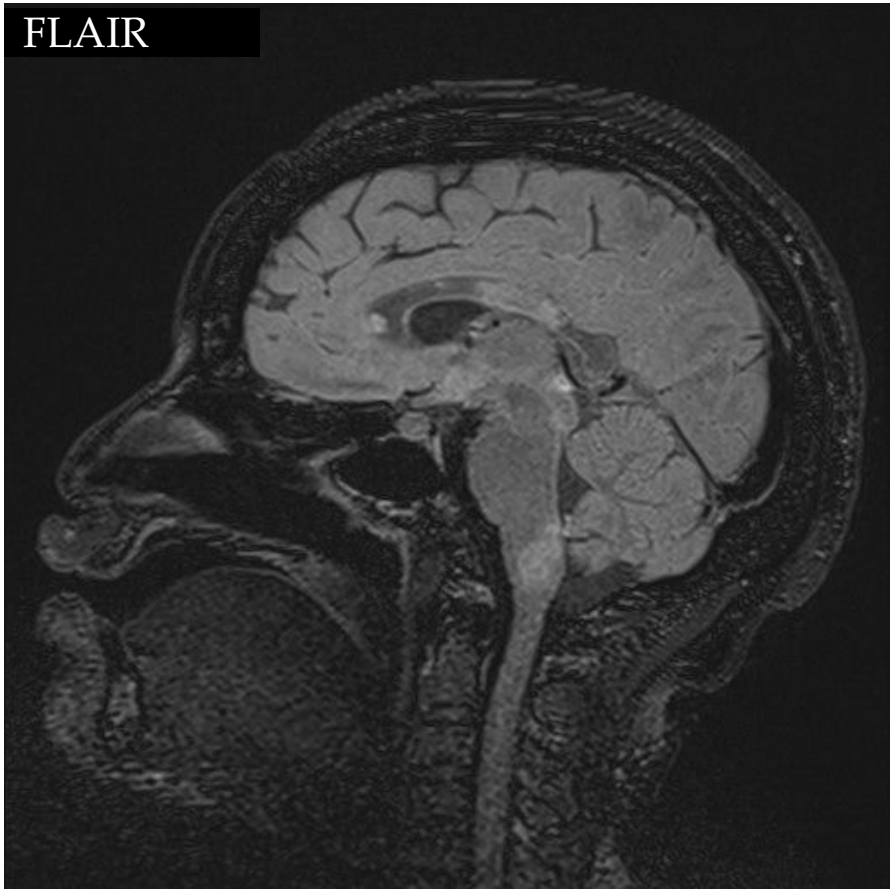
Case report 2

- Female, 26 year-old /African
- No particular medical or family history (minor beta thalassemia)
- January 2021
  - intractable hiccups and vomiting for a week with diffuse abdominal pain
  - pyrexia
  - mesenteric cystic lymphangioma
  - pulmonary embolism

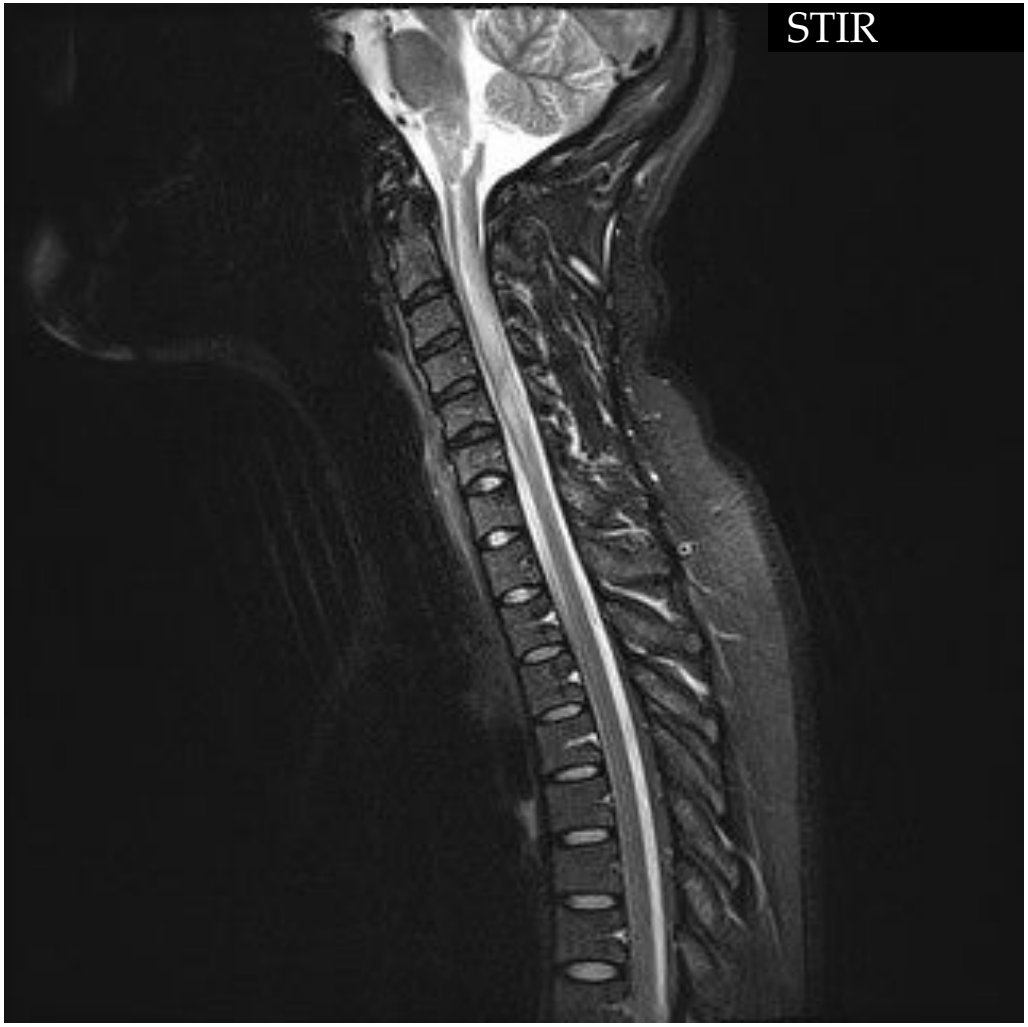
- CSF analysis: 198 WBC (lymphocytes), normal protein and glucose levels, no OCB, negative culture and common PCRs
- AAN SSA + 1/320

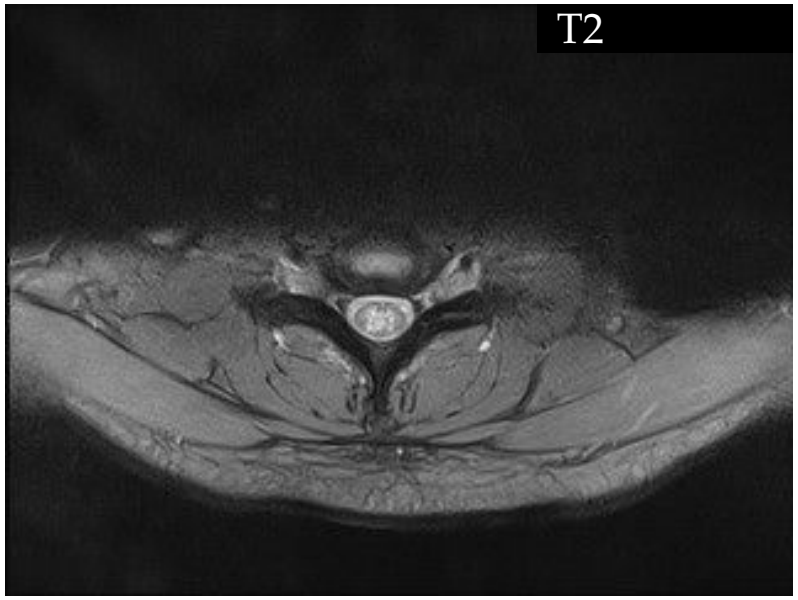
- Brain MRI (8/03/21)





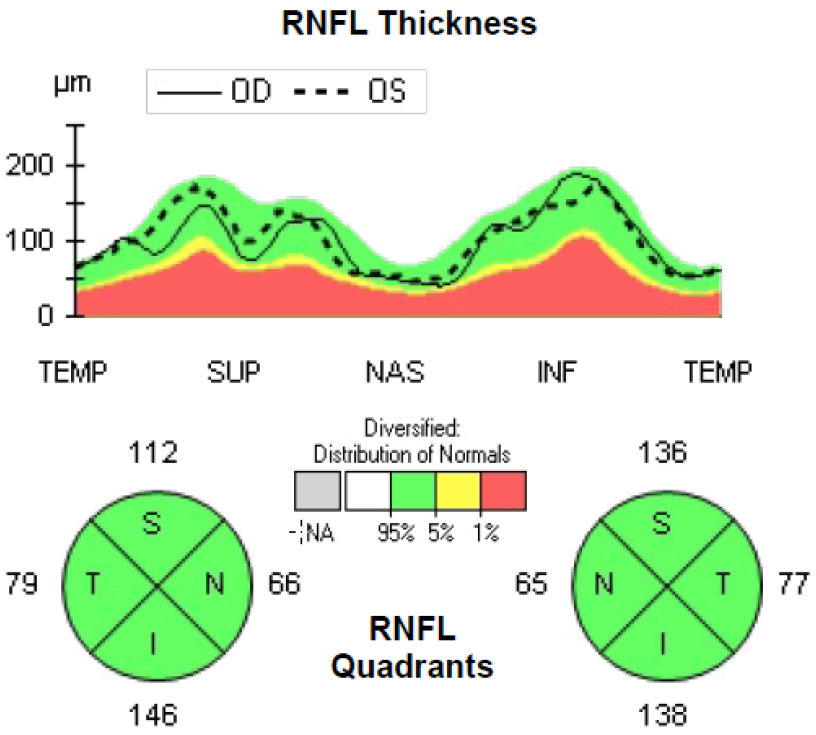
- She developped a right upper limb paresia (distal> proximal)

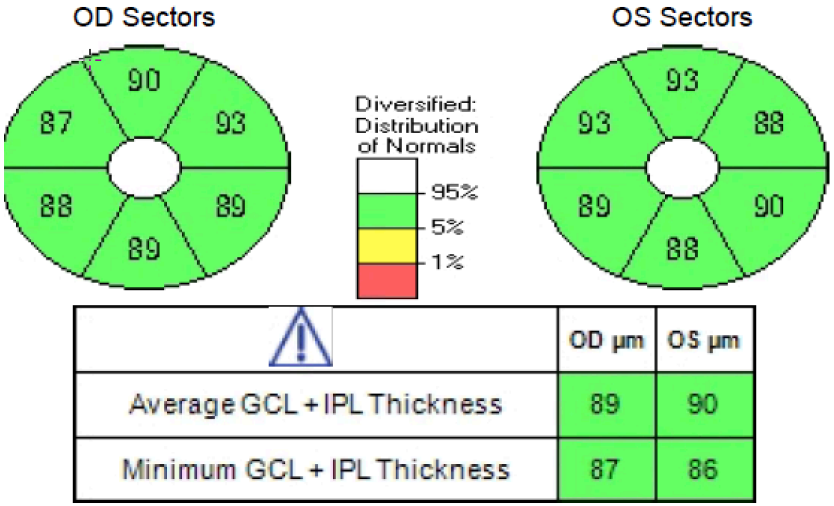


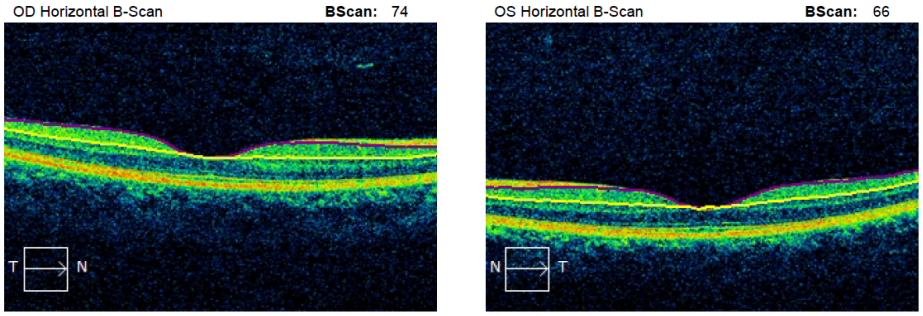


AQP4 IgG+

- Normal ophthalmologic examination







How to treat ?

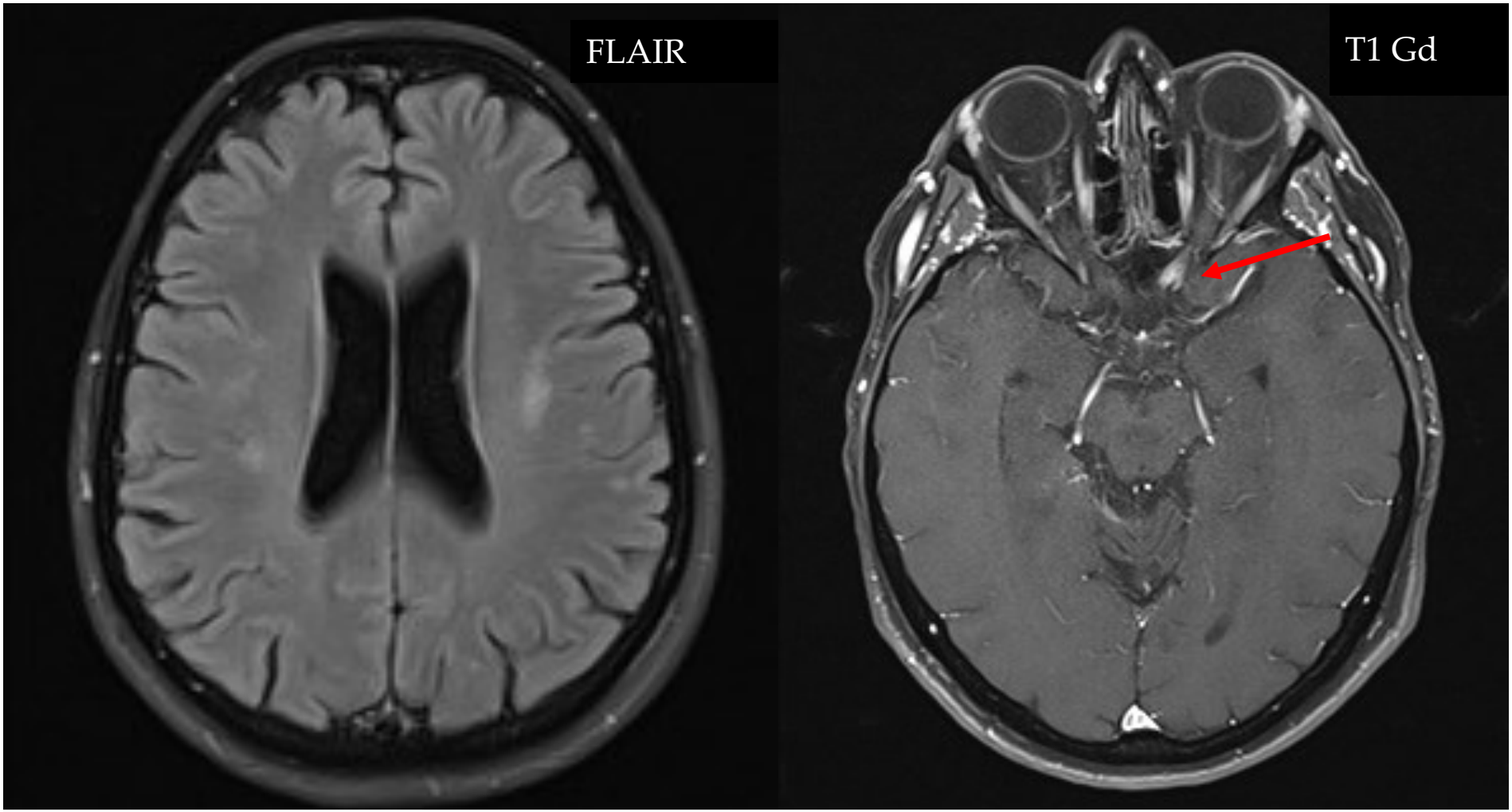
- 9 PLEX
- IV corticosteroids (10 days 1g/d)
- Rituximab: Week 1 and 2: 375 mg/m^2 ➔ Covid19 ➔ 1g

Case report 3

- Female, 62 year-old /Caucasian
- No relevant medical history
- Treatment: cardioaspirin (prophylactic), HRT

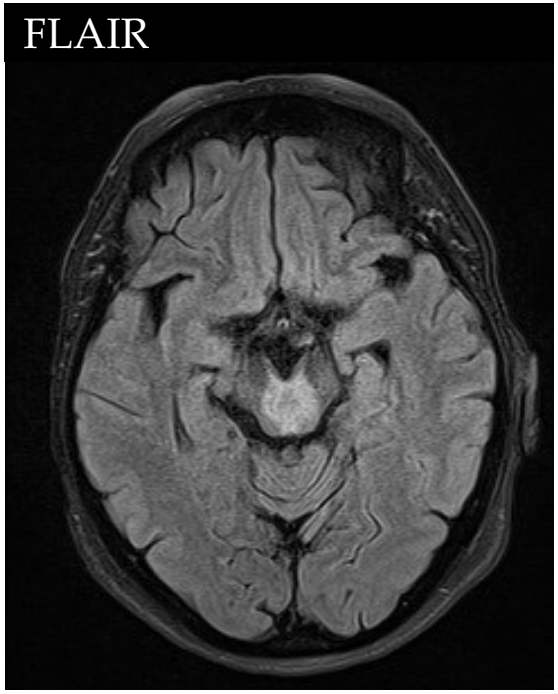
- Severe left VA loss (“hand motion”), normal fundus, no OCT available
- Slow recovery after IV corticosteroids (VA 8,5/10 after 5 months)
- Negative serology and autoimmune screening; AQP4 IgG -
- Normal CSF / No OCB
- PET CT: normal
- Spinal cord MRI: normal

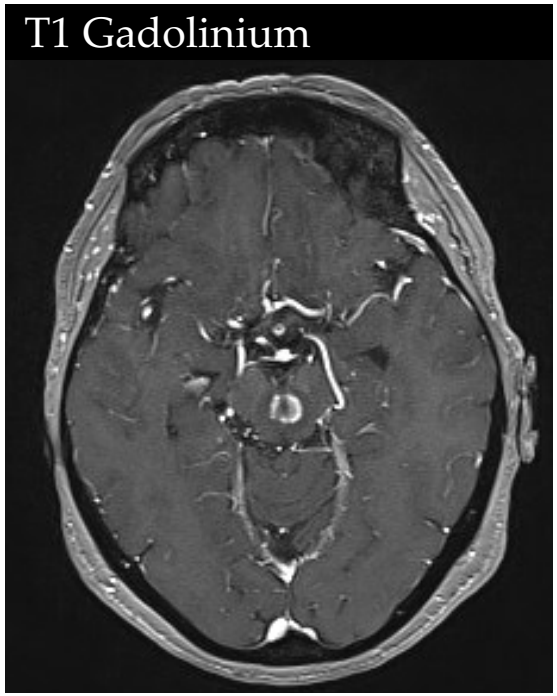
- Brain MRI , June 2012

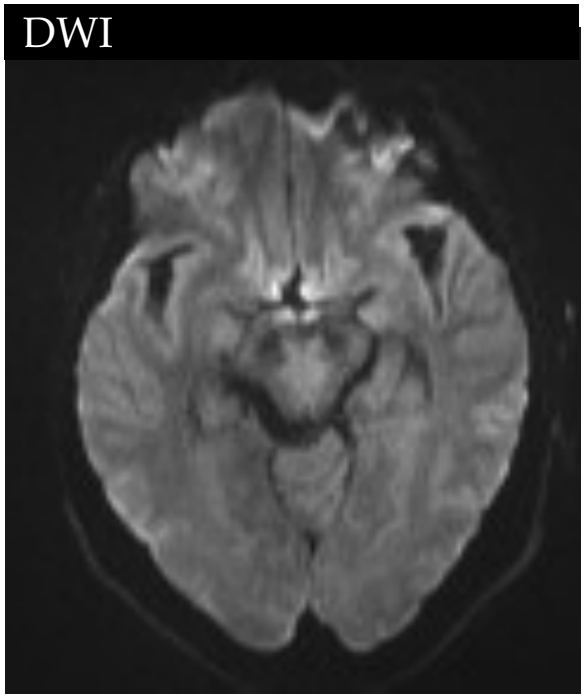


- Painful visual loss in right eye
- VA: **R** 1/10 and **L** 8/10
- Prompt recovery after IV corticosteroids (VA 10/10 R and 8/10 L)
- Negative serology and autoimmune screening (no AQP4 retest)
- PET CT (total body): normal
- Brain MRI : Right ON

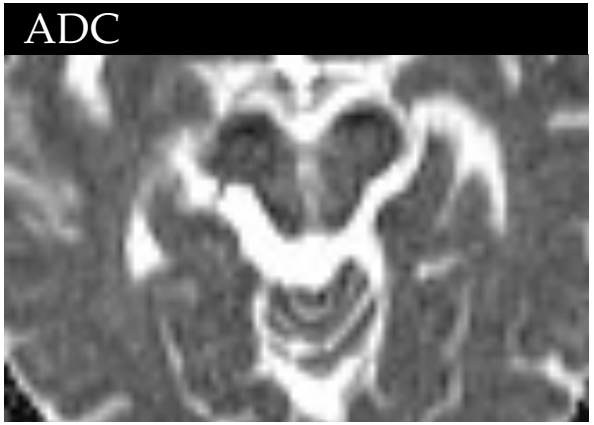
- Diplopia (internuclear ophthalmoplegia) and dysarthria for 4 days
- Cerbellar signs (right upper limb dysmetria and ataxia)
- Dysphagia



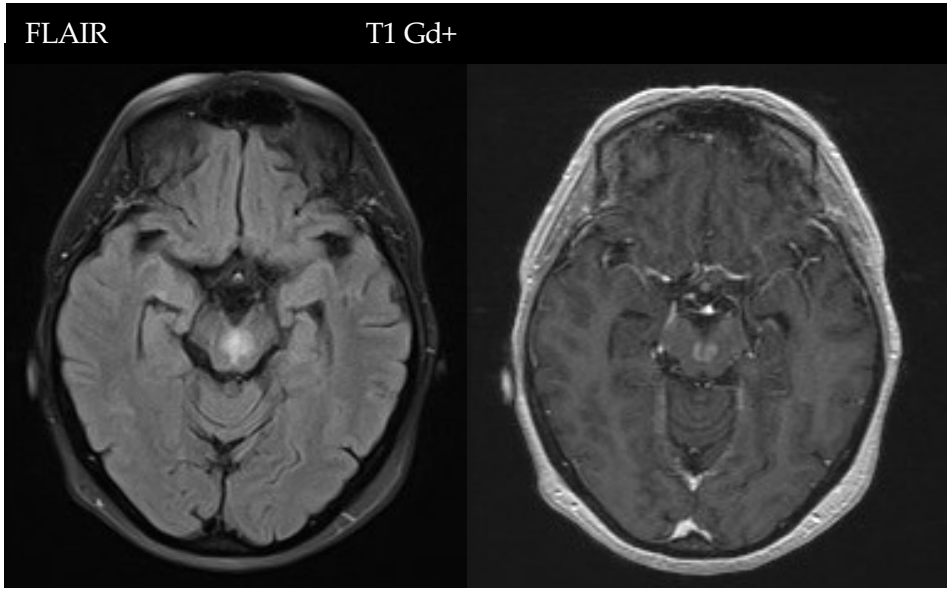




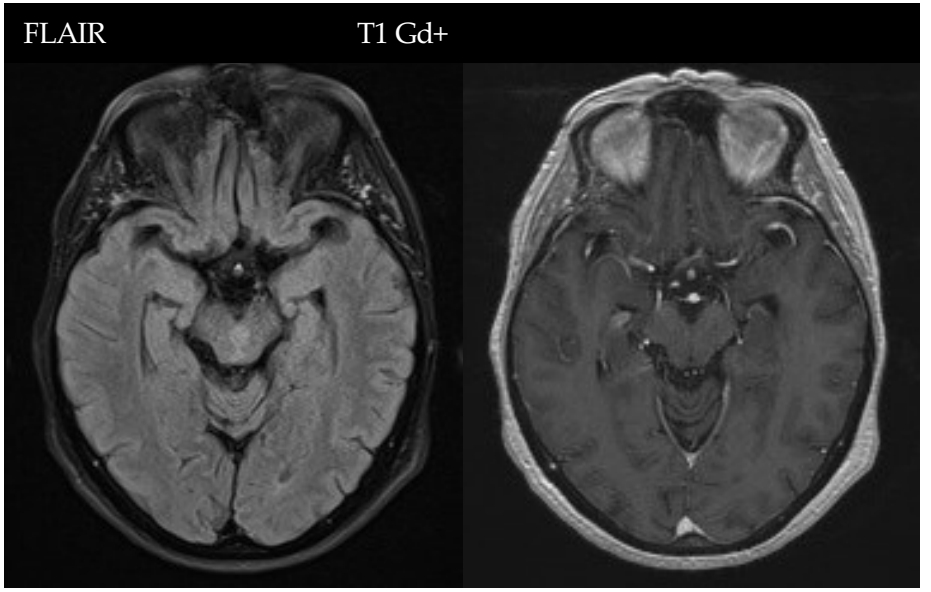
Brain MRI, June 2017



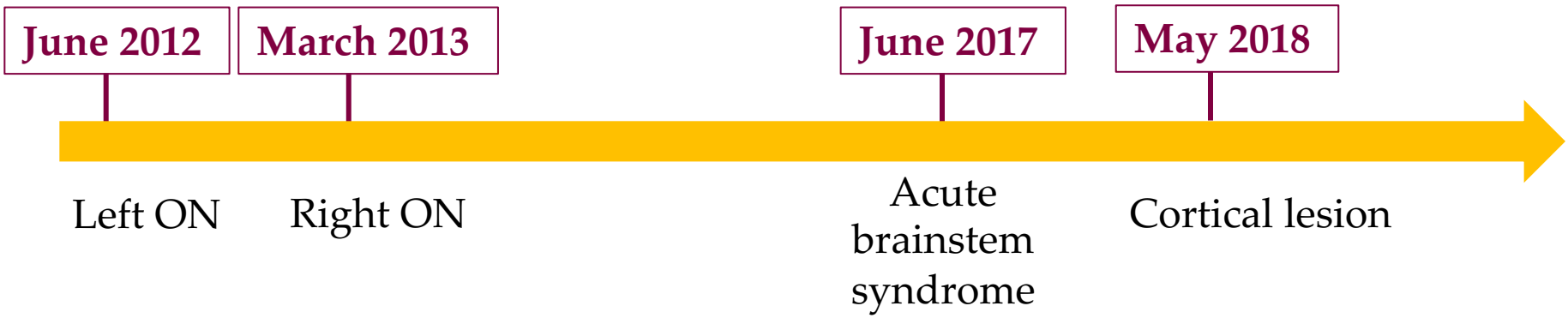
- PET CT (total body): normal
- Cardiac workup (holter and echocardiography): normal
- Spinal cord MRI: normal
- Negative serology and autoimmune screening; AQP4 IgG - ; MOG IgG1 –
- CSF: 0 WBC, protein level 900 mg/L, no OCB, negative PCRs and culture



July 2017 after 10 PLEX

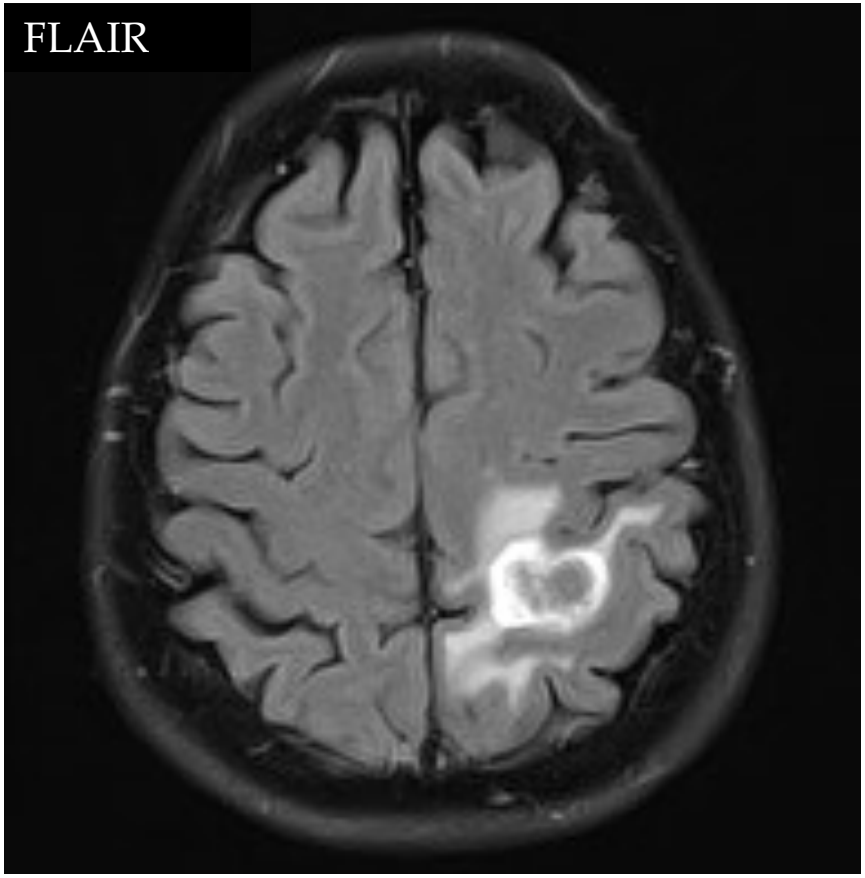


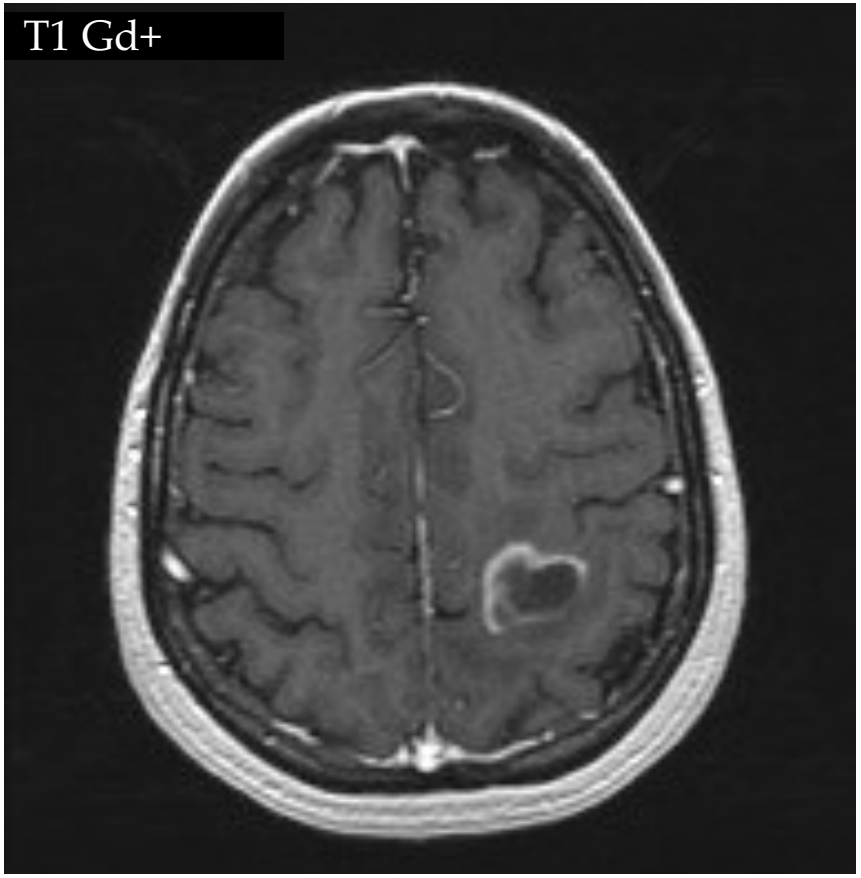
August 2017 mycophenolate mofetil 1g b.i.d initiation



- Right hemiparesis and hemihypoesthesia

Brain MRI, May 2018

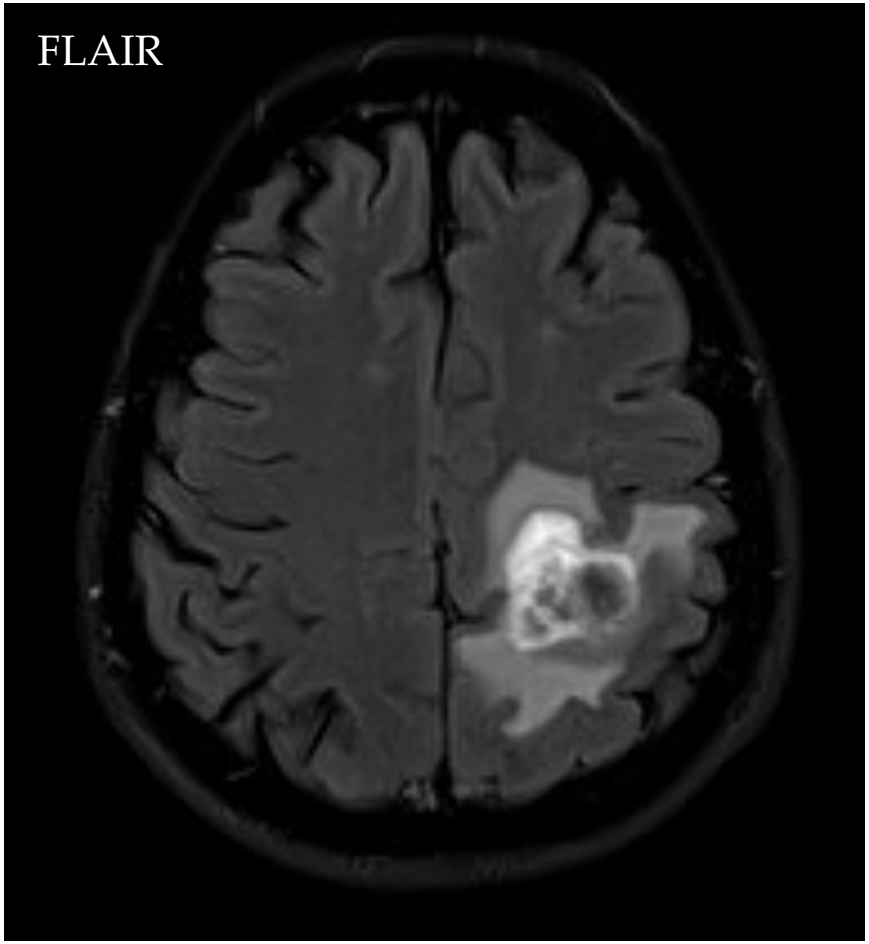


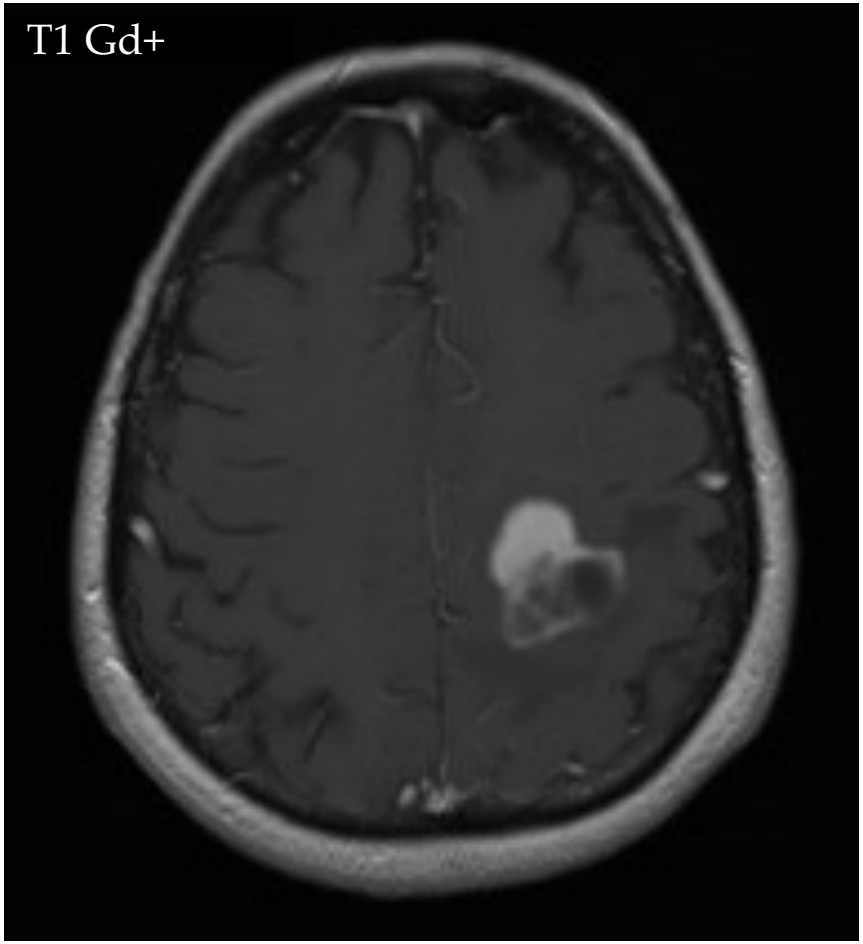


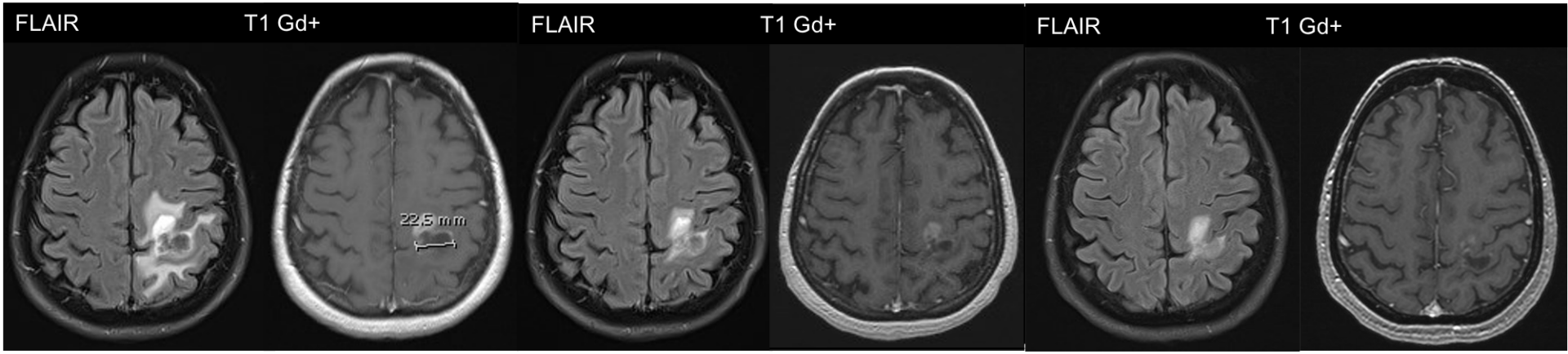
- PET CT (total body): hypermetabolism at the periphery of the parietal lesion
- Spinal cord MRI: normal
- Serology and autoimmune screening negative; AQP4 IgG - ; MOG IgG1 -
- CSF: negative cytology, protein level 750 mg/L, no OCB, negative culture and PCRs
- Prompt recovery of sensorimotor deficit after IV corticosteroids
- Decision to switch from oral IS to Rituximab: first course in June (1000mg two weeks apart, repeated every six months)

… **but** further clinical deterioration

Brain MRI, July 2018



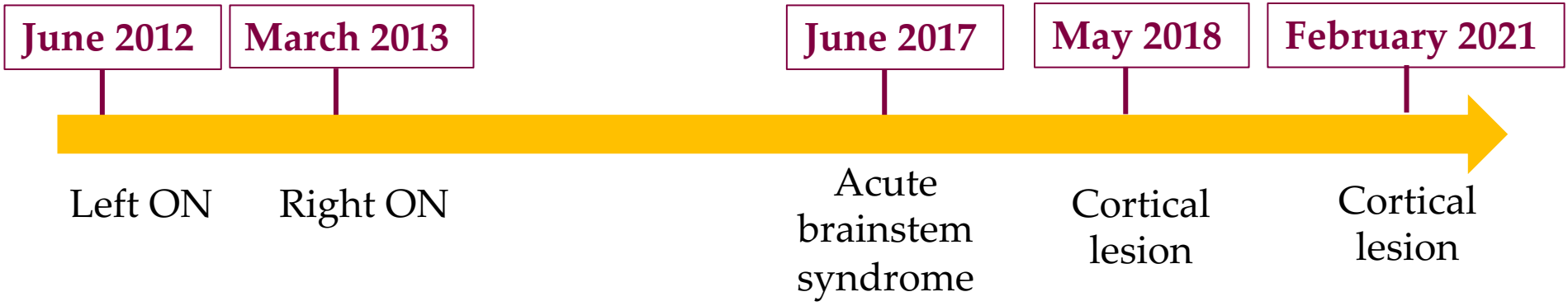




August 2018

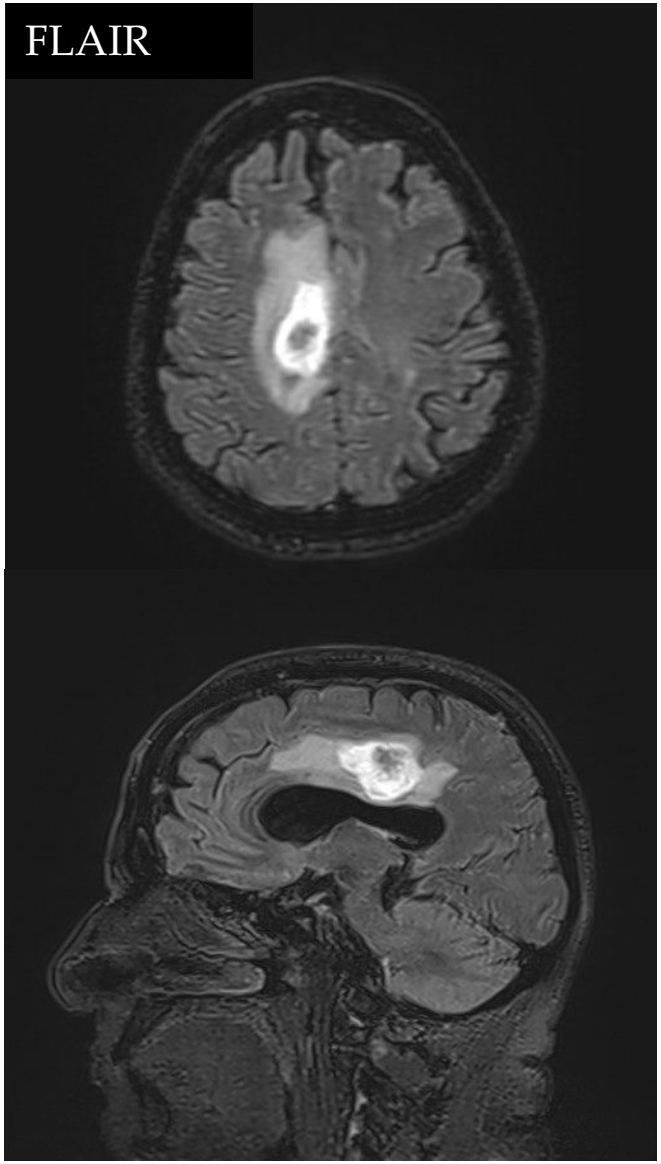
September 2018

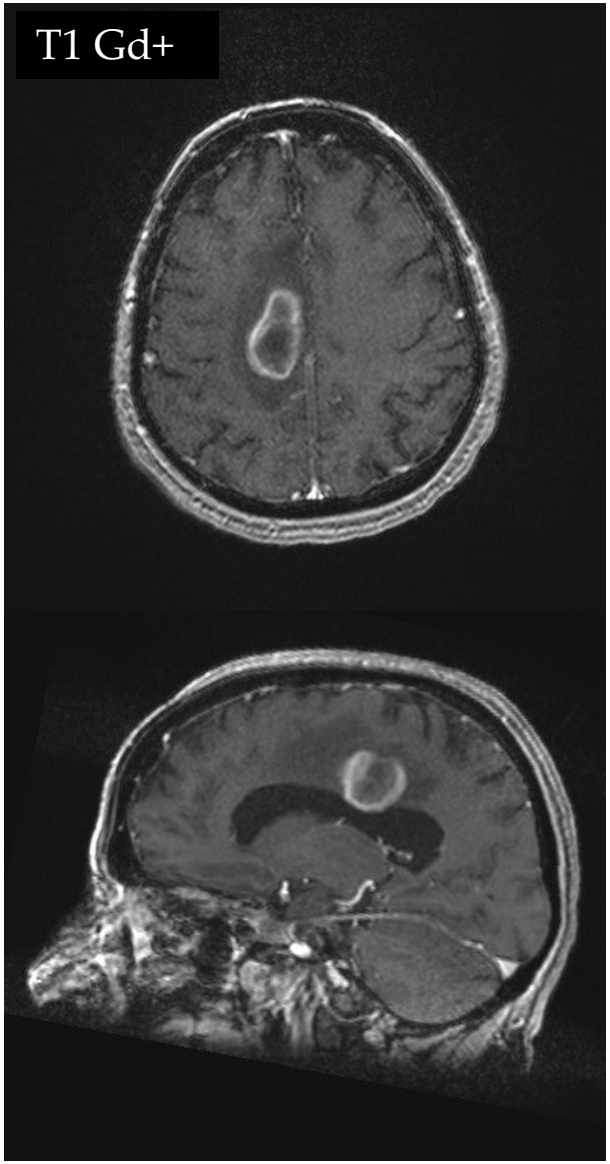
October 2018



- While she is still treated with Rituximab (since May 2018), remaining sensitivo-motor symptoms on right foot subacutly worsened
- Neurological examination shows a severe proprioceptive ataxia

Brain MRI, February 2021





- PET CT (total body): normal
- Spinal cord MRI: normal
- Negative serology and autoimmune screening (AAN 1/80 without characterization); negative antineurones screening; AQP4 IgG - ; MOG IgG-
- CSF: 0 WBC, protein level 1045 mg/L, no OCB, negative PCRs and culture
- Peripheral blood lymphocyte typing: 0% B lymphocyte

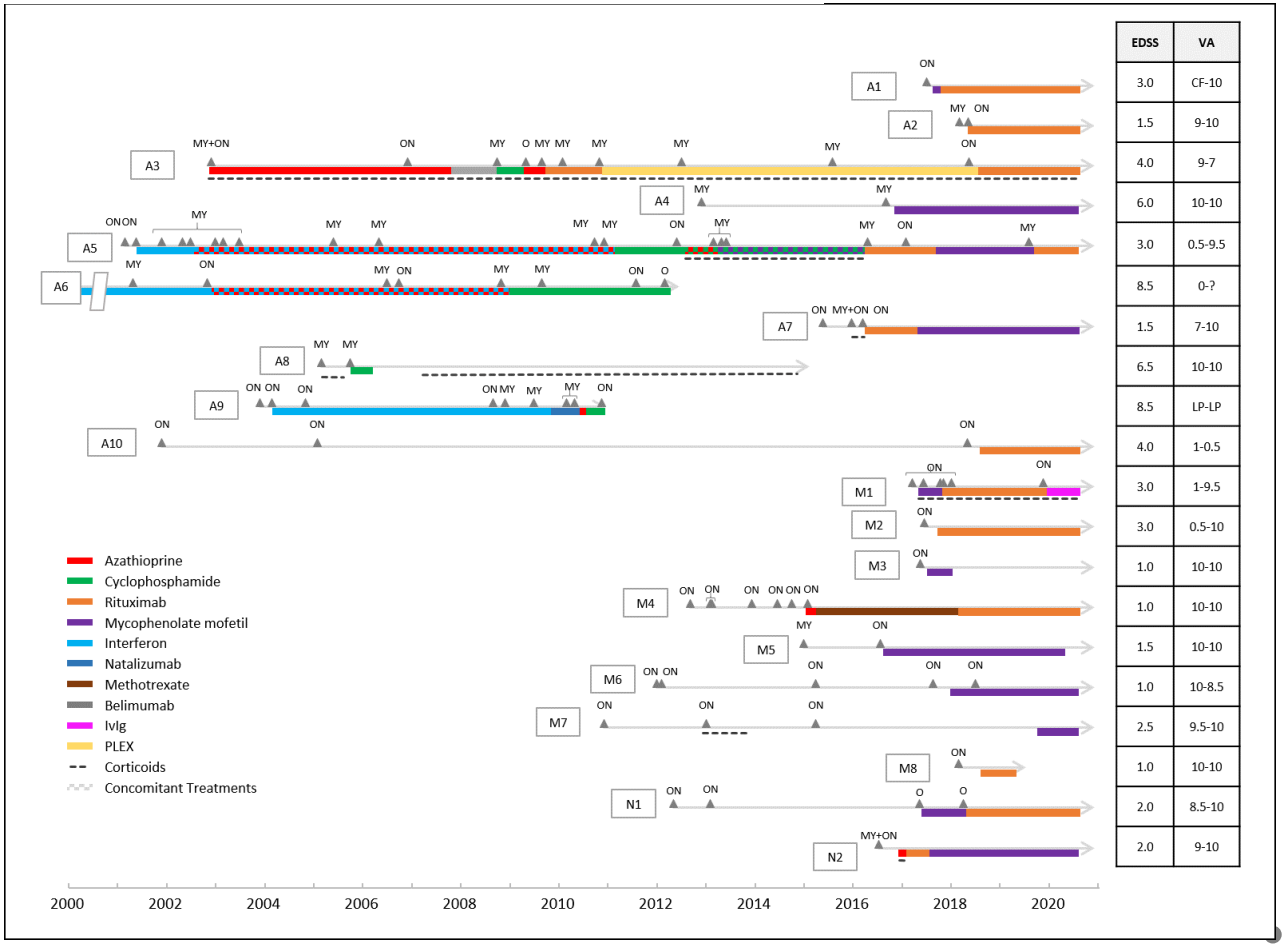
➔ Start Tocilizumab 8 mg/kg every 4 weeks

Acta Neurologica Belgica
https://doi.org/10.1007/s13760-021-01712-3

ORIGINAL ARTICLE

Comparative study of AQP4-NMOSD, MOGAD and seronegative NMOSD: a single-center Belgian cohort

Solène Dauby[1,2] · Dominique Dive[1] · Laurence Lutteri[4] · Cécile Andris[3] · Isabelle Hansen[1] · Pierre Maquet[1,2] · Emilie Lommers[1,2]



EDSS	VA
3.0	CF-10
1.5	9-10
4.0	9-7
6.0	10-10
3.0	0.5-9.5
8.5	0-?
1.5	7-10
6.5	10-10
8.5	LP-LP
4.0	1-0.5
3.0	1-9.5
3.0	0.5-10
1.0	10-10
1.0	10-10
1.5	10-10
1.0	10-8.5
2.5	9.5-10
1.0	10-10
2.0	8.5-10
2.0	9-10

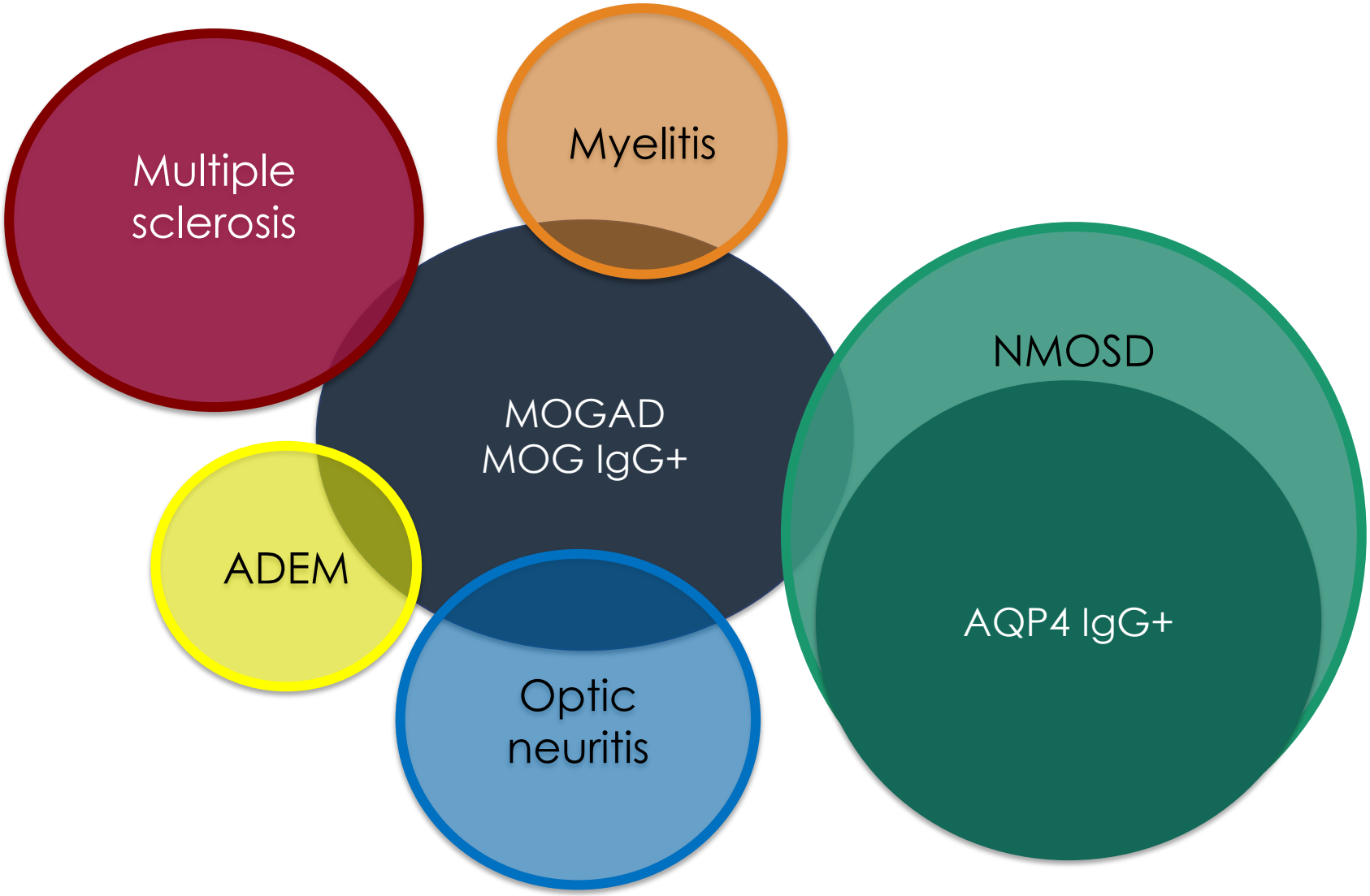
Conclusion

Anti-AQP4 & anti-MOG associated diseases

- Rare diseases
- Different physiopathology
- Common clinical features but MOGAD phenotype is beyond NMOSD
- Relasping/monophasic condition but no progression
- Severe clinical deficit during attack ➔ early and effective treatment to prevent relapse is the key to prevent irreversible disability
- Therapeutic approach: prospective randomized controlled studies needed!
- May fulfill MS diagnostic criteria (especially MOGAD) but atypical presentation!

Be carefull!

Conclusion


Multiple sclerosis
Myelitis
MOGAD
MOG IgG+
NMOSD
AQP4 IgG+
ADEM
Optic neuritis