

Full title: **Clinical presentation and prognosis in myelin oligodendrocyte glycoprotein-antibody disease, analysis of 252 patients from the United Kingdom**

Running title: MOG-antibody disease in the UK

Authors: Maciej Jurynczyk^{*1}, Silvia Messina^{*1}, Mark R. Woodhall^{*1}, Naheed Raza¹, Rosie Everett¹, Adriana Roca-Fernandez¹, George Tackley¹, Shahd Hamid², Angela Sheard¹, Gavin Reynolds¹, Saleel Chandratre¹, Cheryl Hemingway³, Anu Jacob², Angela Vincent¹, M. Isabel Leite¹, Patrick Waters^{**1} & Jacqueline Palace^{**1}

^{*}equally contributing first authors

^{**}equally contributing senior authors

¹Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, UK

²NMO Clinical Service, The Walton Centre, Liverpool, UK

³Department of Neurology, Great Ormond Street Hospital for Children, London, UK

Corresponding author: Jacqueline Palace, Nuffield Department of Clinical Neurosciences, West Wing, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, UK, email: jacqueline.palace@ndcn.ox.ac.uk

Abstract

A condition associated with an autoantibody against myelin oligodendrocyte glycoprotein 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 myelin oligodendrocyte glycoprotein antibody disease on a large cohort of patients from the United Kingdom.

We obtained demographic and clinical data on 252 United Kingdom patients positive for serum immunoglobulin G1 myelin oligodendrocyte glycoprotein 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 ($n = 44$).

Myelin oligodendrocyte glycoprotein antibody disease affects women (57%) slightly more often than men, shows no ethnic bias and typically presents with isolated optic neuritis (55%, bilateral in almost a 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% patients were left with permanent disability in at least one of the following: 16% patients had visual acuity $\leq 6/36$ in at least one eye, mobility was limited in 7% (i.e. expanded disability status scale ≥ 4.0), 5% had expanded disability status scale ≥ 6.0 , 28% had permanent bladder issues, 20% 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.

Myelin oligodendrocyte glycoprotein 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.

Keywords

Demyelination, Neuroinflammation, Multiple sclerosis, Neuromyelitis optica, Acute disseminated encephalomyelitis

Abbreviations

Ab – antibody, Abs – antibodies, ANOVA – analysis of variance, AQP4 – aquaporin 4, CSF – cerebrospinal fluid, EDSS – expanded disability status scale, IgG – immunoglobulin G, IVIG – intravenous immunoglobulins, IVMP – intravenous methylprednisolone, LETM – longitudinally extensive transverse myelitis, MOG - myelin oligodendrocyte glycoprotein, MRI – magnetic resonance imaging, NMDAR – N-methyl-D-aspartate receptor, NMO - neuromyelitis optica, NMOSD - neuromyelitis optica spectrum disorders, ns – not significant, OCB – oligoclonal bands, ON – optic neuritis, PLEX – plasma exchange, TM – transverse myelitis, UK – United Kingdom, VA – visual acuity, WBC – white blood cells

Introduction

A condition associated with the presence of serum anti-MOG Abs has been recently proposed as a new inflammatory disease of the CNS driven by Abs of the IgG1 class,

which target MOG expressed on myelin sheaths and promote demyelination (Reindl *et al.*, 2013). MOG-Ab disease is increasingly recognised as distinct from multiple sclerosis as typical multiple sclerosis patients test negative for the presence of MOG-Abs when novel assays with conformationally intact MOG are used (Waters *et al.*, 2015). Moreover, MOG-Ab disease clinically and radiologically resembles AQP4-Ab NMOSD and ADEM rather than multiple sclerosis (Brilot *et al.*, 2009; Jurynczyk *et al.*, 2017; J. L. Kitley *et al.*, 2012; Kitley *et al.*, 2014; Mader *et al.*, 2011). Although MOG-Ab disease is considered milder and less relapsing than AQP4-Ab 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 the previous studies and biases towards recruiting relapsing patients because monophasic patients could not be diagnosed at onset until the recent discovery of the disease (Jarius, Ruprecht, Kleiter, Borisow, Asgari, Pitarokoili, Pache, Stich, Beume, Martin W. Hümmert, *et al.*, 2016; Kitley *et al.*, 2014).

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

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

–Ab positive patients was registered under the Oxford University Hospitals Trust policy.

MOG-Ab testing

Testing for the presence of serum MOG-Abs 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-Ab-positive patients were negative for AQP4-Abs.

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-Abs 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 ON, bilateral ON, short TM, LETM, ADEM, other), recovery from 1st attack (full, good, moderate or poor), maintenance prednisolone or immunosuppression treatment (none, yes for less than 3 months, between 3 and 6 months, longer than 6 months), number of attacks, date of 1st 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 Supplementary Material 1). Clinicians were asked to specify the onset attack if it 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-Ab cohort: VA \leq 6/36 in at least one eye, EDSS \geq 4.0 (ambulatory without aid or rest for <500 meters), neurogenic bladder dysfunction (urinary incontinence and/or urgency), neurogenic bowel dysfunction (fecal 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-Ab 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 above 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 younger than 20 years, those between 20 and 45 years and those older than 45 years at disease onset (Fig. 1A) (and Supplementary Fig. 1A). Male and female patients had comparable general characteristics with similar mean onset age, ethnicity and similar disease duration although there were more onset ON + TM in males (14% vs 6%, ns, 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 ON; 24% bilateral, 18% had isolated TM; 14% were longitudinally extensive and 4% short-segment, 9% had simultaneous ON and TM and 18% had an ADEM or ADEM-like presentation (including brainstem attacks). Patients with ADEM/ADEM-like presentations were younger than other groups (Fig. 1B, Table 2) and in patients with disease onset < 20 years of age it was the most prevalent presentation (36% patients). Patients with disease onset between 20 and 45 years of age most often presented with unilateral ON (36%), while patients with disease onset above 45 years of age with bilateral ON (39%). Short TM was more common than LETM in patients older than 45 years at onset (14% vs. 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 five out of 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 TM \pm ON and two had bilateral ON. Brain MRI scans were performed at the time of symptoms in 9/11 patients; three had brainstem lesions adjacent to 4th 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 ON and ADEM-like presentations (Fig. 2A). Younger patients were more likely to fully recover than older adults (Fig. 2B). Patients with ON at onset tended to relapse more frequently than those with TM or ADEM (Table 2).

Disease course in the 'Oxford Incident Cohort'

Time 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 ON and classic Devic's phenotype were more likely to relapse than those with isolated TM or ADEM-like presentation (Fig. 3C, 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 ON (35/44 relapsing patients, 24/26 among those with isolated ON onset and 4/7 among those with isolated TM at onset).

NMOSD, ADEM and MS criteria in the 'Oxford Total Cohort'

Of the 53 adults (>16 years): 47 fulfilled either the 2006 NMO (Wingerchuk *et al.*, 2006) or 2007 NMOSD (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-Ab-negative), two of whom fulfilled the ADEM criteria defined primarily for children (Krupp *et al.*, 2013). Six patients did

not fulfill any of the aforementioned criteria: five had monophasic unilateral ON with normal brain MRI and one patient had short-segment TM with a single non-specific brain white matter lesion. Assuming LETM attacks do not count as MS relapses, only one patient fulfilled the McDonald 2010 MS criteria (Polman *et al.*, 2011) but with red flags: bilateral ON followed within weeks by a short lateral TM with a low thoracic lesion and typical NMO-like brain lesions (thalamic and brainstem). These lesions resolved (MS patients would be expected to increase lesion load over time) and OCB 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 of whom two 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-Ab patients fulfilled distinct disease criteria is shown on Supplementary Fig. 5A and 5B (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 to 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 Incident Cohort’. 45/75 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 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% patients did not have any disability at last follow-up but around 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 (0.07), gender ($p = 0.7$), ethnicity ($p = 0.37$) or disease duration ($p = 0.8$).

Disability outcomes in the ‘Oxford Total Cohort’

35/75 patients in the ‘Oxford Total Cohort’ had permanent visual ($VA \leq 6/36$ in at least one eye), motor ($EDSS \geq 4.0$), sphincter or erectile dysfunction at the last follow-up. Twenty-five became disabled from the onset attack (33%) and ten from subsequent attacks (20% of 50 who recovered fully from the onset attacks). We detail these outcomes below.

Visual disability

Twelve out of 75 patients reached the permanent visual outcome of VA 6/36 or worse in at least one eye at last follow-up and all of them had ON during the onset attack (\pm TM or ADEM.) In nine, this was a consequence of the first attack, i.e. nine out of 48 patients who had ON at onset became visually disabled from the onset attack (four had unilateral ON, three bilateral ON and two had ON + ADEM). Seven of the nine were treated at acute attack with IVMP, one with dexamethasone and one was not treated.

Out of the remaining 39 patients with ON onset (\pm TM or ADEM), three became visually impaired from subsequent attacks of isolated (uni- or bilateral) ON attacks. All these three patients recovered fully from the onset ON attacks. At the time of subsequent disabling attacks, two of them were not on background immunosuppression, and one was on reducing dose of prednisolone and methotrexate. In the acute phase of the subsequent disabling ON attacks one patient received IVMP, one had an increase in the dose of oral prednisolone and one was not treated.

Two out of 75 patients had VA 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 vs. 30.6 ± 17.0 , $p = 0.06$). Out of all patients who had ON at onset (\pm TM 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 4B.

Motor disability

All permanent motor disability ($\text{EDSS} \geq 4.0$) at follow-up was associated with TM attacks (+/- ON) and occurred in five patients only (three males, two females). Four of the five had $\text{EDSS} \geq 6$ at last follow-up (5%). In three of five patients disability was related to the onset attack and these three were out of 30 patients with TM at onset, 14 females, 16 males, (15 TM alone, nine ADEM + TM, six ON + TM). Out of these three patients, two were treated at acute onset attack with IVMP, PLEX and IVIG and one was treated with IVMP only. Two patients became disabled from subsequent TM attacks and initially presented with ON or ADEM onset phenotypes. Both of them had stopped short courses of steroids just prior to the disabling TM attack. In the acute TM attack one of them was treated with IVMP followed by oral prednisolone and the other one 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 vs. 28.6 ± 15.9 , ns). 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 on Supplementary Fig. 4C and 4D.

Bladder disability

Permanent bladder dysfunction at follow-up occurred in 21 patients, all related to TM (with or without other features). Males were affected more frequently than females (12/33 vs. 9/42), which was likely to be related to the higher proportion of males having TM (\pm ON or ADEM) than females (16/33 vs. 14/42 onset attacks, respectively). All these patients had lesions affecting the thoracic cord or conus. Fifteen patients had bladder dysfunction from the onset attack. Six were treated with

IVMP only, five with IVMP and PLEX, two with IVMP, PLEX and IVIG and two with oral steroids.

Six patients were disabled from further attacks (two from TM onset phenotype, two from ADEM onset phenotype and two from ON onset attacks). Three were not on background immunosuppression, two stopped steroids within the last two weeks and one was on a reducing dose of prednisolone. During the attack that left them with bladder disability five were treated with IVMP 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 ≥ 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 on Supplementary Fig. 4E and 4F.

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 TM at onset.

Cognitive problems

Six out of 15 (40%) patients with ADEM/ADEM-like onset presentations were left with cognitive problems, three had paediatric and three had adult onset. Within 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. Out 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-Ab 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 TM 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 looked 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-Abs 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-Ab 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%) patients turned negative and then again positive (median disease duration 9 months, range 1-16, Fig. 5). Twenty-four out of 41 (59%) of 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 ON and TM, and ADEM-like phenotypes when compared with those who remained antibody-positive, and were more likely to be monophasic (58% vs. 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-Ab 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-Ab disease can present at any age, most commonly with ON, 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 favorable, 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.

Initial reports indicated that the presence of MOG-Ab typically predicts a monophasic disease but focused on patients presenting with both ON and LETM (J. Kitley, Woodhall, *et al.*, 2012; Kitley *et al.*, 2014), however the phenotype is clearly broader and includes a relapsing disorder (Höftberger *et al.*, 2015; Sato *et al.*, 2014). High risk of relapse over time (around 80%) and high annualized relapse risk (0.92) recently reported (Jarius, Ruprecht, Kleiter, Borisow, Asgari, Pitarokoili, Pache,

Stich, Beume, Martin W. Hümmert, *et al.*, 2016) 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 around 50% over 2 years (Fig. 3A) and lower annual relapse rates. However it is still likely that we are not referred some monophasic patients 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-Ab disease has been a question of debate. In a recent study including 50 MOG-Ab patients, severe visual impairment was present at last follow-up in 36% (defined as VA < 0.5 in one or both eyes) and markedly impaired ambulation in 25% patients (Jarius, Ruprecht, Kleiter, Borisow, Asgari, Pitarokoili, Pache, Stich, Beume, Martin W Hümmert, *et al.*, 2016). Another study reported a more favorable outcome with 19% patients with ON 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 \geq 4 (Sepúlveda *et al.*, 2016). In a study including 17 MOG-Ab patients only one had EDSS \geq 6 at last follow-up (Kim *et al.*, 2015). Analysis of our Oxford cohort showed that permanent visual disability affected only patients with ON at onset and typically was a consequence of the onset attack but could also result from subsequent ON attacks. Motor disability was rarer and might result either from onset or further TM 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 ON 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-Ab ADEM/brainstem disease carried a risk of permanent cognitive impairment (40%).

When compared with our previous work MOG-Ab disease is clearly less disabling than AQP4-Ab NMOSD in terms of visual function and ambulation. After 25 months from onset permanent bilateral visual disability and reduced mobility as defined by EDSS ≥ 6.0 occurred in 1% and 4% of MOG-Ab patients, respectively, as compared with 20% and 25% of AQP4-Ab patients, respectively, from the United Kingdom (J. Kitley, Leite, *et al.*, 2012). Sphincter dysfunction was not assessed in the AQP4-Ab 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-Ab patients presented with symptoms suggestive of area postrema syndrome, which has been thought to be highly specific for AQP4-Ab NMOSD.

Previous studies reported the presence of serum MOG-Abs 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-ON, a known MOG-Ab 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-Ab disease features such as bilateral ON, 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 an MS attack, only one adult patient in the Oxford cohort fulfilled McDonald criteria but with red flags such as NMO-typical brain imaging and absent OCB 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 this is by far the largest national MOG-Ab cohort reported and the UK cohort was very similar to the Oxford cohort suggesting the obtained data was 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 TM. 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-Ab 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.

Acknowledgments

We would like to thank all UK clinicians who provided us with the patient data.

Funding

We gratefully acknowledge the Highly Specialised Commissioning Team for funding the Neuromyelitis Optica service in Oxford. Dr Maciej Jurynczyk received research fellowship from the Polish Ministry of Science and Higher Education programme Mobilnosc Plus (1070/MOB/B/2013/0).

Table 1

	Total cohort	Oxford	
		Total	Incident
No. of patients	252	75	44
Mean age at onset (\pm SD)	30.1 \pm 18.3	29.0 \pm 16.5	32.0 \pm 17.6
Female (%)	57	56	48
Onset attack (%)			
Unilateral ON	31	25	18
Bilateral ON	24	27	27
TM	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 \leq 6/36 in one or both eyes (%)	NA	16	7
Limited walking distance, EDSS \geq 4 (%)	NA	7	9
Permanent bladder dysfunction (%)	NA	28	34
Self or in situ catheterisation (%)	NA	17	25
Permanent bowel dysfunction (%)	NA	20	27
Permanent erectile dysfunction (% males)	NA	21	26
CSF findings	Oxford Total Cohort		
Normal WBC (<10 / μ l)	29/47		
WBC 10-50/ μ l	12/47		
WBC 50-100/ μ l	3/47		
WBC \geq 100/ μ l (range)	3/47 (100-300)		
Normal protein	27/50		
CSF protein, 0.5 - 1 g/L	18/50		
CSF protein, \geq 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		

Comparison of basic demographics, clinical features between the ‘UK Cohort’, ‘Oxford Total Cohort’ and ‘Oxford Incident Cohort’ (diagnosis after the onset attack).

*estimated from Kaplan-Meier curves. CSF findings for the ‘Oxford Total Cohort’ are also shown.

Table 2

	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 \pm SD (range)	28 \pm 16 (7-68)	36 \pm 18 (6-74)	31 \pm 17 (6-73)	53 \pm 16 (22-81)	33 \pm 14 (15-69)	19 \pm 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

Basic clinical information on patients with different onset attack phenotypes in the ‘UK’ and ‘Oxford Incident Cohort’.

Supplementary Table 1

	Females	Males
Mean age at onset (\pm SD)	31 \pm 19	29 \pm 17
Ethnicity (%)		
Caucasian	82	90
Asian	10	4
Afro-Caribbean	4	4
Mixed/Other	5	2

Onset attack (%)		
ON	58	51
TM	18	17
ON + TM	6	14
ADEM / ADEM-like	18	18
Relapsing (%)	45	43
Median disease duration (months)	25	26

Comparison of basic demographic and clinical features in female and male patients with MOG-Ab disease in the UK.

Supplementary Table 2

	Caucasians	Non-Caucasians	p value
Number of patients	197	34	-
Breakdown of ethnicities (number of patients)	-	Asian 17 Afro-Caribbean 9 Mixed 4 Other 4	-
Mean age at onset (\pm SD)	31 \pm 18	25 \pm 17	0.08
Females (%)	54	71	0.08
Onset attack (%)			
ON	52	64	0.2
TM	19	18	-
ON + TM	11	0	-
ADEM / ADEM-	18	18	-
Relapsing (%)	46	33	0.17
Median disease duration in months	26	23	0.28

A comparison of basic demographic and clinical features between Caucasian and non-Caucasian patients with MOG-Ab disease in the United Kingdom.

Supplementary Table 3

	Visual disability (6/36 or worse in at least one eye)	Motor disability (limited walking distance)	Bladder disability
Gender	No difference	No difference	No difference
Onset age	Increases with decreasing age (p=0.04)	No difference	No difference
Onset attack	Optic neuritis more likely than other presentations (p=0.03)	No difference	TM (p < 0.001), ON+TM (p < 0.01) and ADEM (p < 0.01) more likely than ON
Disease duration	More likely with longer disease duration (p = 0.04)	No difference	No difference

Predictors of disability in the 'Oxford Total Cohort'. P values relate to the significance of each predictor coefficient in the binomial logistic regression model.

One model was built for each outcome.

Supplementary Table 4

Demographic and clinical data on patients who became antibody-negative vs. those who remained antibody positive over time.

	Patients who remained antibody-positive	Patients who turned antibody-negative
Number of patients	41	14
Female (%)	48	50
Caucasian (%)	88	79
Mean age at onset (range)	24 (2-61)	25 (1-69)
Onset attack (%)		
Unilateral ON	23	29
Bilateral ON	27	0
Short TM	0	0
LETM	15	14
ON+TM	12	21
ADEM-like	23	36
Median follow-up	29	28

(months)		
Long-term immunosuppression after onset attack (%)		
None	26	36
<3 months	36	36
3-6 months	20	7
>6 months	18	21
Relapsing (%)	58	36

Figure legends

Fig. 1

Age at onset in MOG-Ab 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-Ab onset phenotypes.

Fig. 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.

Fig. 3

Kaplan-Meier curves showing cumulative probability over time of remaining relapse free in the 'Oxford Incident Cohort'. (A) All patients in the Oxford incidence cohort are included. The 95% confidence interval is shown in gray. 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.

Fig. 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: less than 1 month, between 1 and 3 months, between 3 and 6 months and above 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.

Fig. 5

MOG-Ab test results (negative or positive) and the occurrence of relapses over time. Patients 1-14 became MOG-Ab 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.

Supplementary Fig. 1

(A) Following the trimodal distribution of age at onset k-means clustering reveals age groups of patients younger than 20 years of age, between the age of 20 and 45, and older than 45 years old. (B) Onset attack phenotypes in three age groups.

Supplementary Fig. 2

Examples of brain MRI brainstem lesions adjacent to 4th ventricle and involving area postrema in three different Oxford patients with symptoms in keeping with area postrema syndrome.

Supplementary Fig. 3

Cumulative probability of remaining relapse-free over time in patients from the total UK cohort depending on the phenotype of onset attack.

Supplementary Fig. 4

‘Oxford Total Cohort’: Kaplan-Meier curves showing cumulative probability of remaining free from (A, B) visual disability defined as visual acuity 6/36 or worse in at least one eye; (C, D) motor disability defined as EDSS ≥ 4 , i.e. limited walking distance; (E, F) bladder dysfunction. The risk of disability depending on age group (A, C, E) and onset attack phenotype (B, D, F) are shown.

Supplementary Fig. 5

Breakdown of Oxford MOG-Ab patients showing how they fulfilled distinct disease criteria (NMO 2006, NMOSD 2007, NMOSD 2015, ADEM 2013, MS 2010).

References

- Brilot F, Dale RC, Selter RC, Grummel V, Kalluri SR, Aslam M, et al. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. [Internet]. *Ann. Neurol.* 2009; 66: 833–42.
- Hacohen Y, Absoud M, Deiva K, Hemingway C, Nytrova P, Woodhall M, et al. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. [Internet]. *Neurol. Neuroimmunol. neuroinflammation* 2015; 2: e81.
- Höftberger R, Sepulveda M, Armangue T, Blanco Y, Rostásy K, Cobo Calvo A, et al.

Antibodies to MOG and AQP4 in adults with neuromyelitis optica and suspected limited forms of the disease [Internet]. *Mult. Scler. J.* 2015; 21: 866–874.

Hyun J-W, Woodhall MR, Kim S-H, Jeong IH, Kong B, Kim G, et al. Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases. *J. Neurol. Neurosurg. Psychiatry* 2017: jnnp-2017-315998.

Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, Pache F, Stich O, Beume L-A, Hümmert MW, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. *J. Neuroinflammation* 2016; 13: 279.

Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, Pache F, Stich O, Beume L-A, Hümmert MW, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. *J. Neuroinflammation* 2016; 13: 280.

Jurynczyk M, Geraldes R, Probert F, Woodhall MR, Waters P, Tackley G, et al. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. *Brain* 2017; 140: 617–627.

Kim S-M, Woodhall MR, Kim J-S, Kim S-J, Park KS, Vincent A, et al. Antibodies to MOG in adults with inflammatory demyelinating disease of the CNS. *Neurol. Neuroimmunol. neuroinflammation* 2015; 2: e163.

Kitley J, Leite MI, Nakashima I, Waters P, McNeill B, Brown R, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain* 2012; 135: 1834–49.

Kitley J, Waters P, Woodhall M, Leite MI, Murchison A, George J, et al. Neuromyelitis Optica Spectrum Disorders With Aquaporin-4 and Myelin-Oligodendrocyte Glycoprotein Antibodies: A Comparative Study. *JAMA Neurol.* 2014; 1–8.

Kitley J, Woodhall M, Waters P, Leite MI, Devenney E, Craig J, et al. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. *Neurology* 2012; 79: 1273–7.

Kitley JL, Leite MI, George JS, Palace J a. The differential diagnosis of longitudinally extensive transverse myelitis. *Mult. Scler.* 2012; 18: 271–85.

Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult. Scler. J.* 2013; 19: 1261–1267.

Mader S, Gredler V, Schanda K, Rostasy K, Dujmovic I, Pfaller K, et al. Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. *J. Neuroinflammation* 2011; 8: 184.

MILLER H, SIMPSON CA, YEATES WK. BLADDER DYSFUNCTION IN MULTIPLE SCLEROSIS. *Br. Med. J.* 1965; 1: 1265–9.

Polman CH, Reingold SC, Banwell B, Clanet M, Cohen J a, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann. Neurol.* 2011; 69: 292–302.

Reindl M, Di Pauli F, Rostásy K, Berger T. The spectrum of MOG autoantibody-associated demyelinating diseases. *Nat. Rev. Neurol.* 2013; 9: 455–461.

Sato DK, Callegaro D, Lana-Peixoto MA, Waters PJ, Jorge FMDH, Takahashi T, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO

spectrum disorders. *Neurology* 2014; 82: 474–81.

Sepúlveda M, Armangue T, Martinez-Hernandez E, Arrambide G, Sola-Valls N, Sabater L, et al. Clinical spectrum associated with MOG autoimmunity in adults: significance of sharing rodent MOG epitopes [Internet]. *J. Neurol.* 2016; 263: 1349–1360.

Spadaro M, Gerdes LA, Krumbholz M, Ertl-Wagner B, Thaler FS, Schuh E, et al. Autoantibodies to MOG in a distinct subgroup of adult multiple sclerosis. [Internet]. *Neurol. Neuroimmunol. neuroinflammation* 2016; 3: e257.

Waters P, Woodhall M, O'Connor KC, Reindl M, Lang B, Sato DK, et al. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. *Neurol. Neuroimmunol. Neuroinflammation* 2015; 2: e89.

Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015; 85:177.

Wingerchuk DM, Lennon V a, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. [Internet]. *Lancet Neurol.* 2007; 6: 805–15.

Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006; 66: 1485–9.