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Predictors of relapse in MOG antibody associated disease- a cohort study

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Title- Predictors of relapse in MOG antibody associated disease- a cohort study

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Abstract

Objective To identify factors predictive of relapse risk and disability in myelin oligodendrocyte glycoprotein associated disease (MOGAD).

Setting Patients were seen by the neuromyelitis optica spectrum disorders (NMOSD) service in Liverpool, UK, a national referral centre for adult patients with MOGAD, NMOSD and related conditions.

Participants MOGAD patients=76 from England, Northern Ireland and Scotland were included in this cohort study.

Methods We retrospectively analysed clinical, radiological, and serological data from MOGAD patients. Univariable and multivariable analyses were used to identify prognostic factors for risk of relapse, time to relapse, visual and overall disability.

Results Relapsing disease was observed in 55% (42/76) of cases. Steroid treatment ≥1 month (OR 0.2, 95%CI: 0.05-0.80; p=0.022), transverse myelitis (TM) at 1st attack (OR 0.03, 95%CI: 0.004- 0.23; p=0.001), and male sex (OR 0.16, 95%CI: 0.04-0.68; p=0.014) were associated with monophasic disease (AUC=0.85). Male sex (HR 0.46, 95%CI: 0.24-0.89; p=0.011) and TM at disease onset (HR 0.42, 95%CI: 0.22-0.82; p=0.011) were also associated with an increased latency to 1st relapse. Disappearance of MOG-Abs was observed in 45% (32/71) patients and was associated with a lower relapse risk (RR 0.11 95%CI 0.05-0.26; p<0.001). No specific factors were predictive of visual or overall disability.

Conclusions Male patients with spinal cord involvement at disease onset have a lower risk of relapsing disease and longer latency to 1st relapse. Steroid treatment for at least 1 month with the 1st attack was also associated with a monophasic disease course. MOG-Ab negative seroconversion was associated with a lower risk of relapse and may help inform treatment decisions and duration.

Article Summary

Strengths and Limitations

- This national UK cohort study (n=76) identified prognostic factors associated with relapsing disease and time to 1st relapse in myelin oligodendrocyte glycoprotein associated disease (MOGAD).
- Steroid treatment ≥1 month at 1st attack, transverse myelitis (TM) at disease onset, and male sex were associated with monophasic disease.
- Male sex and TM at onset were associated with an increased latency to first relapse.
- Disappearance of MOG antibodies was observed in 45% of cases and was associated with a reduction in relapse risk.
- A limitation of this study was the shorter duration of follow-up in monophasic MOGAD patients.

INTRODUCTION

Myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) is associated with central nervous system inflammation, typically acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), transverse myelitis (TM), and brainstem inflammation.[1-7] In retrospective studies, a relapsing disease course has been reported in 27-80% of patients, which may over-report the proportion of relapsing patients by virtue of differential follow-up of monophasic versus relapsing patients.[1-5] Indeed in two studies using incident cohorts, rates of relapsing disease were at the lower end (27-36%).[1,2] Although MOGAD is associated with a better prognosis compared to neuromyelitis optica spectrum disorder (NMOSD), persistent visual, motor or sphincter disturbances have been reported.[1,7] These studies collectively support the presence of a subgroup of MOGAD patients with lower risk of relapse and minimal if any long-term disability. This has understandably led to equipoise amongst international experts on when to introduce chronic immunotherapy and the duration

of treatment.[8] Identifying prognostic factors for risk of a) early relapse, b) any relapse, and c) permanent disability will help individualise MOGAD treatment.

Cohort description

Study design

All patients were seen by the NMOSD UK service at the Walton Centre NHS Foundation Trust in Liverpool, UK, a national referral centre for adult patients with NMOSD, MOGAD, and other non-multiple sclerosis atypical CNS inflammatory/demyelinating syndromes. Patients from England, Northern Ireland and Scotland were included.

Between January 2010 and January 2020, patients with an acute demyelinating syndrome, at least one serum MOG-IgG1 positive assay result, and a minimum of 12 months follow-up were included. Serum MOG-IgG1 Abs were detected using a live cell based assay employing full length human MOG (α1 isoform; Oxford Autoimmune Neurology Group).[9] The study was approved by the Research Ethics Service, NRES Committee London- Hampstead, Ref. no. 15/LO/1433. All patients provided written informed consent.

Demographic, clinical details of attacks, cerebrospinal fluid and MRI results, treatment, and longitudinal MOG-Ab results were collected. Childhood onset was defined as disease onset at age ≤16 years. Patients were considered 'monophasic' if no relapses were observed after the 1st clinical attack for the duration of follow-up (at least 12 months) and were compared to relapsing MOGAD patients. Patients where the diagnosis was made shortly after onset and prior to relapse were designated as 'incident' cases. The following outcomes were examined: 1) relapse at any time, 2) visual acuity ≤6/36 (one or both eyes at last follow-up), 3) time between 1st and 2nd attack, and 4) impact of MOG-Ab serostatus on relapse frequency.

Statistical Analysis

Continuous covariates are summarised as median (interquartile range) unless otherwise stated with categorical covariates summarised as frequencies with associated percentages. For comparisons of covariates across groups Fisher's exact tests and Mann-Whitney U-tests were applied for categorical and continuous data respectively.

To evaluate the impact of covariates on each endpoint, univariable and multivariable modelling were applied. Multivariable models for binary endpoints were constructed using a generalised linear model assuming a binomial distribution and a logistic link function and using a forward stepwise approach. Model evaluations were performed using Akaike Information Criterion (AIC). Model performance were assessed by comparing the linear predictors against the model outcome using Receiver Operating Curve (ROC) and Area Under the Curve (AUC). Model results are presented in terms of odds ratios with associated 95% confidence intervals. For the time-to-event outcome, estimates of the probability of relapse were obtained using the Kaplan Meier method. Univariable and multivariable analyses were performed using Cox proportional hazards models with an equivalent procedure used to evaluate univariate models and construct multivariable models. Results are presented in terms of hazard ratios with 95% confidence intervals. The longitudinal impact of MOG-Ab negativity on patient relapse was investigated using a random effects Poisson regression model. Here MOG-Ab negativity was included as a fixed effect and the time included in the model as a (log) offset. Patient identifier was included as a random effect. Results are presented as relative and absolute risk for observing a relapse with 95% confidence intervals. A threshold of $p<0.05$ was applied for statistical significance. All analyses were performed using R (Version 3).

Patient and public involvement

Clinical data from patients were included in this study. The development of the research question was driven by our patient's uncertainty over future relapse risk following a first

presentation of MOGAD. The patients and public were not explicitly involved the design or conduct of this study. Results will be disseminated at the NMO UK patient day where patients, relatives, and caregivers will be in attendance.

RESULTS

Demographic features

We identified 76 MOGAD patients with a median onset age of 27 (IQR 19-45), 54% were female and 17% had disease onset in childhood (age ≤16years). The geographic distribution of patients is shown in supplementary figure 1. In total 42 relapsing patients (total no of relapses=140) and 34 monophasic patients were identified. The clinical profile of patients and respective univariable analyses are presented in Table 1 and supplementary Table 1.

Overall, there was a slight female predominance (54%) and although the proportion of male patients did not reach statistical significance in the univariable analysis, male sex was associated with a lower overall risk of relapsing disease (OR 0.16 95% CI: 0.04-0.68; p=0.014) and time to 1st relapse (HR 0.46 95% CI: 0.24-0.89; p=0.011) in multivariable analyses (Figure 1A, Table 2 supplementary). The majority of patients (93%) were white; there were no racial differences between the groups. The median age of relapsing patients was lower than monophasic patients (26 (16-40) vs 37 (27-51) years; p=0.001). Development of MOGAD after the age of 16 years was associated with a lower risk of relapsing disease in the multivariable analysis (OR 12.54 (1.81-87.17; p=0.011), but 12/13 children had relapses, suggesting a bias towards follow-up of children into adulthood with relapsing disease.

	Relapsing=42	Monophasic=34	p-value	Incident cohort=38	Total cohort=76
Demographics (%)					
Female (%)	64 (27/42)	41 (14/34)	0.064	47 (18/38)	54 (41/76)
White (%)	98 (41/42)	88 (30/34)	0.166	87 (33/38)	93 (71/76)
Onset attack characteristics % (n/total)					
Median onset age years (IQR)	26 (16-40)	37 (27-51)	0.001†*	37 (27-45)	27 (19-45)
Age≤16yrs at onset	29 (12/42)	3 (1/34)	0.004*	3 (1/38)	17 (13/76)
ADEM	12 (5/42)	0 (0/34)	0.061	3 (1/38)	7 (5/76)
ON	62 (26/42)	59 (20/34)	0.817	50 (19/38)	61 (46/76)
bON	31 (13/42)	41 (14/34)	0.470	32 (12/38)	36 (27/76)
TM	26 (11/42)	62 (21/34)	0.002*	58 (22/38)	42 (32/76)
LETM	17 (7/42)	41 (14/34)	0.022*	40 (15/38)	28 (21/76)
ON+TM	14 (6/42)	24 (8/34)	0.377	21 (8/38)	18 (14/76)
Brain involvement	29 (12/42)	21 (7/34)	0.595	29 (11/38)	25 (19/76)
≥2 CNS sites	17 (7/42)	25 (12/34)	0.109	32 (12/38)	25 (19/76)
Infective trigger	8 (1/13)	40 (6/15)	0.084	35 (6/17)	25 (7/28)
EDSS≥3 at nadir	83 (33/40)	91 (31/34)	0.326	92 (35/38)	87 (64/74)
EDSS≥3 6m	17 (7/41)	27 (9/34)	0.400	24 (9/38)	21 (16/75)
Treatment (IS)	67 (28/42)	91 (31/34)	0.013*	87 (33/38)	68 (59/76)
Steroids≥1m	37 (15/41)	76 (25/33)	0.001*	70 (26/37)	38 (40/74)
Steroids≥3m	32 (13/41)	55 (18/33)	0.060	49 (18/37)	35 (31/74)
non-steroid IS	5 (2/42)	27 (7/33)	0.038*	19 (7/37)	12 (9/75)
Comparison % (n/total)					
Relapsing	-	-	-	18 (7/38)	55 (42/76)
Relapse<12m	52 (22/42)	-	-	86 (6/7)	29 (22/76)
>2 attacks	62 (26/42)	-	-	43 (3/7)	34 (26/76)
>3 attacks	43 (18/42)	-	-	1 (1/7)	24 (18/76)
Median ARR (range)	0.45 (0.07-5.43)	-	-	0.66 (0.18-2.04)	0.45 (0.07-5.43)
ADEM ever	15 (5/42)	0 (0/34)	0.061	3 (1/38)	7 (5/76)
ON ever	88 (37/42)	59 (20/34)	0.007*	55 (21/38)	75 (57/76)
bON ever	55 (23/42)	38 (13/34)	0.172	40 (15/38)	47 (36/76)
TM ever	52 (22/42)	62 (21/34)	0.488	61 (23/38)	57 (43/76)
LETM ever	29 (12/42)	38 (13/34)	0.064	40 (15/38)	33 (25/76)
ON+TM ever	50 (21/42)	27 (9/34)	0.058	26 (10/38)	39 (30/76)
Brain involvement ever	41 (17/42)	24 (8/34)	0.150	32 (12/38)	33 (25/76)
>1 CNS site ever	67 (28/42)	41 (14/34)	0.597	45 (17/38)	55 (42/76)
Other Abs present (e.g., ANA, ENA)	16 (6/38)	18 (5/28)	1.00	19 (6/32)	17 (11/66)
MRI brain abnormality	50 (20/40)	44 (15/34)	0.647	47 (18/38)	47 (35/74)
MRI spine abnormality	56 (23/41)	69 (20/29)	0.325	67 (22/33)	61 (43/70)
CSF Protein median (range)	0.47 (0.18-2.27)	0.44 (0.16-1.66)	0.954†	0.43 (0.16-1.66)	0.45 (0.16-2.27)
CSF WBC median (range)	2.5 (0-550)	30 (0-937)	0.008†*	25 (0-937)	10 (0-937)

Unmatched oligoclonal bands	7 (2/28)	6 (1/17)	1.00	14 (3/22)	7 (3/45)
At follow-up % (n/total)					
VA≤6/36 in at least one eye at fu	30 (12/40)	3 (1/34)	0.002*	3 (1/37)	18 (13/74)
EDSS≥4 at last FU	22 (9/41)	15 (5/34)	0.555	16 (6/38)	19 14/75)
EDSS≥3 at last FU	44 (18/41)	21 (7/34)	0.049*	24 (9/38)	33 (25/75)
Bladder dysfunction	32 (13/41)	33 (11/34)	1.00	34 (13/38)	32 (24/75)
Urinary catheter use	15 (6/41)	21 (7/33)	0.545	19 (7/37)	18 (13/74)
Bowel dysfunction	12 (5/41)	29 (10/34)	0.084	26 (10/38)	20 (15/75)
Erectile dysfunction	7 (1/14)	32 (6/19)	0.195	30 (6/20)	21 (7/33)
Current smoker	26 (9/35)	4 (1/27)	0.030*	9 (3/32)	16 (10/62)
Median FU/months (IQR)	107 (44-162)	33.5 (20-56)	<0.001†*	35 (12-77)	49 (28-113)
Treatment % (n/total)					
Prednisolone monotherapy	0 (0/42)	6 (2/34)	0.197	5 (2/38)	3 (2/76)
Prednisolone + other IS	36 (15/42)	6 (2/34)	0.002*	13 (5/38)	22 (17/76)
Azathioprine	12 (5/42)	3 (1/34)	0.216	3 (1/38)	8 (6/76)
Mycophenolate mofetil	33 (14/42)	9 (3/34)	0.013	18 (7/38)	22 (17/76)
Rituximab	7 (3/42)	0 (0/34)	0.248	0 (0/38)	4 (3/76)
IVIg	10 (4/42)	0 (0/34)	0.123	0 (0/38)	5 (4/76)
Tocilizumab	2 (1/42)	0 (0/34)	1.00	0 (0/38)	1 (1/76)
No IS	21 (16/42)	82 (28/34)	<0.001*	74 (28/38)	58 (44/76)
MOG-Ab					
No of patients MOG-Ab(+) at last review	62 (24/39)	47 (15/32)	0.229	51 (19/37)	55 (39/71)
Median no of samples (IQR)	4 (3-6)	3 (2-5.5)	0.407†	3 (3-6)	3 (3-6)
Median time between 1st and last sample/months (IQR)	30 (15.8-43.3)	29.5 (6.3-47)	0.782†	28 (6.5-46.5)	30 (15-46)
Median time to MOG-IgG(-) months (IQR)	103 (30.3-132)	12 (6-50)	0.003†*	11 (7-33)	34 (9-96)
Relapses (within 6 months) of MOG-Ab negative	2 (1/42)	-	-	14 (1/7)	1 (1/76)

Table 1. Univariate analysis of relapsing and monophasic patients with myelin oligodendrocyte glycoprotein antibody associated disease. ADEM; acute disseminated encephalomyelitis, ON; optic neuritis, bON; bilateral ON, TM; transverse myelitis, LETM; longitudinally extensive TM, CNS; central nervous system, NMOSD; neuromyelitis optica spectrum disorder, IPND; international panel for NMOSD diagnosis, Abs; antibodies, VA; visual acuity, EDSS; expanded disability status score, ARR; annualised relapse rate, IS; immunosuppression, IVIg; intravenous immunoglobulin, FU; follow-up, †; Mann-Whitney U-test, *; P<0.05.

Clinical course

Relapsing disease was observed in 18% of incident cases and 55% of the total cohort with a median time to first relapse of 11.5 (IQR 3-46) months. The most common first clinical presentations were optic neuritis (ON; 61%), transverse myelitis (TM; 42%), and bilateral ON (36%); (Table 1). TM and longitudinally extensive transverse myelitis (LETM) were more frequently part of the 1st clinical attack in monophasic patients (62% vs 26%, p=0.002 and 41% vs 17%; p=0.022 respectively). In multivariable analysis, TM with a 1st attack was associated with a lower overall risk of relapse (OR 0.03, 95% CI: 0.00-0.23; p=0.001) and a longer time to 1st relapse (HR 0.42 95%CI: 0.22-0.82; p=0.011; Figure 1B and Table 2 supplementary). Importantly although median follow up duration was longer in relapsing as compared to monophasic patients (107 (44-162) vs 33.5 (20-56) months; p<0.001)), the median follow-up times of these groups of patients with TM specifically were similar (35 (26-62) vs 55 (43-113); p=0.11). In addition, there was no difference in use of steroids>1m in those patients presenting with or without TM (59% vs 50%; p=0.485).

Simultaneous ON+TM at any point was associated with a greater risk of relapsing disease (OR: 12.54 (1.81-87.17); p=0.011), but follow-up duration was shorter in patients with monophasic disease (p=0.018). The proportion of patients presenting with bilateral optic neuritis and multi-CNS site involvement were similar between relapsing and monophasic groups. EDSS at nadir and 6 months after 1st attack were similar in monophasic and relapsing patients. Preceding infective symptoms were more frequent in monophasic patients, but the results did not reach statical significance (40% vs 8%; p=0.084).

Overall >2 attacks and >3 attacks were observed in 34% (26/76) and 24% (18/76) of patients respectively. Only 18% of incident cases relapsed and 86% of first relapses occurred within 12 months of the first attack. Follow-up duration was shorter in the incident cohort as reflected

in the higher annualised relapse rate in these patients as compared to the total cohort (0.66 (0.18-2.04 vs 0.45 (0.07-5.43). Smoking was more frequently noted at follow-up in relapsing patients (26% vs 4%; p=0.030) but median ARR in smokers was similar to non-smokers in the incident MOGAD patients (p=0.533). The most common CNS sites involved in attacks were the optic nerve (57/76; 75%), spinal cord (43/76; 57%), or simultaneous involvement of both these sites (30/76; 39%). The site of CNS involvement was similar between relapsing and monophasic groups with the exception of optic neuritis, which was more common in relapsing patients (88% vs 59%; p=0.007).

Paraclinical tests

In the total cohort MRI abnormalities in brain and spine were observed in 47% and 61% of cases respectively. The frequency of abnormalities on MRI brain (p=0.647) and spinal cord (p=0.325) were similar between relapsing and monophasic patients. CSF white cell count was higher in monophasic patients (p=0.008). Unmatched oligoclonal bands were seen in only 3/45 (7%) cases tested. Non-organ specific autoantibodies (e.g., antinuclear antigen, extractable nuclear antigen) were present in 16% of relapsing and 18% and monophasic patients. None of these variables maintained a significant association in multivariable analysis.

Treatment

Overall, 38% (40/74) of patients received steroid treatment for ≥1month and 12% (9/75) were commenced on non-steroid immunosuppression (IS) following the onset clinical attack. Both steroid treatment for ≥1month (76% vs 37%; p=0.001) and non-steroid IS (27% vs 5%; p=0.038) were associated with monophasic disease. In multivariable analysis, treatment of the 1st attack with steroids ≥1month was associated with a lower overall relapse risk (OR 0.2, 95% CI: 0.05-0.80; p=0.022, Table 2 supplementary). In keeping with current UK practice, steroids ≥1m were more frequently used in incident as compared to non-incident patients (70% vs

39%). Overall, 32/76 (42%) of MOGAD patients received long term IS, and of these patients 26 (81%) had relapsing disease. In order of frequency, the most commonly used non-steroid immunosuppressants were mycophenolate mofetil (22%) and azathioprine (8%). IVIg (5%), rituximab (4%), and tocilizumab (1%) were used as second- and third-line therapies. In 22% of patients, maintenance prednisolone (5-15mg/day) was combined with non-steroid immunosuppression.

An evaluation of the multivariable model to describe monophasic patients was performed using ROC analysis with the following factors- age≥16 years, male sex, TM at onset, steroids ≥1month. Using the linear predictor from the fitted model, an area under the curve of 0.92 was achieved. However, in view of the observer bias relating to age at disease onset, this variable was removed and a high AUC of 0.85 was maintained.

Long term outcome

Poor visual outcome defined by a visual acuity of ≤6/36 in at least one eye at last review was observed in 18% (13/74) of patients after a median of 13.5 years follow-up (Table 1 supplementary). Of those with poor visual outcome, 85% (11/13) had an EDSS ≥3 and 39% (5/13) had an EDSS ≥4. Permanent visual disability was more common in relapsing MOGAD (30% vs 3%; p=0.002) and median follow up duration in these patients was longer (median 161 vs 43 months; p<0.0001). Interestingly patients presenting with TM or LETM at 1st attack were less likely to develop optic nerve involvement (53% vs 91%; p=0.0003 and 38% vs 89%; p=0.0001 respectively) and had a better visual prognosis (49% vs 8%; p=0.006 and 33% vs 0%; p=0.015 respectively, Table 1 supplementary). In the multivariable analysis, TM with the 1st MOGAD clinical attack was associated with a favourable visual prognosis (OR 0.09 (0.01-0.70); p=0.022, Table 2 supplementary). To determine whether this simply reflected less optic nerve involvement in patients with TM at onset we analysed onset TM patients with subsequent

ON attacks (17/32; 53%) and the remaining patients that developed ON only after first attack (12/30; 40%). Although the results were not significant, there was a trend towards better visual outcome in patients that presented with TM and had subsequent optic nerve involvement (6% versus 36%; p=0.06).

Patients with relapsing disease (92% vs 46%; p=0.002), >3 relapses (83% vs 29%; p=0.002), or a history of bilateral ON (77% vs 43%; p=0.033) had worse visual outcomes but these factors and others (MOG-Ab seronegative status and long term IS) did not maintain a significant association in multivariable analysis. A visual acuity ≤6/36 in at least one eye at last review was more frequently observed with childhood onset MOGAD (46% vs 12%; p=0.008). As with findings related to higher relapse rate, this observation likely relates to preferential follow-up of children with more severe disease.

An EDSS≥3 was recorded in 33% (25/76) of patients at last review after a median of 6.6 years follow-up. Follow-up duration was longer in patients with an EDSS≥3 (median 79 vs. 44 months; p=0.004). Approximately a third of relapsing and monophasic patients had bladder dysfunction at last review. Rates of bowel and erectile dysfunction were not significantly different between relapsing and monophasic patients. Patients who received IVIg had worse EDSS (and visual) scores at follow-up due to refractory relapsing clinical disease with severe disability prior to treatment commencement. No clinical feature was associated with overall disability (EDSS≥3) in multivariable analysis.

MOG-Ab serostatus

In total 71 patients had more than 1 serum sample for MOG-Ab testing (Table 1). The median number of samples in relapsing and monophasic groups (4 (IQR: 3-6) vs 3 (IQR: 2-5.5); p=0.407) and patients with and without persistent MOG-Abs (3 (IQR: 3-6) vs 4 (IQR: 3-6);

p=0.563) were similar (Tables 1 and 2 supplementary). The median time between 1st and last sampling (30 (15.8-43.3) vs 29.5 (21-53.8) months; p=0.782) was also similar.

Persistent MOG-Ab detection was observed in 55% (39/71) of patients. In 2 patients MOG-Ab serostatus was initially negative and then became positive. In 5 patients a fluctuating MOG-Ab serostatus was noted- following a positive MOG-Ab result 3 patients became transiently negative and then persistently positive and 2 patients became negative, positive and then persistently negative. The median time to negative MOG-Ab serostatus was 34 (9-96) months and as expected was shorter in the incident cohort (11 (7-33) months). The time interval was also shorter in the monophasic as compared to relapsing patient group (12 (6-50) vs 103 (30.3-132) months; p=0.003). Relapse within 6 months of a negative MOG-Ab assay was recorded in only 1 patient. Two further patients had a relapse after a negative result, but MOG-Ab testing was done more than 6 months prior to attack and undetected MOG-Ab positive seroconversion could not be excluded. Figure 3 summarises the longitudinal MOG-Ab serostatus in relation to clinical attacks.

To assess the impact of MOG-Ab serostatus on clinical course we first analysed the risk of relapsing disease in those patients who became seronegative. Patients that became MOG-Ab seronegative were just as likely to have relapsing disease as those who remained MOG-Ab positive (45% vs 62%; p=0.229). To determine if longitudinal MOG-Ab serostatus influenced relapse rate we used a random effects Poisson regression model. The monthly risk of relapse was approximately 4% and reduced to 0.5% following MOG-Ab negative seroconversion (RR 0.11 (0.048-0.259); p<0.001, supplementary Table 3). Figure 2 illustrates clinical course of patients in relation to longitudinal MOG-Ab serostatus. Unfortunately, it was not possible to assess the impact of MOG titre on risk of relapsing and monophasic disease as these data were not available in all patients.

In univariable analysis, patients were more likely to become MOG-Ab negative if they presented with transverse myelitis (p=0.018), had an infective trigger (p=0.041), or had less 3 attacks (p=0.039) overall (Supplementary Table 1). A trend towards MOG-Ab negative seroconversion was noted with long term immunosuppression (72% vs 33%; p=0.057) but no specific treatment was associated with a higher likelihood of subsequent negative MOG-Ab serostatus. Longitudinal MOG-Ab serostatus was not associated with overall disability (p=0.802) or visual disability (p=0.067). In the multivariable analysis, transverse myelitis at onset was associated with MOG-Ab negative seroconversion (OR 2.85 (1.11-7.30); p=0.029).

DISCUSSION

In this study that included myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) cases from across the UK, we found that male patients receiving ≥1 month of steroid treatment at disease onset and spinal cord involvement at 1st presentation had a lower risk of relapsing disease. A transition to MOG-antibody negative serostatus occurred in around half of patients and was associated with a lower risk of relapse. Spinal cord involvement at onset was associated with negative MOG-Ab seroconversion.

There is wide variation in the reported rates of relapsing MOGAD in retrospective cohorts (27-80%).[1-5] Unsurprisingly the highest proportion of relapsing disease has been observed in studies with longer follow-up duration. The stratification of relapse risk at disease onset is important when considering the long-term approach to MOGAD treatment. In this study we analysed relapsing and monophasic patients to identify prognostic factors related to relapse and disability. We also included an incident cohort analysis to assess for observer bias.

The clinical characteristics of these MOGAD patients were similar to previous reports, with relapsing disease observed in 55% of cases.[1-6,11] A relapse rate of 18% in incident cases was lower than other reported studies (27-36%).[1,2,6] It has been shown previously that the

risk of relapse is highest in the first year and in this study only cases with at least 12 months follow-up were included.[1] Furthermore the median follow-up duration of incident cases was almost 3 years though it is noteworthy that the risk of relapse in one study was 45% at 2 years and 62% at 5 years.[2]

We found that in male patients the time to 1st relapse was longer and the overall risk of relapsing disease was lower. This is similar to the findings of a recent large French study in childhood onset MOGAD.[6] The explanation for this finding is uncertain, particularly as unlike other autoimmune diseases such as neuromyelitis optica spectrum disorder, the female predominance in MOGAD is less marked.[7] In our cohort patients presenting with spinal cord involvement at disease onset had a lower risk of relapsing disease and a longer latency to 1st relapse, reproducing findings from an Indian cohort study.[5] Importantly relapsing and monophasic patients with spinal cord involvement at disease onset were treated similarly with regards to steroid taper and had similar disease duration. As has been previously reported, a prolonged steroid taper with a first MOGAD attack was associated with a lower risk of relapsing disease. [1,5,11] In keeping with UK recommendations for MOGAD treatment, a prolonged steroid taper was more frequently observed in the incident cases.[12] As mentioned previously, these cases were followed for a median of 3 years and the lower relapse rates (18%) in this cohort may relate to the use of corticosteroids but also to disease duration. Paradoxically and in contrast to the findings by Cobo Calvo et al., childhood onset disease was associated with relapsing disease and disability.[6] This finding is explained by the preferential follow-up of children with more severe MOGAD who transition into adult neurological services. Accordingly, this parameter was excluded from the ROC analysis but a high area under the curve of 0.85 was maintained for predicting patients less likely to develop relapsing disease using features identifiable at 1st clinical presentation (male sex, spinal cord involvement, steroids ≥1 month).

Visual disability (VA≤6/36) in at least one eye was observed in 17% of the total cohort, comparable to rates of 13% and 17% from other studies.[1,6] In the multivariable analysis, spinal cord onset was associated with a better visual prognosis at follow-up. This relates to less optic nerve involvement in these cases but there was also a trend towards better visual outcome in patients presenting with transverse myelitis with subsequent optic nerve involvement. Further exploration of this finding in a larger dataset would be of interest. Spinal cord involvement in MOGAD is frequently associated with residual bladder, bowel and erectile dysfunction and the former was present in around a third of patients in this study.[1,13] As expected, in the univariable analysis transverse myelitis was also associated with an EDSS>3 at long term follow-up. Comparable to the 33% and 24% of patients presented here, 27% of a total MOGAD cohort and 22% of an incident cohort had an EDSS≥3 in 2 large French studies.[2,6] Several factors of interest were identified in univariable but not multivariable analyses of visual disability (relapsing disease, number of relapses, and a history of bilateral optic neuritis) and overall disability (number of relapses and spinal cord involvement) that could be explored further.

In this study we were able to analyse the longitudinal profile of patients in relation to MOG-Ab serostatus. MOG-Abs became negative in 45% of cases which is higher than rates reported in other studies of MOGAD, particularly adults (28-57%).[1,6,14] This finding may relate to longer follow-up times; the median time to negative serostatus in this study was almost 3 years. Although final MOG-Ab serostatus was not associated with a relapsing disease course, longitudinal analysis of serostatus showed a reduction of 4% to 0.5% in monthly relapse risk with MOG-Ab negative serostatus. Only 1 patient relapsed within 6 months of a negative MOG-Ab assay. These findings support the prognostic value of serial antibody testing and consideration of MOG-Ab serostatus in long term treatment decisions.

This study benefited from the national catchment of patients across the UK that were followed in a single centre but is not without limitation. As with previous studies, higher relapse rates were observed in the total cohort as compared to incident cases. In particular, childhood onset patients had higher rates of disability with longer follow-up duration due to follow-up bias. In addition, relapsing patients had a longer duration follow-up as compared to monophasic cases. With a larger incident cohort, a separate analysis could have been performed to address this. However, prognostic factors related to male sex, onset attack topography, onset attack treatment, and MOG-Ab serostatus were less likely to be influenced by these differences and are the key findings of this study. Importantly subgroup analyses were performed to assess for the impact of differences in disease duration and were factored into data interpretation. In this study we defined MOGAD on the basis of serum MOG-Abs rather than serum and CSF. Intrathecal synthesis of MOG-Ab has been reported and it would be interesting to explore this further in a prospective study that includes CSF analysis.[15] In a specialised centre referral bias towards a more severe relapsing disease is also a likely factor, though similar numbers of relapsing and monophasic patients were present overall making group comparisons possible. As with all observational studies the results of the analyses do not hold the same weight as those of randomised controlled studies. In particular, for the analysis of observational datasets, the onus is on accounting for possible confounding when drawing conclusions on possible causal effects. While multivariable modelling is a powerful tool in adjudging for possible confounding, the impact of conclusions is given further weight by external validation against a new dataset and will be the focus of future research.

In summary we have identified that male patients with spinal cord involvement at disease onset have a lower risk of relapsing disease and longer latency to 1st relapse. Steroid treatment for at least 1 month at disease onset was also associated with a monophasic disease course. MOG-

Ab negative seroconversion was associated with a lower risk of relapse and may help inform treatment decisions and duration.

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Patient consent: All patients provided written informed consent.

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Figure 1. Kaplan-Meier analysis of relapse probability and sex

Figure 2. Kaplan-Meier analysis of relapse probability and transverse myelitis

Figure 3. Clinical attacks and longitudinal MOG-Ab serostatus

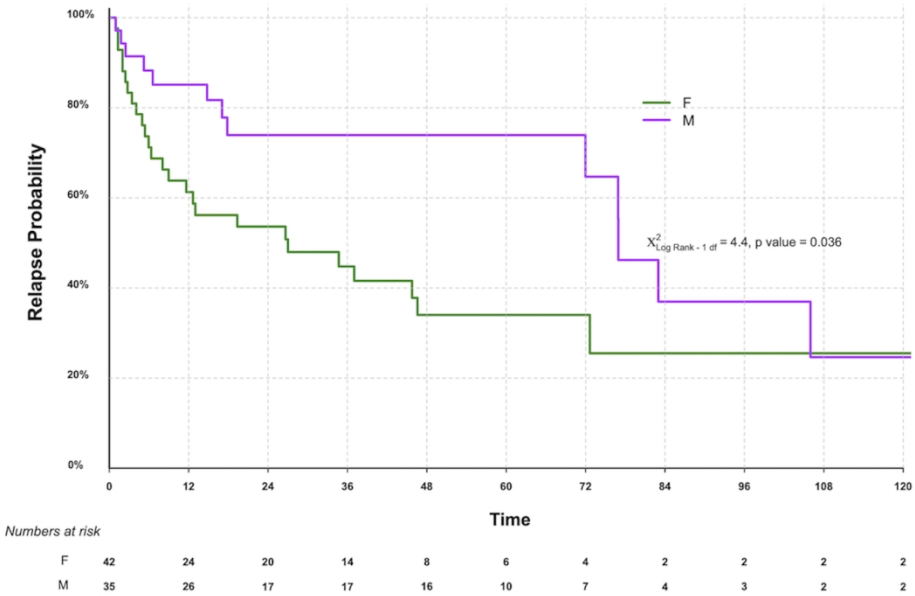

Figure 1. Kaplan-Meier analysis of relapse probability and sex

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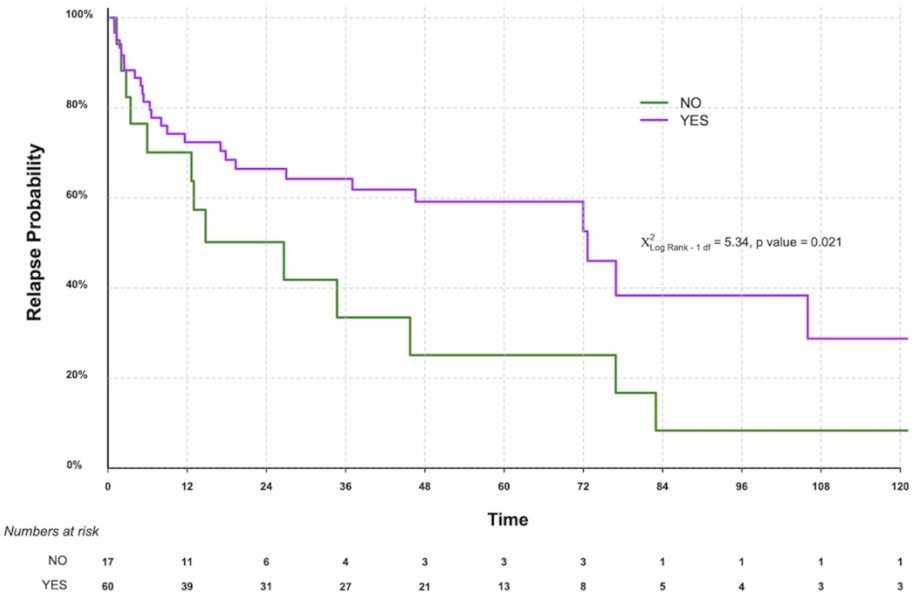

Figure 2. Kaplan-Meier analysis of relapse probability and transverse myelitis

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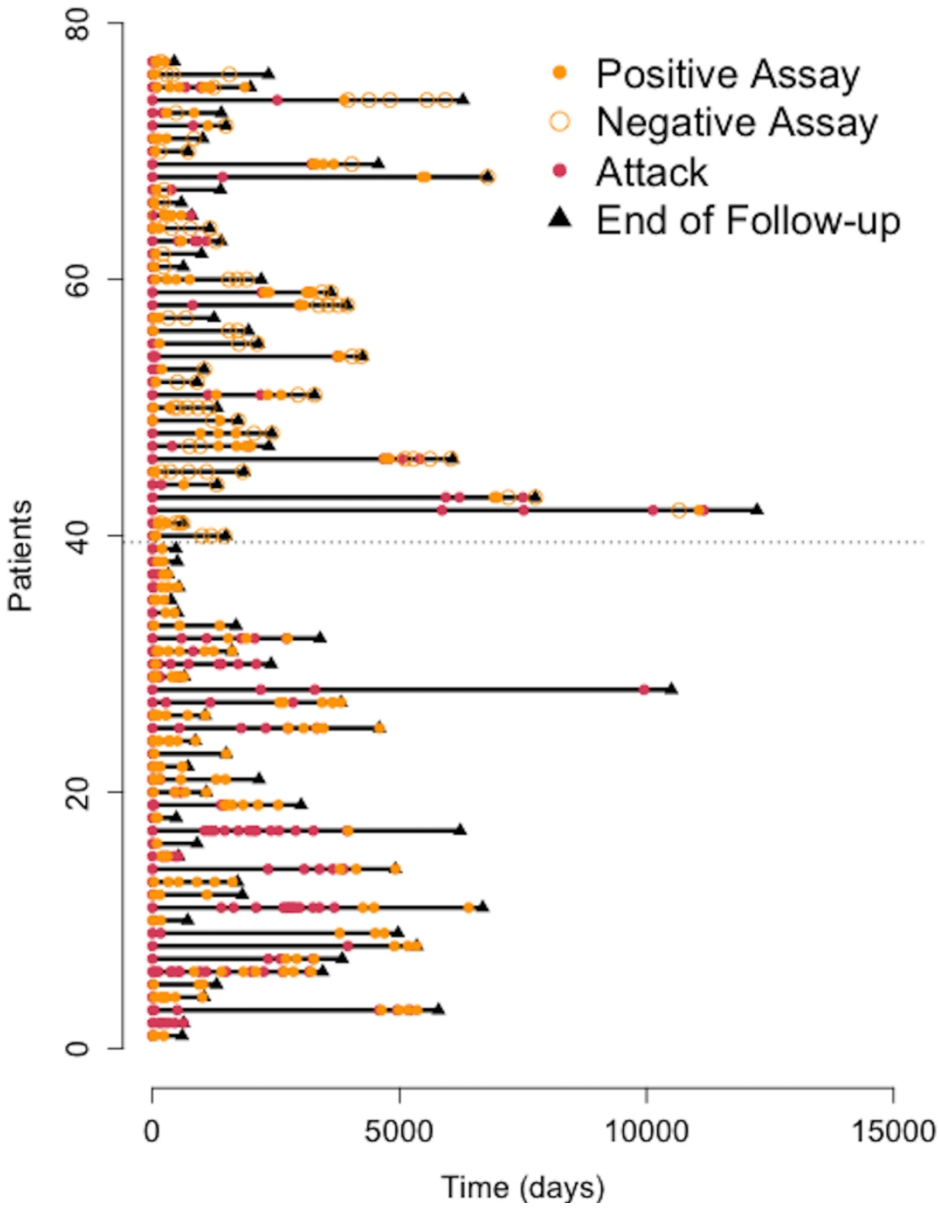

Figure 3. Clinical attacks and longitudinal MOG-Ab serostatus

230x293mm (300 x 300 DPI)

Supplementary material

Supplementary Figure 1. Geographical spread of patients with myelin oligodendroctye glycoprotein antibody associated disease.

	VA≤6/36 at f/u=13	VA>6/36at f/u= 61	p-value	EDSS≥3 at f/u= 25	EDSS<3 at f/u= 50	p-value	MOG-Ab persistent (+)=39	MOG-Ab negative at f/u=32	p-value
Demographics % (n/total)									
Female (%)	54 (7/13)	53 (32/61)	1	60 (15/25)	62 (25/50)	0.463	54 (21/39)	56 (18/32)	1.00
White (%)	100 (13/13)	92 (56/61)	0.579	96 (24/25)	92 (46/50)	0.658	90 (35/39)	97 (31/32)	0.370
1st attack characteristics % (n/total)									
Median onset age years (IQR)	24 (11-38)	33 (20-45)	0.031†	29 (16-51)	30 (23-41)	0.940	29 (17-44)	29 (19-47)	0.985†
Age≤16yrs at onset	46 (6/13)	12 (7/61)	0.008*	32 (8/25)	10 (5/50)	0.025	15 (6/39)	22 (7/32)	0.547
ADEM	15 (2/13)	5 (3/58)	0.210	4 (1/25)	8 (4/50)	0.658	8 (3/39)	6 (2/32)	0.168
ON	69 (9/13)	51 (36/61)	0.550	52 (13/25)	64 (32/50)	0.331	64 (25/39)	50 (16/32)	0.334
bON	46 (6/13)	34 (21/61)	0.530	32 (8/25)	38 (19/50)	0.792	44 (17/39)	22 (7/32)	0.078
TM	8 (1/13)	49 (30/61)	0.006*	40 (10/25)	42 (21/50)	1.00	31 (12/39)	59 (19/32)	0.018*
LETM	0 (0/13)	33 (20/61)	0.015*	32 (8/25)	24 (12/50)	0.581	21 (8/39)	38 (12/32)	0.184
ON+TM	8 (1/13)	20 (12/61)	0.442	8 (2/25)	22 (11/50)	0.196	15 (6/39)	22 7/32)	0.547
Brain involvement	31 (4/13)	23 (14/61)	0.722	32 (8/25)	26 (13/50)	0.596	31 (12/39)	22 (7/32)	0.433
≥2 CNS sites	15 (2/13)	26 (16/61)	1.00	20 (5/25)	26 (13/50)	0.777	21 (8/39)	29 (9/32)	0.578
Infective trigger	0 (0/3)	44 (7/16)	0.540	25 (2/8)	26 (5/19)	1.00	15 (2/13)	62 (8/13)	0.041*
EDSS≥4 at nadir	46 (6/13)	53 (32/61)	0.765	67 (16/24)	46 (23/50)	0.221	55 (21/38)	56 (18/32)	1.00
EDSS≥4 6m	15 (2/13)	15 (9/61)	1.00	40 (10/25)	2 (1/50)	-	13 (5/39)	16 (5/32)	0.460
Treatment	69 (9/13)	80 (49/61)	0.460	84 (21/25)	74 (37/50)	0.393	74 (29/39)	84 (27/32)	1.00
Steroids≥1m	27 (3/11)	61 (37/61)	0.052	52 (13/25)	55 (27/49)	1.00	55 (21/38)	53 (17/32)	1.00
Steroids≥3m	27 (3/11)	46 (28/61)	0.331	52 (13/25)	37 (18/49)	0.222	40 (15/38)	44 (14/32)	0.809
non-steroid IS	8 (1/13)	13 (8/60)	1.00	16 (4/25)	10 (5/49)	0.472	8 (3/39)	19 (6/32)	0.282
Comparison % (n/total)									
Relapsing	92 (12/13)	46 (28/61)	0.002*	72 (18/25)	46 (23/50)	0.043	62 (24/39)	44 (14/32)	0.157
Relapse<12m	33 (4/12)	57 (16/28)	0.301	28 (7/25)	28 (14/50)	1.00	63 (15/24)	36 (5/14)	0.179
>2 attacks	83 (10/12)	57 (16/28)	0.157	52 (13/25)	26 (13/50)	0.039	71 (17/24)	50 (7/14)	0.298
>3 attacks	83 (10/12)	29 (8/28)	0.002*	67 (12/18)	12 (6/50)	0.000*	50 (12/24)	14 (2/14)	0.039*
Median ARR (range)	0.65 (0.08-1.4)	0.38 (0.07-5.43)	0.789†	0.6 (0.07-5.43)	0.037 (0.1-3.4)	0.392	0.66 (0.32-5.43)	0.37 (0.07-1.68)	0.040†
ADEM ever	15 (2/13)	5 (3/61)	0.210	4 (1/25)	8 (4/50)	0.658	8 (3/39)	6 (2/32)	1.00
ON ever	100 (13/13)	69 (42/61)	0.059	72 (18/25)	76 (38/50)	0.787	74 (29/39)	72 (23/32)	1.00

bON ever	77 (10/13)	43 (26/61)	0.033*	52 (13/25)	46 (23/50)	0.63	54 (21/39)	34 (11/32)	0.150
TM ever	62 (8/13)	56 (34/61)	0.766	77 (19/25)	46 (23/50)	0.01	54 (21/39)	66 (21/32)	0.343
LETM ever	15 (2/13)	36 (22/61)	0.201	44 (11/25)	26 (13/50)	0.12	31 (12/39)	28 (12/32)	0.619
ON+TM ever	62 (8/13)	34 (21/61)	0.116	48 (12/25)	34 (17/50)	0.31	41 (16/39)	41 (13/32)	1.00
Brain involvement ever	46 (6/13)	30 (18/61)	0.329	32 (8/25)	34 (17/50)	1.00	44 (17/39)	25 (8/32)	0.136
>1 CNS site ever	77 (10/13)	49 (30/61)	0.123	64 (16/25)	50 (25/50)	0.32	62 (24/39)	53 (17/32)	0.630
Other Abs present (e.g., ANA, ENA)	30 (3/10)	14 (8/56)	0.351	16 (4/25)	17 (7/42)	1.00	21 (7/33)	10 (3/30)	0.308
MRI brain abnormality	54 (7/13)	47 (28/60)	0.763	48 (12/25)	47 (23/49)	1.00	55 (21/38)	41 (13/32)	0.241
MRI spine abnormality	69 (9/13)	61 (34/56)	0.753	76 (19/25)	53 (24/45)	0.09	63 (22/35)	68 (21/31)	0.797
CSF Protein median (range)	0.52 (0.3-1.25)	0.45 (0.16-1.27)	0.714†	0.90 (0.3-1.66)	0.4 (0.16-2.27)	0.029*	0.48 (0.16-2.27)	0.38 (0.18-1.61)	0.337†
CSF WBC median (range)	1 (0-4)	22 (0-937)	0.059†	4 (0-937)	23 (0-550)	0.020*	10 (0-937)	8.5 (0-221)	0.959†
Unmatched oligoclonal bands	0 (0/6)	8 (3/39)	1.00	6 (1/25)	4 (2/50)	1.00	8 (2/20)	4 (1/24)	0.58
At follow-up % (n/total)									
VA≤6/36 in at least one eye at fu	-	-	-	44 (11/25)	4 (2/49)	0.000*	21 (8/39)	3 (1/30)	0.067
EDSS≥4 at fu	39 (5/13)	16 (10/61)	0.122	58 (14/25)	-	-	21 (8/39)	19 (6/32)	1.00
EDSS≥3 at fu	85 (11/13)	23 (14/61)	<0.0001*	-	-	-	31 (12/39)	34 (11/32)	0.802
Bladder dysfunction	31 (4/13)	31 (19/61)	1.00	56 (14/25)	20 (10/50)	0.003	26 (10/39)	44 (14/32)	0.134
Urinary catheter use	23 (3/13)	17 (10/60)	0.690	48 (12/25)	2 (1/49)	0.000	13 (5/39)	25 (8/32)	0.227
Bowel dysfunction	8 (1/13)	23 (14/61)	1.00	40 (10/25)	10 (5/50)	0.003	18 (7/39)	28 (9/32)	0.395
Erectile dysfunction	0 (0/6)	26 (7/27)	0.301	22 (2/9)	21 (5/24)	1.00	12 (2/17)	36 (5/14)	0.198
Current smoker	29 (2/7)	15 (8/53)	0.330	19 (4/21)	15 (6/41)	0.72	15 (5/33)	14 (4/28)	1.00
Median f/u duration months (IQR)	161 (95-212)	43 (23-75)	<0.0001†*	79 (41-194)	44 (23-77)	0.004	49 (21-113)	53 (34-115)	0.275†
Treatment % (n/total)									
Prednisolone monotherapy	0 (0/13)	3 (2/61)	1.00	4 (1/25)	2 (1/50)	1.00	3 (1/39)	3 (1/32)	1.00
Prednisolone + other IS	46 (6/13)	18 (11/61)	0.063	32 (8/25)	18 (9/50)	0.24	28 (11/39)	16 (5/32)	0.260
Azathioprine	8 (1/13)	8 (5/61)	1.00	4 (1/25)	10 (5/50)	0.65	10 (4/39)	6 (2/32)	0.684

Mycophenolate mofetil	39 (5/13)	20 (12/61)	0.160	32 (8/25)	18 (9/50)	0.242	26 (10/39)	13 (4/32)	0.234
Rituximab	15 (2/13)	2 (1/61)	0.078	8 (2/25)	2 (1/50)	0.258	5 (2/39)	6 (2/32)	1.00
IVIg	15 (2/13)	0 (0/61)	0.029*	16 (4/25)	0 (0/50)	0.010*	10 (4/39)	0 (0/39)	0.115
Tocilizumab	0 (0/13)	2 (1/61)	1.00	0 (0/25)	2 (1/50)	1.00	3 (1/39)	0 (0/32)	1.00
No IS	23 (3/13)	66 (40/61)	0.011*	44 (11/25)	66 (33/50)	0.196	33 (19/39)	72 (23/32)	0.057
MOG-Ab									
No of patients MOG-Ab(+) at last review	11 (1/13)	48 (29/60)	0.011*	48 (11/23)	44 (21/48)	0.802	-	-	
Median no of samples (IQR)	3 (1.3-3.8)	4 (3-6)	0.03†	3.5 (2.3-5)	3 (2.8-6)	0.799	3 (3-6)	4 (3-6)	0.563†
Median time between 1st and last sample (IQR)/months	36 (18-65)	29.5 (15.3-45.5)	0.193†	35 (19-47)	28 (7.8-43.8)	0.282	29 (10-40)	29.5 (21-53.8)	0.174†
Median time to MOG-IgG(-) months (IQR)	48*	34 (9.5-103)	-	48 (14-132)	34 (7-103)	0.293	-	38 (9.3-106.5)	-
Relapses whilst MOG-Ab negative	0 (0/1)	7 (2/29)	1.00	9 (1/11)	5 (1/21)	1.00	-	3 (1/32)	-

Supplementary table 1. Univariate analysis of visual outcome, overall disability, and MOG-Ab serostatus. VA; visual acuity, MOG-Ab; myelin oligodendrocyte glycoprotein antibodies, ADEM; acute disseminated encephalomyelitis, ON; optic neuritis, bON; bilateral ON, TM; transverse myelitis, LETM; longitudinally extensive TM, CNS; central nervous system, EDSS; expanded disability status score, IS; immunosuppression, ARR; annualised relapse rate, NMOSD; neuromyelitis optica spectrum disorder, IPND; international panel for NMOSD diagnosis, Abs; antibodies, IVIg; intravenous immunoglobulin, †; Mann-Whitney U test, *; $p<0.05$.

	Relapse (any time)			VA≤6/36			Time between 1st and 2nd Attack		
	est (se)	Odds ratio (95% CI)	P-value	est (se)	Odds ratio (95% CI)	P-value	est (se)	Hazard ratio (95% CI)	p-value
(Intercept)	5.26 (1.5)	-	<0.001*	-0.95 (0.34)	-	0.005*	-	-	-
Steroids 1m	-1.59 (0.695)	0.2 (0.05, 0.80)	0.022*	-	-	-	-	-	-
TM w/ 1st attack	-3.51 (1.032)	0.03 (0.00, 0.23)	0.001*	-2.45 (1.072)	0.09 (0.01, 0.70)	0.022*	-0.86 (0.34)	0.42 (0.22, 0.82)	0.011*
Age	-0.08 (0.028)	0.93 (0.88, 0.98)	0.005*	-	-	-	-	-	-
ON/TM	2.53 (0.989)	12.54 (1.81, 87.17)	0.011*	-	-	-	-	-	-
SexM	-1.86 (0.754)	0.16 (0.04, 0.68)	0.014*	-	-	-	-0.78 (0.34)	0.46 (0.24, 0.89)	0.011*
AUC	-	0.98	-	-	-	-	-	-	-

Supplementary table 2. Multivariable and ROC analysis. VA; visual acuity, CI; confidence interval, m; month, ON; optic neuritis, TM; transverse myelitis, M; male, AUC; area under the curve, *; p<0.05.

	Est (se)	RR (95% CI)	P-value
(Intercept)	-3.3 (0.175)	0.04 (0.026-0.052	<0.001*
MOG-Ab negativity	-2.19 (0.429)	0.11 (0.048-0.259	<0.001*

Supplementary table 3. Results of Poisson regression model and MOG-Ab negativity. MOG-Ab; myelin oligodendrocyte glycoprotein antibody, CI; confidence interval, *; p<0.05.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abst
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine sub ups and interactions
		(*c*) Explain how missing data were addres
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addresse *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Predictors of relapse in MOG antibody associated disease- a cohort study

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Title- Predictors of relapse in MOG antibody associated disease- a cohort study

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Abstract

Objective To identify factors predictive of relapse risk and disability in myelin oligodendrocyte glycoprotein associated disease (MOGAD).

Setting Patients were seen by the neuromyelitis optica spectrum disorders (NMOSD) service in Liverpool, UK, a national referral centre for adult patients with MOGAD, NMOSD and related conditions.

Participants MOGAD patients=76 from England, Northern Ireland and Scotland were included in this cohort study.

Results Relapsing disease was observed in 55% (42/76) of cases. Steroid treatment ≥1 month (OR 0.2, 95%CI: 0.05-0.80; p=0.022), transverse myelitis (TM) at 1st attack (OR 0.03, 95%CI: 0.004- 0.23; p=0.001), and male sex (OR 0.16, 95%CI: 0.04-0.68; p=0.014) were associated with monophasic disease (AUC=0.85). Male sex (HR 0.46, 95%CI: 0.24-0.89; p=0.011) and TM at disease onset (HR 0.42, 95%CI: 0.22-0.82; p=0.011) were also associated with an increased latency to 1st relapse. Disappearance of MOG-Abs was observed in 45% (32/71) patients and in relapsing patients was associated with a lower relapse risk (RR 0.11 95%CI 0.05-0.26; p<0.001). No specific factors were predictive of visual or overall disability.

Conclusions Male patients with spinal cord involvement at disease onset have a lower risk of relapsing disease and longer latency to 1st relapse. Steroid treatment for at least 1 month with the 1st attack was also associated with a monophasic disease course. MOG-Ab negative seroconversion was associated with a lower risk of relapse and may help inform treatment decisions and duration.

Article Summary

Strengths and Limitations

- This UK cohort study of myelin oligodendrocyte glycoprotein associated disease (MOGAD) included 76 patients from England, Northern Ireland, and Scotland.

- Prognostic factors associated with relapsing disease and time to 1st relapse were assessed using univariable and multivariable modelling.
- The longitudinal impact of MOG antibody disappearance on relapse risk was analysed using a Poisson regression model.
- A limitation of this study was the shorter duration of follow-up in monophasic MOGAD patients.

INTRODUCTION

Myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) is associated with central nervous system inflammation, typically acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), transverse myelitis (TM), and brainstem inflammation.[1-7] In retrospective studies, a relapsing disease course has been reported in 27-80% of patients, which may over-report the proportion of relapsing patients by virtue of differential follow-up of monophasic versus relapsing patients.[1-5] Indeed in two studies using incident cohorts, rates of relapsing disease were at the lower end (27-36%).[1,2] Although MOGAD is associated with a better prognosis compared to neuromyelitis optica spectrum disorder (NMOSD), persistent visual, motor or sphincter disturbances have been reported.[1,7] These studies collectively support the presence of a subgroup of MOGAD patients with lower risk of relapse and minimal if any long-term disability. This has understandably led to equipoise amongst international experts on when to introduce chronic immunotherapy and the duration of treatment.[8] Identifying prognostic factors for risk of a) early relapse, b) any relapse, and c) permanent disability will help individualise MOGAD treatment.

Cohort description

Study design

All patients were seen by the NMOSD UK service at the Walton Centre NHS Foundation Trust in Liverpool, UK, a national referral centre for adult patients with NMOSD, MOGAD, and other non-multiple sclerosis atypical CNS inflammatory/demyelinating syndromes. Patients from England, Northern Ireland and Scotland were included.

Between January 2010 and January 2020, patients with an acute demyelinating syndrome, at least one serum MOG-IgG1 positive assay result, and a minimum of 12 months follow-up were included. Serum MOG-IgG1 Abs were detected using a live cell based assay employing full length human MOG (α1 isoform; Oxford Autoimmune Neurology Group).[9] The study was approved by the Research Ethics Service, NRES Committee London- Hampstead, Ref. no. 15/LO/1433. All patients provided written informed consent.

Demographic, clinical details of attacks, cerebrospinal fluid and MRI results, treatment, and longitudinal MOG-Ab results were collected. Childhood onset was defined as disease onset at age $\leq$16 years. Patients were considered 'monophasic' if no relapses were observed after the 1st clinical attack for the duration of follow-up (at least 12 months) and were compared to relapsing MOGAD patients. Patients where the diagnosis was made shortly after onset (< 6months) and prior to relapse were designated as 'incident' cases. The following outcomes were examined: 1) relapse at any time, 2) visual acuity $\leq$6/36 (one or both eyes at last follow-up), 3) time between 1st and 2nd attack, and 4) impact of MOG-Ab serostatus on relapse frequency.

Statistical Analysis

Continuous covariates are summarised as median (interquartile range) unless otherwise stated with categorical covariates summarised as frequencies with associated percentages. For comparisons of covariates across groups Fisher's exact tests and Mann-Whitney U-tests were applied for categorical and continuous data respectively.

To evaluate the impact of covariates on each endpoint, univariable and multivariable modelling were applied. Multivariable models for binary endpoints were constructed using a generalised linear model assuming a binomial distribution and a logistic link function and using a forward stepwise approach. Model evaluations were performed using Akaike Information Criterion (AIC). Model performance were assessed by comparing the linear predictors against the model outcome using Receiver Operating Curve (ROC) and Area Under the Curve (AUC). Model results are presented in terms of odds ratios with associated 95% confidence intervals. For the time-to-event outcome, estimates of the probability of relapse were obtained using the Kaplan Meier method. Univariable and multivariable analyses were performed using Cox proportional hazards models with an equivalent procedure used to evaluate univariate models and construct multivariable models. Results are presented in terms of hazard ratios with 95% confidence intervals. The longitudinal impact of MOG-Ab negativity on patient relapse was investigated using a random effects Poisson regression model. Here MOG-Ab negativity was included as a fixed effect and the time included in the model as a (log) offset. Patient identifier was included as a random effect. Results are presented as relative and absolute risk for observing a relapse with 95% confidence intervals. A threshold of $p<0.05$ was applied for statistical significance. All analyses were performed using R (Version 3).

Patient and public involvement

Clinical data from patients were included in this study. The development of the research question was driven by our patient's uncertainty over future relapse risk following a first presentation of MOGAD. The patients and public were not explicitly involved the design or conduct of this study. Results will be disseminated at the NMO UK patient day where patients, relatives, and caregivers will be in attendance.

RESULTS

Demographic features

We identified 76 MOGAD patients with a median onset age of 27 (IQR 19-45), 54% were female and 17% had disease onset in childhood (age ≤16years). The geographic distribution of patients is shown in supplementary figure 1. In total 42 relapsing patients (total no of relapses=140) and 34 monophasic patients were identified. The median time from 1st clinical attack to diagnosis in the incident cohort (n=38) was 1 month (IQR 0-2 months). The clinical profile of patients and respective univariable analyses are presented in Table 1 and supplementary Table 1.

Overall, there was a slight female predominance (54%) and although the proportion of male patients did not reach statistical significance in the univariable analysis, male sex was associated with a lower overall risk of relapsing disease (OR 0.16 95% CI: 0.04-0.68; p=0.014) and time to 1st relapse (HR 0.46 95% CI: 0.24-0.89; p=0.011) in multivariable analyses (Figure 1, Table 2 supplementary). The majority of patients (93%) were white; there were no racial differences between the groups. The median age of relapsing patients was lower than monophasic patients (26 (16-40) vs 37 (27-51) years; p=0.001). Development of MOGAD after the age of 16 years was associated with a lower risk of relapsing disease in the multivariable analysis (OR 12.54 (1.81-87.17; p=0.011), but 12/13 children had relapses, suggesting a bias towards follow-up of children into adulthood with relapsing disease.

	Relapsing=42	Monophasic=34	p-value	Incident cohort=38	Total cohort=76
Demographics (%)					
Female (%)	64 (27/42)	41 (14/34)	0.064	47 (18/38)	54 (41/76)
White (%)	98 (41/42)	88 (30/34)	0.166	87 (33/38)	93 (71/76)
Onset attack characteristics % (n/total)					
Median onset age years (IQR)	26 (16-40)	37 (27-51)	0.001†*	37 (27-45)	27 (19-45)
Age≤16yrs at onset	29 (12/42)	3 (1/34)	0.004*	3 (1/38)	17 (13/76)
ADEM	12 (5/42)	0 (0/34)	0.061	3 (1/38)	7 (5/76)
ON	62 (26/42)	59 (20/34)	0.817	50 (19/38)	61 (46/76)
bON	31 (13/42)	41 (14/34)	0.470	32 (12/38)	36 (27/76)
TM	26 (11/42)	62 (21/34)	0.002*	58 (22/38)	42 (32/76)
LETM	17 (7/42)	41 (14/34)	0.022*	40 (15/38)	28 (21/76)
ON+TM	14 (6/42)	24 (8/34)	0.377	21 (8/38)	18 (14/76)
Brain involvement	29 (12/42)	21 (7/34)	0.595	29 (11/38)	25 (19/76)
≥2 CNS sites	17 (7/42)	25 (12/34)	0.109	32 (12/38)	25 (19/76)
Infective trigger	8 (1/13)	40 (6/15)	0.084	35 (6/17)	25 (7/28)
EDSS≥3 at nadir	83 (33/40)	91 (31/34)	0.326	92 (35/38)	87 (64/74)
EDSS≥3 6m	17 (7/41)	27 (9/34)	0.400	24 (9/38)	21 (16/75)
Treatment (IS)	67 (28/42)	91 (31/34)	0.013*	87 (33/38)	68 (59/76)
Steroids≥1m	37 (15/41)	76 (25/33)	0.001*	70 (26/37)	38 (40/74)
Steroids≥3m	32 (13/41)	55 (18/33)	0.060	49 (18/37)	35 (31/74)
non-steroid IS	5 (2/42)	27 (7/33)	0.038*	19 (7/37)	12 (9/75)
Comparison % (n/total)					
Relapsing	-	-	-	18 (7/38)	55 (42/76)
Relapse<12m	52 (22/42)	-	-	86 (6/7)	29 (22/76)
≥3 attacks	62 (26/42)	-	-	43 (3/7)	34 (26/76)
≥4 attacks	43 (18/42)	-	-	1 (1/7)	24 (18/76)
Median ARR (range)	0.45 (0.07-5.43)	-	-	0.66 (0.18-2.04)	0.45 (0.07-5.43)
ADEM ever	15 (5/42)	0 (0/34)	0.061	3 (1/38)	7 (5/76)
ON ever	88 (37/42)	59 (20/34)	0.007*	55 (21/38)	75 (57/76)
bON ever	55 (23/42)	38 (13/34)	0.172	40 (15/38)	47 (36/76)
TM ever	52 (22/42)	62 (21/34)	0.488	61 (23/38)	57 (43/76)
LETM ever	29 (12/42)	38 (13/34)	0.064	40 (15/38)	33 (25/76)
ON+TM ever	50 (21/42)	27 (9/34)	0.058	26 (10/38)	39 (30/76)
Brain involvement ever	41 (17/42)	24 (8/34)	0.150	32 (12/38)	33 (25/76)
>1 CNS site ever	67 (28/42)	41 (14/34)	0.597	45 (17/38)	55 (42/76)
Other Abs present (e.g., ANA, ENA)	16 (6/38)	18 (5/28)	1.00	19 (6/32)	17 (11/66)
MRI brain abnormality	50 (20/40)	44 (15/34)	0.647	47 (18/38)	47 (35/74)
MRI spine abnormality	56 (23/41)	69 (20/29)	0.325	67 (22/33)	61 (43/70)
CSF Protein median (range)	0.47 (0.18-2.27)	0.44 (0.16-1.66)	0.954†	0.43 (0.16-1.66)	0.45 (0.16-2.27)
CSF WBC median (range)	2.5 (0-550)	30 (0-937)	0.008†*	25 (0-937)	10 (0-937)
Unmatched oligoclonal bands	7 (2/28)	6 (1/17)	1.00	14 (3/22)	7 (3/45)

At follow-up % (n/total)					
VA≤6/36 in at least one eye at fu	30 (12/40)	3 (1/34)	0.002*	3 (1/37)	18 (13/74)
EDSS≥4 at last FU	22 (9/41)	15 (5/34)	0.555	16 (6/38)	19 14/75)
EDSS≥3 at last FU	44 (18/41)	21 (7/34)	0.049*	24 (9/38)	33 (25/75)
Bladder dysfunction	32 (13/41)	33 (11/34)	1.00	34 (13/38)	32 (24/75)
Urinary catheter use	15 (6/41)	21 (7/33)	0.545	19 (7/37)	18 (13/74)
Bowel dysfunction	12 (5/41)	29 (10/34)	0.084	26 (10/38)	20 (15/75)
Erectile dysfunction	7 (1/14)	32 (6/19)	0.195	30 (6/20)	21 (7/33)
Current smoker	26 (9/35)	4 (1/27)	0.030*	9 (3/32)	16 (10/62)
Median FU/months (IQR)	107 (44-162)	33.5 (20-56)	<0.001†*	35 (12-77)	49 (28-113)
Treatment % (n/total)					
Prednisolone monotherapy	0 (0/42)	6 (2/34)	0.197	5 (2/38)	3 (2/76)
Prednisolone + other IS	36 (15/42)	6 (2/34)	0.002*	13 (5/38)	22 (17/76)
Azathioprine	12 (5/42)	3 (1/34)	0.216	3 (1/38)	8 (6/76)
Mycophenolate mofetil	33 (14/42)	9 (3/34)	0.013	18 (7/38)	22 (17/76)
Rituximab	7 (3/42)	0 (0/34)	0.248	0 (0/38)	4 (3/76)
IVIg	10 (4/42)	0 (0/34)	0.123	0 (0/38)	5 (4/76)
Tocilizumab	2 (1/42)	0 (0/34)	1.00	0 (0/38)	1 (1/76)
No IS	21 (16/42)	82 (28/34)	<0.001*	74 (28/38)	58 (44/76)
MOG-Ab					
No of patients MOG-Ab(+) at last review	62 (24/39)	47 (15/32)	0.229	51 (19/37)	55 (39/71)
Median no of samples (IQR)	4 (3-6)	3 (2-5.5)	0.407†	3 (3-6)	3 (3-6)
Median time between 1st and last sample/months (IQR)	30 (15.8-43.3)	29.5 (6.3-47)	0.782†	28 (6.5-46.5)	30 (15-46)
Median time to MOG-IgG(-) months (IQR)	103 (30.3-132)	12 (6-50)	0.003†*	11 (7-33)	34 (9-96)
Relapses (within 6 months) of MOG-Ab negative	2 (1/42)	-	-	14 (1/7)	1 (1/76)

Table 1. Univariate analysis of relapsing and monophasic patients with myelin oligodendrocyte glycoprotein antibody associated disease. ADEM; acute disseminated encephalomyelitis, ON; optic neuritis, bON; bilateral ON, TM; transverse myelitis, LETM; longitudinally extensive TM, CNS; central nervous system, NMOSD; neuromyelitis optica spectrum disorder, IPND; international panel for NMOSD diagnosis, Abs; antibodies, VA; visual acuity, EDSS; expanded disability status score, ARR; annualised relapse rate, IS; immunosuppression, IVIg; intravenous immunoglobulin, FU; follow-up, †; Mann-Whitney U-test, *; P<0.05.

Clinical course

Relapsing disease was observed in 18% of incident cases and 55% of the total cohort with a median time to first relapse of 11.5 (IQR 3-46) months. A survival analysis for time to 1st

relapse between the incident and total cohort is presented in Supplementary Figure 2. The most common first clinical presentations were optic neuritis (ON; 61%), transverse myelitis (TM; 42%), and bilateral ON (36%); (Table 1). TM and longitudinally extensive transverse myelitis (LETM) were more frequently part of the 1st clinical attack in monophasic patients (62% vs 26%, p=0.002 and 41% vs 17%; p=0.022 respectively). In multivariable analysis, TM with a 1st attack was associated with a lower overall risk of relapse (OR 0.03, 95% CI: 0.00-0.23; p=0.001) and a longer time to 1st relapse (HR 0.42 95%CI: 0.22-0.82; p=0.011; Figure 2 and Table 2 supplementary). Importantly although median follow up duration was longer in relapsing as compared to monophasic patients (107 (44-162) vs 33.5 (20-56) months; p<0.001)), the median follow-up times of these groups of patients with TM specifically were similar (35 (26-62) vs 55 (43-113); p=0.11). In addition, there was no difference in use of steroids>1m in those patients presenting with or without TM (59% vs 50%; p=0.485).

Simultaneous ON+TM at any point was associated with a greater risk of relapsing disease (OR: 12.54 (1.81-87.17); p=0.011), but follow-up duration was shorter in these patients with monophasic disease (p=0.018). The proportion of patients presenting with bilateral optic neuritis and multi-CNS site involvement were similar between relapsing and monophasic groups. Three patients presented with encephalitis and seizures, all of whom had a relapsing disease course. EDSS at nadir and 6 months after 1st attack were similar in monophasic and relapsing patients. Preceding infective symptoms were more frequent in monophasic patients, but the results did not reach statical significance (40% vs 8%; p=0.084).

Overall, more than 2 and 3 attacks were observed in 34% (26/76) and 24% (18/76) of patients respectively. Only 18% of incident cases relapsed and 86% of first relapses occurred within 12 months of the first attack. Follow-up duration was shorter in the incident cohort as reflected in the higher annualised relapse rate in these patients as compared to the total cohort (0.66 (0.18-2.04 vs 0.45 (0.07-5.43). Smoking was more frequently noted at follow-up in relapsing patients

(26% vs 4%; p=0.030) but median ARR in smokers was similar to non-smokers in the incident MOGAD patients (p=0.533). The most common CNS sites involved in attacks were the optic nerve (57/76; 75%), spinal cord (43/76; 57%), or simultaneous involvement of both these sites (30/76; 39%). The site of CNS involvement was similar between relapsing and monophasic groups with the exception of optic neuritis, which was more common in relapsing patients (88% vs 59%; p=0.007).

Paraclinical tests

In the total cohort MRI abnormalities in brain and spine were observed in 47% and 61% of cases respectively. The frequency of abnormalities on MRI brain (p=0.647) and spinal cord (p=0.325) were similar between relapsing and monophasic patients. CSF white cell count was higher in monophasic patients (p=0.008). Unmatched oligoclonal bands were seen in only 3/45 (7%) cases tested. Non-organ specific autoantibodies (e.g., antinuclear antigen, extractable nuclear antigen) were present in 16% of relapsing and 18% and monophasic patients. None of these variables maintained a significant association in multivariable analysis.

Treatment

Overall, 38% (40/74) of patients received steroid treatment for ≥1month and 12% (9/75) were commenced on non-steroid immunosuppression (IS) following the onset clinical attack. Both steroid treatment for ≥1month (76% vs 37%; p=0.001) and non-steroid IS (27% vs 5%; p=0.038) were associated with monophasic disease. In multivariable analysis, treatment of the 1st attack with steroids ≥1month was associated with a lower overall relapse risk (OR 0.2, 95% CI: 0.05-0.80; p=0.022, Table 2 supplementary). In keeping with current UK practice, steroids ≥1m were more frequently used in incident as compared to non-incident patients (70% vs 39%). Overall, 32/76 (42%) of MOGAD patients received long term IS, and of these patients 26 (81%) had relapsing disease. In order of frequency, the most commonly used non-steroid

immunosuppressants were mycophenolate mofetil (22%) and azathioprine (8%). IVIg (5%), rituximab (4%), and tocilizumab (1%) were used as second- and third-line therapies. In 22% of patients, maintenance prednisolone (5-15mg/day) was combined with non-steroid immunosuppression.

An evaluation of the multivariable model to describe monophasic patients was performed using ROC analysis with the following factors- age≥16 years, male sex, TM at onset, steroids ≥1month. Using the linear predictor from the fitted model, an area under the curve of 0.92 was achieved. However, in view of the observer bias relating to age at disease onset, this variable was removed and a high AUC of 0.85 was maintained.

Long term outcome

Poor visual outcome defined by a visual acuity of ≤6/36 in at least one eye at last review was observed in 18% (13/74) of patients after a median of 13.5 years follow-up (Table 1 supplementary). Of those with poor visual outcome, 85% (11/13) had an EDSS ≥3 and 39% (5/13) had an EDSS ≥4. Permanent visual disability was more common in relapsing MOGAD (30% vs 3%; p=0.002) and median follow up duration in these patients was longer (median 161 vs 43 months; p<0.0001). Interestingly patients presenting with TM or LETM at 1st attack were less likely to develop optic nerve involvement (53% vs 91%; p=0.0003 and 38% vs 89%; p=0.0001 respectively) and had a better visual prognosis (49% vs 8%; p=0.006 and 33% vs 0%; p=0.015 respectively, Table 1 supplementary). In the multivariable analysis, TM with the 1st MOGAD clinical attack was associated with a favourable visual prognosis (OR 0.09 (0.01-0.70); p=0.022, Table 2 supplementary). To determine whether this simply reflected less optic nerve involvement in patients with TM at onset we analysed onset TM patients with subsequent ON attacks (17/32; 53%) and the remaining patients that developed ON only after first attack (12/30; 40%). Although the results were not significant, there was a trend towards better

visual outcome in patients that presented with TM and had subsequent optic nerve involvement (6% versus 36%; p=0.06).

Patients with relapsing disease (92% vs 46%; p=0.002), >3 relapses (83% vs 29%; p=0.002), or a history of bilateral ON (77% vs 43%; p=0.033) had worse visual outcomes but these factors and others (MOG-Ab seronegative status and long term IS) did not maintain a significant association in multivariable analysis. A visual acuity ≤6/36 in at least one eye at last review was more frequently observed with childhood onset MOGAD (46% vs 12%; p=0.008). As with findings related to higher relapse rate, this observation likely relates to preferential follow-up of children with more severe disease.

An EDSS≥3 was recorded in 33% (25/76) of patients at last review after a median of 6.6 years follow-up. Follow-up duration was longer in patients with an EDSS≥3 (median 79 vs. 44 months; p=0.004). Approximately a third of relapsing and monophasic patients had bladder dysfunction at last review. Rates of bowel and erectile dysfunction were not significantly different between relapsing and monophasic patients. Patients who received IVIg had worse EDSS (and visual) scores at follow-up due to refractory relapsing clinical disease with severe disability prior to treatment commencement. No clinical feature was associated with overall disability (EDSS≥3) in multivariable analysis.

MOG-Ab serostatus

In total 71 patients had more than 1 serum sample for MOG-Ab testing (Table 1). The median number of samples in relapsing and monophasic groups (4 (IQR: 3-6) vs 3 (IQR: 2-5.5); p=0.407) and patients with and without persistent MOG-Abs (3 (IQR: 3-6) vs 4 (IQR: 3-6); p=0.563) were similar (Tables 1 and 2 supplementary). The median time between 1st and last sampling (30 (15.8-43.3) vs 29.5 (21-53.8) months; p=0.782) was also similar.

Persistent MOG-Ab detection was observed in 55% (39/71) of patients. In 2 patients MOG-Ab serostatus was initially negative and then became positive. In 5 patients a fluctuating MOG-Ab serostatus was noted- following a positive MOG-Ab result 3 patients became transiently negative and then persistently positive and 2 patients became negative, positive and then persistently negative. The median time to negative MOG-Ab serostatus was 34 (9-96) months and as expected was shorter in the incident cohort (11 (7-33) months). The time interval was also shorter in the monophasic as compared to relapsing patient group (12 (6-50) vs 103 (30.3-132) months; p=0.003). Relapse within 6 months of a negative MOG-Ab assay was recorded in only 1 patient. Two further patients had a relapse after a negative result, but MOG-Ab testing was done more than 6 months prior to attack and undetected MOG-Ab positive seroconversion could not be excluded. Figure 3 summarises the longitudinal MOG-Ab serostatus in relation to clinical attacks.

To assess the impact of MOG-Ab serostatus on clinical course we first analysed the risk of relapsing disease in those patients who became seronegative. Patients that became MOG-Ab seronegative were just as likely to have had relapsing disease as those who remained MOG-Ab positive (45% vs 62%; p=0.229). To determine if longitudinal MOG-Ab serostatus influenced relapse rate we used a random effects Poisson regression model. The monthly risk of relapse was approximately 4% and reduced to 0.5% following MOG-Ab negative seroconversion (RR 0.11 (0.048-0.259); p<0.001, supplementary Table 3). Figure 2 illustrates clinical course of patients in relation to longitudinal MOG-Ab serostatus. Unfortunately, it was not possible to assess the impact of MOG titre on risk of relapsing and monophasic disease as these data were not available in all patients.

In univariable analysis, patients were more likely to become MOG-Ab negative if they presented with transverse myelitis (p=0.018), had an infective trigger (p=0.041), or had less 3 attacks (p=0.039) overall (Supplementary Table 1). A trend towards MOG-Ab negative

seroconversion was noted with long term immunosuppression (72% vs 33%; p=0.057) but no specific treatment was associated with a higher likelihood of subsequent negative MOG-Ab serostatus. Longitudinal MOG-Ab serostatus was not associated with overall disability (p=0.802) or visual disability (p=0.067). In the multivariable analysis, transverse myelitis at onset was associated with MOG-Ab negative seroconversion (OR 2.85 (1.11-7.30); p=0.029).

DISCUSSION

In this study that included myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) cases from across the UK, we found that male patients receiving ≥1 month of steroid treatment at disease onset and spinal cord involvement at 1st presentation had a lower risk of relapsing disease. A transition to MOG-antibody negative serostatus occurred in around half of patients and was associated with a lower risk of relapse. Spinal cord involvement at onset was associated with negative MOG-Ab seroconversion.

There is wide variation in the reported rates of relapsing MOGAD in retrospective cohorts (27-80%).[1-5] Unsurprisingly the highest proportion of relapsing disease has been observed in studies with longer follow-up duration. The stratification of relapse risk at disease onset is important when considering the long-term approach to MOGAD treatment. In this study we analysed relapsing and monophasic patients to identify prognostic factors related to relapse and disability. We also included an incident cohort analysis to assess for observer bias.

The clinical characteristics of these MOGAD patients were similar to previous reports, with relapsing disease observed in 55% of cases.[1-6,10] A relapse rate of 18% in incident cases was lower than other reported studies (27-36%).[1,2,6] It has been shown previously that the risk of relapse is highest in the first year and in this study only cases with at least 12 months follow-up were included.[1] Furthermore the median follow-up duration of incident cases was

almost 3 years though it is noteworthy that the risk of relapse in one study was 45% at 2 years and 62% at 5 years.[2]

We found that in male patients the time to 1st relapse was longer and the overall risk of relapsing disease was lower. This is similar to the findings of a recent large French study in childhood onset MOGAD.[6] The explanation for this finding is uncertain, particularly as unlike other autoimmune diseases such as neuromyelitis optica spectrum disorder, the female predominance in MOGAD is less marked.[7] In our cohort patients presenting with spinal cord involvement at disease onset had a lower risk of relapsing disease and a longer latency to 1st relapse, reproducing findings from an Indian cohort study.[5] Importantly relapsing and monophasic patients with spinal cord involvement at disease onset were treated similarly with regards to steroid taper and had similar disease duration. As has been previously reported, a prolonged steroid taper with a first MOGAD attack was associated with a lower risk of relapsing disease.[1,5,10] In keeping with UK recommendations for MOGAD treatment, a prolonged steroid taper was more frequently observed in the incident cases.[11] As mentioned previously, these cases were followed for a median of 3 years and the lower relapse rates (18%) in this cohort may relate to the use of corticosteroids but also to disease duration. Paradoxically and in contrast to the findings by Cobo Calvo et al., childhood onset disease was associated with relapsing disease and disability.[6] This finding is explained by the preferential follow-up of children with more severe MOGAD who transition into adult neurological services. Accordingly, this parameter was excluded from the ROC analysis but a high area under the curve of 0.85 was maintained for predicting patients less likely to develop relapsing disease using features identifiable at 1st clinical presentation (male sex, spinal cord involvement, steroids ≥1 month).

Visual disability (VA≤6/36) in at least one eye was observed in 17% of the total cohort, comparable to rates of 13% and 17% from other studies.[1,6] In the multivariable analysis,

spinal cord onset was associated with a better visual prognosis at follow-up. This relates to less optic nerve involvement in these cases but there was also a trend towards better visual outcome in patients presenting with transverse myelitis with subsequent optic nerve involvement. Further exploration of this finding in a larger dataset would be of interest. Spinal cord involvement in MOGAD is frequently associated with residual bladder, bowel and erectile dysfunction and the former was present in around a third of patients in this study.[1,12] As expected, in the univariable analysis transverse myelitis was also associated with an EDSS>3 at long term follow-up. Comparable to the 33% and 24% of patients presented here, 27% of a total MOGAD cohort and 22% of an incident cohort had an EDSS≥3 in 2 large French studies.[2,6] Several factors of interest were identified in univariable but not multivariable analyses of visual disability (relapsing disease, number of relapses, and a history of bilateral optic neuritis) and overall disability (number of relapses and spinal cord involvement) that could be explored further.

In this study we were able to analyse the longitudinal profile of patients in relation to MOG-Ab serostatus. MOG-Abs became negative in 45% of cases which is higher than rates reported in other studies of MOGAD, particularly adults (28-57%).[1,6,13] This finding may relate to longer follow-up times; the median time to negative serostatus in this study was almost 3 years. Although final MOG-Ab serostatus was not associated with a relapsing disease course, longitudinal analysis of serostatus showed a reduction of 4% to 0.5% in monthly relapse risk with MOG-Ab negative serostatus. Only 1 patient relapsed within 6 months of a negative MOG-Ab assay. These findings support the prognostic value of serial antibody testing and consideration of MOG-Ab serostatus in long term treatment decisions.

This study benefited from a nationwide catchment of patients across the UK that were followed in a single centre but is not without limitation. As with previous studies, higher relapse rates were observed in the total cohort as compared to incident cases. In particular,

childhood onset patients had higher rates of disability with longer follow-up duration due to follow-up bias. Monophasic patients were followed for a median of 3 years which is longer than the median time of 15.8 months to 1st relapse in a nationwide French study.[2] However, relapsing patients had a longer duration of follow-up as compared to monophasic cases. With a larger incident cohort, a separate analysis could have been performed to address this. However, prognostic factors related to male sex, onset attack topography, onset attack treatment, and MOG-Ab serostatus were less likely to be influenced by these differences and are the key findings of this study. Importantly subgroup analyses were performed to assess for the impact of differences in disease duration and were factored into data interpretation. In this study we defined MOGAD on the basis of serum MOG-Abs rather than serum and CSF. Intrathecal synthesis of MOG-Ab has been reported and it would be interesting to explore this further in a prospective study that includes CSF analysis.[14] In a specialised centre referral bias towards a more severe relapsing disease is also a likely factor, though similar numbers of relapsing and monophasic patients were present overall making group comparisons possible. As with all observational studies the results of the analyses do not hold the same weight as those of randomised controlled studies. In particular, for the analysis of observational datasets, the onus is on accounting for possible confounding when drawing conclusions on possible causal effects. While multivariable modelling is a powerful tool in adjudging for possible confounding, the impact of conclusions is given further weight by external validation against a new dataset and will be the focus of future research.

In summary we have identified that male patients with spinal cord involvement at disease onset have a lower risk of relapsing disease and longer latency to 1st relapse. Steroid treatment for at least 1 month at disease onset was also associated with a monophasic disease course. MOG-Ab negative seroconversion was associated with a lower risk of relapse and may help inform treatment decisions and duration.

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Figure 1. Kaplan-Meier analysis of relapse probability and sex

Figure 2. Kaplan-Meier analysis of relapse probability and transverse myelitis

Figure 3. Clinical attacks and longitudinal MOG-Ab serostatu

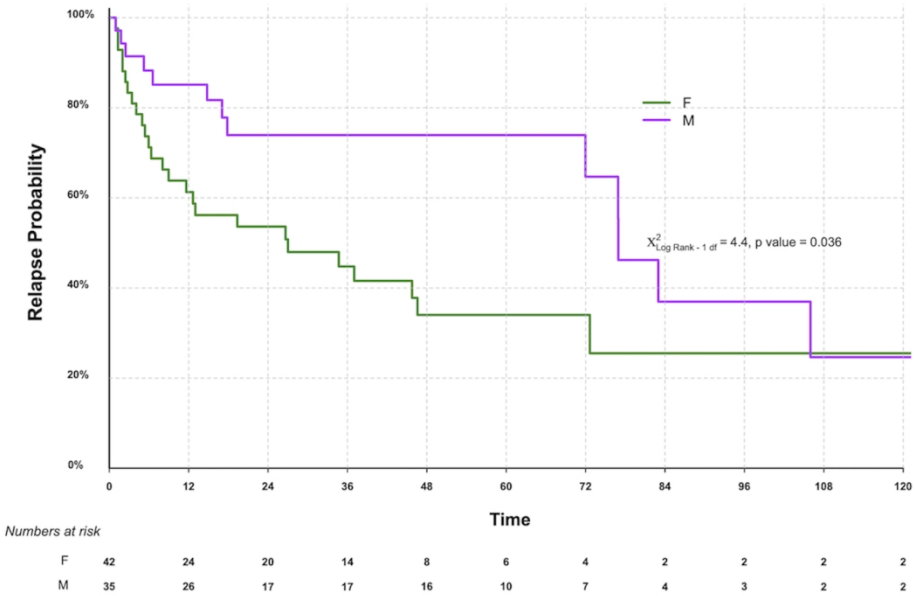

Figure 1. Kaplan-Meier analysis of relapse probability and sex

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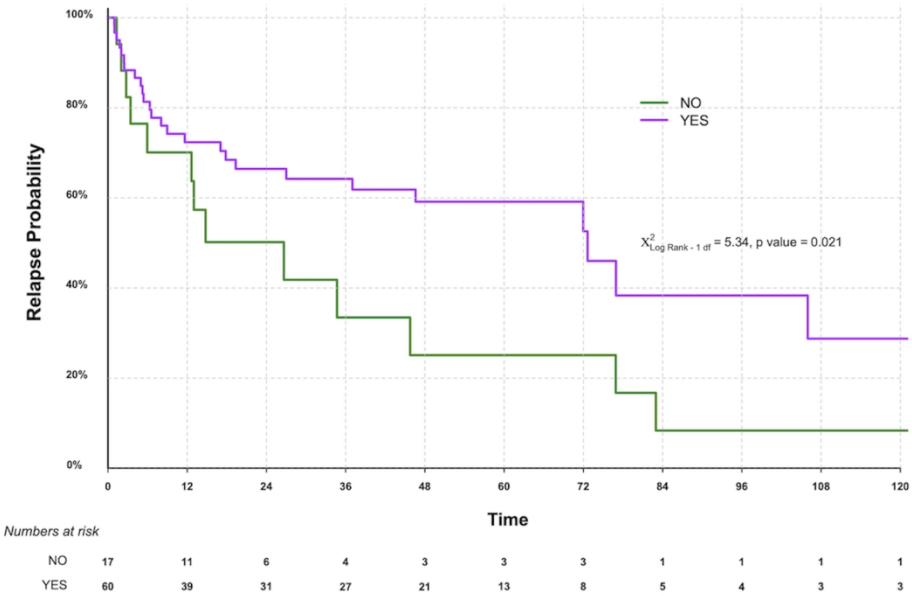

Figure 2. Kaplan-Meier analysis of relapse probability and transverse myelitis

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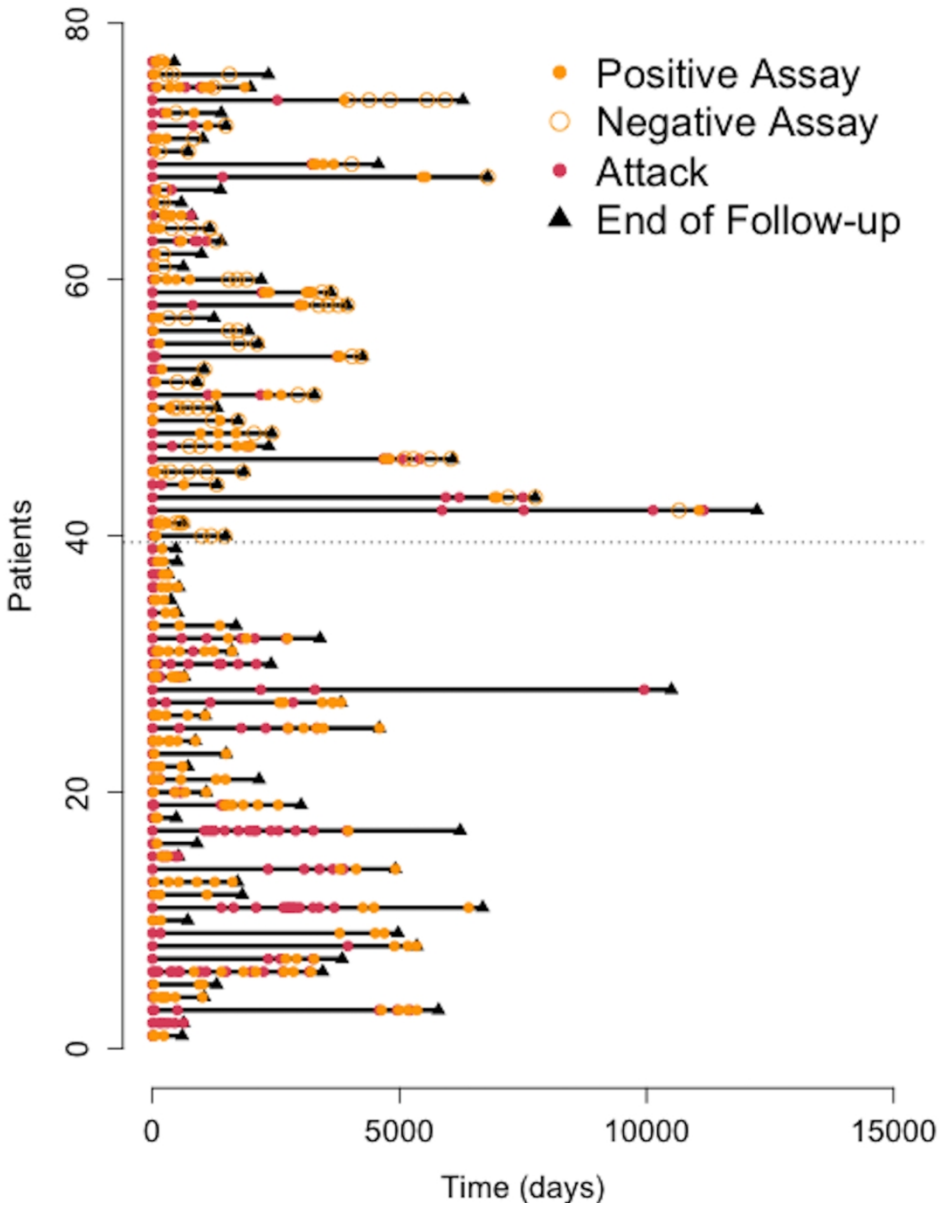

Figure 3. Clinical attacks and longitudinal MOG-Ab serostatus

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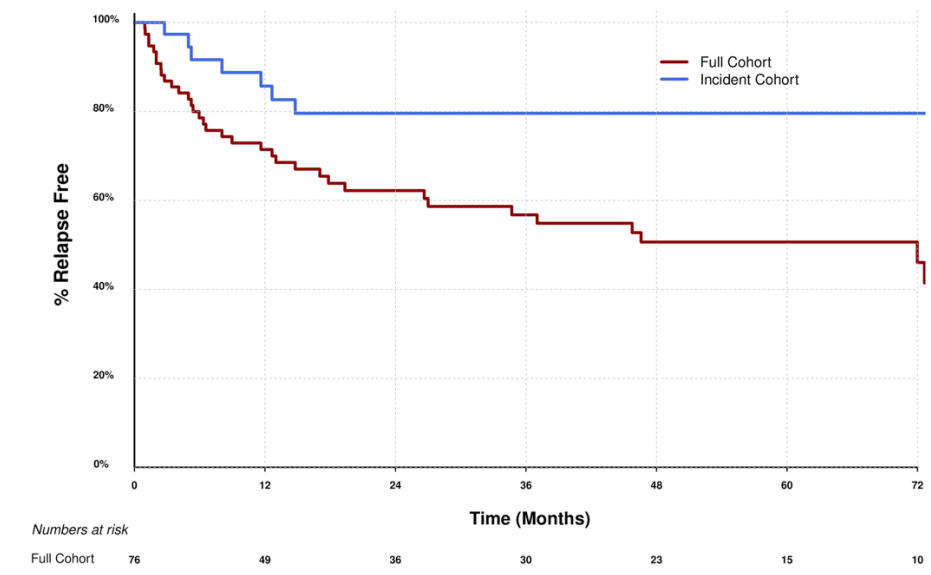
Supplementary material

Supplementary Figure 1. Geographical spread of patients with myelin oligodendroctye glycoprotein antibody associated disease.



Supplementary Figure 2. Kaplan Meier survival analysis of time to 1st relapse in incident and full cohort.

	VA≤6/36 at f/u=13	VA>6/36at f/u= 61	p-value	EDSS≥3 at f/u= 25	EDSS<3 at f/u= 50	p-value	MOG-Ab persistent (+)=39	MOG-Ab negative at f/u=32	p-value
Demographics % (n/total)									
Female (%)	54 (7/13)	53 (32/61)	1	60 (15/25)	62 (25/50)	0.463	54 (21/39)	56 (18/32)	1.00
White (%)	100 (13/13)	92 (56/61)	0.579	96 (24/25)	92 (46/50)	0.658	90 (35/39)	97 (31/32)	0.370
1st attack characteristics % (n/total)									
Median onset age years (IQR)	24 (11-38)	33 (20-45)	0.031†	29 (16-51)	30 (23-41)	0.940	29 (17-44)	29 (19-47)	0.985†
Age≤16yrs at onset	46 (6/13)	12 (7/61)	0.008*	32 (8/25)	10 (5/50)	0.025	15 (6/39)	22 (7/32)	0.547
ADEM	15 (2/13)	5 (3/58)	0.210	4 (1/25)	8 (4/50)	0.658	8 (3/39)	6 (2/32)	0.168
ON	69 (9/13)	51 (36/61)	0.550	52 (13/25)	64 (32/50)	0.331	64 (25/39)	50 (16/32)	0.334
bON	46 (6/13)	34 (21/61)	0.530	32 (8/25)	38 (19/50)	0.792	44 (17/39)	22 (7/32)	0.078
TM	8 (1/13)	49 (30/61)	0.006*	40 (10/25)	42 (21/50)	1.00	31 (12/39)	59 (19/32)	0.018*
LETM	0 (0/13)	33 (20/61)	0.015*	32 (8/25)	24 (12/50)	0.581	21 (8/39)	38 (12/32)	0.184
ON+TM	8 (1/13)	20 (12/61)	0.442	8 (2/25)	22 (11/50)	0.196	15 (6/39)	22 7/32)	0.547
Brain involvement	31 (4/13)	23 (14/61)	0.722	32 (8/25)	26 (13/50)	0.596	31 (12/39)	22 (7/32)	0.433
≥2 CNS sites	15 (2/13)	26 (16/61)	1.00	20 (5/25)	26 (13/50)	0.777	21 (8/39)	29 (9/32)	0.578
Infective trigger	0 (0/3)	44 (7/16)	0.540	25 (2/8)	26 (5/19)	1.00	15 (2/13)	62 (8/13)	0.041*
EDSS≥4 at nadir	46 (6/13)	53 (32/61)	0.765	67 (16/24)	46 (23/50)	0.221	55 (21/38)	56 (18/32)	1.00
EDSS≥4 6m	15 (2/13)	15 (9/61)	1.00	40 (10/25)	2 (1/50)	-	13 (5/39)	16 (5/32)	0.460
Treatment	69 (9/13)	80 (49/61)	0.460	84 (21/25)	74 (37/50)	0.393	74 (29/39)	84 (27/32)	1.00
Steroids≥1m	27 (3/11)	61 (37/61)	0.052	52 (13/25)	55 (27/49)	1.00	55 (21/38)	53 (17/32)	1.00
Steroids≥3m	27 (3/11)	46 (28/61)	0.331	52 (13/25)	37 (18/49)	0.222	40 (15/38)	44 (14/32)	0.809
non-steroid IS	8 (1/13)	13 (8/60)	1.00	16 (4/25)	10 (5/49)	0.472	8 (3/39)	19 (6/32)	0.282
Comparison % (n/total)									
Relapsing	92 (12/13)	46 (28/61)	0.002*	72 (18/25)	46 (23/50)	0.043	62 (24/39)	44 (14/32)	0.157
Relapse<12m	33 (4/12)	57 (16/28)	0.301	28 (7/25)	28 (14/50)	1.00	63 (15/24)	36 (5/14)	0.179
≥3 attacks	83 (10/12)	57 (16/28)	0.157	52 (13/25)	26 (13/50)	0.039	71 (17/24)	50 (7/14)	0.298
≥4 attacks	83 (10/12)	29 (8/28)	0.002*	67 (12/18)	12 (6/50)	0.000*	50 (12/24)	14 (2/14)	0.039*
Median ARR (range)	0.65 (0.08-1.4)	0.38 (0.07-5.43)	0.789†	0.6 (0.07-5.43)	0.037 (0.1-3.4)	0.392	0.66 (0.32-5.43)	0.37 (0.07-1.68)	0.040†
ADEM ever	15 (2/13)	5 (3/61)	0.210	4 (1/25)	8 (4/50)	0.658	8 (3/39)	6 (2/32)	1.00
ON ever	100 (13/13)	69 (42/61)	0.059	72 (18/25)	76 (38/50)	0.787	74 (29/39)	72 (23/32)	1.00

bON ever	77 (10/13)	43 (26/61)	0.033*	52 (13/25)	46 (23/50)	0.63	54 (21/39)	34 (11/32)	0.150
TM ever	62 (8/13)	56 (34/61)	0.766	77 (19/25)	46 (23/50)	0.01	54 (21/39)	66 (21/32)	0.343
LETM ever	15 (2/13)	36 (22/61)	0.201	44 (11/25)	26 (13/50)	0.12	31 (12/39)	28 (12/32)	0.619
ON+TM ever	62 (8/13)	34 (21/61)	0.116	48 (12/25)	34 (17/50)	0.31	41 (16/39)	41 (13/32)	1.00
Brain involvement ever	46 (6/13)	30 (18/61)	0.329	32 (8/25)	34 (17/50)	1.00	44 (17/39)	25 (8/32)	0.136
>1 CNS site ever	77 (10/13)	49 (30/61)	0.123	64 (16/25)	50 (25/50)	0.32	62 (24/39)	53 (17/32)	0.630
Other Abs present (e.g., ANA, ENA)	30 (3/10)	14 (8/56)	0.351	16 (4/25)	17 (7/42)	1.00	21 (7/33)	10 (3/30)	0.308
MRI brain abnormality	54 (7/13)	47 (28/60)	0.763	48 (12/25)	47 (23/49)	1.00	55 (21/38)	41 (13/32)	0.241
MRI spine abnormality	69 (9/13)	61 (34/56)	0.753	76 (19/25)	53 (24/45)	0.09	63 (22/35)	68 (21/31)	0.797
CSF Protein median (range)	0.52 (0.3-1.25)	0.45 (0.16-1.27)	0.714†	0.90 (0.3-1.66)	0.4 (0.16-2.27)	0.029*	0.48 (0.16-2.27)	0.38 (0.18-1.61)	0.337†
CSF WBC median (range)	1 (0-4)	22 (0-937)	0.059†	4 (0-937)	23 (0-550)	0.020*	10 (0-937)	8.5 (0-221)	0.959†
Unmatched oligoclonal bands	0 (0/6)	8 (3/39)	1.00	6 (1/25)	4 (2/50)	1.00	8 (2/20)	4 (1/24)	0.58
At follow-up % (n/total)									
VA≤6/36 in at least one eye at fu	-	-	-	44 (11/25)	4 (2/49)	0.000*	21 (8/39)	3 (1/30)	0.067
EDSS≥4 at fu	39 (5/13)	16 (10/61)	0.122	58 (14/25)	-	-	21 (8/39)	19 (6/32)	1.00
EDSS≥3 at fu	85 (11/13)	23 (14/61)	<0.0001*	-	-	-	31 (12/39)	34 (11/32)	0.802
Bladder dysfunction	31 (4/13)	31 (19/61)	1.00	56 (14/25)	20 (10/50)	0.003	26 (10/39)	44 (14/32)	0.134
Urinary catheter use	23 (3/13)	17 (10/60)	0.690	48 (12/25)	2 (1/49)	0.000	13 (5/39)	25 (8/32)	0.227
Bowel dysfunction	8 (1/13)	23 (14/61)	1.00	40 (10/25)	10 (5/50)	0.003	18 (7/39)	28 (9/32)	0.395
Erectile dysfunction	0 (0/6)	26 (7/27)	0.301	22 (2/9)	21 (5/24)	1.00	12 (2/17)	36 (5/14)	0.198
Current smoker	29 (2/7)	15 (8/53)	0.330	19 (4/21)	15 (6/41)	0.72	15 (5/33)	14 (4/28)	1.00
Median f/u duration months (IQR)	161 (95-212)	43 (23-75)	<0.0001†*	79 (41-194)	44 (23-77)	0.004	49 (21-113)	53 (34-115)	0.275†
Treatment % (n/total)									
Prednisolone monotherapy	0 (0/13)	3 (2/61)	1.00	4 (1/25)	2 (1/50)	1.00	3 (1/39)	3 (1/32)	1.00
Prednisolone + other IS	46 (6/13)	18 (11/61)	0.063	32 (8/25)	18 (9/50)	0.24	28 (11/39)	16 (5/32)	0.260
Azathioprine	8 (1/13)	8 (5/61)	1.00	4 (1/25)	10 (5/50)	0.65	10 (4/39)	6 (2/32)	0.684

Mycophenolate mofetil	39 (5/13)	20 (12/61)	0.160	32 (8/25)	18 (9/50)	0.242	26 (10/39)	13 (4/32)	0.234
Rituximab	15 (2/13)	2 (1/61)	0.078	8 (2/25)	2 (1/50)	0.258	5 (2/39)	6 (2/32)	1.00
IVIg	15 (2/13)	0 (0/61)	0.029*	16 (4/25)	0 (0/50)	0.010*	10 (4/39)	0 (0/39)	0.115
Tocilizumab	0 (0/13)	2 (1/61)	1.00	0 (0/25)	2 (1/50)	1.00	3 (1/39)	0 (0/32)	1.00
No IS	23 (3/13)	66 (40/61)	0.011*	44 (11/25)	66 (33/50)	0.196	33 (19/39)	72 (23/32)	0.057
MOG-Ab									
No of patients MOG-Ab(+) at last review	11 (1/13)	48 (29/60)	0.011*	48 (11/23)	44 (21/48)	0.802	-	-	
Median no of samples (IQR)	3 (1.3-3.8)	4 (3-6)	0.03†	3.5 (2.3-5)	3 (2.8-6)	0.799	3 (3-6)	4 (3-6)	0.563†
Median time between 1st and last sample (IQR)/months	36 (18-65)	29.5 (15.3-45.5)	0.193†	35 (19-47)	28 (7.8-43.8)	0.282	29 (10-40)	29.5 (21-53.8)	0.174†
Median time to MOG-IgG(-) months (IQR)	48*	34 (9.5-103)	-	48 (14-132)	34 (7-103)	0.293	-	38 (9.3-106.5)	-
Relapses whilst MOG-Ab negative	0 (0/1)	7 (2/29)	1.00	9 (1/11)	5 (1/21)	1.00	-	3 (1/32)	-

Supplementary table 1. Univariate analysis of visual outcome, overall disability, and MOG-Ab serostatus. VA; visual acuity, MOG-Ab; myelin oligodendrocyte glycoprotein antibodies, ADEM; acute disseminated encephalomyelitis, ON; optic neuritis, bON; bilateral ON, TM; transverse myelitis, LETM; longitudinally extensive TM, CNS; central nervous system, EDSS; expanded disability status score, IS; immunosuppression, ARR; annualised relapse rate, NMOSD; neuromyelitis optica spectrum disorder, IPND; international panel for NMOSD diagnosis, Abs; antibodies, IVIg; intravenous immunoglobulin, †; Mann-Whitney U test, *; $p<0.05$.

	Relapse (any time)			VA≤6/36			Time between 1st and 2nd Attack		
	est (se)	Odds ratio (95% CI)	P-value	est (se)	Odds ratio (95% CI)	P-value	est (se)	Hazard ratio (95% CI)	p-value
(Intercept)	5.26 (1.5)	-	<0.001*	-0.95 (0.34)	-	0.005*	-	-	-
Steroids 1m	-1.59 (0.695)	0.2 (0.05, 0.80)	0.022*	-	-	-	-	-	-
TM w/ 1st attack	-3.51 (1.032)	0.03 (0.00, 0.23)	0.001*	-2.45 (1.072)	0.09 (0.01, 0.70)	0.022*	-0.86 (0.34)	0.42 (0.22, 0.82)	0.011*
Age	-0.08 (0.028)	0.93 (0.88, 0.98)	0.005*	-	-	-	-	-	-
ON/TM	2.53 (0.989)	12.54 (1.81, 87.17)	0.011*	-	-	-	-	-	-
SexM	-1.86 (0.754)	0.16 (0.04, 0.68)	0.014*	-	-	-	-0.78 (0.34)	0.46 (0.24, 0.89)	0.011*
AUC	-	0.98	-	-	-	-	-	-	-

Supplementary table 2. Multivariable and ROC analysis. VA; visual acuity, CI; confidence interval, m; month, ON; optic neuritis, TM; transverse myelitis, M; male, AUC; area under the curve, *; p<0.05.

	Est (se)	RR (95% CI)	P-value
(Intercept)	-3.3 (0.175)	0.04 (0.026-0.052	<0.001*
MOG-Ab negativity	-2.19 (0.429)	0.11 (0.048-0.259	<0.001*

Supplementary table 3. Results of Poisson regression model and MOG-Ab negativity. MOG-Ab; myelin oligodendrocyte glycoprotein antibody, CI; confidence interval, *; p<0.05.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abst
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine sub ups and interactions
		(*c*) Explain how missing data were addres
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addresse *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.