Evolution of brain MRI lesions in Paediatric Myelin-Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD) and its relevance to disease course

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Abstract

Background: Lesion resolution is often observed in children with MOGAD, and asymptomatic lesions are less commonly reported in MOGAD than in Multiple Sclerosis.

Objective: We aimed to evaluate brain MRI changes over time in paediatric MOGAD.

Methods: Retrospective study in 8 UK paediatric neuroscience centres. Acute brain MRI and available follow-up MRIs were reviewed. Predictors for lesion dynamic were evaluated using multivariable regression and Kaplan-Meier survival analyses were used to predict risk of relapse, disability, and MOG-Ab status.

Results: 200 children were included (MOGAD 97; MS 103). At first MRI post-attack, new symptomatic and asymptomatic lesions were seen more often in MS vs MOGAD (52/103 vs 28/97; p=0.002 and 37/103 vs 11/97; p<0.001); 83% of MOGAD patients showed at least one lesion's resolution at 1st follow-up scan, and 23% had normal MRI. Only 1 MS patient had single lesion resolution; none had normal MRI. Disappearing lesions in MOGAD were seen in 40% after the 2nd attack, 21% after 3rd attack and none after the 4th attack.

New lesions at 1st follow-up scan were associated with increased likelihood of relapse (p=0.02) and persistent MOG-Ab serostatus (p=0.0016) compared to those with no new lesions. Plasma exchange was associated with increased likelihood of lesion resolution (p=0.01). Longer time from symptom onset to steroids was associated with increased likelihood of new lesions; 50% increase at 20 days (p=0.01).

Conclusions and Relevance: These striking differences in lesion dynamics between MOGAD and MS suggest greater potential to repair. Early treatment with steroids and plasma exchange is associated with reduced likelihood of new lesions.

Key messages points:

What is already known on this topic:

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- Patients with myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD), an inflammatory demyelinating disorder different than Multiple Sclerosis (MS), have highly dynamic lesions on brain MRI after attacks.

What this study adds:
- 81/97 (83%) of children with MOGAD had at least one lesion resolve at first follow-up MRI after the initial attack, compared to only 1/103 MS patient who had a single lesion disappear; the proportion of normal brain MRI was reduced after each clinical relapse with disappearing lesions suggesting the ability to repair is reduced in patients with multiple relapses.
- Early treatment with steroids and escalating to plasma exchange is associated with lesion resolution on follow-up imaging.

How this study might affect research, practice, or policy:
- Monitoring lesion resolution in serial imaging can be helpful in clinical practice when trying to differentiate between MS and its mimics including MOGAD.
- Early treatment with steroids and plasma exchange may influence the disease trajectory

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Introduction

Myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a distinct inflammatory demyelinating disorder different than Multiple Sclerosis (MS) and Aquaporin 4-antibody positive Neuromyelitis Optica Spectrum Disorder (AQP4-Ab NMOSD). Both monophasic and relapsing disease courses are seen in children and adults. Brain MRI in MOGAD can be abnormal in more than 50% of patients, regardless of the clinical phenotype at presentation[1]. In general, brain lesions are more widespread in children compared to adults[2, 3].

Radiological parameters to differentiate between MOGAD from AQP4-Ab NMOSD and MS at first presentation have been reported in both adults and children. Our group reported in a large cohort of 110 patients that children with MOG-Ab were less likely to present with area postrema syndrome and cerebellar peduncle lesions than children with AQP4-Ab NMOSD in addition to being younger with lower disability and a longer time to relapse[4]. In a retrospective cross-sectional study of 162 adult MOGAD patients compared to 162 AQP4-Ab NMOSD and 189 MS patients, lesion location in interval non-attack imaging was used to differentiate between the different diagnoses, with temporal lobe lesions, absence of Dawson's fingers and longitudinally extensive lesions in the cervical cord all pointing towards MOGAD[5].

When evaluating serial MRIs over the disease course, asymptomatic or silent brain lesions have been previously reported in 10/74 (14%) paediatric MOGAD patients[6], commonly within the first months post-onset. In another study of 38 MOGAD patients (including adult and children), the brain T2-index lesion resolved completely in 13/18 (72%) of MOGAD patients at first follow-up MRI[7]. A more recent study from the same group demonstrated in paediatric patients that the MRI T2-index lesion resolved more frequently and more completely in children with MOGAD (n=21) compared to MS (n=27) and AQP4-Ab NMOSD (n=8)[8].

The aims of the study were to (i) study the evolution of brain lesions after an acute attack and compare it between paediatric MOGAD and RRMS; (ii) correlate first follow-up MRI with patients' management at presentation, and (iii) evaluate if MRI lesion dynamics early in the disease can predict risk of relapse, disability accrual and MOG-Ab serostatus at follow-up.

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Methods

This project was a multi-institutional, retrospective study run within the UK Childhood Neuroinflammatory Diseases Network and included patients from Great Ormond Street Hospital (London), Evelina Children's Hospital (London), Birmingham Children's Hospital, Addenbrooke's Hospital (Cambridge), Alder Hey Children's Hospital (Liverpool), Royal Manchester Children's Hospital, Great North Children's Hospital (Newcastle) and John Radcliffe Hospital (Oxford). Two cohort of patients with MOGAD and RRMS, consecutively seen in the 8 UK paediatric neuroscience centres between January 2014 to January 2022, were included. All patients (whether tested retrospectively for antibodies or at the time of disease onset) fulfilled their respective MOGAD[9] or MS diagnostic criteria[10]. All MOGAD patients were tested for MOG-IgG as part of the routine clinical care using cell-based assay.

From these cohorts, our inclusion criteria required the following: (1) first clinical attack occurring before 18 years old; (2) available acute brain MRI that revealed parenchymal T2-hyperintense lesion(s), obtained within 4 weeks of the attack nadir; and (3) available follow-up MRI at least 6 weeks after the acute MRI (off steroids).

When multiple acute MRIs were available, the most representative of attack nadir was chosen (most extensive CNS radiological abnormality). Patients with optic neuritis and/or transverse myelitis with normal brain MRI were excluded. Clinical data including demographics, clinical findings, neuroimaging reports, and laboratory results, first and subsequent relapse characteristics, and treatment information were retrospectively reviewed from electronic medical records of patients and entered in a standardized database. Relapses were defined as "new neurological symptom" or "clear acute worsening of previous neurological deficits" with objective clinical signs, lasting for at least 24 hours and attributed to an inflammatory CNS event, and occurring after a period of clinical remission of >1 month, as defined by the International MOGAD Panel proposed criteria[9], confirmed by the treating physician. Asymptomatic lesions were used to only describe lesions occurring outside a clinical attack. Disability assessment was determined from patient electronic medical record review, at all subsequent clinical follow-up timepoints using the Expanded Disability Status Scale (EDSS).

All available MRI were clinically reported by a paediatric neuroradiologist. MRI scans were then independently re-evaluated by two neurologists (O.A.-M. and Y.H.). For patients with a reported initial abnormal brain MRI, subsequent follow-up MRI scans were grouped into the following

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categories: i) Symptomatic lesions (associated with a clinical relapse), ii) New asymptomatic lesions, iii) Stable (no new lesions), iv) Lesion shrinking with at least one lesion resolution, and v) Normal MRI. Patient with coexisting new lesions and shrinking lesions were included in the 'New lesions' groups (either symptomatic or asymptomatic). A maximum of 10 MRIs per patient were evaluated.

For patients with MOGAD, clinical and paraclinical features at presentation were used to predict lesion dynamics at first follow-up MRI. We subsequently evaluated if new lesions on first follow-up MRI predict risk of relapse, disability accrual, and MOG-Ab serostatus at final follow-up.

Statistical analysis

Descriptive statistics were performed on the demographic and clinical variables. Mean, median, SD, and interquartile range (IQR) were reported as appropriate. To compare the demographic, clinical, and paraclinical characteristics between our MOGAD and RRMS cohorts, parametric or non-parametric statistical tests (Mann-Whitney-U and Kruskal-Wallis tests) were used for continuous distributions as appropriate given normality, and Pearson's chi squared test with Yates' continuity correction or Fisher exact tests were used for nominal data. Results associated with a value of p <0.05 were considered significant.

For patients with MOGAD, multivariable logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals for potential confounders between the different MRI groups (including sex, age at presentation, cerebrospinal fluid analysis and acute immunotherapies). Kaplan-Meier survival analyses were used to estimate the cumulative risk of clinical relapses, risk of disability accrual (increase in EDSS score by 1 or more), and risk of seroconversion to MOG-Ab negative status, using the log-rank test to compare patients stratified to two groups: new lesions vs shrinking lesions. Data were analysed with GraphPad Prism 8 (GraphPad Software) and R (version 4.3.1; R Core Team 2020).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by Great Ormond Street Hospital Research and Development Department (reference: 16NC10). As the data analysis was retrospective and no additional data were collected beyond that required for standard medical care of the patient, participants were not required to give informed written consent to participate in the study before taking part. Any data not published within the article will be shared upon request from any senior (tenured) investigator.

Results

Two hundred consecutive children were retrospectively studied (MOGAD 97; RRMS 103). Patients'
demographics are summarized in **Table 1**. The median length of follow-up from first clinical
presentation was 3.8 years (IQR 3-7 years) in the RRMS group and 3.8 years (IQR 2-6) the MOGAD
group. At last follow-up 54/ 97 (56%) MOGAD patients relapses and 29/42 (69%) of the one who
were tested more than once remained MOG-Ab positive.

Comparison between children with RRMS and MOGAD

RRMS patients were older (median 14 yrs for MS vs 5 yrs in MOGAD, p<0.0001) with a greater
female preponderance (73% vs 58%; p=0.01) and more likely to have positive oligoclonal bands
(87/93, 94% vs 13/60, 22%; p<0.0001). No difference was observed in either EDSS at the time of first
follow-up scan or EDSS at final follow-up between MOGAD and RRMS patients (**Table 1**).

Table 1: Comparison between MOGAD vs RRMS paediatric cohorts.

	MOGAD (N=97)	RRMS (n=103)	p-value
Age at presentation (yrs), median (IQR)	5 (4-9.5)	14 (12-14.8)	**<0.0001**
Sex (Male: Female)	41:56	28:75	**0.01**
Demyelinating phenotype at onset			
ON	7	27	**0.0003**
TM	2	4	0.68
CIS -other	0	72	**<0.0001**
ADEM	66	0	**<0.0001**
Cortical encephalitis	22	0	**<0.0001**
Intensive care admission	13	1	**0.0005**
Seizures at presentation	21	0	**<0.0001**
CSF oligoclonal bands	12/57 (21)	87/93 (95)	**<0.0001**
EDSS at time of follow-up scan	1 (0,1.5)	1 (0,1.5)	0.51
MRI lesion location (initial MRI), n (%)			
Brain	97 (100)	102 (99)	0.33
Spinal Cord	35 (36)	60 (59)	**0.002**
Optic nerve	22 (23)	25 (24)	0.79
Contrast enhancement on initial MRI, n (%)	41/65 (63)	46/63 (73)	0.23
EDSS at last follow-up, median (IQR)	1 (0,2)	1 (1,1.5)	0.81
Brain lesion dynamics at first follow-up MRI, n (%)			
New symptomatic lesions	28 (29)	52 (50)	**0.0024**
New asymptomatic lesions	11 (11)	37 (36)	**<0.0001**
Stable (no new lesions)	0 (0)	10 (10)	**<0.0001**
Lesions shrinking with at least 1 lesion resolution	36 (37)	1 (1)	**<0.0001**
Normal MRI	22 (23)	0 (0)	**<0.0001**

During the period, a median of four repeated MRI scans were performed per patient (range 2–10, total MRI scans in RRMS patients 430 and in MOGAD 511). The median length of time between attack MRI and first post-attack/remission follow-up MRI was 0.4 years (IQR 0.2, 1.0). The median length of time between attack MRI and final follow-up MRI was 1.8 years (IQR 0.7, 4.8 yrs, range 0.1 to 12.6 yrs). When evaluating the first post-attack/remission follow-up MRI, patients with paediatric MS when compared to MOGAD had more new symptomatic lesions (50% (52/103) vs 29% (28/97); p=0.002) and asymptomatic lesions (36% (37/103) vs 11% (11/97); p<0.001). Only one patient with RRMS had a single lesion resolve and none had normal MRI. In contrast, 60% (58/97) of MOGAD patients had at least one lesion resolution at first follow-up MRI and 23% (22/97) showed a normal MRI (**Table 1**).

Of the 39 patients with MOGAD with new lesions at the first follow-up scan, 23 (59%) had also at least one lesion disappearing (i.e., they showed a mix picture with both new lesions and disappearing lesions, Figure 1C). When examining the time taken for lesions to disappeared by stratifying the results to when the first follow-up scan was performed , of the 81/97 (83%) patients who had at least one lesion resolved at the first follow-up scan, 25/30 (83%) patients showed lesion resolution when the interval was less than 3 months, 22/28 (79%) when the interval was between 3 and 6 months, 16/17 (94%) in the 6 - 12 months interval and 18/22 (82%) when the first follow-up scan was performed longer than 12 months from baseline.

Predictive factors for lesion changes at first follow-up MRI in MOGAD patients

Examples of lesion changes in patients with MOGAD are illustrated in **Figure 1**. When comparing patients whose first follow-up MRI demonstrated new lesions vs patients with shrinking lesions, there were no differences in demographic, clinical and paraclinical features at onset (**Table 2**). Similarly, no differences were observed between MOGAD patients who received intravenous immunoglobulin (IVIg) and steroids at presentation and those who did not. All patients who received plasma exchange (PLEX) at onset (n=13) had shrinking lesions (with at least one lesion resolution) on follow-up MRI vs none of those who did not (p=0.01). Increased time from symptom onset to starting steroids was associated with increased likelihood of new lesions with 50% increase at 20 days (p=0.01**, Table 2).**

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Table 2: MOGAD patients stratified by different brain lesion dynamics in first follow-up MRI.

	New symptomatic lesions (n=28)	New asymptomatic lesions (n=11)	Lesions shrinking with at least 1 lesion resolution (n=36)	Normal MRI (n=22)	OR (CI) (New lesions vs no new lesions)	p-value*
Age at presentation (yrs), median (IQR)	5 (5.7)	5 (2.8)	5.1 (6.3)	7 (6)	1.03 (0.94-0.15)	0.34
Sex (Male: Female)	15:13	2:9	13:23	11:11	0.91 (0.4-2.0)	0.16
Positive oligoclonal bands (%)	4/14 (29)	2/6 (33)	3/23 (13)	3/14 (21)	0.635 (0.18-2.19)	0.45
Raised CSF protein (%)	7/14(50)	0/4 (0)	11/27 (41)	5/16 (31)	1.03 (0.33-3.31)	0.45
Time from first MRI to second MRI (month), median IQR	12 (2-36)	3.5 (2 - 8)	4 (2.5 – 7.5)	4 (2.5 – 7)	0.95 (0.9-0.97)	**0.03**
Acute management on 1st event						
Steroids (%)	16 (57)	5 (45.5)	27 (75)	17 (77)	2.69 (1.13- 6.54)	0.08
IVIg (%)	8 (29)	5(46)	6 (17)	5 (23)	0.16 (0.02- 0.72)	0.25
PLEX (%)	0	0	7 (19)	6 (27)	**36872171 (0-NA)**	**0.01**
Time to steroids, days (mean)	4.7	38.9	10.8	6.9	**0.46, incr=20days (0.14- 0.98)**	**0.01**

When evaluating brain MRI lesion outcomes after sequential relapses for MOGAD patients in 511 MRI scans, the proportion of normal brain MRI was reduced after each clinical relapse (**Table 3, Figure 2**). Disappearing lesions (lesion shrinking or normalization of MRI) were seen in 40% after the 2nd attack, 21% after 3rd attack and none after the 4th attack. There was a trend to more lesions (symptomatic and asymptomatic) with each subsequent attack. Lesion dynamics throughout the disease course in a patient with MOGAD is illustrated in **Figure 3**.

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Table 3: Normalization of MRI lesions after sequential relapses for MOGAD patients with brain involvement on initial MRI (n=97).

Radiological findings in follow up MRI*s*	1st attack, % (n)	2nd attack, % (n)	3rd attack, % (n)	4th attack, % (n)	5th attack, % (n)
New symptomatic lesions	29% (28)	44% (17)	64% (9)	63% (5)	57% (4)
New asymptomatic lesions	11% (11)	15% (6)	14% (2)	20% (2)	29% (2)
Lesion shrinking including at least 1 lesion resolution	37% (36)	28% (11)	14% (2)	12% (1)	14% (1)
Normal MRI	23% (22)	12% (5)	7% (1)	0	0
Total patients	**97**	**39**	**14**	**8**	**7**

A total of 62 MRIs were performed on 23 MOGAD patients on maintenance immunotherapy (**Supplemetal Table 1**). Of these 19 MRIs were performed on patients on mycophenolate mofetil, MMF (4 new symptomatic lesions, 3 new asymptomatic lesions, 4 stable, 5 lesion shrinking, and 3 normal MRI), 3 on rituximab (all new symptomatic lesions), 12 on azathioprine (4 new symptomatic lesions, 7 stable and 1 lesion shrinking), 7 on IVIg (2 new asymptomatic lesions, one stable, 4 lesion shrinking), 13 on a combination of IVIg and MMF (1 new symptomatic lesion, 4 new asymptomatic, 6 stable and 2 lesion shrinking) and 8 on interferon beta 1a (2 new symptomatic lesions, 1 new asymptomatic and 5 stable). Asymptomatic lesions beyond the first follow-up MRI scan were more common in patients on maintenance immunotherapy than patients on no treatment (16% (10/62) vs 4% (9/255), p=0.009).

New lesions (symptomatic and asymptomatic) at first follow-up scan were associated with increased likelihood of relapse (p=0.02, **Figure 4a)** and persistent MOG-Ab serostatus (p=0.0016, **Figure 4b**), but not with increased disability (EDSS increase >1, p=0.8, **Figure 4c**). Four patients in the group with new lesions and two patients in the group with no new lesions did not have a baseline EDSS and so were excluded from the Kaplan-Meier survival analysis. EDSS at final follow-up was also not different in the two groups with a median of 1.5 (range 0-5) in the group with new lesions vs median 1 (range 0-6) in the group with shrinking lesions (p=0.28). EDSS > 3 was seen in 10% (4/39) of patients in the group with new lesions on first follow-up MRI and 5% (3/58) in the group with no new lesions (p=0.44).

Discussion

In this UK-wide observational study of paediatric MOGAD patients, we observed that 83% of MOGAD cases had at least one lesion resolved on the first follow-up MRI scan. In contrast, in a cohort of paediatric MS presenting in the same epoch to the same centres (n=103), only one patient had one

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lesion resolve on follow-up imaging. The striking difference between lesion resolution between children with MOGAD and RRMS suggest clear pathobiological differences between these two relapsing demyelinating disorders. This can also be useful in clinical practice when trying to differentiate between MS and its mimics; significant lesion resolution will go against the diagnosis of MS. There is a clear need for securing diagnosis given the paradigm shift in clinical practice toward the early use of highly effective disease modifying therapies in paediatric MS[11] after the first attack, hence in patients with diagnostic uncertainty at presentation, our findings suggest it may be helpful to wait until the first follow-up MRI to better inform the diagnostic process. In addition, it is important to consider a multimodal investigative approach, using paraclinical factors such as age at presentation, presence of intrathecal oligoclonal bands and EBV serology to help differentiate cases with diagnostic uncertainty[4].

Most patients with MOGAD had lesion resolution at first follow-up MRI; however, we showed that this became less frequent with sequential relapses, suggesting that the ability for brain repair is reduced following multiple relapses. In these patients, following multiple relapses (most were of the leukodystrophy-like phenotype[12]), new asymptomatic lesions and persistent enhancement were seen outside of clinical attack and may indicate that even within individual patients the disease process changes over time and may respond differently to different medication or interventions. It is also possible that the different lesion evolutions are influenced by environmental factors (e.g., infection or vaccination) which may settle naturally without treatment once the trigger has been removed. Asymptomatic lesions were seen more frequently in patients treated with maintenance immunosuppression, in particular IVIg. As patients on immunosuppression represent a more severe group with more relapses this finding is not unexpected. Nevertheless, it is possible that the treatment may have prevented clinical relapses but was not sufficient to stop the inflammatory disease completely. Of note, children with MOGAD, many of whom require general anaesthesia for MRIs given their younger age, do not have standardized MRI protocols as performed in children with RRMS; this may bias our results to a more severe group of patients being scanned more frequently. The question about treatment escalation in patients with new asymptomatic lesions will need further studies.

Time to initiate steroids and the use of plasma exchange for the acute attack were the strongest predictors of MRI outcome following MOGAD attack. The importance of early steroid treatment was also observed in a retrospective study of 75 children with MOGAD with lower risk of relapse in patients who received immunotherapy <7 days from onset[13]. Although time to steroid was the

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shortest in the group with symptomatic lesions it is likely that the group with new asymptomatic lesion, which had longer time to steroids, has influenced the results of the group comparison. In addition, use of steroids was showing to promote resolution of large T2 lesions (defined as ≥1 cm), but not smaller lesions (<1cm), in a retrospective study of 585 lesions from 55 adult and paediatric MOGAD patients[14]. As current practice for MOGAD is to only perform plasma exchange for severe attacks[15], the data presented here may suggest that early removal of the antibodies may influence the disease trajectory over time and, akin to AQP4-Ab NMOSD[16, 17], plasma exchange should be considered earlier and in more MOGAD patients.

Interestingly new symptomatic and asymptomatic lesions on the first follow-up MRI scan were associated with increased likelihood of further relapses. This is in keeping with a retrospective cohort study, in which 4/107 MOGAD patients with new asymptomatic lesions had a shorter time to next relapse, compared to those without[18]. In contrast, two large study did not find an association between new asymptomatic lesions and shorter time to next relapse[6,19]. It is likely that the conflicting results in the literature are due to the inherit biases of lesion dynamics in MOGAD with new lesions on the first follow-up MRI reflecting disease activity which may developed during the prior attack but may not have been apparent (radiologic lag) or may have developed in the days after the acute MRI was undertaken. This emphasise the importance of rebaslining after the acute attack.

It is important to highlight that by contrast to MRI studies of patients with MS, when studying MOGAD, this lesion dynamic with lesions appearing and disappearing (even within the attacks), differences in timing and outcome may influence comparison across studies. A previous study evaluating lesion dynamics in MOGAD[20] noted resolution of the index lesion (defined as symptomatic or largest lesion) in 60% (9/15) of paediatric MOGAD patients. As our studied focused on children with abnormal brain MRI (acute disseminated encephalomyelitis, ADEM, and ADEM-like phenotypes) who presented with cerebral polyfocal presentation, we were unable to accurately identify the symptomatic lesion. It is possible that the timing and interval between attack and first follow-up neuroimaging (remission MRI) in our cohort (with median 0.4 years) may explain the differences noted in our cohort's frequency of lesion resolution/normalization of MRI compared to previous studies.[8, 21] Longer intervals between attack and remission follow-up imaging are more likely to demonstrate T2-lesion resolution. Furthermore, we compared evolution of lesions between the initial and follow up imaging regardless of whether the second MRI was performed for a further attack/relapse or routine follow-up (remission scan). This differs from the aforementioned studies,

which focused on attack-to-remission scans only. As a result, when evaluating attack-to-attack MRIs, the interpretation of lesion resolution is more complex and may be affected by new lesions occurring in the same region as old residual lesions. Nevertheless, in a real-world setting with young children that may require general anaesthetic for repeated follow-up imaging, it is not always feasible to obtain remission MRI scans outside of clinical attacks.

This study is limited by its retrospective design with a lack of standardized MRI assessments (i.e., at regular time intervals on the same scanner). Nevertheless, this real-world study is reflective of clinical practice where MRIs are undertaken on different scanners and at variable intervals. Although we report a large paediatric MOGAD cohort, the sample size within each first-follow up MRI category was small limiting some of our statistical inferences. We limited our analysis to patients with abnormal brain MRI at onset (regardless of the clinical phenotype at presentation) and did not include MOGAD patients with only optic neuritis or transverse myelitis at onset, which may limit applicability of some of our findings. Nevertheless, we specifically selected to evaluate lesion dynamics in MOGAD children with abnormal brain MRI at presentation to also allow us to better understand pathobiological mechanisms of damage and repair and whether lesions in MOGAD are resulting from oedema or demyelination. In fact, the rapid disappearance of lesions seen at follow-up imaging supports a transient phenomenon such as resolution of myelin oedema rather than remyelination which would be expected to take longer to occur.

Future studies investigating differences in lesion dynamic in patients presenting with non-brain involvement (ON and TM) compared to those with brain involvement (ADEM or cortical presentations) may shed some more light on the heterogeneity of the disease course. Given that EDSS is not a sensitive enough clinical outcome measure in both MS and MOGAD (median score 1.0 at final follow-up for both groups), the use of other clinically relevant outcome measures such as visual acuity or retinal nerve fibre layer (RNFL) thickness in patients with ON and brain involvement may be more informative; however, we did not have systematic data for these measures across our patient cohort.

Our findings have clinical relevance when evaluating children with acquired demyelinating syndromes; for instance, in the cases when there is a diagnostic challenge with overlapping clinical features, lesion disappearance should point to a non-MS diagnosis. This is also of relevance for clinical trials in children with MOGAD; new or enlarging T2 lesions on brain MRI is often used as a primary outcome measure in MS, which relies on lesion persistence over time. In MOGAD this is not

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as straightforward given the dynamic nature of the lesions. Future studies evaluating temporal dynamics between white matter lesion evolution over time and long-term outcomes may help us to better understand the pathobiology of this condition, and act as a platform for further interventions.

The key to improving outcomes in MOGAD is making early diagnosis based on accurate and reproducible detection of MOG-Ab[22], improving our understanding of the mechanisms that lead to relapses and disability, identifying the main treatment targets and clarifying when they should be used. Recent cohort studies and case reports have shown that the disease course is very heterogeneous in terms of the clinical course. The number of clinical relapses itself does not accurately explain the disability accrual at the individual level, possibly because of individual differences in the susceptibility for myelin damage and mechanisms of remyelination and repair. For instance, although younger children are more likely to have a severe brain pathology with higher lesion load detected on conventional imaging than older children[23]; recovery from acute attacks appears faster than in older children and adults. This may not be disease-specific and was also observed in a comparison between adult and children with MS demonstrating that every 10 years of age, there was a reduced EDSS recovery by 0.15 points[24]. This may suggest a therapeutic window particularly in this paediatric age group. With the lack of evidence-based guidelines for the acute treatment of MOGAD, the results presented here not only indicate that time to steroids and the use of plasma exchange are beneficial for early disease trajectory, but they also indicate that optimal management at presentation is a key predictor of long-term outcome.

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Figure legends

Figure 1: Brain imaging of three patients demonstrating patterns of lesion dynamics. Coronal T2-weighted fluid-attenuated inversion recovery (FLAIR) images at onset (A), 3 months (B), 9 months (C) of patient 1 demonstrating appearance of new lesions at three months scan with significant resolution of lesions at 9 months. Axial T2-weighted images at onset (D) and 2 months (E) of patient 2 demonstrating confluent diffuse white matter changes bilaterally at onset with complete lesion resolution at two months. Axial T2-weighted images of patient 3 focusing on the cerebellum at onset (F), 5 months (G), 7 months (H) and 12 months (I) demonstrating a mixed picture with some lesions appearing and some disappearing at the same timepoint.

Figure 2: Lesion dynamics throughout the disease course in 97 patients with MOGAD. Each horizontal line represents an individual patient time course. First follow-up MRI revealed new symptomatic lesions, i.e., associated with a relapse, (red) in 28 patients. New asymptomatic lesions (purple) were seen in 11 patients. Lesion shrinking with at least one lesion disappearing (green) was reported in 36 patients. Completely normal MRI (blue) was seen in 22 patients. Although not seen at first follow-up scan, many of the patients with initial partial lesion resolution remained stable in between attacks (yellow). In patients with multiple clinical relapses, new asymptomatic lesions appeared later in the disease course (purple). This was not seen in patients in whom MRI had previously normalized.

Figure 3: Brain imaging throughout disease course of a MOGAD patient with relapsing acute disseminated encephalomyelitis (ADEM). Acute presentation at age 3 years demonstrating bilateral globus pallidus signal change on T2-weighted imaging (A). Clinical relapse at age 5 with similar semiology, FLAIR-weighted images demonstrating multiple supratentorial T2 hyperintense lesions (B). Follow-up FLAIR-weighted imaging at age 6, demonstrating complete resolution of lesions (C).

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Third CNS attack aged 10 years, FLAIR-weighted imaging demonstrates a single lesion in the left parieto-occipital deep white matter (D); in view of worsening and lack of steroid responsiveness, repeat imaging was performed on day 14 (E) shows interval appearance of extensive multi-lobar bilateral subcortical white matter lesions with these foci showing intense nodular enhancement with a linear pattern of enhancement also apparent. There is no associated restricted diffusion (not shown). Follow up remission imaging at 11 years (F), EDSS 2.0, shows progression of signal abnormality in right frontal lobe subcortical white matter associated with new patchy enhancement. The subcortical signal abnormality elsewhere appears similar in extent.

Figure 4: Kaplan-Meier survival analyses were used to estimate the cumulative risk of clinical relapses (A), of disability accrual (increase in EDSS score by 1 or more, B), and of seroconversion to MOG-Ab negative status (C), using the log-rank test to compare patients stratified to two groups of lesion dynamics on first follow-up MRI (new lesions vs shrinking lesions).