Autoimmune Water Channelopathies/ neuromyelitis optica (NMO)

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Disclosures

Angela Vincent and the University of Oxford hold patents, and receive royalties and payments for antibody tests (not for NMO)

Angela Vincent has recently received honoraria for lectures from UCB Pharma and Serono

Learning objectives

To recognise the clinical features of neuromyelitis optica and the spectrum of related diseases

To understand the pathophysiology of the disease and the role of aquaporin-4 antibodies

To appreciate some of the treatment possibilities and challenges

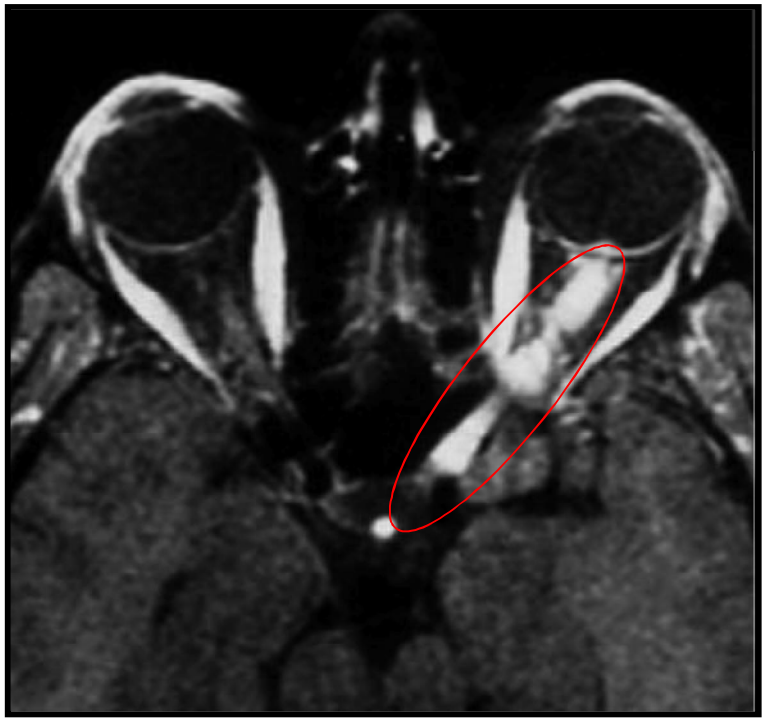
Neuromyelitis optica was traditionally called Devic's disease

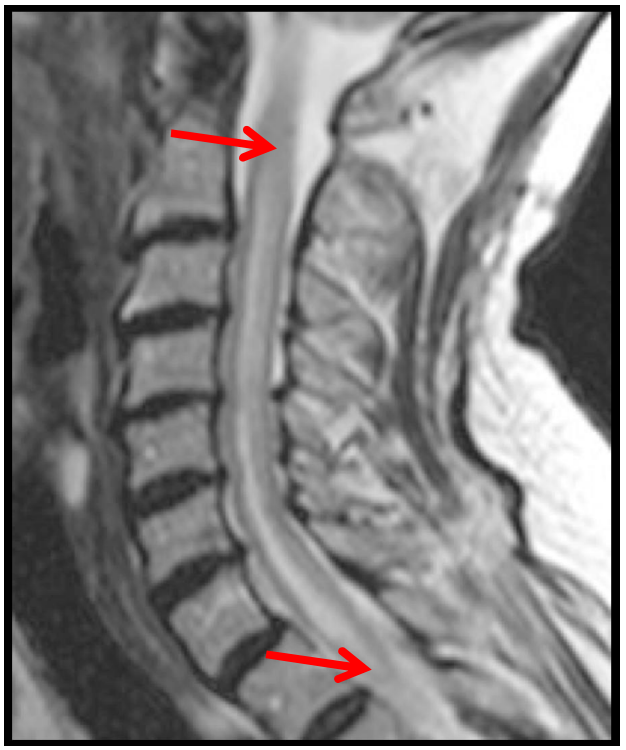
Originally a monophasic disorder causing simultaneous or sequential optic neuritis (ON) and transverse myelitis (TM; Devic 1894)

Patients subsequently described with relapsing disease or temporal separation of ON and TM

Now recognised to be a severe relapsing-remitting disorder of the CNS distinct from MS

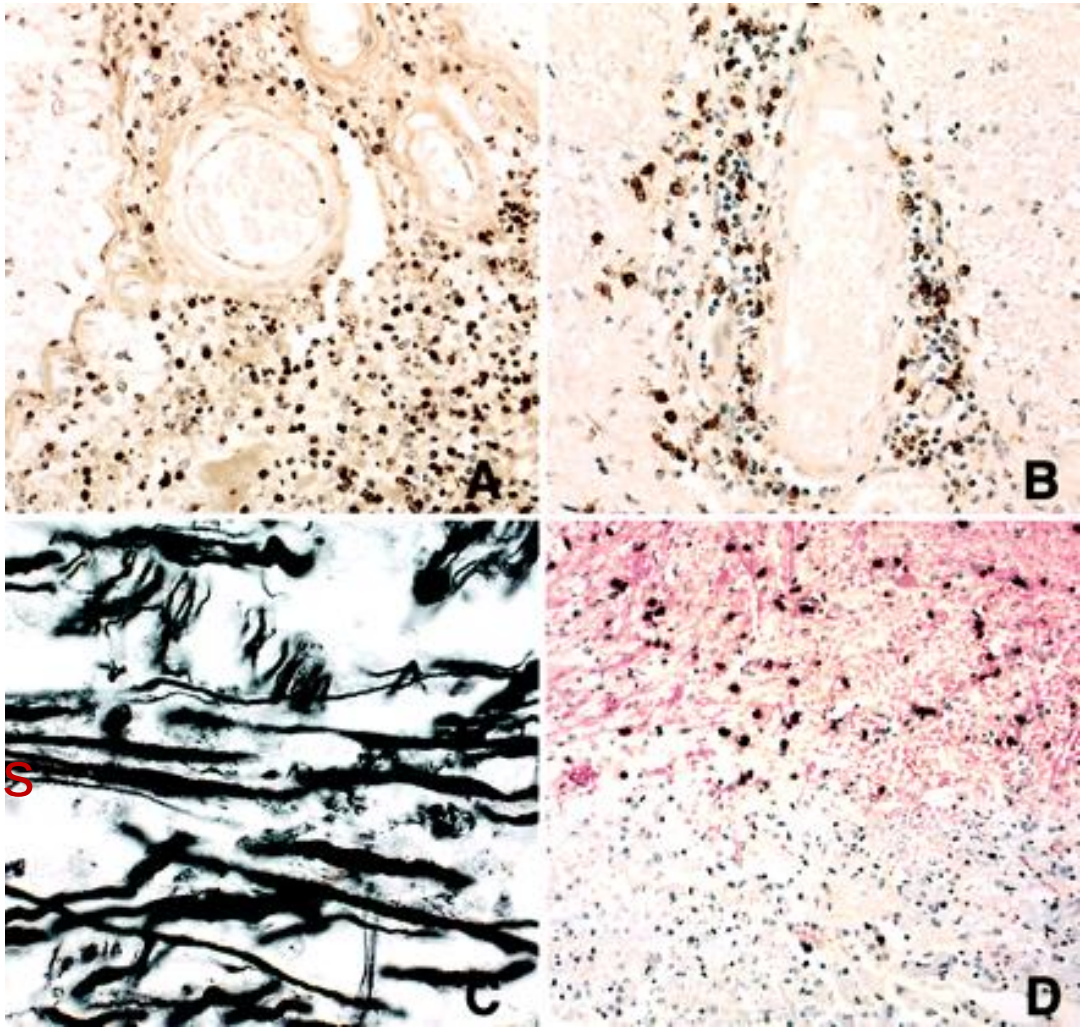
Neuromyelitis optica – Devic’s disease





Lucchinetti
et al Brain 2002

CD3



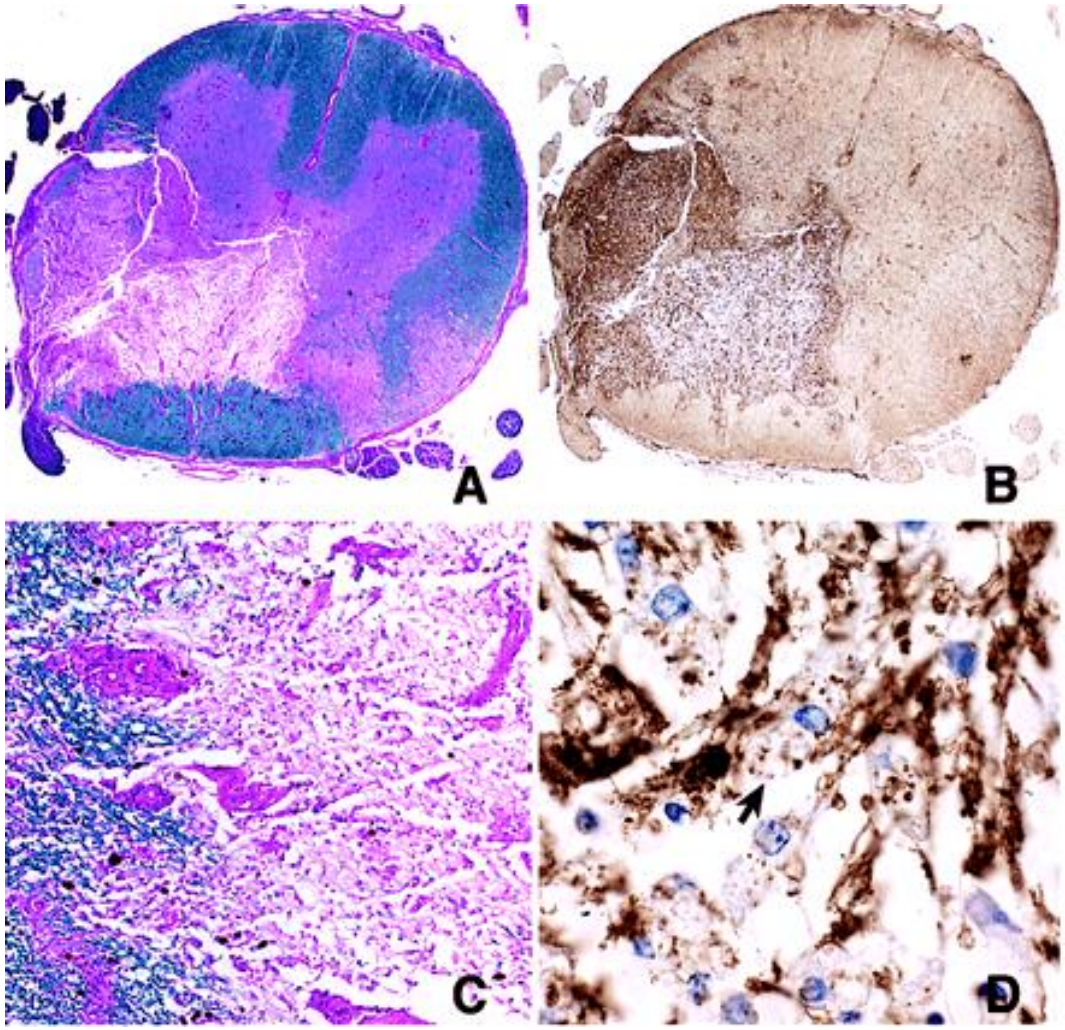
CD8

Axons

Oligos

Perivascular infiltrates with numerous CD3+ T lymphocytes and CD8+ T lymphocytes; axonal loss with swellings and spheroids, reduced oligodendrocytes in the lesion.

Lucchinetti
et al Brain 2002

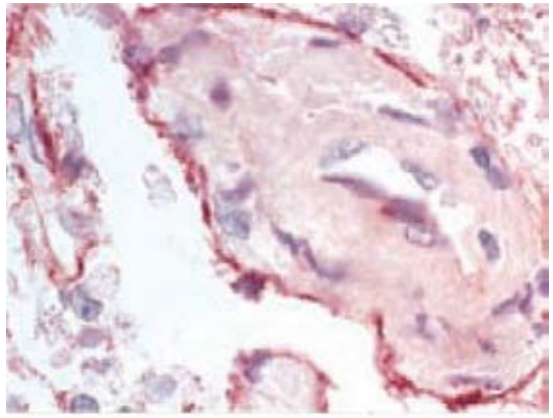


Eosino

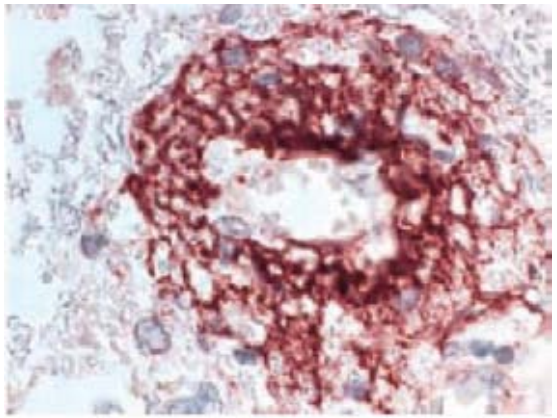
Macro

Demyelination involves both white and grey matter, macrophages, eosinophils and neutrophils in lesions

IgG/M and complement deposits in lesions



IgM



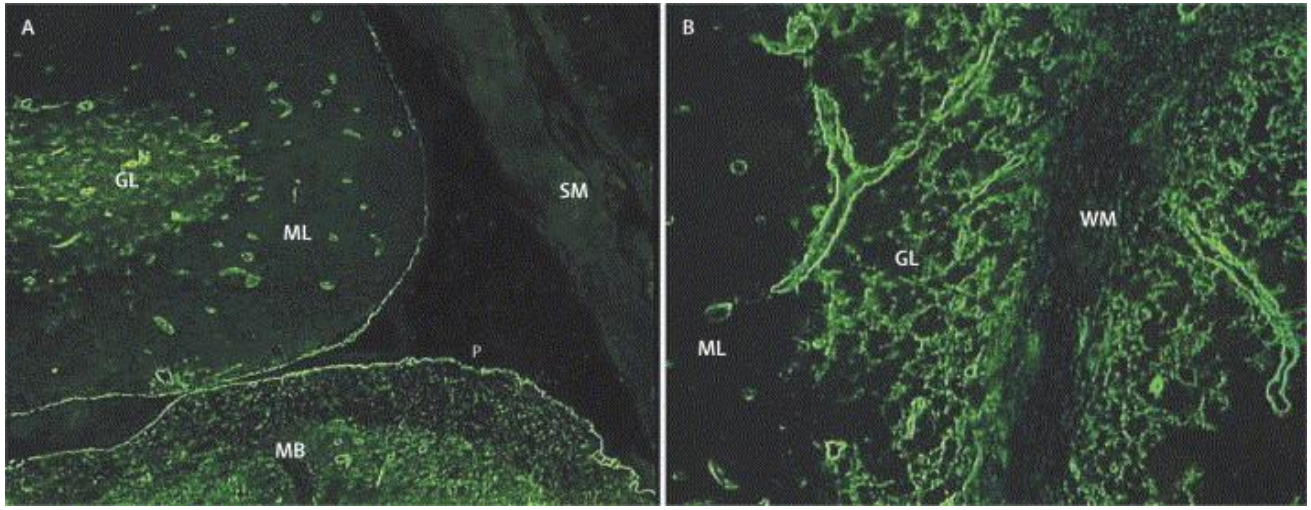
Complement

IgM or C9neo (complement) on perivascular
rim or in rosettes around vessels in NMO

Lucchinetti et al Brain 2002

NMO-IgG

Antibodies binding capillaries, pia and Virchow Robin spaces were first discovered in 2004 in the sera of patients with neuromyelitis optica (NMO)



Lennon et al Lancet 2004

THE IMORTANCE OF THE ANTIBODIES
Aquaporin-4 antibodies in neuromyelitis optica

Lennon et al
NMO-IgG defined, Lancet 2004,
AQP4 identified as the antigen, J Exp Med 2005

Antibodies proving useful in early diagnosis and disease monitoring

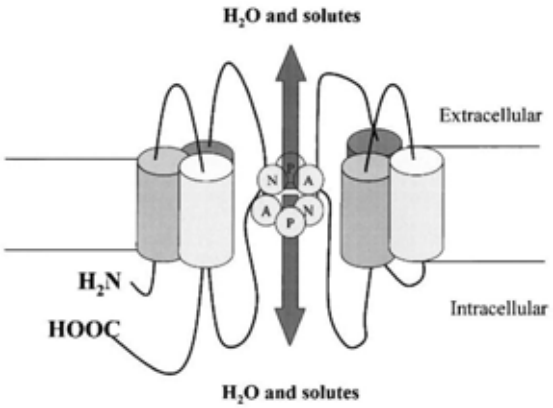
In UK identifying about 1/million new patients each year

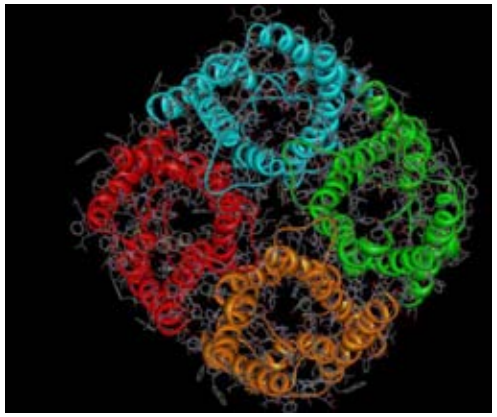
Diagnosis of NMO

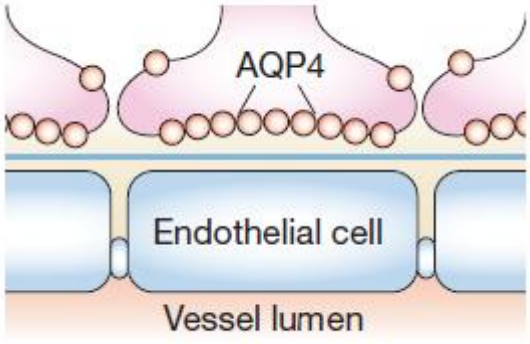
Revised diagnostic criteria (Wingerchuk et al., 2006)

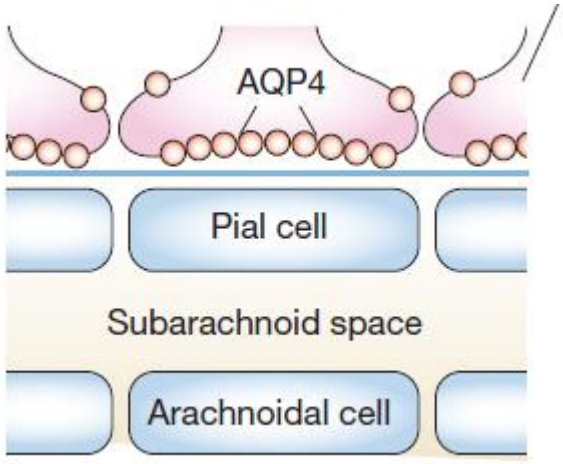
- Two absolute criteria:
  - (i) optic neuritis, (ii) myelitis.
- *And* at least two of three supportive criteria:
  - (i) Spinal cord MRI lesion extending >2 vertebral segments,
  - (ii) MRI criteria not satisfying the revised McDonald diagnostic criteria (Polman et al., 2005) for MS,
  - (iii) AQP4 antibody in serum.

AQP4 – six transmembrane protein
Forms a central water channel
Exists as tetramers
Expressed strongly on astrocyte end-feet abutting the endothelial or pial cells





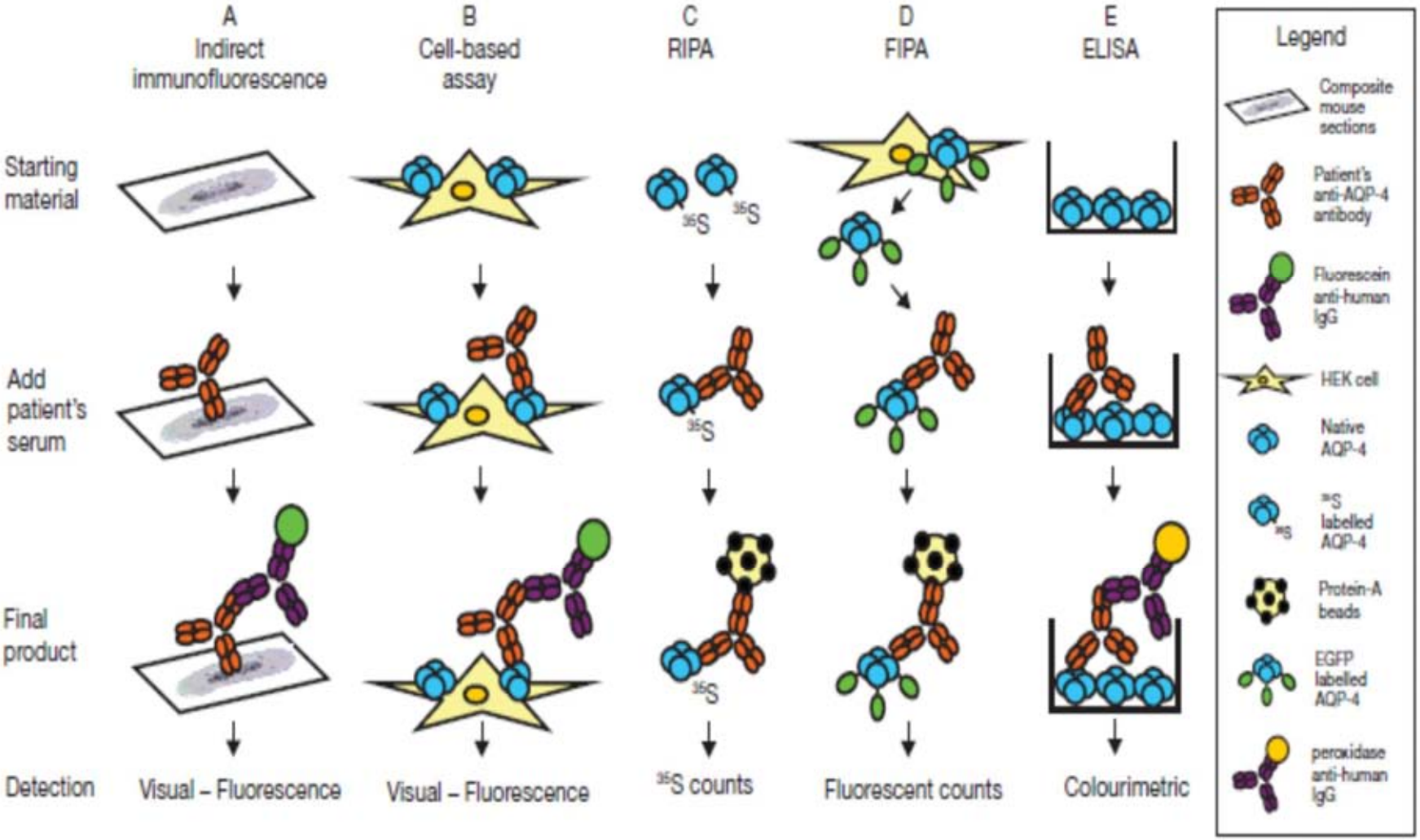




Papdopoulos & Verkmann
Lancet Neurology
2012

Jarius et al
Nat Clin Pract 2008

Techniques employed to detect NMO-IgG



A

Diagnosis	FACS	CBA-O	CBA-E	ELISA (≈1.6)	ELISA	FIPA-0	FIPA-M	IF
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMOSD-TM	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMOSD	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMOSD-ON	+	+	+	+	+	+	+	+
NMOSD-ON	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMOSD	+	+	+	+	+	+	+	+
NMOSD-TM	+	+	+	+	+	+	+	+
NMOSD-ON	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMOSD-TM	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMOSD-TM	+	+	+	+	+	+	+	+
NMOSD-ON	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMOSD-ON	+	+	+	+	+	+	+	+
NMOSD-TM	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	-	+	+	+
NMOSD	+	+	+	+	+	+	+	-
NMOSD-TM	+	+	+	+	+	+	+	-
NMO	+	+	+	+	+	-	-	-
NMOSD-TM	+	+	+	+	+	-	-	-
NMO	+	+	+	+	+	-	-	-
NMOSD-TM	+	+	+	+	+	-	-	-
NMO	+	+	+	+	-	-	-	-
NMO	+	+	+	+	-	-	-	+
NMO	+	+	+	+	-	-	-	-
NMOSD-TM	+	+	+	+	-	-	-	-
NMOSD-TM	+	+	+	-	-	-	-	-
NMO	+	+	-	+	+	-	-	-
NMOSD-TM	+	+	-	+	+	-	+	-
NMO	+	+	-	-	-	-	-	-
NMO	+	+	-	+	-	-	-	-
NMOSD-ON	+	-	+	-	-	-	-	-
NMO	+	-	-	-	-	-	-	-
NMOSD-TM	-	-	-	-	-	+	-	-
NMOSD-TM	-	-	-	-	-	-	-	-
NMOSD-ON	-	-	-	-	-	-	-	-
NMOSD-ON	-	-	-	-	-	-	-	-
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NMO	-	-	-	-	-	-	-	-
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NMO	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
Patients	46/60	44/60	41/60	42/60	36/60	32/60	32/60	29/60
Controls	0/86	0/86	0/86	2/86	0/86	0/86	2/86	0/86
AUC-ROC	0.883	0.867	0.842	0.838	0.800	0.767	0.755	0.742

+ Positive
- Negative
LETM
rON

Results

All highly specific

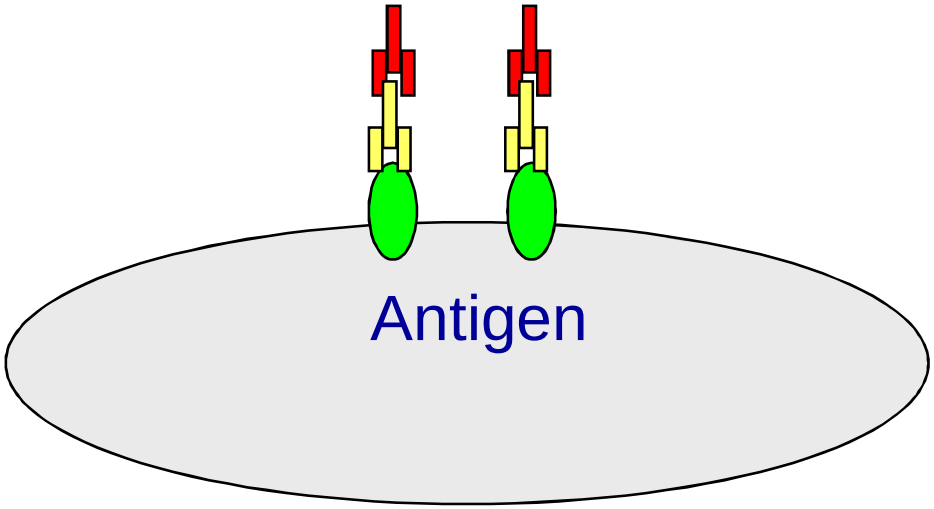
Concordance very good

Sensitivity:

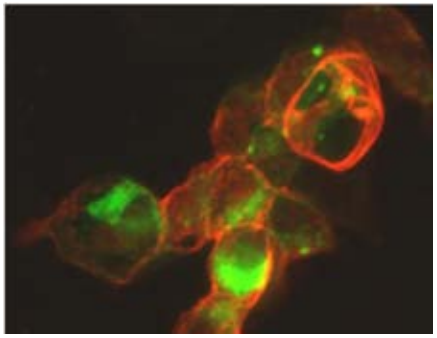
Cell-based assay/FACS with
M23 > ELISA > NMO-IgG IF

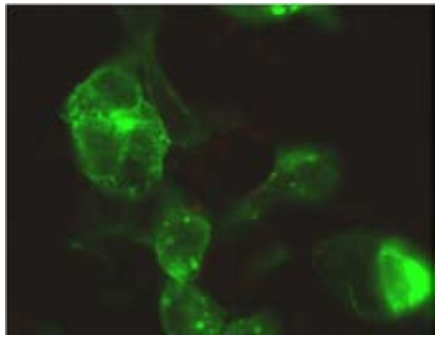
Waters ……Pittock Neurology 2012

What is a cell-based assay?



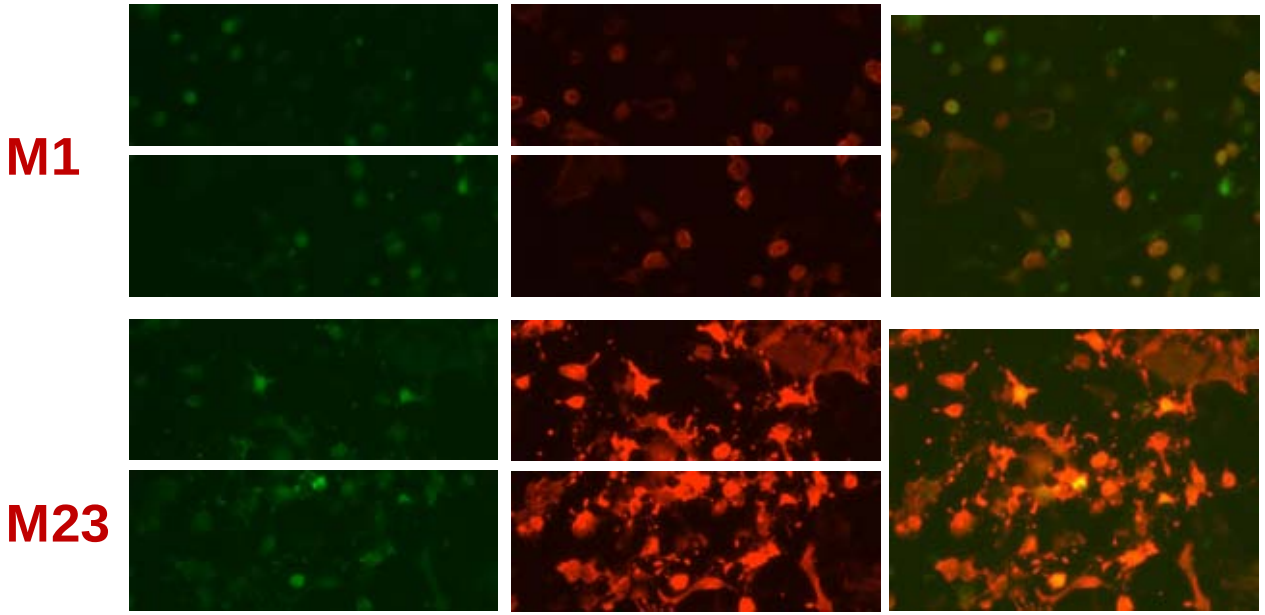
Patient has AQP4 antibodies Intensity of binding can be scored visually





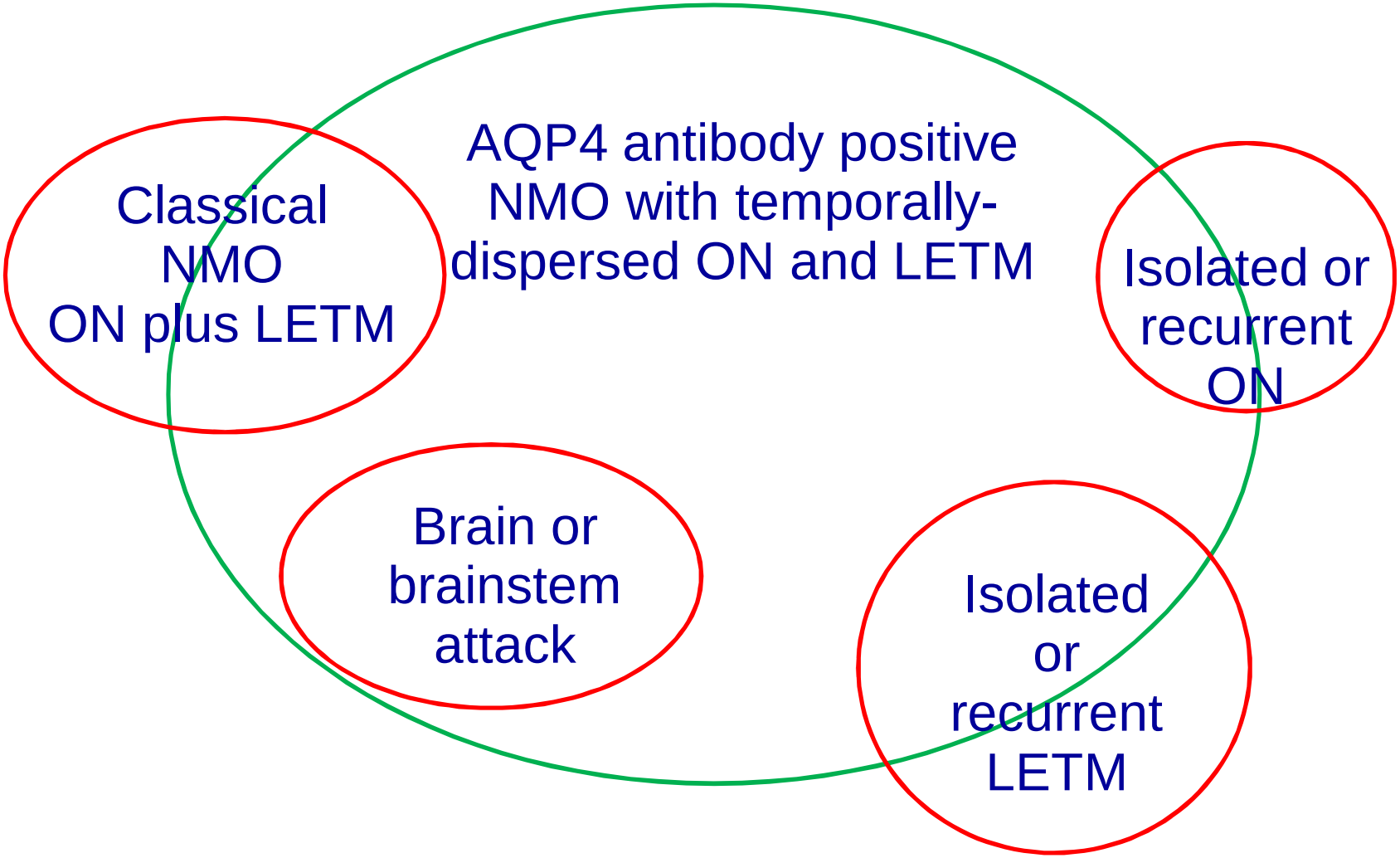
Patient does not have AQP4 antibodies

Two isoforms of AQP4 – M1 and M23
M23 forms orthogonal arrays of proteins (OAPs)
Many patient sera bind more strongly to M23
if expressed on cell lines



Waters et al 2008 unpublished
Also Mader et al Plos One 2010

Spectrum of disease has expanded
To include limited and less typical forms of ‘NMO’
AQP4 antibodies not found in every patient with any one form



DEMOGRAPHICS AND CLINICAL SPECTRUM AQP4-Ab disease

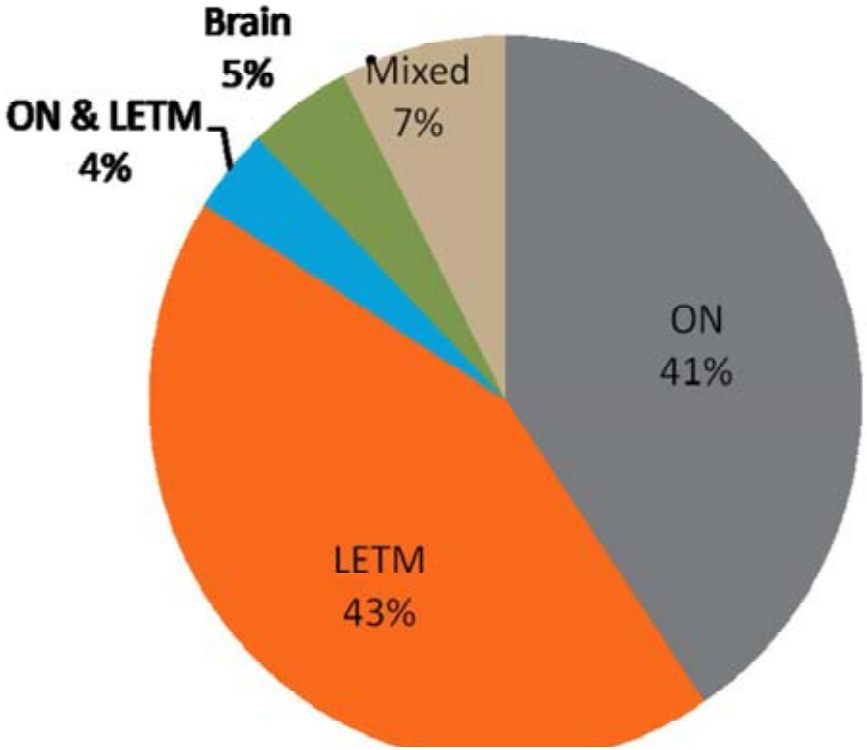
- Rare disorder
  - Prevalence estimated to be 1 to 2% of MS
  - 120-150 new cases in the UK/year
- Strong female preponderance
- Occurs in all ethnic groups
  - Relatively more common in those of Asian or Afro-Caribbean ethnicity
- Mean age at disease onset of ~40 years
  - Can occur at any age

Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan

Joanna Kitley,[1] M. Isabel Leite,[1] Ichiro Nakashima,[2] Patrick Waters,[1] Benjamin McNeillis,[1] Rachel Brown,[1] Yoshiki Takai,[2] Toshiyuki Takahashi,[2] Tatsuro Misu,[2,4] Liene Elsone,[3] Mark Woodhall,[1] Jithin George,[1] Mike Boggild,[3] Angela Vincent,[1] Anu Jacob,[3] Kazuo Fujihara[2,4] and Jacqueline Palace[1]

BRAIN
A JOURNAL OF NEUROLOGY

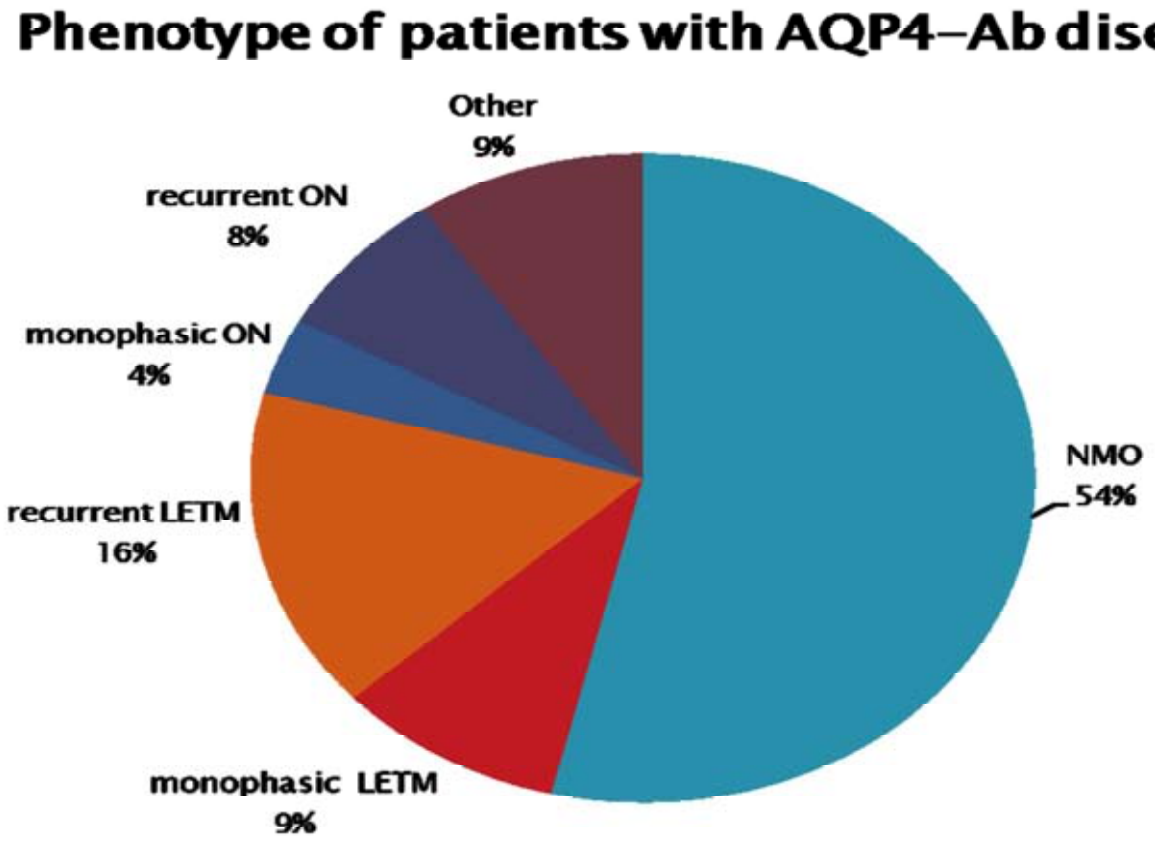
Presenting Feature of AQP4-Ab disease



A ‘classic’ Devic’s syndrome is rare in AQP4-Ab disease AT PRESENTATION

- **80% patients presented with either LETM or ON**
  - **Only 4% presented with both**

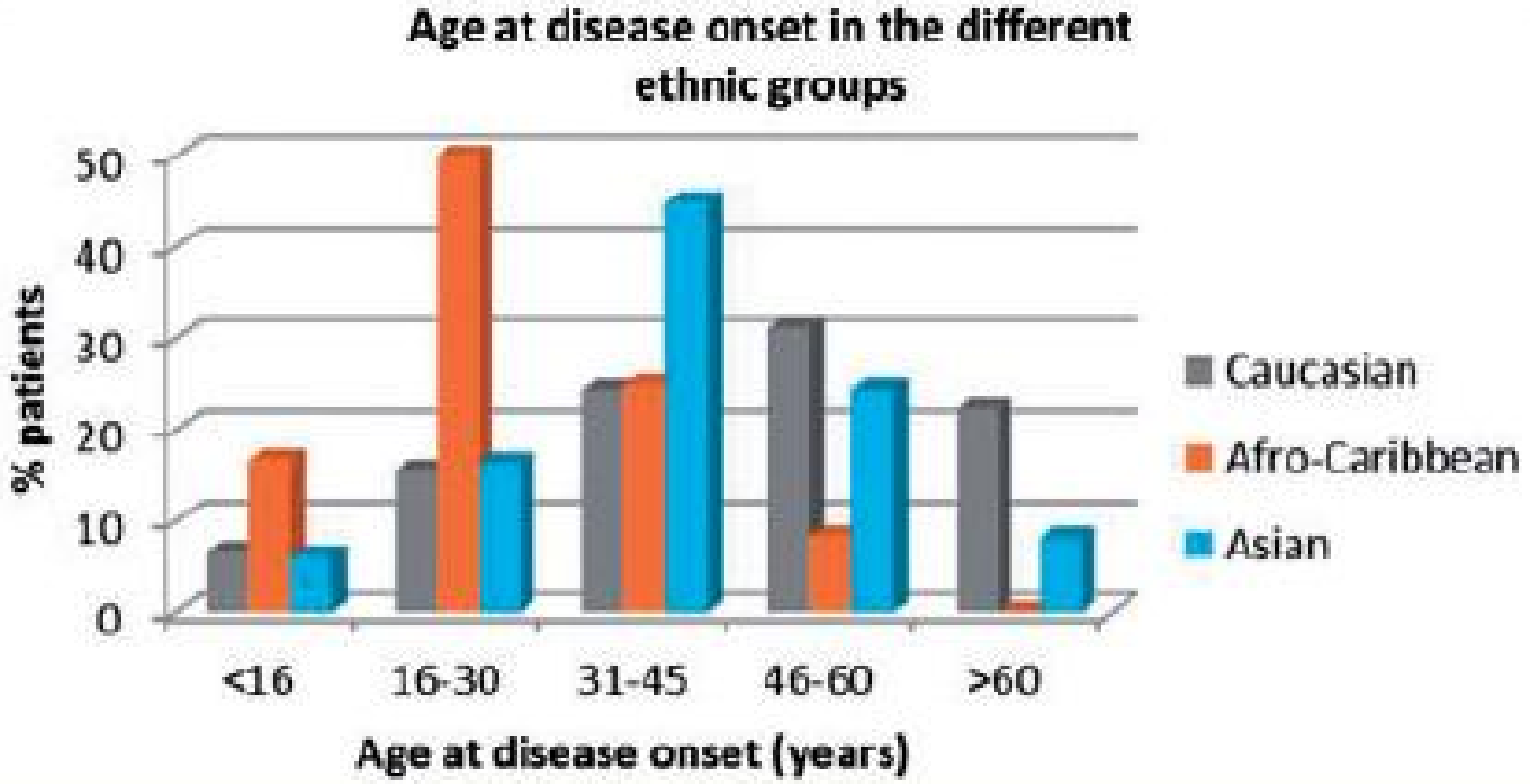
Only half of patients with AQP4-Ab have the full NMO phenotype and this takes time to develop



Kitley et al, Brain 2012

AT LAST FOLLOW-UP

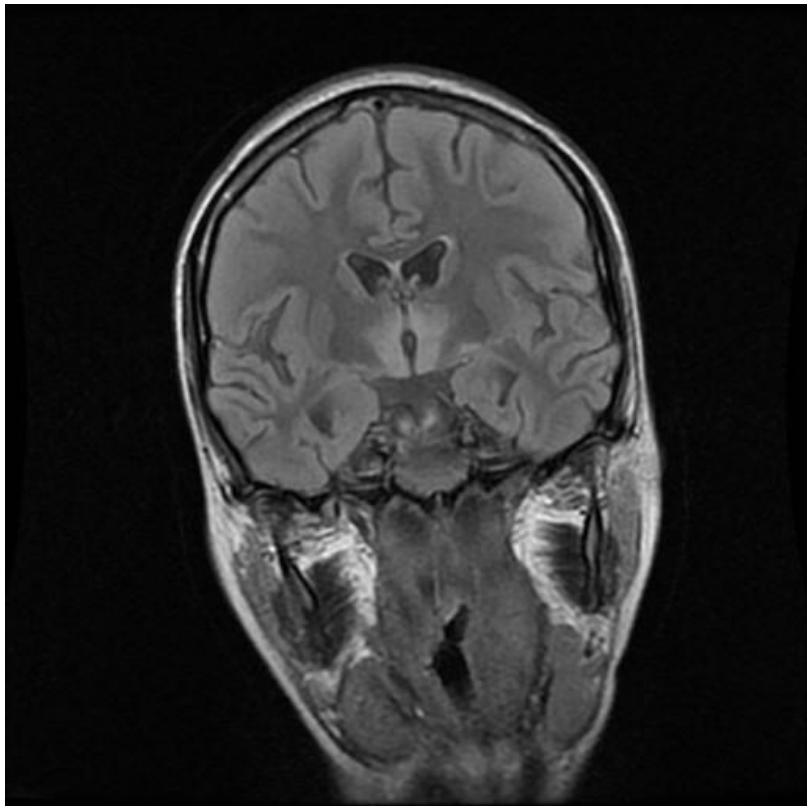
46% patients didn't fulfil current clinical diagnostic criteria for NMO. Development of the full NMO syndrome took a median of 54 months

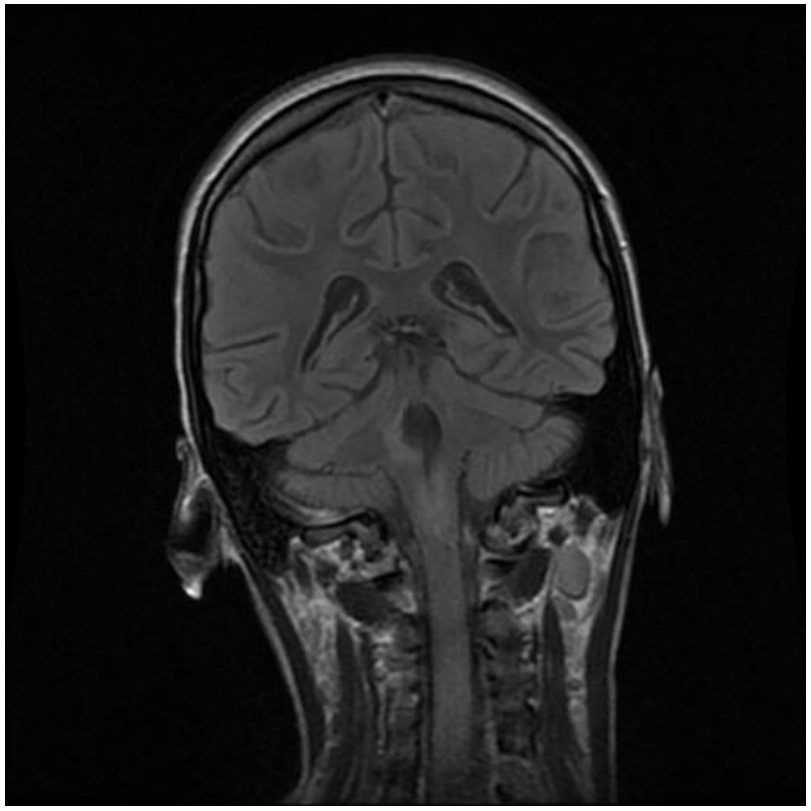

Age at disease onset in the different ethnic groups
% patients
50
40
30
20
10
0
<16
16-30
31-45
46-60
>60
Age at disease onset (years)
Caucasian
Afro-Caribbean
Asian

THE LESIONS
‘Classic’ NMO lesions are uncommon

‘Classic’ NMO lesions occur around the 3rd and 4th ventricles and aqueduct, hypothalamus

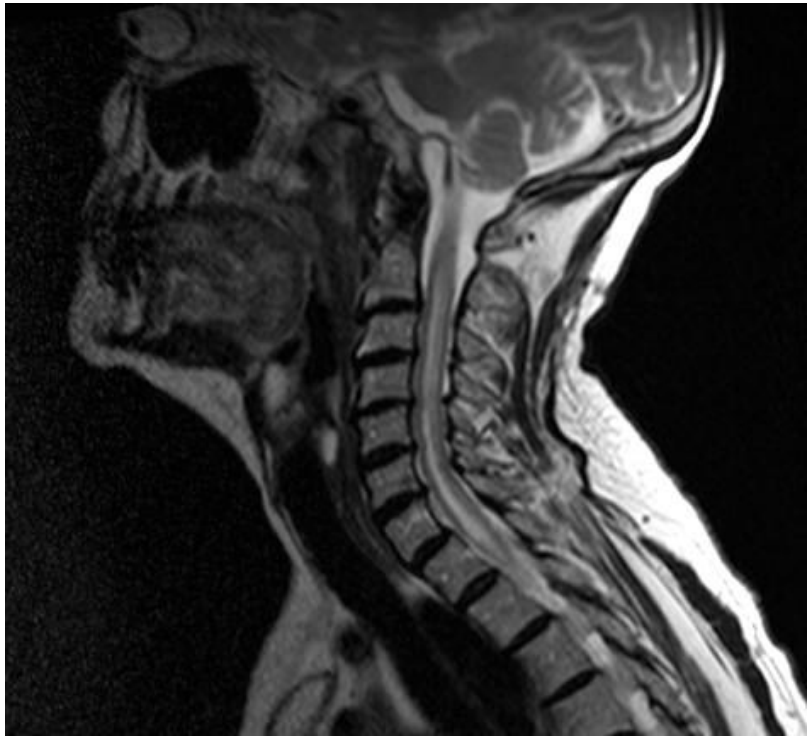
Only occur in ~10% patients

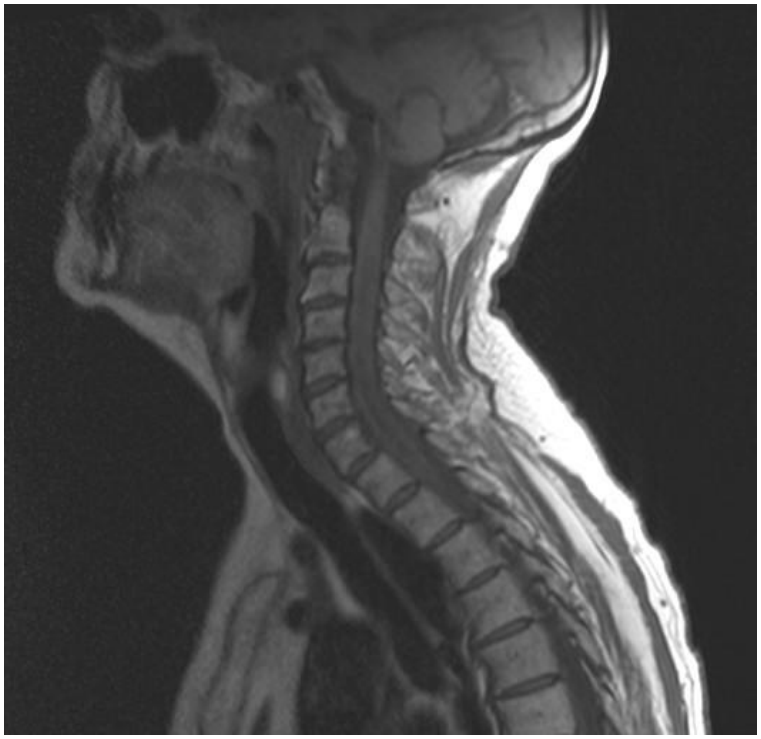


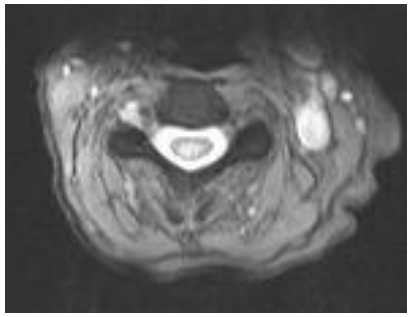


Pittock et al, Arch Neurol 2006; Chan et al, Arch Neurol 2011; Kim et al J Neurol Sci 2011

NMO cord lesions are typically cervical or thoracic and central on axial imaging





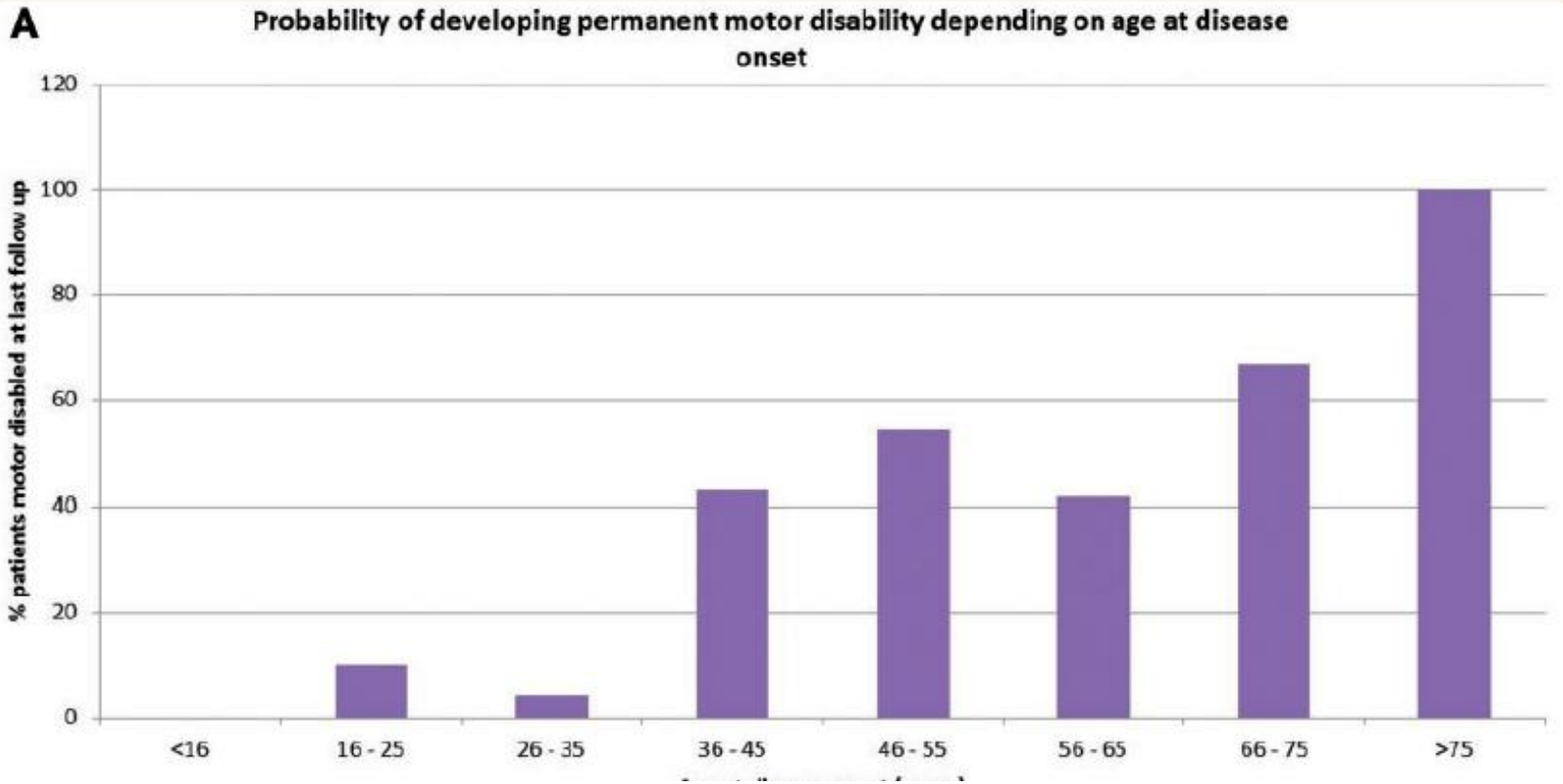


T1 hypointensity is common
Lower thoracic/conus involvement rare
Short lesions can occur

Myelitis in AQP4-Ab disease

- Speed of onset is highly variable
  - Acute onset mimicking spinal cord infarction
  - Typical subacute onset
  - Stuttering onset over weeks
- May be preceded by hiccoughs and/or intractable vomiting
  - Can last days/weeks/months before development of other symptoms
  - First presentation in 12% patients (Appiwatanakul et al, Arch Neurol 2010)
- Severe back/neck pain may precede or accompany onset
- Dystonic spasms can be severe
  - Can be exquisitely sensitive to carbamazepine but often intractable if not

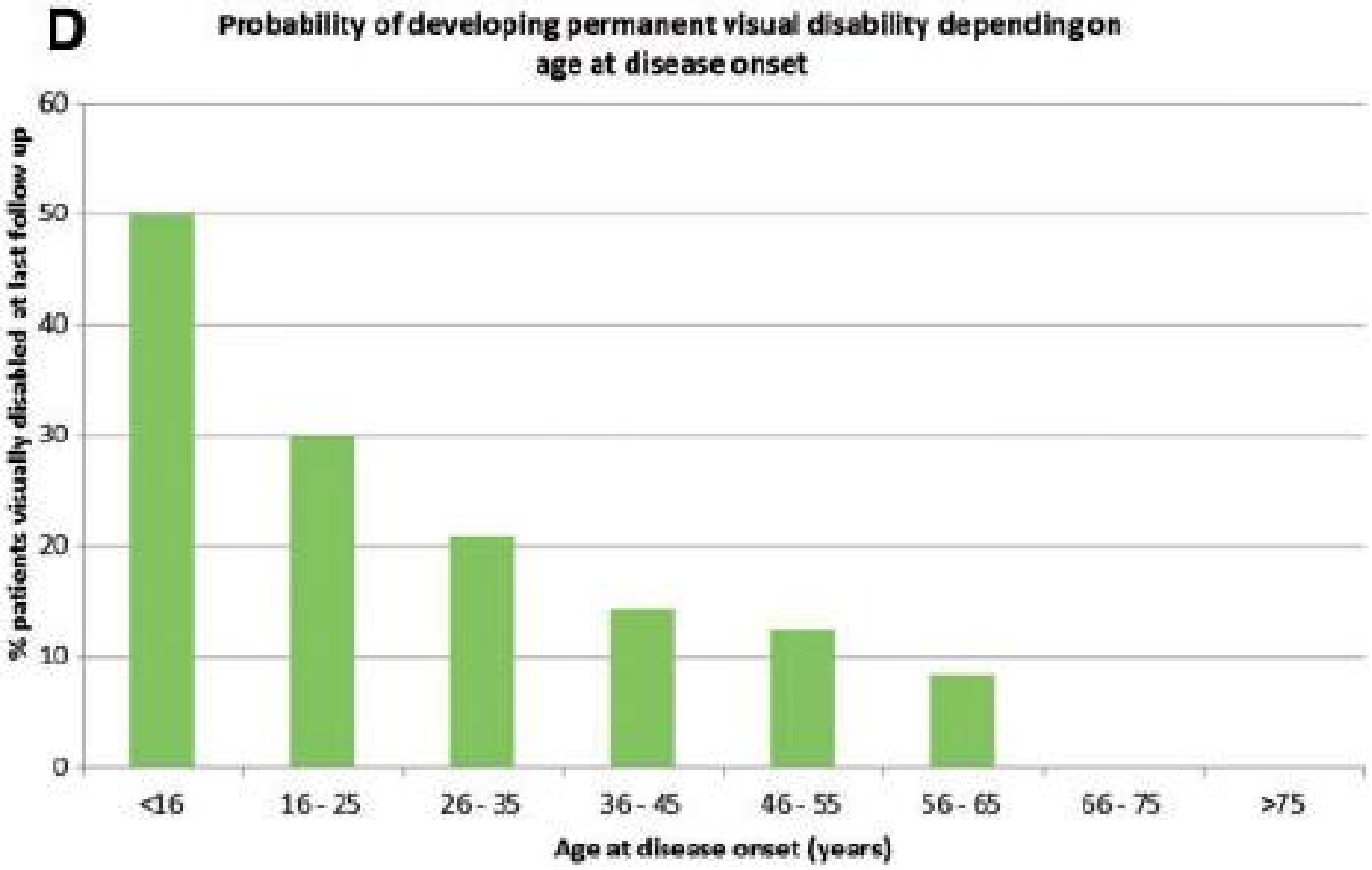
Permanent motor disability less likely in children



Optic neuritis in AQP4-Ab disease

- Usually unilateral
- May be painful or painless
- Usually retrobulbar
- Patients with ON onset attacks are significantly younger than patients with LETM onset attacks
  - 61% with disease onset <30 yrs presented with ON
  - 66% with disease onset >50 yrs presented with LETM

Permanent visual disability is more common in children



Be aware of brain/brainstem attacks as first presentation

28 year old Afro-Caribbean man

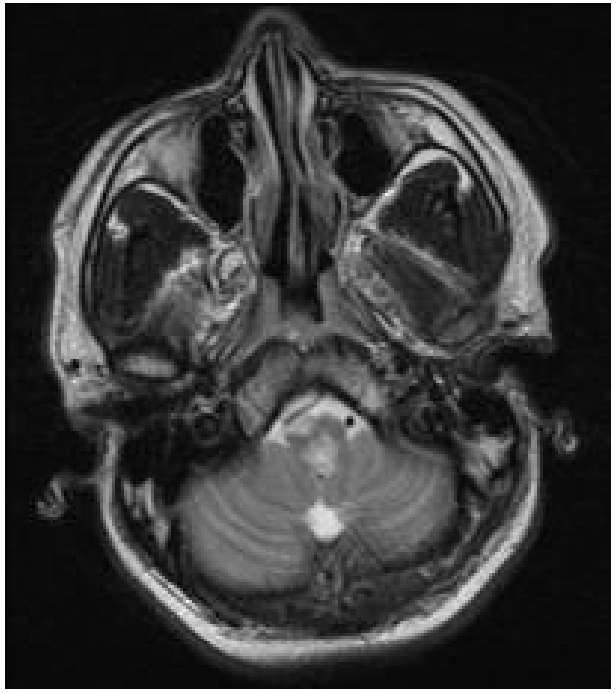
Fatigue, fever, hiccoughs and vomiting

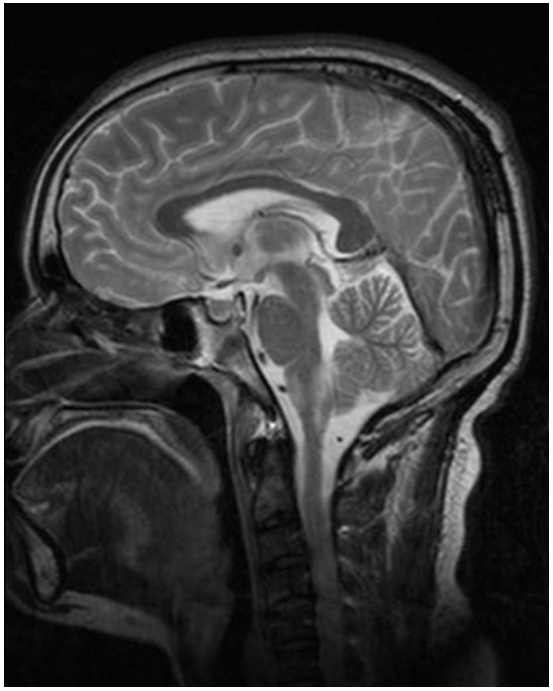
Tetraparesis and bulbar dysfunction after several days

Low GCS and respiratory failure requiring ITU admission

Lesions in pons and medulla and short cord lesion at C3/4

On waking from coma noted to be blind

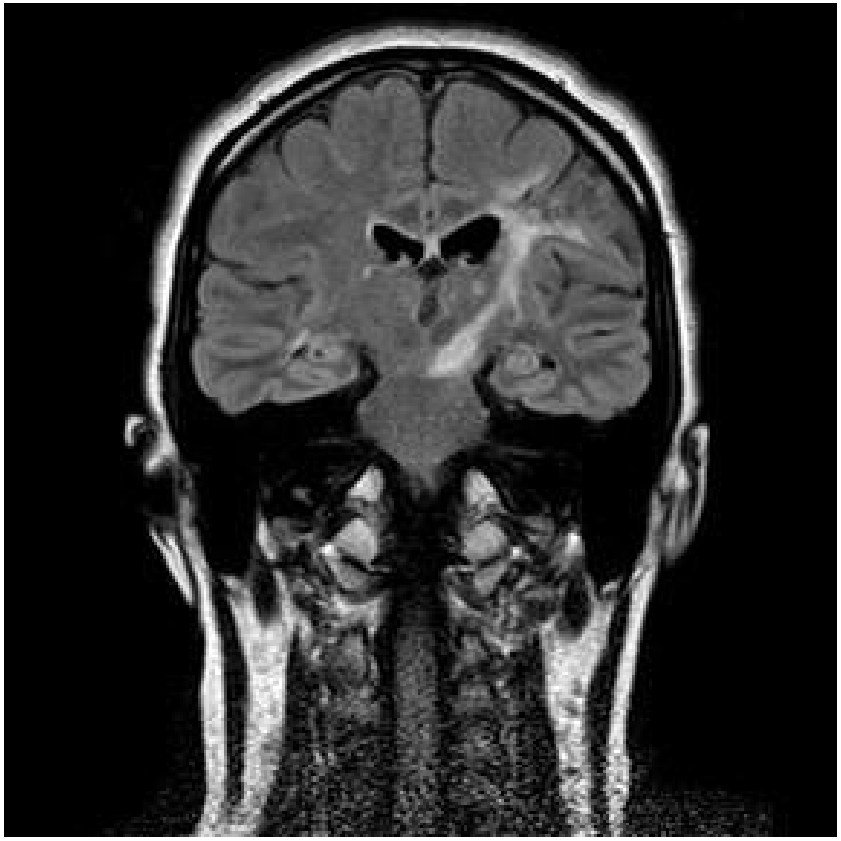


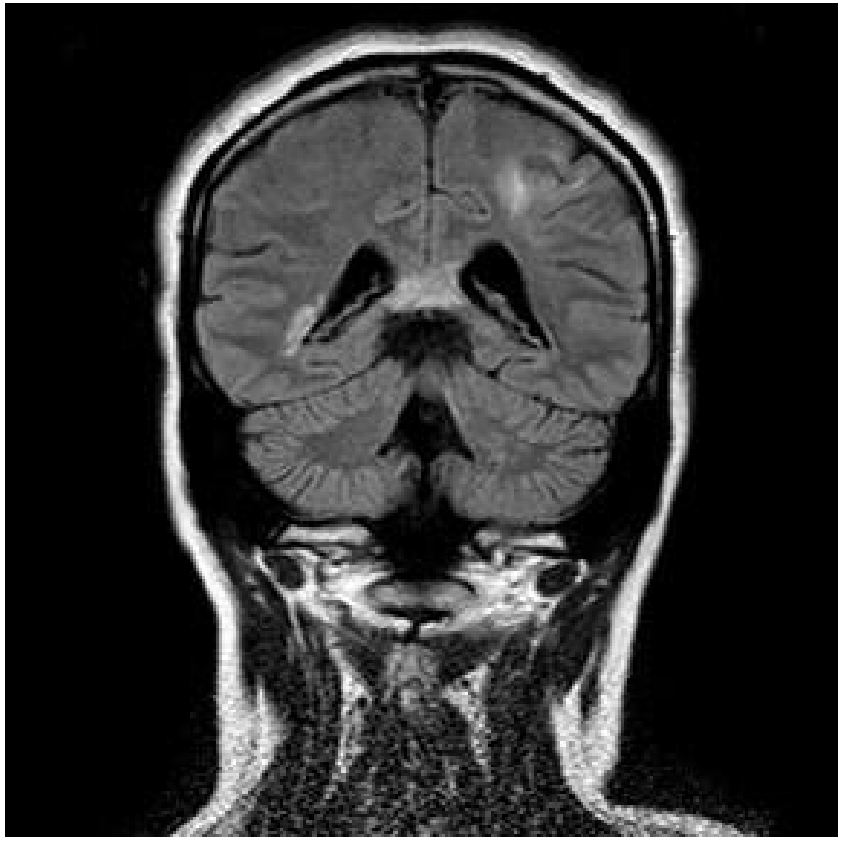


Brain disease in AQP4-Ab disease

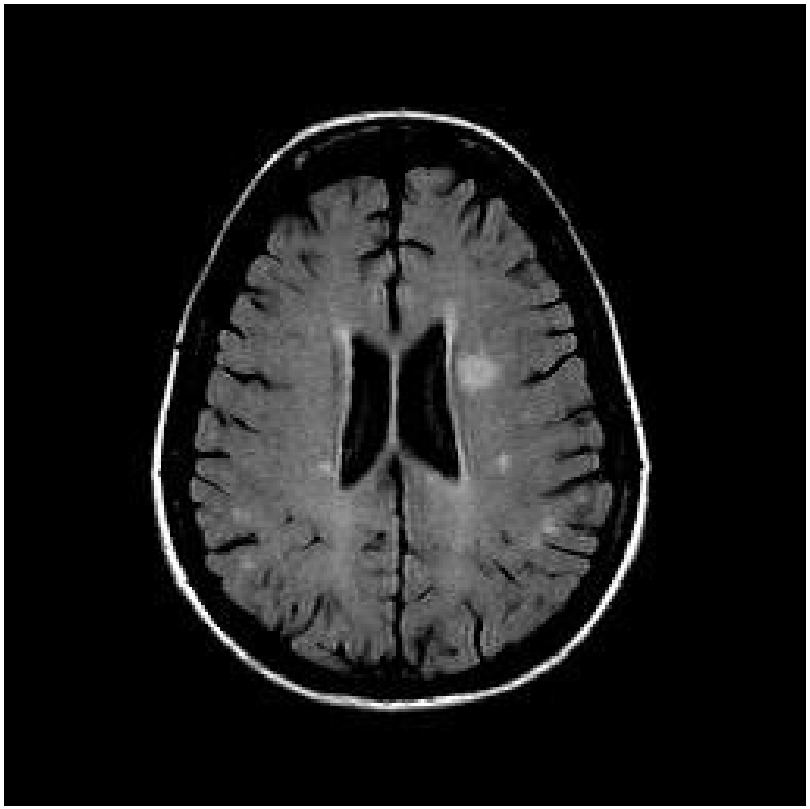
- Brain or brainstem attacks can be presenting feature of NMO
- Rare in Caucasians
- More common in children, Asians and Afro-Caribbeans
  - Up to 25% in Asia (Chan et al, Arch Neurol 2011; Kim et al, Neurology 2012)
- Can occur in the absence of ON and TM

Tumefactive lesions can also occur





MS-like lesions can be seen in up to 1/3



Periventricular lesions usually not Dawson's fingers

Black holes said to be uncommon

Matsushita et al, J Neurol Sci 2010; Chan et al, Arch Neurol 2011

ARE ANTIBODIES CAUSATIVE?

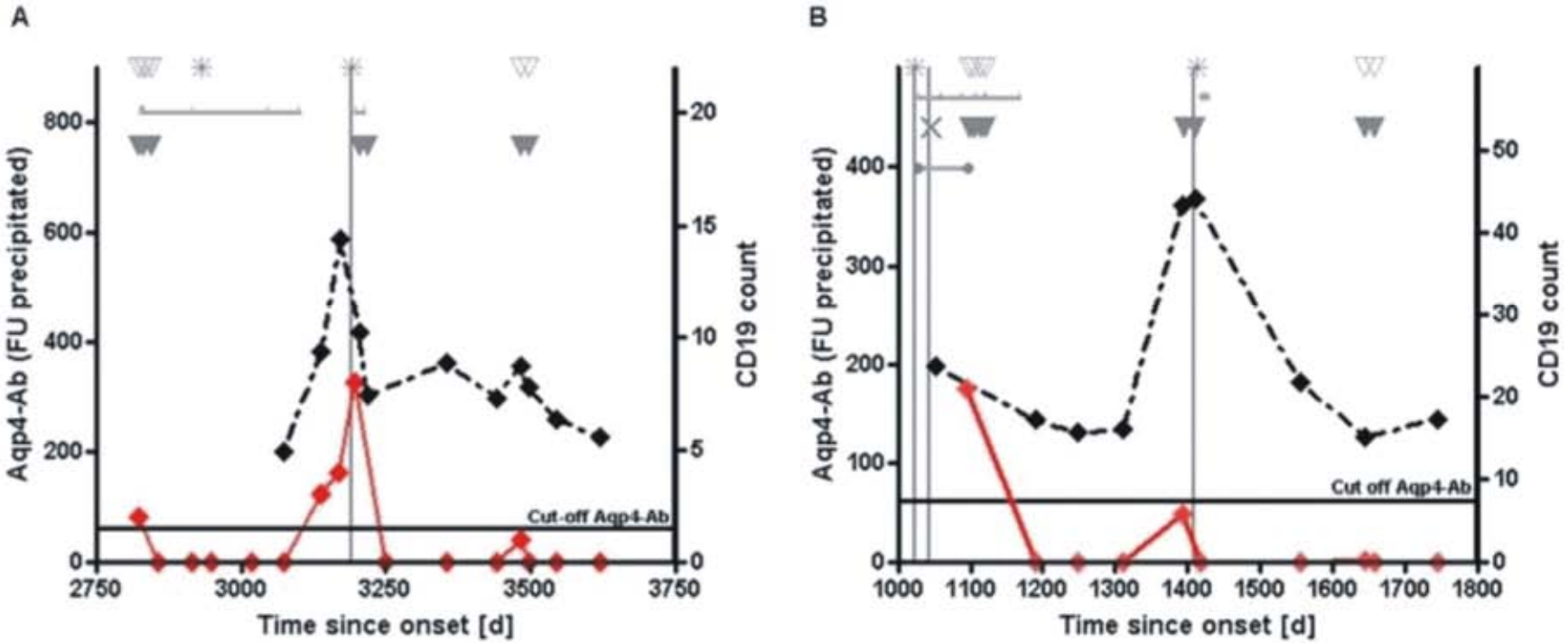
Is NMO an antibody-mediated disease?

Do antibody levels correlate with relapses?

Do the patients respond to immunotherapies?

Can one transfer disease to experimental antibodies with antibodies alone?

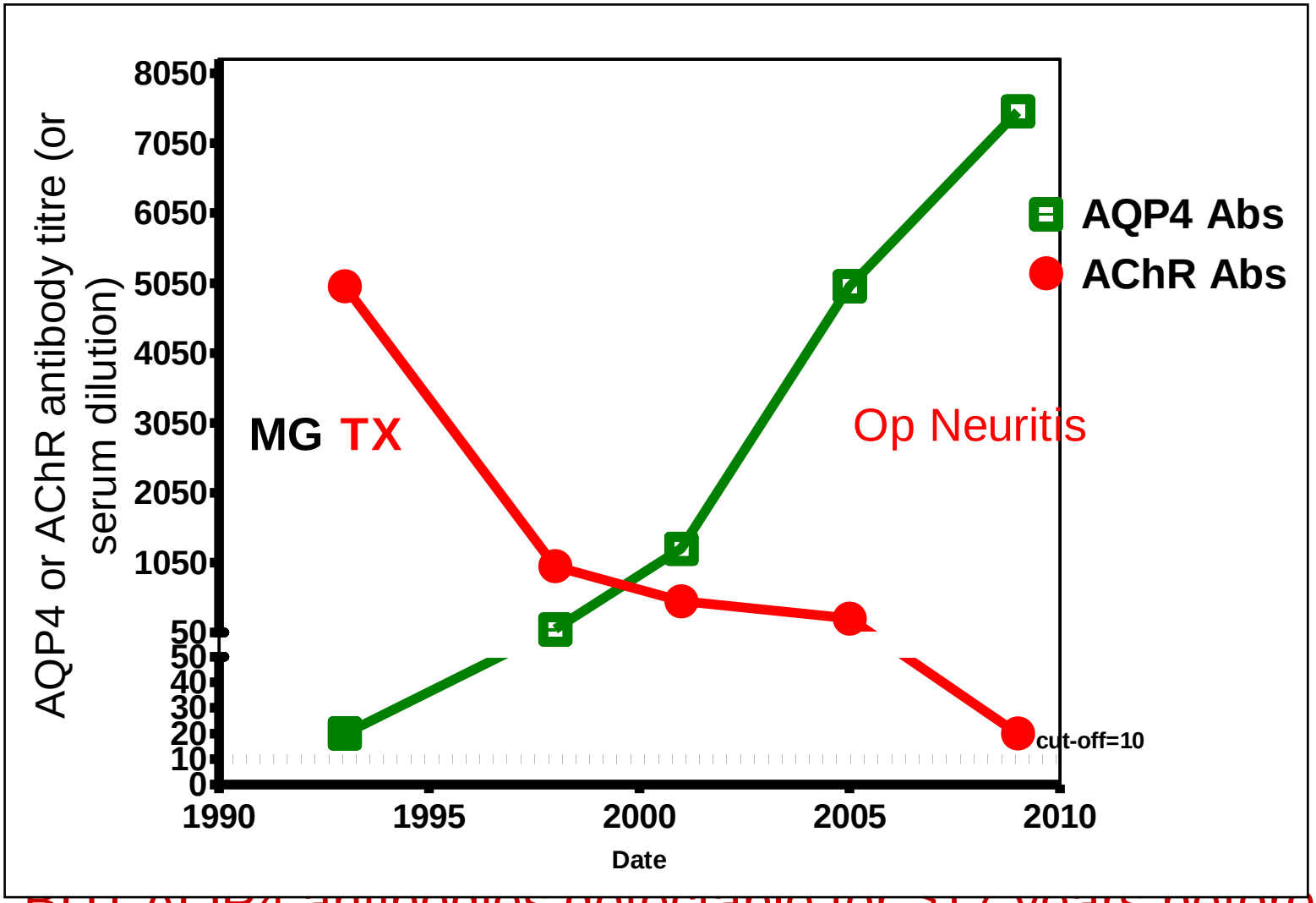
Do antibody levels correlate with relapses?



; u = **CD19 cell counts**; u = **AQP4 antibodies**
I = clinical relapse; q = **rituximab;**

Jarius ……..Kristoferitsch Brain 2008

AChR and AQP4 antibody levels run in opposite directions, "mirroring" clinical manifestations



BUT AQP4 antibodies detectable for >17 years before her first manifestation of NMO!

Are the AQP4 Abs pathogenic in vivo?
Two model types

Peripheral injection into mice with existing
T cell immunity to myelin proteins

Kinoshito et al Biochem Biophys Res Comm 2009

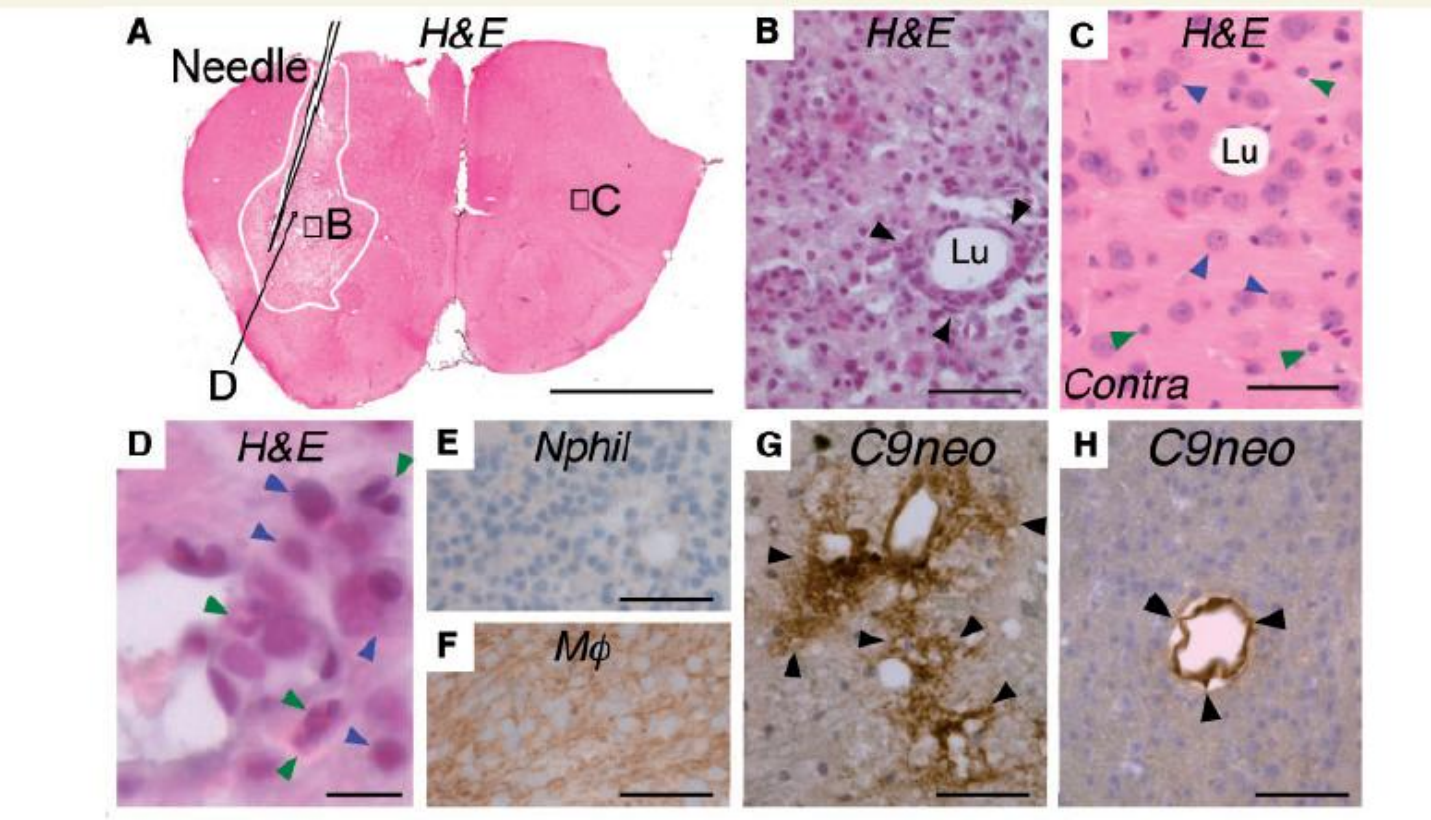
Bradl et al Ann Neurol 2010

Bennett et al Ann Neurol 2010

Intracerebral injection with human complement

Saadoun et al Brain 2010

Are AQP4 antibodies alone pathogenic and what other factors are required? Intracerebral injection



AQP4 Abs alone did not produce NMO lesions
AQP4 plus human complement produced NMO lesions
Saadoun ……Papadopoulos Brain 2010

TREATMENT
The majority of patients with AQP4-Ab follow a relapsing course

- The presence of AQP4-Ab confers a high risk of relapsing disease

- More than half of patients presenting with first event LETM will go on to relapse within a year (Weinshenker et al, Ann Neurol 2006)

- 86 % relapsing-remitting course in our cohort
  - 49% relapse within 1 yr (61% untreated)
  - 70% relapse within 2 yrs (81% untreated)

Acute relapses must be treated aggressively

- IVMP 1g/day for 5/7 ASAP
  - Do not delay IVMP to wait for MRI etc
  - Commence oral prednisolone 60mg od and reduce by 5mg/month to maintenance 20mg alternate days
- Plasma exchange if no improvement after 5/7 or if previous poor recovery
- IVIG is an alternative to plasma exchange

Treatment is long term

- Azathioprine first line agent (2.5mg/kg)
- Alternatives are methotrexate (15 – 20mg weekly) or mycophenolate mofetil
- Many patients seem very responsive to and dependent on steroids
  - Maintenance prednisolone 20mg alternate days
- Rituximab second line agent for refractory NMO but would still give concomitant oral prednisolone
- No prospective studies looking at treatment withdrawal but would generally keep on long term immunosuppression and only consider withdrawal if relapse free for >7 years

Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study

Sean J Pittock, Vanda A Lennon, Andrew McKeon, Jay Mandrekar, Brian G Weinshenker, Claudia F Lucchinetti, Orna O'Toole, Dean M Wingerchuk

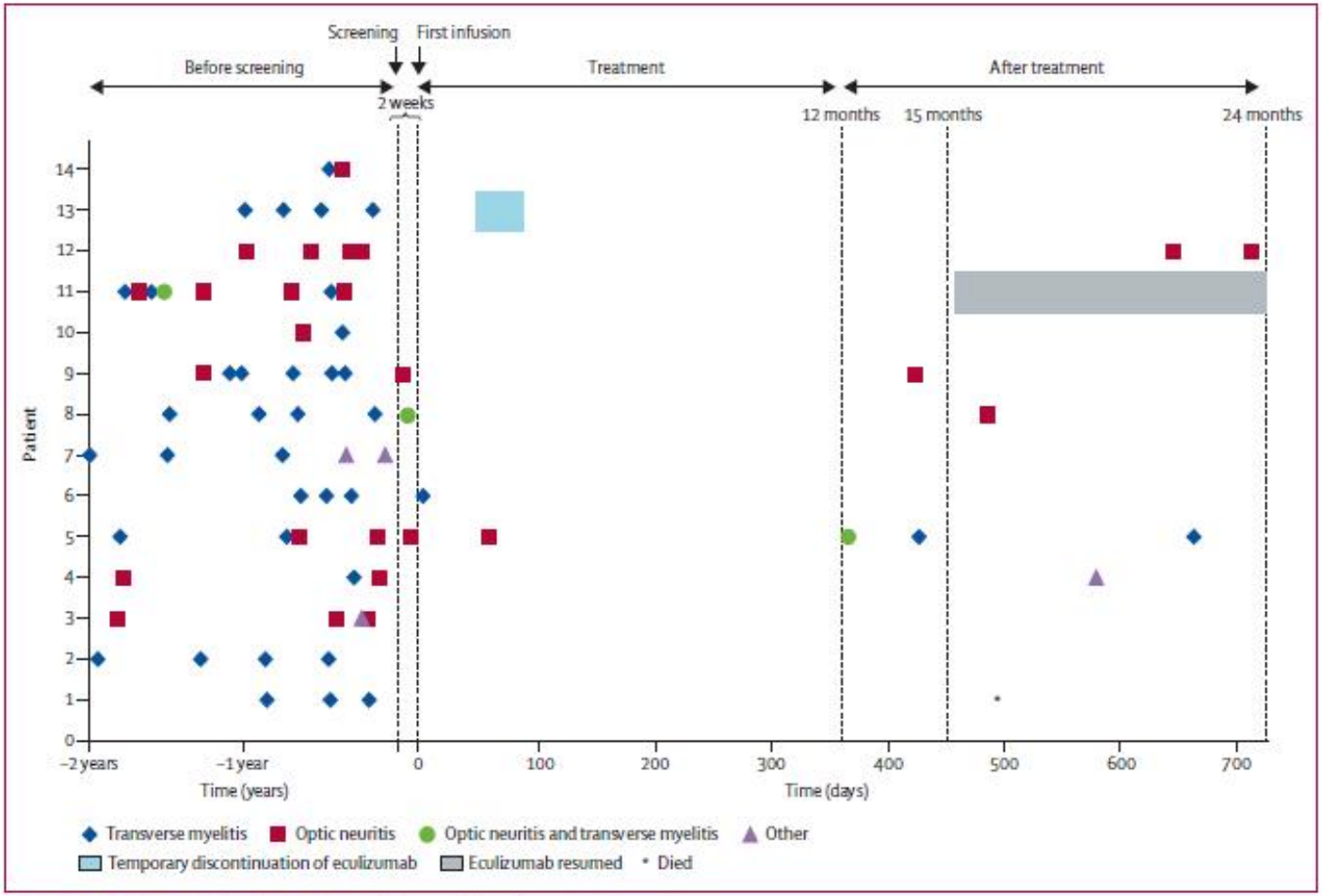


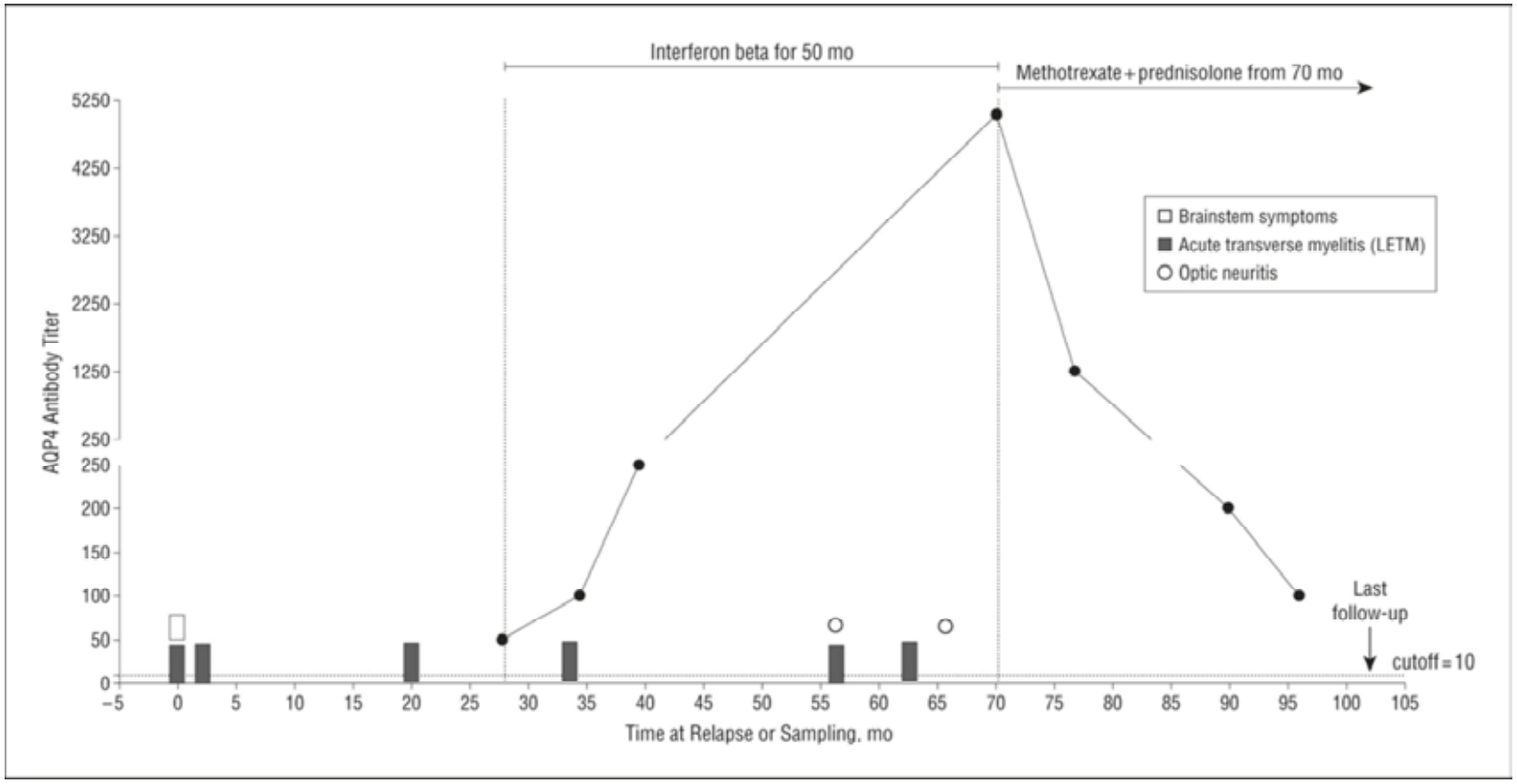
Figure 1: Attack frequency before, during, and after eculizumab treatment

www.thelancet.com/neurology **Published online April 26, 2013** http://dx.doi.org/10.1016/S1474-4422(13)70076-0

OSMS/Seronegative NMO overlap syndromes

- MS therapies to avoid
  - Natalizumab (Barnett et al, Mult Scler 2012)
  - Fingolimod: isolated case report of severe exacerbation of NMO (Min et al, Mult Scler 2012)
  - Alemtuzumab: known to exacerbate autoimmune disorders
  - Interferon (Tanaka et al, Eur Neurol 2009; Palace et al Arch Neurol 2010; Shimizu et al, Neurology 2010)
- Drugs to consider
  - Copaxone
  - Mitoxantrone
  - Azathioprine/methotrexate
  - Rituximab

56 year old woman with multiple attacks of myelitis and ‘MS-like’ MRI brain



Palace et al. Arch Neurol 2010

SERONEGATIVE NMO

Is it a different disease?

Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients

Jarius et al J Neuroinflammation 2012

Kitley, Leite, Palace et al submitted

More males

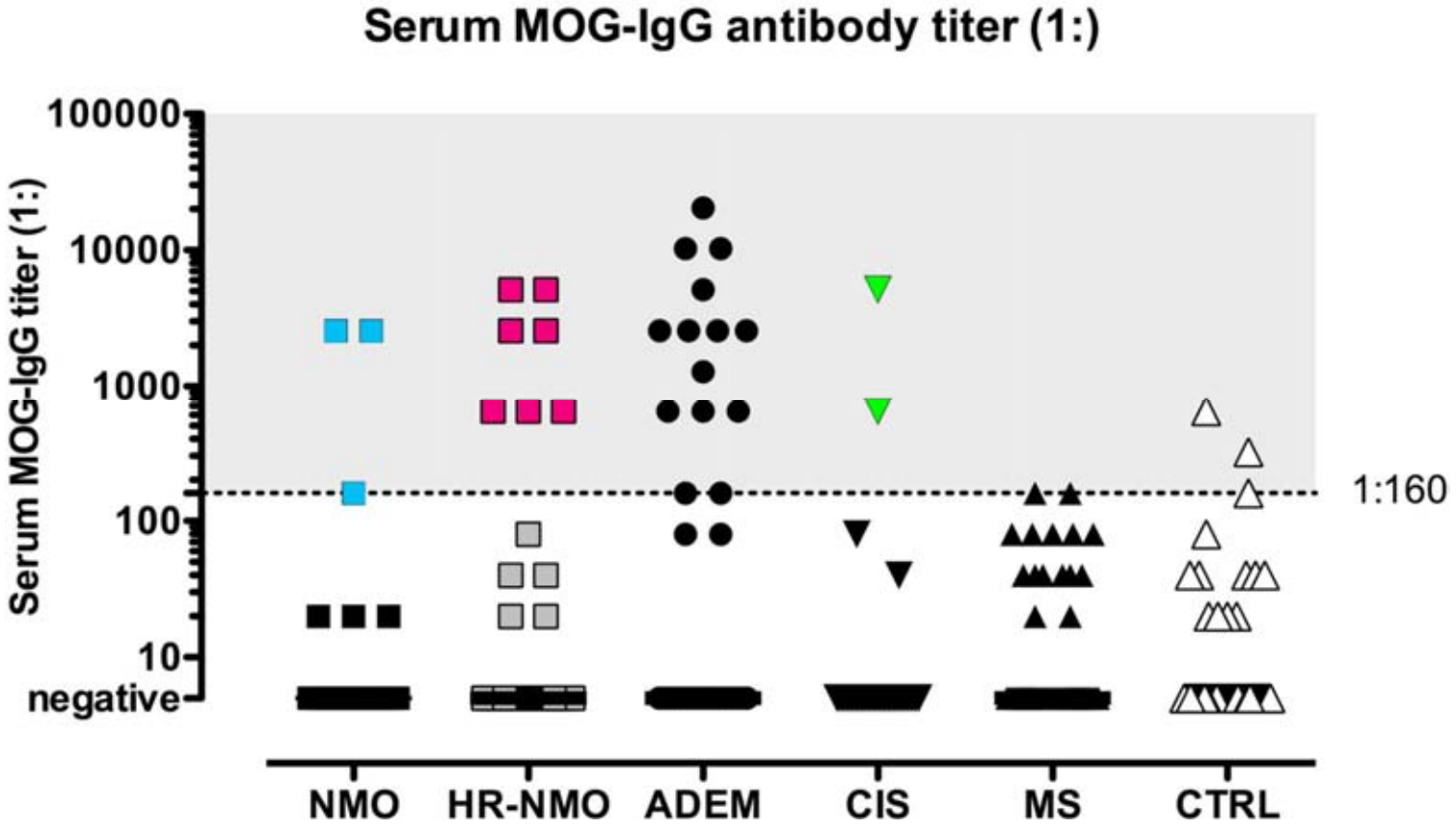
Lower EDSS

ON and LETM simultaneously

More monophasic

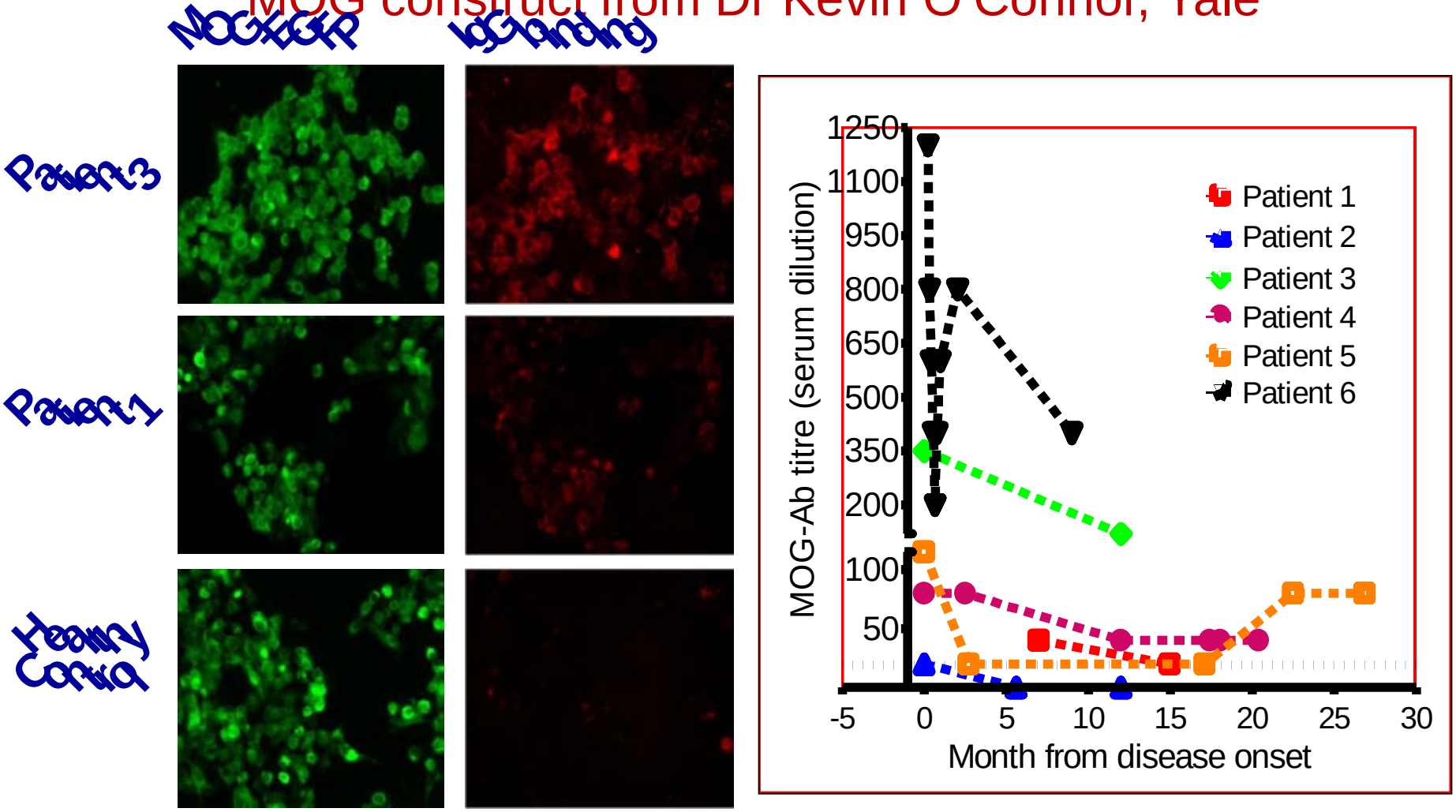
But do some have another antibody?

Antibodies to myelin-oligodendrocyte glycoprotein (MOG) Found in proportion of AQP4-Ab negative NMO



Mader et al J Neuroinflammation 2011

Antibodies to myelin-oligodendrocyte glycoprotein (MOG) in four adults with “NMO”
MOG construct from Dr Kevin O’Connor, Yale



Kitley, Woodhall et al Neurology and unpublished 2012

MOG antibody-associated NMO/NMO spectrum disorder

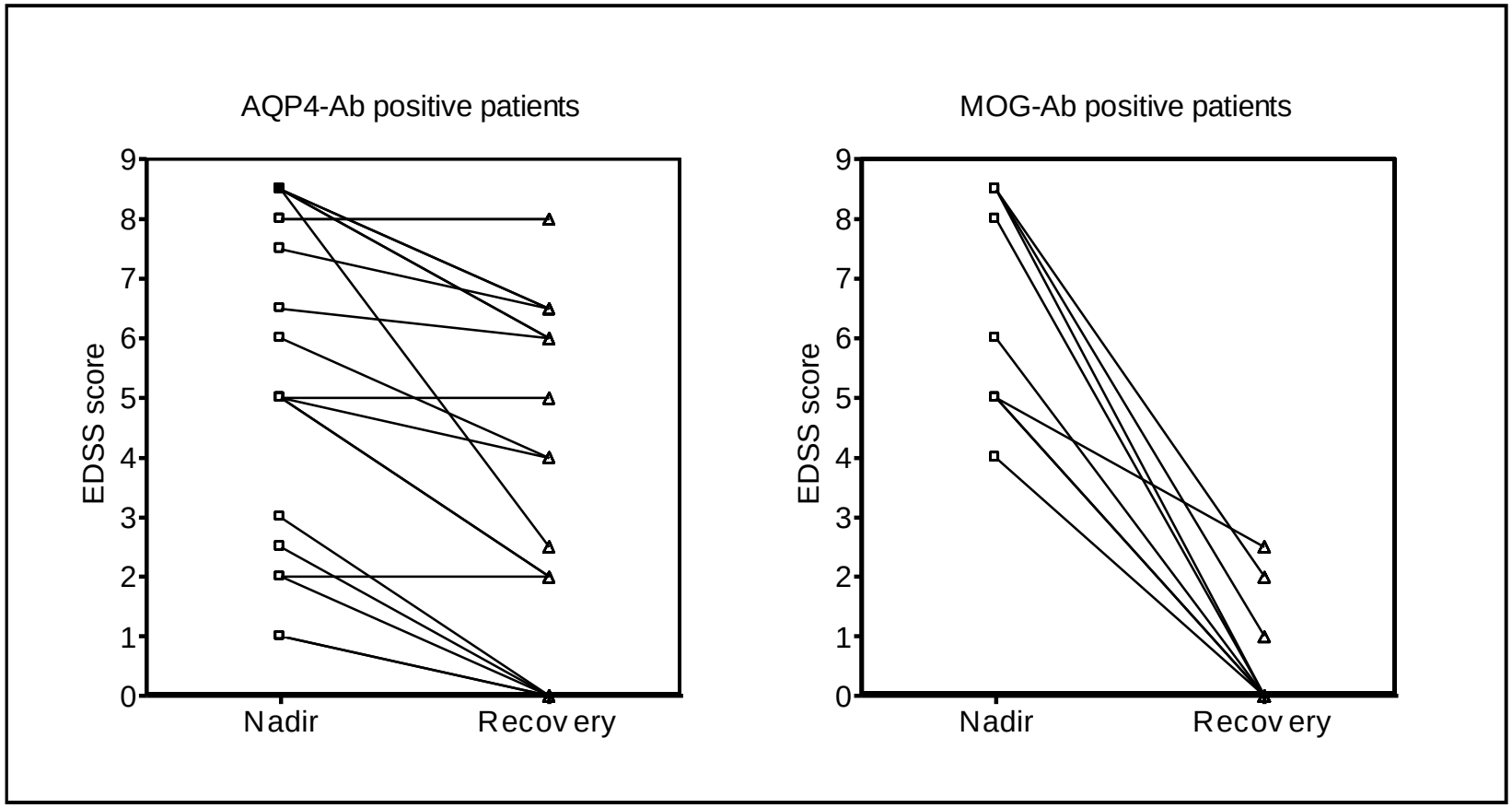
Younger age than AQP4-Ab positive NMOSD;

M>F

Myelitis involving the conus

Long segments of optic nerve involved

Good response to treatment.



Comparison between pre and post retreatment EDSS
In AQP4 and MOG antibody patients with
NMO/NMO-like disease
J Kitley in preparation

Summary

- AQP4-Ab disease is a severe relapsing remitting inflammatory disorder warranting prompt, aggressive and long-term treatment
- Be aware of atypical and limited phenotypes e.g. Afro-Caribbean patients with brain-only disease, brainstem encephalitis-like presentations, intractable hiccoughs and vomiting
- Avoid MS immunomodulatory therapies in OSMS/NMO overlap syndromes as well as in AQP4-Ab disease
- Seronegative NMO is likely a heterogeneous group of disorders
  - Test for MOG-Abs in all NMO patients who are AQP4-Ab negative

NMO and related diseases

A widening spectrum of antibody-mediated conditions

Poor or adverse response to typical DMTs in typical AQP4-Ab positive patients

Require aggressive and sustained immunotherapies to prevent accumulation of disability

MOG antibodies with NMO-type phenotype may indicate a more monophasic and treatment-responsive disease

Acknowledgements

The National Health System support for NMO

Dr Anu Jacob (Liverpool), Dr Jackie Palace (Oxford)

Dr Joanna Kitley, Clinical Fellow, Oxford