
UK Nationally Commissioned NMO team

Setting the Scene: Neuromyelitis Optica

epidemiology, population variability, subgroups: relapsing/monophasic, Ab +ve/-ve, NMO/SD, treated/untreated

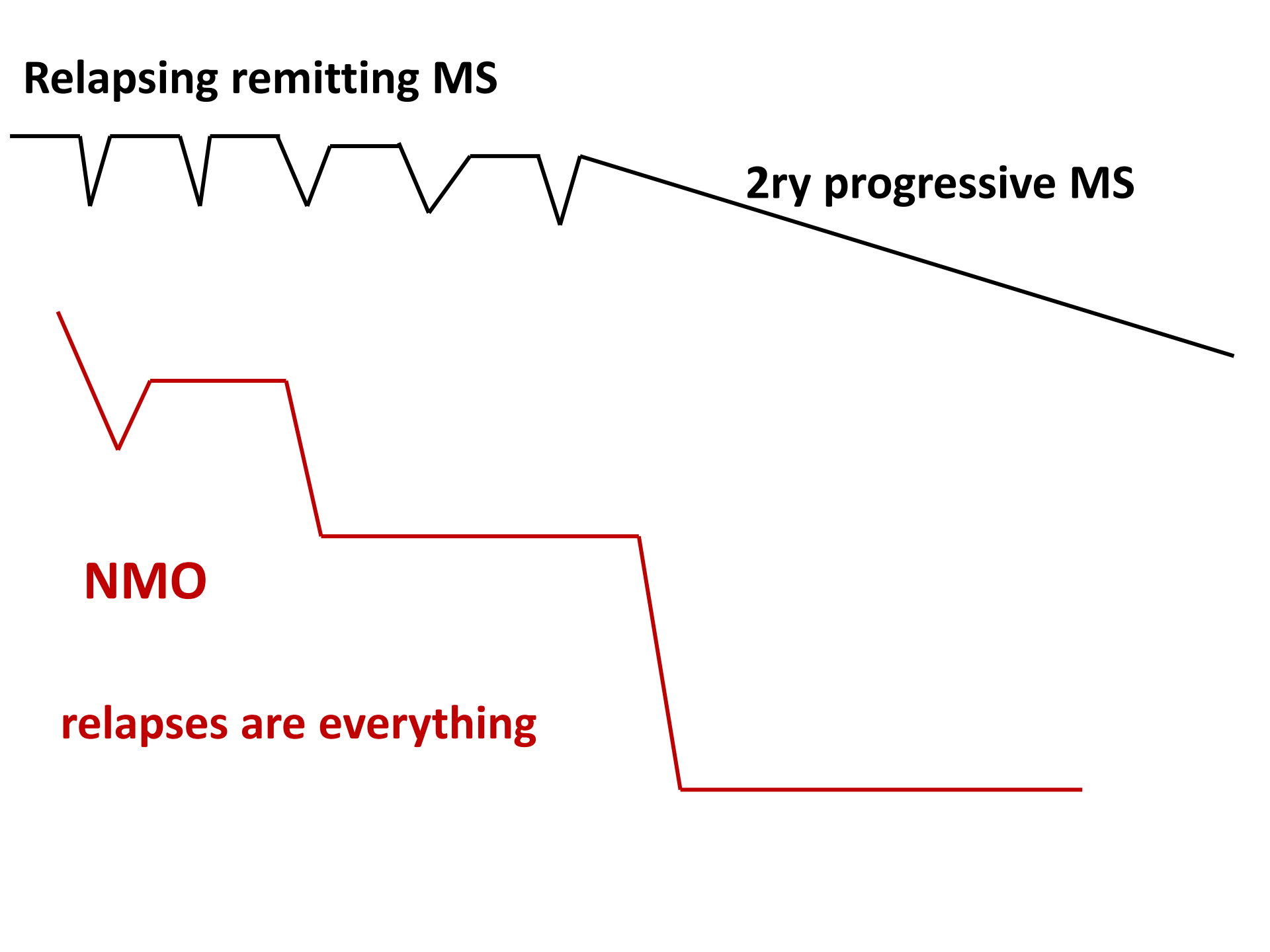
Jackie Palace

Disclosures

J. Palace is partly funded by highly specialised services to run a national congenital myasthenia service and a neuromyelitis service. She has received support for scientific meetings and honorariums for advisory work from Merck Serono, Biogen Idec, Novartis, Teva, Chugai Pharma and Bayer Schering, and unrestricted grants from Merck Serono, Novartis, Biogen Idec and Bayer Schering. Her hospital trust receives funds for her role as clinical lead for the RSS, and she has received grants from the MS society and Guthie Jackson Foundation for unrelated research studies.

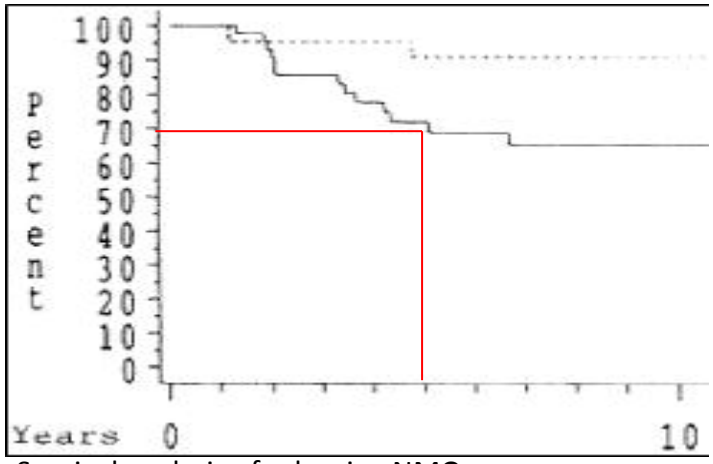
Multiple Sclerosis

NMO: ON + LETM


Relapsing remitting MS
2ry progressive MS
NMO
relapses are everything

HIGH MORTALITY AND MORBIDITY

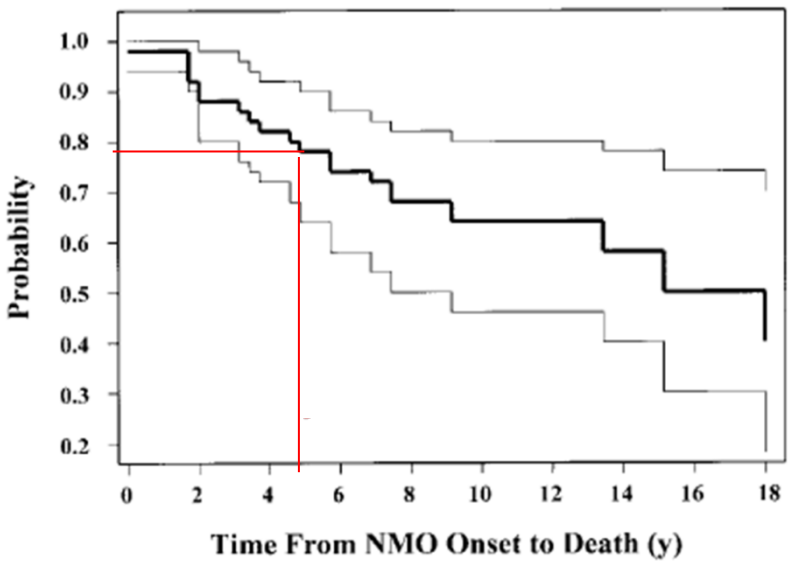
1999 **30% 5yr mortality**



Survival analysis of relapsing NMO

2003 **22% 5yr mortality**

Wingerchuk et al, NEUROLOGY 2003;60:848–853



Brain 2012 Jun;135(6):1834-49 2012 **14% 5yr mortality** (ab positive, many undiagnosed)

UK cohort

29% wheelchair dependant (> in elderly)

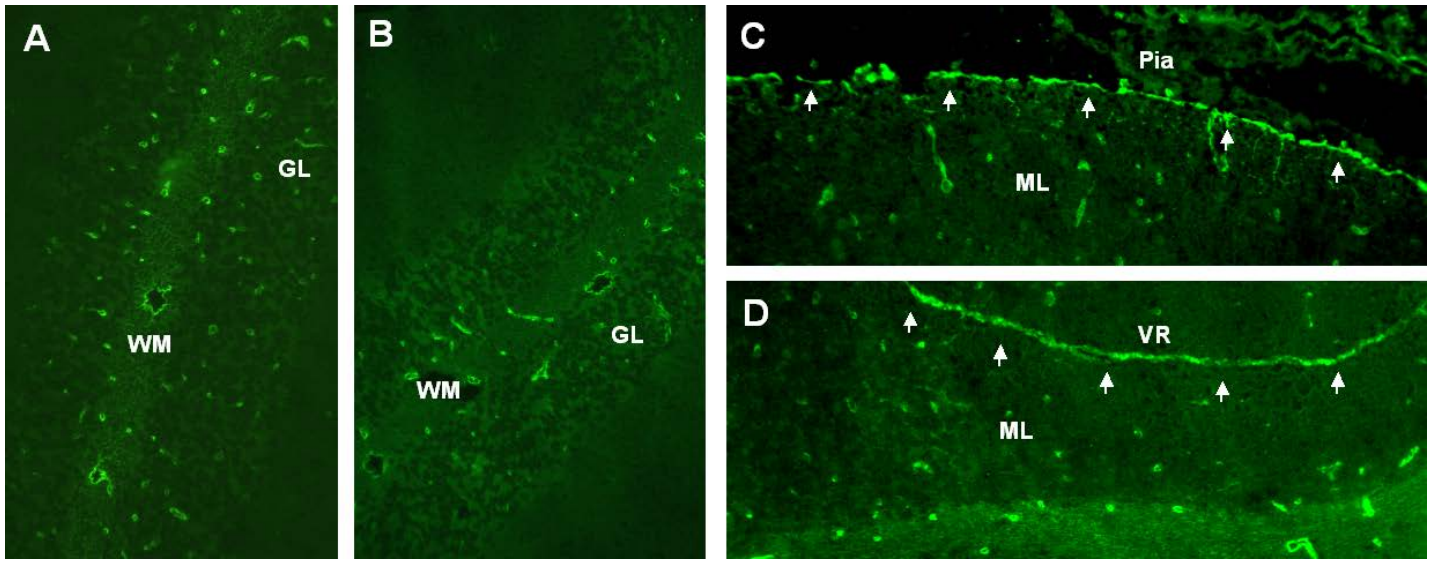
22% severe bilateral visual impairment (> young)

Time to 1st relapse: on treatment median 57 months mean 74.1

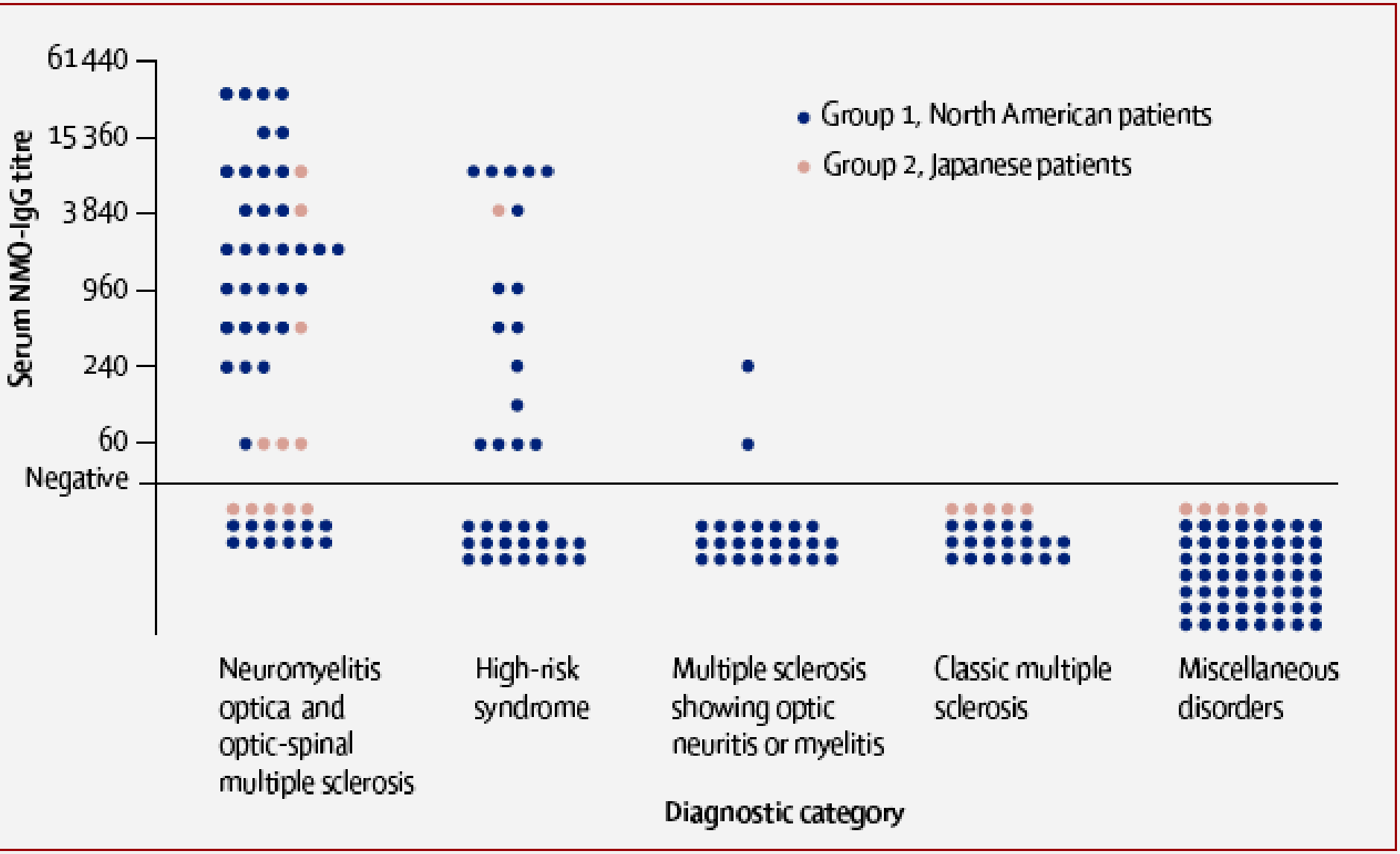
off treatment median 9 months mean 20.4 months (p< .001].

Auto-antibody in neuromyelitis optica

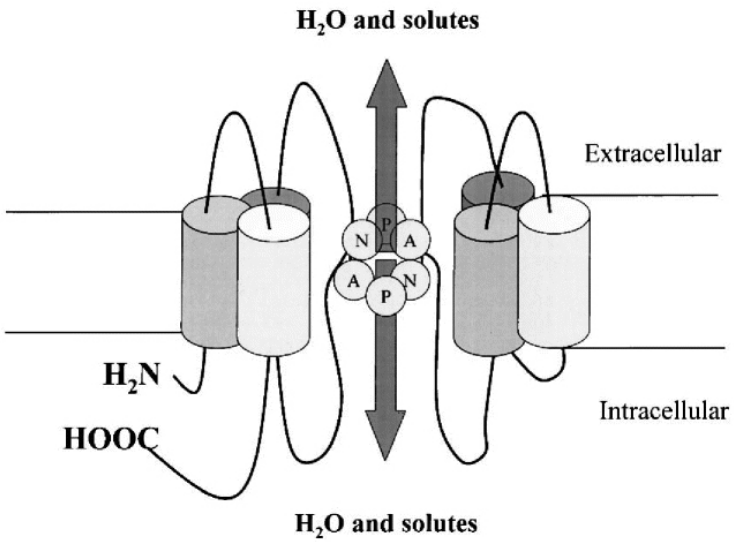
NMO IgG assay: First reported by Lennon et al, Lancet 2004; detected by immuofluorescence

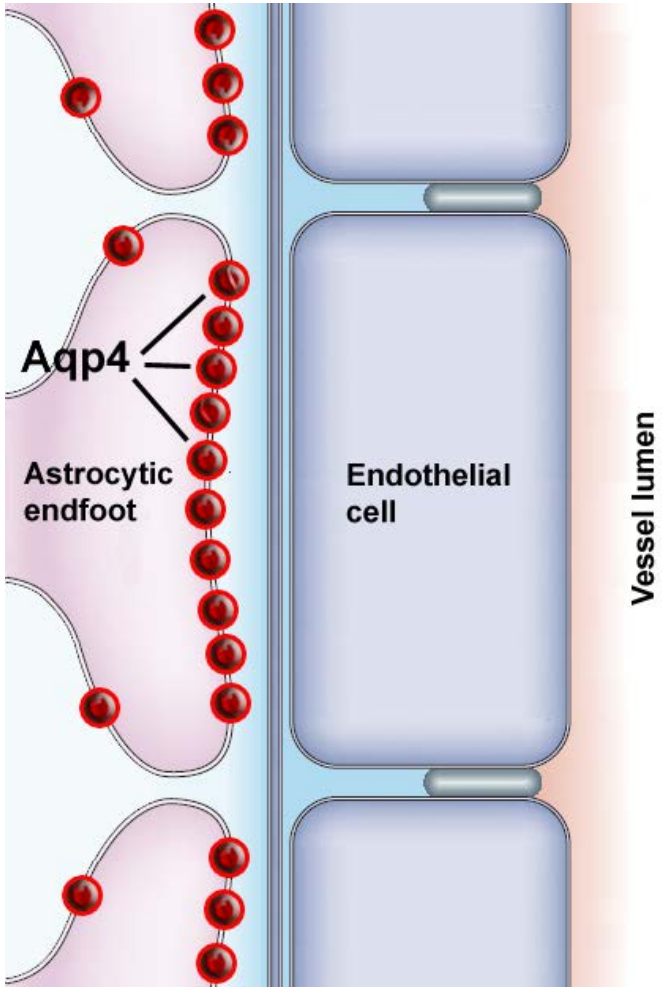


Serum contains IgG binds to mouse cerebellum in a characteristic pattern: microvessels, pia & Virchow Robin spaces


61 440
15 360
3 840
960
240
60
Negative
Serum NMO-IgG titre
Group 1, North American patients
Group 2, Japanese patients
Neuromyelitis optica and optic-spinal multiple sclerosis
High-risk syndrome
Multiple sclerosis showing optic neuritis or myelitis
Classic multiple sclerosis
Miscellaneous disorders
Diagnostic category

Aquaporin-4 identified as antigen

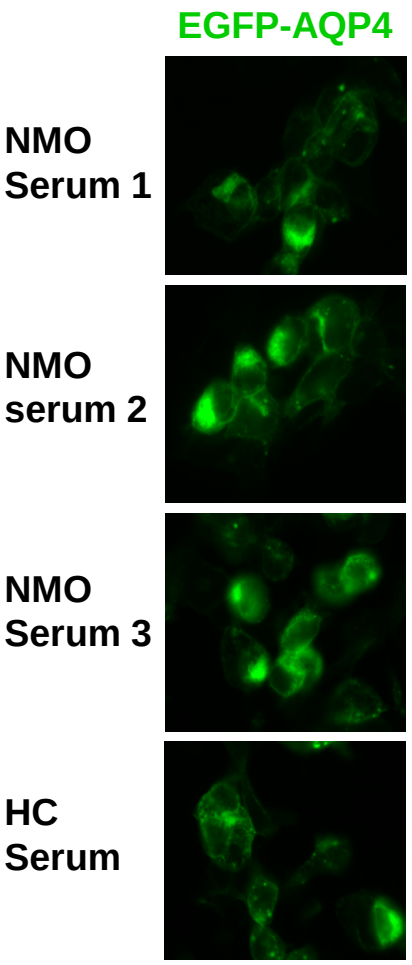


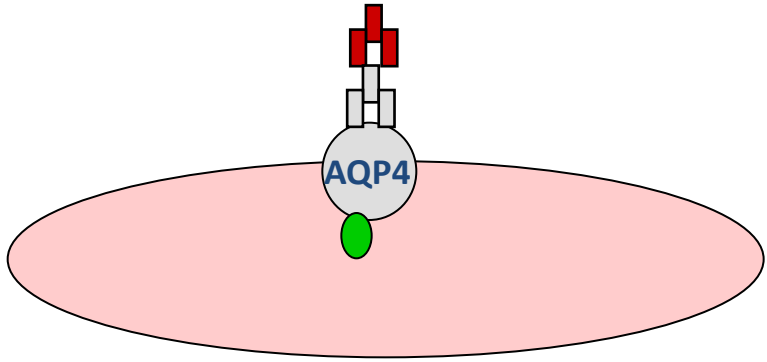


most abundant water channel in CNS
Concentrated in astrocytic foot processes

Lennon et al Lancet 2004; J Ex Med 2005

Cell Based Assay (CBA) for AQP4 antibodies: qualitative, sensitive, specific





HEK cells transfected with EGFP-AQP4

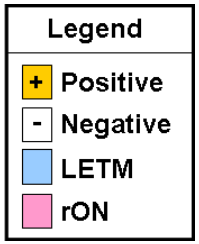
IgG from NMO patient binds to green tagged AQP4 on surface of HEK cells

Marked variability in the NMO antibody assay

Sensitivity depends on:

- Assay Technique
- Isoform of AQP4 used
- Observer or Kit
- Laboratory

Diagnosis	FACS	CBA-O	CBA-E	ELISA-R (<1.6)	ELISA-R (5.0)	FIPA-0	FIPA-M	IIF
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMO	+	+	+	+	+	+	+	+
NMOSD-TM	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	-
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	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
NMO	-	-	-	-	-	-	-	-
Positive	46/60	44/60	41/60	42/60	36/60	32/60	32/60	29/60
Negative	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



Waters et al,
Neurology. 2012 Feb 28;78(9):665-71

Multiple Sclerosis

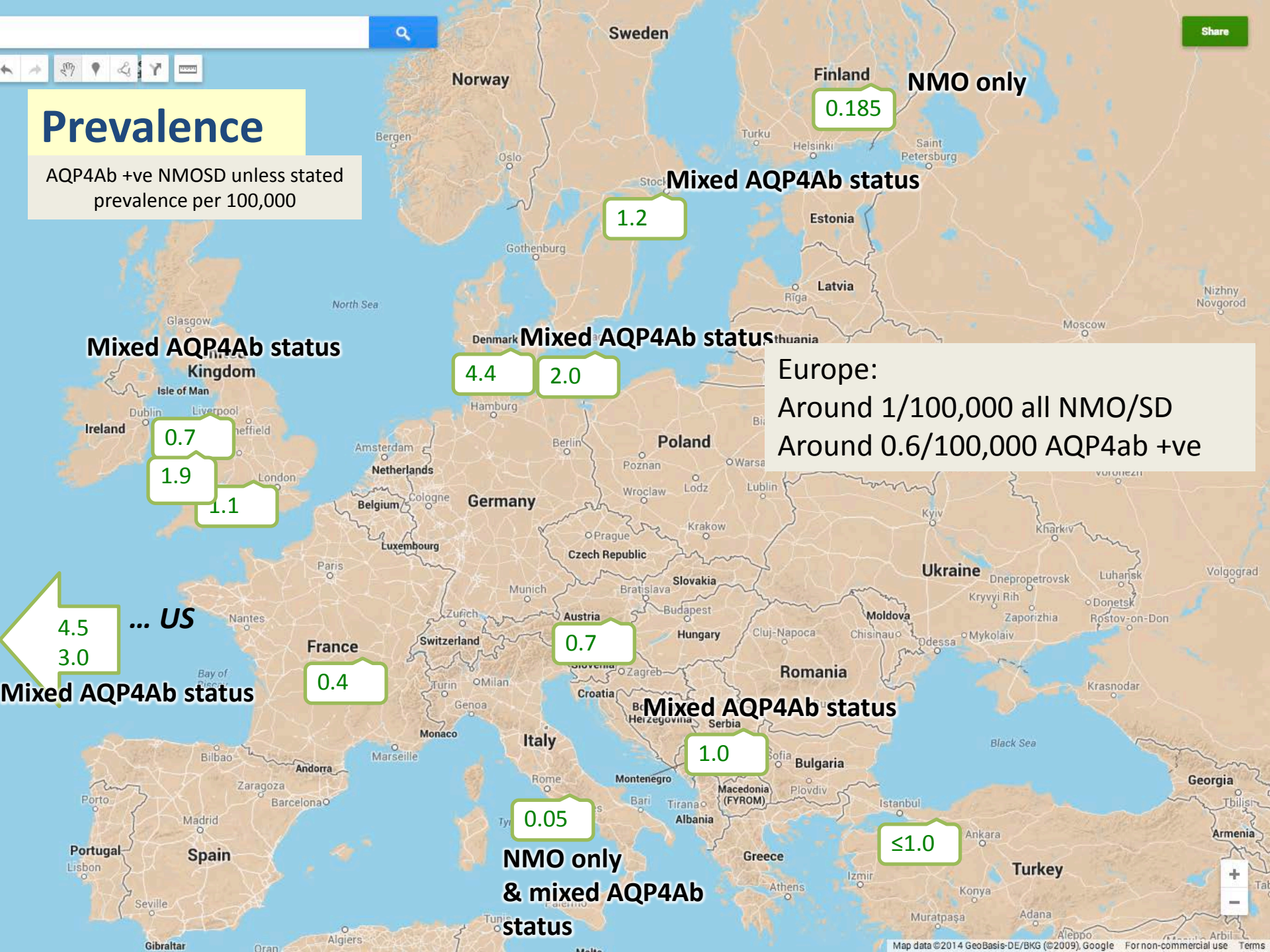
NMO

NMOSD

LETM
Longitudinally extensive transverse myelitis

ON:
recurrent
simultaneous bilateral
w auto-immune disease
w NMO typical brain lesions
poor visual outcome

Inflammatory brain lesions with AQP4 abs


Prevalence
AQP4Ab +ve NMOSD unless stated
prevalence per 100,000
NMO only
0.185
Mixed AQP4Ab status
1.2
Mixed AQP4Ab status
4.4
2.0
Mixed AQP4Ab status
0.7
1.9
1.1
4.5
3.0
… US
Mixed AQP4Ab status
0.4
0.7
Mixed AQP4Ab status
1.0
0.05
NMO only
& mixed AQP4Ab
status
≤1.0
Europe:
Around 1/100,000 all NMO/SD
Around 0.6/100,000 AQP4ab +ve
Sweden
Norway
Finland
Estonia
Latvia
Denmark
Ireland
Isle of Man
Netherlands
Belgium
Germany
Poland
Czech Republic
Slovakia
Austria
Hungary
Switzerland
France
Luxembourg
Ukraine
Moldova
Romania
Croatia
Serbia
Bulgaria
Italy
Monaco
Spain
Portugal
Andorra
Montenegro
Albania
Greece
Turkey
Georgia
Armenia
North Sea
Black Sea
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NMO/NMOSD

Females:

80-90% AQP4 ab +ve, 50% ab negative

World wise disease

Rarer than MS

1:30 – 1:100 West

1:2 -1:10 Asia

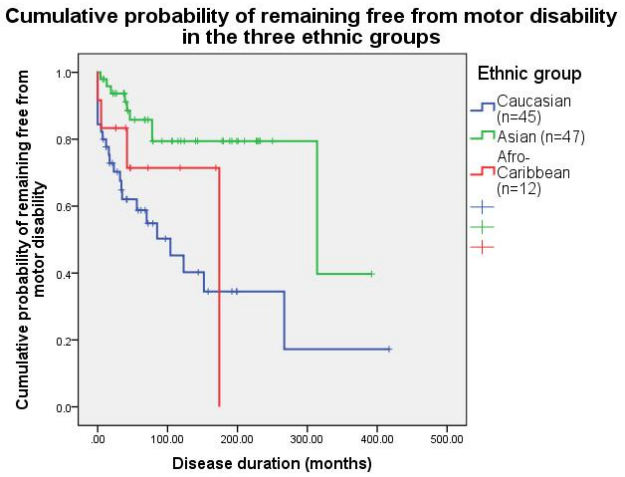
Afro-Caribbeans over represented in Europe and US

Ethnic effect on outcome

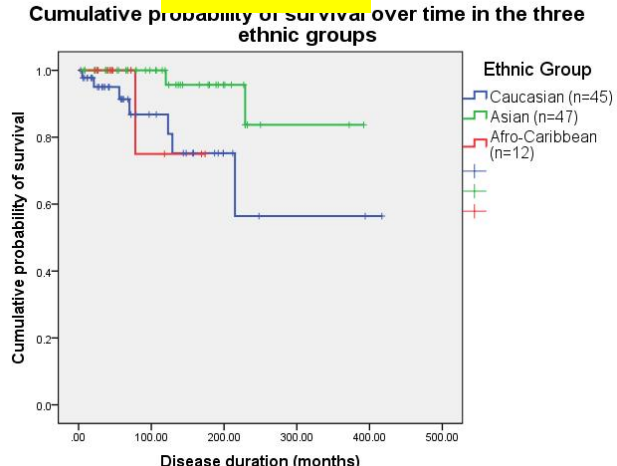
UK: n=59 Caucasian and Afro-caribbean Japan: n= 47 all Asian

worse in Caucasians

Motor disability

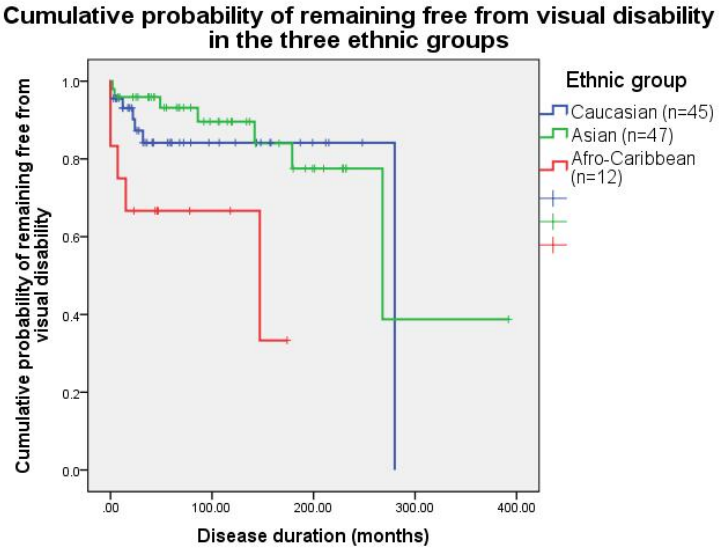


Survival



worse in Afro-Caribbeans

Visual disability



Brain 2012 Jun;135(Pt 6):1834-49

Age onset around 40yr (range 3-81)

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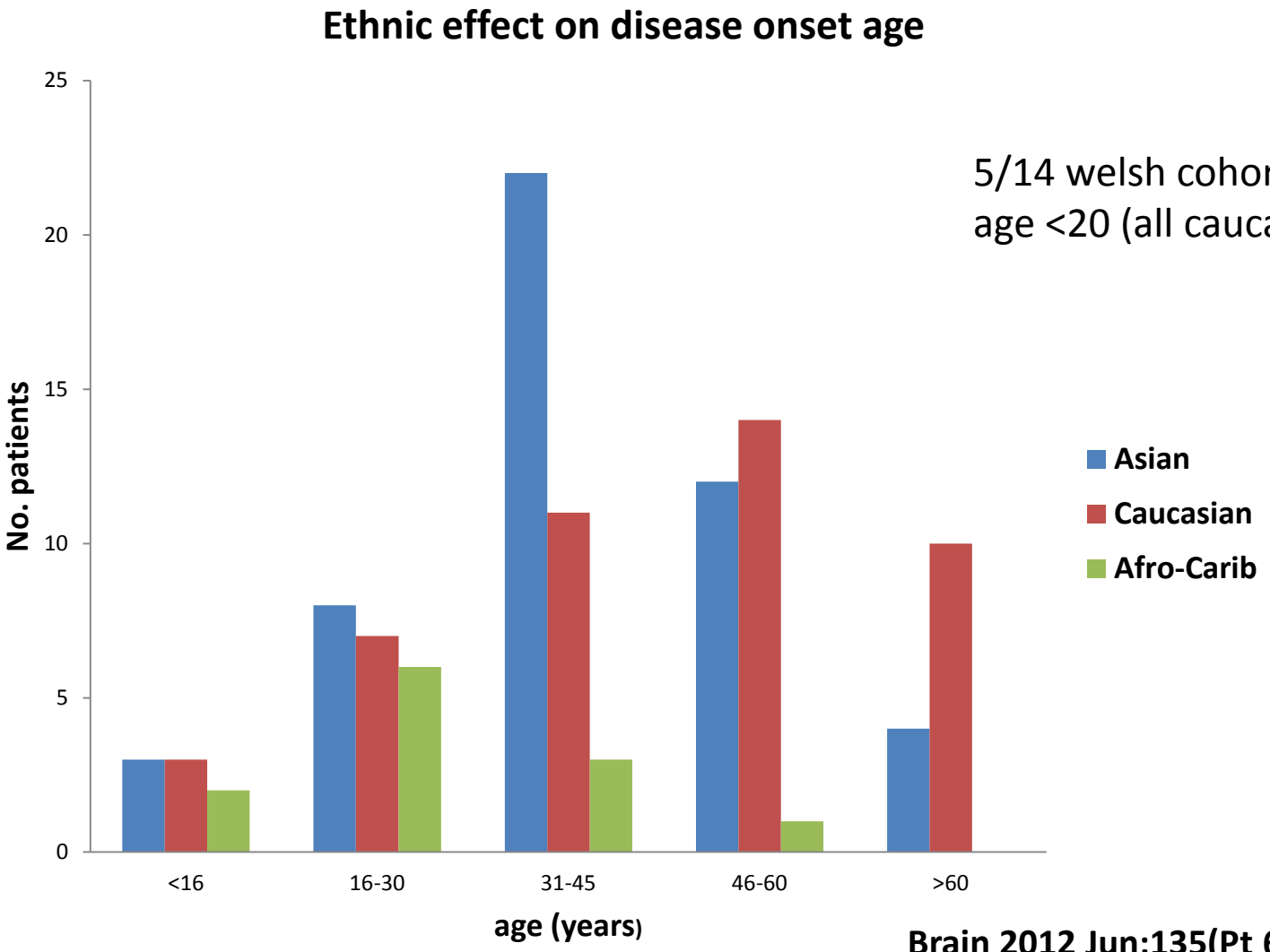
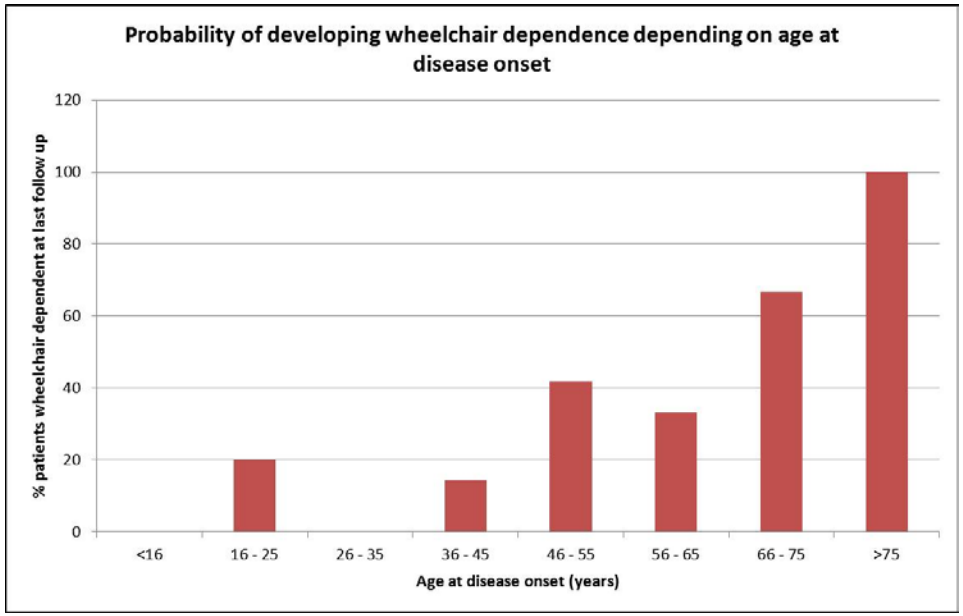


5/14 welsh cohort onset age <20 (all caucasian)

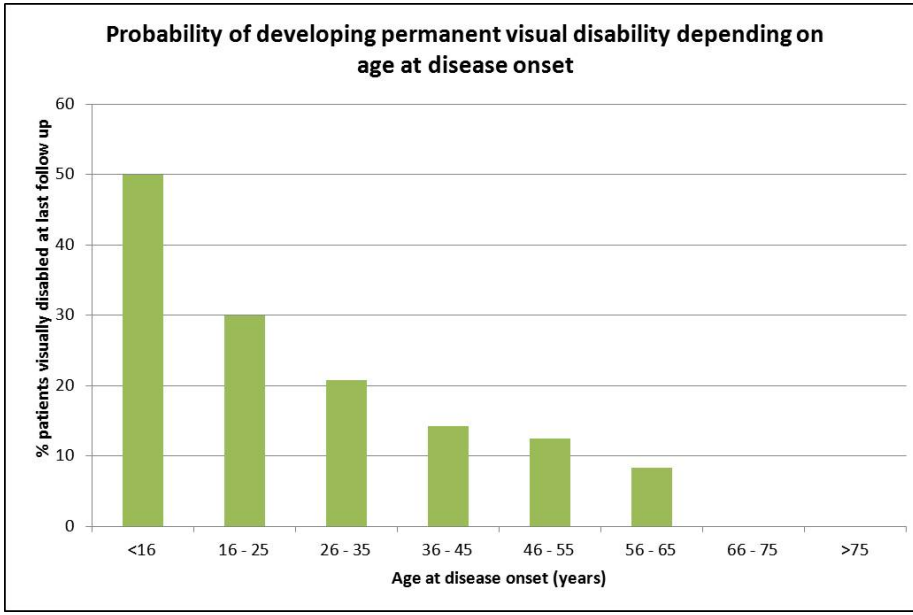
Brain 2012 Jun;135(Pt 6):1834-49

Onset age and outcome

Motor disability

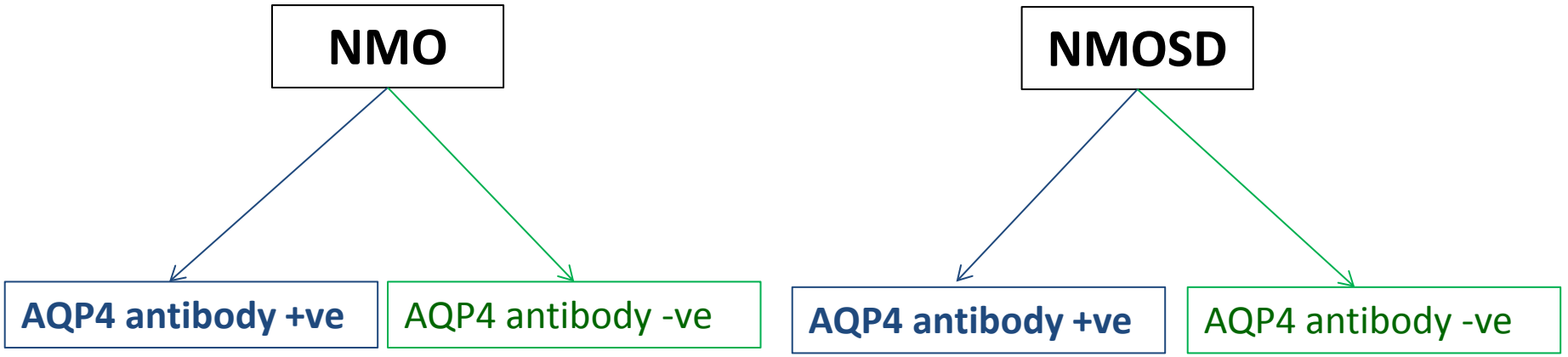


Visual disability



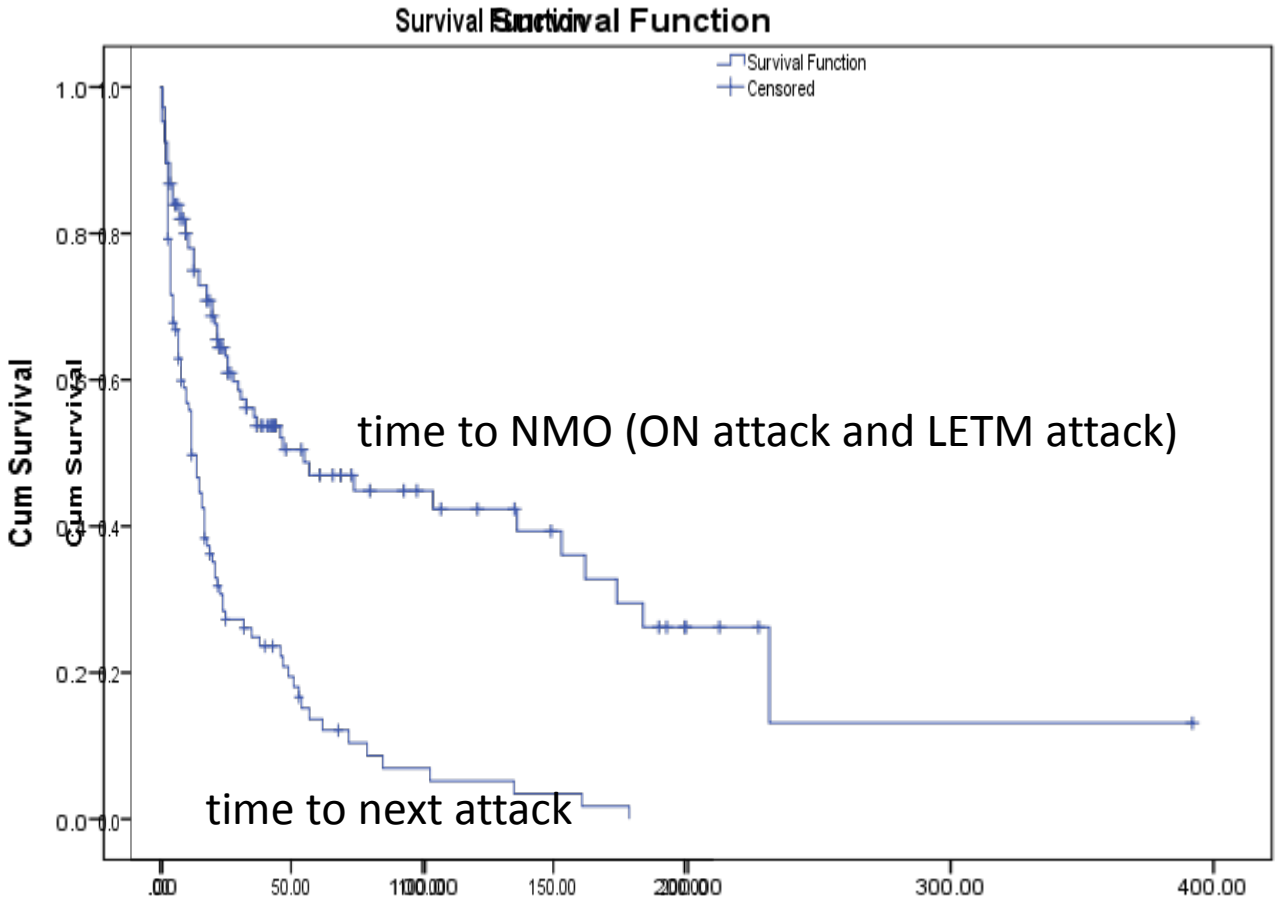
Brain 2012 Jun;135(Pt 6):1834-49

The Spectrum



55% all NMO/NMOSD

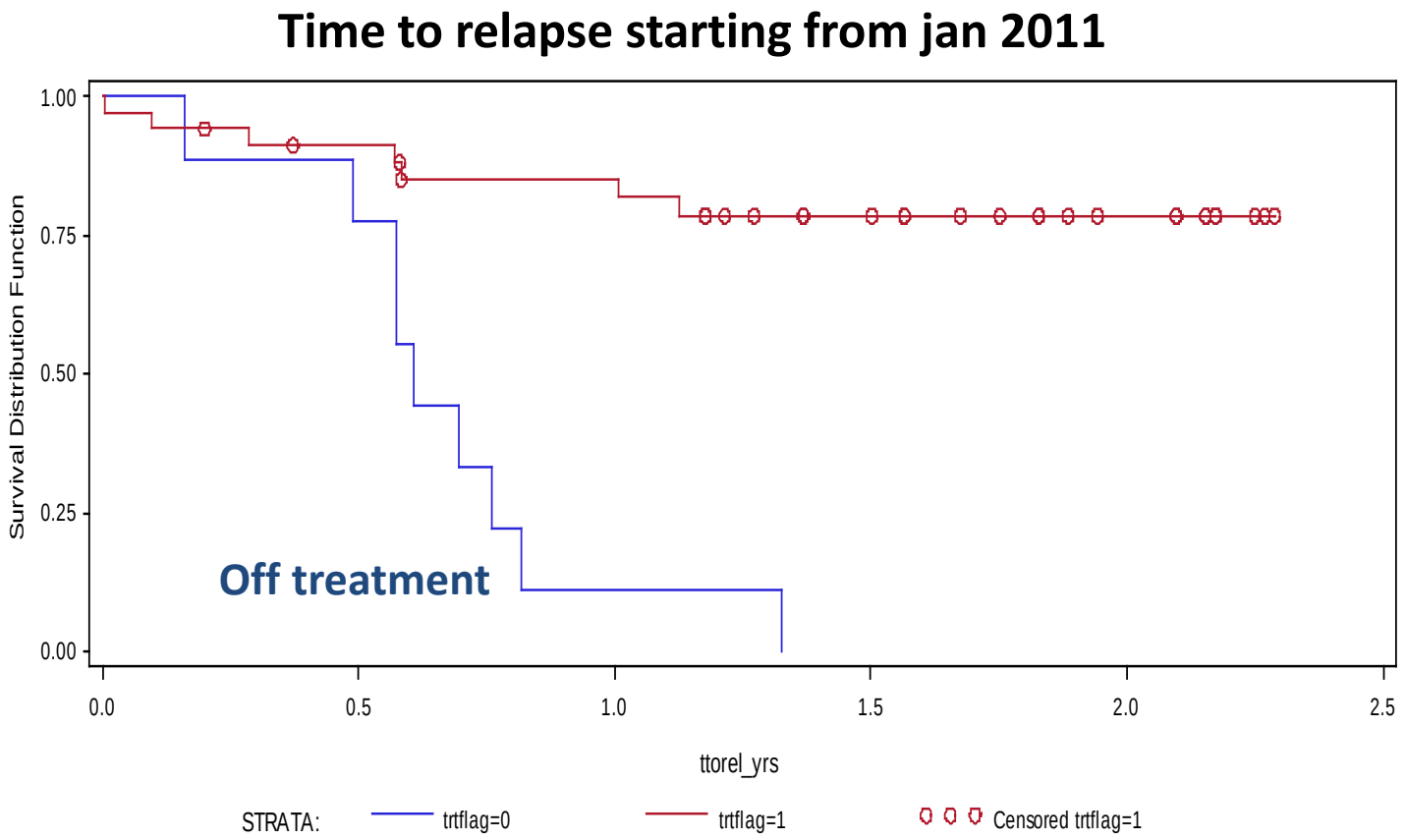
AQP4ab +ve NMO and NMOSD the same disease
96% start as NMOSD



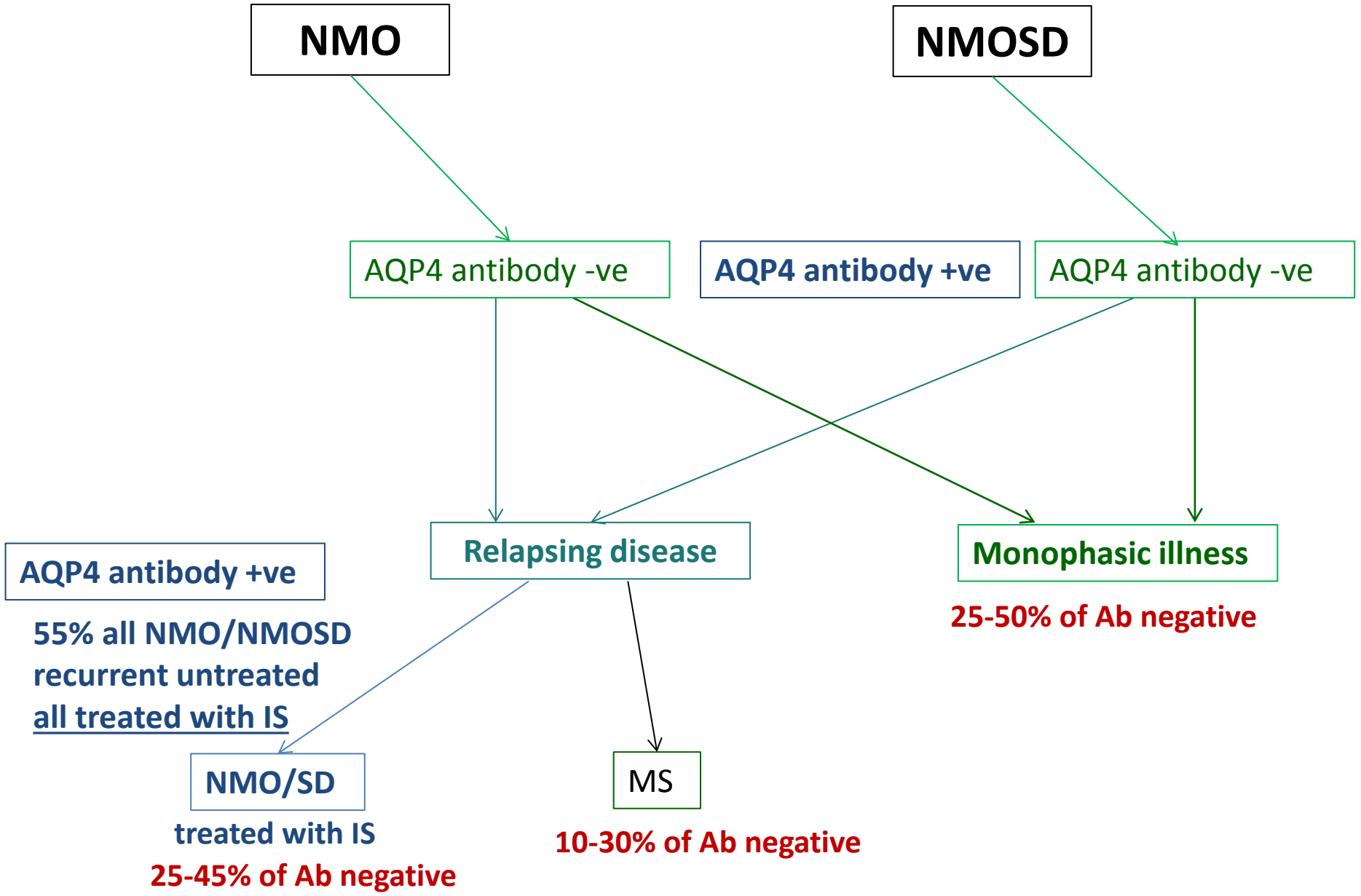
106 AQP4 + patients

Brain 2012 Jun;135(Pt 6):1834-49

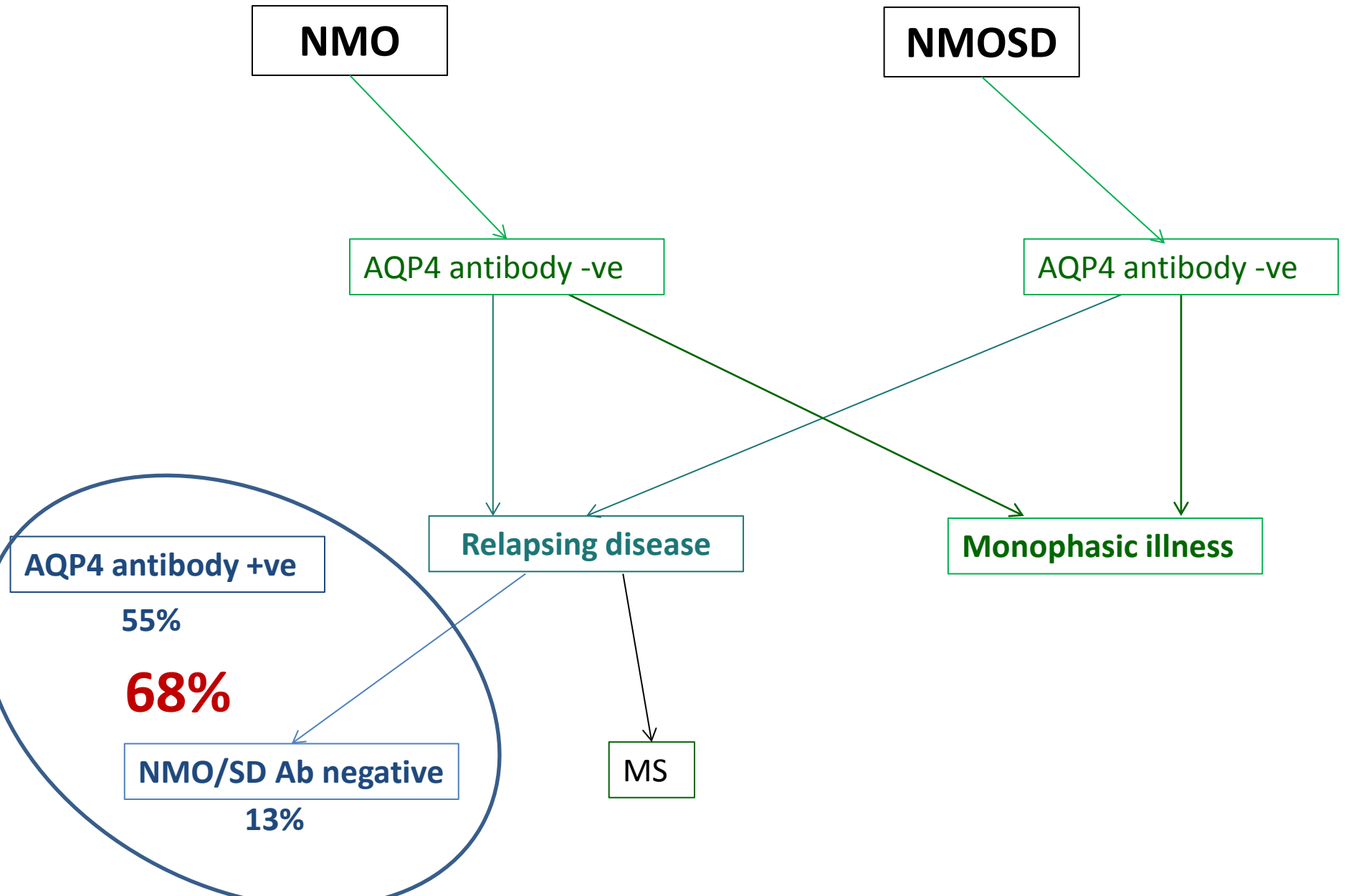
AQP4 ab disease is a relapsing disease (untreated)



The Spectrum



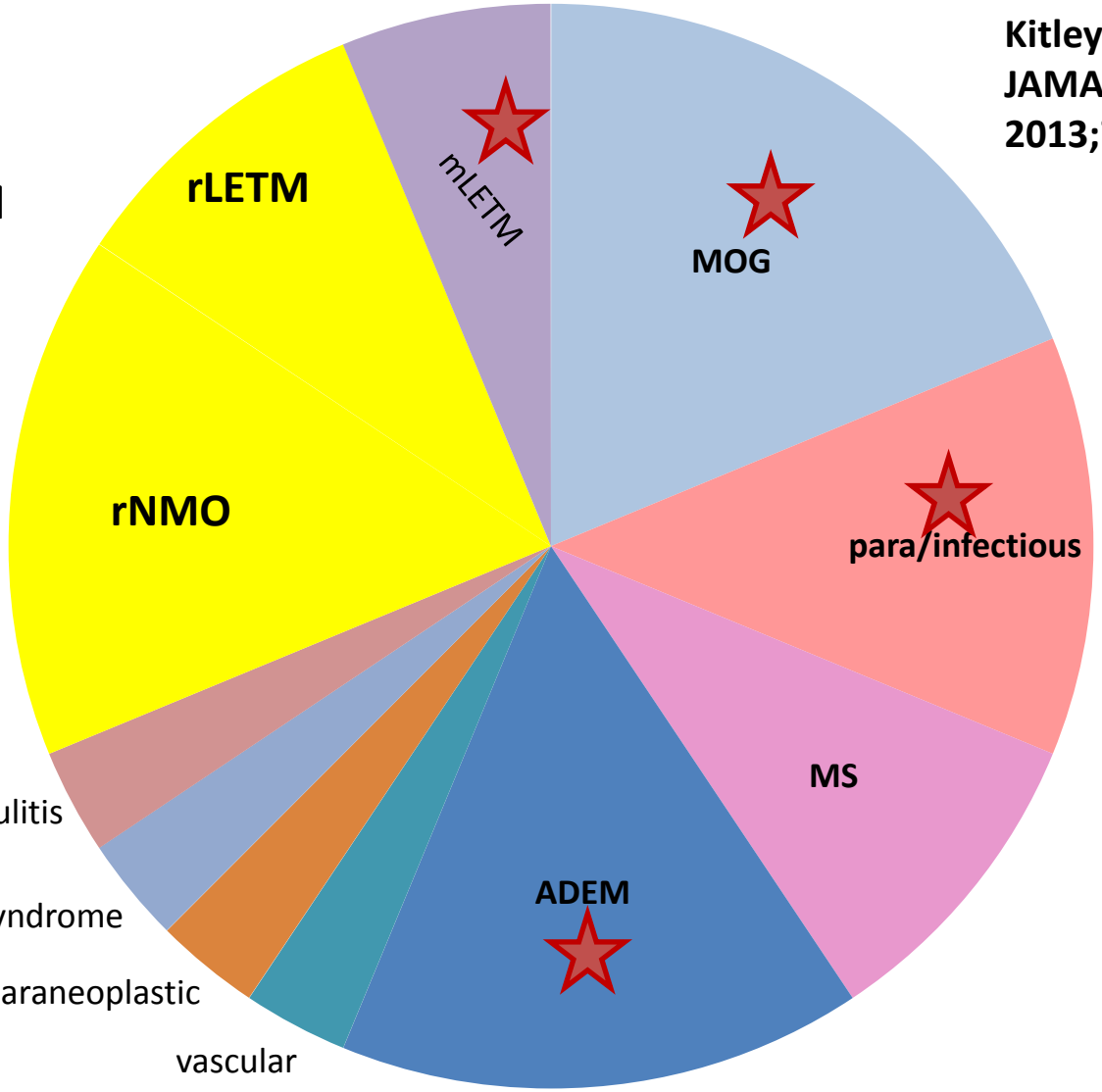
The Spectrum



Majority of seronegative NMO/LETM have alternative diagnoses

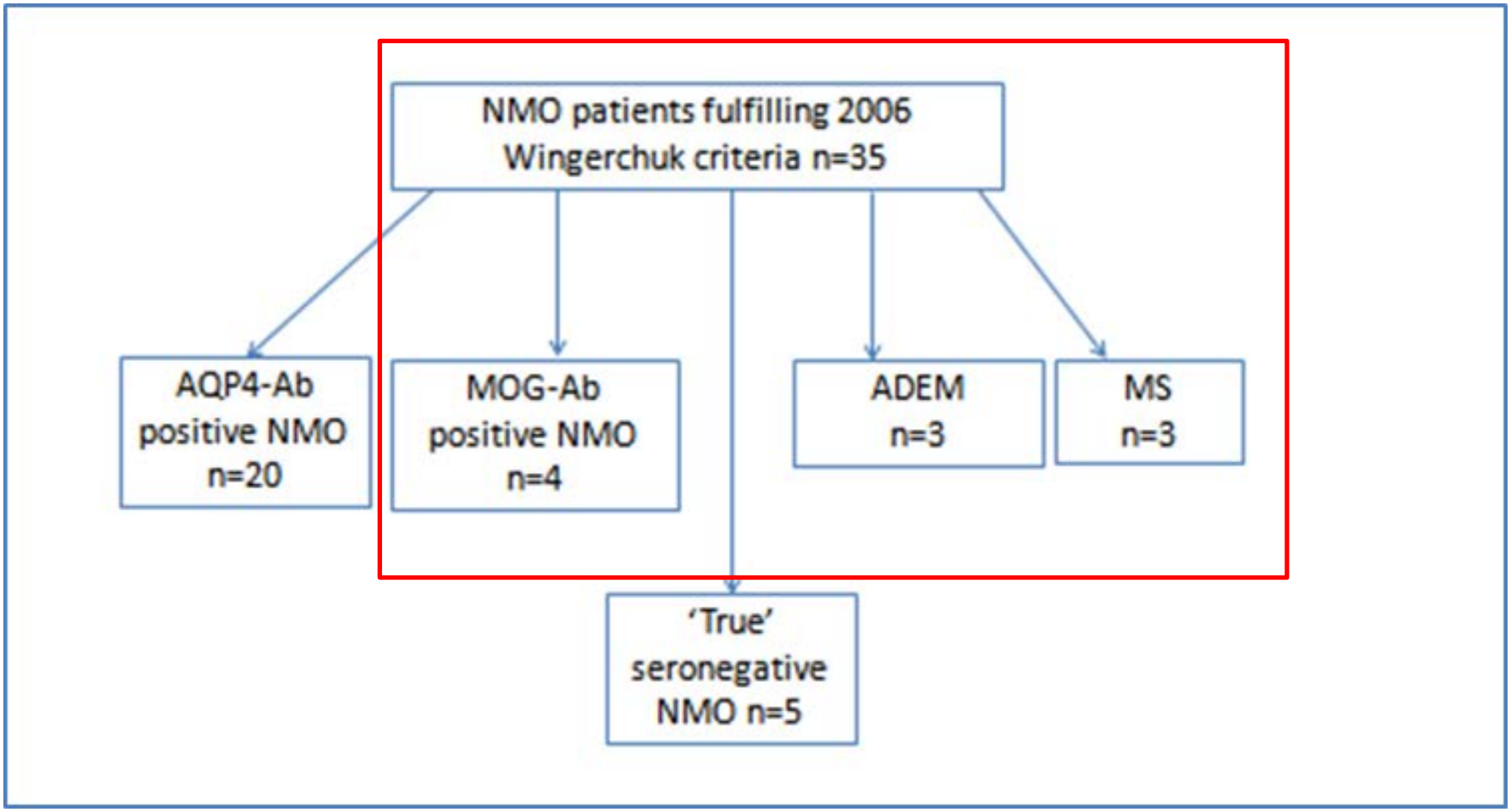
Kitley et al
JAMA Neurol.
2013;70(11):1375-1381

36 AQP4 ab -veM



MANY MONOPHASIC

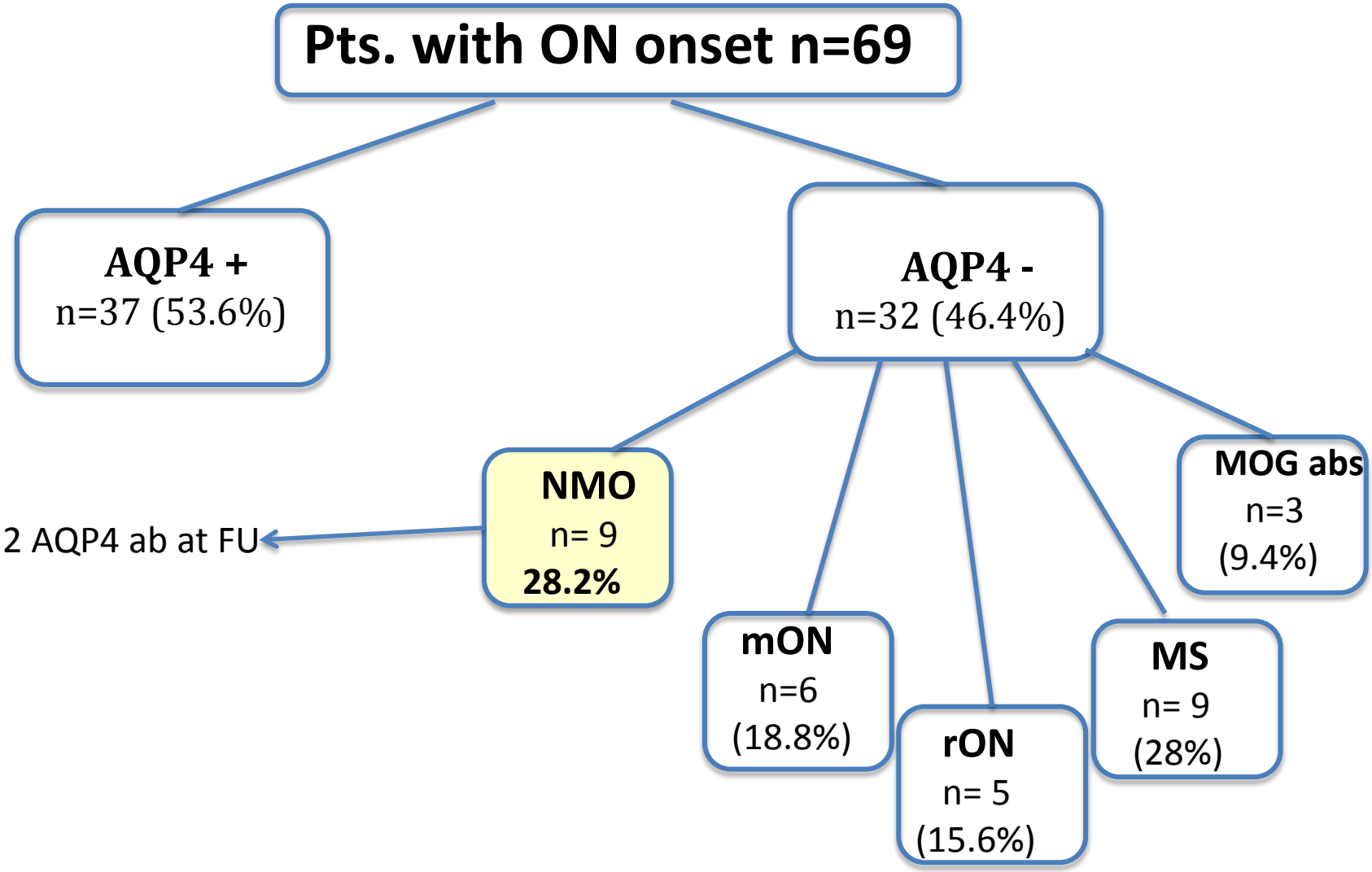
66% of ab-neg fulfilling 2006 criteria for NMO had other diseases



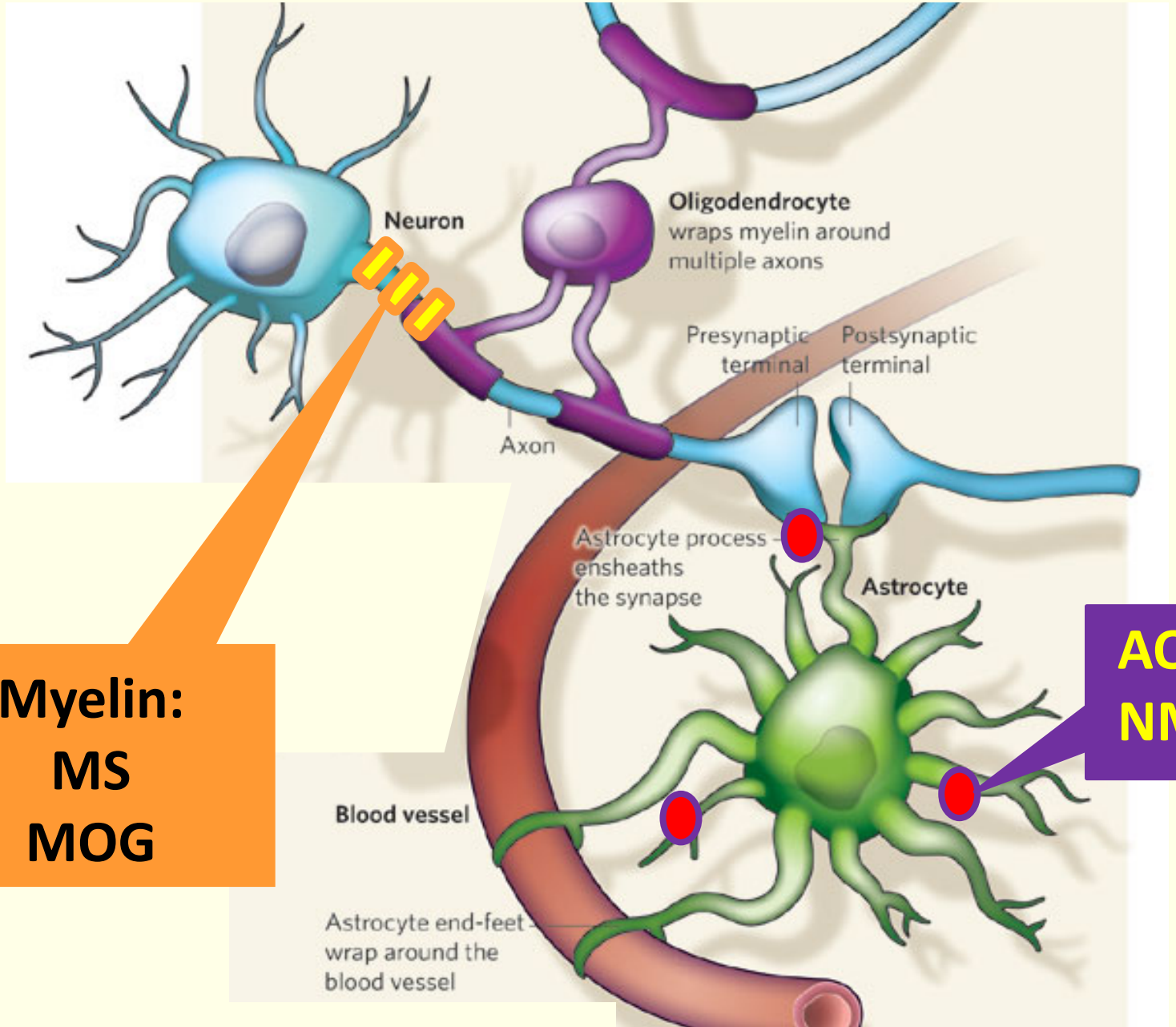
Majority of seronegative ON onset patients in Oxford NMO service

(severe and/or bilateral and/or recurrent)

have alternative conditions



AQP4 and MOG on different CNS locations



Myelin:
MS
MOG

AQP4
NMO

MOG antibody disease: a monophasic LE TM ± ON with full recovery

Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype
Joanna Kitley, Mark Woodhall, Patrick Waters, et al.
Neurology 2012;79:1273-1277 Published Online before print August 22, 2012

Sex/ Age	Clinical features	Diagnostic criteria	Treatment	Outcome (clinical, MRI, VEPs)
F 32	Severe unilateral ON + LETM Brain lesions	NMO	IVMP oral pred + aza	Mild bladder symptoms
M 27	Severe LETM	NMOSD	IVMP & PE oral pred	Full recovery
M 34	Severe bilateral ON + mild TM (LETM) Brain lesions	NMO	IVMP	Full recovery
M 16	Severe bilateral ON + mild TM (LETM) w ADEM like rebound	NMO	IVMP po steroids	Full recovery
M30	Bilat ON severe LETM	NMO	IVMPred & PE	Full recovery
M3	Severe bilat ON Asymptomatic LETM		IVMpred	Full recovery

MOG antibody disease: monophasic NMO

- Always AQP4 ab negative
- Male predominant

- Usual: monophasic, classic 'Devics' disease (ON + LETM)
- Virtual complete recovery w MPred ± PLEX

- Caution: exception childhood: MS, ADEM,
  some MOG assays find in young adults 'MS' like disease

Key Messages

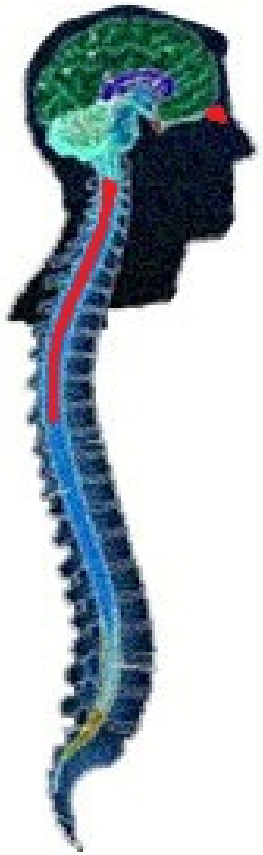
NMOSD we are interested in:

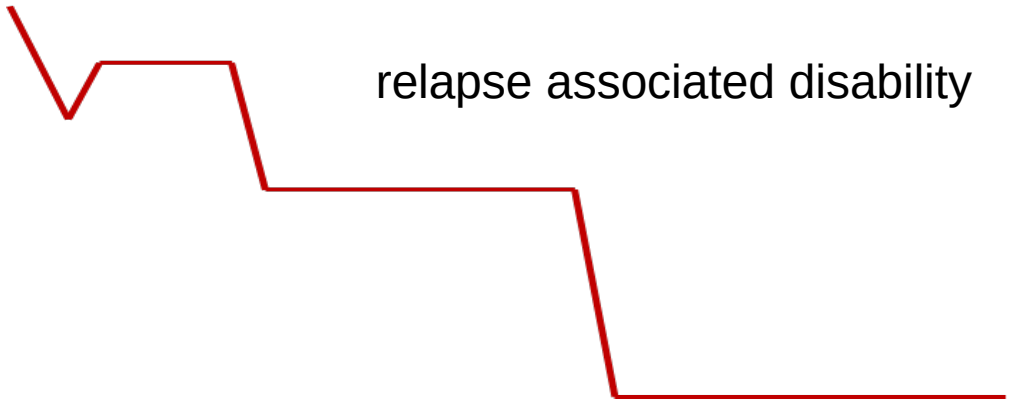
- Worldwide disease
- All ages
- Female predominant
- Afro-Caribbean susceptible

- AQP4ab +ve: relapsing disease, high mortality & morbidity,
- Relapses are total cause disability

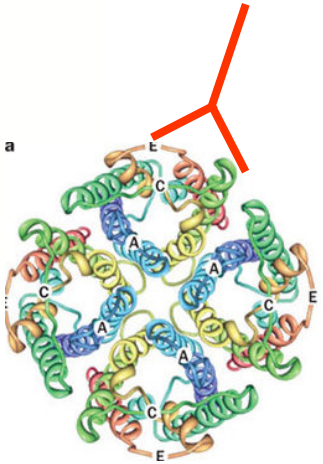
- Antibody negative patients many different conditions ,
  often monophasic, 25-45% being 'true' NMOSD,
- AQP4ab+ve and relapsing NMOSD are immunosuppressed

- Prevalence Europe about 1:100,000
- ~ 68% of total have true NMO/NMOSD:
  all AQP4ab+ve (55%) + ~ 1/3 ab negative (13%)





Antibodies



CNS water channel AQP4

Wingerchuk et al, NEUROLOGY 2003;60:848–853