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Clinical presentation and prognosis in MOG-antibody disease: a UK study

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A condition associated with an autoantibody against MOG has been recently recognized as a new inflammatory disease of the central nervous system, but the disease course and disability outcomes are largely unknown. In this study we investigated clinical characteristics of MOG-antibody disease on a large cohort of patients from the UK. We obtained demographic and clinical data on 252 UK patients positive for serum immunoglobulin G1 MOG antibodies as tested by the Autoimmune Neurology Group in Oxford. Disability outcomes and disease course were analysed in more detail in a cohort followed in the Neuromyelitis Optica Oxford Service ($n = 75$), and this included an incident cohort who were diagnosed at disease onset ($n = 44$). MOG-antibody disease affects females (57%) slightly more often than males, shows no ethnic bias and typically presents with isolated optic neuritis (55%, bilateral in almost half), transverse myelitis (18%) or acute disseminated encephalomyelitis-like presentations (18%). In the total Oxford cohort after a median disease duration of 28 months, 47% of patients were left with permanent disability in at least one of the following: 16% patients had visual acuity $\leqslant$6/36 in at least one eye, mobility was limited in 7% (i.e. Expanded Disability Status Scale $\geqslant$ 4.0), 5% had Expanded Disability Status Scale $\geqslant$ 6.0, 28% had permanent bladder issues, 20% had bowel dysfunction, and 21% of males had erectile dysfunction. Transverse myelitis at onset was a significant predictor of long-term disability. In the incident cohort 36% relapsed after median disease duration of 16 months. The annualized relapse rate was 0.2. Immunosuppression longer than 3 months following the onset attack was associated with a lower risk of a second relapse. MOG-antibody disease has a moderate relapse risk, which might be mitigated by medium term immunosuppression at onset. Permanent disability occurs in about half of patients and more often involves sphincter and erectile functions than vision or mobility.

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Abbreviations: ADEM = acute demyelinating encephalomyelitis; EDSS = Expanded Disability Status Scale; LETM = longitudinally extensive transverse myelitis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders

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Introduction

A condition associated with the presence of serum anti-MOG antibodies has been recently proposed as a new inflammatory disease of the CNS driven by antibodies of the IgG1 class, which target MOG expressed on myelin sheaths and promote demyelination (Reindl *et al.*, 2013). MOG-antibody disease is increasingly recognized as distinct from multiple sclerosis as typical multiple sclerosis patients test negative for the presence of MOG antibodies when novel assays with conformationally intact MOG are used (Waters *et al.*, 2015). Moreover, MOG-antibody disease clinically and radiologically resembles AQP4-antibody neuromyelitis optica spectrum disorders (NMOSD) and acute demyelinating encephalomyelitis (ADEM) rather than multiple sclerosis (Brilot *et al.*, 2009; Mader *et al.*, 2011; Kitley *et al.*, 2012*b*, 2014; Jurynczyk *et al.*, 2017). Although MOG-antibody disease is considered milder and less relapsing than AQP4-antibody NMOSD (Kitley *et al.*, 2014; Sato *et al.*, 2014), the clinical course, predictors of relapses and clinical outcomes remain largely unknown due to a relatively small number of patients included in previous studies and biases towards recruiting relapsing patients because monophasic patients could not be diagnosed at onset until the recent discovery of the disease (Kitley *et al.*, 2014; Jarius *et al.*, 2016*a*).

In this study we examined demographics, disease presentation, disease course and clinical outcomes in a large cohort of patients from the UK ($n = 252$), who tested positive for serum IgG1 MOG antibodies. Clinical outcomes and predictors of relapses were studied in more detail in a cohort followed-up in the neuromyelitis optica (NMO) Specialist Clinic in Oxford ($n = 75$), including patients who were diagnosed with MOG-antibody disease at onset ($n = 44$).

Materials and methods

Ethics

All patients followed in Oxford signed written consent of the NMO Tissue Bank (Oxford Research Ethics Committee C Ref: 10/H0606/56) and the audit of the MOG antibody-positive patients was registered under the Oxford University Hospitals Trust policy.

MOG antibody testing

Testing for the presence of serum MOG antibodies was performed in the Autoimmune Neurology laboratory in Oxford using a cell-based assay (M.W.) as described previously (Waters *et al.*, 2015). All MOG antibody-positive patients were negative for AQP4 antibodies.

Cohorts

We selected three different cohorts to analyse: the 'UK Cohort', which was the largest but least detailed and objective dataset; the 'Oxford Total Cohort' with more detailed uniformly and prospectively collected data; and an 'Oxford Incident Cohort' where only those diagnosed at onset were included.

UK cohort

Questionnaires on 494 samples positive for MOG antibodies were sent out to hospitals, or requesting clinicians (where they were identifiable), which included 12 basic questions on year of birth, ethnicity (Caucasian, Asian, Afro-Caribbean, Mixed or Other), date of onset attack, onset attack type [unilateral optic neuritis, bilateral optic neuritis, short transverse myelitis, longitudinally extensive transverse myelitis (LETM), ADEM, other], recovery from first attack (full, good, moderate or poor), maintenance prednisolone or immunosuppression treatment (none, yes for <3 months, 3–6 months, >6 months), number of attacks, date of first relapse, date of last relapse, end date of follow-up, disability at last follow-up (none, mild, moderate, severe) and current diagnosis (the questionnaire is shown in the Supplementary material). Clinicians were asked to specify if the onset attack was in the 'other' category. ADEM-like presentations (e.g. brainstem attack) were merged with ADEM attacks and analysed as one group. Complete questionnaires were returned on 252 patients.

Oxford total cohort

More extensive prospectively collected data from 75 patients seen within the specialist Neuromyelitis Optica Clinic in Oxford were available and included treatment, disability outcomes, disease course and phenotype. We selected disability outcomes that were prevalent enough in the MOG-antibody cohort: visual acuity $\leqslant 6/36$ in at least one eye, Expanded Disability Status Scale (EDSS) $\geqslant 4.0$ (ambulatory without aid or rest for <500 m), neurogenic bladder dysfunction (urinary incontinence and/or urgency), neurogenic bowel dysfunction (faecal incontinence and/or constipation) and erectile dysfunction. Outcomes were considered in the analysis if they persisted for at least 6 months and were present at last follow-up. Cognitive problems were noted when reported but were not systematically assessed and thus not analysed.

Oxford incident cohort

Because MOG-antibody disease is a recent discovery and thus the diagnosis was not possible until the past 5 years, patients captured in prevalence cohorts with longer follow-up are likely to have been diagnosed if they present with relapses. To avoid this relapse risk bias, a 44-patient incident cohort from the Oxford cohort were identified where the diagnosis was made shortly after onset and before the second relapse. The onset dates were all after January 2012, once the diagnostic MOG-IgG1 assay became available.

Statistical analysis

Statistical analysis was performed using R. Unpaired *t*-tests or Mann-Whitney U-tests were used when comparing two groups. ANOVA or Kruskal-Wallis tests were used when comparing multiple groups (e.g. patients with distinct onset presentations). The Kaplan-Meier method was used for estimating relapse risk and disability outcomes. Binomial and logistic regression was used to identify predictors of relapses and

disability. K-means clustering was used to identify patient subgroups according to age of onset.

Results

Demographic data

The demographics of the UK cohort, the Oxford total cohort and Oxford incident cohort are shown in Table 1. There were no obvious differences between the three cohort sets except for shorter follow-up periods and lower relapse rate in the Oxford incident cohort.

In the UK cohort, the ethnic breakdown was as expected in the general population. There was a slight female predominance of 57% and a broad onset age range of 1–81 years with a trimodal appearing distribution identified from the modelling analysis, with the age clusters being <20 years, 20–45 years and >45 years at disease onset (Fig. 1A and Supplementary Fig. 1A). Male and female patients

Table 1 Comparison of basic demographics, clinical features between the UK cohort, Oxford total cohort and Oxford incident cohort (diagnosis after the onset attack)

	Total cohort	Oxford	
		Total	Incident
Patients, *n*	252	75	44
Mean age at onset ± SD	30.1 ± 18.3	29.0 ± 16.5	32.0 ± 17.6
Female, %	57	56	48
Onset attack, %			
Unilateral ON	31	25	18
Bilateral ON	24	27	27
Transverse myelitis	18	20	21
ADEM or ADEM-like	18	20	25
Simultaneous ON and TM	9	8	9
With short TM	4	1	0
With LETM	5	7	9
Disease course, %			
Monophasic	56	41	64
Relapsing	44	59	36
Phenotype at follow-up, %			
ON	NA	37	36
TM	NA	12	18
ADEM/ADEM-like	NA	24	32
ON + TM	NA	27	14
Median disease duration in months (range)	26 (0–492)	28 (1–437)	15.5 (1–57)
Time until relapse, months			
1st quartile	14	7	5
Median	40*	27	44*
Reaching endpoints			
VA ⩽6/36 in one or both eyes, %	NA	16	7
Limited walking distance, EDSS ⩾4, %	NA	7	9
Permanent bladder dysfunction, %	NA	28	34
Self or *in situ* catheterization, %	NA	17	25
Permanent bowel dysfunction, %	NA	20	27
Permanent erectile dysfunction, % males	NA	21	26
CSF findings		Oxford total cohort	
Normal WBC (<10/μl)		29/47	
WBC 10–50/μl		12/47	
WBC 50–100/μl		3/47	
WBC ⩾100/μl (range)		3/47 (100–300)	
Normal protein		27/50	
CSF protein, 0.5–1 g/l		18/50	
CSF protein, ⩾1 g/l (range)		5/50 (1–2.9)	
Elevated protein with normal WBC (protein range)		4/39 (0.6–1.7)	
Unmatched OCB		7/57	

*Estimated from Kaplan-Meier curves.

OCB = oligoclonal bands; ON = optic neuritis; TM = transverse myelitis; VA = visual acuity; WBC = white blood cells.

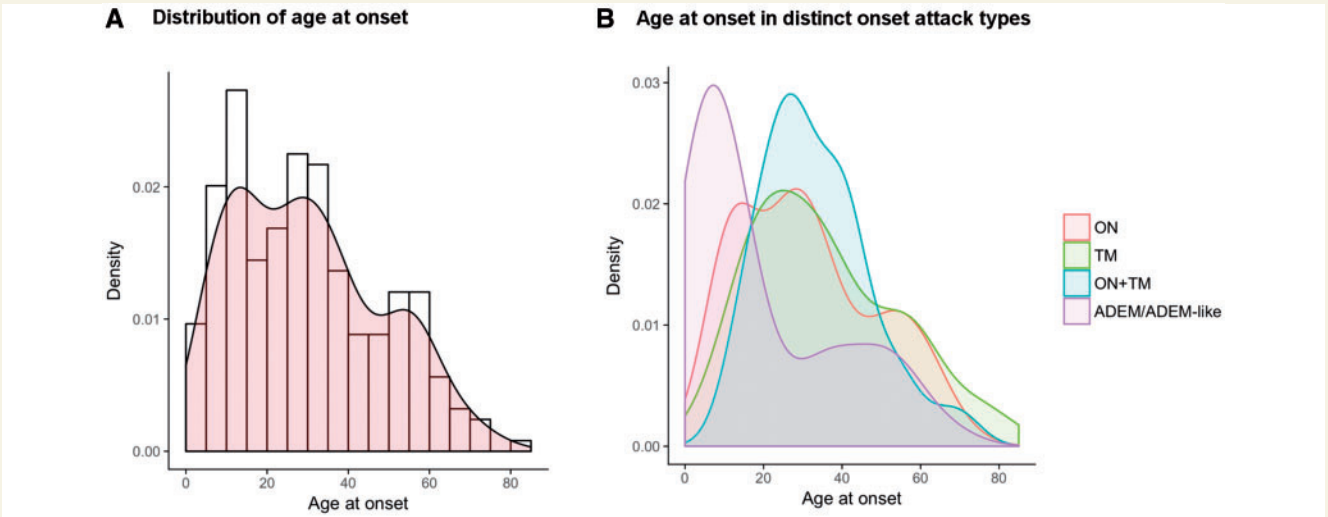

Figure 1 Age at onset in MOG-antibody patients in the UK. (**A**) Distribution of age at onset shown as a histogram overlaid with a density plot (pink). (**B**) Age at onset in distinct MOG-antibody onset phenotypes. ON = optic neuritis; TM = transverse myelitis.

Table 2 Basic clinical information on patients with different onset attack phenotypes in the UK and Oxford incident cohorts

	Unilateral ON	Bilateral ON	LETM	Short TM	ON + TM	ADEM/ ADEM-like
UK cohort (*n* = 252)						
Patients, %	31	24	14	4	9	18
Mean age at onset in years ± SD (range)	28 ± 16 (7–68)	36 ± 18 (6–74)	31 ± 17 (6–73)	53 ± 16 (22–81)	33 ± 14 (15–69)	19 ± 19 (1–67)
Median disease duration in months (range)	27 (2–432)	17 (1–355)	26 (0–287)	28 (5–108)	24 (3–312)	26 (8–492)
Relapsing, %	53	43	31	22	39	46
Oxford incident cohort (*n* = 44)						
Patients, %	18	27	18	2	9	25
Median disease duration in months (range)	25 (2–43)	10 (3–20)	6.5 (1–57)	9	31 (11–37)	37 (8–53)
Relapsing, %	50	42	12	0	50	36

ON = optic neuritis; SD = standard deviation; TM = transverse myelitis.

had comparable general characteristics with similar mean onset age, ethnicity and similar disease duration although there were more onset optic neuritis + transverse myelitis in males (14% versus 6%, not significant, Supplementary Table 1). There was a trend towards higher proportion of female patients and younger age at onset in non-Caucasian patients when compared with Caucasians (Supplementary Table 2).

Disease presentation

In the UK cohort the majority of patients (55%) presented with optic neuritis: 24% bilateral, 18% had isolated transverse myelitis; 14% were longitudinally extensive and 4% short-segment; 9% had simultaneous optic neuritis and transverse myelitis; and 18% had an ADEM or ADEM-like presentation (including brainstem attacks). Patients with ADEM/ADEM-like presentations were younger than the other groups (Fig. 1B and Table 2) and in patients with disease onset <20 years of age it was the most prevalent presentation (36% of patients). Patients with disease onset between 20 and 45 years of age most often presented with unilateral optic neuritis (36%), while patients with disease onset above 45 years of age presented with bilateral optic neuritis (39%). Short transverse myelitis was more common than LETM in patients older than 45 years at onset (14% versus 9%), but was exceptional in younger patients. Onset presentations in different age groups are shown on Supplementary Fig. 1B.

In the Oxford Total cohort, where more detailed history was available, 11/75 patients experienced symptoms in keeping with area postrema syndrome (nausea, vomiting,

hiccups), most of them (91%) at onset attacks. In 5/11 patients, area postrema symptoms preceded the recognized onset attack symptoms. Vomiting was the most frequent symptom (nine patients), followed by hiccups (one), and cough (one). Five had ADEM/ADEM-like presentations, four had transverse myelitis ± optic neuritis and two had bilateral optic neuritis. Brain MRI scans were performed at the time of symptoms in 9/11 patients; three had brainstem lesions adjacent to fourth ventricle (Supplementary Fig. 2), one had cerebellar lesions, three had brain lesions without brainstem or cerebellar involvement and two had normal brain MRI.

Recovery from relapses

In the UK cohort, recovery from the onset attack was full or good in 78%, with full recovery more frequent in patients with unilateral optic neuritis and ADEM-like presentations (Fig. 2A). Younger patients were more likely to fully recover than older adults (Fig. 2B). Patients with optic neuritis at onset tended to relapse more frequently than those with transverse myelitis or ADEM (Table 2).

Disease course in the Oxford incident cohort

Time taken until 25% of patients relapsed was 5 months (Fig. 3A), with 36% relapsing at final follow-up. In those who were followed-up for at least 24 months ($n = 16$), the annualized relapse rate (excluding the onset attack) was 0.2. There was a tendency for more relapses in younger patients (Fig. 3B).

Patients presenting with optic neuritis and classic Devic's phenotype were more likely to relapse than those with isolated transverse myelitis or ADEM-like presentation (Fig. 3C and Table 2). The same phenomenon was observed in the total UK cohort (Supplementary Fig. 3).

Second attacks in the Oxford total cohort

Second attacks were predominantly optic neuritis (35/44 relapsing patients, 24/26 among those with isolated optic neuritis onset and 4/7 among those with isolated transverse myelitis at onset).

NMOSD, ADEM and multiple sclerosis criteria in the Oxford total cohort

Of the 53 adults (>16 years), 47 fulfilled either the NMO 2006 (Wingerchuk *et al.*, 2006) or NMOSD 2007 (Wingerchuk *et al.*, 2007) criteria but only 17 fulfilled the NMOSD 2015 (Wingerchuk *et al.*, 2015) criteria (because of the requirement for more than one area to be involved if AQP4 antibody-negative), two of whom fulfilled the ADEM criteria defined primarily for children (Krupp *et al.*, 2013). Six patients did not fulfil any of the aforementioned criteria: five had monophasic unilateral optic neuritis with normal brain MRI and one patient had short-segment transverse myelitis with a single non-specific brain white matter lesion. Assuming LETM attacks do not count as multiple sclerosis relapses, only one patient fulfilled the McDonald 2010 multiple sclerosis criteria

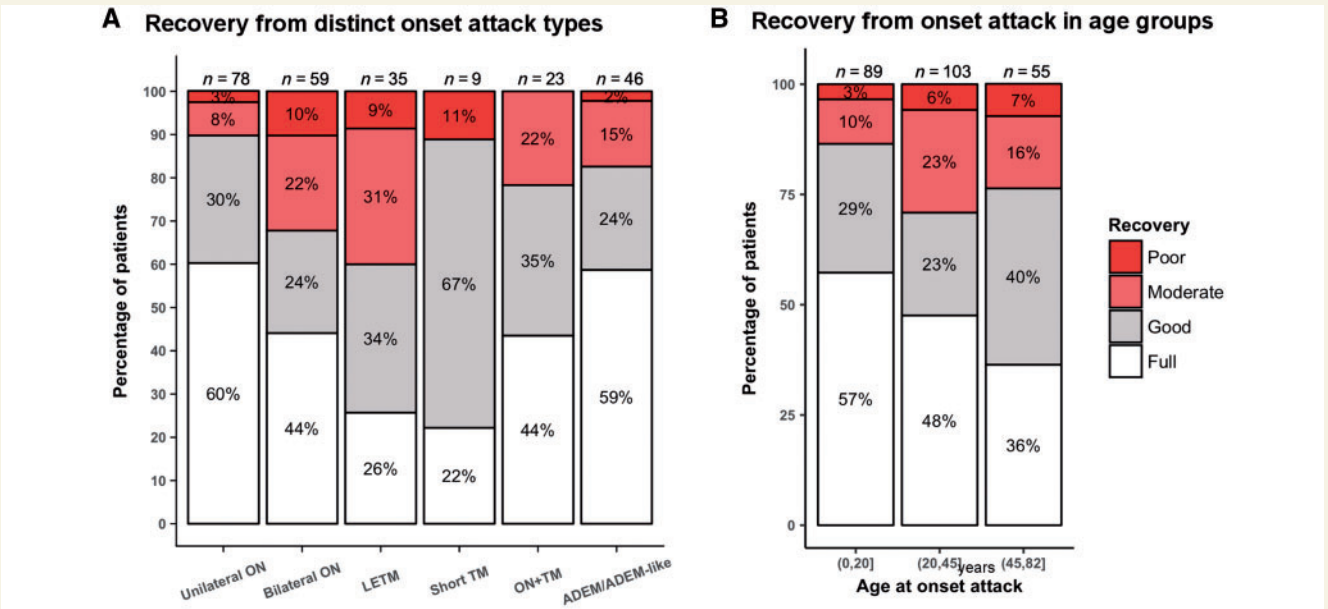

Figure 2 Recovery from the onset attack in the UK cohort. (**A**) Depending on the onset attack phenotype; (**B**) in different age groups. The total number of patients in each group is shown above the bar. ON = optic neuritis; TM = transverse myelitis.

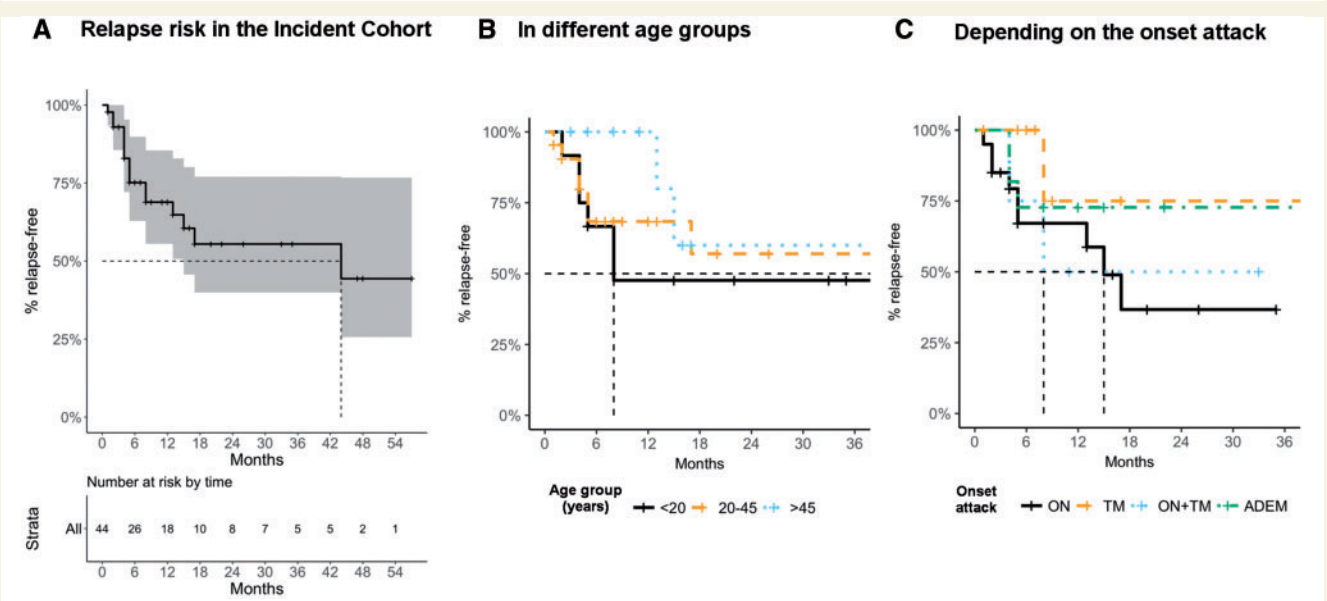

Figure 3 Kaplan-Meier curves showing cumulative probability over time of remaining relapse free in the Oxford incident cohort. (**A**) All patients in the Oxford incident cohort are included. The 95% confidence interval is shown in grey. The dashed line represents the number of months until 50% patients relapsed. The risk table shows the number of patients at risk of the relapse at each time point, (**B**) depending on the age at onset; (**C**) depending on the onset phenotype. ON = optic neuritis; TM = transverse myelitis.

(Polman *et al.*, 2011) but with red flags: bilateral optic neuritis followed within weeks by a short lateral transverse myelitis with a low thoracic lesion and typical NMO-like brain lesions (thalamic and brainstem). These lesions resolved (multiple sclerosis patients would be expected to increase lesion load over time) and oligoclonal bands were not detected in the CSF.

Of the 22 paediatric patients, 19 fulfilled the 2006 NMO or 2007 NMOSD criteria but only 13 fulfilled the 2015 NMOSD criteria, two of whom fulfilled the ADEM criteria. A further two fulfilled the ADEM criteria alone and another two had a diagnosable ADEM attack but because of other relapses these could not be diagnosed as ADEM at follow-up.

A detailed breakdown of how MOG-antibody patients fulfilled distinct disease criteria is shown in Supplementary Fig. 5A and B (adults and children, respectively).

Treatment duration and relapse risk

In the UK cohort, 40% did not receive long-term immunosuppression after the first attack, 34% were treated for less than 3 months, 11% from 3–6 months and 15% for more than 6 months. The risk of relapse was higher in those who were not immunosuppressed or immunosuppressed for less than 3 months (53% and 47%, respectively) when compared with those treated for 3 to 6 months or longer than 6 months (22% and 26%, respectively).

We then assessed this in more detail in the Oxford total cohort. Forty-five of 75 patients received long-term immunosuppression after their onset attack. Of those, 38 were treated with oral prednisolone, six with oral prednisolone and azathioprine and one with oral prednisolone and methotrexate. The risk of relapse was significantly lower in patients who were treated for more than 3 months in comparison to those treated for less than 3 months ($P = 0.005$, Cox regression, Fig. 4A). It was clear that relapses tended to occur early and often shortly after stopping corticosteroids (Fig. 4B).

Disability outcome in the UK cohort

In the UK cohort, where disability was subjectively scored by the referring clinician, 41% of patients did not have any disability at last follow-up but approximately a quarter had moderate to severe disability. Logistic regression showed that disability at last follow-up was significantly worse with number of attacks ($P < 0.01$) and worse recovery from the onset attack ($P < 0.01$), but was not significantly influenced by age at onset ($P = 0.07$), gender ($P = 0.7$), ethnicity ($P = 0.37$) or disease duration ($P = 0.8$).

Disability outcomes in the Oxford total cohort

Thirty-five of 75 patients in the Oxford total cohort had permanent visual (visual acuity $\leqslant$6/36 in at least one eye), motor (EDSS $\geqslant$4.0), sphincter or erectile dysfunction at the last follow-up. Twenty-five became disabled from the onset attack (33%) and 10 from subsequent attacks (20% of 50 who recovered fully from the onset attacks). We detail these outcomes below.

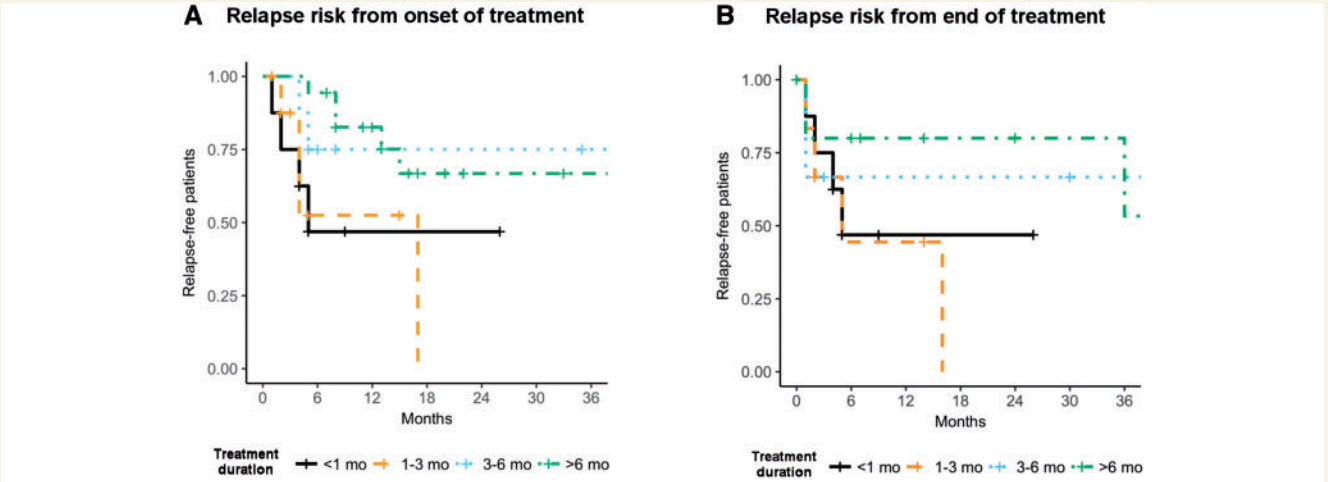

Figure 4 Risk of relapse depending on the duration of treatment in the Oxford incident cohort. (**A**) Kaplan-Meier curve showing cumulative probability over time of remaining relapse-free depending on how long patients were treated with immunosuppression after the onset attack: < 1 month, between 1 and 3 months, between 3 and 6 months and > 6 months. (**B**) Cumulative probability of remaining relapse-free over time depending on the duration of immunosuppression with baseline of observation at the moment when immunosuppression was discontinued. ON = optic neuritis; TM = transverse myelitis.

Visual disability

Twelve of 75 patients reached the permanent visual outcome of visual acuity 6/36 or worse in at least one eye at last follow-up and all of them had optic neuritis during the onset attack (± transverse myelitis or ADEM.) In nine, this was a consequence of the first attack, i.e. 9 of 48 patients who had optic neuritis at onset became visually disabled from the onset attack (four had unilateral optic neuritis, three bilateral optic neuritis and two had optic neuritis + ADEM). Seven of the nine were treated at acute attack with intravenous methylprednisolone, one with dexamethasone and one was not treated.

Of the remaining 39 patients with optic neuritis onset (± transverse myelitis or ADEM), three became visually impaired from subsequent attacks of isolated (uni- or bilateral) optic neuritis attacks. These three patients all recovered fully from the onset optic neuritis attacks. At the time of subsequent disabling attacks, two of them were not on background immunosuppression, and one was on a reducing dose of prednisolone and methotrexate. In the acute phase of the subsequent disabling optic neuritis attacks one patient received intravenous methylprednisolone, one had an increase in the dose of oral prednisolone and one was not treated.

Two of 75 patients had visual acuity 6/36 or worse in the best eye at last follow-up. Older patients were less likely to develop permanent visual disability at follow-up (Supplementary Table 3 and Supplementary Fig. 4A). Accordingly, patients who reached the visual disability endpoint were younger at disease onset than those who did not (mean 20.8 ± 11.3 versus 30.6 ± 17.0, $P = 0.06$). Of all patients who had optic neuritis at onset (± transverse myelitis or ADEM, $n = 48$) visual disability occurred in 12/39 (31%) patients younger than 45, and 0/9 (0%) older than 45 years of age. Cumulative probability of remaining free from visual disability is shown on Supplementary Fig. 4A and B.

Motor disability

All permanent motor disability (EDSS $\geqslant 4.0$) at follow-up was associated with transverse myelitis attacks (± optic neuritis) and occurred in five patients only (three males, two females). Four of the five had EDSS $\geqslant 6$ at last follow-up (5%). In three of five patients, disability was related to the onset attack and these three were of 30 patients with transverse myelitis at onset, 14 females, 16 males (15 transverse myelitis alone, nine ADEM + transverse myelitis, six optic neuritis + transverse myelitis). Of these three patients, two were treated at acute onset attack with intravenous methylprednisolone, plasma exchange and intravenous immunoglobulins and one was treated with intravenous methylprednisolone only. Two patients became disabled from subsequent transverse myelitis attacks and initially presented with optic neuritis or ADEM onset phenotypes. Both had stopped short courses of steroids just prior to the disabling transverse myelitis attack. In the acute transverse myelitis attack one of them was treated with intravenous methylprednisolone followed by oral prednisolone and the other had no acute treatment, but was started on interferon-β.

Those who had limited walking distance at last follow-up were slightly older than those without walking disability (36.3 ± 22.7 versus 28.6 ± 15.9, not significant). However, age of onset was not a significant predictor of final motor disability, neither was gender, disease duration or type of onset attack (Supplementary Table 3).

Cumulative probability of remaining free from motor disability is shown in Supplementary Fig. 4C and >D.

Bladder disability

Permanent bladder dysfunction at follow-up occurred in 21 patients, all related to transverse myelitis (with or without other features). Males were affected more frequently than females (12/33 versus 9/42), which was likely to be related to the higher proportion of males having transverse myelitis (± optic neuritis or ADEM) than females (16/33 versus 14/42 onset attacks, respectively). All of these patients had lesions affecting the thoracic cord or conus. Fifteen patients had bladder dysfunction from the onset attack. Six were treated with intravenous methylprednisolone only, five with intravenous methylprednisolone and plasma exchange, two with intravenous methylprednisolone, plasma exchange and intravenous immunoglobulins and two with oral steroids.

Six patients were disabled from further attacks (two from transverse myelitis onset phenotype, two from ADEM onset phenotype and two from optic neuritis onset attacks). Three were not on background immunosuppression, two stopped steroids within the last 2 weeks and one was on a reducing dose of prednisolone. During the attack that left them with bladder disability, five were treated with intravenous methylprednisolone and one with oral methylprednisolone.

Thirteen patients required long-term catheterization (5/42 females and 8/33 males) at last follow-up. Only two of these patients had ambulation problems (EDSS $\geqslant$4.0) at the same time.

Overall bladder outcome was not significantly affected by age of onset, disease duration or gender (Supplementary Table 3). Cumulative probability of remaining free from bladder disability is shown in Supplementary Fig. 4E and F.

Bowel and erectile dysfunction

Bowel and erectile dysfunction only occurred in those with bladder disability. Bowel dysfunction occurred in 15 patients (six females and nine males). Erectile dysfunction occurred in 21% of males, or 44% of males presenting with transverse myelitis at onset.

Cognitive problems

Six of 15 (40%) patients with ADEM/ADEM-like onset presentations were left with cognitive problems, three had paediatric and three had adult onset. Within the ADEM/ADEM-like group, age at onset was similar between those left with and without residual cognitive problems. Cognition was not affected in patients with other onset presentations. Of the paediatric patients, one showed poor concentration, one learning difficulties and one psychiatric (mania, hallucinations) and memory problems. In particular, the last patient was also positive for NMDAR-antibody encephalitis. Among adult patients, one showed memory impairment and low mood, one poor concentration and one drowsiness.

Poor outcome predictors in the Oxford total cohort

Onset attack involving transverse myelitis was a predictor of poor outcome (visual, motor, bladder, bowel or erectile) in the Oxford cohort ($P = 0.02$). This was not the case for the age at onset, gender or Caucasian ethnicity.

Importantly, when taking the 50 patients who did not reach poor outcome from the onset attack and looking for predictors of a subsequent poor outcome we found none among onset attack type, age at onset, gender, Caucasian ethnicity and poor recovery from onset attack.

Test positivity over time and relapse risk

We assessed whether the persistence of MOG antibodies on follow-up testing might be correlated with the risk of further relapses. We obtained information on 57 patients who had at least two MOG antibody tests over time, at least 6 months apart (all patients included in the group who showed persistence of the antibody in the serum had testing performed at least 6 months apart). Forty-one (72%) remained positive over time (median disease duration 37 months, range 17–57), 14 (25%) became negative on follow-up testing and two (3%) turned negative and then again positive (median disease duration 9 months, range 1–16, Fig. 5). Twenty-four of 41 (59%) patients in whom the antibody remained positive over time had further relapses. All patients who became negative over time remained relapse-free. Two patients who became negative and then positive (Fig. 5) did not have further attacks.

Patients who became antibody-negative over time more often presented with simultaneous optic neuritis and transverse myelitis, and ADEM-like phenotypes when compared with those who remained antibody-positive, and were more likely to be monophasic (58% versus 36%), but the differences were not statistically significant (Supplementary Table 4). The duration of immunosuppression after the onset attack did not seem to predict the antibody status.

Discussion

This is the largest MOG-antibody study reported and incorporates a national unselected patient cohort, the largest single centre cohort with more detailed clinical data and also a large incident cohort. We show that MOG-antibody disease can present at any age, most commonly with optic neuritis, shows slight female preponderance and no ethnic bias. It is often a relapsing disease with the risk of relapse affected by the duration of immunosuppression initiated after the onset attack. The prognosis is typically favourable, but patients can be left with significant sphincter and erectile dysfunction, cognitive impairment and poor visual acuity. The majority of this disability originates from the onset attack.

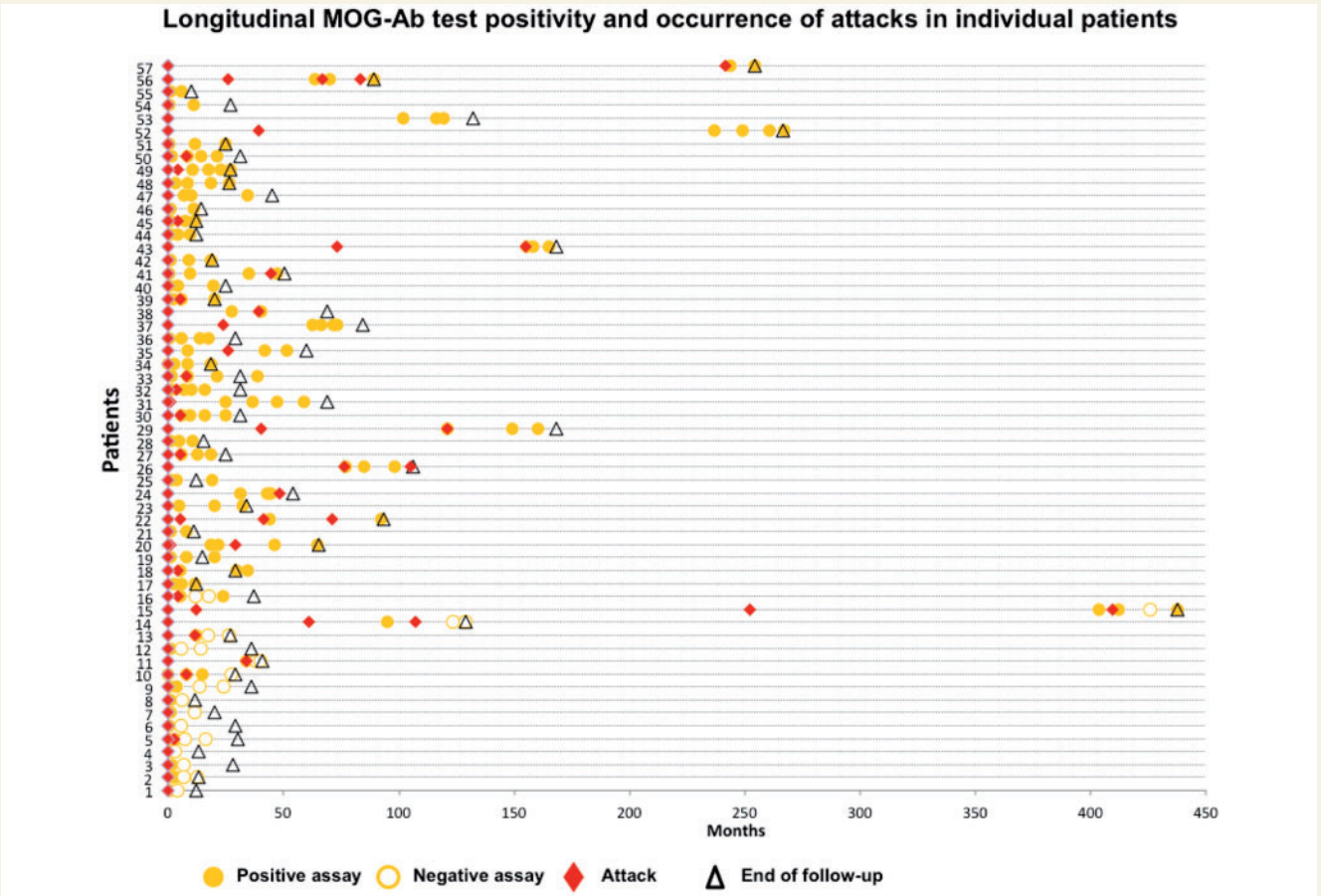

Figure 5 MOG-antibody test results (negative or positive) and the occurrence of relapses over time. Patients 1–14 became MOG antibody-negative at last follow-up, Patients 15 and 16 turned negative and then positive again, and Patients 15–57 remained positive at each assay over time. There were no relapses in patients who became negative.

Initial reports indicated that the presence of MOG antibody typically predicts a monophasic disease but focused on patients presenting with both optic neuritis and LETM (Kitley *et al.*, 2012*b*, 2014); however, the phenotype is clearly broader and includes a relapsing disorder (Sato *et al.*, 2014; Höftberger *et al.*, 2015). High risk of relapse over time (~80%) and high annualized relapse risk (0.92) recently reported (Jarius *et al.*, 2016*a*) may be overestimated because patients with onset prior to the availability of the antibody test will ordinarily only re-present and thus be diagnosed, if they relapse. Additionally, there is likely to be a bias towards testing patients with relapses. Our study, using an incident cohort with our policy of treating patients at onset with >6 months prednisolone (which appears to reduce the risk of relapse), may explain the lower risk of relapse of ~50% over 2 years (Fig. 3A) and lower annual relapse rates. However, it is still likely that some monophasic patients were not referred and thus the true risk of relapse may be even lower. It is also worth mentioning that none of the patients who turned antibody-negative on repetitive testing experienced further relapses during follow-up, which is in line with a recent report (Hyun *et al.*, 2017).

The prognosis in MOG-antibody disease has been a question of debate. In a recent study including 50 MOG-antibody patients, severe visual impairment was present at last follow-up in 36% (defined as visual acuity <0.5 in one or both eyes) and markedly impaired ambulation in 25% patients (Jarius *et al.*, 2016*b*). Another study reported a more favourable outcome with 19% patients with optic neuritis visually impaired (sustained visual acuity <0.2) at last follow-up (Sepúlveda *et al.*, 2016), which compares with our figure of 16%. Only 11% patients had EDSS ⩾4 (Sepúlveda *et al.*, 2016). In a study including 17 MOG-antibody patients only one had EDSS ⩾6 at last follow-up (Kim *et al.*, 2015). Analysis of our Oxford cohort showed that permanent visual disability affected only patients with optic neuritis at onset and typically was a consequence of the onset attack but could also result from subsequent optic neuritis attacks. Motor disability was rarer and might result either from onset or further transverse myelitis attacks. Interestingly, permanent bladder and

erectile dysfunction was more prevalent than motor disability at follow-up (28% and 21%, respectively), and this observation may be an important indicator to test for MOG antibodies, as in multiple sclerosis the occurrence of urogenital symptoms is considered similar to that of lower limb dysfunction (Miller *et al.*, 1965). Importantly our study indicates that patients with good recovery from the onset attacks are still potentially at risk of disabling attacks and that although it is difficult to predict who will have a future disabling attack, longer-term immunosuppression could be considered in patients presenting with optic neuritis because even among those who recovered there was an 8% risk of developing visual disability over the next 28 months. It is also worth noting that MOG-antibody ADEM/brainstem disease carried a risk of permanent cognitive impairment (40%).

When compared with our previous work MOG-antibody disease is clearly less disabling than AQP4-antibody NMOSD in terms of visual function and ambulation. After 25 months from onset permanent bilateral visual disability and reduced mobility as defined by EDSS $\geqslant$6.0 occurred in 1% and 4% of MOG-antibody patients, respectively, as compared with 20% and 25% of AQP4-antibody patients from the UK (Kitley *et al.*, 2012*a*). Sphincter dysfunction was not assessed in the AQP4-antibody cohort, but from our experience it is typically associated with motor disability rather than stand alone. It is also worth noting that a sizeable proportion (roughly 15%) of MOG-antibody patients presented with symptoms suggestive of area postrema syndrome, which has been thought to be highly specific for AQP4-antibody NMOSD.

Previous studies reported the presence of serum MOG antibodies in rare cases of paediatric and adult multiple sclerosis (Hacohen *et al.*, 2015; Spadaro *et al.*, 2016) although the paediatric cases have had their diagnoses revised to ADEM-optic neuritis, a known MOG-antibody phenotype (personal communication, Hacohen) and the adults had atypical multiple sclerosis phenotypes. In our UK cohort, 17/252 patients were diagnosed with multiple sclerosis by the referring clinicians but all had typical MOG-antibody disease features such as bilateral optic neuritis, LETM, ADEM-like presentation including brainstem involvement, lack of progressive disease, and brain MRI not typical of multiple sclerosis, including the absence of silent brain lesions. Assuming that LETM is not considered as a multiple sclerosis attack, only one adult patient in the Oxford cohort fulfilled McDonald criteria but with red flags such as NMO-typical brain imaging and absent oligoclonal bands in the CSF.

There are several strengths and limitations to our study. The main limitation of the study is the lack of information from all clinicians who requested testing. This was mainly due to the difficulty in identifying the responsible clinicians from the request forms because their in-house laboratories transpose request details when sending samples for external testing. However, we cannot think of a likely bias towards completing questionnaires for some phenotypes over others. The strength is that this is by far the largest national MOG-antibody cohort reported and the UK cohort was very similar to the Oxford cohort suggesting the obtained data were representative of the whole. Additionally, auditing results obtained from a single UK assay service allowed a wider range of patients to be assessed, thus included paediatric and adult populations, ADEM as well as NMOSD phenotypes, and we were able to identify the not uncommon presentation of short transverse myelitis. Further strengths of our study include: an incident cohort to reduce the risk of bias towards relapsing patients in those with onset before the availability of the antibody test and the largest single centre cohort ($n = 75$) ensuring homogeneous detailed data collection.

In conclusion, MOG-antibody disease is a newly identified CNS inflammatory condition, distinct from multiple sclerosis and is associated with attacks involving the optic nerve, spinal cord, brainstem and the brain. The risk of a relapsing disease is moderate and might be mitigated by prolonged immunosuppression. The prognosis is typically good, but a subset of patients might be left with some degree of sphincter, erectile, cognitive or visual dysfunction.

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Supplementary material

Supplementary material is available at *Brain* online.

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