

## Brain Foundation Final Progress Report

A longitudinal cohort study of myelin oligodendrocyte glycoprotein antibody-demyelination: defining the clinical course, therapeutic responses, and outcomes

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### Summary:

#### *Background*

Myelin is the electrically insulating material that forms a sheath around the axons of neurons in the central nervous system, and increases the speed at which impulses are propagated. Diseases related to the damage of myelin are referred to as demyelinating disorders. Multiple sclerosis (MS) is the most prevalent demyelinating condition with recurrent attacks of inflammation of the central nervous system that can result in accumulated disability including blindness and paralysis over time. However, it is increasingly recognised that there are patients with demyelination who have a different mechanism of action to MS. Antibodies to myelin oligodendrocyte glycoprotein (MOG), a protein found in myelin, have been described since 2007 in some children with demyelination, but until recently were not identified in adults.

In the last four years, our group has been instrumental in identifying a subgroup of adult patients with demyelination who have antibodies to MOG, and correlating MOG antibody seropositivity as having a strong association with inflammation of the optic nerve resulting in blindness (optic neuritis or ON)<sup>1</sup>. We have provided some of the first descriptions in the literature specifically highlighting the association of MOG antibodies in both children and adults with simultaneous bilateral optic neuritis (BON) and detailing the clinical and radiological phenotype of these patients<sup>1-5</sup>. This has enabled clinicians to make an earlier and more accurate diagnosis for their patients and distinguish this condition from MS. Our team has also provided some of the early results into looking at mechanisms of actions of MOG antibodies in humans, and how they may affect the central nervous system<sup>3</sup>.

Patients with MOG antibody-associated demyelination can have relapsing disease that can result in blindness and paralysis. There is currently no guidance in the literature on the best way to treat this newly identified group of patients.

### *Aims & Hypotheses*

The overall vision of our 2016 Brain Foundation Grant was to study a cohort of children and adults with relapsing MOG antibody-associated demyelination with the following aims in mind:

Aim 1: To describe the clinical course, and identify clinical phenotypes associated with this condition

- *Hypothesis: MOG antibody seropositivity will be strongly associated with ON in both children and adults, and acute disseminated encephalomyelitis (ADEM) in children*

Aim 2: To evaluate the therapeutic responses of patients to different immunotherapeutic agents

- *Hypothesis: patients with MOG antibodies will be steroid responsive and dependent*

Aim 3: To identify long-term outcomes in patients with relapsing MOG antibody-associated demyelination

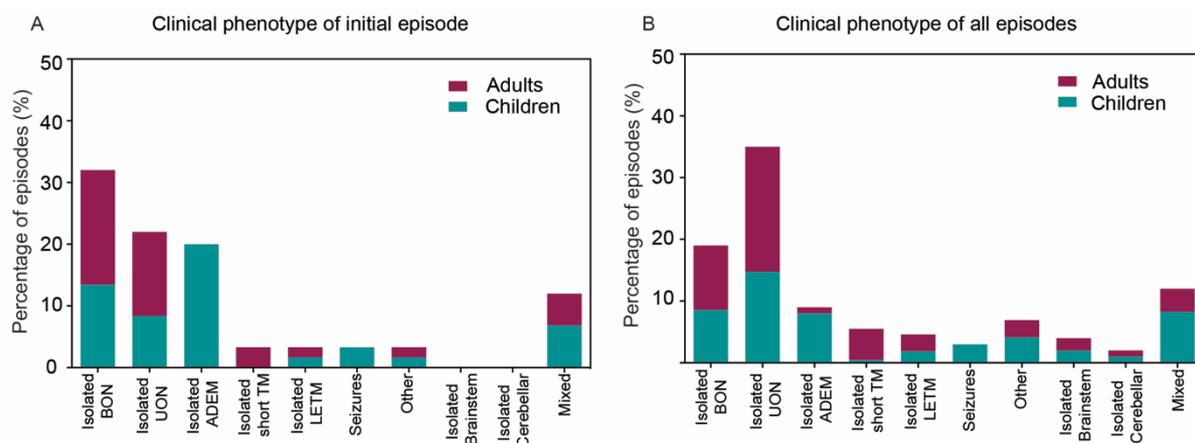
- *Hypothesis: some patients with relapsing demyelination may have sustained disability, highlighting the need for early diagnosis and targeted treatment*

## Results

Our research team is currently the only group in Australasia that offers the gold standard diagnostic laboratory test for detecting MOG antibodies in patient serum. We have been receiving over 1500 samples/ year to test for MOG antibodies, from over 100 paediatric and adult neurologists throughout Australia, New Zealand, and South East Asia. We have identified over 250 MOG antibody-positive children since 2008, and over 300 MOG antibody-positive adults since 2013. We identified that the opportunity existed for a unique platform for national collaboration and in 2015 we initiated the Australasian and New Zealand MOG Study Group.

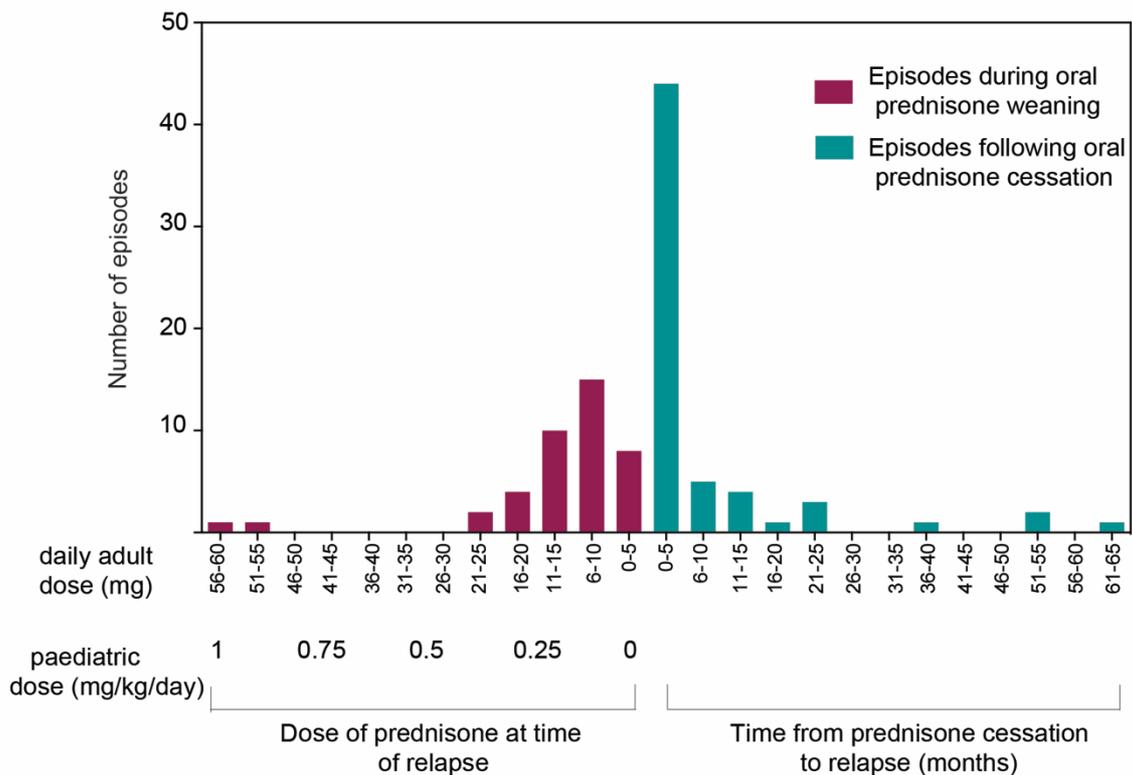
As a consequence of the research efforts of this Study Group we were able to identify 59 patients (33 children and 26 adults) who had relapsing MOG antibody associated-demyelination, and obtained detailed clinical information on the cohort with follow-up for an average of five years. These patients had a collective 218 clinical episodes of demyelination during the time of follow-up, and the clinical data we studied provided invaluable information on the clinical course, treatment responses, and outcomes in this condition.

We firstly confirmed that ON, and particularly bilateral ON, was the most common initial presentation in the total cohort (Figure 1A). In children, ADEM was the most common initial presentation. When we looked at the clinical presentations throughout the disease course, ON remained the most common phenotype, but it was more often unilateral (Figure 1B).



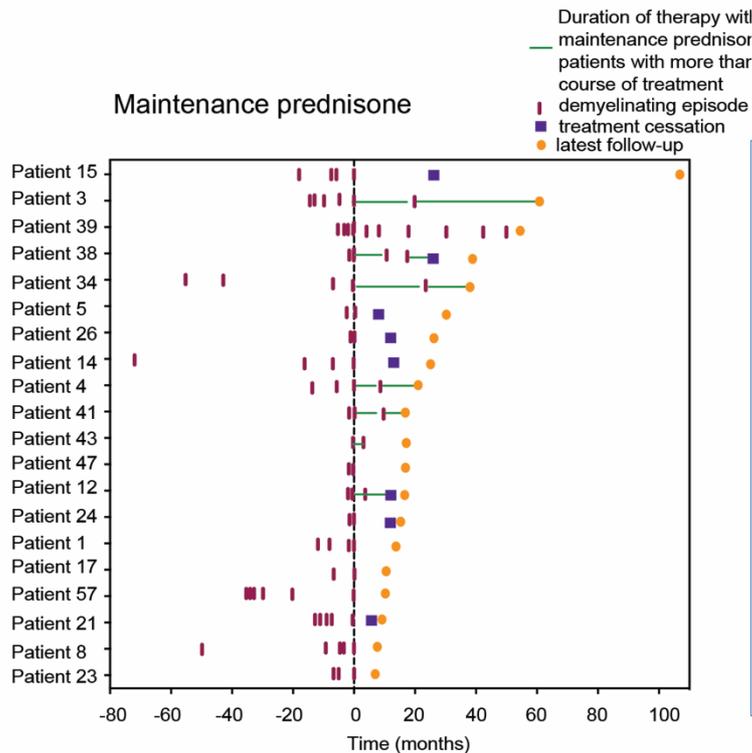
**Figure 1: The clinical phenotypes in relapsing MOG antibody-associated demyelination** (A) Illustration of the clinical phenotype at first presentation of all patients in the cohort, with a breakdown reflecting the distribution of each clinical phenotype in the paediatric age group (0-16 years at disease onset), and adult group (>16 years at disease onset). (B) Illustration of the clinical phenotype at all presentations (n=218, initial presentation plus relapses) in the cohort, with a breakdown reflecting the distribution of each clinical phenotype in the paediatric and adult group. ADEM: acute disseminated encephalomyelitis; BON: bilateral optic neuritis; LETM: longitudinally extensive transverse myelitis; TM: transverse myelitis; UON: unilateral optic neuritis.

We then identified that the majority of episodes (181/218) were treated with courses of oral steroids (prednisone). However, 70% of episodes treated with steroids relapsed when the daily dose of prednisone dropped below 10 mg/day, or within the first two months of ceasing steroids (Figure 2). This result is important as it informs clinicians treating these patients that they should taper steroid courses with caution, over a longer period of time than they might otherwise do, in order to reduce the chance of a patient relapsing.



**Figure 2: The steroid response in relapsing MOG antibody-associated demyelination** An illustration of the number of relapses that occurred during tapering oral prednisone (and the dose of prednisone at which these relapses occurred), or following the cessation of an oral prednisone taper (and the time frame at which these relapses occurred).

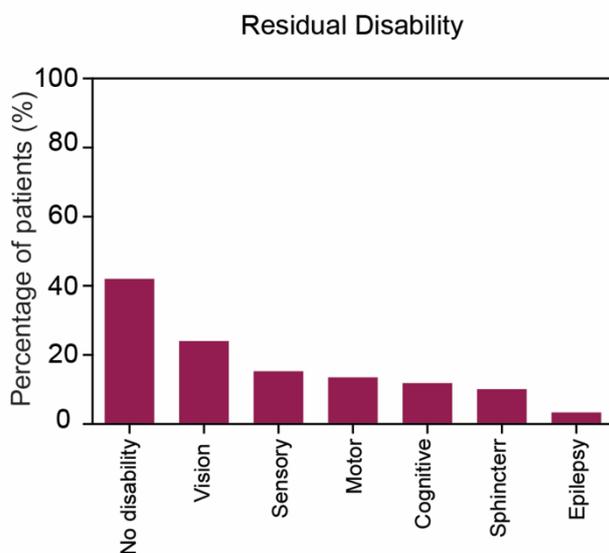
Using steroids was a very effective treatment, with many patients achieving relapse freedom on maintenance prednisone (Figure 3). However, given the long-term adverse effects of steroid use (including increasing cardiovascular and metabolic risks, and the affect on bone health and growth), we also evaluated the efficacy of alternate immunotherapy on patients including monthly intravenous immunoglobulin, mycophenolate, and rituximab. We identified that all these agents reduced relapse risk while on treatment compared to pre-treatment, thereby providing treatment options for patients and clinicians. However, treatment failure rates were lower in patients on maintenance steroids (1/20, 5%) compared to patients on all trials of non-steroidal maintenance immunosuppression (11/29, 38%) [including mycophenolate (7/16), IVIg (3/7), and rituximab (1/6) (P value = 0.016)].



**Figure 3: Disease activity of MOG antibody-positive patients on maintenance prednisone therapy.**

Depictions of the clinical course and disease activity in patients who underwent therapy with maintenance prednisone (commencing at time point 0). In patients who had more than two courses of maintenance prednisone lasting  $\geq 6$  months each, the green lines depict the duration of each course of maintenance corticosteroid therapy. The magenta lines represent a demyelinating episode. The purple squares represent time of switched treatment cessation. The orange circles represent time of latest clinical follow-up.

While MOG antibody-associated demyelination has been previously described as a relatively benign condition, we identified that in patients with relapsing disease, only 40% of patients have no disability at latest clinical follow-up, with 60% of patients having deficits in one or more domains including vision, motor function, bladder and bowel function, etc (Figure 4).



**Figure 4. Outcomes in relapsing MOG antibody-associated demyelination.** Percentage of patients with residual disability in a particular domain.

### *Unanswered Questions*

All published studies to date on MOG antibody-positive patients have focused on patients diagnosed retrospectively, hence standardised outcome measures have not been able to be performed at regular intervals and patients have sometimes been treated with multiple agents simultaneously, or therapy more suitable to MS, rendering it difficult to extrapolate the isolated influence of specific immunosuppressive agents. These are accepted caveats of any study where patients are diagnosed retrospectively. As we are now managing one of the largest cohorts of MOG antibody-positive patients internationally, and with our existing collaborations, we are ideally placed to commence prospective recruitment of patients which will help to definitively answer questions regarding the incidence and prevalence of this newly described condition, and identify optimal therapeutic strategies in these patients. Further work from a basic science perspective which will enable us to understand the underlying mechanisms of action of MOG antibodies, will provide vital insights into managing these complex patients.

### *What these research outcomes mean*

**Our results over the last year highlight the importance of the early recognition and diagnosis of this condition, and the need for the institution of appropriate immunotherapy, in order to improve the outcomes and prognosis of this vulnerable group of patients. Our results have been accepted for publication as an original article in the Journal of Neurology, Neurosurgery, and Psychiatry (In Press October 2017), and will assist clinicians in the recognition and management of this condition.**



Russell Dale, Fabienne Brilot, and Darshi Ramanathan work as part of the Clinical Neuroimmunology and Brain Autoimmunity Groups at the Institute For Neuroscience and Muscle Research, at the Children's Hospital at Westmead. They greatly appreciate the support from the Brain Foundation towards their research.

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