What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients

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Abstract Antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) have been described in patients with neuromyelitis optica spectrum disorders (NMO) without aquaporin-4 antibodies (AQP4-IgG). We aimed to identify the proportion of AQP4-IgG-negative NMO patients who are seropositive for MOG-IgG. In a cross sectional study, we reviewed all patients seen in the National NMO clinic over the last 4 years (after the availability of MOG-IgG testing), including clinical information, MRI, and antibody tests. 261 unique patients were identified. 132 cases satisfied the 2015 NMO diagnostic criteria. Of these, 96 (73%) were AQP4-IgG positive and 36 (27%) were AQP4-IgG negative. These 36 patients were tested for MOG-IgG and 15/36 (42%) tested positive. 20% (25/125) of the patients who did not satisfy NMO criteria had MOG-IgG. Approximately half of seronegative NMO is MOG-Ig seropositive and one in five of non-NMO/non-MS demyelination is MOG-IgG positive. Since MOG-associated demyelinating disease is likely different from AQP4-IgG disease in terms of underlying disease mechanisms, relapse risk and possibly treatment, testing for MOG-IgG in patients with AQP4-IgG-negative NMO and other non-MS demyelination may have significant implications to management and clinical trials.

Keywords Neuromyelitis optica · Aquaporin-4 antibodies · Myelin oligodendrocytes glycoprotein

Introduction

73–90% of neuromyelitis optica spectrum disorder (NMO) patients diagnosed according to the 2015 International panel on NMO diagnosis have aquaporin-4 antibodies (AQP4-IgG) [1, 2]. It is presumed that at least a proportion of the remaining 10–27% of patients, classified as seronegative NMO have another disease specific antibody. Antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) have been increasingly reported in a variety of CNS neuroinflammatory conditions including patients with phenotypes typical for NMO [3]. We aimed to determine the prevalence of MOG-IgG in AQP4-IgG-negative NMO.

Methods

The Walton Centre Neurosciences NHS Trust in Liverpool, United Kingdom, is a tertiary neurology hospital that hosts...
one of the two national multidisciplinary specialist clinics for patients with NMOSD and non-MS demyelinating disorders as part of the UK NMOSD service. We systematically reviewed all patients seen in this clinic over the last 4 years (after the availability of MOG-IgG testing), including clinical information, MRI, and antibody tests. Both AQP4-IgG and MOG-IgG were tested using a validated live cell-based assay with high specificity (John Radcliffe Hospital, Oxford, UK) [4, 5]. This study was approved by Research Ethics Service, NRES Committee London—Hampstead, Ref. no. 15/LO/1433.

**Results**

261 unique patients with non-MS/atypical CNS inflammatory conditions attended the clinic and were assessed for NMOSD. All patients were tested for AQP4-IgG. 132 cases satisfied the 2015 NMOSD diagnostic criteria. Of these, 96 (73%) were AQP4-IgG positive and 36 (27%) AQP4-IgG negative. These 36 patients, were tested for MOG-IgG and 15/36 (42%) tested positive. This would account for 11% (15/132) of the total cohort of NMOSD patients (Fig. 1; Table 1). All MOG-IgG-negative patients were Caucasians with a median age of onset of 18 years (8–44 years) and median disease duration of 4.7 years (2–16 years). The predominant clinical phenotype of the demyelinating event was ON (60%), TM (21%), brain (12%), and brainstem (4%).

While we tested all AQP4-IgG-negative patients for MOG-IgG (n = 36), only a proportion (33%) of AQP4-IgG-positive patients (n = 32) were tested (as double positives are exceptionally rare) (Fig. 1). None were definitely positive. However, one patient was ‘low positive/possibly negative. This patient with one episode of long myelitis also had antinuclear antibodies (1/80 titre with homogenous pattern (nuclear antigens all negative) and was ‘low positive’ for anti-glycine antibodies too. The significance of the MOG-IgG in the context of these additional antibodies is uncertain and may reflect a heightened humoral autoimmune response rather than truly pathogenic dual positivity. This patient has not been included in the MOG cohort in this paper.

We also tested the majority of patients with a demyelinating syndrome referred to the service who did not fulfill the NMOSD criteria (125/129, 97%). Twenty-five (20%) were positive for MOG-IgG. Details of these cases will be the subject of an upcoming separate research paper and are not discussed further here.

We also assessed how many of the MOG-IgG patients with NMOSD phenotype had a relapsing course. Thirteen patients (86%) had a relapsing course. However, a relapsing course was the reason for referral to the clinic in the first place (n = 13/13). The median duration of illness for the relapsing patients was 4.7 years (2–16 years). The median inter-attack interval was 1 year (0.16–17) and median EDSS in the relapsing MOG group at last follow-up was 3 (0–9, Table 1). All relapsing patients are on immunosuppressants (Table 1).

We also assessed the proportion of patients with optic neuritis and long myelitis who fulfill Wingerchuk 2006 criteria [6] that are MOG-IgG positive, as this is a clinical question often posed. Of the whole cohort of 261 patients, 75 patients had long myelitis and optic neuritis. Of these 49 were AQP4-IgG positive (66%) and 10 were MOG-IgG positive (13%, or 38% of AQP4-IgG-negative patients) and 16 remained seronegative (21%). Serial testing where done in 14/15 patients (13 relapsing); MOG-IgG was detected in all. Treatment with steroid or immunosuppression does not seem to have an effect on MOG-IgG serostatus in this cohort of predominantly relapsing patients (Table 2).
| Patient no. | Age  | Sex | Age at onset | Disease duration (years) | Course | Total no. of events | Clinical phenotype (no. of attacks) | First inter-attack interval | Spinal MRI | Baseline brain MRI | CSF oligoclonal bands | EDSS | Current treatment |
|------------|------|-----|--------------|--------------------------|--------|---------------------|-------------------------------------|----------------------------|-------------|-----------------|----------------------|-------|-------------------|
| 1          | 31   | F   | 18           | 13.4                     | R      | 13                  | ON (13) TM (1)                      | 3 years                   | LETM        | Normal          | Negative            | 4     | Subcutaneous IGs (immunoglobulins) and oral prednisolone |
| 2          | 55   | M   | 44           | 11                       | R      | 7                   | ON (2) TM (1) brain-stem (1) brain syndrome (5) | 7 years                   | Short mid thoracic lesion | Brain stem, cortical and subcortical extensive demy | Positive | 3.5 | Steroid & mycophenolate |
| 3          | 31   | F   | 15           | 16.4                     | R      | 2                   | ON (1) TM (1)                       | 4 years                   | LETM        | Normal          | Negative            | 9     | Azathioprine and oral prednisolone |
| 4          | 21   | M   | 18           | 2.5                      | R      | 5                   | Brain stem (1) Brain syndrome (1) TM (1) ON (5) | 2 months                  | Multiple short lesions on thoracic cord | Large area of high T2 signal in the posterior brainstem both sides of mid brain | Negative | 1.5 | Azathioprine switched to rituximab |
| 5          | 22   | M   | 17           | 4.7                      | R      | >7                  | ON (>7) and TM (2)                  | 2 months                  | LETM        | Normal          | Unknown              | 3     | Tocilizumab, IVIG six weekly and oral prednisolone |
| 6          | 30   | F   | 28           | 2                        | R      | 2                   | ON (1) TM (1)                       | 1 year                    | LETM        | Cerebral ring enhancing lesion supracallosal subcortical | Negative | 0   | Mycophenolate       |
| 7          | 23   | F   | 8            | 14.4                     | R      | 3                   | ON (2) TM (2) Brain syndrome (1)     | 3 years                   | LETM        | Multiple non-specific white matter lesions | Negative | 6   | Azathioprine and oral prednisolone |
| 8          | 24   | F   | 17           | 6.9                      | R      | 2                   | ON (1) TM (1) Brain syndrome (1)    | 3 months                  | LETM        | Brainstem, left cerebral peduncle, and few non-specific white matter lesions | Negative | 1   | Azathioprine and oral prednisolone |
| 9          | 14   | F   | 10           | 4                        | R      | 3                   | Brain syndrome (1) ON (3) TM (1)    | 3 months                  | LETM        | Bilateral hemispheric white matter changes | Negative | 2.5 | Rituximab and mycophenolate |
In a cohort of well-characterised NMOSD patients \((n = 132)\), 73% were AQP4-IgG and 11% were MOG-IgG seropositive and 16% remained seronegative. MOG-IgG disease accounts for 42% of the AQP4 IgG-negative seronegative cohort. MOG-IgG was present in 38% of patients with long myelitis and optic neuritis who do not have AQP4 IgG.

86% \((13/15)\) of our patients who satisfy criteria for NMOSD who are MOG-IgG-positive patients have relapsing disease, similar to a recent study [7] who reported that 80% of their MOG-IgG-positive cohort \((n = 50)\) followed a relapsing course. However, a relapsing course was the reason for referral to the clinic in the first place \((n = 13/13)\) making this a biased sample. Long-term follow-ups of a cohort of MOG-IgG-positive patients after the very first event is required to obtain the true risk of relapse.

Importantly, 20% of patients with non-MS/atypical demyelination who do not satisfy criteria for NMOSD tested positive for MOG-IgG (Fig. 1). Double positive cases (both AQP4-IgG and MOG-IgG) are rare [8–10] with none of the tested patients were definite positives. Since we have tested only 52% \((68/132)\) of the total NMOSD cohort for MOG-IgG, this requires further clarification in future studies.

In conclusion, our study provides the best possible answers at the current time on several questions on the frequency of MOG-IgG patients: NMOSD who are AQP4-IgG negative and MOG-IgG positive (42%), NMO (as per Wingerchuk 2006) with optic neuritis and long myelitis who are AQP4-IgG negative but MOG-IgG (13%). We also found that MOG-IgG is found in 20% of non-NMOSD/non-MS demyelination. It is also estimated that at least 11% of all NMOSD (as per 2015 criteria) is MOG-IgG positive.

Our study has important practical implications. First, the definite diagnosis of MOG-IgG-associated disease offers patients and physicians a better diagnostic label than seronegative NMOSD. Second, as nearly one in every two of seronegative NMOSD, and 1/5 of atypical non-MS demyelination is MOG-Ig positive, testing for these cohorts will be of high yield and worthwhile, compared to testing every demyelination (which in most Caucasian predominant populations is likely to be MS) with attendant costs and risk of false-positive results. Third, it is likely that the long-term disease course and therefore treatment strategies of AQP4-IgG and MOG-IgG is different. If this is the case, MOG-IgG status, should be part of inclusion/exclusion criteria or a variable for stratification in clinical trials. The latter issue may have importance for currently recruiting trials that include seronegative NMOSD.
| Patient no. | Date of onset | Date of first relapse | Last relapse | Date of start on steroid | Date of start on maintenance immunosuppressive treatment | First-positive MOG-IgG test | Subsequent MOG test year | Titre | Comments |
|------------|--------------|----------------------|--------------|--------------------------|----------------------------------------------------------|---------------------------|-------------------------|------|----------|
| 1          | Jan 02       | May 05               | Jul 05       | Jan 08                   | 2009                                                     | 2011                      | 2013, 2014 both positive | NA   | Data not clear if was on steroid in first or last relapse, but was on immunosuppressant when tested positive for MOG-IgG |
| 2          | 2004         | 2011                 | 2015         | 2014                     | 2014                                                     | 2014                      | 2015, 2016, 2017 all positive | 300  | Patient was not on steroid in first or last relapses, but was on immunosuppressant when tested positive for MOG-IgG after diagnosis and remained positive |
| 3          | Jan 99       | Apr 03               | May 03       | Unknown                  | 2003                                                     | Apr 14                    | Jul 14 positive          | NA   | Data not clear if was on steroid in first or last relapse, but was on immunosuppressant when tested positive for MOG-IgG subsequently |
| 4          | Sep 14       | Nov 14               | May 17       | Nov 14                   | Dec 14                                                   | 2014                      | 2015 positive            | 300  | Patient was not on steroid in first relapse, but was on steroid and immunosuppressant in last relapse and when MOG-IgG tested and remained positive |
| 5          | Sep 10       | Oct 10               | Jul 13       | At onset                 | 2011                                                     | 2012                      | 2014, 2015, 2016 all positive | NA   | Patient was on reducing dose of steroid in first relapse, and on immunosuppressant and steroid in last relapse and when MOG-IgG was tested and remained positive |
| 6          | Aug 13       | Sep 14               | Sep 14       | May 15                   | Sep 14                                                   | 2016, 2017 both positive | NA                      | Patient was not on steroid in first relapse, was on steroid when tested for MOG-IgG initially and in 2016 but off steroid in 2017 and remained positive |
| 7          | 2001         | 2004                 | 2010         | At onset                 | 2010                                                     | 2013                      | 2014, 2016 both positive | NA   | Patient was not on steroid in first or last relapse, she was on immunosuppressant when tested for MOG-IgG subsequently. |
Table 2 (continued)

| Patient no. | Date of onset | Date of first relapse | Last relapse | Date of start on steroid | Date of start on maintenance immunosuppressive treatment | First-positive MOG-IgG test | Subsequent MOG test year | MOG test | Comments |
|-------------|---------------|----------------------|--------------|--------------------------|-------------------------------------------------|----------------------------|---------------------------|-----------|----------|
| 8           | Jul 08        | Nov 08               | Nov 08       | At onset                 | Nov 08                                          | Apr 11                     | May 11 positive           | NA        | Data unavailable if patient was on steroid in first relapse, she was on immunosuppressant when tested positive for MOG-IgG. |
| 9           | Apr 12        | Jul 12               | Aug 15       | At onset                 | 2012                                            | 2012                       | 2015, 2016 positive       | NA        | Patient was on steroid in first relapse and when tested positive for MOG-IgG. She was also positive when on steroid and immunosuppressant in subsequent relapses. |
| 10          | Mar 07        | Jul 13               | Dec 15       | At onset                 | Jul-14                                          | Apr 14                     | 2016 positive             | NA        | Patient was not on steroid in first relapse, or first MOG-IgG test. He was on immunosuppressant in last relapse and when remained positive in subsequent testing. |
| 11          | 1984          | 2001                 | Mar 13       | At onset                 | 2013                                            | 2015                       | No further tests          | NA        | No available data whether patient was on steroid in first or last relapse, but he was on immunosuppressant when tested positive for MOG-IgG. |
| 12          | May 12        | Aug 14               | Aug 14       | At onset                 | May 15                                          | May 15                     | 2016 positive             | NA        | Patient was not on steroid in first relapse, but was on steroid when tested positive for MOG-IgG and was on immunosuppressant on subsequent positive test. |
| 13          | Oct 12        | Jan 13               | Jan 13       | At onset                 | Aug 13                                          | Jul 13                     | 2014 negative 2015 positive | NA        | Patient was on steroid in first relapse, however, immunosuppressant was initiated after MOG-IgG returned positive in 2013, later test one year apart was negative in 2014, and subsequent test in 2015 was positive while still on immunosuppressant. |
| 14          | Mar 14        |                      | At onset     | Apr 14                   | Apr 14                                          | Apr 14                     | 2015, 2016, 2017 all positive | NA        | Only one event but patient chose to go on treatment |
| 15          | Jun 12        |                      | At onset     | Not on immunosuppressant | Jun 12                                          | 2015 positive              | NA                        | Not on immunosuppression |
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Compliance with ethical standards

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Conflicts of interest All authors declare no conflict of interest.

Ethical standards This study meets UK ethical standards.

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