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BRIEF COMMUNICATION

Seroprevalence of anti-myelin oligodendrocyte glycoprotein antibodies in adults with myelitis

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Abstract

Although myelitis is the second most common presentation in adults with myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD), studies on MOG-IgG seroprevalence in patients with myelitis episodes are sparse. Herein, we investigated MOG-IgG seroprevalence in Korean adults who exhibited myelitis since 2017. Among 151 adults with acute myelitis, 11 (7.3%) tested positive for MOG-IgG by the initial screening and 10 (6.6%) patients were finally diagnosed with MOGAD during the study period. This study is the first to provide data on MOG-IgG seroprevalence in adults with myelitis and supports the clinical utility and importance of MOG-IgG testing in myelitis episodes.

Introduction

Antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) have been established as a disease-specific biomarker for MOG-IgG-associated disease (MOGAD), a distinct demyelinating disease of the central nervous system (CNS).[1] MOGAD has broad clinical manifestations, including optic neuritis, myelitis, acute disseminated encephalomyelitis, and other brain syndromes. Myelitis is the second most common presentation in adults with MOGAD, accounting for 18–37% of cases, and the proportion increases up to more than a half during entire disease course.[1–7] Current international consensus for MOGAD diagnosis recommends an MOG-IgG test with live cell-based assays for patients with suspected CNS-inflammatory demyelinating diseases (IDDs), except in cases with typical multiple sclerosis (MS) or a progressive disease course.[8] Therefore, serological test for MOG-IgG is becoming increasingly essential in cases with myelitis for precise diagnosis and proper treatment.

MOG-IgG seroprevalence in patients with CNS-IDDs or seronegative neuromyelitis optica spectrum disorder (NMOSD) has been studied. Approximately 4–6% of adults with CNS-IDDs,[4,9–11] and 10–45% of NMOSD patients without aquaporin-4 antibodies (AQP4-IgG) exhibit MOG-IgG seropositivity.[12–14] Regarding AQP4-IgG-negative longitudinally extensive transverse myelitis (LETM), 7–23% patients are reportedly MOG-IgG-seropositive.[15,16] However, investigations on MOG-IgG seroprevalence in patients with myelitis are sparse. A recent study reported that 6.6% (11/166) of patients with acute myelopathy were MOG-IgG-seropositive; however, that study included patients with all etiologies of myelopathy and did not provide clinical information specifically associated with myelitis.[17]

Investigating MOG-IgG seroprevalence among patients with myelitis can help in determining the pre-test probability of MOG-IgG positivity in cases with myelitis. Thus, we aimed to evaluate MOG-IgG seroprevalence in Korean adults with acute myelitis from the National Cancer Center (NCC) registry for CNS-IDDs.

Patients and Methods

A flow diagram of subject inclusion is displayed in Figure 1. During the study period from January 2017 to

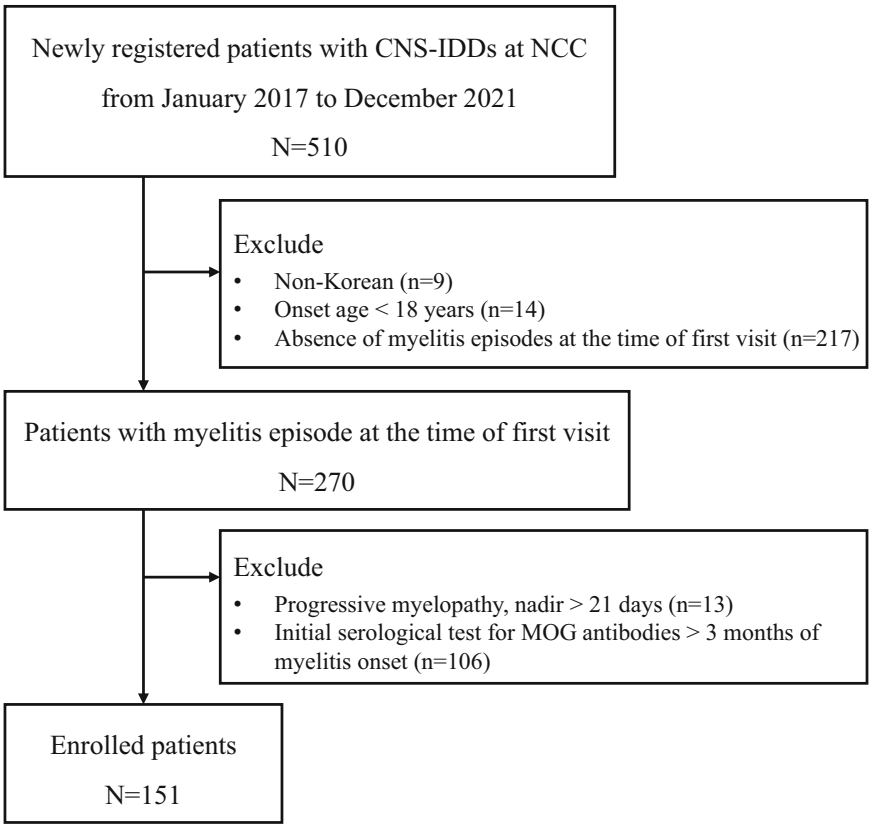

Figure 1. A flow diagram of patients. During the study period, 510 patients with CNS-IDDs were newly registered, and 151 patients who fulfilled the inclusion criteria were selected. CNS-IDDs, inflammatory demyelinating diseases of the central nervous system.

December 2021, 510 patients were newly registered in the NCC registry for CNS-IDDs. Of 510 patients with CNS-IDDs, nine non-Korean adults and 14 participants aged below 18 years were excluded, and 270 experienced myelitis episodes at the time of their first visit. All patients with myelitis episode presented with sensory, motor, or autonomic deficits (one or any combination) referable to the spinal cord, which develops over hours to days. A diagnosis of inflammatory myelitis is supported by MRI evidence of T2 hyperintense signal of the spinal cord with or without gadolinium enhancement, CSF pleocytosis and by the exclusion of vascular, compressive, cancer-related, infectious, and metabolic causes. The inclusion criteria were as follows: (1) history of acute myelitis (nadir ≤21 days) at the time of first visit and (2) the presence of MOG and AQP4-IgG test performed in acute stage of myelitis (within 3 months of myelitis onset). Based on the above criteria, 151 Korean adults with myelitis were included in this study.

Serological tests for MOG and AQP4-IgG were performed in all patients with CNS-IDDs at the time of their first visit since 2017. The presence of these antibodies was determined in the serum using the in-house live cell-based immunofluorescence assay as described in our previous reports.[14,18] The immunofluorescence intensity score (IF-score) was semi-quantitatively graded from 1 to 4. In double-seronegative myelitis other than typical MS by initial serologic test, a follow-up serologic examination was performed at relapses or 3–6 months later, in cases where serum samples were available. Of 56 patients with double-seronegative myelitis, 25 (44.6%) undertook the follow-up serology test for MOG-IgG.

Medical records were reviewed to collect the demographic, clinical, and radiological information of patients with myelitis episodes. Patients were categorized as having MS according to the 2017 McDonald criteria, including typical MS lesions on magnetic resonance imaging (MRI)[19,20]; NMOSD according to the 2015 criteria[21]; and MOGAD according to the international recommendations for diagnosis.[8] The remaining patients who did not fulfill these diagnostic criteria were classified as having unclassified CNS-IDDs, including monophasic or relapsing isolated myelitis and myelitis combined with other phenotypes (optic neuritis or brain demyelinating syndrome). Myelitis was defined as having acute myelopathy due to inflammation for which other definitive etiologies

or a better explanation could not be revealed. The final diagnosis was primarily determined by treating neurologists (H. J. Kim, S.-H. Kim) and confirmed by other neurologists (K. H. Kim, J.-W. Hyun).

The Institutional Review Board of the NCC approved this study (NCC2014-0146), and written consent was obtained from all participants.

Results

Of 151 adults with acute myelitis, 11 (7.3%) tested positive for MOG-IgG while 42 (27.8%) tested positive for AQP4-IgG by the initial serological test. At the time of the initial test, 103 (68.2%) patients already had received the acute treatment and 63 (41.7%) were on maintenance immunotherapy. When limited to the first myelitis episode, four (5.2%) of the 77 patient who had experienced myelitis as a presenting feature were MOG-IgG-positive. Among AQP-IgG-negative patients with myelitis, 9.2% (10/109) were found to be MOG-IgG positive. When excluding patients with typical MS and AQP4-IgG-positive NMOSD, 13.8% (9/65) were positive for MOG-IgG. Of 53 patients with LETM, three (5.7%) showed MOG-IgG seropositivity, while 31 (58.5%) showed AQP-IgG seropositivity. Among 15 patients who satisfied the diagnostic criteria for AQP4-IgG-negative NMOSD on their first visit, 2 (13.3%) were MOG-IgG positive. Table 1 shows the demographic and clinical information of the enrolled patients along with the results of the MOG-IgG test.

Among the 11 patients who were initially MOG-IgG positive, nine were diagnosed with MOGAD (IF-score 3+, $n = 3$; 2+, $n = 2$; 1+, $n = 4$); one patient with MRI lesions, typical for MS, was diagnosed with MS (IF-score 1+), and one double-seropositive patient with LETM was classified as AQP4-IgG-positive NMOSD based on the clinical (painful tonic spasm) and MRI (highly edematous LETM with brighter spotty lesion) findings highly suggestive of NMOSD than MOGAD.[22,23] In addition to the above, a marked difference in each of the antibody titers favored the diagnosis of NMOSD: AQP-IgG was strongly positive (IF-score 4+), while MOG-IgG was weakly positive (IF-score 1+). A follow-up MOG-IgG test was performed on 25 patients diagnosed with double-seronegative myelitis by initial serological test. Among them, one (4%) patient became MOG-IgG-positive during re-evaluation after 5 months (IF-score 3+). Thus, a total of 10 (6.6%) patients were finally diagnosed with MOGAD during the study period.

Of 10 patients with MOGAD, six underwent the follow-up MOG-IgG test to check for serostatus change, and one (16.7%) of them showed negative seroconversion on the follow-up serological test after 5 months (IF-score 1+ ➜ negative). The final diagnosis of the enrolled patients is summarized in Table 2.

Table 1. Demographic characteristics, clinical information, and serology results of enrolled patients with myelitis.

Enrolled patients with myelitis episode	*N* = 151
Sex, female	110 (72.8)
Age at myelitis episode, years	42.9 ± 14.7
Acute treatment at the time of initial sampling	103 (68.2)
IVMP only	93
IVMP + plasma exchange	8
IVMP + intravenous immunoglobulin	2
Maintenance therapy at the time of initial sampling	63 (41.7)
Azathioprine	17
Mycophenolate mofetil	14
Rituximab	3
Interferon-beta	11
Teriflunomide	8
Glatiramer acetate	4
Dimethyl fumarate	4
Fingolimod	1
Natalizumab	1
AQP4-IgG-seropositive	42 (27.8)
Among LETM phenotype	31/53 (58.5)
MOG-IgG-seropositive	11 (7.3)
Among patients with presenting myelitis	4/77 (5.2)
Excluding AQP-IgG-positive NMOSD	10/109 (9.2)
Excluding typical MS and AQP-IgG-positive NMOSD	9/65 (13.8)
Among LETM phenotype	3/53 (5.7)
Among AQP-IgG-negative NMOSD[1]	2/15 (13.3)
Double seropositive for AQP4-IgG and MOG-IgG	1 (0.6)

Data are presented as mean ± standard deviation or *N* (%) value. IVMP, Intravenous methylprednisolone; LETM, longitudinally extensive transverse myelitis; NMOSD, neuromyelitis optica spectrum disorder.
[1]Patients who satisfied the 2015 diagnostic criteria for AQP4-IgG-negative NMOSD at the time of their first visit.

Discussion

Our study showed MOG-IgG seroprevalence in Korean adults with myelitis: 7.3% of patients with myelitis were found to be MOG-IgG positive at the initial screening, and 6.6% were diagnosed with MOGAD during the study period. When excluding typical MS and AQP4-IgG-positive NMOSD, MOG-IgG seroprevalence increased up to 13.8% in patients with myelitis. This result provides a pre-test probability of MOG-IgG positivity in cases with myelitis, which supports the utility of MOG-IgG testing in patients with myelitis episodes following current international recommendations.[8]

In this study, MOG-IgG seroprevalence of patients with myelitis was found to be comparable to that of overall CNS-IDDs cohort in previous studies. Of 586 Korean adults with CNS-IDDs, 6.1% tested positive for MOG-IgG.[4] Likewise, MOG-IgG positivity was detected in 6.7%

Table 2. Final diagnosis based on serology tests in Korean patients with a myelitis episode.

		Positive MOG-IgG			
Final diagnosis	*N* = 151	Initial (*n*)	IF score	Detection during f/u (*n*)	IF score
MS	42 (27.8)	1	1+, *n* = 1		
AQP-IgG-positive NMOSD	44 (29.1)	1	1+, *n* = 1		
AQP-IgG-negative NMOSD	13 (8.6)	0			
MOGAD	10 (6.6)	9	1+, *n* = 4 2+, *n* = 2 3+, *n* = 3	1	3+, *n* = 1
Other CNS-IDDs with myelitis	42 (27.8)	0			
Monophasic isolated myelitis	20	0			
Relapsing isolated myelitis	10	0			
Combined with optic neuritis	9	0			
Combined with brain syndrome	3	0			

Data are presented as *N* (%) value. CNS-IDDs, central nervous system-inflammatory demyelinating diseases; MS, multiple sclerosis; MOGAD, MOG-antibody-associated disorder; NMOSD, neuromyelitis optica spectrum disorder; IF score, the immunofluorescence intensity score of MOG-IgG test.

of 447 adults with CNS-IDDs in a study conducted in Israel,[24] in 5.3% of 1081 adults in a national Dutch study,[25] and in 6.5% of 13736 adults in a US study from Mayo Clinic.[11] In addition, MOG-IgG positivity in patients with myelitis was approximately three times lower than AQP4-IgG positivity (7.3% vs. 27.8%), which is in concordance with the findings of previous studies on Asian adults that reported lower MOG-IgG seroprevalence than AQP4-IgG seroprevalence in Asian populations.[4,10,26] In contrast, a large cohort study conducted on the Western population reported almost 3 times higher seroprevalence of MOG-IgG than that of AQP-IgG.[11] Given the noticeable difference in MOG/AQP4-IgG seroprevalence ratio between Asian and Western adults with CNS-IDDs, further investigations on MOG-IgG seroprevalence among diverse racial groups are warranted.

Interestingly, two patients with myelitis who were initially MOG-IgG positive were finally diagnosed as having MS or NMOSD, rather than MOGAD. As low-titers of MOG-IgG can be found in patients with otherwise typical MS,[27] the identification of Dawson's finger or ovoid periventricular lesions, suggestive of MS, can help identify the probability of false-positive results. Additionally, one (0.6%) of our patients was double seropositive for MOG-IgG and AQP4-IgG, which is consistent with previous reports demonstrating that the incidence of double seropositivity is extremely rare.[9–11] Currently, the implication of the coexistence of MOG-IgG in AQP-IgG-positive patients with typical clinical manifestations of NMOSD remains unclear. As the diagnostic criteria for MOGAD are yet to be established, careful interpretation of MOG-IgG positivity with low-titers is required for MOGAD diagnosis in clinical practice.

This study has several limitations. First, we enrolled patients from a single referral center which might have resulted in selection bias. Second, more than two-thirds of the enrolled patients had undertaken acute treatment before sampling; therefore, MOG-IgG seroprevalence might have been underestimated, as MOG-IgG serostatus is affected by treatment and the timing of sampling.[9,28] However, the follow-up tests for MOG-IgG were conducted after 3–6 months in double-seronegative patients with myelitis, which may partially reduce the treatment effect on MOG-IgG seroprevalence. Despite these limitations, our study is the first to report MOG-IgG seroprevalence in adult patients with myelitis, which supports the importance of MOG-IgG testing for patients with acute myelitis.[8]

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Author Contributions

Ho Jin Kim was involved in conceptualization. All authors were involved in resources and writing—review and editing. Su-Hyun Kim and Ho Jin Kim were involved in supervision. Ki Hoon Kim was involved in visualization. Ki Hoon Kim was involved in writing—original draft.

Conflict of Interest

K. H. Kim, Y. Kim, and H. Park report no disclosures. S.-H. Kim has lectured, consulted, and received honoraria from Bayer Schering Pharma, Biogen, Genzyme, Merck Serono, and UCB and received a grant from the National Research Foundation of Korea. J.-W. Hyun has received a grant from the National Research Foundation of Korea. H. J. Kim received a grant from the National Research Foundation of Korea and research support from Aprilbio and Eisai; received consultancy/speaker fees from Alexion, Aprilbio, Biogen, Celltrion, Daewoong, Eisai, GC Pharma,

HanAll BioPharma, Horizon Therapeutics (foremly Viela Bio), MDimune, Merck Serono, Novartis, Roche, Sanofi Genzyme, Teva-Handok, and UCB; is a co-editor for the *Multiple Sclerosis Journal* and an associate editor for the *Journal of Clinical Neurology*.

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