XXII World Congress of Neurology
Santiago - Chile 2015
Changing Neurology Worldwide

Santiago, Chile, October 31 - November 5, 2015

WCN 2015

Teaching Course: *Neuroimmunology And Multiple Sclerosis* TC14
(Cordillera-2, 15:00-16:00, November 1, 2015)

UPDATE IN NMO

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Disclosure (Kazuo Fujihara, M.D.)

Scientific Advisory Boards

Bayer Schering, Biogen Idec, Mitsubishi Tanabe, Novartis, Chugai, Ono, Nihon, Merck Serono, Alexion, Medimmune, Medical Review

Speaker Honoraria

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Research Support

Bayer Schering, Biogen Idec, Asahi Kasei, Chemo-Sero-Therapeutic Research Institute, Teva, Mitsubishi Tanabe, Teijin, Chugai, Ono, Nihon, Genzyme Japan

Government Funding

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"Prevalence of NMOSD is fairly constant in the world "

- **Worldwide** 0.5 ~ $5/10^5$

- **Japan (Nation-wide)** (2013)
  Definite NMO $1.9/10^5$, NMOSD $3/10^5$
- **India (Mangalore)** (Pandit, MSJ 2014)
  NMOSD $2.6/10^5$

- **Southern Denmark** (Asgari, Neurology 2011)
  NMOSD $4.4/10^5$
- **Northern California** (Pittock, JAMA Neurol 2014)
  NMOSD $3/10^5$

"NMO:MS Ratio is high in Asia"

Taiwan (Chang, MSJ 2006)
- OSMS:CMS = 42:33 (OSMS 56%)

Bangkok (Siritho, Neurology 2011)
- NMO:MS&IIDD = 53:82 (NMO 39%)

Hong Kong (Chan, Neuroimmunol 2013)
- NMO:MS = 47:88 (NMO 35%)

Kuala Lumpur (Viswanathan, MS Int 2013)
- NMO:MS = 77: 104 (NMO 43%)

  Malays 38:55 (41%), Chinese 32:19 (63%), Indians 7:28 (20%)

Mangalore, India (Pandit, MSJ 2014)
- NMO:MS = 11:35 (NMO 24%)

Tianjin, China (Yang, CNS Neurosci Ther 2014)
- NMO:MS = 51:63 (NMO 45%)

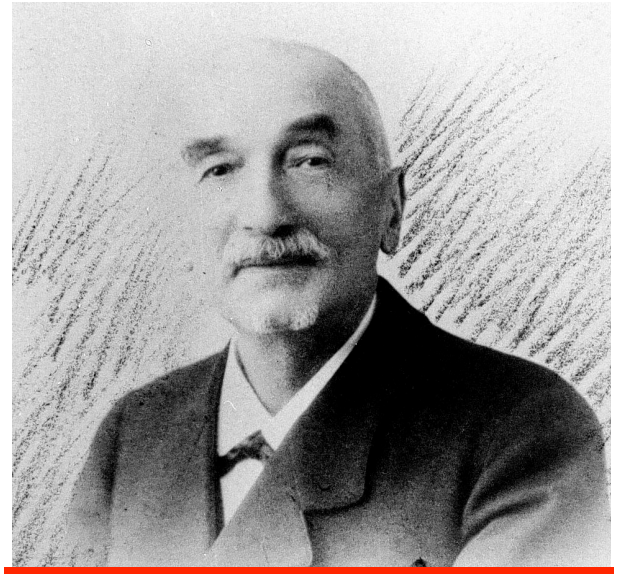
Southern Denmark (Asgari, Neurology 2011)
- NMOSD:MS = 42:258 (NMO 14%)

Northern California (Pittock, JAMA Neurol 2014)
- NMOSD:MS = 98:3293 (NMO 3%)

“Myélite subaiguë compliquée de névrite optique”

(Bull Med 8;1033-1034, 1894)

Eugène Devic (1858-1930)



(from Miyazawa et al. J Neurol 2002)

45y.o.woman
*Severe ON & TM
*Severe Demyelination & Necrosis in ON and SC
*No Brain Lesions

Analysis of 17 Reported Cases of NMO

Age at Onset (y)	30.6 (12-52)
Male : Female	1.66 : 1
Initial Symptom	ON (9), M (6)
Interval of ON & M	<30d (10), 1-6m (4)
Optic Neuritis	Bilateral (15)
Myelitis	ATM (4)
Other CNS signs	Cerebral(3)
	Brainstem (3)
Course	Monophasic (14)
	Relapsing (3)

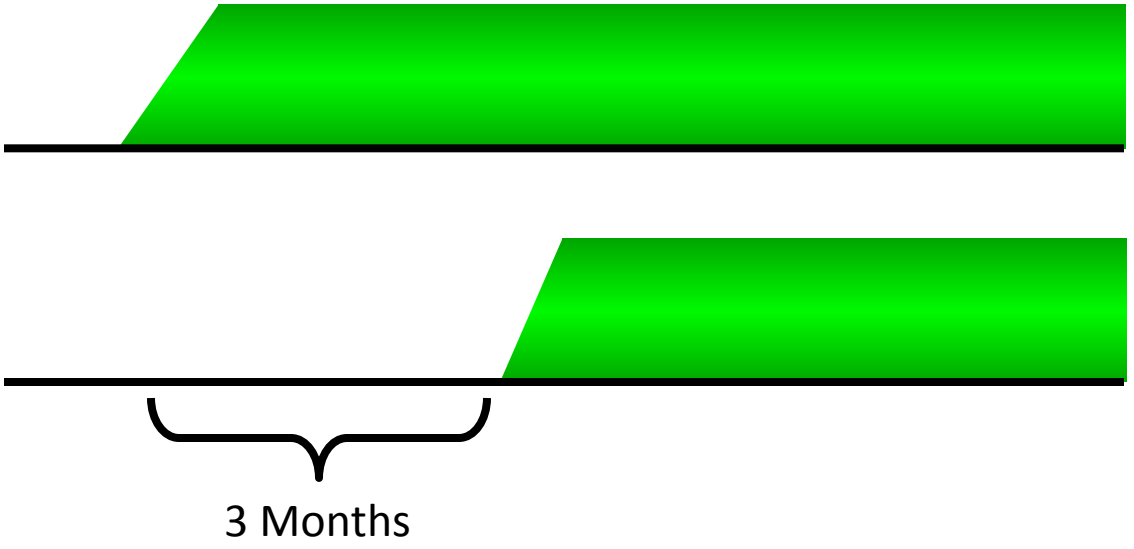
(Devic and Gault,1894)

NMO or Opticospinal MS ?

36y.o. woman

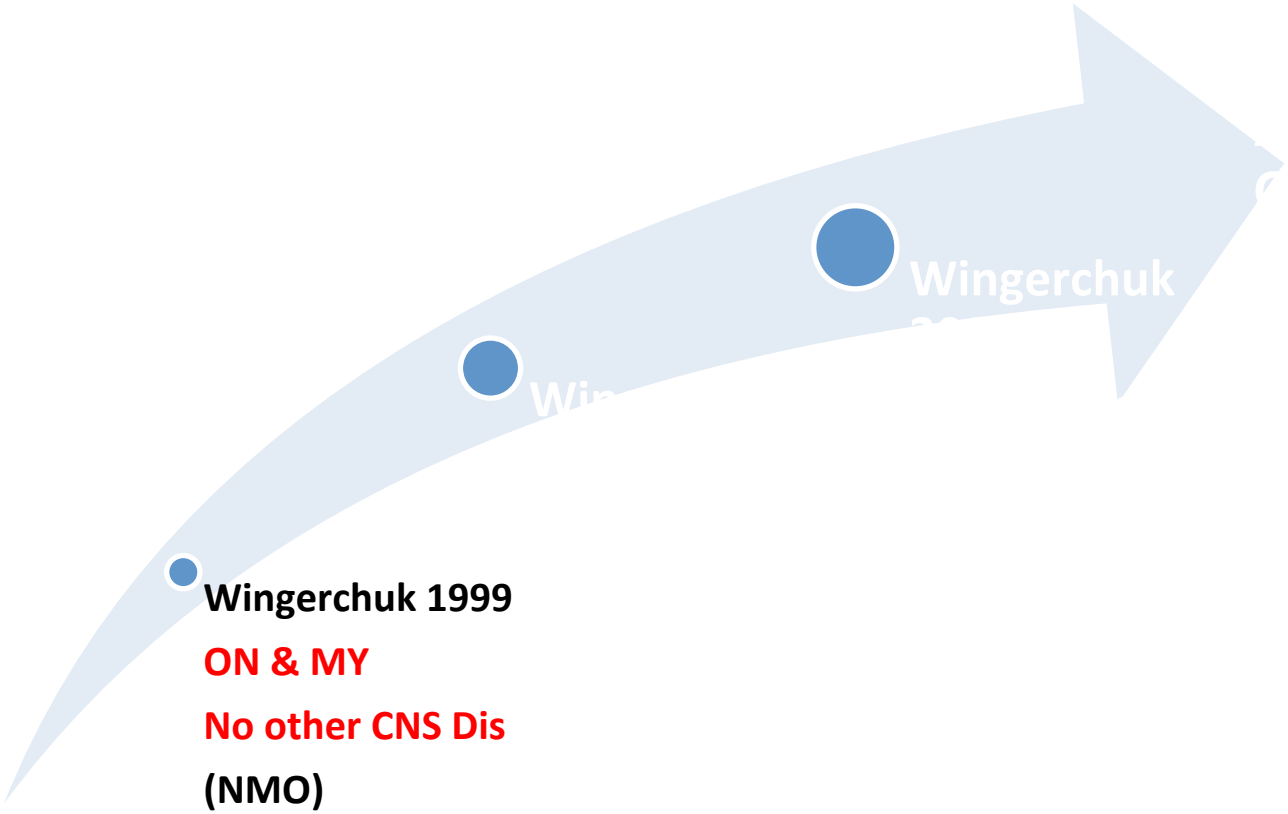
Total Blindness

Paraplegia



Head CT: normal

Evolving Diagnostic Criteria of NMOSD



Wingerchuk 1999

ON & MY

No other CNS Dis

(NMO)

Devic

1894

ON & MY

No other CNS Dis

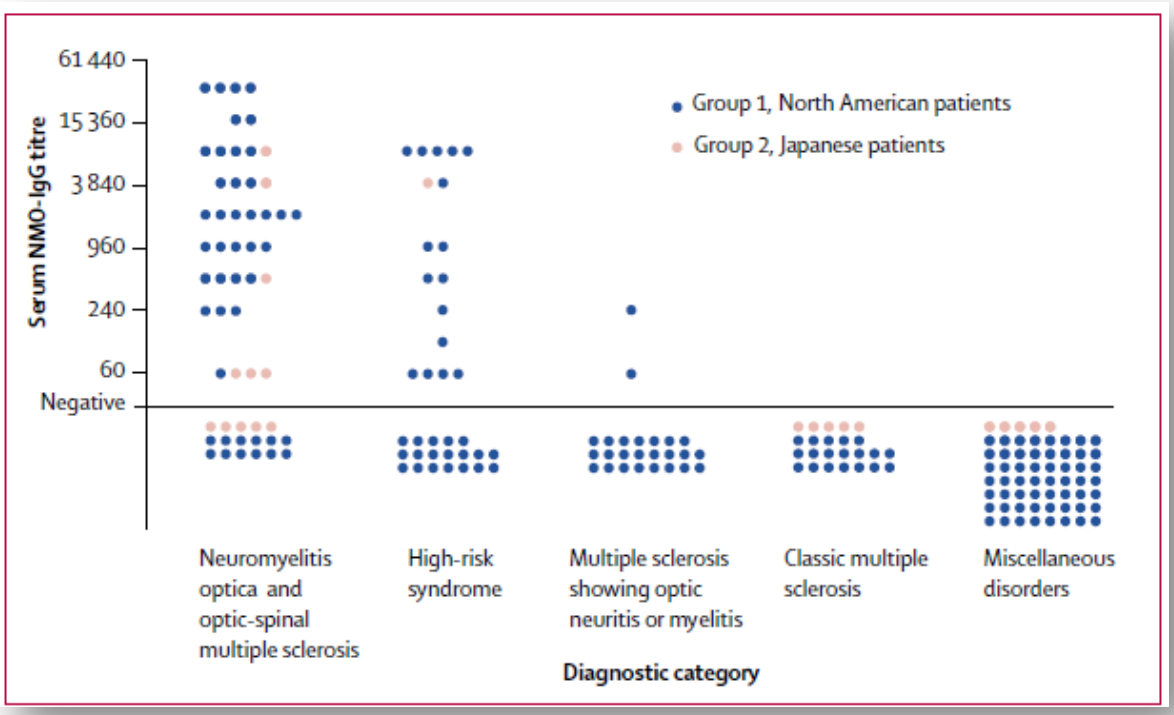
ON: optic neuritis, MY: acute myelitis (>3VS), Syn: syndrome

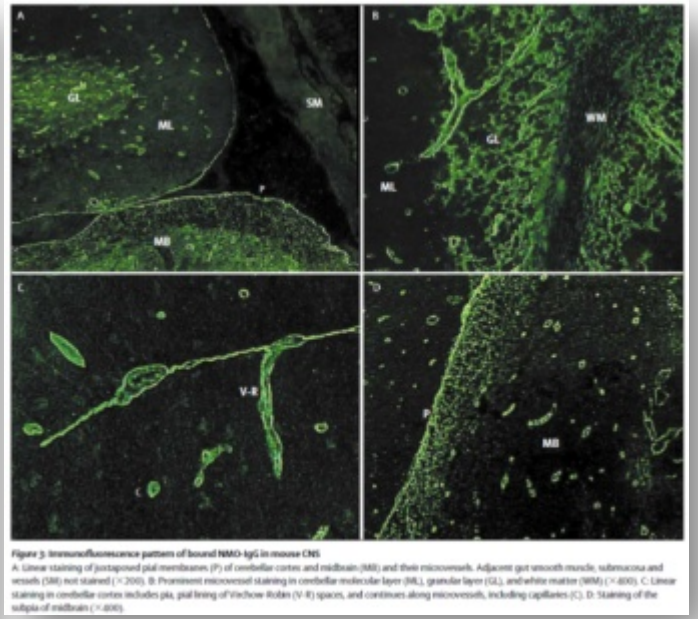
Red items are absolute requirements for Dx.

Discovery of NMO-IgG, an NMO-specific autoantibody

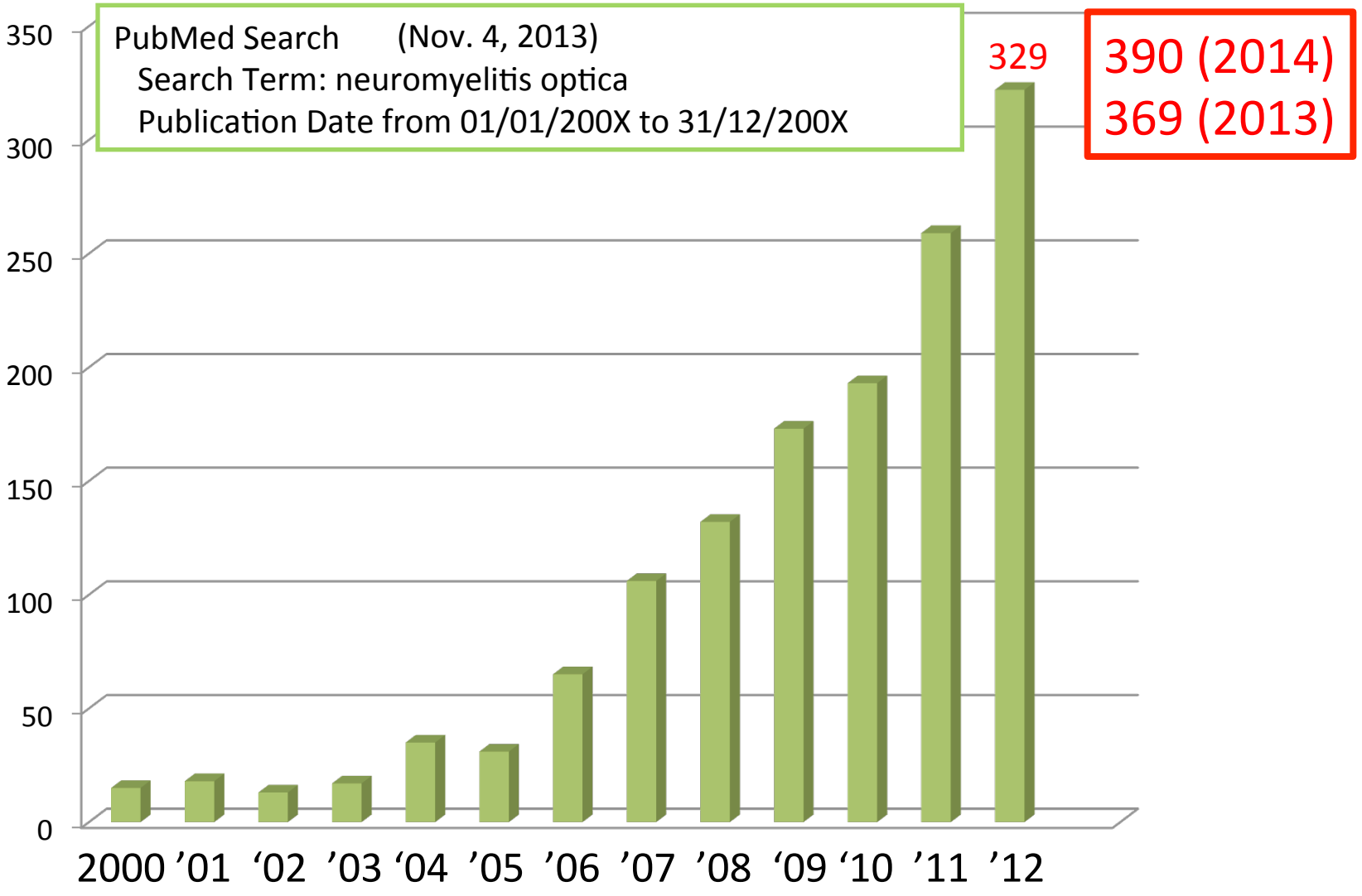
A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis

Lancet 2004; 364: 2106–12 *Vanda A Lennon, Dean M Wingerchuk, Thomas J Kryzer, Sean J Pittock, Claudia F Lucchinetti, Kazuo Fujihara, Ichiro Nakashima, Brian G Weinshenker*





Recent Explosion of NMO-related Publications



(Fujihara, Lucchinetti, Brain Pathol 2013)

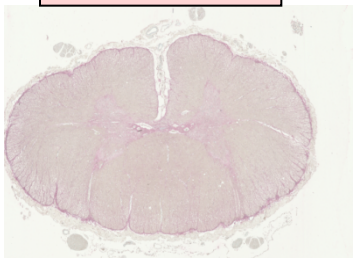
Aquaporin 4 (AQP4) and AQP4-IgG

1. NMO-IgG = AQP4-IgG (Lennon et al, JEM 2005)

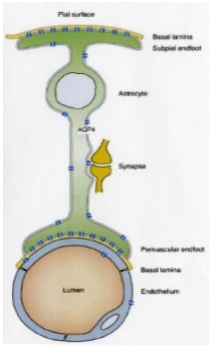
2. AQP4 is a water channel richly expressed in CNS

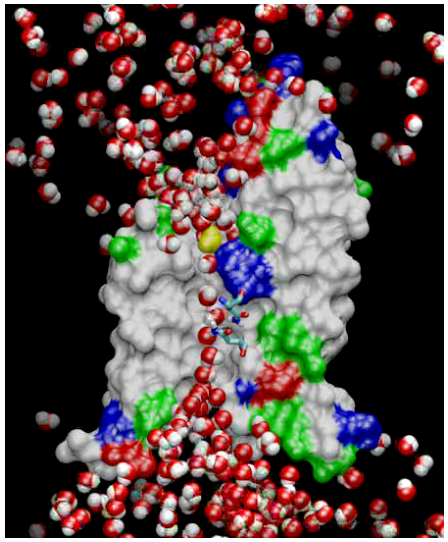
esp. in periventricular regions,
spinal gray matter, and
endfeet of astrocytes.

AQP4 (pink)

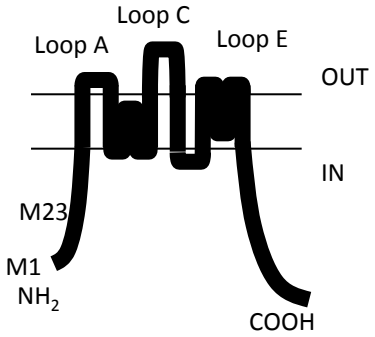


Astrocyte

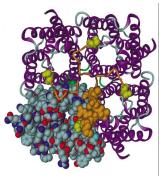




3. AQP4-IgG binds to the extracellular domains of AQP4.

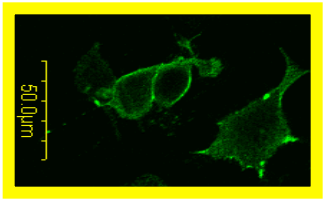


AQP4 Tetramer



AQP4-transfected Cells
NMO-Patient's IgG

(Takahashi et al, Brain 2006)

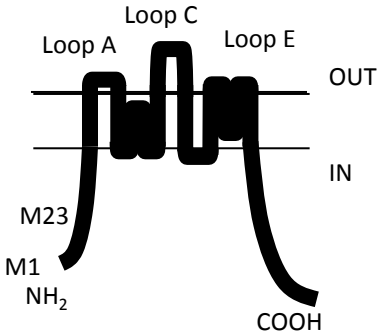


4. AQP4-IgG predicts relapse. (Weinshenker, et al Ann Neurol 2006)

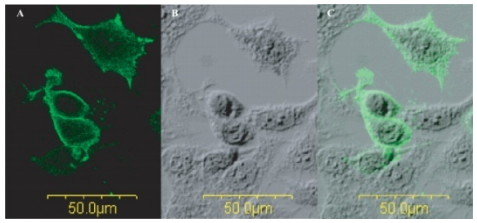
Factors To Influence Sensitivity In AQP4-IgG Assay

1. Cell-Based Assay > ELISA > Mouse Tissue-Based Assay
2. M23 > M1 (M23 forms orthogonal array of particles)
3. Other factors to lower sensitivity in Cell-Based Assay
   (1) Pre-fixed cells, (2) GFP tagging at N-terminus

AQP4: Transmembrane protein

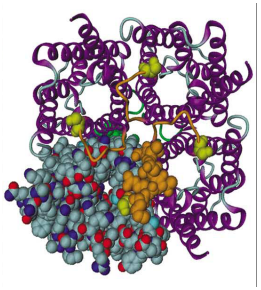


Cell-Based Assay



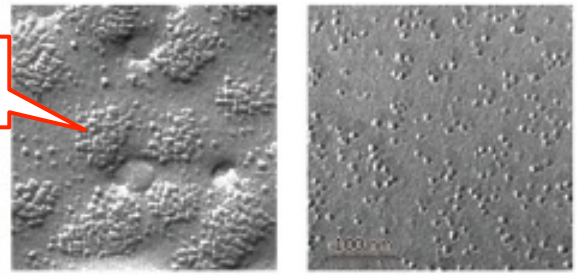
(Takahashi et al, Brain 2007)

AQP4 : Tetramer



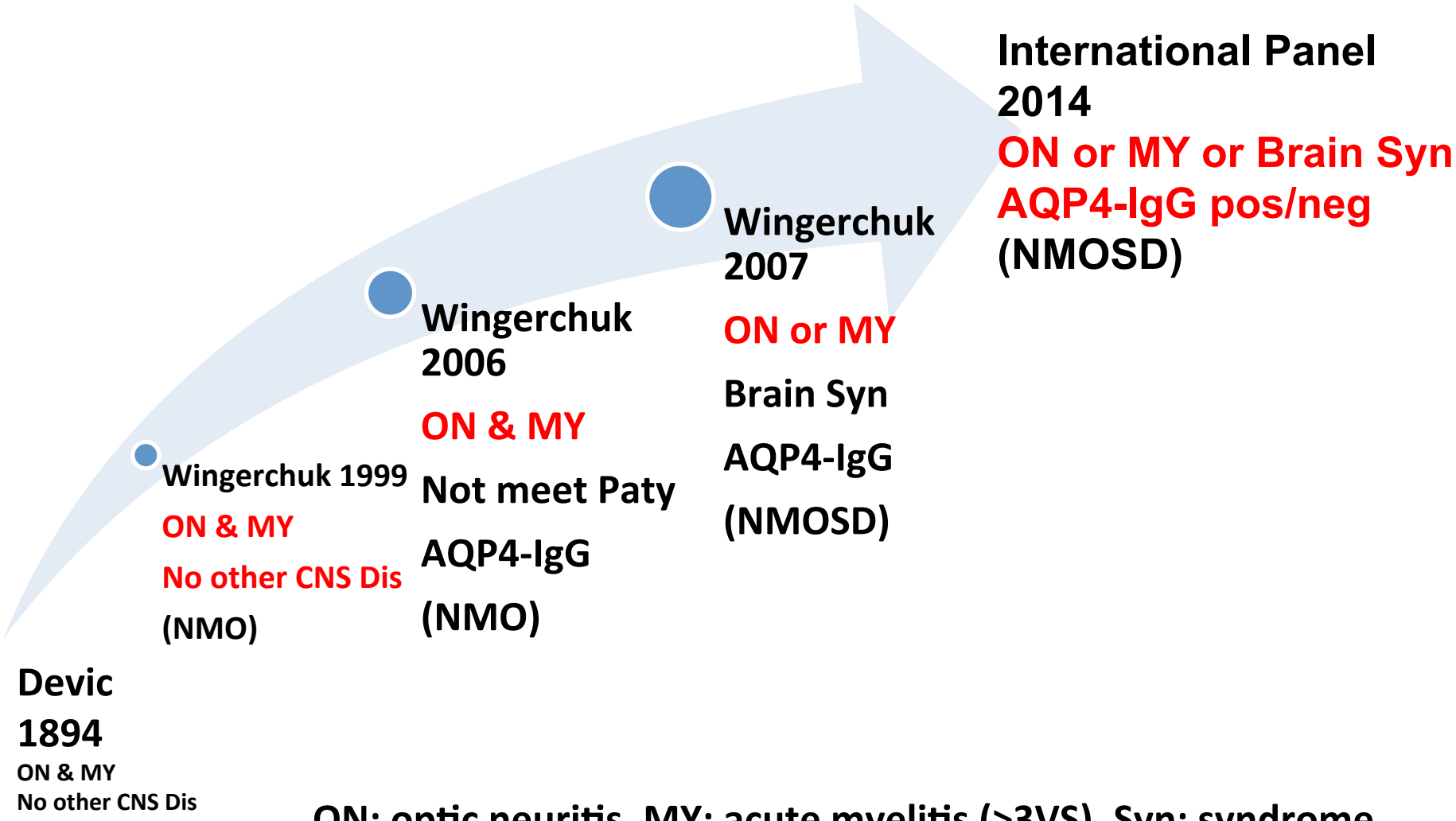
Orthogonal Array of Particles (OAP)

AQP4-M23 AQP4-M1



(Verkman et al, Methods Enzymol2012)

Evolving Diagnostic Criteria of NMOSD



ON: optic neuritis, MY: acute myelitis (>3VS), Syn: syndrome

Red items are absolute requirements for Dx.

International Consensus Diagnostic Criteria of NMOSD

NMOSD, the unifying term for the entire clin spectrum

1) NMOSD with AQP4-IgG

One Core Clinical Characteristic (ON, Acute MY, Brain Synd)

2) NMOSD without AQP4-IgG (or unknown)

Two or more Core Clinical Characteristics

Additional requirements (One of ON/MY/AP Synd, DIS, MRI)

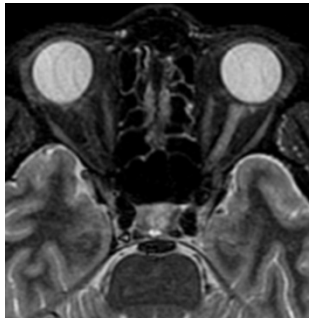
No better explanation for the clin synd

Red-flags: Findings atypical for NMOSD (OCB neg, <3VS, etc)

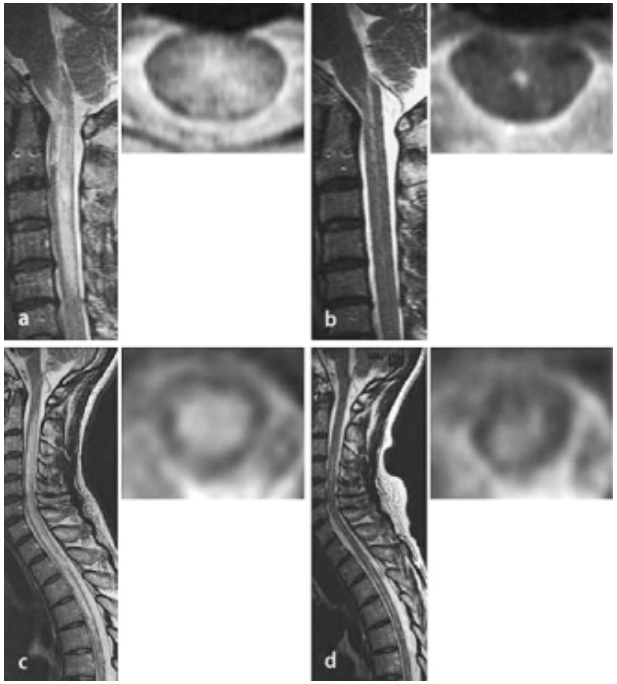
(Wingerchuk et al. Neurology 2015)

Core Clinical Characteristics of NMOSD

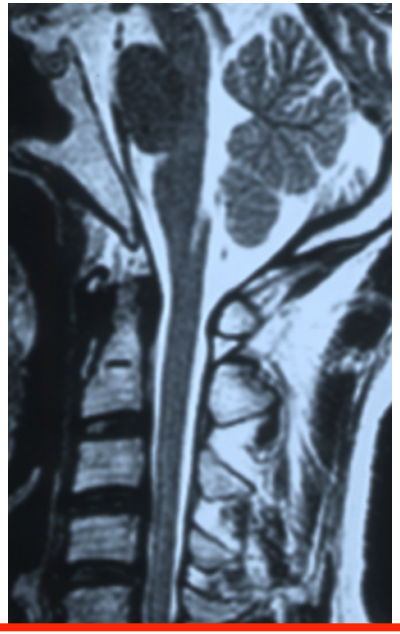
Optic neuritis (Severe, Chiasmal)



Acute myelitis (Transverse, > 3 VS)

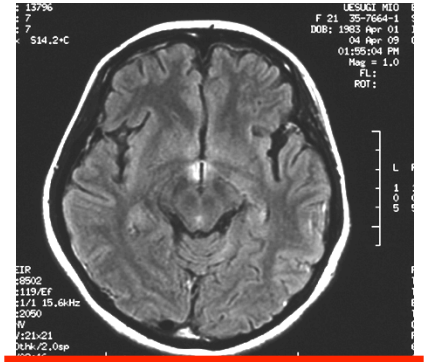


Area postrema syndrome



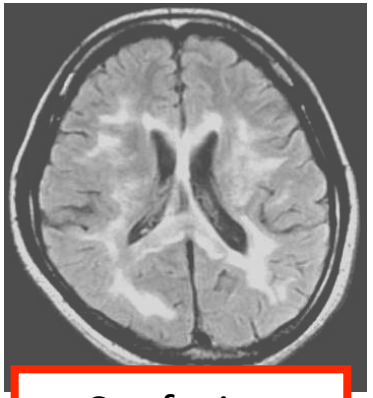
Intractable Hiccup, Nausea & Vomiting

Symptomatic narcolepsy



Hypersomnia
(low CSF-orexin A level)

Symptomatic cerebral syndrome



Confusion

(Misu, Neurology 2005; Nakashima, JNNP 2006; Takahashi, Brain 2007; Nakamura, J Neurol 2009)

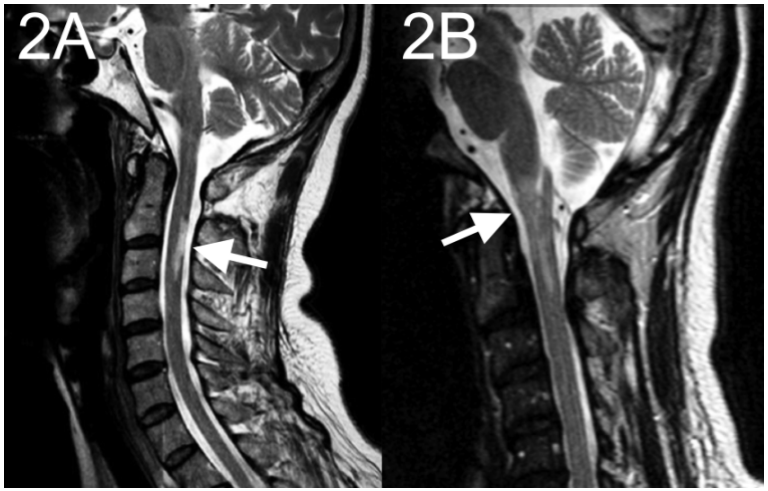
Red Flags (Conventional Neuroimaging):

2) Spinal Cord MRI

a) Characteristics more suggestive of MS than NMOSD

- Lesions < 3 complete VS on saggital T2WI
- Lesions located predominantly (> 70%) in the peripheral cord
- Diffuse, indistinct Proton Density- or T2- signal change (longstanding or progressive MS)

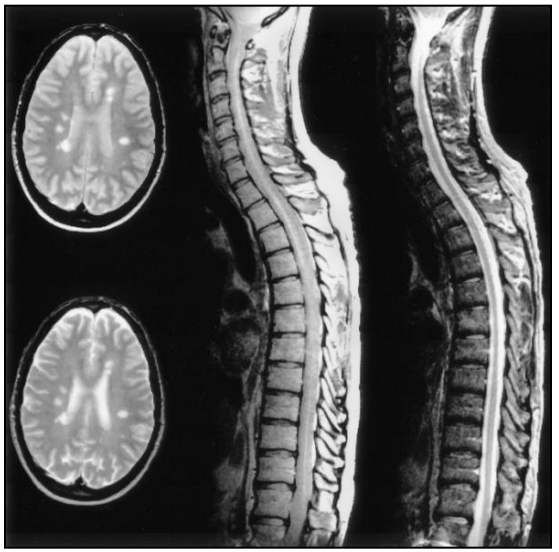
Short Myelitis in AQP4-IgG+Pt



(Sato et al. Neurology 2013)

PPMS (M, 41yo)

PD T2



(Bot et al. Neurology 2004)

Differential Diagnosis of Longitudinally Extensive Transverse Myelitis (LETM)

1. Autoimmune:
- NMO, SLE, Sjogren syndrome, Antiphospholipid syndrome

2. Infllammatory:
- MS, ADEM, NeuroBechet's disease, Neurosarcoidosis

3. Infectious:
- Parainfectious:
  - EBV, CMV, HSV, VZV, Mycoplasma
- Syphilis, Tuberculosis, HIV, HTLV-I, Schistosomiasis

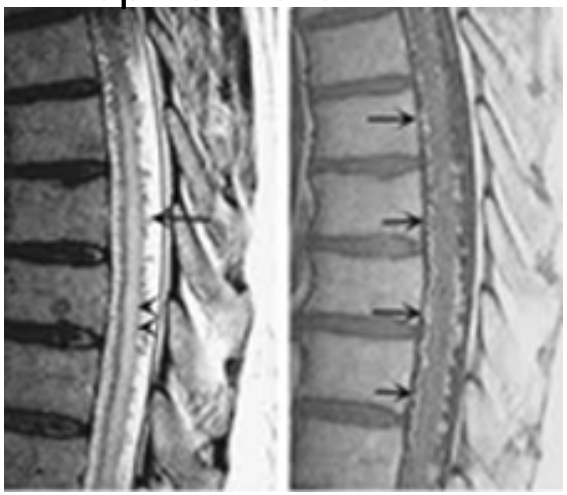
4. Neoplastic:
- Paraneoplastic, particularly CRPMS
- Intramedullary tumor:
  - Ependymoma, Lymphoma
- Intramedullary metastasis

5. Metabolic:
- Vitamin B12 deficiency, Copper deficiency

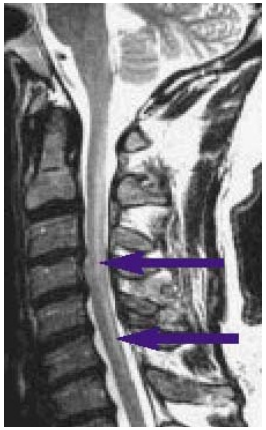
6. Vascular:
- Spinal cord infarction/ischemia
- Dural fistula

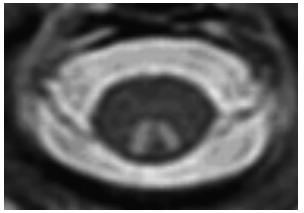
7. Other:
- Radiotherapy

Spinal Dural AVF



Subacute combined degeneration (Vit.B12 deficiency)





(Kitley, Mult Scler 2011)

International Panel meeting on McDonald Criteria (RCPI, Dublin, 21st – 22nd May, 2010)

Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,[1] Stephen C. Reingold, PhD,[2] Brenda Banwell, MD,[3] Michel Clanet, MD,[4] Jeffrey A. Cohen, MD,[5] Massimo Filippi, MD,[6] Kazuo Fujihara, MD,[7] Eva Havrdova, MD, PhD,[8] Michael Hutchinson, MD,[9] Ludwig Kappos, MD,[10] Fred D. Lublin, MD,[11] Xavier Montalban, MD,[12] Paul O'Connor, MD,[13] Magnhild Sandberg-Wollheim, MD, PhD,[14] Alan J. Thompson, MD,[15] Emmanuelle Waubant, MD, PhD,[16] Brian Weinshenker, MD,[17] and Jerry S. Wolinsky, MD[18]

New evidence and consensus has led to further revision of the McDonald Criteria for diagnosis of multiple sclerosis. The use of imaging for demonstration of dissemination of central nervous system lesions in space and time has been simplified, and in some circumstances dissemination in space and time can be established by a single scan. These revisions simplify the Criteria, preserve their diagnostic sensitivity and specificity, address their applicability across populations, and may allow earlier diagnosis and more uniform and widespread use.

ANN NEUROL 2011;69:292–302

(courtesy of Prof. Michael Hutchinson)

2010 Revisions to the McDonald Criteria

There was agreement that this phenotype (NMO) should be separated from typical MS because of different clinical course, prognosis, and underlying pathophysiology and poor response to some available MS disease-modifying therapies.

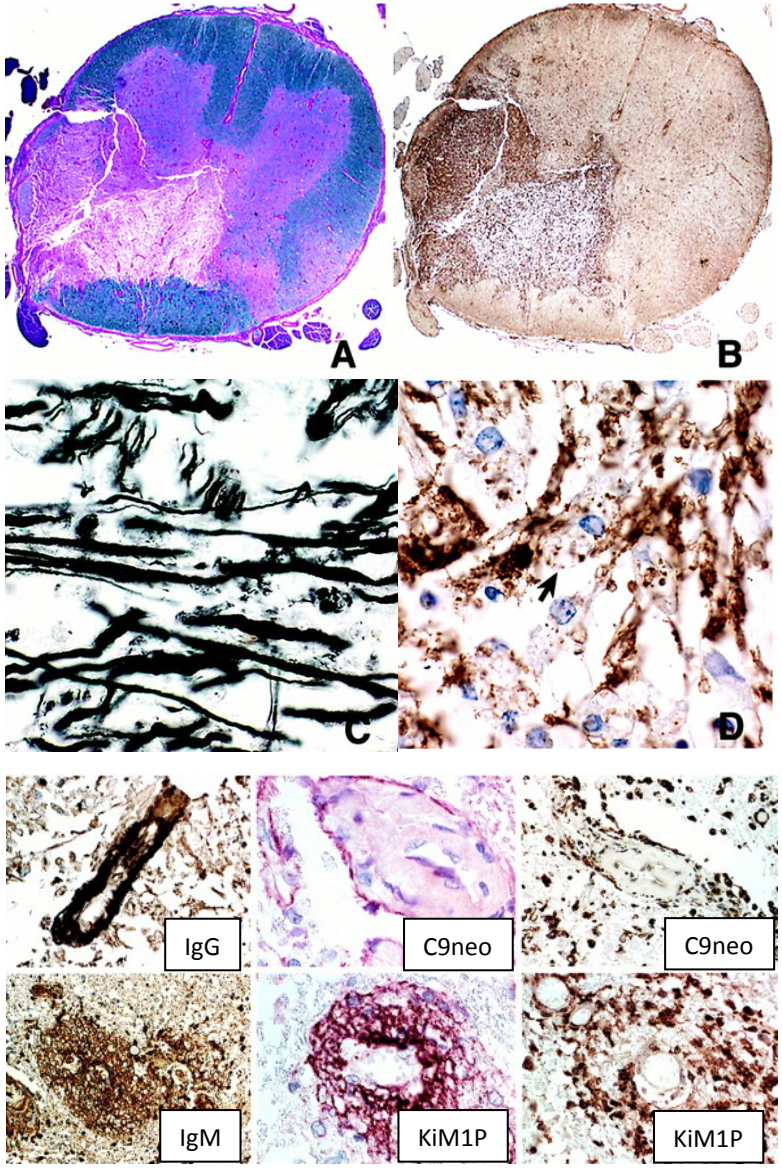
(Polman et al, Ann Neurol 2011)

What is the definition of "demyelinating disease" ?

Medical Dictionary
"disease of myelin"

Prof. Hans Lassmann (Med. Univ. Vienna)
"Myelin damage is more severe than neuronal damage."

Pathological Features of NMO



General Features:

- Severe Demyelination
- Edema, Necrosis & Cavity
- Acute axonal swelling, Spheroids
- Myelin-laden Macrophages

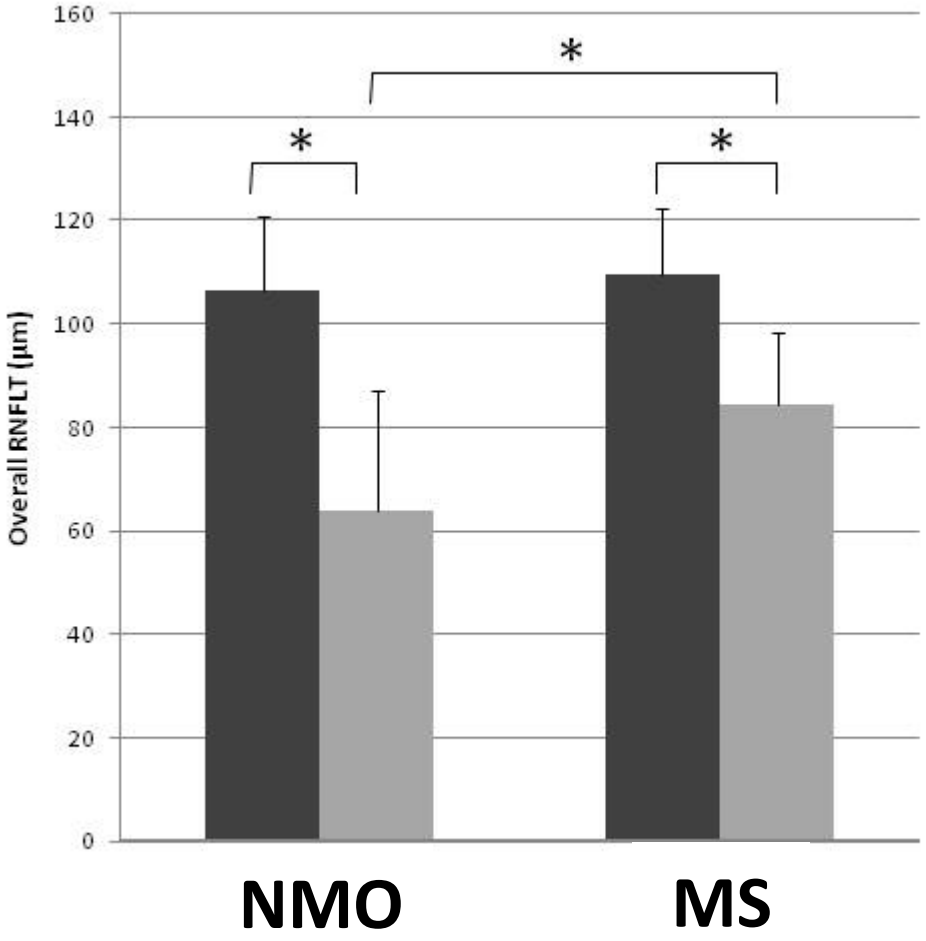
Humoral Immunity & Vascular Pathology

- Deposition of Immunoglobulins and Complements in Vasculocentric Pattern
- Thickened and Hyalinized Vessel Walls

(Lucchinetti et al, Brain 2002)

Optical Coherence Tomography (OCT)

Retinal Nerve Fiber Layer Thickness (RNFLT) in eyes with NMO and MS with episodes of optic neuritis (ON)



*: P<0.05

Eyes without ON

Eyes with ON

(Nakamura, 2010)

Two Distinct Pathologies in NMOSD

1) Severe Astrocytic Damage in AQP4-IgG+NMOSD

a) Astrocyte Pathology (AQP4 Loss, etc) in the Lesions

b) Pathogenicity of AQP4 Ab *in vitro* and *in vivo*

c) Low Myo-Isositol/Creatine Value on ^{1}H-MRS

d) Remarkable High CSF-GFAP in Relapse

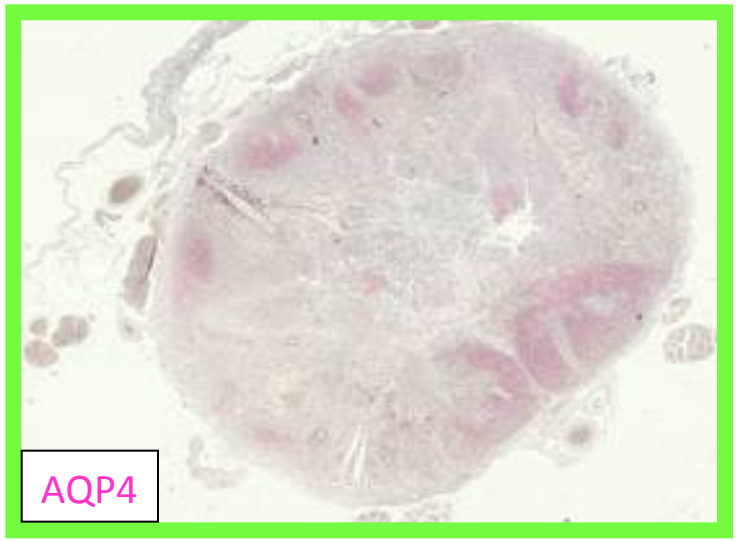
GFAP: glial fibrillary acidic protein (an astrocytic protein)

2) Severe Demyelination in MOG-IgG+NMOSD

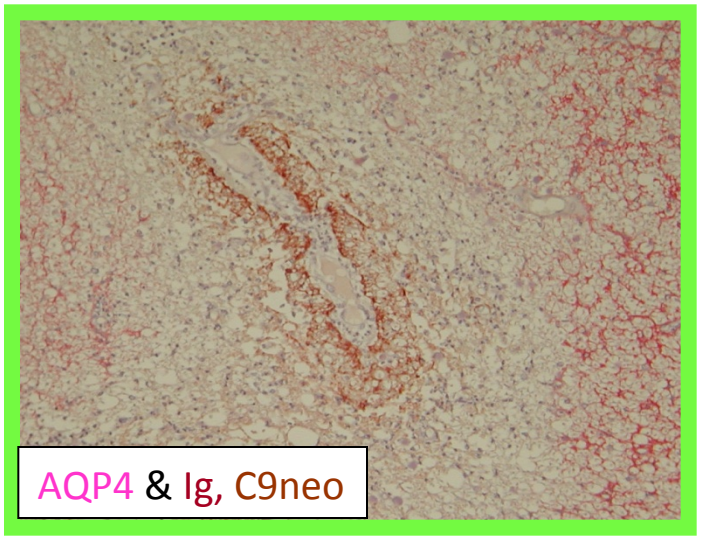
a) High CSF-MBP, but Normal CSF-GFAP in Relapse

b) Severe Demyelinating Lesions (MS-type II Pathology)

Extensive Loss of AQP4 and Perivascular Deposition of Humoral Immune Factors in NMO



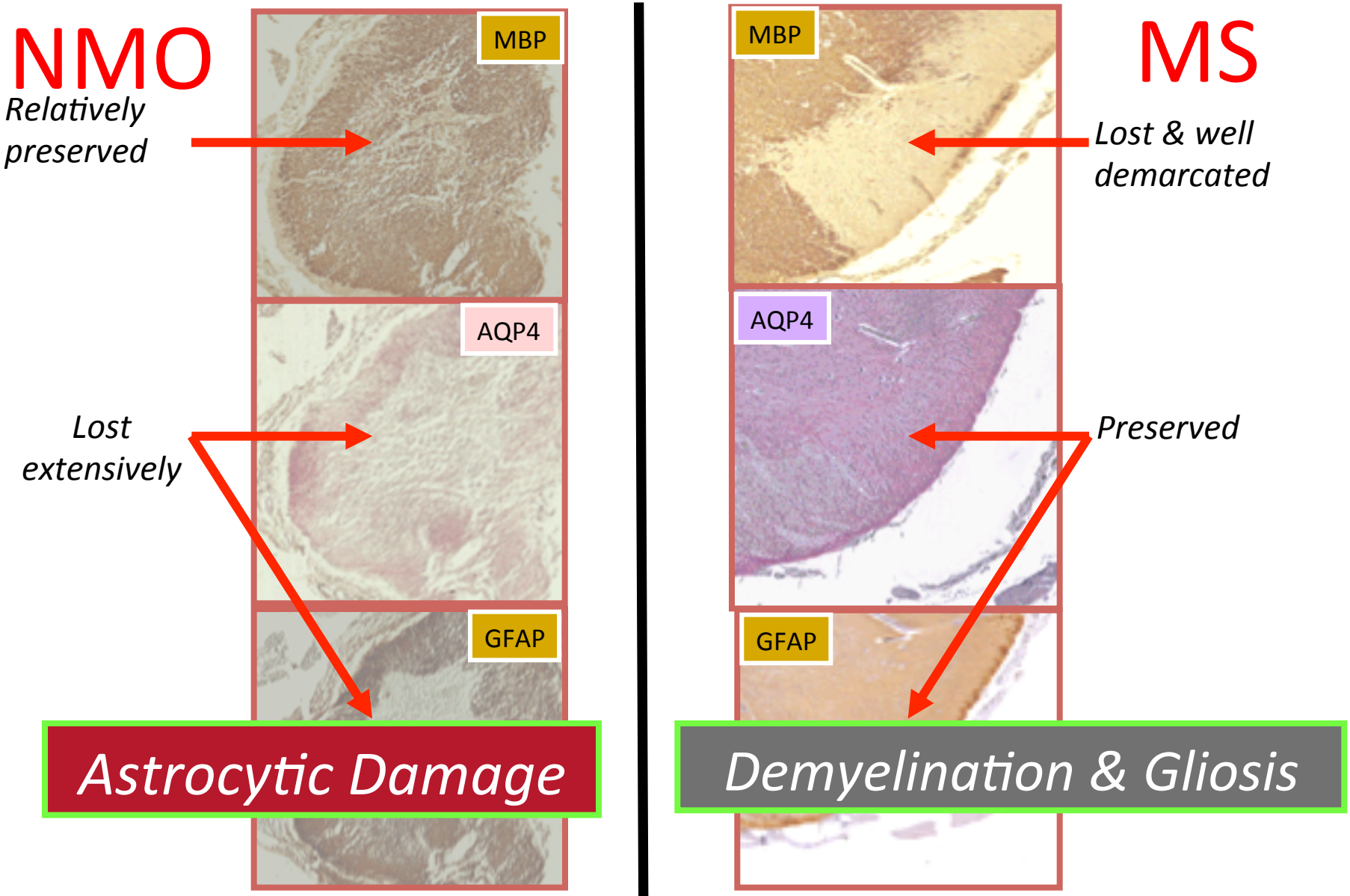
Extensive Loss of AQP4



Perivascular Deposition of Ig & C9neo and Loss of AQP4

(Misu et al. TJEM 2006, Brain 2007)

Loss of AQP4 & GFAP in NMO Lesions



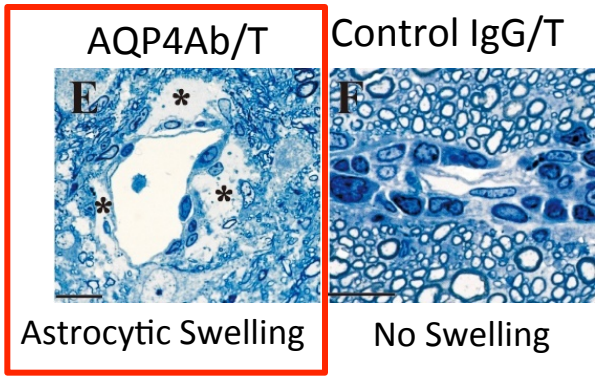
(Misu, TJEM 2006, Brain 2007)

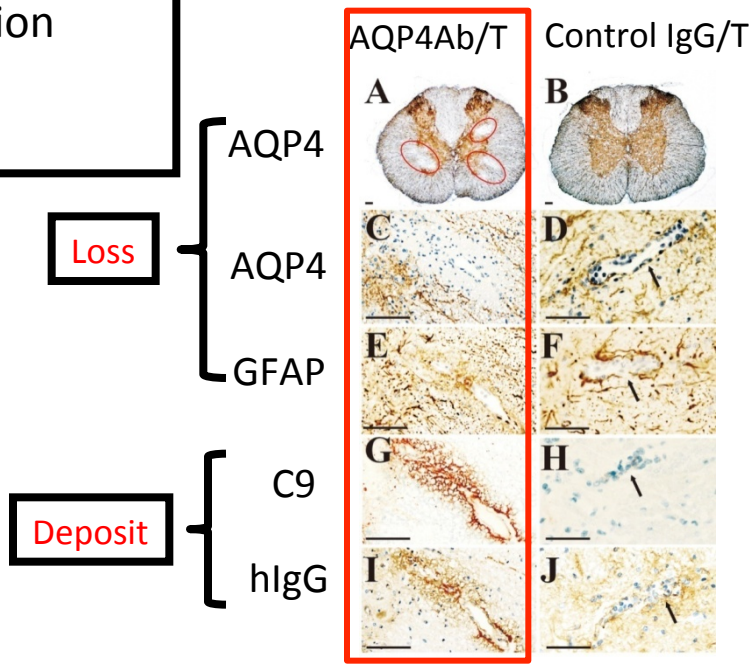
Pathogenicity of AQP4 Ab *in vitro* and *in vivo*

1. AQP4-Ab + Complements Damage AQP4-transfected Cells and Astrocytes in Culture (Hinson 2007; Vincent, 2008; Kinoshita, 2009, etc)

2. AQP4 Ab can induce NMO-like lesions in transfer EAE

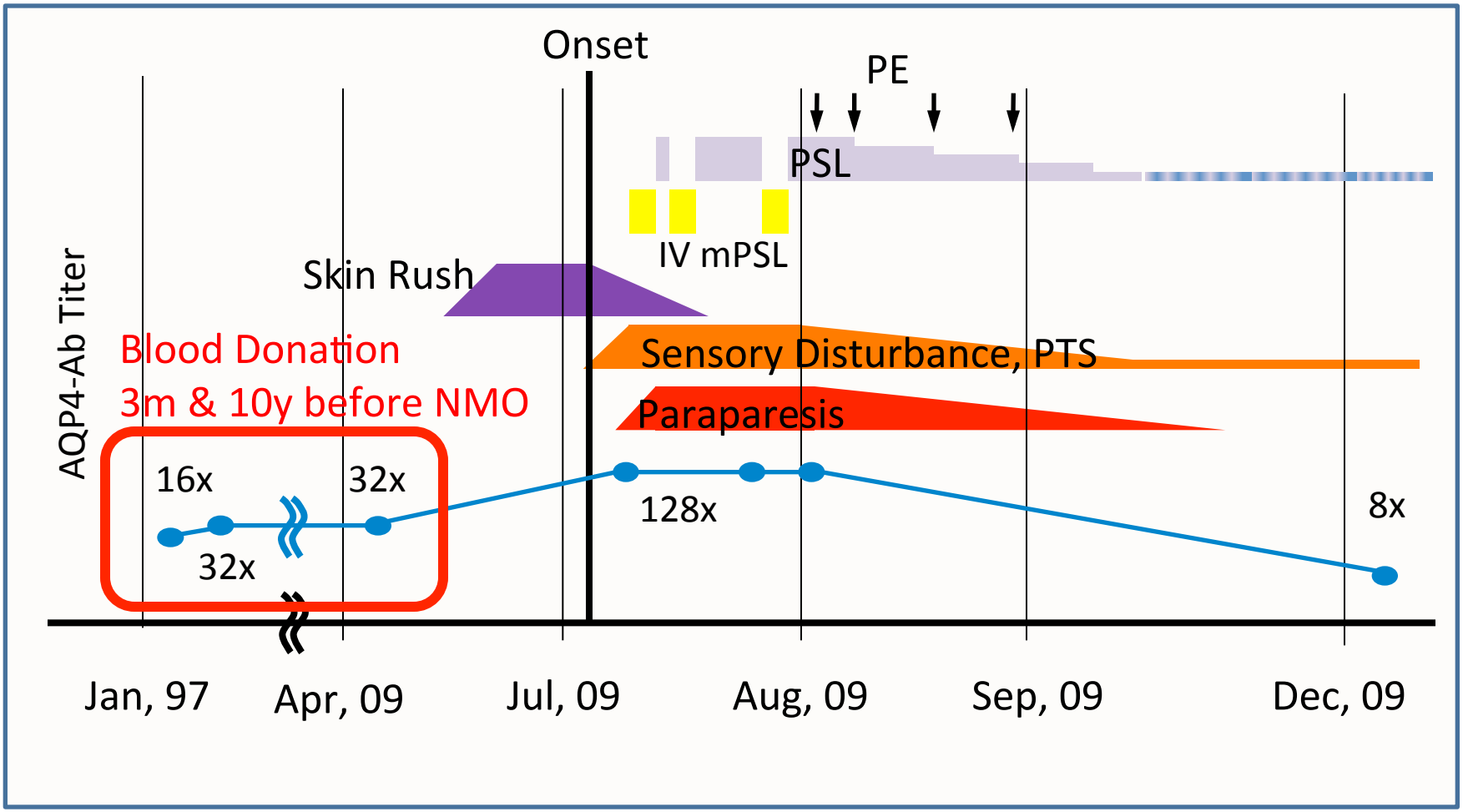
1) AQP4-Ab + MBP-T Cells → NMO-like lesion
2) Control IgG + MBP-T Cells → No lesion
3) AQP4-Ab alone → No lesion





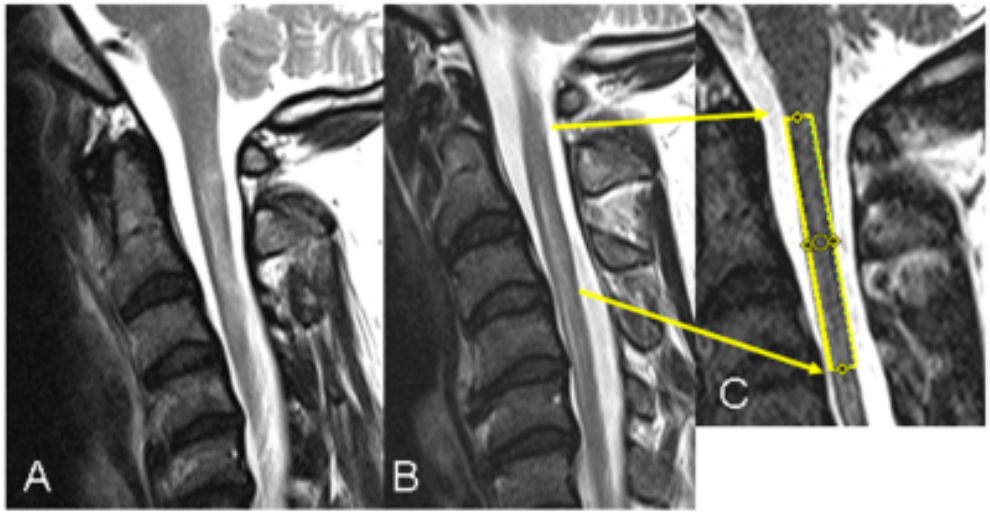
(Bradl et al, Ann Neurol 2009)

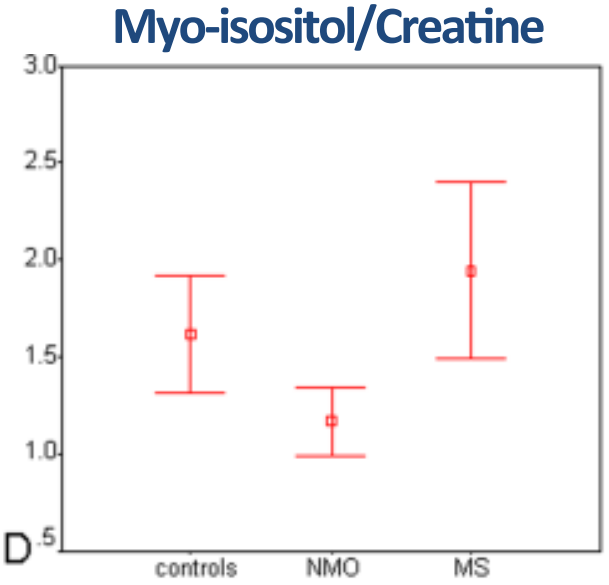
Detection of AQP4-Ab Before the Onset of NMO

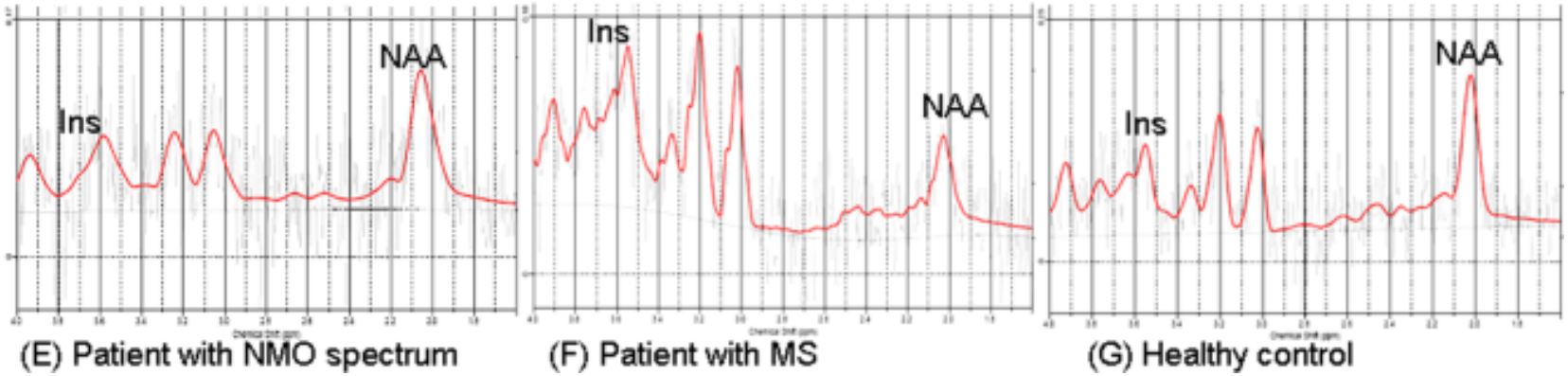


(Nishiyama, Neurology 2009)

Low Myo-inositol indicating astrocytic damage in NMO
- ^{1}H-MR Spectroscopy Study-





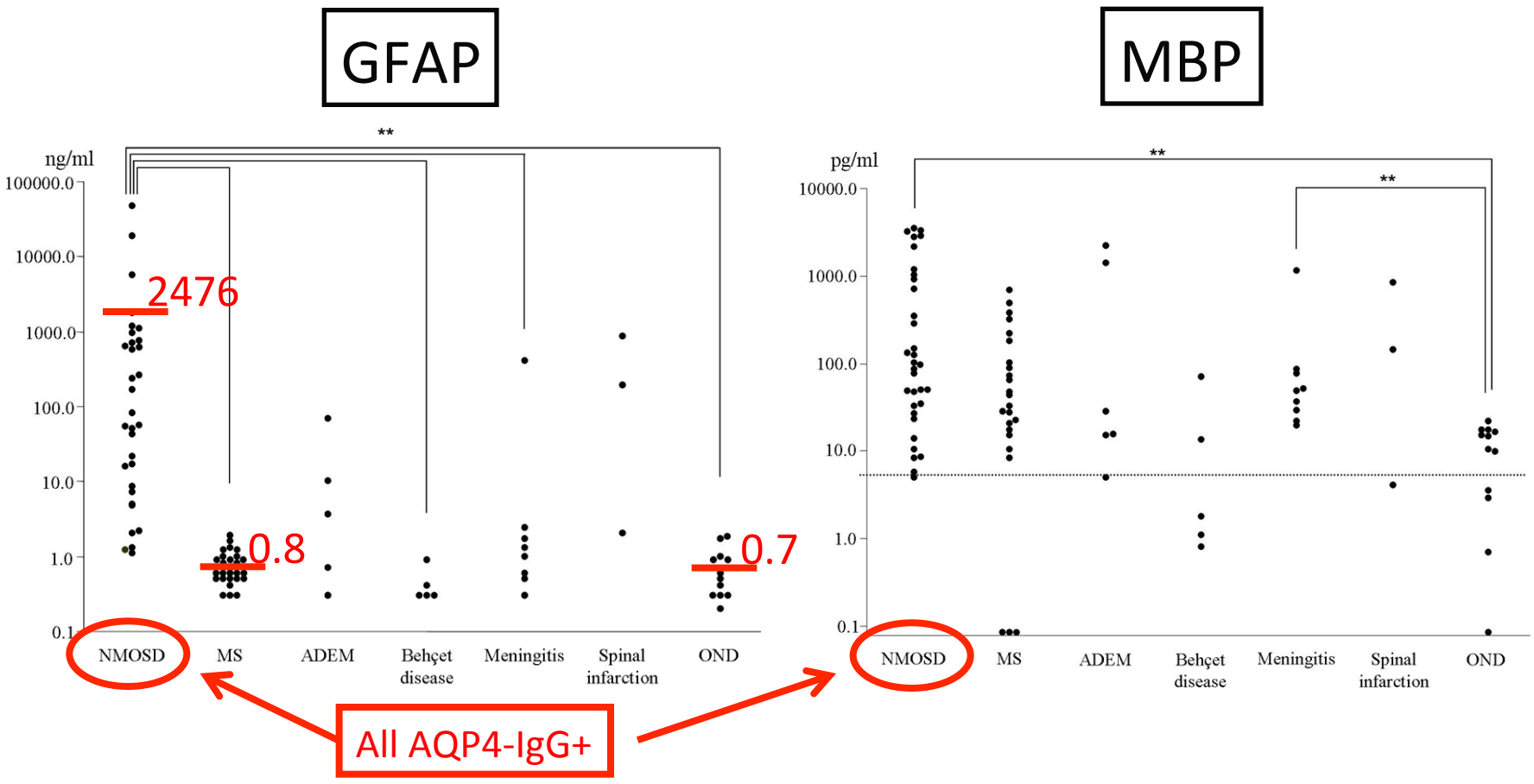


(E) Patient with NMO spectrum (F) Patient with MS (G) Healthy control

(Ciccarelli et al, Ann Neurol 2013)

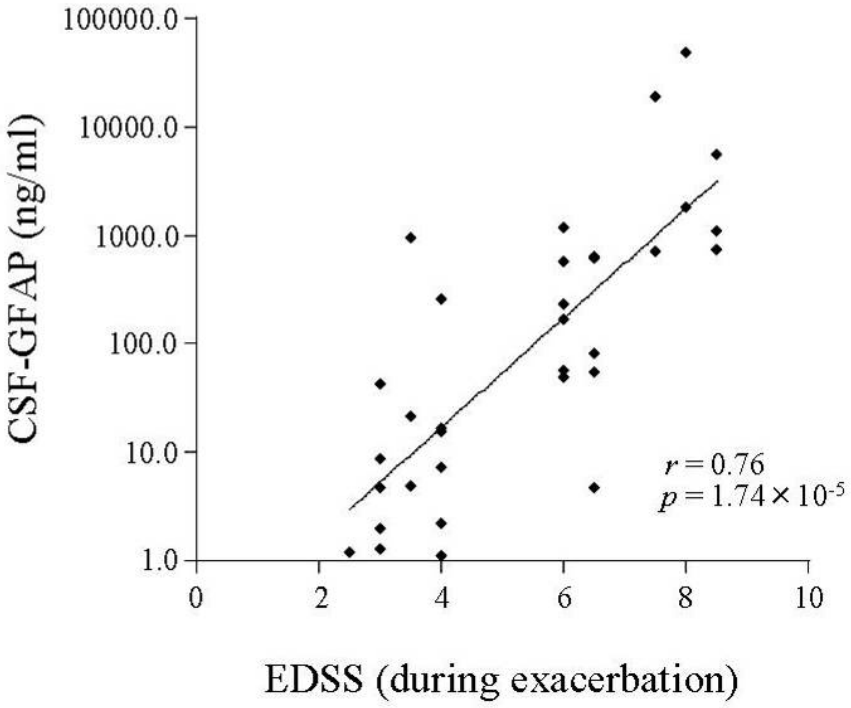
Astrocytic damage is far more severe than demylination in NMOSD

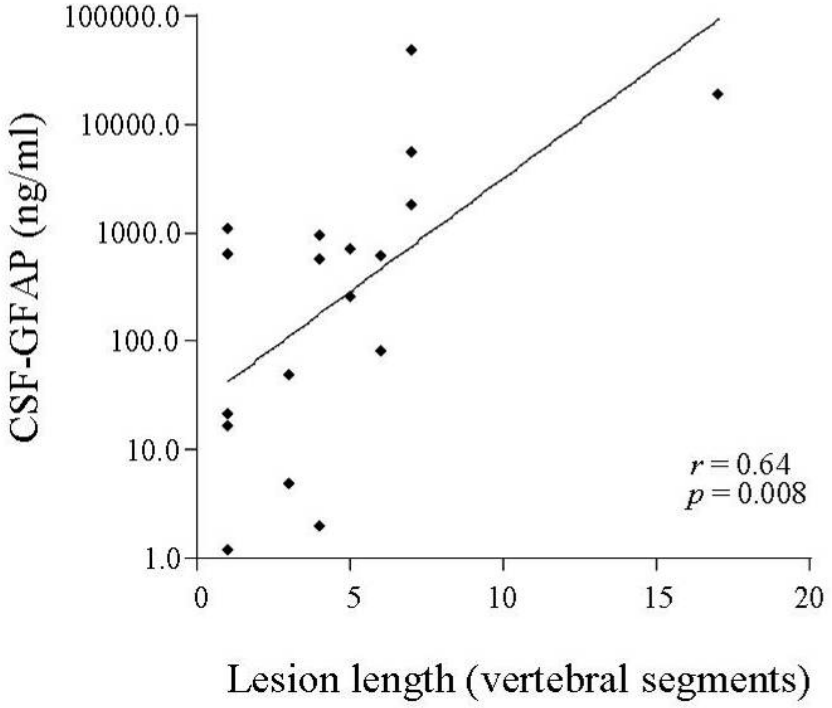
Remarkably Elevated CSF-GFAP Levels in NMOSD



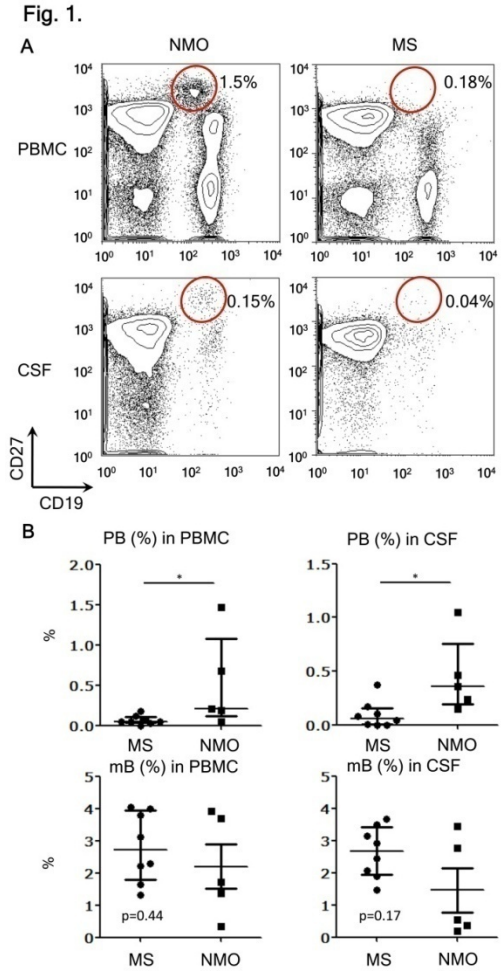
(Takano et al, Neurology 2011)

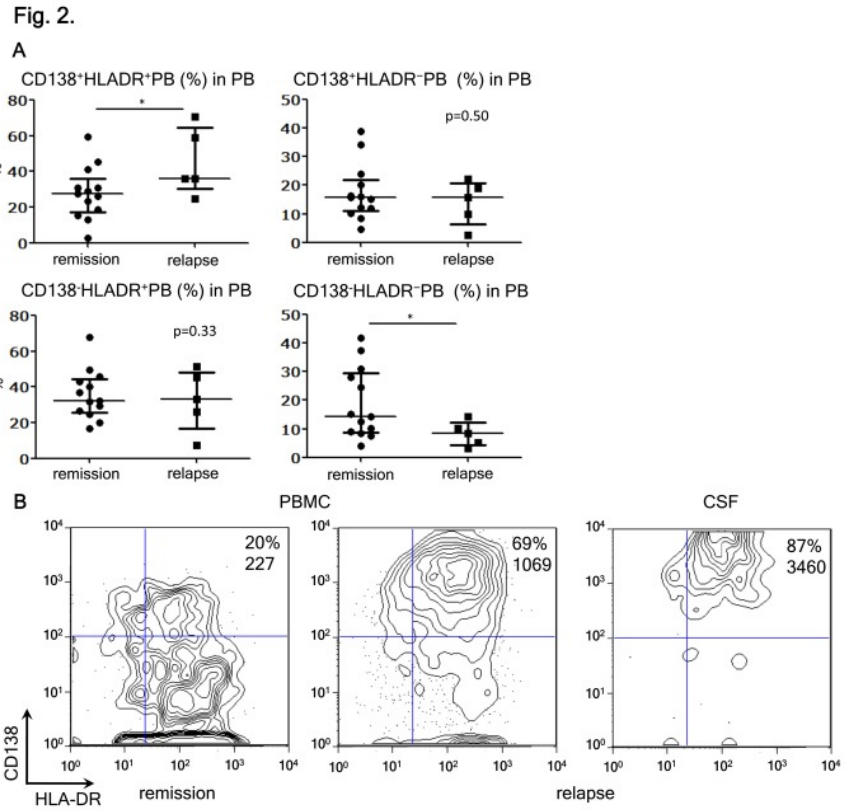
Significant Correlation between CSF-GFAP Levels and EDSS or Cord Lesion Length in NMO





CD138+HLA-DR+ Plasmablasts, a subset of IgG-producing cells, are increased in Blood and are enriched among CSF Lym in Relapse





(Chihara et al, PLOS ONE 2013)

IL-6 promotes AQP4-IgG production from plasmablasts in NMOSD

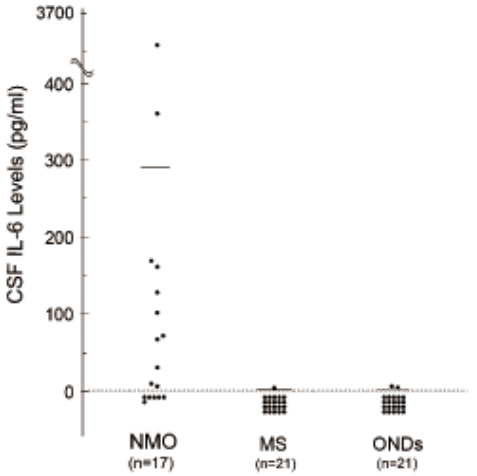
(Chihara et al, PNAS 2011)

CSF-GFAP, IL-6 and AQP4-IgG in NMOSD

1) Significant elevation of CSF-IL-6, IL-8, Il-13, G-CSF, and IL-1R antagonist in NMOSD

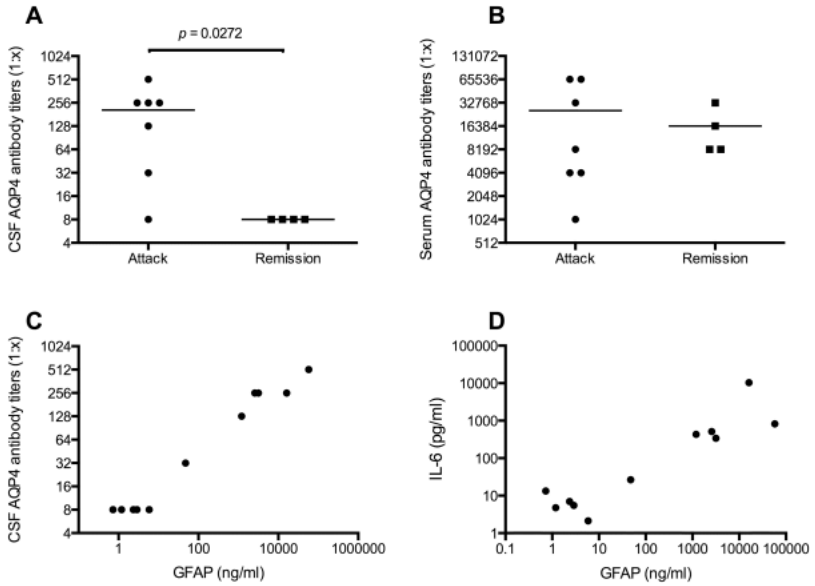
2) Significant correlation of CSF-IL-6 and CSF-GFAP

(Uzawa et al, J Neurol 2009, Mult Scler 2010)

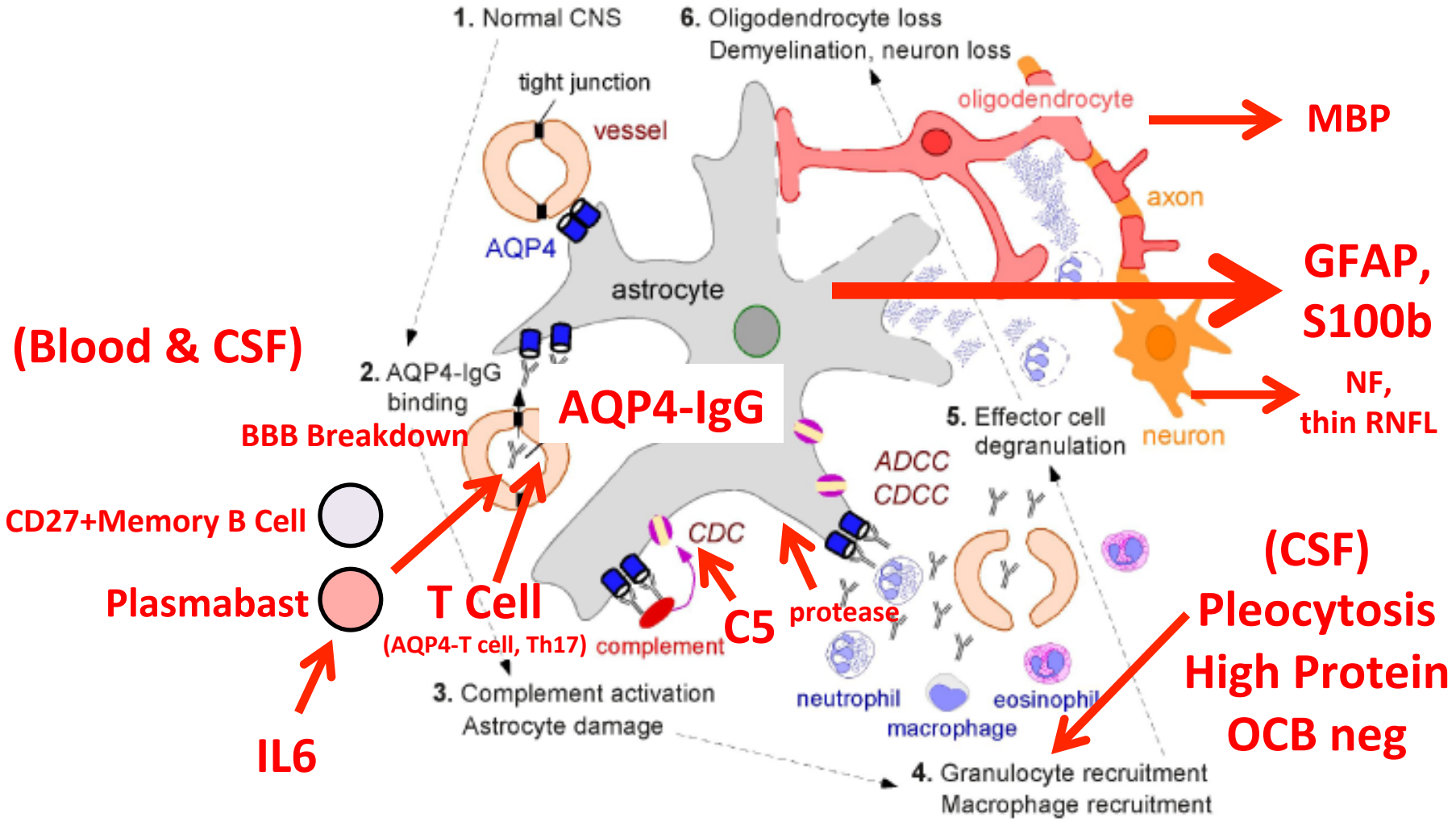


3) CSF-AQP4-IgG titers and CSF-IL6 correlates GFAP in NMOSD.

(Sato et al, Ann Neurol 2014)



Pathomechanisms of AQP4-IgG+NMOSD



(modified from Verkman et al, Brain Pathol 2013)

Six Different Lesion Types in NMO

Complement-mediated cytotoxicity, necrotic

Type 1: Active NMO lesions with C activation and Gra infiltration

Type 2: Cystic lesions with extensive tissue destruction

Type 3: Lesions resembling secondary Wallerian degeneration

Type 4: Lesions with selective loss of AQP4

Type 5: Active NMO lesions with astrocytic clasmatodendrosis

Type 6: Lesions with astrocyte dystrophy and primary demyelination

(Misu et al, Acta Neuropathol 2013)

No complement deposition, apoptosis-like

Host and Environmental Factors in NMOSD

1. Host Factors

1) Autoimmune backgroud (AQP4-Ab and other auto-Ab)

2) Female preponderance (F:M = 9:1 in AQP4-Ab+Cases)

3) Familial NMO (>16 multiplex families)

4) HLA-DRB1*1501 -- no association with NMOSD

5) Genetic susceptibility: HLA-DPB1, HLADRB1*03:01,
PD-1.3A allele of PTPN22, CD226 Gly307Ser
Protective: CYP7A1 gene G/G genotype

2. Environmental Factors

1) Infections

Para- or Post-infectious -- case reports

CMV, VZV, EBV, HAV, HIV, Dengue, Mycoplasma p, Tbc

Clostridium perfringens ABC transporter (homology to T cell epitope of AQP4)

Treatment of NMOSD

Dilemma

1. Scientific evidences -- insufficient
2. Debates on clinical trial design (placebo, add-on, active comparator)

(Weinshenker et al. Neurology 2015)

Therapeutic approach

1. Acute exacerbation

   IV-Methlprednisolen → Plasma Exchange

2. Relapse prevention

   PSL, Azathioprine, MMF, Rituximab (CD20), Methotrexate, Mitoxantrone, Tocilizumab (IL6R), Eculizumab (C5), CD19 mAb, etc

   [IFNβ, Natalizumab, and Fingolimod can aggravate NMOSD !]

3. Symptomatic therapy

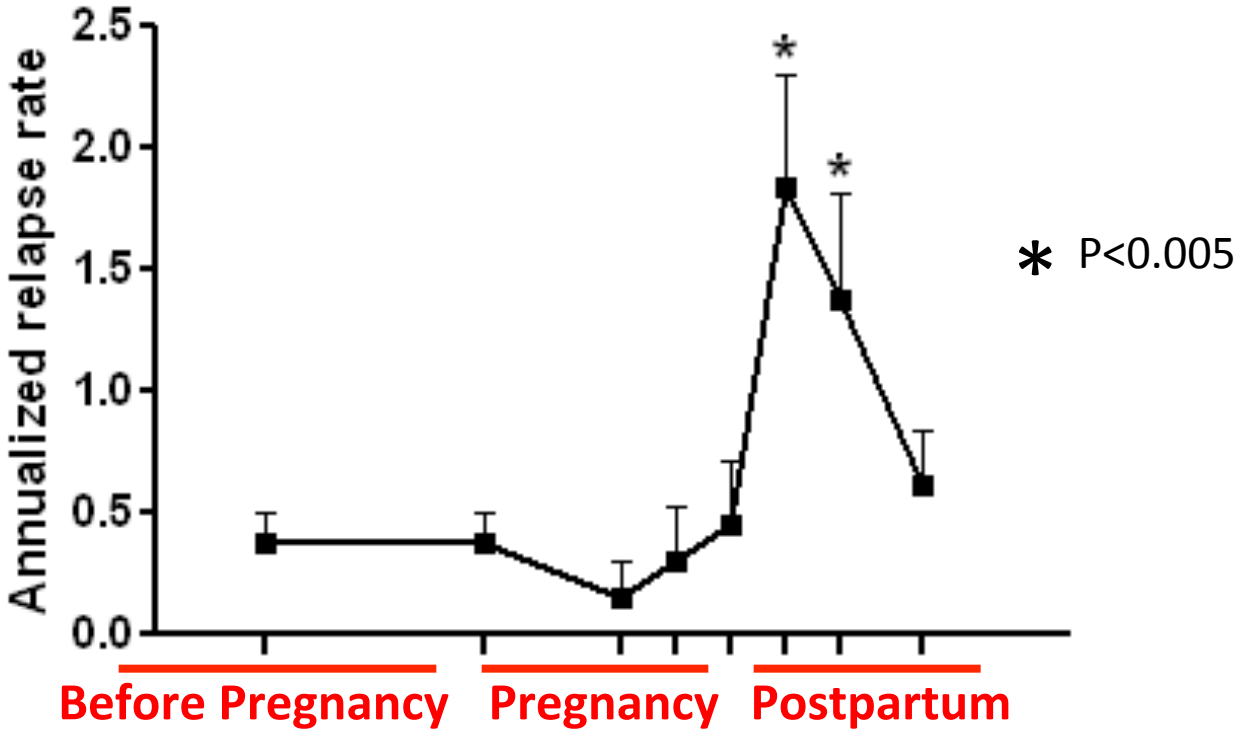
   Pain & Tonic spasm, Neurogenic bladder, Constipation, etc

(Kimbrough, Mult Scler Relat Disord 2012; Araki, Neurology 2014; Pittock, Lancet Neurol 2013, Bradl, Nat Rev Neurol 2014, etc)

Pregnancy and AQP4-IgG+NMOSD

1) Increase of relapse in 6 months postpartum

- An International Collaboration of Korea, Japan, UK and Portugal -



(Kim et al, Neurology 2011)

2) Higher rate of miscarriage (Nour et al, Neurology in press)

Experimental Study: AQP4-IgG can cause placental inflammation & fetal death (Saadoun et al, J Immunol 2013)

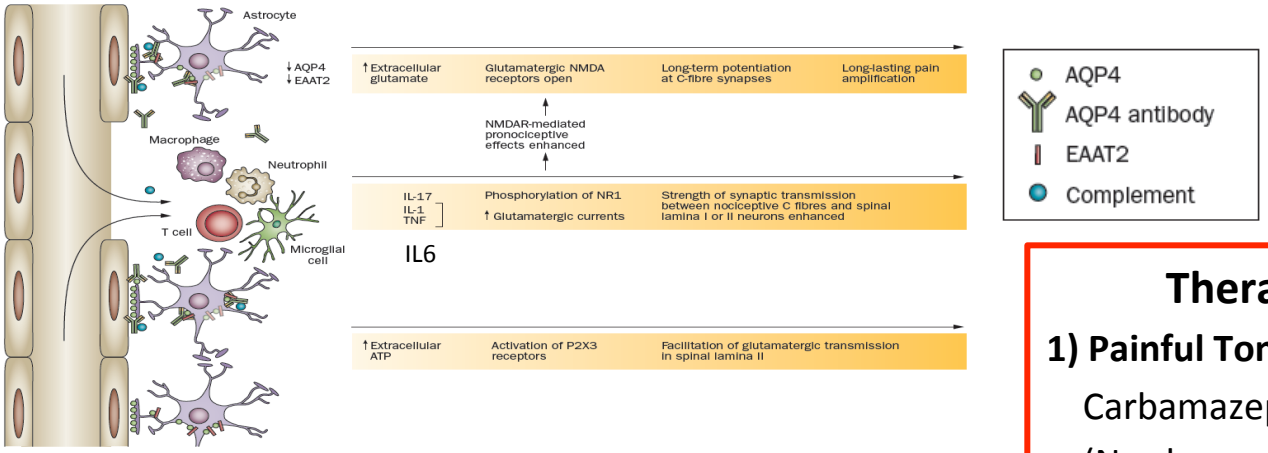
Brief Pain Inventory in NMO and MS

	NMO (n=37)	MS (n=51)	
Pain Severity Index	**3.6 ± 2.8**	**1.5±2.1**	**＜0.0001**
Categorized Pain Severity Index rating	n (%)	n (%)	
none (0)	6 (16.2)	27 (52.9)	
mild (1-3)	14 (37.8)	14 (27.5)	
moderate (4-6)	9 (24.3)	8 (15.7)	
severe (7-10)	8 (21.6)	2 (3.9)	
Pain-related interference(1-10)			
General activity	3.3 ± 3.8	2.0 ± 3.0	ns
Mood	3.5 ± 3.3	2.4 ± 3.2	ns
Walking ability	**3.2 ± 3.8**	**1.6 ± 2.6**	**0.02**
Normal work	3.4 ± 3.8	2.3 ± 3.4	ns
Relation with other people	3.0 ± 3.7	1.7 ± 2.9	ns
Sleep	3.5 ± 3.6	2.2 ± 3.1	ns
Enjoyment of life	**3.7 ± 3.8**	**2.0 ± 3.0**	**0.02**
total	23.3 ± 23.8	14.7 ± 19.4	ns

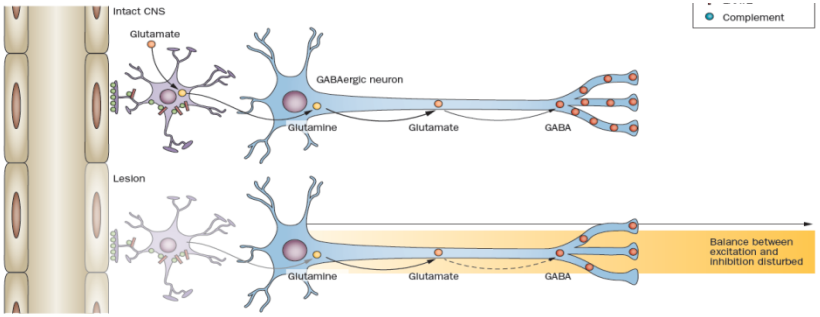
mean ± SD
ns, not significant

(Kanamori, Neurology 2011)

Stages of NMO lesions and key players & events in the development of Pain



In early lesions, long-lasting pain amplification results from the excitatory action & excessive extracellular glutamate



In old lesions, loss of astrocytes, an exclusive source of glutamine in CNS, interrupts the glutamine-glutamate-GABA axis, disrupting the excitation & inhibition balance in nociceptive pathways

Therapy of Pain in NMO

1) Painful Tonic Spasm

Carbamazepine, Gabapentinem etc

(Na channel blocking anti-Epi agents)

2) On-going Neuropathic Pain -- refractory

Pregabalin (binds to VGCC, reduce Glu release)

Baclofen (GABA receptor agonist)

Amitriptyline (tricyclic antidepressants)

Tramadol (binds to μ-opioid R, inhibits 5HT&NE reuptake

Tocilizumab (anti-IL6R)

Bradl, M. *et al. Nat. Rev. Neurol.* advance online publication 29 July 2014; doi:10.1038/nrneurol.2014.129

"Seronegative Definite NMO"

The most sensitive assay for AQP4-IgG

Cell-based assay, M23, No prefixing, No GFP tagging

Sensitivity (74.4%) and Specificity (100%)

Seronegative vs. Seropositive NMO

1) No female preponderance (Female/Male 1.2 vs 9.8)
2) Caucasian ethnicity (100% vs 73.6%)
3) Opticomyelitis at onset (27% vs 6%)
4) Less frequent severe visual impairment (12% vs 54%)

(Marignier et al, Neurology 2013)

MOG-IgG detection and MOG-IgG+cases

- Cell-Based Assays to detect conformation-sensitive myelin-oligodendrocyte glycoprotein (MOG)-IgG

  (O'Connor, **Nat Med** 2007)

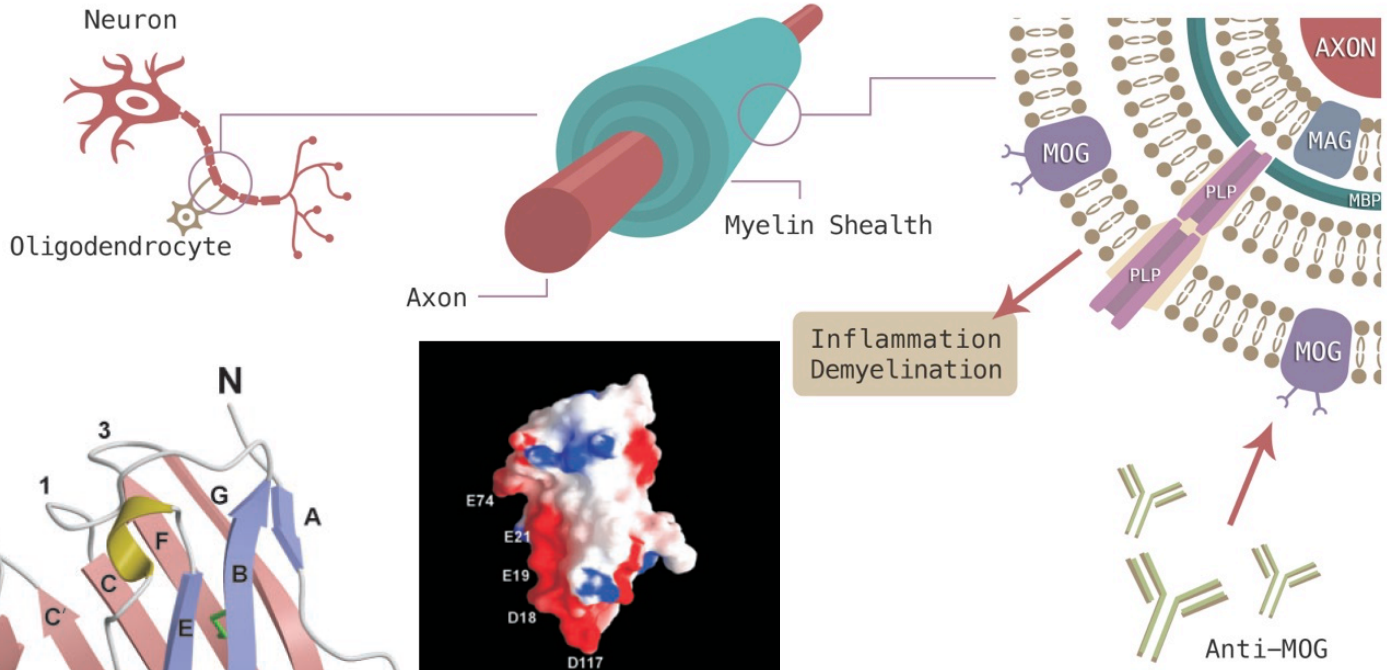
- MOG-IgG+ inflammatory CNS diseases, especially pediatric ADEM etc

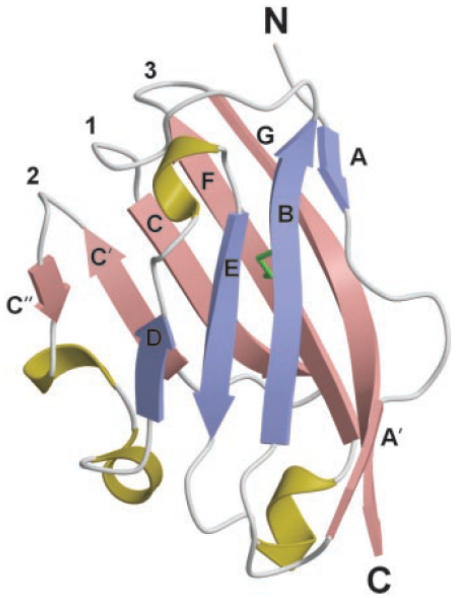
  (Pröbstel, **Neurology** 2011; Reindl, **Nat Rev Neurol** 2013)

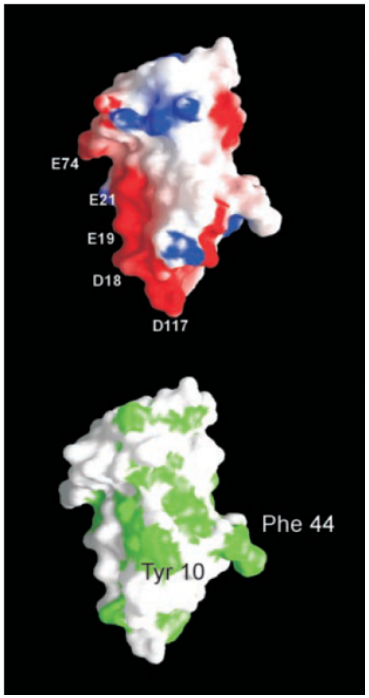
- **MOG-IgG in some AQP4-IgG-seronegative NMOSD**

  (Mader, **J Neuroinflamm** 2011; Kitley, **Neurology** 2012; Sato, **Neurology** 2014; Kitley, **JAMA Neurol** 2014)

Myelin Oligodendrocyte Glycoprotein (MOG)







(Clements, PNAS 2003)

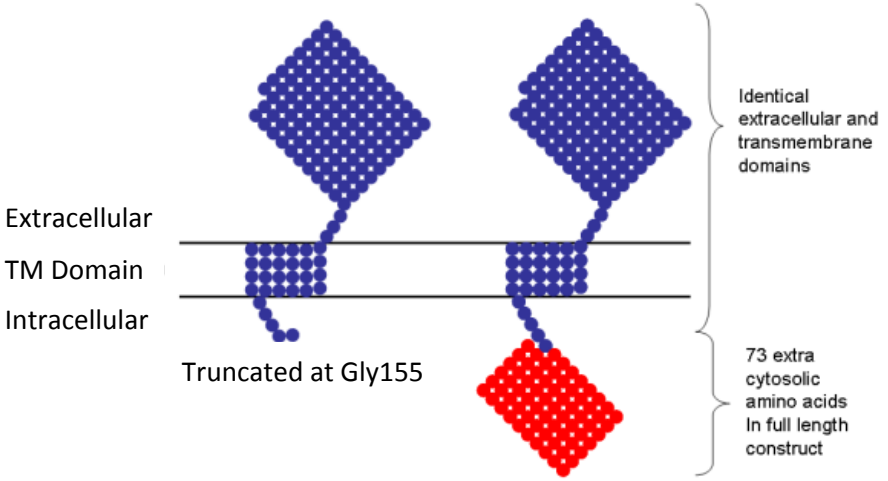
MOG protein

- **Outermost lamellae of the myelin sheath**
- Single Ig V extracellular domain
- Adhesion molecule ?
- Immune function? C1q binding
- **MOG peptides are encephalitogenic**

(Sato et al, AAN 2014)

MOG Antibodies measured using anti-human IgG (H+L)

A Myelin Oligodendrocyte Glycoprotein (MOG)



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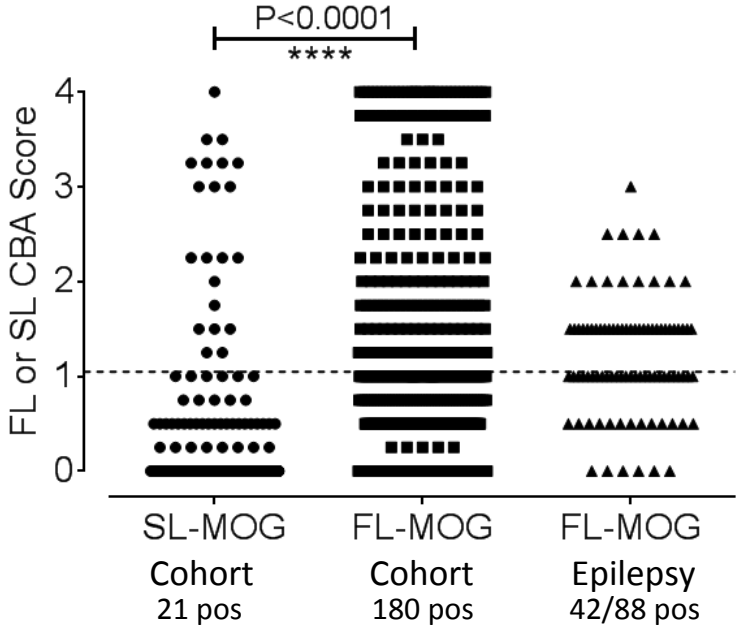
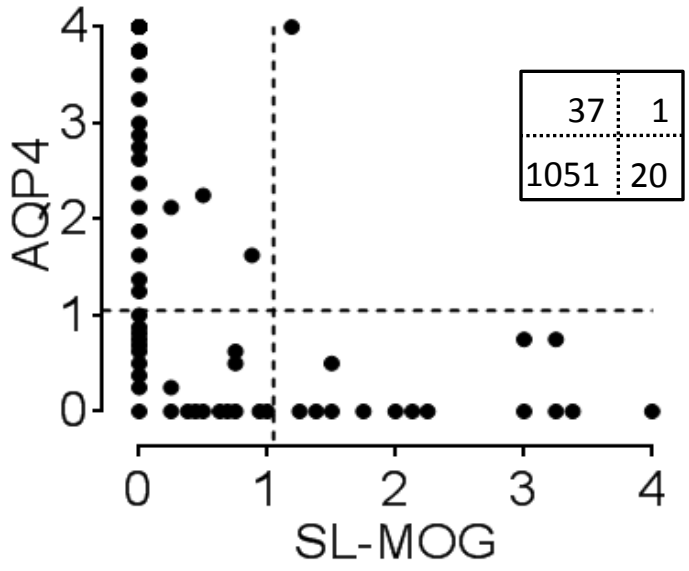
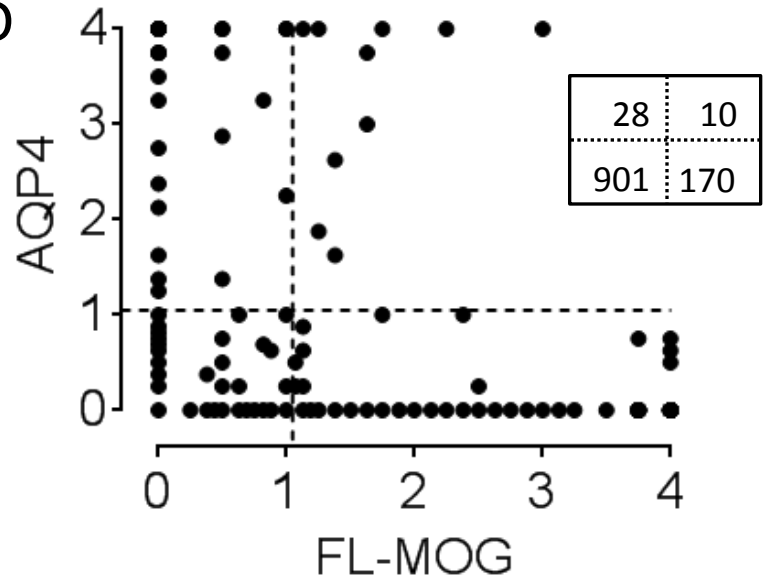


C

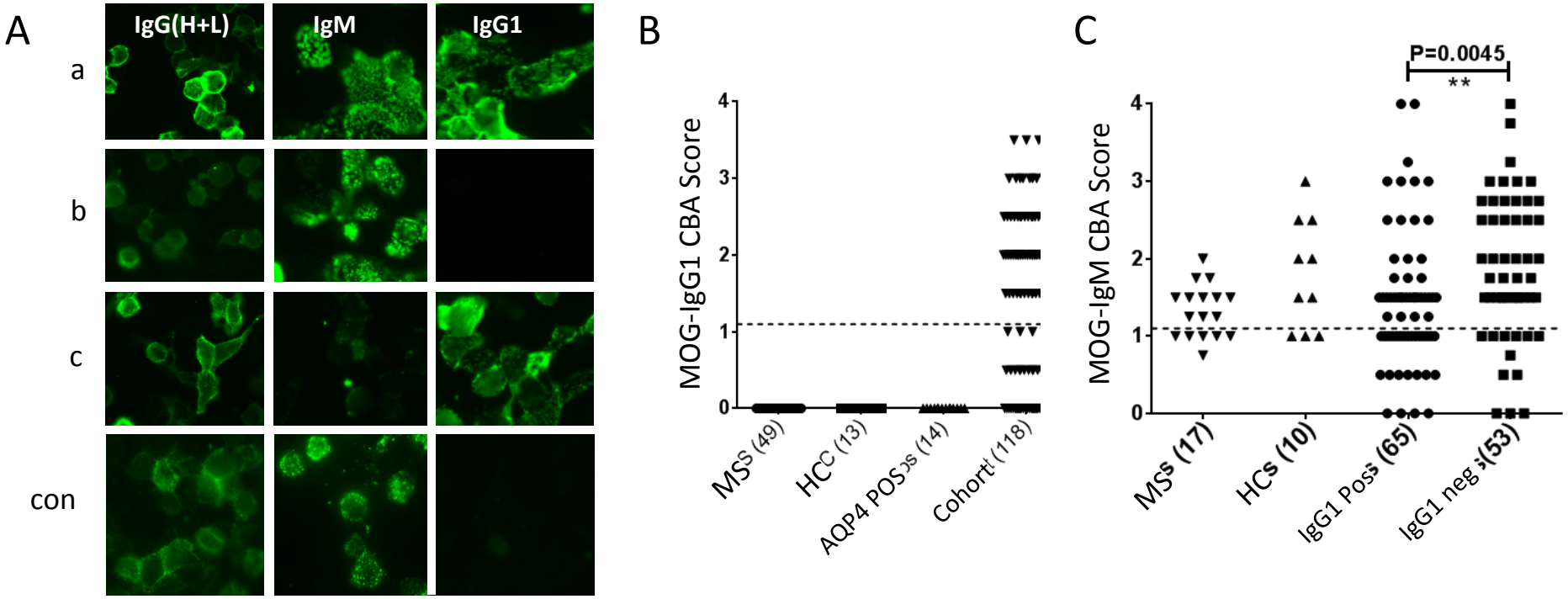


D



(Waters et al, Neurology N2, 2015)

MOG Antibodies detected by anti-human IgG (H+L), IgG1 or IgM



MOG Antibodies by FL-MOG + anti-human IgG1

Positive: ON, AQP4-IgG-negative NMOSD, ADEM

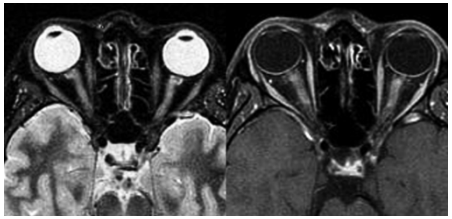
Negative: MS, AQP4-IgG-positive NMOSD, Controls

(Waters et al, Neurology N2, 2015)

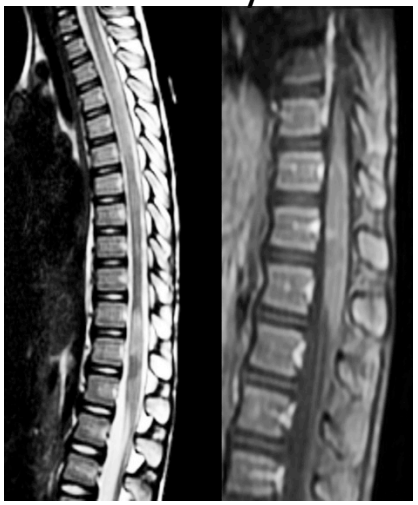
Features of MOG-IgG+NMOSD

	Anti-AQP4+ (n = 166)	Anti-MOG+ (n = 35)	Seronegative (n = 89)	*p* value
Onset Age	36 (4 – 78)	**35 (3 – 79)**	33 (10 – 80)	0.6770
Female Sex	88.6% (147)	**54.3% (19)**	64.0% (57)	<.0001
Single Attack	16.3% (27)	**42.9% (15)**	38.2% (34)	<.0001
Clinical Phenotype				
NMO	60.8% (101)	**11.4% (4)**	21.4% (19)	
LETM	29.5% (49)	**25.7% (9)**	55.1% (49)	<.0001
Recur ON / Bil ON	9.7% (16)	**62.9% (22)**	23.6% (21)	
EDSS (last visit)				
Monophasic	6 (2 – 8.5)	**2 (0 – 6)**	4 (0 – 8.5)	0.0009
Recurrent	5 (1 – 8.5)	**2 (0 – 8)**	4 (0 – 7)	<.0001

Simult Bil ON



Caudal Myelitis



(Sato et al, AAN, Neurology 2014)

MRI and OCT in anti-MOG+ vs anti-AQP4+ ON

	Anti-MOG+ ON eyes (n=19)	Anti-AQP4+ ON eyes (n=9)	Seronegative ON eyes (n=9)	p Value (anti-MOG+ vs anti-AQP4+)	p Value (anti-MOG+ vs seronegative)
Optic nerve segments with STIR or T2WI hyperintensity					
Orbital, n (%)	14/19 (73.7)	8/9 (88.9)	8/9 (88.9)	NS	NS
Canalicular, n (%)	19/19 (100)	4/9 (44.4)	6/9 (66.7)	0.0013	0.0445
Intracranial, n (%)	19/19 (100)	4/9 (44.4)	1/9 (11.1)	0.0013	<0.0001
Chiasm, n (%)	0/19 (0)	4/9 (44.4)	1/9 (11.1)	0.0062	NS
Optic tract, n (%)	0/19 (0)	1/9 (11.1)	0/9 (0)	NS	NS
Lesion extension in segments, median (range)	3 (2–3)	1 (1–5)	2 (1–3)	0.0829	0.0005
Severe optic nerve swelling at onset, n (%)	16/17 (94.1)	1/9 (11.1)	1/9 (11.1)	0.0001	0.0001
Optic nerve lesions with CE, n (%)	14/17 (82.4)	7/9 (77.7)	1/9 (11.1)	NS	<0.0001
Extension of inflammation to intraorbital tissues with CE, n (%)	8/17 (47.1)	2/9 (22.2)	2/9 (22.2)	NS	NS

Anti-MOG, antimyelin oligodendrocyte glycoprotein; CE, contrast enhancement; NS, not significant; ON, optic neuritis; STIR, short T1 inversion recovery; T2WI, T2-weighted imaging.

OCT (Anti-MOG+ vs Anti-AQP4+ ON eyes, 6 month follow-up)

- cpRNFL 90.2 ± 10.5 vs 74.1 ± 14.9 µm ($P = 0.022$)
- GCIP 57.0 ± 6.2 vs 46.1 ± 12.3 µm ($P = 0.027$)

(Akaishi T, J Neurol Neurosurg Psychiatry 2015)

Severe Demyelination but No Astrocytopathy in MOG-IgG-Positive Definite NMO

31year-old man

Rt ON (VA 20/200)

Rapid recovery after IVMP

Acute Myelitis (2 weeks later)

T2 sensory level, dysuria

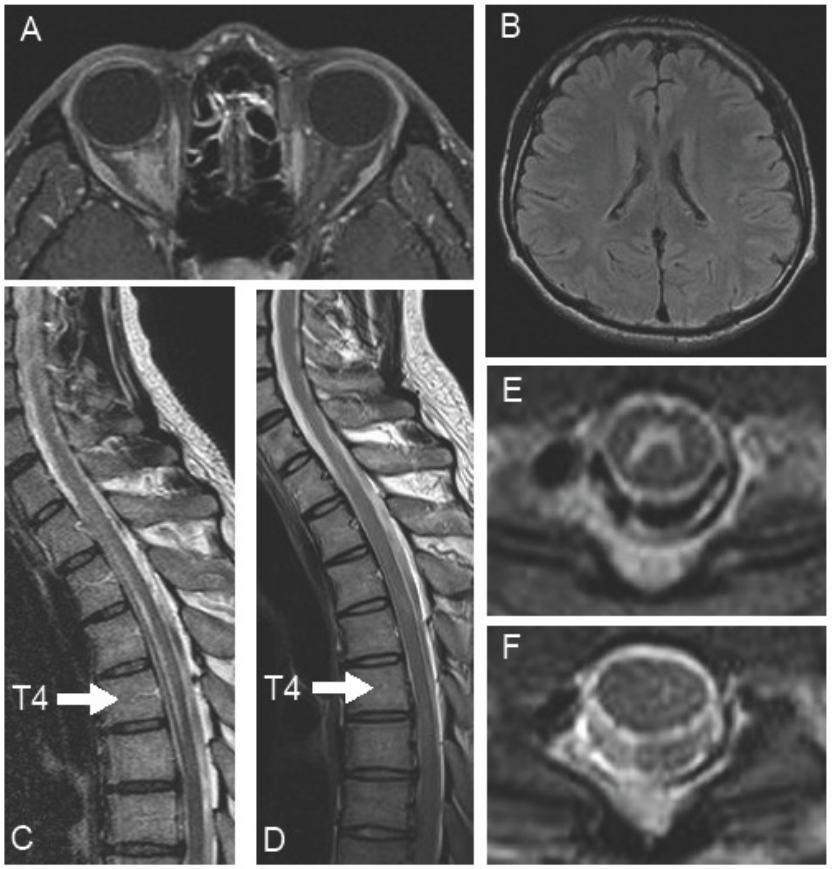
CSF pleocytosis (90), OCB negative

T2 lesions in C3-5, **C6-T5** (central)

AQP4-IgG-Neg, MOG-IgG-Pos

Good recovery after IVMP

CSF-MBP 1190pg/ml (normal <102)
CSF-GFAP < 0.004ng/ml

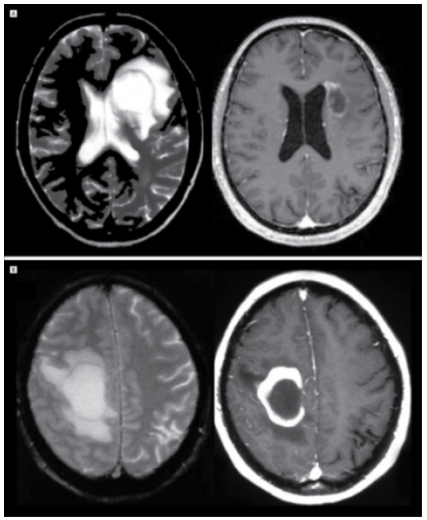


(Ikeda et al, Mult Scler, 2015)

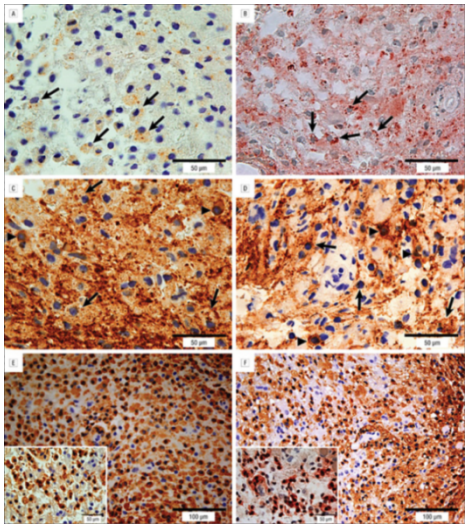
I. MS type- II Pathology in biopsied brains of MOG-IgG-positive cases

1. Konig et al. Arch Neurol. 2008

49-yo white woman
"CD-RRMS", MOG-IgG positive



Early active inflammatory demyelination with deposition of Ig & C



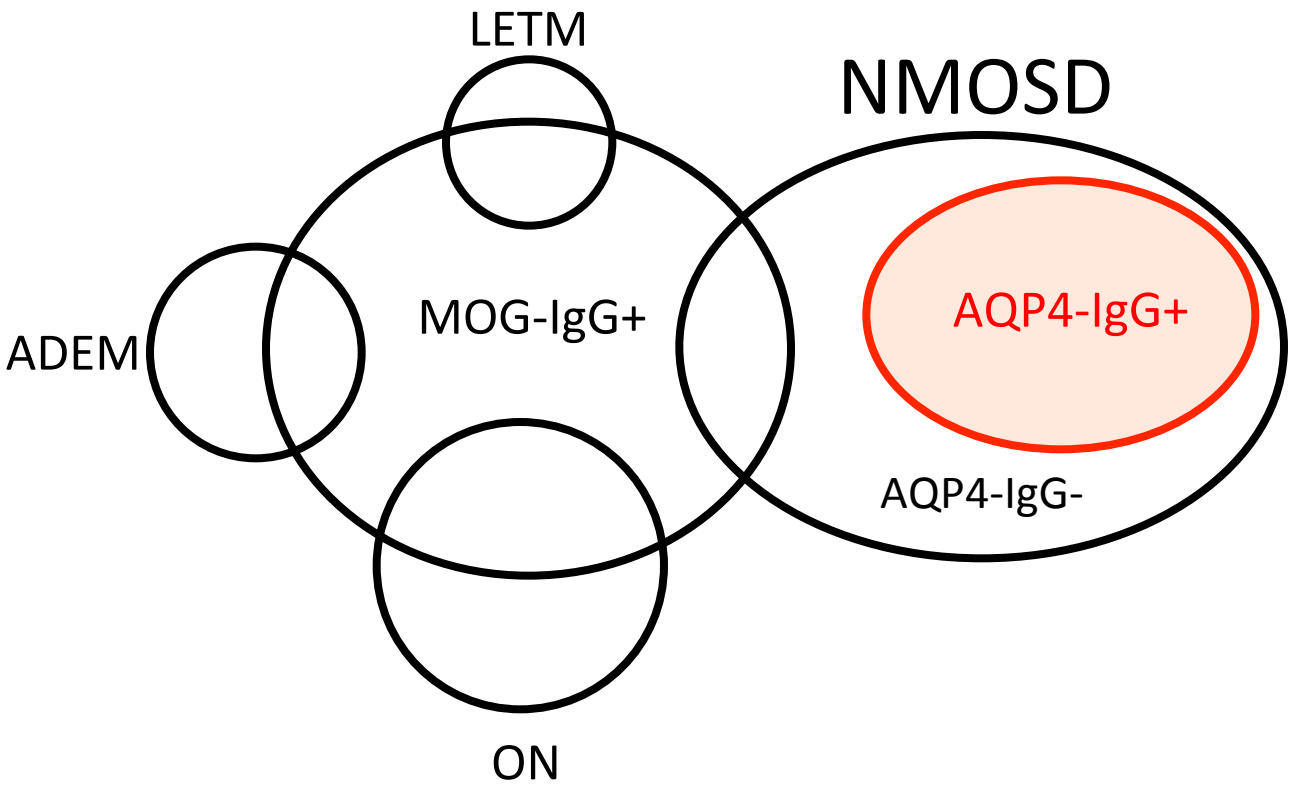
2. Spadalo M, et al. Ann Clin Transl Neurol, 2015

II. Pathogenicity of MOG-IgG

1. MOG-IgG activates complements (Mader et al. J Neuroinflammation. 2011)
2. MOG-IgG affects oligodendrocyte cytoskeleton (Dale et al. Neurol N2. 2014)

MOG-IgG and NMOSD

(Demyelinating and Astorcytopathic Diseases)



NMOSD includes astrocytopathic disease (AQP4-IgG+) and demyelinating disease (MOG-IgG+)

Traditional Classification

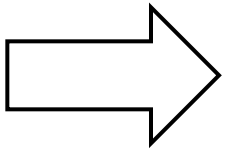
I. Demyelinating Disease
- **1. MS**
- **2. NMO**
- **3. …..**
- **4. …..**

II. …..

or

I. Demyelinating Disease
- **1. MS**
  - **1) …..**
  - **2) NMO**
  - **3) …..**
- **2. …..**
- **3. …..**

II. …..



Newly Proposed Classification

I. Demyelinating Disease
- **1. MS**
- **2. MOG-IgG-associated Disease (including NMOSD)**
- **3. …..**

II. Astrocytopathic Disease
- **1. AQP4-IgG+NMOSD**

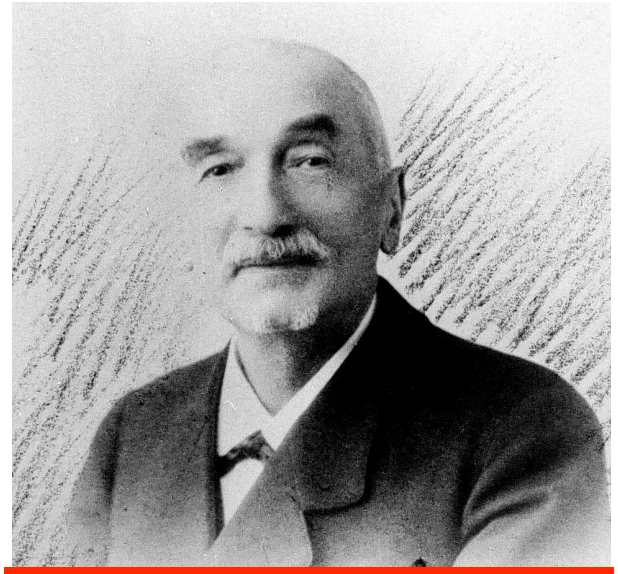
III. …..

(modified from Fujihara et al, Clin Exp Neuroimmunol 2012)

“Myélite subaiguë compliquée de névrite optique”

(Bull Med 8;1033-1034, 1894)

Eugène Devic (1858-1930)



(from Miyazawa et al. J Neurol 2002)

45y.o.woman
*Severe ON & TM
*Severe Demyelination & Necrosis in ON and SC
*No Brain Lesions

Analysis of 17 Reported Cases of NMO

Age at Onset (y)	30.6 (12-52)
Male : Female	1.66 : 1
Initial Symptom	ON (9), M (6)
Interval of ON & M	< 30d (10), 1-6m (4)
Optic Neuritis	Bilateral (15)
Myelitis	ATM (4)
Other CNS signs	Cerebral(3)
	Brainstem (3)
Course	Monophasic (14)
	Relapsing (3)

(Devic and Gault,1894)

Summary: NMOSD

1. NMOSD is distributed world-wide (Prevalence ~5/10$^{5)}$.
   NMOSD:MS ratios are high in Asian countries.

2. NMOSD has evolved, and the new Criteria will facilitate early Dx.

3. mAb are expected to be new therapeutic options.
   Pain & Pregnancy-related attack are therapeutic challenges.

4. MOG-IgG+ (AQP4-IgG negative) cases have unique features.

5. NMOSD includes astrocytopathic and demyelinating diseases.
   (AQP4-IgG+) **(MOG-IgG+)**

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