Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases

Authors: Jae-Won Hyun,[1] Mark R. Woodhall,[2] Su-Hyun Kim,[1] In Hye Jeong,[1] Byeong-Su Kong,[1] Gayoung Kim,[1] Yeseul Kim,[1] Min Su Park,[3] Sarosh R Irani,[2] Patrick Waters,[2#] Ho Jin Kim[1#]

Affiliations: [1]Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, Korea. [2]Autoimmune Neurology group, Nuffield Department of Clinical Neurosciences, Oxford University, Oxford, UK. [3]Department of Neurology, College of Medicine, Yeungnam University College of Medicine, Daegu, Korea,

Word count of title: 101

Word count of abstract: 210

Total word count for the text: 2,110

Number of references: 35

Number of Tables: 3

Number of figures: 3

Key words: Myelin oligodendrocyte glycoprotein antibody; Longitudinal

Correspondence:

Ho Jin Kim, PhD

Department of Neurology, Research Institute and Hospital of National Cancer Center

323 Ilsan Street, Ilsandong-gu, Goyang-si, Gyeonggi-do, Korea

Tel: 82-31-920-2438 Fax: 82-31-905-5524

E-mail:hojinkim@ncc.re.kr

Or

Patrick Waters, PhD

Nuffield Department of Clinical Neurosciences

Level 3, West wing, John Radcliffe Hospital, Oxford, UK

Tel: 44-1865-227840

Email: paddy.waters@ndcn.ox.ac.uk

Contributions of authors:

HJ Kim, and P. Waters contributed equally to this paper as corresponding authors. HJ Kim, and P. Waters had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hyun, SH Kim, HJ Kim and P. Waters. Acquisition, analysis or interpretation of data: All authors. Drafting of manuscript: Hyun, HJ Kim and P. Waters. Critical revision of manuscript for important intellectual content: All authors. Study supervision: HJ Kim and P Waters.

Conflict of Interest

Hyun JW, Woodhall MR, Kim SH, Jeong IH, Kong BS, Kim KY, Kim YS report no disclosures. S. Irani is supported by the Wellcome Trust, British Medical Association Research grant, Vera Down grant and Epilepsy Research UK. P. Waters has received honoria from Biogen Idec Japan, Euroimmun AG, Germany and Mereo Biopharma, UK; SRI and PW are named co-inventors and receive royalties for assays for the detection of antibodies. Kim HJ has lectured, consulted, and received honoraria from Bayer Schering Pharma, Biogen, Genzyme, HanAll BioPharma, MedImmune, Merck Serono, Novartis, Teva-Handok, and UCB; received a grant from the Ministry of Science, ICT & Future Planning; and accepted research funding from Genzyme, Kael-GemVax, Merck Serono, Teva-Handok, and UCB; serves on a steering committee for MedImmune; is a co-editor for the Multiple Sclerosis Journal – Experimental, Translational, and Clinical, and an associated editor for the Journal of Clinical Neurology.

Abstract

Background: We evaluated the seroprevalence of myelin oligodendrocyte glycoprotein immunoglobulin G1 (MOG-IgG) and associated clinical features of patients from a large adult predominant unselected cohort with mainly relapsing central nervous system (CNS) inflammatory diseases. We also investigate the clinical relevance of MOG-IgG through a longitudinal analysis of serological status over a 2-year follow-up period.

Methods: Serum samples from 505 patients with CNS inflammatory diseases at the National Cancer Center were analyzed using cell based assays for MOG-IgG and aquaporin-4 immunoglobulin G (AQP4-IgG). MOG-IgG serostatus was longitudinally assessed in seropositive patients with available serum samples and at least 2 years follow-up.

Results: Twenty-two of 505 (4.4%) patients with CNS inflammatory diseases were positive for MOG-IgG. Patients with MOG-IgG had neuromyelitis optica spectrum disorder (NMOSD, n=10), idiopathic AQP4-IgG negative myelitis (n=4), idiopathic AQP4-IgG negative optic neuritis (n=4), other demyelinating syndromes (n=3), and multiple sclerosis (n=1). No relapses were seen in patients when they became MOG-IgG seronegative, whereas a persistent positive serological status was observed in patients with clinical relapses despite immunotherapy.

Conclusions: In a large adult predominant unselected cohort of mainly relapsing CNS inflammatory diseases, we confirmed that NMOSD phenotype was most commonly observed in patients with MOG-IgG. A longitudinal analysis with 2-year follow-up suggested persistence of MOG-IgG is associated with relapses.

Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a component of myelin proteins in the central nervous system (CNS).[1] MOG is predominantly located in the outermost surface of myelin sheaths and is a biologically accessible antigenic target for circulating auto-antibodies.[1] The contribution of MOG and anti-MOG immunoglobulin G (MOG-IgG) in CNS demyelination has been studied using animal models immunized with MOG.[2,3]

In humans, the role of MOG-IgG is still emerging. Indeed, diverse clinical manifestations of patients with MOG-IgG have been described in inflammatory CNS diseases with benign to fulminant features, including monophasic or relapsing clinical courses.[4-27] Additionally, the phenotype can include neuromyelitis optica spectrum disorder (NMOSD), acute disseminated encephalomyelitis (ADEM), and rarely multiple sclerosis (MS) in both the adult and pediatric population.[4-27]

The majority of previous studies that characterize patients with MOG-IgG have been performed in cohorts selected with specific disease or phenotype.[7-24] More importantly, the clinical implication of MOG-IgG status for prognosis and treatment has not been fully elucidated. Understanding risk factors for relapses would allow more directed patient treatment, hence, in the present study, we evaluated the seroprevalence of MOG-IgG and clinical spectrum of associated disorders in a large unselected cohort of inflammatory CNS diseases. We also investigated the clinical relevance of MOG-IgG in relapses through the longitudinal analysis of serological status.

Methods

Patients

Between 2005 and 2016 at the department of neurology of the National Cancer Center (NCC) in Korea, 505 consecutive patients with suspected inflammatory demyelinating CNS diseases who had available serum samples were enrolled; 199 had paired cerebrospinal fluid (CSF) available. Serum and CSF samples from all participants were stored at -80° C before analysis. The enrolled patients presented with the following diagnoses determined at their last visit: 243 with NMOSD; 130 with MS; 104 with idiopathic AQP4-IgG negative myelitis; 9 with idiopathic AQP4-IgG negative optic neuritis; and 19 with other demyelinating syndromes that did not fit either NMOSD or MS. Diagnoses of NMOSD or MS was based on the 2015 International Panel for NMO Diagnosis (IPND) criteria or the 2010 McDonald criteria, respectively.[28,29] Patients with idiopathic AQP4-IgG negative myelitis or optic neuritis had the lesion(s) confined to spinal cord or optic nerve, respectively. The clinical, laboratory, and radiological data of these patients were reviewed retrospectively.

The Institutional Review Board of NCC approved the present study and written informed consent was obtained from all participants.

MOG-IgG cell based assays

Serum samples were evaluated by detecting IgG1 antibodies targeting full-length MOG using a cell based assay (CBA) at Oxford University UK, as previously described.[30] AQP4-IgG was examined using an in-house at the NCC and/or commercial cell-based assay (Euroimmun, Luebeck, AG, Germany).[31,32] AQP4-IgG was evaluated on at least two independent tests and by two independent investigators (KYK and YSK). To confirm the simultaneous presence of

both MOG-IgG and AQP4-IgG, MOG-IgG-positive samples were re-examined for AQP4-IgG status at Oxford University.[33] The testing investigators were blind to the diagnosis and clinical data for the both MOG-IgG and AQP-IgG assays. In MOG-IgG-positive patients who had available serum samples with at least 2 years of follow-up, longitudinal analysis of MOG-IgG was subsequently performed.

Results

Clinical characteristics of patients with MOG-IgG

MOG-IgG was positive in 22 of 505 patients (4.4%) and AQP4-IgG was positive in 212 of 505 patients (42%). One of 505 patients (0.2%) was positive for both antibodies. Of the 22 patients with MOG-IgG, 21 patients had paired serum and CSF samples. Of them, 3 patients showed MOG-IgG positivity in both serum and CSF, while 18 patients were positive only in serum.

The demographics and clinical characteristics of 22 MOG-IgG positive patients are shown in Table 1. The median age at the onset was 30 years with a range of 4 to 50 years, and 14 patients were female. The median follow-up duration was 63 months (range of 7-200 months). Seventeen had relapsing clinical courses (77.3%) within the median follow-up duration of 71 months (range of 23-200 months), while only 5 patients had a monophasic clinical course (median follow-up duration of 34 months (range of 7-113 months)). At last follow-up the EDSS score was highly variable, ranging from 0 to 7.0 (median 2.0), and the median number of attacks was 3 (range of 1-16). Twenty-two MOG positive patients had the following diagnoses at the last visit: 10 with NMOSD; 4 with idiopathic AQP4-IgG negative myelitis; 4 with idiopathic AQP4-IgG negative optic neuritis; 3 with other demyelinating syndromes; and 1 with MS. The most common initial clinical phenotype was optic neuritis (36%) followed by myelitis (27%), brain involvement (23%), and multifocal involvement (14%).

The serological status of MOG-IgG and AQP4-IgG according to the clinical diagnosis at the last follow-up is shown in Figure 1. Of the 243 NMOSD patients who fulfilled the IPND criteria, 212 (87.2%) were positive for AQP4-IgG, 10 (4.1%) were positive for MOG-IgG, 22 (9.1%) were double negative, and 1 (0.4%) were double positive for both AQP4-IgG and MOG-IgG. The double positive patient exhibited typical NMOSD features characterized by

recurrent episodes of optic neuritis and longitudinally extensive transverse myelitis (LETM). One (0.8%) of 130 patients with MS was MOG-IgG positive. This MOG-IgG positive MS patient demonstrated the clinical and radiologic features (Figure 2) consistent with relapsing MS, and responded well to interferon-ß therapy. Additionally, she revealed CSF restricted oligoclonal bands and a new enhancing lesion on brain MRI was observed between clinical relapses. Four of 104 (3.8%) patients with idiopathic AQP4-IgG negative myelitis, 4 of 9 (44.4%) patients with idiopathic AQP4-IgG negative optic neuritis, and 3 of 19 (15.8%) patients with other demyelinating syndromes were positive for MOG-IgG. The detailed clinical features of individual patients with MOG-IgG are shown in Table 2.

Longitudinal analysis of patients with MOG-IgG

Longitudinal serum samples were obtained in 10 of 22 MOG-IgG seropositive patients with median follow-up of 39 months (range 27-92), and all 10 patients were treated with maintenance immunotherapy including immunosuppressive and immune-modulating therapy. Longitudinal analysis of 10 patients with MOG-IgG was demonstrated in figure 3 (patients 1-10 are shown as A-J, respectively) and the detailed clinical characteristics of these 10 patients are shown in Table 2. Of 10 patients, 5 (50%, Figure 3A-E) showed persistent MOG-IgG positivity during a median of 33 months follow-up (range of 28-73 months), and one (Figure 3F) patient became seronegative but returned to seropositive status during 28 months of follow-up. Four patients (40%, Figure 3G-J) became MOG-IgG negative during a median of 73 months follow-up (range of 48-100 months).

Of the 5 (50%) patients with a persistent MOG-IgG-positive status, 2 patients had recurrent attacks despite immunotherapy with rituximab (Figure 3A, B). In contrast, no patient who

became MOG-IgG seronegative showed clinical relapses after undergoing immunotherapy (Figure 3G-J; Table 2). Table 3 revealed MOG-IgG findings at the individual time points of longitudinal tests according to the relapse and remission status. After exclusion of post-steroid pulse therapy samples, all of the MOG-IgG serological statuses at clinical relapse were positive.

Four of 7 samples from the time of relapse and post steroid-pulse therapy converted MOG-IgG negative (Figure 3F, G, I). Two MOG-IgG-positive patients underwent plasmapheresis, and after plasmapheresis, the serological status level of MOG-IgG decreased (Figure 3G, H). Three of six persistent MOG-IgG-positive patients were treated with azathioprine (Figure 3C, D, F), while all of 4 patients that became seronegative were treated with rituximab or had history of treatment with mitoxantrone (Figure 3G-J).

Discussion

The MOG-IgG-positive patients of our large unselected cohort with CNS inflammatory diseases had diverse clinical phenotypes and courses. In this cohort, MOG-IgG was detected in 4.4% (22/505) of patients and 4.1% (10/243) of NMOSD patients who fulfilled the IPND criteria. Seroprevalence of MOG-IgG was comparable with that of one previous study based on an unselected cohort with CNS inflammatory diseases (17/270, 6.3%),[25] but was slightly lower than those of previous studies based on the selected NMOSD cohorts, which varied from 5.6 to 38%.[7-13] However, the prevalence of NMOSD in patients with MOG-IgG could not be directly compared because the previous study was performed before introduction of the IPND criteria.

Not surprisingly, the NMOSD clinical phenotype according to the IPND criteria was most commonly observed in patients with MOG-IgG (10/22, 45.5%), comparable with a recent study (16/50, 32%).[14] Double positivity for both MOG-IgG and AQP4-IgG was rarely observed in patients with NMOSD (0.4%), consistent with previous studies using cell-based assays (1-2.9% double positivity in patients with NMOSD).[7,12,21] These patients have typical clinical manifestations of NMOSD and it is unclear the added impact of MOG antibodies in this context. The double-positive patient in our cohort had the highest EDSS of any of the MOG-positive patients, but this may simply be related to the AQP4-IgG mediated damage. Longitudinal studies on double positive patients may help clarify their temporal association. Previous studies have demonstrated that AQP4-IgG autoimmunity was associated with astrocyte damage, while MOG-IgG autoimmunity was usually associated with myelin injury, therefore using the term NMOSD in patients with MOG-IgG is a matter of debate.[34,35]

Notably, based on a longitudinal analysis over 2 years, we observed that patients did not experience a clinical relapse after conversion to seronegativity under maintenance immunotherapy, but a relapsing clinical course was observed in subset of patients with a persistent MOG-IgG-positive status. After exclusion of acute treatment effect, MOG-IgG was positive in all serum samples that were obtained during relapses, consistent with previous studies.[9,13,18,19] These findings give us a good reason to follow-up MOG-IgG positive patients under immunotherapy, but the one patient who returns to seropositive status does encourage caution. In previous studies,[16,18-20,23] negative serological conversion of MOG-IgG was observed in patients with a benign clinical course that included monophasic features. However, other studies report that patients with negative serological conversion of MOG-IgG do experience clinical relapse.[12,24] Additionally, a persistent MOG-IgG-positive status has been observed in patients with relapsing clinical courses,[9,10,17,20] but was not always.[12,20,24] These contradictory results may be explained by study differences in sample size, follow-up duration, and analysis of the treatment effect.

Interestingly, changes of MOG-IgG status tended to be influenced by acute or maintenance therapeutic regimen. A MOG-IgG-negative status was observed in 4 of 7 serum samples at the relapse status after steroid pulse therapy, and MOG-IgG CBA scores decreased after plasmapheresis. All 4 patients that became MOG-IgG seronegative had a history of potent immunotherapy that included rituximab or mitoxantrone. However, 2 patients with a persistent MOG-IgG-positive status despite rituximab therapy experienced clinical relapses. Similar findings were observed in several previous studies,[14,18,19] but future studies with larger cohorts and an individual therapeutic regimen are necessary to clarify the therapeutic implication of MOG-IgG status in clinical practice.

The presence of MOG-IgG in adult patients with MS has been debated.[4,6,7,11,12,15,16,25,30] This is largely due to assay methodology. Most recent studies, where testing against native protein in cell based diagnostic systems was utilised, demonstrated very low or no reactivity to MOG-IgG in adult patients with MS.[7,11,12,15,16,25,30] However, a recent study showed that MOG-IgG could be detected in a subgroup of adult patients with MS (1% in a unselected MS cohort and 5% in a selected MS cohort with concomitant initial spinal cord and brainstem involvement). All patients in this subgroup showed a typical relapsing-remitting clinical course and 2 of these patients stabilized with natalizumab therapy.[24] In the present study, 1 adult patients (0.8% of adult MS patients) showed the clinical and MRI features consistent with relapsing MS, and CSF restricted oligoclonal bands. She responded well to disease modifying therapy for MS, but after discontinuation of therapy she experienced a series of relapses, which subsided after re-administration of disease modifying therapy. She appeared to become MOG positive during this treatment break after three relapses and reverted to seronegative between 6 and 15 months later. However, the only available samples at earlier time-points, which were negative, were post steroid pulse-therapy.

Retrospective design of the current study entails several methodological limitations including inconsistent and incomplete sampling. Additionally, only 2% of the samples (11/505) were obtained at clinical onset, therefore the clinical implications of MOG-IgG status during an early phase of disease remains unknown. Lastly, the inclusion of patients from a single referral center and patients with available serum samples resulted in an unintentional selection bias, including the preferred enrollment of patients with relapsing clinical courses and/or high disease activity. For the same reason, no pediatric ADEM or monophasic isolated optic neuritis patient with MOG-IgG could be enrolled. Further prospective multicenter

studies that include both adult and pediatric patients and regular assessment for MOG-IgG status with longer follow-up from an early stage of disease, are warranted.

In conclusion, we confirmed that the clinical phenotype of NMOSD was most commonly observed in MOG-IgG-positive patients from a large unselected cohort with CNS inflammatory diseases. Measurements during long-term follow-up suggested that persistent positivity of MOG-IgG is associated with clinical relapses.

References

1. Schluesener HJ, Sobel RA, Linington C, Weiner HL. A monoclonal antibody against a myelin oligodendrocyte glycoprotein induces relapses and demyelination in central nervous system autoimmune disease. J Immunol 1987;139:4016–21.

2. Brunner C, Lassmann H, Waehneldt TV, Matthieu JM, Linington C. Differential ultrastructural localization of myelin basic protein, myelin/oligodendroglial glycoprotein, and 2′,3′-cyclic nucleotide 3′-phosphodiesterase in the CNS of adult rats. J Neurochem 1989;52:296–304.

3. Linington C, Bradl M, Lassmann H, Brunner C, Vass K. Augmentation of demyelination in rat acute allergic encephalomyelitis by circulating mouse monoclonal antibodies directed against a myelin/oligodendrocyte glycoprotein. Am J Pathol 1988;130:443–54.

4. Ramanathan S, Dale R, Brilot F. Anti-MOG antibody: The history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmune Rev 2016;15:307-24.

5. Zamvil SS, Slavin AJ. Does MOG Ig-positive AQP4-seronegative opticospinal inflammatory disease justify a diagnosis of NMO spectrum disorder? Neurol Neuroimmunol Neuroinflamm 2015;2: e62.

6. Reindl M, Pauli FD, Rostasy K, Berger T. The spectrum of MOG autoantibody associated demyelinating diseases. Nat Rev Neurol 2013;9:455-61.

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

8. Kitley J, Woodhall M, Waters P, et al. Myelinoligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. Neurology 2012;79:1273–7.

9. Rostasy K, Mader S, Hennes EM, et al. Persisting myelin oligodendrocyte glycoprotein antibodies in aquaporin-4 antibody negative pediatric neuromyelitis optica. Mult Scler 2013;19:1052–9.

10. Sato DK, Callegaro D, Lana-Peixoto MA, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology 2014;82:474–81.

11. Tanaka M, Tanaka K. Anti-MOG antibodies in adult patients with demyelinating disorders of the central nervous system. J Neuroimmunol 2014;270:98–9.

12. Hoftberger R, Sepulveda M, Armangue T, et al. Antibodies to MOG and AQP4 in adults with neuromyelitis optica and suspected limited forms of the disease. Mult Scler 2015;21:866–74.

13. Probstel AK, Rudolf G, Dornmair K, et al. Anti-MOG antibodies are present in a subgroup of patients with a neuromyelitis optica phenotype. J Neuroinflammation 2015;12:46.

14. Jarius S, Ruprecht K, Kleiter I, 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.

15. Di Pauli F, Mader S, Rostasy K, et al. Temporal dynamics of anti-MOG antibodies in CNS demyelinating diseases. Clin Immunol 2011;138:247–54.

16. Probstel AK, Dornmair K, Bittner R, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. Neurology 2011;77:580–8.

17. Baumann M, Sahin K, Lechner C, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. J Neurol Neurosurg Psychiatry 2015;86:265–72.

18. Dale RC, Tantsis E, Merheb V, et al. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. Neurol Neuroimmunol Neuroinflamm 2014;1:e12.

19. Ramanathan S, Reddel SW, Henderson A, et al. Antibodies to myelin oligodendrocyte glycoprotein in bilateral and recurrent optic neuritis. Neurol Neuroimmunol Neuroinflamm 2014;1:e40.

20. Cobo-Calvo A, SepulvedaM, Bernard-Valnet R, et al. Antibodies tomyelin oligodendrocyte glycoprotein in aquaporin 4 antibody seronegative longitudinally extensive transverse myelitis: clinical and prognostic implications. Mult Scler 2015;22:312-9.

21. Pauli FD, Hoftberger R, Reindl M, et al. Fulminant demyelinating encephalomyelitis. Neurol Neuroimmunol Neuroinflamm 2015;2:175.

22. Lechner C, Baumann M, Hennes EM, et al. Antibodies to MOG and AQP4 in children with neuromyelitis optica and limited forms of the disease. J Neurol Neurosurg Psychiatry 2016;87:897–905.

23. Baumann M, Hennes EM, Schanda K, et al. Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG): Extending the spectrum of MOG antibody positive diseases. Mult Scler. 2016;22:1821-9.

24. Spadaro M, Gerdes LA, Krumbholz M, et al. Autoantibodies to MOG in a distinct subgroup of adult multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 2016;3: e257.

25. Kim SM, Woodhall MR, Kim JS, et al. Antibodies to MOG in adults with inflammatory demyelinating disease of the CNS. Neurol Neuroimmunol Neuroinflamm 2015;2:e163.

26. Fujimori J, Takai Y, Nakashima I. Bilateral frontal cortex encephalitis and paraparesis in a patient with anti-MOG antibodies. J Neurol Neurosurg Psychiatry. 2017 Feb 16

27. Reindl M, Jarius S, Rostasy K, Berger T. Myelin oligodendrocyte glycoprotein antibodies: How clinically useful are they? Curr Opin Neurol. 2017 Feb 28.

28. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-89.

29. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.

30. Waters P, Woodhall M, O'Connor KC, et al. MOG cell based assay detects non-MS patients with inflammatory neurologic disease. Neurol Neuroimmunol Neuroinflamm 2015;2:e89.

31. Kim Y, Kim G, Kong BS, et al. Large scale in-house cell based assay for the evaluation of serostatus in patients with neuromyelitis optica spectrum disorder based on new diagnostic criteria. J Clin Neurol 2017(in press)

32. Jarius S, Probst C, Borowski K, et al. Standardized method for the detection of antibodies to aquaporin-4 based on a highly sensitive immunofluorescence assay employing recombinant target antigen. J Neurol Sci 2010;291:52-6.

33. Waters PJ, McKeon A, Leite MI, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. Neurology 2012;78:665–71.

34. Ikeda K, Kiyota N, Kuroda H, et al. Severe demyelination but no astrocytopathy in clinically definite neuromyelitis optica with anti-myelin-oligodendrocyte glycoprotein antibody. Mult Scler. 2015;21:656-9.

35. Kaneko K, Sato DK, Nakashima I, et al. Myelin injury without astrocytopathy in neuroinflammatory disorders with MOG antibodies. J Neurol Neurosurg Psychiatry. 2016;87:1257-9.

Table 1. Demographics and clinical features of 22 patients with MOG-IgG

Female: male ratio	14:8
Median age at symptom onset (years, range)	30 (4-50)
AQP4-IgG positivity	1 (4.5%)
Median follow-up duration (months, range)	63 (7-200)
Clinical course	
Monophasic	5 (22.7%)
Multiphasic	17 (77.3%)
Median EDSS at last follow-up (range)	2.0 (0.0-7.0)
Median number of attacks (range)	3 (1-16)
Diagnosis at last follow-up	
Neuromyelitis optica spectrum disorder	10 (45.5%)
Multiple sclerosis	1 (4.5%)
Idiopathic AQP4-IgG negative optic neuritis	4 (18%)
Idiopathic AQP4-IgG negative myelitis	4 (18%)
Other demyelinating syndrome	3 (14%)
Clinical phenotype at the onset	
O	8 (36%)
M	6 (27%)
B	5 (23%)
Multifocal involvement	3 (14%)
O+M	2/3 (67%)
O+B	1/3 (33%)

Abbreviation: MOG, myelin oligodendrocyte protein; APQ4, aquaporin 4; O, optic neuritis; M, myelitis; B, Brain; EDSS, Expanded Disability Status Scale

Table 2. Clinical characteristics of 22 individual patients with MOG-IgG

	Gender	Age at onset	Ethnicity	MOG-IgG1 CBA Score	AQP4-IgG CBA Score	Negative conversion of MOG-IgG at last FU	Onset phenotype	Phenotypes at last follow-up	Clinical diagnosis at last FU	No. of attack	Current EDSS	OCB status	Other autoimmune serology	VEP/OCT	brain MRI lesion localization	Follow-up duration (months)	Disease duration (months)	Current Treatment
1	F	41	Korean	1	0	No	O	O	Idiopathic AQP4-IgG negative ON	6	3	N	anti-nuclear Ab (+), homogenous pattern	VEP: delayed P100 latency	None	49	49	RTX
2	F	8	Korean	3	0	No	O(b)+B	O(b)+B	Seronegative NMOSD	11	2	N/A	negative	OCT: RNFL thinning	SC, DGM	194	195	RTX
3	F	46	Korean	3.5	0	No	B	B	Seronegative NMOSD	1	3	N/A	anti-SS-A Ab (+)	VEP: normal	PV	34	50	AZA
4	F	30	Korean	3	0	No	O	O+M(l)+B	Seronegative NMOSD	4	1	N	anti-nuclear Ab (+), speckled pattern	OCT: RNFL thinning	JC, SC	65	68	AZA
5	F	29	Korean	3	0	No	O	O+B	Seronegative NMOSD	4	2	N	negative	VEP: delayed P100 latency, OCT: RNFL thinning	Bs	30	53	MMF
6	M	50	Korean	1	0	No	B	B+M	Other demyelinating syndrome	2	2	N	negative	VEP: normal	SC	32	34	AZA
7	F	35	Korean	3	0	Yes	M	M+B	RRMS	5	3	P	negative	VEP: normal	PV, JC, Bs	106	107	IFNβ
8	F	24	Korean	2	0	Yes	B	B+O(b)+M	Other demyelinating syndrome	4	6	P	anti-nuclear Ab (+), speckled pattern	VEP: delayed P100 latency	PV, SC	200	201	MMF
9	M	42	Korean	1	0	Yes	M(l)	M(l)	Idiopathic AQP4-IgG negative myelitis	5	6.5	P	negative	VEP: normal	None	135	136	AZA
10	M	33	Korean	1	0	Yes	O(b)+M	O(b)+M+B	Seronegative NMOSD	3	1.5	N	negative	VEP: delayed P100 latency, OCT: RNFL thinning	Bs	94	95	RTX
11	F	29	Korean	2	0	NA	O+M(l)	O+M(l)	Seronegative NMOSD	1	0	N	negative	N/A	None	7	126	None
12	F	4	Korean	2	0	NA	O	O+B	Seronegative NMOSD	16	3	N	negative	N/A	PV, Bs, DGM	114	240	AZA
13	F	34	Korean	4	0	NA	O(b)	O(b)	Idiopathic AQP4-IgG negative ON	2	1	N	negative	VEP: delayed P100 latency	None	41	119	None
14	F	27	Korean	3	0	NA	O	O	Idiopathic AQP4-IgG negative ON	3	1	P	negative	VEP: delayed P101 latency	None	61	153	None
15	F	10	Korean	2	0	NA	B	B	Other demyelinating syndrome	2	0	N/A	negative	N/A	Bs, DGM	23	128	NA
16	M	32	Korean	2	3.5	NA	M(l)	M(l)+O	Seropositive NMOSD	4	7	N/A	anti-SS-A Ab (+), anti-nuclear Ab (+), speckled pattern	VEP: delayed P101 latency	None	85	136	AZA
17	M	30	Korean	1	0	NA	M(l)	M(l)	Idiopathic AQP4-IgG negative myelitis	1	0	N/A	negative	VEP: normal	None	113	160	None
18	F	28	Korean	1	0.5	NA	B	B+M(l)	Seronegative NMOSD	2	5.5	N	anti-ds DNA Ab (+)	VEP: normal	PV, Bs	71	105	AZA
19	M	30	Korean	2	0	NA	M	M	Idiopathic AQP4-IgG negative myelitis	1	2.5	P	negative	VEP: normal	None	44	68	NA
20	F	7	Korean	3	0	NA	O	O+B	Seronegative NMOSD	2	0	N	negative	VEP: delayed P100 latency, OCT: RNFL thinning	SC	28	28	MMF
21	M	31	Korean	3	0	NA	M(l)	M(l)	Idiopathic AQP4-IgG negative myelitis	1	2.5	N	negative	VEP: normal	None	23	24	MMF
22	M	21	Korean	3.5	0	NA	O	O(b)	Idiopathic AQP4-IgG negative ON	4	1	N	negative	VEP: delayed P100 latency	None	88	88	MMF

Abbreviation: CBA: cell based assay; a score of less than 1 is negative, a score of 1-1.5 is considered borderline/low positive and above 1.5 is positive; EDSS: Expanded Disability Status Scale; OCB: oligoclonal band; VEP: visual evoked potential; OCT: optical coherence tomography; O: optic neuritis; B: brain; b: simultaneous bilateral; M: myelitis; l: longitudinally extensive transverse myelitis; AQP4-IgG: aquaporin-4 immunoglobulin G; NMOSD: neuromyelitis optic spectrum disorder; RRMS: relapsing remission multiple sclerosis; N: negative; N/A: not available; P: positive; Ab: antibody; RNFL: retinal nerve fiber layer; SC: subcortical white matter; DGM: deep gray matter; PV: periventricular white matter; JC: juxtacortical white matter, Bs: brainstem; RTX: rituximab; AZA: azathioprine; MMF: mycophenolate mofetil; IFNβ; interferon-beta

Table 3. MOG-IgG findings at the individual time points of longitudinal tests according to the relapse and remission status, after exclusion of post-steroid pulse samples (p-value = 0.0022 by Fisher's exact test, follow-up samples for 10 patients were available.)

	Relapse	Remission	
MOG-IgG (+)	12	23	35
MOG-IgG (-)	0	20	20
	12	43	55

Figure legends

Figure 1. Patient diagnosis at last follow-up with serological status of MOG-IgG and AQP4-IgG (NMOSD, neuromyelitis optica spectrum disorder; AQP4, aquaporin-4 antibody; MOG, myelin oligodendrocyte glycoprotein antibody; MS, multiple sclerosis)

Figure 2. Representative MRI findings of the patient with multiple sclerosis juxtacortical (A,B), periventricular (A,C,F), infra-tentorial (A,D,E), inferior temporal (D), U-fiber (A,B), and nodular enhancing periventricular (F) lesions. These images were taken at 44 (A), 45 (B-E) and 47 (G) months after onset, and are highlighted on figure 3G as B1, B2 and B3.

Figure 3. Longitudinal analysis of 10 patients with MOG-IgG Persistent MOG-IgG positivity was observed in 6 patients and 4 patients showed negative serological conversion of MOG-IgG. **(**Black squares represented serial MOG antibody status, downward solid arrowheads represented clinical relapse, downward empty arrowheads represented serum samples which obtained after steroid pulse therapy, upward arrows represented plasmapheresis, and horizontal arrows showed time points of the representative MRI taken in figure 2, cut-off value for positivity: dotted line (score 1); the MOG-IgG cell based assay (CBA) is scored visually in a semi-quantitative manner: a CBA score of less than 1 is negative, a score of 1-1.5 is considered borderline/low positive and above 1.5 is positive, MMF, mycophenolate mofetil; RTX, rituximab; AZA, azathioprine; IFNβ, interferon-beta; Mitox, mitoxantrone; P, plasmapheresis; preg, pregnant)