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Do Early Relapses Predict the Risk of LongTerm Relapsing Disease in an Adult and Paediatric Cohort with <scp>MOGAD</scp>?

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Do early relapses predict the risk of long-term relapsing disease in MOGAD?

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ABSTRACT

IMPORTANCE Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) can range from a monophasic to a relapsing condition, with early relapse being a feature. However, the relevance of early relapse on longer term relapse risk is unknown and thus it is not clear when to start long-term immunosuppression.

OBJECTIVE To determine whether early relapses increase the risk of longer-term relapses in patients with MOGAD.

DESIGN, SETTING, AND PARTICIPANTS A retrospective analysis of 289 MOGAD patients followed for at least 2 years (median disease duration 24-540 months) in 6 specialised referral centres (5 UK centres, Mayo clinic, US). Patients started on long-term immunosuppression from onset were excluded except for patients given early prednisolone tapers which was adjusted in the model.

MAIN OUTCOMES AND MEASURES 'Early relapse' was defined as an attack within the first 12 months from onset, with a 'very early relapse' defined within 30-90 days from onset, and 'delayed early relapse' defined from 90 days to 12 months from onset. 'Long-term relapse' was defined as a relapse beyond 12 months. The long-term relapse risk was estimated using Cox regression multivariate modelling and the relapse rates were calculated by Kaplan-Meier survival analysis.

RESULTS Sixty-seven patients (23.2%) had early relapses with a median number of 1 (range, 1-4) events, which had a high frequency in the first 3 months. Seventy-one patients (24.6%) received a corticosteroid taper with a median duration of 13 (range, 1-49) months. Univariate analysis revealed an elevated risk for long-term relapses if "any early relapses" were present (hazard ratio [HR] 2.11, $p<0.001$), whether occurring during the first 3 months (HR 2.70, $p<0.001$) or the remaining 9 months, with similar results yielded in the multivariate analysis. Individuals of non-white race tended to have a higher risk of long-term relapses compared with white people in whether univariate (HR: 1.5, $p=0.060$) or multivariate (HR: 1.51, $p=0.055$) analysis. In children with onset below aged 12 years, only delayed early relapses were associated with an increased risk of long-term relapses (HR

2.64, p=0.026). Early corticosteroid treatment failed to reduce the risk of the long-term relapses (HR 1.00, p=0.959).

CONCLUSIONS AND RELEVANCE The presence of very early relapses and delayed early relapses within 12 months of onset in MOGAD patients increased the risk of long-term relapsing disease with similar HRs, however a relapse within 90 days appears not to indicate a chronic inflammatory process in young paediatric onset disease. Although a minority of patients received corticosteroid treatment and many for a short period only, it did not appear to influence the risk of long-term relapse.

Keywords: Myelin oligodendrocyte glycoprotein antibody-associated disease; early relapse; long-term relapse;

INTRODUCTION

Myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) is a recently defined autoimmune demyelinating syndrome associated with autoantibodies against myelin oligodendrocyte glycoprotein (MOG-ab), a protein that lies predominantly on the myelin surface in the central nervous system[1]. Disability and, thus prognosis, in MOGAD is intrinsically linked to the presence of relapses and the subsequent risk of neurological sequelae[2-4]. However, MOGAD can range from a monophasic to a long-term relapsing condition, with early relapses being a feature[4-8]. It is not clear if such early relapses necessarily reflect a chronic relapsing condition. In paediatric patients with acute disseminated encephalomyelomyelitis (ADEM) (where MOG-ab are present in around 50%[9]), further attacks have not been considered as relapses if they occur within 90 days from onset[10], because it is assumed that these simply reflect residual inflammatory activity associated with the onset attack. Additionally, early corticosteroid treatment has been reported to reduce the time to first relapse[11] and to be associated with relapse when withdrawn[4,12]. We aimed to assess if early relapses necessarily predict chronic relapsing disease or could represent early inflammatory activity which settles spontaneously and may not need consideration of long-term immunosuppression, accounting for other likely influencing factors.

METHODS

Data were collected prospectively from January 1973 to June 2022 from 5 healthcare services in the UK (Oxford NMO service, Liverpool NMO service, Neurology service Cardiff, Children's Hospital in Birmingham, Evelina London Children's Hospital, and Great Ormond Street Hospital for Children (REC: 10/H0606/56, REC: 15/LO/1344, REC: 17/SC/0224, REC: 19/WA/0289, REC:09/H1202/92)) and the Mayo Clinic (Rochester, Minnesota, USA). Patients with confirmed MOGAD based upon the history of typical neurological demyelinating episodes and a positive live cell-based IgG1 assay[13,14] in the Oxford Autoimmune Neurology Diagnostic and Mayo Clinic Neuroimmunology Laboratories, respectively. To assess the relevance of early relapses on the relapse after one year, we only included patients with at least 2 years of follow-up from the onset, and no long-term non-corticosteroid

immunosuppressive treatment (IST) prior to the late relapse was evaluated. Prednisolone courses were allowed and studied as a covariate.

We investigated if patients with early relapses (defined as relapses within 12 months after onset excluding new symptoms within the first 30 days[15]) were at risk of long-term relapses (defined as relapses beyond 12 months from onset). We included other factors that may be associated with relapse risk such as sex, disease onset age, self-identified race, onset phenotype ('brain onset phenotype' was defined as anyone with ADEM, brain or brainstem plus syndromes) and 'any transverse myelitis' (TM) at onset (with or without other clinical symptoms) because this phenotype was previously associated with a lower risk of second attack[16,17], and use (at least 4 weeks) and duration (in months) of oral corticosteroids taper from the initial acute onset attack treatment excluding the first 30 days[16]. We further sub-grouped the early relapses into 'very early' relapses occurring during 1-3 months versus 'delayed early' relapses during 4-12 months to allow for independent assessment in patients who had attacks in both periods. Additionally, the number of early relapses was also analysed. We also performed subgroup analysis examining this relationship in the young paediatric onset group (≤12 years old) with the rest of the cohort to see if they behaved differently.

Statistical analysis

Kaplan-Meier survival curves with Log-rank test, time-to-relapse analyses, and Cox-regression models were performed, with the hazard ratio (HR), 95% confidential interval (CI), and a p value of each independent variable estimated. The dependent variable for all analyses was the long-term relapse. Multivariate analyses included those factors found to have a p value of less than 0.1 in the univariate analysis. Statistical analyses were performed using R Statistical Software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Cohort description

We included 289 MOGAD patients with ≥2 years of disease duration, of whom 185 (64%) were relapsing at any stage **(Figure 1).** Baseline features were shown in **Table 1**, where 117 (40.5%) were male, 242 (83.7%) were White, the median age at disease onset was 26 years (range, 1-73), and the median follow-up from the onset was 64 months (range, 24-540). Sixty-seven patients (23.2%) had early relapses with a median number of 1 event (range, 1-4), with a higher monthly attack rate during 1-3 months than 4-12 months. Seventy-one patients (24.6%) received a corticosteroid taper with a median duration of 13 months (range, 1-49).

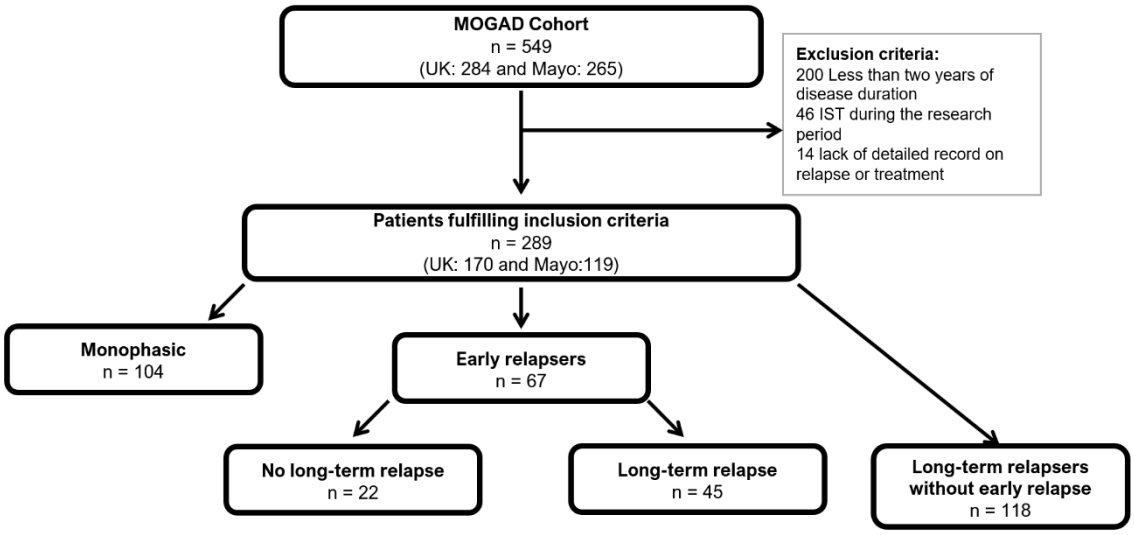

Figure 1: Enrollment profile

Characteristics	Total cohort (N=289)	Adult onset (N=177) (Age at onset ≥ 18 years)	Pediatric onset (N=78) (Age at onset ≤12 years)
Female, N (%)	172 (59.5)	103 (58.2)	44 (56.4)
White, N (%)	242 (83.7)	151 (85.3)	63 (80.8)
Age at onset, median (range)	26 (1-73)	36 (18-73)	7 (1-12)
Disease duration, median (range)	64 (24-540)	53 (24-460)	82 (24-540)
Phenotype at onset, N (%)			
ON	138 (47.8)	99 (55.9)	25 (32.1)
brain	69 (23.9)	17 (9.6)	44 (56.4)
NMO	27 (9.3)	18 (10.2)	5 (6.4)
TM	55 (19.0)	43 (24.3)	4 (5.1)
Any TM	151 (52.2)	78 (44.1)	53 (67.9)
Early relapse, N (%)	67 (23.2)	39 (22.0)	15 (19.2)
No. of early relapse, N (%)			
0	222 (76.8)	138 (78.0)	63 (80.8)
1	47 (16.3)	24 (13.6)	13 (16.7)
2	13 (4.5)	9 (5.1)	2 (2.6)
≥3	7 (2.4)	6 (3.4)	-
Relapse during month 1-3, N (%)	30 (10.4)	20 (11.3)	4 (5.1)
Relapse during month 4-12, N (%)	50 (17.3)	29 (16.4)	11 (14.1)
Relapsing form, N (%)	185 (64.0)	103 (58.2)	56 (71.8)
Use of corticosteroids, N (%)			
No	218 (75.4)	128 (72.3)	65 (83.3)
Yes	71 (24.6)	49 (27.7)	13 (16.7)
Corticosteroid treatment duration, median (range)	0 (0-49)	0 (0-49)	0 (0-18)
Treatment duration in patients receiving corticosteroids, median (range)	13 (1-49）	14 (1-49)	6 (1-18)

Table 1 Demographic and Baseline Clinical Characteristics of Patients

ON = optic neuritis; NMO = neuromyelitis optica (i.e., optic neuritis and myelitis); TM = myelitis

Early relapses: defined as relapses within 12 months after onset excluding new symptoms within the first 30 days.

Total Cohort

Univariate analysis **(Table 2)** revealed an increased risk for long-term relapses if 'any early relapses' were present (HR 2.11, 95% CI 1.49-3.00, p<0.001), if the 'number of early relapses'

increased (all HRs > 1.50 and p values < 0.05), if the patients had 'very early relapses' (HR 2.70, CI 1.73-4.20, p<0.001) or 'delayed early relapses' (HR 1.88, CI 1.28-2.77, p=0.001). There was a trend towards significance in people of non-White race (HR 1.50, CI 0.98-2.29, p=0.06). The use of corticosteroids (HR 0.98, CI 0.65-1.47, p=0.903) and the duration of corticosteroids treatment from onset did not reduce the time to long-term relapses (HR 1.00, CI 0.98-1.02, p=0.959). Age (HR 1.00, CI 0.99-1.01, p=0.434) and phenotype at onset (including any TM) (all p values > 0.1) were not associated with an increased risk of long-term relapse.

Variables		**Total cohort**	
		N (%)	HR (95% CI, p)
Sex	Female	172 (59.5)	-
	Male	117 (40.5)	0.99 (0.72-1.36, p=0.967)
Race	White	242 (83.7)	-
	Non-white	47 (16.3)	1.50 (0.98-2.29, p=0.060)
Age at onset	Mean (SD)	27.4 (18.2)	1.00 (0.99-1.01, p=0.434)
Phenotype	ON	138 (47.8)	-
	brain	69 (23.9)	0.87 (0.59-1.27, p=0.463)
	NMO	27 (9.3)	0.62 (0.34-1.14, p=0.124)
	TM	55 (19.0)	0.89 (0.58-1.35, p=0.581)
	Any TM	151 (52.2)	0.83 (0.61-1.13, p=0.227)
Early relapse	No	222 (76.8)	-
	Yes	67 (23.2)	**2.11 (1.49-3.00, p<0.001)**
No. of early relapse	0	222 (76.8)	-
	1	47 (16.3)	**1.91 (1.28-2.87, p=0.002)**
	2	13 (4.5)	**2.48 (1.25-4.94, p=0.010)**
	3 or more	7 (2.4)	**3.05 (1.33-6.96, p=0.008)**
Relapse during month 1-3	No	259 (89.6)	-
	Yes	30 (10.4)	**2.70 (1.73-4.20, p<0.001)**
Relapse during month 4-12	No	239 (82.7)	-
	Yes	50 (17.3)	**1.88 (1.28-2.77, p=0.001)**
Use of corticosteroids	No	218 (75.4)	-
	Yes	71 (24.6)	0.98 (0.65-1.47, p=0.903)
Corticosteroid treatment duration	Mean (SD)	3.6 (8.1)	1.00 (0.98-1.02, p=0.959)

Table 2 Univariate Analysis of long-term Relapse Risk

ON = optic neuritis; NMO = neuromyelitis optica (i.e., optic neuritis and myelitis); TM = myelitis

Early relapses: defined as relapses within 12 months after onset excluding new symptoms within the first 30 days.

Multivariate Cox regression models for the long-term relapse (shown in **Table 3)** were performed to evaluate the effect of the presence, the number, and the timing of the early relapses**.** The presence, number of early relapses, 'very early relapses', and 'delayed early relapses' remained significant while non-White race was significant in two of the models.

Models	Variables		Multivariable analysis	
			No (%)	HR (95% CI, p)
model 1	Race	White	242 (83.7)	-
		Non-white	47 (16.3)	1.51 (0.99-2.31, p=0.055)
	Early relapse	No	222 (76.8)	-
		Yes	67 (23.2)	**2.12 (1.49-3.01, p<0.001)**
model 2	Race	White	242 (83.7)	-
		Non-white	47 (16.3)	**1.54 (1.01-2.36, p=0.046)**
	No. of early relapses	0	222 (76.8)	-
		1	47 (16.3)	**1.91 (1.27-2.87, p=0.002)**
		2	13 (4.5)	**2.46 (1.24-4.89, p=0.010)**
		3 or more	7 (2.4)	**3.29 (1.43-7.55, p=0.005)**
model 3	Race	White	242 (83.7)	-
		Non-white	47 (16.3)	**1.55 (1.02-2.37, p=0.042)**
	Relapse during month 1-3	No	259 (89.6)	-
		Yes	30 (10.4)	**2.38 (1.49-3.80, p<0.001)**
	Relapse during month 4-12	No	239 (82.7)	-
		Yes	50 (17.3)	**1.56 (1.03-2.34, p=0.034)**

Table 3 Multivariate Analysis of long-term Relapse Risk

Given that the number of early relapses was associated with long-term relapses (**Figure 2**), we then calculated the probability of patients having a long-term relapse over the next 4 years based upon the number of early relapses they had using the Kaplan-Meier curve analysis. Patients with any early relapse had a 68.8% risk of long-term relapse within the following 4 years (or 5 years from onset). While this figure was 40.6% for non-early relapsers. Further, patients with 2 or more early relapses had a 75.0% risk of long-term relapse over the next 4 years (or 5 years of follow up). (**Supplementary figure 1**).

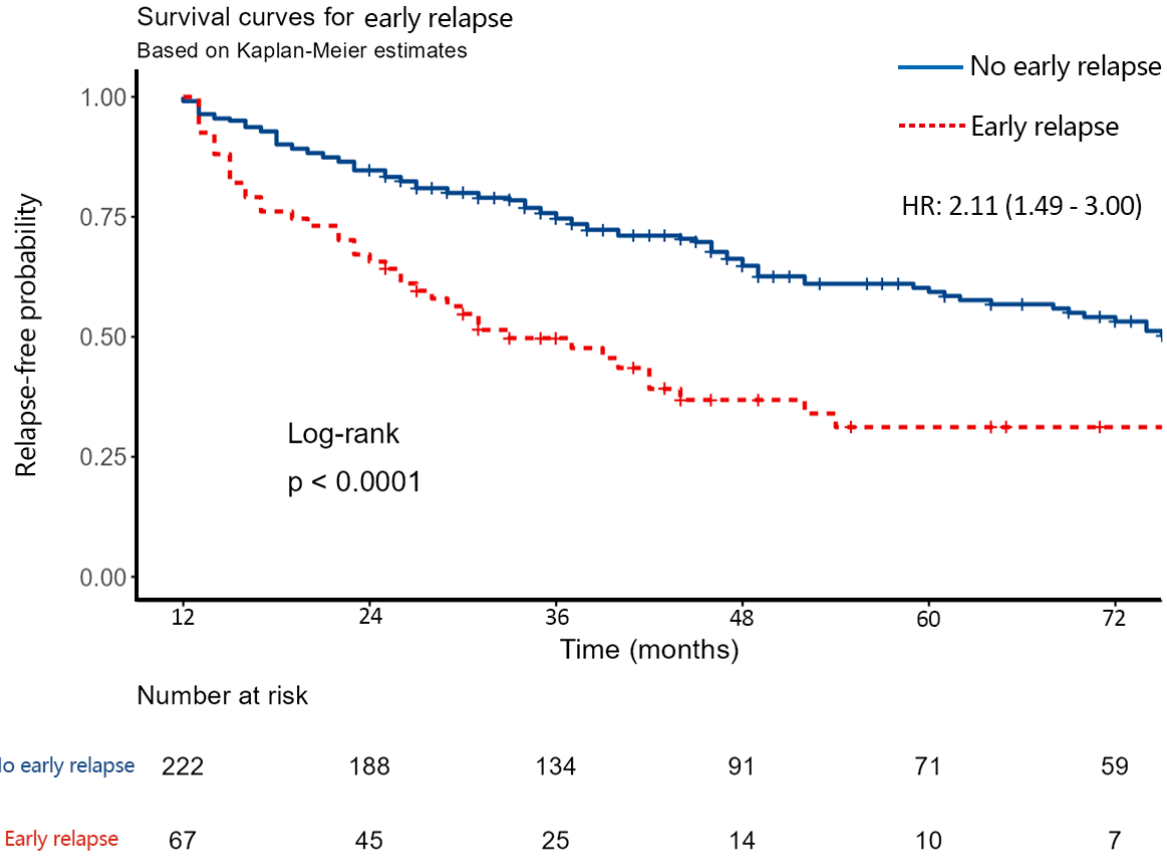

Figure 2 Kaplan–Meier estimates of time to late relapse based on the early relapse

*Paediatric population (**Table 4**)*

We identified 78 patients with disease onset ≤ 12 years, of whom 44 (56.4%) (**Table 1**) had an ADEM/brain/brainstem onset phenotype. The median disease duration or follow-up time was longer in this group and the ADEM subgroup (82 months [Range: 24-540] for ≤12 years and 87 months [24-540] for ≤ 12 years, respectively) than that in the whole cohort (64 [24-540] months and 79 [24-540] months, respectively). Of note, very few children (13/78) received

corticosteroids for longer than 30 days. **Table 4** demonstrated that there was a trend for an increased risk of long-term relapses with 'any' early relapse (HR 1.96, CI 0.92-4.18, p=0.080) which appeared to be related to those who had a relapse during the 4^{th}-12^{th} month (HR 2.64, CI 1.12-6.19, p=0.026) in the univariate analysis rather than early relapses within the first 3 months (0.95, CI 0.23-3.93, p=0.942) although the number of patients who relapsed within 1-3 months was low (n= 4, **Table 4**). Multivariate analysis was not performed as only one independent variable was significant in the univariate analysis (**Table 4**).

Variables		Child-onset cohort (Age at onset ≤12 years)		Adult-onset cohort (Age at onset ≥ 18 years)	
		N (%)	HR (95% CI, p)	N (%)	HR (95% CI, p)
Sex	Female	44 (56.4)	-	103 (58.2)	-
	Male	34 (43.6)	1.11 (0.63-1.97, p=0.711)	74 (41.8)	0.99 (0.65-1.50, p=0.949)
Race	White	63 (80.8)	-	151 (85.3)	-
	Non-white	15 (19.2)	1.38 (0.65-2.92, p=0.396)	26 (14.7)	1.60 (0.91-2.82, p=0.101)
Age at onset	Mean (SD)	6.8 (3.2)	1.00 (0.93-1.09, p=0.919)	38.9 (13.6)	0.99 (0.98-1.01, p=0.436)
Phenotype	ON	25 (32.1)	-	99 (55.9)	-
	brain	44 (56.4)	0.97 (0.52-1.79, p=0.917)	17 (9.6)	0.58 (0.26-1.28, p=0.175)
	NMO	5 (6.4)	1.39 (0.40-4.85, p=0.603)	18 (10.2)	**0.44 (0.20-0.97, p=0.043)**
	TM	4 (5.1)	0.78 (0.18-3.43, p=0.745)	43 (24.3)	0.89 (0.55-1.45, p=0.644)
Early relapse	No	63 (80.8)	-	138 (78.0)	-
	Yes	15 (19.2)	1.96 (0.92-4.18, p=0.080)	39 (22.0)	**1.86 (1.18-2.95, p=0.008)**
No. of early relapse	0	63 (80.8)	-	138 (78.0)	-
	1	13 (16.7)	2.13 (0.96-4.71, p=0.062)	24 (13.6)	1.52 (0.86-2.67, p=0.148)
	2	2 (2.6)	1.22 (0.17-8.96, p=0.847)	9 (5.1)	**2.87 (1.23-6.72, p=0.015)**
	3 or more	-	-	6 (3.4)	**2.58 (1.03-6.45, p=0.043)**
Relapse during month 1-3	No	74 (94.9)	-	157 (88.7)	-
	Yes	4 (5.1)	0.95 (0.23-3.93, p=0.942)	20 (11.3)	**3.14 (1.80-5.49, p<0.001)**
Relapse during month 4-12	No	67 (85.9)	-	148 (83.6)	-
	Yes	11 (14.1)	**2.64 (1.12-6.19, p=0.026)**	29 (16.4)	1.53 (0.92-2.55, p=0.100)
Use of corticosteroids	No	65 (83.3)	-	128 (72.3)	-
	Yes	13 (16.7)	1.39 (0.61-3.15, p=0.434)	49 (27.7)	0.89 (0.52-1.52, p=0.669)

Corticosteroid treatment duration	Mean (SD)	1.3 (3.5)	1.04 (0.96-1.14, p=0.315)	4.4 (8.9)	0.99 (0.97-1.02, p=0.654)

Table 2 Univariate analysis of late relapse risk in the paediatric- and adult-onset cohort

ON = optic neuritis; NMO = neuromyelitis optica (i.e., optic neuritis and myelitis); TM = myelitis

Early relapses: defined as relapses within 12 months after onset excluding new symptoms within the first 30 days.

DISCUSSION

Our study provides a novel analysis examining the effect of early relapses on the later relapse activity in MOGAD patients. We have shown that in a large cohort, including adults and children, and followed for a median disease duration of over 5 years, the presence and the number of relapses within 12 months from onset (including those between 30 and 90 days from onset), are predictors of further relapses beyond one year. Our findings have important implications for MOGAD treatments and upcoming clinical trials as attack-prevention maintenance treatments are generally reserved for those with relapsing disease. If the current 90-day cut-off for defining a new attack in the ADEM diagnostic criteria was applied to all MOGAD patients, these early relapsing MOGAD patients would be labeled as monophasic and would not receive chronic treatment or be eligible for upcoming MOGAD clinical trials which require relapsing disease for enrollment. Our findings support the use of a 30-day cut-off for relapse in the recently published International MOGAD panel diagnostic criteria (in press Lancet Neurology).

However, the 90-day rule for ADEM may be generally appropriate for younger children with MOGAD as when we analysed the ≤12-year sub-cohort (to capture as many prepubescent patients as possible), and in contrast to the adult cohort, we found that early relapses within 90 days from onset did not predict later relapse activity. This supports the previous proposal in ADEM[10] that at least in younger children a MOGAD relapse within 90 days appears not to indicate a chronic inflammatory process. However, delayed early relapses beyond the 90-day time point did increase the risk of later relapse activity as in adults. In contrast, in adults, very

early relapses appeared to be a stronger predictor of long-term relapses than delayed early relapses. The higher proportion of children with early relapses having long-term relapses (64.1%) than in the whole cohort (56.4%) was related to their longer follow up.

Additionally, non-White race appeared to be a significant risk factor for increased risk of long-term relapse in most models herein and this has not previously been studied. Race was not found to be associated with time to first relapse[16] but White race was reported to be associated with a lower relapse rate in those treated with maintenance intravenous immunoglobulin[18]. The reason for the poorer outcome is not clear but early prednisolone treatment was accounted for in the model. Further studies are needed to explore this.

Jurynczyk et al[4] reported that prednisolone treatment for less than 3 months was associated with a higher risk of relapse (47%) when compared with those receiving treatment for 3-6 months (22%), or longer than 6 months (26%). Another study has shown prednisolone dosage sensitivity in patients with MOGAD[12]. Our study did not show that a prednisolone course reduced the risk of long-term relapse, however, only a minority received treatment for a short period. Nevertheless, 35% of patients who did not receive corticosteroids remained relapse-free, which is not different from 39% given corticosteroids, although this study was not powered to analyze the different lengths and doses. Further studies are required to see if the benefits from corticosteroids for a subgroup outweigh the risks and side effects overall.

There are limitations and strengths of our study. Firstly, we defined long-term relapsing MOGAD based upon our practice to treat patients who relapsed beyond one year. This does not mean such patients will continue indefinitely to be at risk of relapses, and a recent analysis suggests a reduction (not stopping) of relapse risk over time in MOGAD in contrast to AQP4-IgG-seropositive NMOSD[19]. The strengths are that this is a large MOGAD cohort including all ages with a long follow-up period answering an important question which rejects our idea that early inflammatory activity is not a risk for long-term activity. Additionally, we did not limit it to only incident patients i.e., those diagnosed from the onset, and this may have led to an over-representation of relapsing patients in those without early relapses. This would actually have underestimated the hazard ratio of early relapse on the long-term relapse

risk. Exclusion of those on maintenance immunosuppressant treatment prior to the late relapse may have led to the under-representation of more severe MOGAD cases.

In summary, our results suggest that early relapses within the first 12 months in MOGAD patients increase the risk of long-term relapsing disease, although in younger children very early relapses within 3 months did not show this effect. Longer early corticosteroid courses may not reduce the risk of longer-term relapse and adults with early relapses should be considered for long-term immunosuppressants particularly if they have multiple early attacks. Long-term studies on relapse risk after withdrawing immune suppression are needed to assess if there is a safe or optimal time to stop immunosuppressants in relapsing patients.

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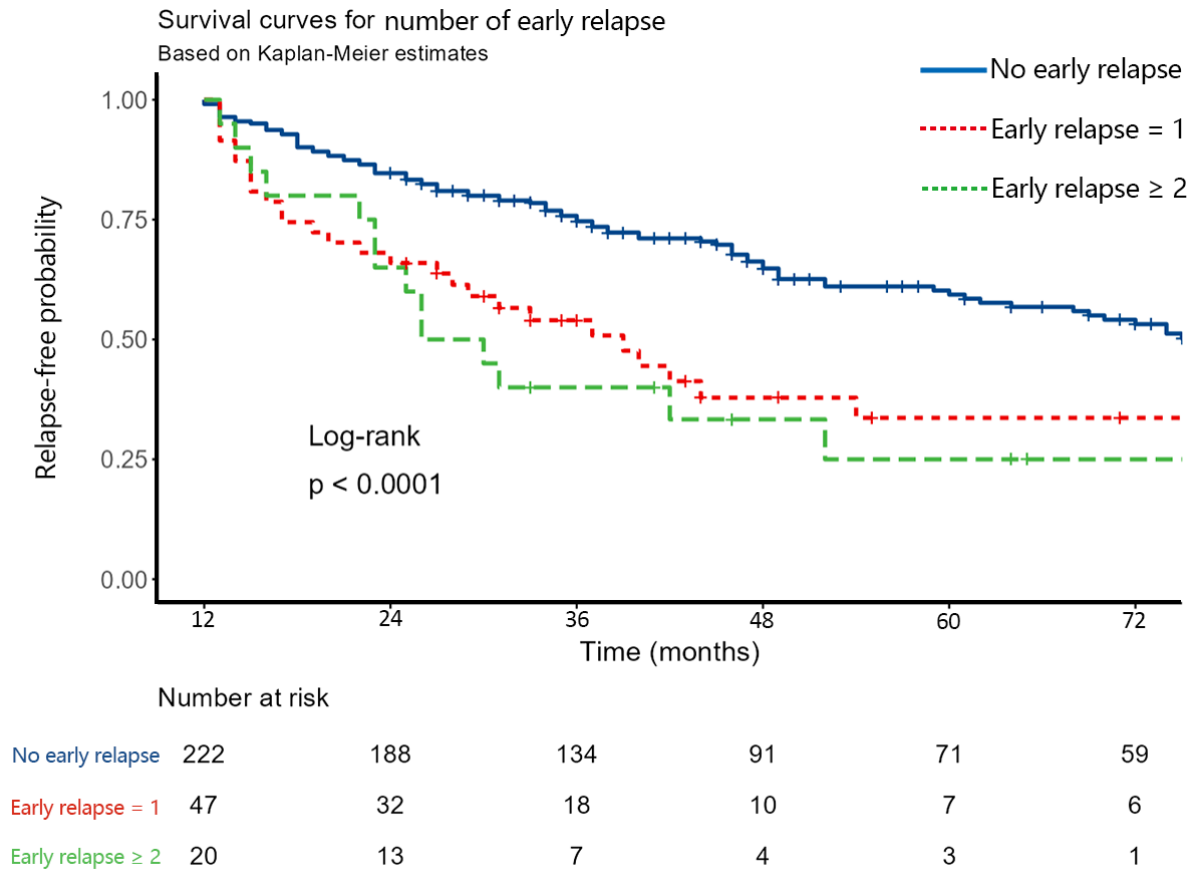

Supplementary figure 1 Kaplan–Meier estimates of time to late relapse based on the number of early relapses