Results of a Survey on Diagnostic Procedures and Treatment Choices for Neuromyelitis Optica Spectrum Disorder in Korea: Beyond the Context of Current Clinical Guidelines

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Background and Purpose Neuromyelitis optica spectrum disorder (NMOSD) is a rare demyelinating disease of the central nervous system (CNS). We investigated the medical behaviors of experts in Korea when they are diagnosing and treating NMOSD.

Methods An anonymous questionnaire on the diagnosis and treatment of NMOSD was distributed to experts in CNS demyelinating diseases.

Results Most respondents used the 2015 diagnostic criteria for NMOSD and applied a cerebrospinal fluid examination, magnetic resonance imaging (MRI) of the brain and spine, and anti-aquaporin-4 antibody testing to all suspected cases of NMOSD. All respondents prescribed steroid pulse therapy as a first-line therapy in the acute phase of NMOSD, and 67% prescribed azathioprine for maintenance therapy in NMOSD. However, details regarding monitoring, the tapering period of oral steroids, second-line therapy use in refractory cases, management during pregnancy, and schedule of follow-up MRI differed according to the circumstances of individual patients. We analyzed the differences in response rates between two groups of respondents according to the annual number of NMOSD patients that they treated. The group that had been treating $\geq 10$ NMOSD patients annually preferred rituximab more often as the second-line therapy ($p=0.011$) and had more experience with rituximab treatment ($p=0.015$) compared with the group that had been treating $<10$ NMOSD patients.

Conclusions This study has revealed that NMOSD experts in Korea principally follow the available treatment guidelines. However, the differences in specific clinical practices applied to uncertain cases that have been revealed will need to be investigated further in order to formulate suitable recommendations.

Keywords neuromyelitis optica spectrum disorder; survey; expert opinion; guideline.

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic demyelinating disease of the central nervous system (CNS). Approximately 80% of patients with NMOSD have pathognomonic antibodies known as aquaporin-4 antibodies (AQP4-Abs).\textsuperscript{1} The diagnostic criteria and therapeutic options for NMOSD have evolved remarkably over the past decade and have recently been updated.\textsuperscript{2} Treatment options have diversified in recent years, with several emerging drugs approved in 2019, including eculizumab, satralizumab, and inebilizumab.\textsuperscript{3} However, there is a scarcity of reports on the clinical diagnosis and treatment of NMOSD.\textsuperscript{4-7}

While NMOSD is rare in the Republic of Korea, a clinical registry and research network for multiple sclerosis (MS) and NMOSD (the MS-NMO NETWORK) comprising experts in CNS demyelinating diseases from 32 hospitals was formed. This network has been...
supported by the Korea Disease Control Agency since 2014.4-10 We conducted a survey of the diagnostic procedures and treatment protocols adopted by experts in the MS-NMO NETWORK. We aimed to identify current clinical practices and controversial aspects of the treatment strategies used by NMOSD experts. Furthermore, we aimed to identify any aspects of the current treatment guidelines for Korea that need to be addressed in future research on treatment guidelines.

METHODS

The questionnaire utilized in this study comprised two parts: 1) diagnostic procedures and laboratory tests, and 2) treatment strategies for NMOSD. We did not differentiate between seronegative and seropositive NMOSD, and specifically included only items related to seronegative NMOSD in the questionnaire. The following information was obtained: 1) center setting and the number of NMOSD patients seen each year, 2) diagnostic procedures performed, 3) procedures applied to patients with acute attacks and to those refractory to first-line therapy, 4) procedures applied after acute therapy for further prevention, 5) first- and second-line preventive therapies administered, and 6) routine management of patients with NMOSD. The draft questionnaire was reviewed by all of the authors and finalized accordingly. The questionnaire was distributed to experts in the MS-NMO NETWORK as an anonymous survey.

We used descriptive statistics to report the response rates for each questionnaire item. We divided participants into two groups according to hospital size (secondary versus tertiary hospital), medical experience as a neurologist (<10 years versus ≥10 years), and the number of NMOSD patients followed up annually at their hospital (≥10 versus <10). Statistical differences in response rates for each questionnaire were analyzed using Fisher’s exact test.

This study was approved by the Institutional Review Board of Korea University Guro Hospital (approval number 2017 GR0257). We received 27 responses between January 2019 and August 2019, corresponding to a response rate of 75% (27/36). The requirement of informed consent was waived by the institutional review board. SPSS (version 21; IBM Corporation, Armonk, NY, USA) was used for descriptive statistical analyses.

RESULTS

Participants

Most participants were from referral hospitals: 59% (n=16) of the participants worked at a tertiary hospital and 37% (n=10) worked at a secondary hospital. All respondents were neurologists specializing in CNS demyelinating disease, and 59% (n=16) had been practicing as clinical neurologists for at least 10 years. Approximately 41% (n=11) of the respondents had been treating ≥10 NMOSD patients annually (Fig. 1A).

Diagnostic workup

Most respondents (85%, n=23) solely followed the 2015 NMOSD diagnostic criteria, while others followed either the 2006 revised diagnostic criteria or the 2015 NMOSD diagnostic criteria depending on the individual patient (15%, n=4).2,6,11 Approximately 89% (n=24) of the participants applied AQP4-Ab tests to all patients with optic neuritis, myelitis, or acute encephalitis, while 11% (n=3) applied tests only to patients suspected of having NMOSD. The AQP4-Ab test was performed using cell-based assays (CBAs) and tissue-based indirect immunofluorescence assays by 67% (n=18) and 21% (n=6) of the participants, respectively (Fig. 2). Two participants used flow cytometry to analyze the CBA. Furthermore, 22% (n=6) applied tests for the antimyelin oligodendrocyte glycoprotein (MOG) antibody in order to differentially diagnose myelin oligodendrocyte glycoprotein-associated disease, and 93% (n=25) applied tests for systemic autoantibodies, including antinuclear antibody and antineutrophil cytoplasmic antibody, to identify other concurrent autoimmune diseases such as Sjogren’s disease.

All participants performed brain and spinal magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) examinations on all patients suspected of having NMOSD. Approximately 93% (n=25) performed evoked potential tests, such as of visual evoked, somatosensory evoked, and brainstem auditory evoked potentials. Optical coherence tomography was ordered by 74% (n=20) of the participants.

Treatment for acute attacks

All respondents prescribed high-dose steroid pulse therapy for a suspected acute NMOSD attack. After the initial steroid pulse therapy, 44% (n=12) of the respondents monitored the patients for approximately 1 week, while 48% (n=13) did not apply an observational period in cases refractory to steroid pulse therapy, defined as Expanded Disability Status Scale score ≥5.0, Medical Research Council grade ≤3.0, or corrected visual acuity ≤0.2. In refractory cases, 74% (n=20) of the participants opted for plasmapheresis as the second-line therapy for the acute phase, while 19% (n=5) repeated the steroid pulse therapy. Furthermore, 70% (n=19) of the respondents used plasmapheresis as the second-line therapy, even in cases with seronegative NMOSD, while 26% (n=7) did not. In cases with less-severe clinical symptoms remaining after steroid pulse therapy, 41% (n=11) of the participants...
Fig. 1. Characteristics of participants. A: Most of the participants worked in secondary or tertiary hospitals. About 59% of the participants had ≥10 years of medical experience as a neurologist. B: Acute management of NMOSD patients. All respondents selected steroid pulse therapy as the first-line therapy for an NMOSD attack. However, the observation period after the initial steroid pulse therapy varied. In addition, they applied diverse secondary treatments to NMOSD patients with mild remaining symptoms after an acute attack. C: Maintenance therapy for NMOSD patients. Approximately 67% of the participants selected azathioprine as the first-line therapy for maintenance in seropositive NMOSD, but second-line therapy selections were more diverse. D: Imaging monitoring of NMOSD patients. Approximately 60% of participants selected regular brain MRI every year, while spinal MRI was performed by only 11% of the participants. IVIG, intravenous immune globulin; NMOSD, neuromyelitis optica spectrum disorder.
Furthermore, 67% (n=18) of the respondents prescribed azathioprine with or without oral steroids as the initial therapy for preventive management, while 30% (n=8) prescribed mycophenolate mofetil with or without oral steroids as the initial therapy (Fig. 1C). In the event of recurrence after first-line therapy had been applied for an adequate period, 70% of the respondents preferred prescribing rituximab as the second-line therapy in response to the question regarding the use of secondary drugs that allowed multiple responses. Among those who chose azathioprine as the primary drug, 14 selected rituximab and the rest chose mycophenolate mofetil as the secondary drug. Among those who chose mycophenolate mofetil as the first-line drug, five selected rituximab and two selected azathioprine as the second-line drug.

Moreover, 37% (n=10) of the respondents reported that they switched to second-line therapy in 10%–30% of patients, while 30% (n=8) reported this in 30%–50% of patients. In addition, 63% (n=17) of the respondents answered that the average duration before drug change was 1–3 years.

For preventive therapy, 59% (n=16) of the respondents had experience of administering rituximab, among which 93% (n=14) claimed that rituximab was more effective than other oral immunosuppressive agents. Furthermore, 37% (n=10) of the respondents reported that cost and coverage by the national health insurance system were the most important considerations for prescribing rituximab. Before re-initiating rituximab treatment, 75% (n=12) of the respondents evaluated B-cell or memory-B-cell counts in the serum, and when such counts were not available, retreatment was prescribed at regular intervals of 6–9 months.

Monitoring
In total, 59% (n=16) of the respondents performed regular brain MRI monitoring during preventive treatment of NMOSD patients, with the most common follow-up period for brain MRI being 1 year. The remaining 41% (n=11) of the respondents did not perform regular brain MRI unless new clinical symptoms appeared. Only three (11%) respondents performed regular spinal MRI follow-ups despite the absence of new clinical symptoms, while the remaining respondents did not apply regular spinal MRI follow-ups (Fig. 1D).

Regarding treatment discontinuation, 78% (n=21) of the respondents reported that maintenance treatment for NMOSD patients would not be discontinued even if there were no relapses, while 22% (n=6) reported that they would consider discontinuation if previous symptoms were not severe and if no relapse occurred for >5 years. Among them, two respondents based their decisions on the patient’s individual condition, while another did not submit a response about what they would do in a special situation.

**Preventive therapy**
Immunosuppressants were prescribed by 85% (n=23) of the participants after the first attack in patients with seropositive NMOSD. In seronegative cases of suspected NMOSD with longitudinally extensive transverse myelitis, optic neuritis, or encephalitis, 78% (n=21) of the participants considered prescribing immunosuppressants, including oral steroid agents, for severe symptomatic cases, and did not consider prescribing any maintenance treatment if the symptoms were mild. In cases without AQP4-Abs, 22% (n=6) of the respondents did not prescribe maintenance drugs regardless of the presence of severe clinical symptoms; however, 89% (n=24) considered using immunosuppressant therapy in cases of recurrence, even in patients who were negative for AQP4-Abs (Fig. 1B).
Lee HL et al.

For patients undergoing preventive treatment who had plans to conceive, 44% (n=12) of the respondents recommended that immunosuppression treatment should be discontinued before pregnancy, while 26% (n=7) recommended continuing rituximab and planning for conception after 2–3 months of observation. In addition, 15% (n=4) of the respondents reported that they would encourage patients to refrain from pregnancy or would prescribe either azathioprine or a minimum dose of oral steroids until pregnancy was confirmed.

### Analysis of influencing factors

An analysis of differences in response rates for diagnostic procedures, the application of first- and second-line therapies, and regular monitoring for NMOSD patients between the two groups of hospital size and medical experience as a neurologist revealed no significant differences. However, there were differences between the two groups of the annual number of followed-up NMOSD patients. That is, the group that had been treating ≥10 NMOSD patients annually selected rituximab more often as the second-line therapy (p=0.011) and they had more experience with rituximab treatment (p=0.015) (Table 1).

### DISCUSSION

This study investigated the diagnostic and treatment approaches adopted in clinical practice for patients with NMOSD in Korea. The participants in our survey were specialists at referral hospitals involved in the care of patients with NMOSD. The main results of this survey were homogenous with respect to the diagnostic procedures followed. Most participants performed brain and spinal MRI, AQP4-Ab tests using CBAs and CSF examinations, and autoimmune antibody tests in cases of suspected NMOSD. The MOG antibody test was not commercially available in Korea until 2019, and so only 22% of the participants had applied the MOG antibody test. All respondents selected steroid pulse therapy as the first-line treatment for episodes of NMOSD. Azathioprine was the most common first-line immunosuppressant applied to patients with seropositive NMOSD.

A previous international survey similarly attempted to understand medical behaviors during the clinical diagnosis of NMOSD, but since the respondents were from different countries, their responses were heterogeneous due to the availability and access to diagnostic procedures differing among hospitals located in North America and Europe. In contrast, the present study revealed broadly uniform medical behavior among Korean experts in the diagnosis of NMOSD. There were no significant differences between the groups according to hospital size or medical experience. This is not only because the hospitals that participated in the survey were referral hospitals and had good access to neuroimaging devices, including MRI, but also because the clinical practice guidelines for NMOSD were released by the Korean MS Society in 2012.

Despite the guidelines lacking detailed and updated information, they have been used by many Korean neurologists as a reference for the clinical management of NMOSD. The guidelines are based on the 2006 neuromyelitis optica (NMO) diagnostic criteria and recommend using brain MRI, spine MRI, serologic testing for NMO IgG, and CSF examinations as diagnostic procedures. Steroid pulse therapy and azathioprine were recommended as the first-line acute and maintenance treatments for NMOSD, respectively. In cases that are refractory to steroid pulse therapy, an observational period of at least 1 week is needed, and a second-line acute therapy such as plasmapheresis should be considered. Moreover, medical practices in Korea are greatly influenced by the national health insurance policy. For example, despite myco-

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**Table 1. Preferences of physicians regarding the application of first- and second-line therapies to neuromyelitis optica spectrum disorder (NMOSD) patients**

| Experience of treating <10 NMOSD patients annually (n=11) | Experience of treating ≥10 NMOSD patients annually (n=16) | p     |
|--------------------------------------------------------|----------------------------------------------------------|-------|
| First-line therapy                                     |                                                         |       |
| Azathioprine                                           | 9                                                       | 9     | 0.239 |
| Mycophenolate mofetil                                  | 3                                                       | 6     | 0.618 |
| Oral steroid                                           | 1                                                       | 3     | 0.624 |
| Second-line therapy                                    |                                                         |       |
| Azathioprine                                           | 4                                                       | 2     | 0.187 |
| Mycophenolate mofetil                                  | 6                                                       | 5     | 0.130 |
| Rituximab                                              | 4                                                       | 14    | 0.011 |
| Methotrexate                                           | 1                                                       | 0     | 0.407 |
| Experience of rituximab                                | 3                                                       | 13    | 0.015 |
phenolinate mofetil showing a noninferior treatment effect compared with azathioprine, some physicians prefer using azathioprine because of concern about insurance reductions for mycophenolate mofetil by the national health insurance policy. A similar issue was observed with rituximab: if rituximab is used by the physician without clear justification, the hospital and patient must take the risk of the payment being refused by the national health insurance system.13,14

A recent international survey found that brain or spine MRI was performed by around 10% of participants,15 whereas 59% (16/27) of the present participants performed regular brain MRI and 11% (3/27) of them performed spinal MRI in Korea. Several studies have examined when and how to measure disease activity in MS using MRI,16,17 but this has not been studied previously in NMOSD. A recent study of asymptomatic brain lesions in NMOSD did not elucidate their clinical significance.17

The criteria used in decision-making about treatment discontinuation remain controversial. In the present survey, 78% of the respondents did not consider discontinuation of the maintenance drug, while the remaining 22% considered discontinuation if there was no recurrence. There have been several recent reports on whether drugs can be discontinued based on consideration of the long-term side effects or risk of relapse in NMOSD, but further studies are needed.18,19

Since the current guidelines do not address clinical characteristics in detail, many physicians depend on personal experience when deciding about how to treat patients with NMOSD. We therefore attempted to obtain detailed information from neuroimmunologic experts regarding clinical decisions for the diagnosis and treatment of NMOSD, such as the observational period, duration of steroid tapering, and secondary treatment options. In particular, rituximab was preferred as a secondary treatment agent for preventive therapy in refractory cases. The group that had been treating ≥10 NMOSD patients annually showed the same tendency in this study. The efficacy and safety of rituximab for NMOSD have been established in previous studies.20-22 In addition, rituximab has been covered by medical insurance in Korea since 2015 as a second-line drug, and so it was presumed that many physicians would prefer prescribing it as a secondary treatment for NMOSD in current practice. However, only 59% of the respondents had experience in prescribing rituximab due to concerns about the coverage of medical insurance, and so we expect that the use of rituximab will increase in the future. Moreover, rituximab was selected as the preferred drug for females considering pregnancy, because other immunosuppressive drugs carry a risk of teratogenicity. Rituximab also belongs to drug category C, but its longer interval before repeat therapy is an additional benefit.21,22

Studies have investigated the potential efficacy and tolerability of rituximab as the first-line disease-modifying drug for NMOSD, and other novel drugs are expected to emerge.23 This is not reflected in the current clinical guidelines for NMOSD in Korea,24,25 and so we expect that recommendations for more treatment options will appear in the clinical guidelines for NMOSD in the future.

This study had a few limitations. First, the number of respondents was small. The survey was sent to 36 neurologists, and only 27 of them responded. However, since all of the respondents were experts in NMOSD and had been overseeing clinical care for MS and NMOSD, we assume that their answers reliably reflect real clinical practice in Korea. Furthermore, only 74 participants have been previously surveyed in international studies, including from North America and Europe, because NMOSD is a very rare neurologic disease. Second, the survey was performed only in Korea, and the answers of the respondents may have been greatly influenced by the coverage of national health insurance and the single treatment guidelines for NMOSD in Korea. However, we were able to identify clinical aspects that the current guidelines do not address. These results are potentially useful for planning retrospective studies on treatment effects or the quality of life of NMOSD patients.

The results of this survey of national experts in the MS-NMO NETWORK indicate that diagnostic procedures and acute treatments are implemented relatively consistently for NMOSD. However, the treatment strategies for second-line therapy or maintenance drugs for seronegative NMOSD, including the duration of steroid tapering, and the interval between imaging studies for NMOSD patients remain controversial. This study has confirmed the lack of current treatment guidelines regarding clinical practices for medication changes, including the duration of steroid use in regular follow-up or specific considerations such as pregnancy. Validation through studies with larger cohorts using big data such as from the national health insurance system or clinical registry is warranted to obtain more detailed clinical information on diverse cases in the future. It is also necessary to conduct studies comparing the effects of emerging drugs and traditional drugs. Some respondents in this survey cited shifting to a new drug or applying more aggressive treatments such as plasmapheresis as their biggest concern about insurance reductions. Future guidelines should include rationales about emerging drugs and treatments and reduce restrictions of physicians’ choices due to insurance reductions, in order to become a practical basis for the management for NMOSD patients.

Availability of Data and Material
The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.
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Conflicts of Interest

Author Contributions

Conceptualization: Ho Jin Kim, Su-Hyun Kim. Data curation: Hye Lim Lee, Jin Myoung Seok. Formal analysis: Hye Lim Lee. Funding acquisition: Hye Lim Lee, Byoung Joon Kim. Investigation: Byung Jo Kim. Supervision: Byoung Joon Kim. Writing—original draft: Hye Lim Lee. Writing—review & editing: Byung Jo Kim, Byoung Joon Kim.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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