Epidemiology of Neuromyelitis Optica Spectrum Disorder and Its Prevalence and Incidence Worldwide

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Neuromyelitis optica spectrum disorder (NMOSD) is an uncommon inflammatory disease of the central nervous system, manifesting clinically as optic neuritis, myelitis, and certain brain and brainstem syndromes. Cases clinically diagnosed as NMOSD may include aquaporin 4 (AQP4)-antibody-seropositive autoimmune astrocytopathic disease, myelin oligodendrocyte glycoprotein (MOG)-antibody-seropositive inflammatory demyelinating disease, and double-seronegative disease. AQP4-antibody disease has a high female-to-male ratio (up to 9:1), and its mean age at onset of ∼40 years is later than that seen in multiple sclerosis. For MOG-antibody disease, its gender ratio is closer to 1:1, and it is more common in children than in adults. Its clinical phenotypes differ but overlap with those of AQP4-antibody disease and include acute disseminated encephalomyelitis, brainstem and cerebral cortical encephalitis, as well as optic neuritis and myelitis. Double-seronegative disease requires further research and clarification. Population-based studies over the past two decades report the prevalence and incidence of NMOSD in different populations worldwide. One relevant finding is the varying prevalence observed in different racial groups. Consistently, the prevalence of NMOSD among Whites is ∼1/100,000 population, with an annual incidence of <1/million population.

Among East Asians, the prevalence is higher, at ~3.5/100,000 population, while the prevalence in Blacks may be up to 10/100,000 population. For MOG-antibody disease, hospital-based studies largely do not observe any significant racial preponderance so far. This disorder comprises a significant proportion of NMOSD cases that are AQP4-antibody-seronegative. A recent Dutch nationwide study reported the annual incidence of MOG-antibody disease as 1.6/million population (adult: 1.3/million, children: 3.1/million). Clinical and radiological differences between AQP4-antibody and MOG-antibody associated diseases have led to interest in the revisions of NMOSD definition and expanded stratification based on detection of a specific autoantibody biomarker. More population-based studies in different geographical regions and racial groups will be useful to further inform the prevalence and incidence of NMOSD and their antibody-specific subgroups. Accessibility to AQP4-antibody and MOG-antibody testing, which is limited in many centers, is a challenge to overcome. Environmental and genetic studies will be useful accompaniments to identify other potential pathogenetic factors and specific biomarkers in NMOSD.

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an uncommon inflammatory disease of the central nervous system, with clinical features of optic neuritis, myelitis, and certain brain, and brainstem syndromes. Although it had long been debated whether NMOSD is a severe variant of multiple sclerosis (MS), the discovery of NMOSD-specific aquaporin 4 (AQP4) antibody, and the subsequent clinical, immunological, and pathological data have established that NMOSD is indeed a distinct entity (1–3). Currently, cases clinically diagnosed as NMOSD may include AQP4-antibody-seropositive autoimmune astrocytopathic disease, myelin oligodendrocyte glycoprotein (MOG)-antibody-seropositive inflammatory demyelinating disease, and double-seronegative disease (4).

AQP4-antibody-seropositive NMOSD has a high female-to-male ratio (up to 9:1) (5), and its mean age at onset is around 40 years (6, 7), older than in MS. Pathologically, it is primarily an astrocytopathic disease rather than a demyelinating disease (3, 8). For MOG-antibody disease, the sex ratio is close to 1:1, and it is more common in children than in adults (9, 10). Its clinical manifestations overlap with those of AQP4-antibody disease but there are differences about which there is emerging consensus. Besides optic neuritis and myelitis, its clinical phenotypes also include acute or multiphasic disseminated encephalomyelitis (ADEM/MDEM), brainstem and cerebral cortical encephalitis, and cranial nerve involvement (11–14). Double (AQP4- and MOG-antibodies)-seronegative disease is enigmatic at present and requires further clinical and laboratory research for specific classification.

There have been several editions of the diagnostic criteria for NMOSD since 1999 (15, 16), with the latest being the 2015 International Panel on NMO Diagnosis (IPND) criteria (17). In the meantime, laboratory assays for AQP4 antibody and MOG antibody have also improved over time, with increased sensitivity and specificity (18, 19). These factors have contributed to the improvement in the accuracy of the diagnosis of NMOSD cases.

In this article, we review current data on the worldwide epidemiology of NMOSD, specifically on the population-based studies of NMOSD to determine its prevalence and incidence among different populations and racial groups. We emphasize that the field of NMOSD is undergoing a rapid evolution, making epidemiological estimates tentative. Additionally, different levels of diagnostic rigor to exclude NMOSD mimics and access to medical care in study populations can bias the epidemiological survey results in the disease, which makes the interpretation and comparison of the findings in and across the studies difficult. Nonetheless, the best known of current knowledge is being presented.

Search Strategy and Selection Criteria

The PubMed database was searched for population-based studies on NMOSD with prevalence data, from 1st January 2000 till 11th March 2020. A combination of the following search terms was used: "neuromyelitis optica," "NMO," "NMOSD," "aquaporin 4," "AQP4," "myelin oligodendrocyte glycoprotein," "MOG," "optico-spinal multiple sclerosis," "OSMS," "idiopathic inflammatory demyelinating disease," "IIDD," "epidemiology," "prevalence," "population," and "demographic." The reference lists in published articles on NMOSD were also queried to identify further studies. Additionally, recent conference proceedings of major neurology and MS congresses, including the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the Pan-Asian Committee for Treatment and Research in Multiple Sclerosis (PACTRIMS), were searched for relevant abstracts where the full studies are not yet published. Population-based studies with information on the prevalence of NMOSD in English language were reviewed.

The final list of publications was selected on the basis of relevance to the topic.

Prevalence of NMOSD

The prevalence range of NMOSD is ~0.5–4/100,000, and may be up to 10/100,000 in certain racial groups. Nevertheless, this prevalence range is rather small relative to that of MS, which ranges from 1–2/100,000 in the equatorial region, to 150–200/100,000 in Canada and northern part of Europe (20, 21).

Over the past two decades, population-based studies of NMOSD have provided important insights into its prevalence. The earliest population-based studies were conducted in French West Indies (Martinique) (22, 23), Cuba (24), Denmark (25), and Tokachi Province on Hokkaido Island in Japan (26). Interestingly, the majority of these early studies were conducted on island populations, which facilitate population-based studies by providing well-delimited boundaries of the study area. Two of the studies (Martinique and Hokkaido) (22, 23, 26) have since been updated by the original groups of researchers.

Since 2017, several new population-based studies were published, expanding knowledge of NMOSD in diverse populations around the world. Inter-racial variation in prevalence, as summarized in **Table 1**, is notable and consistent across geographical regions. More recently, the Australia/New Zealand group has also re-analyzed the data from their 2017 study (47) to provide further information with regards to the prevalence among different racial groups in their large continent (46). **Figure 1** is a map showing population-based prevalence studies of NMOSD around the world.

East Asians

East Asians (Japanese, Chinese, and Koreans) appear to have a higher prevalence of NMOSD (around 3.5/100,000) as compared to Whites and other Asian racial groups. The study in Hokkaido, Japan recorded a prevalence of 4.1/100,000 (36), while the Japanese nationwide survey estimated a prevalence of 3.42/100,000 (40). Meanwhile, a study conducted in the multi-racial population in Penang Island, Malaysia showed that the prevalence among Chinese was 3.31/100,000 (39). These results were in line with the genetic studies that showed that Japanese and Chinese share the same HLA risk genes for NMOSD, namely, HLA-DPB1*05:01 and HLA-DRB1*16:02 (49–51). In a very recent study from South Korea, by using a nationwide health insurance research dataset, it was calculated that the prevalence among Koreans was 3.56/100,000 in 2017 (48). More studies, especially from China, Taiwan, and Hong Kong will be useful to further inform the prevalence of NMOSD among the East Asians.

Blacks

In 1971, a study conducted in a single hospital in the sub-Saharan African city of Ibadan (Nigeria) reported 95 cases of NMO, 22 cases of acute transverse myelitis, 11 cases of bilateral retrobulbar neuritis, and only two cases of MS over 12 years of hospital admissions (1957–1969) (52). During the same period, there were nine cases of non-Nigerians with MS (in eight Europeans and one Indian). It estimated that NMO cases made up 0.43/1000 (or 430/100,000) of the hospital population.

Population-based studies over the past two decades showed that Blacks also have a higher NMOSD prevalence than Whites. A study conducted in Liverpool, UK reported a prevalence rate of 1.8/100,000 among Blacks (29). The Australia/New Zealand study estimated a prevalence rate of 1.84/100,000 in those with African ancestry (46). The study conducted in the French Martinique Island in the Caribbean reported a very high prevalence of 11.5/100,000 among its Black population (34), and this was the highest prevalence reported so far. In population-based studies, within the same localities, prevalence among Blacks is always higher than in Whites, as seen in Cuba (24), Liverpool (UK) (29), Olmsted county (USA) (34), Martinique Island (34), and Australia/New Zealand (46).

As Blacks are genetically diverse, more data from different geographical regions are needed, and especially those from the African continent. Although no population-based studies of NMOSD have been published from Africa, recently there have been reports of NMOSD cases from various African countries that are to be compiled and reported elsewhere.

Whites/Caucasians

In recent nationwide and region-wide studies, the prevalence of NMOSD among Whites has consistently been ~1/100,000. The prevalence was 0.55/100,000 in Australia and New Zealand (46, 47), 0.89/100,000 in Catalonia (38), 1.09/100,000 in Denmark (42), and 1.04/100,000 in Sweden (43). Also recently, a re-analysis of the data of an earlier study from South Denmark has reported the prevalence of AQP4-antibody-positive NMOSD as 1.68/100,000, and the prevalence of the total clinical phenotype including AQP4-antibody-negative and MOG-antibody-positive subsets was 4.4/100,000 (25, 27).

Interestingly, the prevalence among Hungarians was slightly higher, at 1.91/100,000 (45). This has brought up the notion of whether there are some admixtures of Asian genes (from North East Asia) among the Hungarians (53). Furthermore, there is scarcity of prevalence data from Central Asia, and such data from this region will be informative.

Other Asians
South Indians

If the 2015 IPND criteria were applied, the prevalence among South Indians in Mangalore was 0.72/100,000 (31). No cases were found among the 10% South Indian population in Penang Island, Malaysia (39), suggesting a low prevalence.

Austronesian Peoples

The Austronesian peoples reside in the Philippines, Malaysia, Indonesia, the Pacific Islands (Polynesia, Micronesia, and Hawaii), down to New Zealand, and also to the west in Madagascar. The study conducted in the multi-racial Penang Island, Malaysia (39) found that the prevalence of an Austronesian group, the Malays, was ~0.80/100,000 (this was revised from 0.43/100,000 as reported earlier, after a new case was diagnosed). The prevalence data from another Austronesian group was available recently, namely, the Māoris in New Zealand, with an estimated prevalence of 1.50/100,000 (46). Nevertheless, in the same study, no cases of NMOSD were found among

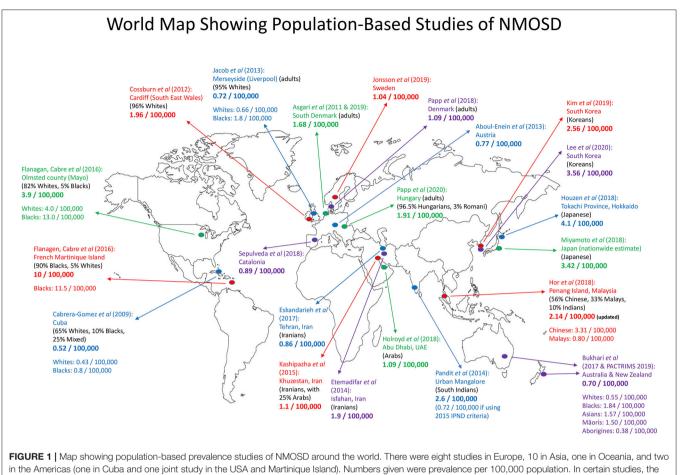**TABLE 1 |** Population-based prevalence and incidence studies of NMOSD.

Population-based study	Geographical location	Prevalence of NMOSD (per 100,000 population), as according to racial groups				Incidence (per million population)	AQP4-ab testing methods	AQP4-ab positivity	Female-to-male ratio
		Whites/ Caucasians	Blacks	East Asians	Other Asians/Other Races				
Cabrera-Gomez et al. (2009) (24)	Cuba	0.43	0.80			0.53	Not tested	Not tested	7.3:1
Asgari et al. (2011) (25) (re-analyzed 2019) (27)	South Denmark	1.68*				1.5	CBA	62%	5.3:1
Cossburn et al. (2012) (28)	South East Wales	1.96				NR	NR	71%	6:1
Jacob et al. (2013) (29)	Merseyside, England	0.66*	1.8*			0.8	Oxford CBA	88%	3:1
Aboul-Enein et al. (2013) (30)	Austria	0.77				0.54	Innsbruck CBA	100%	7:1
Pandit and Kundapur (2014) (31)	Mangalore, India				South Indians: 2.6 (0.72 if using 2015 IPND criteria)	NR	NR	27%	1.2:1
Etemadifar et al. (2014) (32)	Isfahan, Iran	1.9				NR	NR	66%	2.3:1
Kashipazha et al. (2015) (33)	Khuzestan, Iran	1.1				NR	NR	54%	7.5:1
Flanagan et al. (2016) (34)	Olmsted county, USA	4.0	13.0			0.7	Mayo CBA	83%	5:1
	French Martinique Island	6.1 (single case, AQP4-ab negative)	11.5			7.3	Mayo CBA	79%	8.8:1
van Pelt et al. (2016) (35)	Netherlands	—				0.9	CBA	NA	4.9:1
Houzen et al. (2017) (36)	Tokachi, Hokkaido, Japan			Japanese: 4.1		NR	Sendai CBA	79%	6:1
Eskandarieh et al. (2017) (37)	Tehran, Iran	0.86				NR	ELISA	47%	5.1:1
Sepúlveda et al. (2018) (38)	Catalonia	0.89				0.63	Mainly CBA (96%)	73%	3.1:1

(Continued)

TABLE 1 | Continued

Population-based study	Geographical location	Prevalence of NMOSD (per 100,000 population), as according to racial groups				Incidence (per million population)	AQP4-ab testing methods	AQP4-ab positivity	Female-to-male ratio
		Whites/Caucasians	Blacks	East Asians	Other Asians/Other Races				
Hor et al. (2018) (39)	Penang Island, Malaysia			Chinese: 3.31	Malays: 0.80 (revised)	NR	Euroimmun CBA	100%	14:1
Miyamoto et al. (2018) (40)	Japan (nationwide estimate)			Japanese: 3.42		NR	NA	NA	6.4:1
Holroyd et al. (2018) (41)	Abu Dhabi, UAE				Arabs: 1.09	1.16	NR	83%	All females
Papp et al. (2018) (42)	De nmark	1.09*				0.70	Various, incl. CBA	70%	4.5:1
Jonsson et al. (2019) (43)	Sweden	1.04				0.79	Immunoblot and CBA	NR	2.8:1
Kim et al. (2019) (44)	South Korea			Koreans: 2.56		7.3	CBA	NA	2.37:1
Papp et al. (2020) (45)	Hungary	Hungarians: 1.91*				1.32	CBA	83%	8.8:1
Bukhari et al. (PACTRIMS 2019) (46) (updated from 2017 study) (47)	Australia and New Zealand	0.55	1.84		Asians: 1.57 Māoris: 1.50 Australian Aborigines: 0.38	0.37	IF tissue assay, some also ELISA and CBAs	>90%	6:1
Lee et al. (2020) (48)	South Korea			Koreans: 3.56		4.1–6.5	NA	NA	4.7:1

*Only consider adult population. (As AQP4-antibody-positive NMOSD is rare in children, thus, if full population is considered, the prevalence will be slightly lower).

NMOSD, neuromyelitis optica spectrum disorder; AQP4-ab, aquaporin 4-antibody; CBA, cell-based assay; IF, immunofluorescence; NA, not applicable; NR, not reported.

FIGURE 1 | Map showing population-based prevalence studies of NMOSD around the world. There were eight studies in Europe, 10 in Asia, one in Oceania, and two in the Americas (one in Cuba and one joint study in the USA and Martinique Island). Numbers given were prevalence per 100,000 population. In certain studies, the prevalence according to racial groups was given. Adults, only adult population was studied.

the ~295,000 Pacific Islanders (Pasifika) (46). More data from other Austronesian groups in other localities will be useful to clarify this.

Arabs

A study from Abu Dhabi, United Arab Emirates reported six cases of NMOSD among its citizens, consistent with a prevalence of 1.09/100,000 (AQP4-antibody seropositivity: 83%, all six cases were females) (41). If only adult citizens aged ≥20 years were considered (a total of five cases), the prevalence is higher at 1.76/100,000. Data on Arabs in other regions of Middle East and North Africa will be very informative.

Australian Aborigines

The Australian Aborigines are one of the oldest populations in the world, with their ancestors having migrated to Australia around 50,000 years ago. There is evidence of some admixture of Denisovan genes in the Aborigines (Denisovans are an extinct species or subspecies of humans of the genus *Homo*). It is interesting to note that MS rarely exists in the Aborigines (54, 55). Recent data showed that NMOSD is also rare among the Aborigines, with a prevalence of 0.38/100,000 (46). However, the

paper cautioned whether inequality in health care access may lead to this low figure.

Native Americans

MS is less common among Native Americans than in Whites in North America. Prior to AQP4-antibody discovery, a study conducted among the Native Canadians in Manitoba (56) found seven cases of "MS," of which five cases were of NMO phenotypes, while the other two had brainstem involvement. Autopsy of one patient showed eosinophil infiltration in the cervical cord lesion, and retrospectively, this pathological finding suggests that this case was likely to be NMOSD. Genetically, Native Americans may be more closely related to early East Asians, and thus they may also have a higher prevalence than Whites. A re-look at these native populations will be helpful to confirm the results, though may be practically difficult.

Latin America

After the arrival of Europeans in the 1500's, the indigenous populations of Latin American had dwindled rapidly. Today, along with the indigenous peoples, there is a large proportion of Whites, Blacks, and mixed races in Latin America.

In an earlier study from a tertiary hospital in Mexico City (57), using 1999 Wingerchuk criteria, a total of 34 cases of NMO were identified, with all patients being Mestizos (mixed race). By calculating the ratio of MS and NMO in the hospital, and by using the estimated MS prevalence in the country at that time, it was extrapolated that the prevalence of NMO among Mexican Mestizos was around 1.3/100,000. With the availability of AQP4-antibody assays, and the newer diagnostic criteria that include NMOSD cases, this prevalence rate is likely to be higher.

From the preliminary findings of a recent study involving seven general hospitals in Venezuela presented at a conference (58), it was estimated that the prevalence of NMOSD in Venezuela was 2.2/100,000, with a female-to-male ratio of 4:1, and again Mestizos formed the majority of those patients.

Studies from other representative populations will be useful to further inform the prevalence of NMOSD in Latin America.

North Africa

The populations of North Africa consist mainly of Amazighs (Berbers) and Arabs. As in Whites/Caucasian populations, there appear to be much higher number of MS than NMOSD cases in North Africa (59, 60). There have been no population-based studies on NMOSD in North Africa so far. There is only one population-based study on Arabs in the Middle East (Abu Dhabi) (41), and the prevalence data among Amazighs are awaited.

Incidence of NMOSD

Table 1 summarizes the incidence reported in the available population-based studies. Among Whites, the annual incidence of NMOSD is generally reported to be around 0.5–0.8/million (30, 38, 42, 43). In populations with a higher prevalence, the incidence is also higher. For instance, Blacks in Martinique have a high prevalence of 11.5/100,000, and its incidence was also reported to be high, at 7.3/million (34). Recently, the data from South Korea also showed a high incidence, ranging from 4.1 to 7.3/million for the period 2013–2017 (44, 48). Other populations with a prevalence higher than 1/100,000 also reported an incidence higher than 1/million [for example, 1.16/million in Arabs (41), and 1.32/million in Hungarians (45)].

A limitation regarding incidence calculation is that, if a new antibody test becomes available in the study region, or when there is increased awareness among clinicians, then the number of newly diagnosed cases in that particular year will be higher, leading to a higher incidence rate, even though the disease could have started many years earlier in some cases. Nevertheless, if researchers are able to calculate the incidence rates over the past few years (e.g., past 5 years) and average them, it is likely to be more accurate.

For pediatric NMOSD, there were two recent nationwide/region-wide studies that reported on its incidence. In the Danish study, the incidence of pediatric NMOSD was calculated as 0.31/million (61). In the Taiwanese study using the national health insurance research database, over the period from 2011 to 2015, the average annual incidence was reported as 1.1/million (62). Again, this higher incidence in Taiwan as compared to Denmark is not surprising as NMOSD is more prevalent among East Asians than Whites.

Age and Racial Differences in the Clinical Features and Severity of NMOSD

Some studies have analyzed how the clinical features and disability are affected by onset age and racial differences. Patients with young-onset NMOSD were more likely to have optic neuritis as onset attack, while older-onset patients often developed myelitis as the initial presentation (63). Furthermore, young-onset patients with optic neuritis were more likely to develop not only recurrent optic neuritis but also higher likelihood of developing blindness, as compared to older-onset patients with optic neuritis (63, 64). Conversely, older-onset patients with myelitis often had poor recovery, while most young-onset patients with myelitis recovered well without permanent motor disability (63, 64).

There also appears to be some differences in the clinical features of NMOSD among different races. Blacks and Asians tended to have lower mean ages at onset than Whites (Blacks: around 28–33 years, Asians: 35–40 years, vs. Whites: 44 years) (63, 65). Black and Asian patients were more likely to have brain and brainstem attacks and abnormalities on brain MRI as compared to Whites (64, 65). Overall, the risk of relapse was lowest in Japanese than in Whites and Blacks (63, 64).

Blacks were found to have a greater likelihood of developing visual disability with time than Whites and Japanese (63, 64). On the other hand, Whites had a higher probability of developing severe motor disability or wheelchair dependence as compared to Japanese (63). Severe attacks were more frequent in Blacks than in Asians and Whites, and therefore Blacks were at a higher risk of severe disability in the early course of the disease (65). In a study from the USA, patients with African ancestry were also found to have a higher mortality rate (15.4%) as compared to the overall mortality rate (7.0%) (66). Nonetheless, while race affected the clinical phenotype, age at onset, and severity of attacks, the overall outcomes were mostly dependent on early and effective immunosuppressive treatment (65).

MOG-Antibody-Associated Disease: Prevalence and Incidence

After the discovery of the AQP4 antibody, a majority of NMO cases have been found positive for this antibody. Nevertheless, there is still a proportion of cases with an NMO phenotype that are persistently tested negative for AQP4 antibody, despite using the most sensitive cell-based assays available. It was later realized that some of these AQP4-antibody-negative NMOSD cases were in fact seropositive for MOG antibody. This so-called MOG-antibody-associated disease consists of a significant proportion of NMOSD cases that are AQP4-antibody seronegative, ranging from 7 to 42% (7, 67–70).

Interestingly, for MOG-antibody-associated disease, besides NMO phenotype, optic neuritis, and myelitis, some of these MOG-antibody-positive cases also have clinical phenotypes beyond the current NMOSD spectrum, such as ADEM/MDEM-like presentation (71), cerebral cortical encephalitis (12), and cranial nerve involvement (14). Pathologically, MOG-antibody-associated disease is a type of demyelinating disease, as opposed

to astrocytopathic disease seen in AQP4-antibody-positive NMOSD (72, 73).

A recent Dutch nationwide study reported the incidence of MOG-antibody-associated disease as 1.6/million, with 1.3/million in adults, and a higher incidence of 3.1/million in children (74). It should be noted that this incidence rate of 1.6/million is higher than the incidence rate of 0.5–0.8/million in NMOSD (mostly AQP4-antibody-positive) among Whites.

So far, hospital-based studies largely did not observe any significant racial preponderance for MOG-antibody-associated disease. For instance, in the UK cohort, the racial breakdown was as expected in the general population (9). Nevertheless, from the annual report of the Oxford NMO Service, there were 145 patients with AQP4-antibody-positive NMOSD, 111 patients with MOG-antibody disease, and 28 patients who were double-seronegative. The proportion of MOG-antibody

disease within the NMOSD spectrum was rather significant (75). Additionally, a study from Mayo Clinic on AQP4- and MOG-antibody testing for 15,598 patients showed higher positivity rate for MOG antibody (1291 patients, 8.3%) than for AQP4 antibody (387 patients, 2.3%). Of the adults, 6.5% were MOG-antibody positive vs. 2.6% for AQP4 antibody, while in children, 21.1% were positive for MOG antibody as compared to 1.9% for AQP4 antibody (76). Similarly, one study in Sri Lanka, in collaboration with the Mayo Clinic, also reported more MOG-antibody-positive cases (126 patients) than AQP4-antibody-positive cases (36 patients) (77). On the other hand, MOG-antibody-associated disease was relatively uncommon in the non-Caucasian population in Rio de Janeiro (Brazil) (70).

The preliminary findings of a population-based prevalence study of MOG-antibody-associated disease, jointly conducted at

TABLE 2 | Epidemiological and clinical comparison between AQP4-antibody-seropositive NMOSD, MOG-antibody disease, and MS.

	AQP4-antibody disease	MOG-antibody disease	MS
Mean age at onset	40 years	More common in children than in adults	30 years
Female:male ratio	9:1	Around 1:1	2–4:1
North–South gradient	No increased prevalence with increasing latitude	No data	Increased prevalence with increasing latitude from the equator (either toward North or South)
Prevalence	East Asians: 3.5/100,000 Whites: 1/100,000 Blacks: range from 1.8 to 10/100,000	More common in children than in adults	Up to 100–200/100,000 in White populations, but <5–50/100,000 in many Asian and African countries Rising in most parts of the world
Annual incidence	Around 0.5–0.8/million in Whites Higher annual incidence in non-White populations	Dutch nationwide study: 1.6/million; adults: 1.3/million; children: 3.1/million More data are needed	Up to 100/million in White populations, but was low in many equatorial countries
Disease course	Relapsing	Monophasic or relapsing	Relapsing, with the majority eventually converting to a secondary progressive disease Up to 15% are primary progressive in Whites
Clinical manifestations	Optic neuritis Myelitis Area postrema syndrome Other brain syndromes	Optic neuritis Myelitis ADEM/MDEM Brainstem/cerebral cortical encephalitis Cranial nerve involvement	Optic neuritis Myelitis Brain syndromes
Optic neuritis	Unilateral/chiasmal, long (>1/2 of optic nerve)	Unilateral/simultaneous bilateral, long; frequent optic disc swelling (papillitis)	Unilateral, short
Myelitis	Long (>3 vertebral segments) in 85%; centrally located; affects cervical or thoracic cord	Often long, but may be <3 vertebral segments; gadolinium enhancement less common than AQP4-antibody disease; relatively more common in the lumbosacral region	Non-transverse, short; peripheral/dorsolateral
Attack severity	Moderate to severe	Mild to moderate	Mild to moderate
Recovery	Variable, but commonly poor	Fair to good	Fair to good
Disability	Attack-related	Attack-related	Mainly due to progression
Pathology	Astrocytopathy	Demyelination	Demyelination
Treatment	Immunosuppressants; some MS drugs may be harmful	Consider immunosuppressants if recurrent; some MS drugs may be ineffective	MS disease-modifying drugs

ADEM/MDEM, acute disseminated encephalomyelitis/multiphasic disseminated encephalomyelitis; AQP4, aquaporin 4; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

Olmsted county (USA) and Martinique Island, were recently presented at a conference (ECTRIMS 2019) (78). In Olmsted county, the prevalence was calculated to be 3.42/100,000, with an incidence of 2.39/million, while at Martinique, the prevalence was 1.6/100,000, with an incidence of 1.12/million.

In the Catalonia NMOSD prevalence study, 12% of cases were MOG-antibody-positive (38). However, the cases in this study were required to strictly fulfill the 2015 IPND criteria, and thus only those with an NMO phenotype were analyzed (The prevalence of MOG-antibody-positive NMO was calculated to be 0.11/100,000.). Needless to say, if MOG-antibody-positive cases with optic neuritis alone or myelitis alone and those with ADEM-like presentation are included, the prevalence of MOG-antibody disease is likely to be higher.

More data from different geographical areas are clearly in need to further inform about the prevalence and incidence of MOG-antibody-associated disease.

Some demographic and epidemiological data and clinical features of AQP4-antibody-positive NMOSD and MOG-antibody-associated disease in comparison with MS are shown in **Table 2**.

CONCLUSION

There appears to be varying prevalence rates of NMOSD, most cases of which are AQP4-antibody-positive cases, among the different racial groups worldwide, with East Asians and Blacks having a higher prevalence than Whites. In most regions, these prevalence rates are lower than that of MS. In AQP4-antibody-positive NMOSD, female preponderance is definite (up to 90%) and the majority of the cases are adults. Moreover, the clinical features of NMOSD and disability accrual may be influenced by onset age and race. The data suggest that certain genetic and environmental factors associated with race may be involved in the pathogenesis of NMOSD. More well-designed population-based and longitudinal studies in different geographical areas and racial groups will be useful to clarify the issue, and to shed new lights onto this unique neuroinflammatory disease. Among AQP4-antibody-negative NMOSD, some patients are MOG-antibody-positive, and unlike AQP4-antibody-positive NMOSD, males, and females are equally affected by MOG-antibody-associated disease and the prevalence may be higher in children than in adults. However, the prevalence data of MOG-antibody-associated disease including the ones with an NMOSD phenotype are still insufficient and being accumulated. Accessibility to AQP4-antibody and MOG-antibody testing, which is currently limited in many regions, is a challenge to overcome.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet*. (2004) 364:2106–12. doi: 10.1016/S0140-6736(04)17551-X

2. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med*. (2005) 202:473–7. doi: 10.1084/jem.20050304

3. Fujihara K, Misu T, Nakashima I, Takahashi T, Bradl M, Lassmann H, et al. Neuromyelitis optica should be classified as an astrocytopathic disease rather than a demyelinating disease. *Clin Exp Neuroimmunol*. (2012) 3:58–73. doi: 10.1111/j.1759-1961.2012.00030.x

4. Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. *Curr Opin Neurol*. (2019) 32:385–94. doi: 10.1097/WCO.0000000000000694

5. Gold SM, Willing A, Leypoldt F, Paul F, Friese MA. Sex differences in autoimmune disorders of the central nervous system. *Semin Immunopathol*. (2019) 41:177–88. doi: 10.1007/s00281-018-0723-8

6. Kitley J, Waters P, Woodhall M, Leite MI, Murchison A, George J, et al. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study. *JAMA Neurol*. (2014) 71:276–83. doi: 10.1001/jamaneurol.2013.5857

7. Sato DK, Callegaro D, Lana-Peixoto MA, Waters PJ, de Haider Jorge FM, Takahashi T, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. *Neurology*. (2014) 82:474–81. doi: 10.1212/WNL.0000000000000101

8. Kawachi I, Lassmann H. Neurodegeneration in multiple sclerosis and neuromyelitis optica. *J Neurol Neurosurg Psychiatry*. (2017) 88:137–45. doi: 10.1136/jnnp-2016-313300

9. Jurynczyk M, Messina S, Woodhall MR, Raza N, Everett R, Roca-Fernandez A, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. *Brain*. (2017) 140:3128–38. doi: 10.1093/brain/awx276

10. Cobo-Calvo A, Ruiz A, Maillart E, Audoin B, Zephir H, Bourre B, et al. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: the MOGADOR study. *Neurology*. (2018) 90:e1858–69. doi: 10.1212/WNL.0000000000005560

11. Nakashima I. Anti-myelin oligodendrocyte glycoprotein antibody in demyelinating diseases. *Clin Exp Neuroimmunol*. (2015) 6(Suppl.1):59–63. doi: 10.1111/cen3.12262

12. Ogawa R, Nakashima I, Takahashi T, Kaneko K, Akaishi T, Takai Y, et al. MOG antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. *Neurol Neuroimmunol Neuroinflamm*. (2017) 4:e322. doi: 10.1212/NXI.0000000000000322

13. Fujihara K, Sato DK, Nakashima I, Takahashi T, Kaneko K, Ogawa R, et al. Myelin oligodendrocyte glycoprotein immunoglobulin G-associated disease: an overview. *Clin Exp Neuroimmunol*. (2018) 9(Suppl.1):48–55. doi: 10.1111/cen3.12434

14. Cobo-Calvo A, Ayrignac X, Kerschen P, Horellou P, Cotton F, Labauge P, et al. Cranial nerve involvement in patients with MOG antibody-associated disease. *Neurol Neuroimmunol Neuroinflamm*. (2019) 6:e543. doi: 10.1212/NXI.0000000000000543

15. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology*. (1999) 53:1107–14.

16. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology*. (2006) 66:1485–9.

17. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. (2015) 85:177–89. doi: 10.1212/WNL.0000000000001729

18. Waters P, Reindl M, Saiz A, Schanda K, Tuller F, Kral V, et al. Multicentre comparison of a diagnostic assay: aquaporin-4 antibodies in neuromyelitis optica. *J Neurol Neurosurg Psychiatry*. (2016) 87:1005–15. doi: 10.1136/jnnp-2015-312601

19. Reindl M, Schanda K, Woodhall M, Tea F, Ramanathan S, Sagen J, et al. International multicenter examination of MOG antibody assays. *Neurol Neuroimmunol Neuroinflamm*. (2020) 7:e674. doi: 10.1212/NXI.0000000000000674

20. Evans C, Beland SG, Kulaga S, Wolfson C, Kingwell E, Marriott J, et al. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. *Neuroepidemiology*. (2013) 40:195–210. doi: 10.1159/000342779

21. Kingwell E, Marriott JJ, Jetté N, Pringsheim T, Makhani N, Morrow SA, et al. Incidence and prevalence of multiple sclerosis in europe: a systematic review. *BMC Neurol*. (2013) 13:128. doi: 10.1186/1471-2377-13-128

22. Cabre P, Heinzlef O, Merle H, Buisson GG, Bera O, Bellance R, et al. MS and neuromyelitis optica in Martinique (French West Indies). *Neurology*. (2001) 56:507–14. doi: 10.1212/wnl.56.4.507

23. Cabre P, Gonzalez-Quevedo A, Lannuzel A, Bonnan M, Merle H, Olindo S, et al. Descriptive epidemiology of neuromyelitis optica in the caribbean basin [article in french, with english abstract]. *Rev Neurol*. (2009) 165:676–83. doi: 10.1016/j.neurol.2009.02.012

24. Cabrera-Gómez JA, Kurtzke JF, Gonzalez-Quevedo A, Lara-Rodríguez R. An epidemiological study on neuromyelitis optica in Cuba. *J Neurol*. (2009) 256:35–44. doi: 10.1007/s00415-009-0009-0

25. Asgari N, Lillevang ST, Skejoe HP, Falah M, Stenager E, Kyvik KO. A population-based study of neuromyelitis optica in Caucasians. *Neurology*. (2011)76:1589–95. doi: 10.1212/WNL.0b013e3182190f74

26. Houzen H, Niino M, Hirotani M, Fukazawa T, Kikuchi S, Tanaka K, et al. Increased prevalence, incidence, and female predominance of multiple sclerosis in northern Japan. *J Neurol Sci*. (2012) 323:117–22. doi: 10.1016/j.jns.2012.08.032

27. Asgari N, Lillevang ST, Skejoe HP, Kyvik KO. Epidemiology of neuromyelitis optica spectrum disorder in Denmark (1998–2008, 2007–2014). *Brain Behav*. (2019) 9:e01338. doi: 10.1002/brb3.1338

28. Cossburn M, Tackley G, Baker K, Ingram G, Burtonwood M, Malik G, et al. The prevalence of neuromyelitis optica in south east wales. *Eur J Neurol*. (2012) 19:655–9. doi: 10.1111/j.1468-1331.2011.03529.x

29. Jacob A, Panicker J, Lythgoe D, Elsone L, Mutch K, Wilson M, et al. The epidemiology of neuromyelitis optica amongst adults in the merseyside county of United Kingdom. *J Neurol*. (2013) 260:2134–7. doi: 10.1007/s00415-013-6926-y

30. Aboul-Enein F, Seifert-Held T, Mader S, Kuenz B, Lutterotti A, Rauschka H, et al. Neuromyelitis optica in Austria in 2011: to bridge the gap between neuroepidemiological research and practice in a study population of 8.4 million people. *PLoS ONE*. (2013) 8:e79649. doi: 10.1371/journal.pone.0079649

31. Pandit L, Kundapur R. Prevalence and patterns of demyelinating central nervous system disorders in urban Mangalore, South India. *Mult Scler*. (2014) 20:1651–3. doi: 10.1177/1352458514521503

32. Etemadifar M, Dashti M, Vosoughi R, Abtahi SH, Ramagopalan SV, Nasr Z. An epidemiological study of neuromyelitis optica in Isfahan. *Mult Scler*. (2014) 20:1920–2. doi: 10.1177/1352458514537699

33. Kashipazha D, Mohammadianinejad SE, Majdinasab N, Azizi M, Jafari M. A descriptive study of prevalence, clinical features and other findings of neuromyelitis optica and neuromyelitis optica spectrum disorder in khuzestan province, Iran. *Iran J Neurol*. (2015) 14:204–10.

34. Flanagan EP, Cabre P, Weinshenker BG, St Sauver J, Jacobson DJ, Majed M, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. *Ann Neurol*. (2016) 79:775–83. doi: 10.1002/ana.24617

35. van Pelt ED, Wong YY, Ketelslegers IA, Siepman DA, Hamann D, Hintzen RQ. Incidence of AQP4-IgG seropositive neuromyelitis optica spectrum disorders in the Netherlands: about one in a million. *Mult Scler Exp Transl Clin*. (2016) 2:2055217315625652. doi: 10.1177/2055217315625652

36. Houzen H, Kondo K, Niino M, Horiuchi K, Takahashi T, Nakashima I, et al. Prevalence and clinical features of neuromyelitis optica spectrum disorders in northern Japan. *Neurology*. (2017) 89:1995–2001. doi: 10.1212/WNL.0000000000004611

37. Eskandarieh S, Nedjat S, Azimi AR, Moghadasi AN, Sahraian MA. Neuromyelitis optica spectrum disorders in Iran. *Mult Scler Relat Disord*. (2017) 18:209–12. doi: 10.1016/j.msard.2017.10.007

38. Sepúlveda M, Aldea M, Escudero D, Llufriu S, Arrambide G, Otero-Romero S, et al. Epidemiology of NMOSD in catalonia: influence of the new 2015 criteria in incidence and prevalence estimates. *Mult Scler*. (2018) 24:1843–51. doi: 10.1177/1352458517735191

39. Hor JY, Lim TT, Chia YK, Ching YM, Cheah CF, Tan K, et al. Prevalence of neuromyelitis optica spectrum disorder in the multi-ethnic penang island, malaysia, and a review of worldwide prevalence. *Mult Scler Relat Disord*. (2018) 19:20–4. doi: 10.1016/j.msard.2017.10.015

40. Miyamoto K, Fujihara K, Kira JI, Kuriyama N, Matsui M, Tamakoshi A, et al. Nationwide epidemiological study of neuromyelitis optica in Japan. *J Neurol Neurosurg Psychiatry*. (2018) 89:667–8. doi: 10.1136/jnnp-2017-317321

41. Holroyd KB, Aziz F, Szolics M, Alsaadi T, Levy M, Schiess N. Prevalence and characteristics of transverse myelitis and neuromyelitis optica spectrum disorders in the United Arab Emirates: a multicenter, retrospective study. *Clin Exp Neuroimmunol*. (2018) 9:155–61. doi: 10.1111/cen3.12458

42. Papp V, Illes Z, Magyari M, Koch-Henriksen N, Kant M, Pfleger CC, et al. Nationwide prevalence and incidence study of neuromyelitis optica spectrum disorder in Denmark. *Neurology*. (2018) 91:e2265–75. doi: 10.1212/WNL.0000000000006645

43. Jonsson DI, Sveinsson O, Hakim R, Brundin L. Epidemiology of NMOSD in Sweden from 1987 to 2013: a nationwide population-based study. *Neurology*. (2019) 93:e181–9. doi: 10.1212/WNL.0000000000007746

44. Kim JE, Park SH, Han K, Kim HJ, Shin DW, Kim SM. Prevalence and incidence of neuromyelitis optica spectrum disorder and multiple sclerosis in Korea. *Mult Scler*. (2019) 352458519888609. doi: 10.1177/1352458519888609. [Epub ahead of print].

45. Papp V, Iljicsov A, Rajda C, Magyari M, Koch-Henriksen N, Petersen T, et al. A population-based epidemiological study of neuromyelitis optica spectrum disorder in hungary. *Eur J Neurol*. (2020) 27:308–17. doi: 10.1111/ene.14079

46. Bukhari W, Khalilidehkordi E, Mason D, Barnett M, Taylor B, Fabis-Pedrini M, et al. NMOSD and MS prevalence in the indigenous populations of Australia and New Zealand. *Presented at the 12th Congress of the Pan-Asian Committee for Treatment and Research in Multiple Sclerosis (PACTRIMS)*, Singapore (2019).

47. Bukhari W, Prain KM, Waters P, Woodhall M, O'Gorman CM, Clarke L, et al. Incidence and prevalence of NMOSD in Australia and New Zealand. *J Neurol Neurosurg Psychiatry*. (2017)88:632–8. doi: 10.1136/jnnp-2016-314839

48. Lee HL, Kim JY, Seok JM, Hong YH, Lim NG, Shin HY, et at. Prevalence and incidence of neuromyelitis optica spectrum disorder in Korea: population based study. *J Korean Med Sci*. (2020) 35:e115. doi: 10.3346/jkms.2020.35.e115

49. Matsushita T, Matsuoka T, Isobe N, Kawano Y, Minohara M, Shi N, et al. Association of the HLA-DPB1*0501 allele with anti-aquaporin-4 antibody positivity in Japanese patients with idiopathic central nervous system demyelinating disorders. *Tissue Antigens*. (2009) 73:171–6. doi: 10.1111/j.1399-0039.2008.01172.x

50. Wang H, Dai Y, Qiu W, Zhong X, Wu A, Wang Y, et al. HLA-DPB1*0501 is associated with susceptibility to anti-aquaporin-4 antibodies positive neuromyelitis optica in Southern Han Chinese. *J Neuroimmunol*. (2011) 233:181–4. doi: 10.1016/j.jneuroim.2010.11.004

51. Yoshimura S, Isobe N, Matsushita T, Yonekawa T, Masaki K, Sato S, et al. Distinct genetic and infectious profiles in Japanese neuromyelitis optica patients according to anti-aquaporin-4 antibody status. *J Neurol Neurosurg Psychiatry*. (2013) 84:29–34. doi: 10.1136/jnnp-2012-302925

52. Osuntokun BO. The pattern of neurological illness in tropical Africa: experience at Ibadan, Nigeria. *J Neurol Sci*. (1971) 12:417–42.

53. Hellenthal G, Busby GB, Band G, Wilson JF, Capelli C, Falush D, et al. A genetic atlas of human admixture history. *Science*. (2014) 343:747–51. doi: 10.1126/science.1243518

54. Hammond SR, de Wytt C, Maxwell IC, Landy PJ, English D, McLeod JG, et al. The epidemiology of multiple sclerosis in Queensland, Australia. *J Neurol Sci*. (1987) 80:185–204.

55. McLeod JG, Hammond SR, Hallpike JF. Epidemiology of multiple sclerosis in Australia: with NSW and SA survey results. *Med J Aust*. (1994) 160:117–22.

56. Mirsattari SM, Johnston JB, McKenna R, Del Bigio MR, Orr P, Ross RT, et al. Aboriginals with multiple sclerosis: HLA types and predominance of neuromyelitis optica. *Neurology*. (2001) 56:317–23.

57. Rivera JF, Kurtzke JF, Booth VJ, Corona T. Characteristics of devic's disease (neuromyelitis optica) in Mexico. *J Neurol*. (2008) 255:710–5. doi: 10.1007/s00415-008-0781-2

58. Soto de Castillo I, Molina O, Soto A, Armas E, Mendoza S, Castillo MC, et al. Neuromyelitis optica spectrum disorders: epidemiologic study in Venezuela. *Presented at the 11th International NMO Roundtable Conference*, Los Angeles (2019).

59. Daoudi S, Bouzar M. Neuromyelitis optica spectrum disorders in algeria: a preliminary study in the region of tizi ouzou. *Mult Scler Relat Disord*. (2016) 6:37–40. doi: 10.1016/j.msard.2015.12.005

60. Salama S, Marouf H, Reda MI, Mansour AR, El Khory O, Levy M. Clinical and radiological characteristics of neuromyelitis optica spectrum disorder in the North Egyptian Nile Delta. *J Neuroimmunol*. (2018) 324:22–5. doi: 10.1016/j.jneuroim.2018.08.014

61. Boesen MS, Jensen PE, Born AP, Magyari M, Nilsson AC, Hoei-Hansen C, et al. Incidence of pediatric neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein antibody-associated disease in Denmark 2008 - 2018: a nationwide, population-based cohort study. *Mult Scler Relat Disord*. (2019) 33:162–7. doi: 10.1016/j.msard.2019.06.002

62. Lin WS, Wang HP, Chen HM, Lin JW, Lee WT. Epidemiology of pediatric multiple sclerosis, neuromyelitis optica, and optic neuritis in Taiwan. *J Neurol*. (2019). 267:925–32. doi: 10.1007/s00415-019-09647-9

63. Kitley J, Leite MI, Nakashima I, Waters P, McNeillis B, Brown R, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain*. (2012) 135:1834–49. doi: 10.1093/brain/aws109

64. Palace J, Lin DY, Zeng D, Majed M, Elsone L, Hamid S, et al. Outcome prediction models in AQP4-IgG positive neuromyelitis optica spectrums disorders. *Brain*. (2019) 142:1310–23. doi: 10.1093/brain/awz054

65. Kim SH, Mealy MA, Levy M, Schmidt F, Ruprecht K, Paul F, et al. Racial differences in neuromyelitis optica spectrum disorder. *Neurology*. (2018) 91:e2089–99. doi: 10.1212/WNL.0000000000006574

66. Mealy MA, Kessler RA, Rimler Z, Reid A, Totonis L, Cutter G, et al. Mortality in neuromyelitis optica is strongly associated with African ancestry. *Neurol Neuroimmunol Neuroinflamm*. (2018) 5:e468. doi: 10.1212/NXI.0000000000000468

67. Kitley J, Woodhall M, Waters P, Leite MI, Devenney E, Craig J, et al. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. *Neurology*. (2012) 79:1273–7. doi: 10.1212/WNL.0b013e31826aac4e

68. Siritho S, Sato DK, Kaneko K, Fujihara K, Prayoonwiwat N. The clinical spectrum associated with myelin oligodendrocyte glycoprotein antibodies (anti-MOG-Ab) in Thai patients. *Mult Scler*. (2016) 22:964–8. doi: 10.1177/1352458515614093

69. Hamid SH, Whittam D, Mutch K, Linaker S, Solomon T, Das K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. *J Neurol*. (2017) 264:2088–94. doi: 10.1007/s00415-017-8596-7

70. Papais-Alvarenga RM, Neri VC, de Araújo e Araújo AC, da Silva EB, Alvarenga MP, Pereira AB, et al. Lower frequency of antibodies to MOG in Brazilian patients with demyelinating diseases: an ethnicity influence? *Mult Scler Relat Disord*. (2018) 25:87–94. doi: 10.1016/j.msard.2018.07.026

71. Misu T, Fujihara K. Neuromyelitis optica spectrum and myelin oligodendrocyte glycoprotein antibody-related disseminated encephalomyelitis. *Clin Exp Neuroimmunol*. (2019) 10:9–17. doi: 10.1111/cen3.12491

72. Zamvil SS, Slavin AJ. Does MOG Ig-positive AQP4-seronegative opticospinal inflammatory disease justify a diagnosis of NMO spectrum disorder? *Neurol Neuroimmunol Neuroinflamm*. (2015) 2:e62. doi: 10.1212/NXI.0000000000000062

73. Narayan R, Simpson A, Fritsche K, Salama S, Pardo S, Mealy M, et al. MOG antibody disease: a review of MOG antibody seropositive neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord*. (2018) 25:66–72. doi: 10.1016/j.msard.2018.07.025

74. de Mol CL, Wong YY, van Pelt ED, Wokke BH, Siepman TA, Neuteboom RF, et al. The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults. *Mult Scler*. (2019). 1352458519845112. doi: 10.1177/1352458519845112. [Epub ahead of print].

75. Oxford University Hospitals NHS Foundation Trust. *Diagnostic and Advisory Service for Neuromyelitis Optica (NMO) Annual Report 2018*. Oxford University Hospitals NHS Foundation Trust (2018).

76. Kunchok A, Chen JJ, McKeon A, Mills JR, Flanagan EP, Pittock SJ. Coexistence of myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies in adult and pediatric patients. *JAMA Neurol*. (2020) 77:257–9. doi: 10.1001/jamaneurol.2019.3656

77. Senanayake B, Jitprapaikulsan J, Aravinthan M, Wijesekera JC, Ranawaka UK, Riffsy MT, et al. Seroprevalence and clinical phenotype of MOG-IgG-associated disorders in Sri Lanka. *J Neurol Neurosurg Psychiatry*. (2019) 90:1381–3. doi: 10.1136/jnnp-2018-320243

78. Flanagan E, Cabre P, St Sauver J, Chen J, Fryer J, Smith C, et al. The epidemiology of myelin oligodendrocyte glycoprotein antibody associated disorders. *Mult Scler*. (2019) 25(Suppl.2):160.