

15th GJCF NMO Roundtable Conference

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Global Epidemiology of NMOSD, MOGAD & Seronegative Disease (SND)

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Disclosure (Kazuo Fujihara, M.D.)

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Biogen, Eisai, Mitsubishi Tanabe, Novartis, Astellas, Takeda, Asahi Kasei Medical, Daiichi Sankyo, Nihon, Teijin, VielaBio

Speaker honoraria:

Biogen, Eisai, Mitsubishi Tanabe, Novartis, Astellas, Takeda, Asahi Kasei Medical, Daiichi Sankyo, Nihon, Teijin. Roche, Chugai, Alexion

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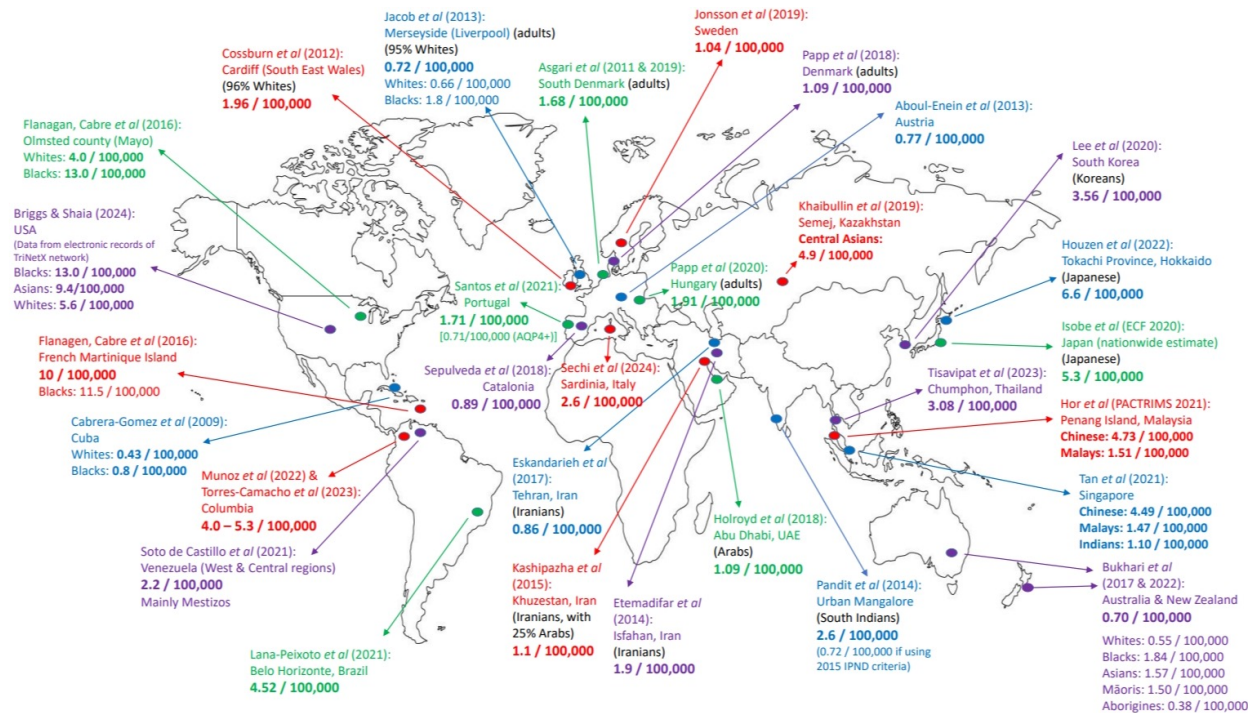
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Key clinical & MRI features of MOGAD, AQP4-IgG NMOSD, SND and MS

	MOGAD	AQP4+NMOSD	SND	MS
Pediatric onset	Frequent	Extremely rare		infrequent
Sex distribution	F=M	F>M		F>M (after puberty)
Disease course	Monophasic/relapsing	Most often relapsing		Relapsing/progressive
Optic nerve	Severe, good recovery Bil, anterior, longitudinally extensive, ON sheath, ON head edema	Severe, poor recovery, Bil/Unil, posterior, longitudinally extensive, chiasmal		Mild~moderate, favorable recovery, Unil, anterior, short
Spinal cord	Severe, excellent recovery, LETM, H sign, conus lesion	Severe, poor recovery, LETM Bright spotty lesion		Mild~moderate, often good recovery, Multiple focal cord lesions;
Brain	Encephalopathy (eg, ADEM), seizures and cerebral cortical encephalitis WM, deep GM, middle cerebellar peduncle, large BS, and confluent cortical	APS, hypersomnolence Peri-IIIrd and -IVth ventricle, callosal splenium, internal capsule, and WM		Focal/polyfocal neurological deficits common, Multifocal, ovoid T2-WM lesions, Dawson's fingers, U- fibre lesions; CVS, SEL

(Modified from Banwell *et al.* Lancet Neurol 2023)

Population-based prevalence studies of NMOSD in the World



NO LATITUDE GRADIENT

Prevalence (per 100,000):

Whites: 1 - 2

Blacks: ~10

East Asians: ~5

Austronesians: ~2

South Indians: ~1

Central Asians: ~5

LATAM: 2.2 - 5

Africa (estimates):

0.004 (Ethiopia) ~ 0.14 (Morocco)

(Modified from Hor *et al.* Front Neurol 2020, Papp *et al.* Neurology 2021, Musubire *et al.* N2 2021, Kissani *et al.* OALIB J, Bukhari *et al.* JNNP 2017, Miyamoto *et al.* JNNP 2018)

F:M ratio: 8.89 : 1 (higher when AQP4+ case proportion is higher)

Mean onset age: 41.7 years (increases with population life expectancy)

(Arnett *et al.* J Neurol 2024)

Increasing prevalence (total n of Pts) over time in some studies

	Prevalence of NMOSD per 100,000 population		
	2007	2016	
Martinique Island (Black population)	4.2	11.5	
	2011	2016	2021
Hokkaido, Japan	0.9	4.1	6.1
	2017	2020	2023
Penang Island, Malaysia (Chinese)	3.3	4.7	6.9
	2013	2022	
Sardinia	1.1	2.6	

In early years, likely due to increased detection & changing definition (NMO -> NMOSD)

But more recently, likely due to improved survival

Relatively stable annual incidence (new cases/year) over the years

A systematic review (Papp *et al.* Neurology 2021) :
 French West Indies (1992-2007)
 British Columbia (1986-2010)
 Netherlands (6 years)
 Abu Dhabi (7 years),
 Denmark (7 years)
 Catalonia (10 years)
 Hungary (10 years)

Annual incidence

among:

Whites: 0.37 – 1.32 / million

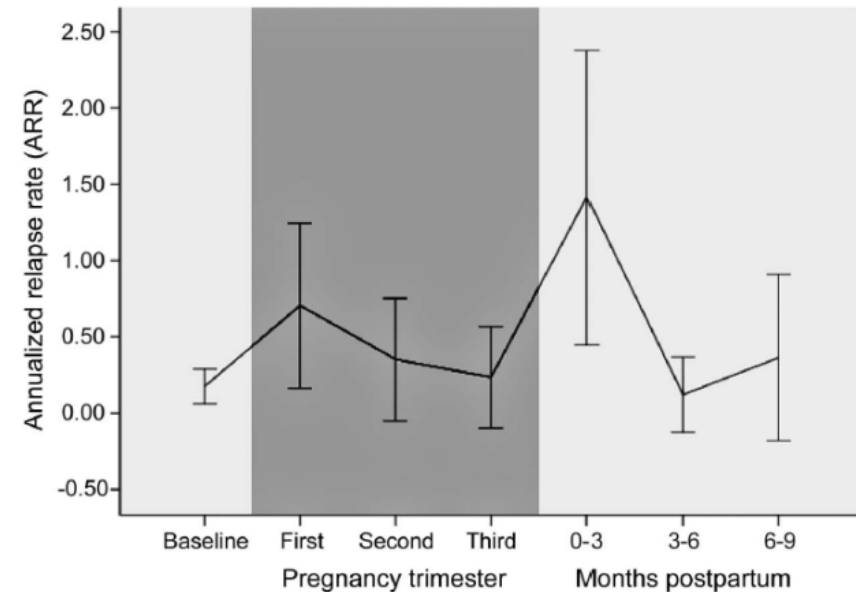
African-Caribbean: up to 7 / million

East Asians: ~ 3 – 4 / million

Pregnancy

- High risk of relapse in **early post-partum period**
- Risk of relapse during pregnancy is not low

(Kim *et al.* 2012, Nour *et al.* 2016, Shimizu *et al.* 2016, Klawiter *et al.* 2017, Collongues *et al.* 2021)



Vitamin D:

- **Inconclusive**
- Some studies reported impact on disease activity and disability, but others reported negative associations

(Min *et al.* 2014, Shan *et al.* 2016, Jitprapaikulsan *et al.* 2016, Kusumadewi *et al.* 2018, Gao *et al.* 2019)

Smoking:

- Does not increase relapse rate, but may cause worse disability due to poor relapse recovery
- (Messina *et al.* 2021)

Rheumatic and autoimmune diseases in NMOSD

1. Systemic

Sjogren, SLE, RA, Anti-PL-Ab

2. Organ-specific

2.1. Neurological organ-specific

MG, AE, Neuropathies (AIDP, CIDP), etc

2.2. Non-neurological organ-specific

Thyroid (Hashimoto, Graves')

GI and liver (AH, UC, etc)

Skin (Raynaud, DM, Psoriasis, etc)

Blood (AHA, etc)

(Shahmohammadi S, *et al.* MSARD 2019)

SLE was significantly associated with AQP4-IgG+NMOSD but not with MOGAD (P<0.037) (Kunchok *et al.* MSJ 2021)

A link of AQP4-IgG+ with SLE but not with MS

Type I IFN signature (Feng X, *et al.* J Neurol Sci 2011),

A whole-genome sequence (Estrada K, *et al.* Nat Commun 2018)

Neoplastic diseases in NMOSD

BRIEF COMMUNICATION

Paraneoplastic neuromyelitis optica spectrum disorders: a case series

Eleonora Virgilio¹  • Domizia Vecchio^{1,2} • Marco Vercellino³ • Paola Naldi¹ • Fabiana Tesser⁴ • Roberto Cantello¹ • Paola Cavalla³ • Cristoforo Comi^{2,4}

(Neurol Sci 2021)



3~25% of NMOSD cases – paraneoplastic?
cancer (breast, lung, uterine, etc), carcinoid, B cell lymphoma, monoclonal gammopathy, etc

(Pittock, Lennon. Arch Neurol 2008)

Topical Review

Double-negative neuromyelitis optica spectrum disorder

Yan Wu, Ruth Geraldese , Maciej Juryńczyk and Jacqueline Palace

- **A rare entity**
- **A syndrome rather than a single disease**
monophasic illness ~ chronic syndrome (AQP4+like/other mimics, eg. MS)

(Wu et al. Mult Scler 2023)

Three cohort studies of Double-seronegative NMOSD defined by the 2015 Criteria

1) Catalonia Population-based Study

	AQP4+ NMOSD (n=54)	MOG+ NMOSD (n=9)	Double seronegative NMOSD (n=11)
Prevalence	~0.64 / 100,000	~0.12 / 100,000	~0.13 / 100,000
Female	44 (82%)	5 (56%)	7 (64%)
<u>Ethnicity:</u>			
White	42 (78%)	9 (100%)	9 (82%)
Hispanic	6 (11%)	0	2 (18%)
Black	2 (4%)	0	0
Asian	2 (4%)	0	0
Arab	2 (4%)	0	0
Age of onset	43y (10-76)	43y (18-63)	35y (13-60)
<u>Onset attacks:</u>			
Optic neuritis	22 (41%)	3 (33%)	3 (27%)
Myelitis	25 (46%)	2 (22%)	3 (27%)
ON + myelitis	3 (6%)	3 (33%)	4 (36%)
Area postrema syndrome	2 (4%)	1 (11%)	0
Brainstem syndrome	2 (4%)	0	1 (9%)
Relapsing forms	51 (94%)	7 (77%)	5 (55%)

(Sepulveda *et al.*, MSJ 2018)

2) Portuguese Nationwide Study

AQP4 ab+ NMOSD n=77
 MOG ab+ NMOSD n=67
 Seronegative NMOSD n=36



Female: 61%
 Mean age of onset: 38 yrs

Onset attack:

Myelitis: n=21 (58%)
 ON: n=9 (25%)
 Myelitis & ON: n=1 (3%)
 Brainstem syndrome: n=1
 Supratentorial: n=1
 Myelitis & brainstem: n=2
 Myelitis & supratentorial: n=1

Relapse : 100%

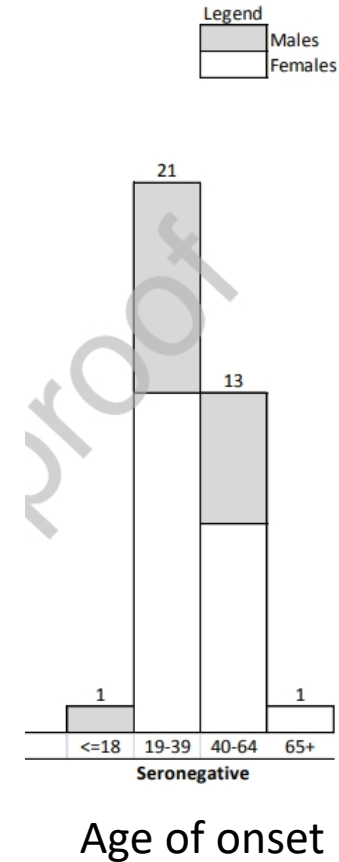
CSF OCB positivity: n=5 (17%)

Prevalence

0.71 / 10⁵

0.65 / 10⁵

0.35 / 10⁵



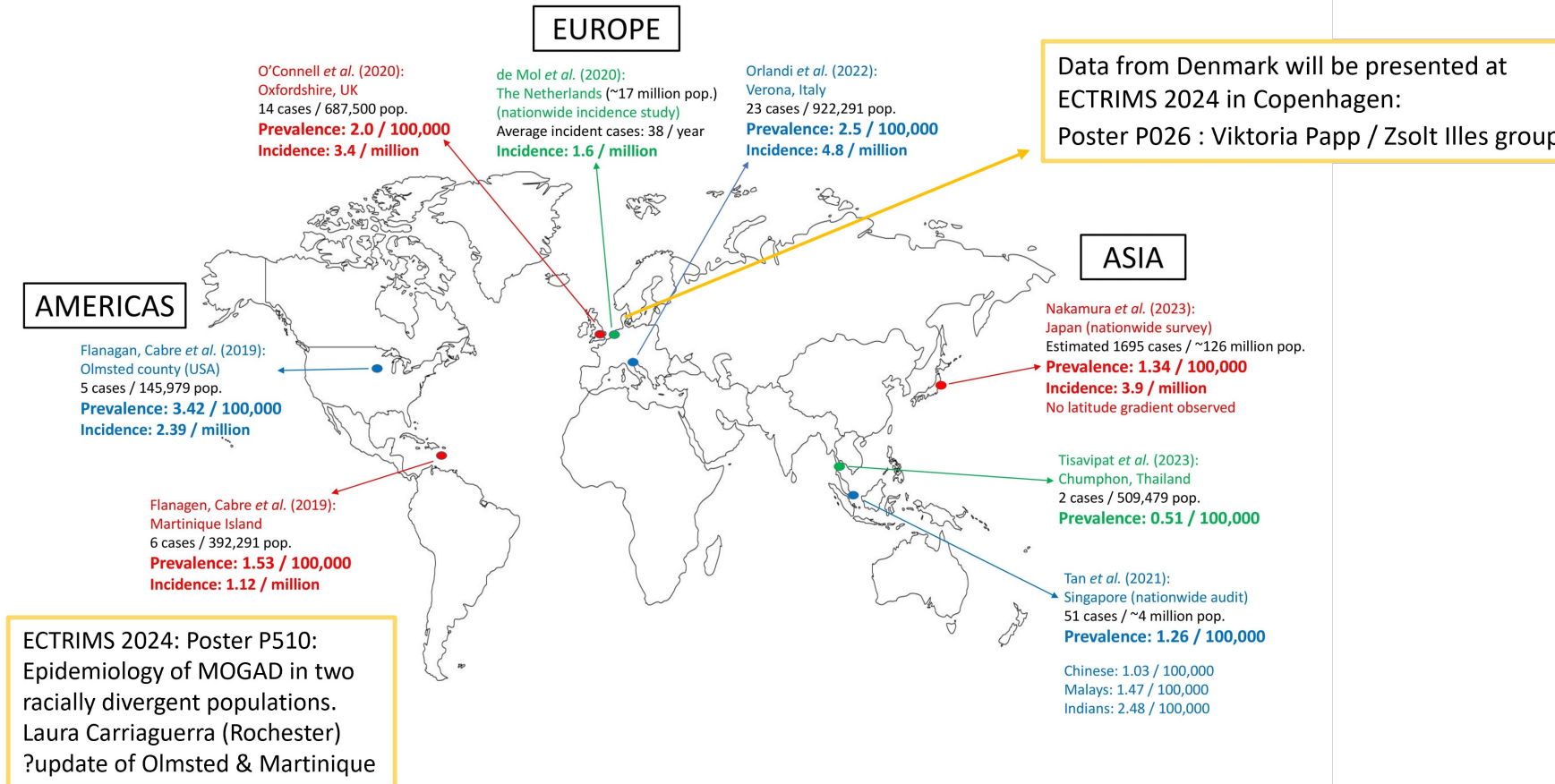
(Santos *et al.*, MSARD 2021)

3) Population-based study in Chumphon Province, Thailand

AQP4+ NMOSD: n=12
 MOGA: n=2
 Seronegative NMOSD: n=1

(Tisavipat *et al.*, MSARD 2023)

World Map Showing Population-Based Prevalence / Incidence Studies of MOGAD



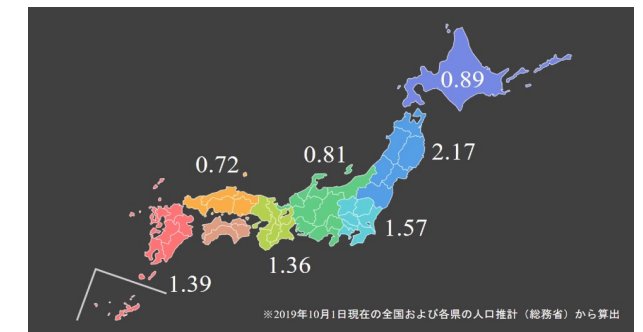
(Hor *et al.* Front Neurol 2023)

No latitude gradient between northern and southern Japan

(Nakamura *et al.* MSJ 2023)

Prevalence:
~1 – 2.5 / 100,000

Annual incidence:
~3 – 4.8 / million



Prevalence & Incidence of MOGAD

	Prevalence (per 100,000)	Incidence (per million)	Compare with prevalence (per 100,000) of AQP4+ NMOSD
<u>Europe:</u>			
• Oxfordshire, UK	1.9	3.4	1.0
• Verona, Italy	2.2	4.8	
<u>Asia:</u>			
• Japan	1.34	3.9	5.3
• Singapore			
• Chinese	1.03		
• Malays	1.47		
• Indians	2.48		

(O'Connell *et al.* JNNP 2020; Orlandi *et al.* 2022; Nakamura *et al.* MSJ 2023; Tan *et al.* Neurol Clin Neurosci 2021)

Genetic / HLA Associations in MOGAD:

Dutch & UK studies: No strong HLA association

(Bruijstens *et al.* Neurol N2 2020; Grant-Peters *et al.* Ann Clin Transl Neurol 2021)

Guangzhou (China):

(1) DQB1*05:02-DRB1*16:02 haplotype in pediatric-onset MOGAD,

but no HLA association in adult-onset MOGAD

(Sun *et al.* JNNP 2020)

(2) Non-HLA susceptibility loci: *BANK1*, *RNASET2*, *TNIP1* polymorphisms (Shu *et al.* J Neuroimmunol 2022)

Precedent Infection

~ 20 – 40% of MOGAD cases had infectious prodrome or precedent infection.

(Hor *et al.* Front Neurol 2023)

In Japan nationwide MOGAD survey, precedent infection was more common in pediatric-onset group (39% in aged < 10 yrs) than in adult-onset group (13.5%).

(Nakamura *et al.* MSJ 2023)

common cold
pharyngolaryngitis
bronchitis
pneumonia
gastroenteritis
infections related to
influenza
mycoplasma
streptococcus
chlamydia

Post-vaccination

A small number of MOGAD cases had onset post-vaccination

Reported vaccines include:

Influenza

Japanese encephalitis

Measles / rubella

Diphtheria / tetanus / pertussis

COVID-19

Post-COVID19 vaccination:

UK study:

25 patients developed
acute CNS inflammatory disease:



12 : **MOG-IgG+**

2 : AQP4-IgG+

11 : seronegative

RESEARCH ARTICLE OPEN ACCESS

Acute Inflammatory Diseases of the Central Nervous System After SARS-CoV-2 Vaccination

Anna G. Francis, BMBCh,* Karlem Elhadd, MBBS, Valentina Camera, MD, Monica Ferreira dos Santos, MD, Chiara Rocchi, MD, Poneh Adib-Samii, MBBS, PhD, Bal Atthwal, FRCP, Kathrine Attfield, PhD, Andrew Barritt, MBBS, PhD, Matthew Craner, PhD, Leonora Fisniku, MD, Astrid K.N. Iversen, MD, PhD,* Oliver Leach, MBChB, Lucy Matthews, MRCP, DPhil, Ian Redmond, FRCP, Jonathan O'Riordan, MD, Antonio Scalfari, MD, PhD, Radu Tanasescu, MD, PhD, Damian Wren, DM, Salf Huda, DPhil, Maria Isabel Leite, MD, DPhil,* Lars Fugger, MD, PhD,* and Jacqueline Palace, MD, PhD*

Neural Neuroimmunol Neuroinflamm 2023;10:e200063. doi:10.1212/NXI.0000000000000063

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Korean study:
10 patients



2 : Multiple sclerosis

2 : NMOSD

3 : **MOGAD**

3 : unclassified CNS-IDD

Multiple Sclerosis and Related Disorders 68 (2022) 104141

Contents lists available at ScienceDirect



ELSEVIER

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Onset of various CNS inflammatory demyelination diseases following COVID-19 vaccinations

Ki Hoon Kim, Su-Hyun Kim, Na Young Park, Jae-Won Hyun, Ho Jin Kim *

MOGAD and pregnancy

ARR decreased from 0.67 (95% CI: 0.40–1.10) during the pre-pregnancy period to 0 (0–0.21) during pregnancy and to 0.22 (0.09–0.53) during the first year post-partum.

(Carra-Dalliere et al. MSJ 2022)

MOGAD and neoplasm

MOG-antibody is a low-risk antibody for paraneoplastic neurological syndrome.

In an Italian cohort, **only 2 (1.3%) of 150 MOGAD** patients had **tumor association**

– (1) 59y.o. male – non-Hodgkin lymphoma; (2) 64y.o. male – melanoma

In a literature review – 17 cases were identified

– commonest association: teratoma (4 cases)

(Trentinaglia et al. Front Neurol 2023)

MOGAD and co-existing antibodies

NMDAR-ab is the commonest co-existing neuronal surface antibodies.

In a lab study, 14 of 376 (**3.7%**) samples (serum or CSF) positive for MOG ab also positive for NMDAR ab.

>200 cases were reported in the literature of dual positivity of MOG ab and NMDAR ab.

(Kunchok et al. MSJ 2021; Molazadeh et al. MSJ-ETC 2022)

Some issues of MOG-IgG detection in the diagnosis of MOGAD

1) CSF-restricted MOG-IgG positivity

MOG-IgG	Seropositive, CSF-negative	Seropositive, CSF-positive	Seronegative, CSF-positive
Italy (n=16), Mariotto, Neurology 2019	31%	50%	19%
UK (n=118), Pace, JNNP 2021	56%	41%	3%
Korea (n=40), Kwon, N2 2023	30%	47%	23%
Japan (n=133), Matsumoto, Brain 2023	13%	71%	17%
Multicentor (n= 255), Carta, Neurology 2023	31%	57%	12%
Italy (n=55), Greco, JNNP 2024	58%	35%	7%
Canada (n=28), Burton, J Neurol 2024	82%	18%	0%
US (n=83), Redenbaugh, Neurology 2024.	10%	79%	11%
Australia (n=114), Reynolds, Ann Clin Transl Neurol 2024	45%	52%	3%

(prepared by Dr. Yuki Matsumoto)

2) Isolated MOG-IgA positivity

In DN for AQP4-IgG and MOG-IgG (1126/1339; 84%),

isolated MOG-IgA was identified 6% (3/50) of NMOSD, 2% (5/228) of other CNS demyel dis, and 1% (10/848) of MS but in none of HC (0/110).

(Gomes *et al.* JAMA Neurol 2023)

3) Exclusive or predominant MOG-IgG3 serpositivity

(Jarius *et al.* J Neurol 2024)

Comparison of AQP4+NMOSD, MOGAD & SND

	MOGAD	AQP4+NMOSD	SND
Pediatric onset	Frequent	Extremely rare	Infrequent (Onset 32~43y)
Sex distribution	F=M	F>M	F=or>M
Disease course	Monophasic/relapsing	Most often relapsing	Monophasic/relapsing (24~100%)
Optic nerve	Severe, good recovery Bil, anterior, longi ext, ON sheath, ON head edema	Severe, poor recovery, Bil/Unil, posterior, longi ext, chiasmal	Moderate~severe, relatively poor recovery, Unil in many, Rare chiasmal involvement
Spinal cord	Severe, excellent recovery, LETM, H sign, conus lesion	Severe, poor recovery, LETM Bright spotty lesion	Moderate~severe, relatively poor recovery, LETM
Brain	Encephalopathy (eg, ADEM), cerebral cortical encephalitis	APS, hypersomnolence	Lesions in some, rare/no APS
Prevalence	Relatively constant	Higher in Blacks, East Asians and Native Americans Probably increasing (stable incid)	Lower than MOGAD/AQP4+
N-S gradient	no	no	?
ARR in postpartum	Not increased	Higher	?
Post-infection/vaccine	20~40%/in some	Relatively rare	?
Coexisting AI/neoplasm	Uncommon (except NMDAR-ab)	Not uncommon	AI 12.9%