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A study of referral bias in NMOSD and MOGAD cohorts

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Highlights

- Relapsing rate in MOGAD is overestimated in cohorts from specialised centres.
- Clinical presentation does not differ across local, regional, or national cohorts.
- Comparisons across cohorts may be reasonable if diagnostic definition is the same.

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Abstract

Background

Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) are rare disorders often seen in highly specialized services or tertiary centres. We aimed to assess if cohort characteristics depend on the origin of the referral catchment areas serviced by our centre (i.e. local, regional or national).

Methods

Retrospective cohort study using a national referral service database including local (Oxfordshire), regional (Oxfordshire and neighbouring counties), and national patients. We included patients with the diagnosis of NMOSD, seronegative NMOSD or MOGAD, followed at the Oxford Neuromyelitis Optica Service.

Results

We included 720 patients (331 with MOGAD, 333 with aquaporin-4 antibody (AQP4)-NMOSD, and 56 with seronegative NMOSD. The distribution of diagnoses was similar across referral cohorts. There were no significant differences in the proportion of pediatric onset patients, sex, or onset phenotype; more White AQP4-NMOSD patients were present in the local than in the national cohort (81% vs 52%). Despite no differences in follow-up time, more relapsing MOGAD disease was present in the national than in the local cohort (42.9% vs. 24%, p=0.029).

Conclusion

This is the first study assessing the impact of potential referral bias in cohorts of NMOSD or MOGAD. The racial difference in the AQP4-NMOSD cohorts likely reflects the variation in the population demographics rather than a referral bias. The over representation of relapsing MOGAD patients in the national cohort probably is a true referral bias and highlights the need to analyze incident cohorts when describing disease course and prognosis. It seems reasonable therefore to compare MOGAD and NMOSD patients seen withing specialised centres to general neurology services appears reasonable, provided both use similar antibody assays.

Manuscript

Introduction

Myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD), aquaporin-4 antibody–positive neuromyelitis spectrum disorder (AQP4-NMOSD), and seronegative NMOSD are rare autoimmune disorders of the central nervous system (CNS) [1, 2]. Unlike more prevalent inflammatory disorders of the CNS like multiple sclerosis, published cohorts including patients with MOGAD and NMOSD derive from a more variable range of services. These include combining data from local or regional services, single regional service data, combined data from across different countries, or specialised centres covering more widespread or national communities."

Observational data is prone to several types of bias that pose threats to the internal and external validity of studies, including selection bias in which there is a systematic error related to subject selection or participation. Clinical features of patients referred into tertiary or academic centres may differ from those in the overall patient population[3, 4], which could cause a selection bias in the literature. In addition, in a rare disease, small centre data may be prone to both random misrepresentation due to small numbers and heterogeneity in cohort selection when combined across sites.

We set out to explore if cohort characteristics depend on the origin of the referral catchment areas serviced by the centre.

Methods

This study used a database of prospectively collected data of patients referred to and followed at the Oxford Neuromyelitis Optica Service. Patients were included if they had a diagnosis of MOGAD[5], AQP4-NMOSD[6], or seronegative NMOSD (i.e. NMOSD without antibodies for AQP4 or MOG)[6]. Antibody status of patients was based on live cell-based assays[5, 6] and no patients fulfilled the Multiple Sclerosis diagnostic criteria[7].

Clinical data included sex, self-identified race, age at onset of disease, date of service referral, clinical presentation at onset and during the disease course, number of relapses, relapsing status, disability data including first recorded Expanded Disability Status Scale (EDSS) integer or European Database for Multiple Sclerosis (EDMUS) scores, and postcode area. Self-identified race was collected since race distribution may differ between groups and may affect outcomes in AQP4-NMOSD[8]. Clinical

presentation at onset was categorized into 6 clinical subgroups: acute disseminated encephalomyelitis, autoimmune encephalitis, brain or brainstem (ADEM, brain or BS) only; unilateral or bilateral optic neuritis (uON or bON); ON and transverse myelitis (ON+TM); TM only; or other (including combinations of the first 5 types or other clinical presentations). We retrieved patients' addresses and postal codes, matched them to a U.K. County, and used patient's county of origin as a proxy for how the patient was referred to our clinic. Patients were grouped into three areas: local patients covered by the local hospital (Oxfordshire), regional patients in the usual catchment area of the Oxford neuroscience centre (Oxfordshire plus the neighbouring counties of Buckinghamshire, Berkshire, Northamptonshire, and Wiltshire), and national patients (all patients followed at our centre, including those coming from outside the regional area, mostly from the south of England but also including patients from the north of England, Wales, Scotland, and Northern Ireland). Univariate (χ^2 test, ANOVA) analyses were performed for demographic and clinical factors. A multivariate logistic regression analysis was conducted to assess the effect of cohort of origin on relapsing disease, adjusted for possible confounders (age of onset, initial clinical presentation). A $p<0.05$ was considered statistically significant. Stata statistical software version 15.1 (StataCorp) packages were used for analysis.

Results

Among 720 patients who met our inclusion criteria, we included 331 (45.9%) patients with MOGAD, 333 (46.3%) with AQP4-NMOSD, and 56 (7.8%) with seronegative NMOSD. Of these patients, 48 (6.7%) were local patients and 109 (15.1%) were regional. The distribution of the 3 diagnoses did not differ between cohorts. Due to the low number of seronegative NMOSD patients in the local (n=3) and regional (n=6) cohorts, we did not perform comparative analysis for this subset of patients. Table 1 summarizes demographic and baseline data for the MOGAD and AQP4-NMOSD patients across cohort. The full analysis, including non-significant values, is presented in Supplementary Table 1. There were no statistically significant differences in proportion of young pediatric onset (≤12 years), late onset patients (≥50 years), or sex. There was a higher proportion of white patients in the local AQP4-NMOSD cohort compared to the national AQP4-NMOSD cohort (81% vs 52%), although overall race distribution did not differ significantly between cohorts.

Table 1. Demographic and clinical characteristics of MOGAD and AQP4-NMOSD patients.

	MOGAD (N=331)			**AQP4-NMOSD (N=333)**		
	Local (N=29)	**Regional (N=59)**	**National (N=331)**	**Local (N=16)**	**Regional (N=44)**	**National (N=333)**
Age at onset, y						
Mean (SD)	37.6 (18.4)	31.3 (18.6)	31.1 (17.0)	44.2 (21.5)	46.7 (21.4)	42.0 (18.5)
Median (range)	37 (5-75)	32 (1-75)	30 (1-78)	44 (11-84)	47.5 (11-84)	42 (3-85)
≤12 onset, No. (%)	3 (10)	12 (20)	55 (16.6)	2 (13)	3 (7)	20 (6.0)
≥50 onset, No. (%)	7 (24)	5 (8)	47 (14.2)	6 (38)	15 (34)	104 (31.2)
Female, No. (%)	16 (55)	33 (56)	205 (61.9)	14 (88)	38 (86)	288 (86.5)
Race, No. (%)						
No. with data	26	51	217	16	41	264
Asian[a]	4 (15)	6 (12)	18 (11.1)	0 (0)	5 (12)	39 (14.8)
Black	0 (0)	0 (0)	13 (5.9)	3 (19)	8 (20)	73 (27.6)
White	21 (81)	43 (84)	171 (78.8)	13 (81)	27 (66)	137 (51.8)
Mixed or other race[b]	1 (4)	2 (4)	7 (4.1)	0 (0)	1 (2.4)	15 (5.7)
Follow up time, mo., median (range)						
Since disease onset[c]	31 (5-447)	42 (5-447)	41 (1-504)	97 (18-337)	85 (8-337)	84 (0-516)
Since referral[d]	28 (0-	26 (0-	17 (0-	71 (9-	64 (0-	43 (0-141)

	141)	141)	141)	130)	141)	
Onset phenotype, No. (%)						
ADEM, Brain or BS	4 (14)	10 (17)	48 (14.5)	1 (6)	5 (11)	50 (15.0)
Unilateral ON	12 (41)	18 (31)	117 (35.4)	4 (25)	9 (20)	95 (28.5)
Bilateral ON	7 (24)	13 (22)	72 (21.8)	0	3 (7)	20 (6.0)
ON+TM	1 (3)	3 (5)	22 (6.7)	2 (13)	2 (5)	11 (3.3)
TM	5 (17)	12 (20)	58 (17.5)	6 (38)	21 (48)	128 (38.4)
Other[e]	0	3 (5)	14 (4.2)	3 (19)	4 (9)	29 (8.7)
Relapses						
Number of relapses before service referral, mean (SD)[f]	1.3 (0.8)*	1.7 (1.9)*	1.9 (1.7)*	3.0 (2.8)	2.5 (2.1)	2.7 (2.9)
Total number of relapses, mean (SD)[f]	1.5 (0.9)*	1.9 (2.0)*	2.2 (2.1)*	3.7 (3.0)	3.4 (2.8)	3.1 (3.1)
EDSS, median (IQR)[g]	2 (0-3)	2 (0-3)	2 (1-3)	4 (1.5-6.5)	3 (2-6)	3 (1-6)

Legend:

*For both the MOGAD and NMOSD cohorts, differences between groups for age at onset, proportion of female patients, race distribution, follow-up time, onset phenotype, and EDSS were non-significant. In the MOGAD cohort, there was a difference in number of relapses before service referral ($p<0.001$) and in the number of total relapses ($p<0.001$), with fewer relapses in the local patients.

[a] Asian race includes individuals who self-identified with South Asian or East Asian.

[b] Individuals with mixed race and other race were those who self-identified as others outside of the categories listed in this table. Mixed race and other race were combined owing to low numbers. Mixed race was a specific term used in data collection.

[c] Data available for 323/331 (97.5%) MOGAD patients and 311/333 (93.3%) AQP4-NMOSD patients

[d] Data available for 296/331 (89.4%) MOGAD patients and 287/333 (86.2%) AQP4-NMOSD patients

[e] Includes individuals who presented with a combination of the first 4 types of disease onset (e.g. unilateral optic neuritis and brainstem syndrome) or other clinical presentation.

[f] Data available for 299/331 (90.3%) MOGAD patients and 288/333 (86.5%) AQP4-NMOSD patients

[g] Data available for 237/331 (72%) MOGAD patients and 236 (71%) AQP4-NMOSD patients

AQP4-NMOSD: aquaporin-4 antibody–positive neuromyelitis spectrum disorder (AQP4-NMOSD); BS: brainstem; EDSS: Expanded Disability Status Scale; IQR: interquartile range; mo.: months; MOGAD: myelin oligodendrocyte glycoprotein antibody–associated disease; No.: number; SD: standard deviation; ON: optic neuritis; ON+TM: optic neuritis and transverse myelitis; TM: transverse myelitis.

There were no differences in the onset clinical presentation across cohorts (Table 1 and Figure 1), with a similar proportion of patients presenting with uON and bON across cohorts. Clinical phenotype during the disease course was also similar across cohorts. The relapsing disease was more common in MOGAD patients from the national cohort than the local cohort (42.9% vs. 24%, p=0.029) (Table 1 and Figure 2) despite disease duration being comparable across the referral cohorts within the disease groups, and even when adjusted for possible confounding factors (age of onset, initial clinical presentation; p=0.041). There were no significant differences in the proportion of relapsing AQP4-NMOSD patients or the number of relapses across cohorts either before or after referral to Oxford. Disability was similar across MOGAD or AQP4-NMOSD.

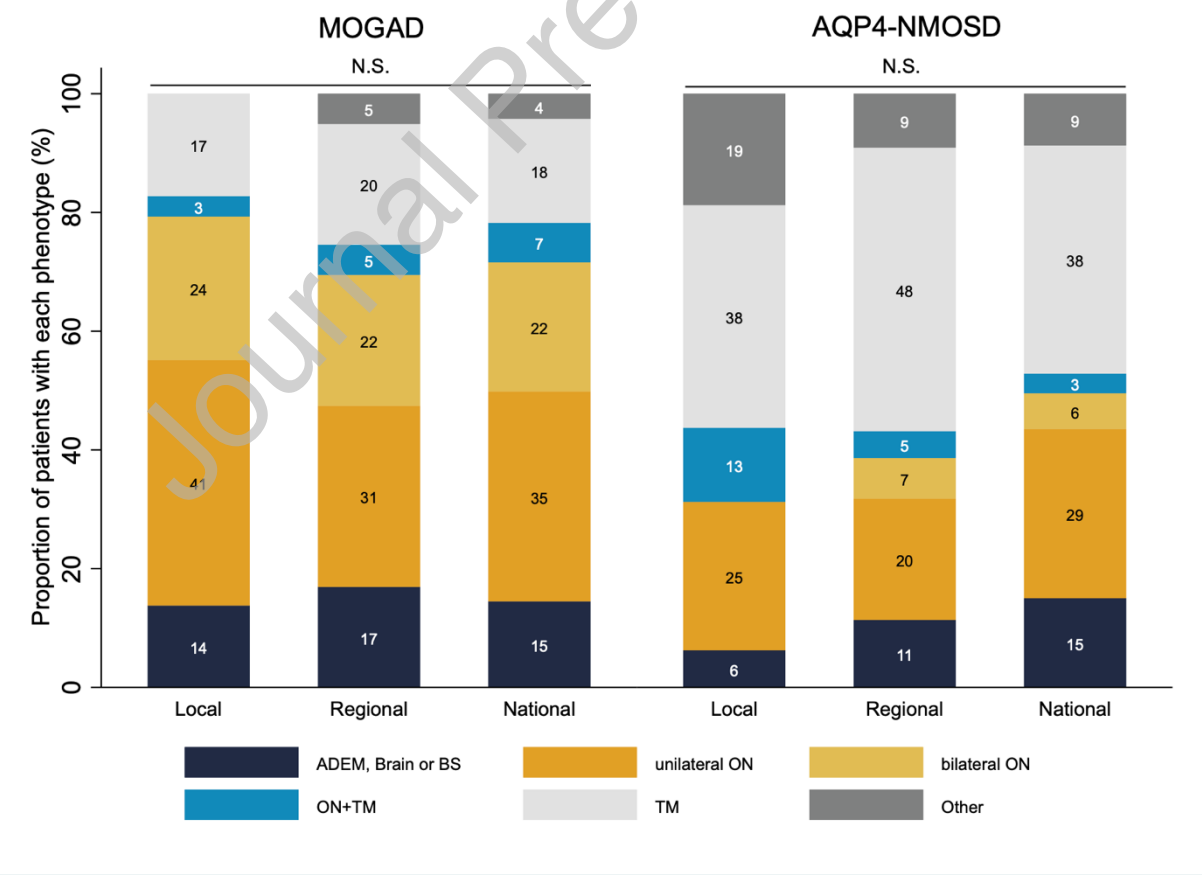

Fig. 1 Onset presentation in patients with MOGAD and AQP4-NMOSD across regions. AQP4-NMOSD: aquaporin-4 antibody–positive neuromyelitis spectrum disorder; ADEM: acute disseminated encephalomyelitis;

bON: bilateral optic neuritis; BS: brainstem; MOGAD: myelin oligodendrocyte glycoprotein antibody–associated disease; NS: non-significant difference; TM: transverse myelitis; uON: unilateral optic neuritis

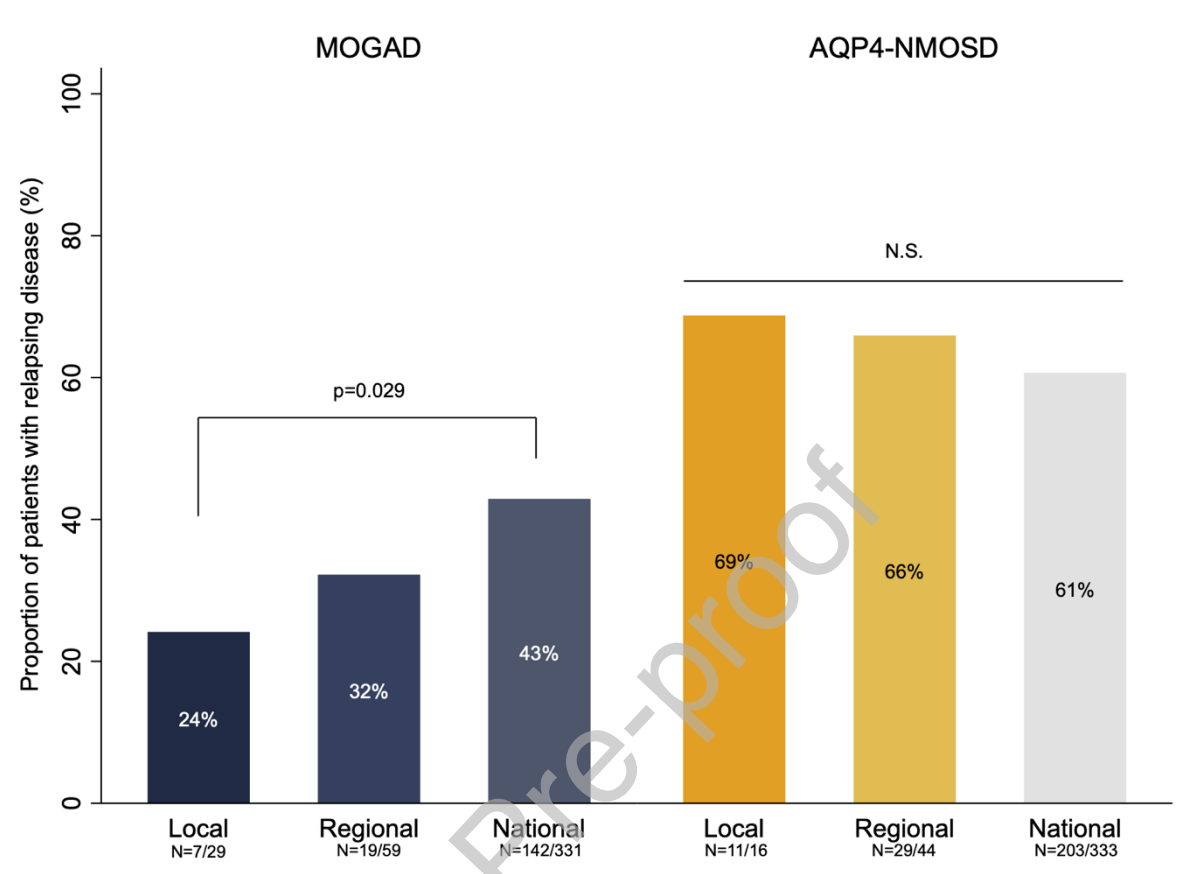

Fig. 2 Proportion of MOGAD and AQP4-NMOSD patients with relapsing disease in each zone. Relapsing disease was more common in MOGAD patients from the national cohort than the local cohort (42.9% vs. 24%, p=0.029). AQP4-NMOSD: aquaporin-4 antibody–positive neuromyelitis spectrum disorder; MOGAD: myelin oligodendrocyte glycoprotein antibody–associated disease; N.S.: non-significant difference.

Discussion

This is the first study assessing the impact of referral bias in cohorts of MOGAD or NMOSD. We observed some differences in potential scientific and clinical impact between cohorts.

Firstly, demographic features and diagnoses distribution did not significantly vary across cohorts except for the racial difference in the AQP4-NMOSD cohorts which is probably due to variation in population demographics rather than a referral bias[9–11].

Despite a similar follow-up time, there was an over-representation of relapsing vs. monophasic MOGAD patients in the national cohort which likely reflects a true referral bias. This may be either

because monophasic MOGAD may be underdiagnosed in the outlying non-specialist hospitals or because more challenging relapsing patients are more likely to be referred to the specialist centre. Additionally, our treatment strategy is to cover patients with a course of prednisolone from the onset attack, with courses of at least 3 months have been reported to reduce early relapse risk[12]. Thus, differences in early-treatment care protocols between centres may affect relapse rates.

Because of the enrichment of relapsing patients in secondary or tertiary cohorts, disease course should be preferentially analyzed in incident cohorts (i.e., in which disease onset occurs after the cohort baseline date) and not in prevalent cohorts (i.e., where already prevalent disease is followed forward in time), so as to not inflate the relapse risk of MOGAD patients[13,14].

In contrast, the proportion of relapsing AQP4-NMOSD patients was similar across cohorts which may reflect the fact that, in contrast to MOGAD, AQP4-NMOSD is a long-term relapsing disease and does not have a monophasic phenotype if untreated. Additionally, AQP4-NMOSD generally results in greater residual relapse disability than MOGAD, and thus AQP4-NMOSD patients may be more likely to be referred to expert centres.

Our study limitations include: low numbers of antibody negative NMOSD which could not be analysed separately; the small numbers in the local population of these rare diseases mean there is limited power to detect differences; the relatively low population diversity in the local and regional cohorts in the AQP4-NMOSD patient group; the non-inclusion of private fee paying patients as the NMO service is fully funded by NHS England, which limits the generalization of our finding to countries where patients can be selected based on their income and where other biases that we have not predicted may exist; disability was assed based on the first EDSS or EDMUS value recorded in our database, regardless of date, which disregards the possibility for improvement since referral until evaluation; and that we cannot identify the exact reason for the greater relapsing MOGAD patients in the national referral cohort.

Other than a risk for overestimation of relapsing MOGAD patients, it is reassuring that the other characteristics did not differ, suggesting that comparisons across NMOSD and MOGAD cohorts may be reasonable, even across specialized care to general neurology services where the clinical and laboratory diagnostic definition is the same. The separate analysis of incident cohorts may be a strategy to limit the impact of referral bias in observational studies on MOGAD or NMOSD.

Data sharing statement: Data not provided in the article may be shared anonymized at the request of any qualified investigator for purposes of collaborative research.

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Conflicts of interest

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