RESEARCH ARTICLE OPEN ACCESS

Effects of the COVID-19 Pandemic on Patients With NMO Spectrum Disorders and MOG-Antibody–Associated Diseases

COPANMO(G)-Study

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Neurol Neuroimmunol Neuroinflamm 2023;10:e200082. doi:10.1212/NXI.0000000000200082

Abstract

Background and Objectives

To evaluate the effects of the coronavirus disease 2019 (COVID-19) pandemic on the life of patients with neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody–associated diseases (MOGAD).

Methods

This multicenter, cross-sectional study included data of 187 patients recruited from 19 different German and Austrian Neuromyelitis Optica Study Group (NEMOS) centers between July 2021 and March 2022. The effects of the pandemic on immunotherapeutic treatment and access to care, the possible severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and the potential effect of vaccination against SARS-CoV-2 on disease incidence and relapse risk were assessed using a patient questionnaire. Health-related quality of life (HRQoL) was measured with the EuroQoL Group 5-Dimension 5-Level Scale (EQ-5D-5L). Demographic and clinical characteristics were retrieved from the NEMOS database.

Results

One hundred eighty-seven patients (75% women; median age 47 [range 21–86] years; median disease duration 5.5 [range 0–67] years; median Expanded Disability Status Scale 2.0 [range 0–8.0];

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Neuromyelitis Optica Study Group (NEMOS) coinvestigators are listed in the appendix at the end of the article.

Glossary

ADEM = acute disseminated encephalomyelitis; **AQP4-IgG** = aquaporin-4 immunoglobulin G; **EDSS** = Expanded Disability Status Scale; **EQ-5D-5L** = EuroQoL Group 5-Dimension 5-Level Scale; **HRQoL** = health-related quality of life; **IVIG** = IV immunoglobulin; **MOG-IgG** = myelin oligodendrocyte glycoprotein immunoglobulin G; **MOGAD** = myelin oligodendrocyte glycoprotein antibody–associated diseases; **mRNA** = messenger RNA; **NEMOS** = Neuromyelitis Optica Study Group; **NMOSD** = neuromyelitis optica spectrum disorders.

51% aquaporin-4 immunoglobulin G (AQP4-IgG)-positive, 36% myelin oligodendrocyte glycoprotein (MOG)-IgG-positive 13% double-seronegative) were analyzed. Most patients maintained excellent access to healthcare services throughout the pandemic. Immunotherapy was not changed in 88% of patients. Ninety-one percent of all patients were satisfied with medical care during the pandemic. Nearly two-thirds (64%) of patients rated their risk of infection with SARS-CoV-2 as low or moderate. Among this study sample, 23 patients (12%) knowingly acquired an infection with SARS-CoV-2 and predominantly had a nonsevere course of illness (n = 22/23, 96%). The SARS-CoV-2 vaccination rate was 89%, with 4 cases of confirmed attack or first manifestation of NMOSD/MOGAD occurring in temporal association with the vaccination (range 2–9 days). The reported HRQoL did not decline compared with a prepandemic assessment (mean EQ-5D-5L index value 0.76, 95% bootstrap confidence interval [CI] 0.72–0.80; mean EQ-VAS 66.5, 95% bootstrap CI 63.5–69.3).

Discussion

This study demonstrates that, overall, patients with NMOSD/MOGAD affiliated with specialized centers received ongoing medical care during the pandemic. Patients' satisfaction with medical care and HRQoL did not decrease.

Neuromyelitis optica spectrum disorders (NMOSD) are rare autoimmune inflammatory conditions of the CNS, primarily involving the optic nerves and spinal cord, which can be further stratified by serologic testing for aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) into AQP4-IgG–positive and AQP4-IgG–negative NMOSD.[1] Myelin oligodendrocyte glycoprotein antibody–associated diseases (MOGAD; also termed MOG encephalomyelitis) are a new clinical entity with considerable clinical overlap with NMOSD and detection of myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (MOG-IgG) antibodies.[2,3] Attacks of both, NMOSD and MOGAD, can result in severe disability.[4,5] Therefore, the most patients receive long-term immunosuppressive or immunomodulatory treatment to prevent relapses, increasing the risk of infections.[6-9]

Owing to the COVID-19 pandemic, patients with NMOSD and MOGAD and their caregivers have been faced with numerous challenges: from infection prevention to the management of SARS-CoV-2 infections and the general restrictions the pandemic imposed on medical care (e.g., medical staff shortages, lack of medications, and protective gear).[10]

Several studies investigated the severity of SARS-CoV-2 infection in patients with NMOSD/MOGAD and immunotherapy demonstrating that most patients had a mild disease course. Comorbidities and B-cell–depleting therapies such as rituximab might be potential factors for unfavorable outcomes.[11-13] However, the role of rituximab remains controversial.[14] In patients treated with B-cell–depleting therapies, the humoral immune response to SARS-CoV-2 infection and vaccination has been shown to be reduced, but T-cell response seems to be largely unaffected.[15,16] The SARS-CoV-2 infection-related or vaccination-related risk of immune-mediated worsening of the underlying disease was found to be low,[17] but temporal association of CNS demyelinating disease relapse or, very rarely, first-time manifestations of NMOSD or MOGAD with SARS-CoV-2 vaccination has been reported.[18,19] Overall, vaccination hesitancy among patients with neuroinflammatory diseases was described as low.[20-22] A recently published evaluation of further influence of the early pandemic phase on NMOSD in a study sample of Chinese patients found that fear of infection often led to postponement of follow-up appointments (71%), alteration or cancellation of rehabilitation plans (25%), and discontinuation of immunotherapy at the patient's initiative (6%).[23]

However, only relatively few data exist on the pandemic's overall personal effect on Central European patients with NMOSD and MOGAD. In addition, there is a lack of data on medical care, quality of life, and satisfaction from a patient perspective during the pandemic. Thus, this multicenter study was initiated within the Neuromyelitis Optica Study Group (NEMOS) to investigate the burden of the COVID-19 pandemic on patients with NMOSD and MOGAD (COPANMO(G)-Study).

Methods

Study Design and Study Population

We performed an exploratory cross-sectional study based on a patient questionnaire from July 1, 2021, to March 15, 2022. Inclusion criteria were adult patients (≥18 years) with diagnoses of NMOSD according to the International Panel for NMO Diagnosis criteria 2015[1] or MOGAD.[3] Exclusion criteria were severe cognitive impairment and inability to provide informed consent. Patients were identified within the

NEMOS (nemos-net.de) at 19 specialized centers in Germany and Austria. NEMOS centers are neurologic centers specialized in the diagnosis and treatment of NMOSD and MOGAD, committed to the standardized acquisition of clinical, demographic, radiologic, and serologic data by evaluating patients in annual visits by trained physicians in the field of neuroimmunology. A total of 205 questionnaires were returned; after exclusion of unsuitable questionnaires (missing data: n = 15; wrong initial diagnosis: n = 2; double entry: n = 1), 187 questionnaires could be analyzed.

Patient Questionnaire

From January to March 2021, an expert panel of 13 senior researchers from the NEMOS network developed the patient questionnaire in 5 meetings. An online-based and a paper-based version was available for patients starting June 21, 2021. The questionnaire consisted of 5 main categories: (1) demographic and clinical data (age, sex, weight, height, disease, disease duration, comorbidities, and current immunotherapy), (2) effects of the pandemic (changes of immunotherapy, restrictions on medical care, satisfaction with medical care during the pandemic, and personal risk assessment concerning infection with SARS-CoV-2), (3) possible SARS-CoV-2 infection (severity, SARS-CoV-2 laboratory test, symptoms, relapse of underlying disease, and changes of immunotherapy during infection), (4) SARS-CoV-2 vaccination (vaccination status, reasons for vaccination hesitancy, influences on vaccination decision, and attack of underlying disease/first-time manifestation after vaccination), and (5) health-related quality of life (HRQoL; captured by the EuroQoL Group 5-Dimension 5-Level Scale [EQ-5D-5L] and visual analog scale EQ-VAS questionnaire).[24] A translated version of the questionnaire is included in the supplement (eQuestionnaire, links.lww.com/NXI/A793). Patients were pseudonymized using a center-specific patient ID. The pseudonym was used to retrieve data from the NEMOS database. Data collection was centralized. Patients could leave a contact information for inquiries, but as well, participate anonymously.

Clinical Data

Data on serostatus and Expanded Disability Status Scale (EDSS) were obtained from the NEMOS database, an electronic registry for NMOSD and MOGAD. All EDSS values in the database were assessed by trained physicians during annual visits. Data on disease duration were cross-checked with the NEMOS database. Owing to online participation, in some cases, patient ID was missing for the database. In these cases, patients who left contact information for inquiries were contacted by telephone to obtain serostatus and EDSS from the respective center. Any patient-reported relapse event or first manifestation of the disease in temporal association with vaccination against or infection with SARS-CoV-2 was evaluated by contacting the treating NEMOS center and contacting the respective patient by telephone. On neurologic confirmation of the relapse event/first manifestation, further clinical data on symptoms, MRI, antibody titers, treatment, and treatment outcome (EDSS acute and after treatment) were retrieved from the responsible centers treating these patients.

Statistical Analyses

The paper-based and web-based data were transferred to an SPSS database by independent double data entry. Statistical analysis was performed using SPSS Statistics, Version 27, SPSS Inc., an IBM Company. Statistical significance was set to $p < 0.05$. Sample data were characterized using descriptive statistics. Differences between groups were evaluated for statistical significance using the Mann-Whitney test for nonparametric variables (care satisfaction, EQ-5D-5L dimensions, index value, and EQ-VAS for the COPANMO(G) patient study sample vs a prepandemic patient study sample; differences of age, body mass index, disease duration, and EDSS in patients with or without COVID-19) and the χ^2 test or, respectively, Fisher test for nominal variables (changes of immunotherapy for NMOSD vs MOGAD; differences in proportion of sex, disease, antibody status, comorbidities, and immunotherapy in patients with or without COVID-19; differences in proportion of sex, disease, antibody status, comorbidities, and immunotherapy in unvaccinated and vaccinated patients). Correlations between nonparametric variables were analyzed using the Spearman test (ρ) (risk assessment for contracting SARS-CoV-2 with EQ-5D-5L dimensions), and associations between nominal variables are described with Cramer V (basis of vaccination decision and vaccination status). As this was an exploratory study, we did not correct for multiple testing. Missing data lead to different numbers of patients analyzed and are indicated at the appropriate site.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the ethics boards of the Hannover Medical School (No. 9721_BO_K_2021). All patients gave their written informed consent before enrolment.

Patients represented in the case series gave additional written informed consent and agreed to the publication of their cases.

Data Availability

The data sets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Results

Patient Characteristics

Data sets from 187 patients, 120 (64%) with NMOSD and 67 (36%) with MOGAD with a median disease duration of 5.5 (range 0–67) years, were analyzed. The median EDSS was 2 (range 0–8). Patients were predominantly female (75%). More than 1 in 2 patients (55%) reported at least 1 comorbidity, and 89% received immunotherapy (Table 1). Details of the spectrum of comorbidities and immunotherapy are included in the supplement (eTable 1 and eTable 2, links.lww.com/NXI/A794 respectively).

Table 1 Sample Characteristics

	All patients	AQP4-IgG$^+$ NMOSD	Double-seronegative NMOSD	MOGAD
N (%)	187 (100)	95 (51)	25 (13)	67 (36)
Demographic characteristics				
Age, median (IQR), y	47 (36–58)	53 (41–62)	46 (40–58)	38 (29–53)
Range of age, y	21–86	21–86	24–70	21–70
Female sex, n (%)	140 (75)	85 (90)	17 (68)	38 (57)
Clinical characteristics				
Disease duration, median (IQR), y[a]	5.5 (3–11)	6 (3–13)	10 (4–12)	4 (2–8)
Range of disease duration, y	0–67	0–67	1.5–32	0–35
EDSS, median (IQR)[b]	2 (1–4)	3 (2–5)	2 (1–5)	2 (1–3)
Range of EDSS	0–8	0–8	0–8	0–8
Immunotherapy, n (%)[c]	166 (89)	89 (94)	22 (88)	55 (82)
Rituximab	93 (50)	51 (54)	17 (68)	25 (37)
Azathioprine	30 (16)	10 (11)	4 (16)	16 (24)
Oral corticosteroids	21 (11)	9 (10)	1 (4)	11 (16)
Eculizumab	13 (7)	12 (13)	1 (4)	—
Tocilizumab	10 (5)	6 (6)	—	4 (6)
Methotrexate	7 (4)	1 (1)	1 (4)	5 (8)
Satralizumab	5 (3)	5 (5)	—	—
Mycophenolate mofetil	3 (2)	1 (1)	—	2 (3)
IVIG	2 (1)	—	—	2 (3)
Glatiramer acetate	1 (<1)	—	—	1 (1)
Ruxolitinib	1 (<1)	1 (1)	—	—
Ocrelizumab	1 (<1)	1 (1)	—	—
Comorbidities, n (%)[d]				
No comorbidity	80 (44)	31 (34)	11 (46)	38 (58)
1 comorbidity	60 (33)	31 (34)	10 (42)	19 (29)
≥2 comorbidities	40 (22)	28 (31)	3 (13)	9 (14)

Abbreviations: AQP4-IgG = aquaporin-4 immunoglobulin G; EDSS = Expanded Disability Status Scale; IVIG = IV immunoglobulin; MOGAD = MOG-antibody–associated diseases; NMOSD = neuromyelitis optica spectrum disorders.
Percentages may not add exactly to 100% because of rounding.
[a] Data on disease duration were missing for 1 case in the MOGAD group.
[b] EDSS values of 4 patients were missing, all in the MOGAD group.
[c] 166 patients (89%) were treated with 1 or more immunotherapies (see also eTable 2, links.lww.com/NXI/A794 for details); 21 patients (11%) did not receive immunotherapy.
[d] Data on comorbidities were missing in 7 cases: 5 cases in the AQP4-IgG$^+$, 1 in the double-seronegative NMOSD group, and 1 case in the MOGAD group, respectively.

Effects of the Pandemic on Medical Care

Most of the patients (89%, n = 162/183) stated keeping up doctor's appointments as usual. Changes were primarily implemented because of the potential risk of infection (67%, n = 14/21, Table 2).

Access to therapeutic healing remained broadly available (Table 2): 88% (n = 148/169) could attend physiotherapy, with even higher rates for speech therapy (98%, n = 128/130) and other therapy forms, mainly occupational therapy (93%, n = 111/118). The main reason for changes was, again, the risk of infection (38%, n = 11/29), followed by facility shutdown (31%, n = 9/29) and appointment difficulties (24%, n = 7/29).

In accordance with recommendations on the use of immunotherapies during the pandemic,[25] most of the patients (88%, n = 160/181) maintained their therapeutic regimen

Table 2 Restrictions on Medical Care Due to the Pandemic

	n (%)	Available n
Physiotherapy		169
No change	148 (88)	
Change	22 (13)	
Speech therapy		130
No change	128 (98)	
Change	2 (2)	
Other therapies		118
No change	110 (93)	
Change	8 (7)	
Reasons for change (free-text option); grouped		29
Risk of infection	11 (38)	
Facility closed	9 (31)	
Appointment difficulties/capacity reduction	7 (24)	
Exclusively telemedical offer	1 (4)	
Access restrictions (vaccination status)	1 (4)	
Doctor's appointments		183
No change	162 (89)	
Change	21 (11)	
Reasons for change (free-text option), grouped		21
Risk of infection	14 (67)	
Appointment difficulties/capacity reduction	3 (14)	
Only telemedical offer for consulting hour	1 (5)	
Other	3 (14)	

Percentages may not add exactly to 100% because of rounding.

(eTable 3, links.lww.com/NXI/A794). If changes were made (12%, n = 21/181), they were initiated primarily by their supervising neurologist (43%, n = 9/21), by the patients themselves (24%, n = 5/21), or by the NEMOS center (19%, n = 4/21), with no difference between patients with NMOSD and MOGAD (p = 0.235).

A large majority of patients was satisfied with medical care during the pandemic (91%, n = 165/182), half of the patients (50%, n = 91/182) even declared to be very satisfied (eTable 4, links.lww.com/NXI/A794). The level of satisfaction did not decline compared with a prepandemic survey of our study group (p = 0.989).[26] Every fifth patient (19%, n = 36/187) made suggestions for improvement (eTable 5, links.lww.com/NXI/A794), mainly asking for more information about influences of SARS-CoV-2 infection or vaccination on NMOSD/MOGAD (n = 10/36).

SARS-CoV-2 Infection

Two-thirds of patients estimated their personal risk of infection with SARS-CoV-2 to be low to moderate (64%, n = 117/184, eTable 6, links.lww.com/NXI/A794). Among the study sample, 23 patients (12%, n = 23/187) reported having had a SARS-CoV-2 infection. There were no relevant differences in the demographic and clinical characteristics of this subgroup (eTable 7, links.lww.com/NXI/A794) compared with the not knowingly infected rest of the study population. Almost all patients with SARS-CoV-2 infection (96%, n = 22/23) had a nonsevere course of infection[27] (see eTable 8, links.lww.com/NXI/A794 for details of symptoms). Four patients were hospitalized (17%, n = 4/23), only 1 required supportive oxygen. However, no therapy in the intensive care unit was reported. Hospitalized patients did not indicate any comorbidities except for 2 cases of hypothyroidism. In 2 cases (9%, n = 2/22), the immunotherapy regimen was changed because of the infection (rituximab administration postponed). Two patients (9%, n = 2/22) indicated having had a relapse of the underlying disease in temporal association with COVID-19, which could be classified as pseudorelapses on further investigation by a neurologist. More than a third of the cases (39%, n = 9/23) occurred during the omicron-wave (from calendar week 52/2021 on), 7 (30%) during the delta-wave (calendar week 31–51/2021), 1 (4%) during the alpha-wave (calendar week 9 to 23/2021), 5 (22%) during the second wave (calendar week 40/2020 to 8/2021), and 1 (4%) during the first wave (calendar week 10–20/2020).[28]

Vaccination Against SARS-CoV-2

Most of the patients (89%, n = 167/187) had received vaccination against SARS-CoV-2. One patient did not provide information on vaccination status. The rate of unvaccinated patients was twice as high in the NMOSD group compared with the MOGAD group (NMOSD 13% vs MOGAD 6%, p = 0.208). Unvaccinated patients were more often female (95%, n = 18/19, p = 0.047) and more frequently taking oral corticosteroids (26%, n = 5/19, p = 0.45) compared with vaccinated patients (female: 72%, n = 121/167; oral corticosteroids: 10%, n = 16/167). Of those who were unvaccinated, 47% (n = 9/19) refused SARS-CoV-2 vaccination in general. Patients who made their vaccination decision based on a consultation at a NEMOS center were more likely to be vaccinated ($\chi^2[1] = 7.808$, p = 0.006, V = 0.205). The main reason for vaccine hesitancy was the fear of vaccination side effects that could negatively affect NMOSD or MOGAD (48%, n = 11/23).

Sixteen patients (9%, n = 16/187) stated having had a relapse or disease onset of NMOSD or MOGAD in temporal association with receiving vaccination. By taking a detailed medical history and contacting the respective center, a relapse could be excluded in 12 of these cases by a neurologist. Four cases were verified clinically and paraclinically; the patients

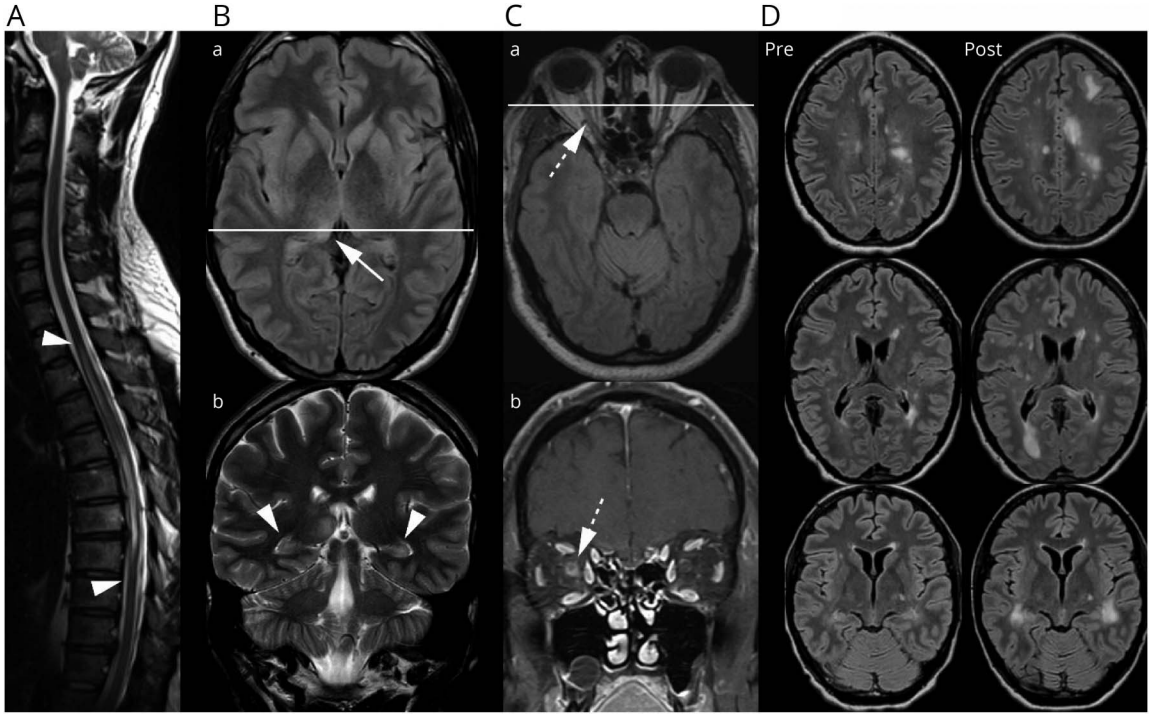
presented with MOG-IgG–positive longitudinal extensive transverse myelitis (Figure 1A), MOG-IgG–positive encephalomyelitis (Figure 1B), MOG-IgG–positive longitudinal optic neuritis (Figure 1C), and an NMOSD relapse with novel large demyelinating lesions (Figure 1D) (detailed characteristics are summarized in Table 3). In the 3 patients with new-onset MOGAD after vaccination (all male, age 34, 35, and 64 years), symptoms occurred for the first time shortly (2–8 days) after the first vector-based dose and third dose of an mRNA-based vaccine, respectively. The fourth patient was a 36-year-old woman with double-seronegative NMOSD and a disease duration of 4 years who relapsed 9 days after the third dose of an messenger RNA (mRNA)-based vaccine. On admission, SARS-CoV-2 infection was excluded through PCR testing in all 4 patients. A comprehensive differential diagnostic laboratory workup was performed, and there was no evidence of connective tissue disease, vasculitis, or other known paraneoplastic or autoimmune encephalitis-associated antibodies including against aquaporin-4 (see eTable 9, links.lww.com/NXI/A794 for details of laboratory testing). All patients were treated with IV methylprednisolone. One patient additionally received 5 cycles of plasmapheresis. Three patients partially recovered after the treatment, and 1 patient showed complete recovery.

Health-Related Quality of Life

More than half of the patients reported limitations in their HRQoL concerning the EQ-5D-5L dimensions mobility (55%, n = 103/187), usual activities (62%, n = 115/186), and anxiety/depression (57%, n = 106/186) at study inclusion. Only 22% (n = 40/184) of patients were impaired in self-care, but 75% (n = 136/181) described feeling pain/discomfort (Figure 2).

The mean EQ-5D-5L index value was 0.760 (95% bootstrap confidence interval [CI] 0.72–0.80) applying the German value set; the mean EQ-VAS was 66.5 (95% bootstrap CI 63.5–69.3). Patients who reported higher levels of HRQoL impairment on the EQ-5D-5L dimensions of pain/discomfort ($\rho = -0.219$, $p = 0.003$) or anxiety/depression ($\rho = -0.225$, $p = 0.002$) also rated their personal risk of contracting SARS-CoV-2 higher. No substantial differences between the various serologic subgroups were found concerning the EQ-5D-5L dimensions, the index value, or EQ-VAS. Compared with the prepandemic CHANCE^{NMO} study sample of our study group with a mean index value of 0.693 (95% CI 0.65–0.73) and an EQ-VAS of 60.9 (95% CI 58.0–64.0),[26] the patients of the COPANMO(G)-Study stated a better or stable HRQoL along all dimensions of the EQ-5D-5L (mobility: $p = 0.004$; self-care: $p = 0.002$; usual activities: $p = 0.013$; pain/discomfort: $p = 0.086$; anxiety/depression: $p = 0.279$). Accordingly, the index value and

Figure 1 Pathologic MRI Findings in Temporal Association With Vaccination Against SARS-CoV-2 in 4 Different Patients (A–D)



Further details in Table 3. (A) Sagittal T2-weighted spinal MRI disclosed a longitudinally extensive spinal cord lesion extending from T2-T8 (arrowheads indicate the start and end of the lesion) in a patient with new-onset MOG-IgG–positive myelitis. (B) Axial FLAIR imaging reveals a lesion in the right thalamus (arrow, B.a) and coronal T2-weighted imaging bilateral hyperintense lesions in the hippocampus (arrowheads, B.b) in another patient with new-onset MOGAD. (C) Longitudinal hyperintense signal of the optic nerve (axial FLAIR imaging, C.a) with gadolinium enhancement (coronal postgadolinium T1-weighted image, C.b) in a third patient with new-onset MOGAD. (D) Three different axial FLAIR layers show several new large lesions after vaccination (post) vs before vaccination (pre). The lines in the axial images indicate the localization of the respective coronal layer. FLAIR = fluid-attenuated inversion recovery; MOG-IgG = myelin oligodendrocyte glycoprotein immunoglobulin G; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated diseases.

Table 3 Characteristics of Cases Presenting With Onset or Relapse of MOGAD/NMOSD in Temporal Association With Vaccination Against SARS-CoV-2

Age	Sex	Vaccine (type, dose, heterologous/ homologous)	Interval between vaccination and onset	Symptoms	MRI findings	Disease type, serostatus	CSF findings	Treatment	Outcome (EDSS acute and after treatment)	History of autoimmune disease
34	M	COVID-19 mRNA vaccine (nucleoside-modified) (Spikevax, Moderna), 3rd dose, heterologous-previous doses COVID-19 mRNA vaccine (nucleoside-modified) (Comirnaty, BioNTech/Pfizer)	2 d	Urinary retention, hypesthesia starting at Th7, spastic paraparesis accentuated on the left side with gait disturbance	Brain MRI: normal, spinal MRI: T2 hyperintense lesion Th2-8, no Gd-enhancement (Figure 1A)	New-onset MOGAD (LETM), MOG-IgG: 1:100 (confirmed by 2 different cell-based assays; borderline positive at follow-up: 1:10 3 mo after initial attack and under immunotherapy with azathioprine)	Pleocytosis (13/µL), elevated protein (73.1 mg/dL), lactate (2.1 mmol/L), Q-albumin (9.39×10^{-3}), OCBs negative (type 4), MRZ reaction negative, no bacterial or viral infection	IV methylprednisolone, in total 9 g over 5 d; 5 cycles of plasmapheresis, initiation of immunotherapy with azathioprine for secondary prevention	Partial recovery EDSS 7.5 and 2.5	none
35	m	COVID-19 vaccine (ChAdOx1-S [recombinant]) (Vaxzevria, AstraZeneca), 1st dose	8 d	Holocephalic headache, fatigue, fever, phonophobia/ photophobia, psychomotor retardation, perseverations, spastic paraparesis with gait disturbance, urinary retention	Brain MRI: T2 hyperintense bilateral hippocampus lesions, lesion in the right thalamus, no Gd-enhancement (Figure 1B), spinal MRI: T2 hyperintense lesions Th3/4 and Th11/12, no Gd-enhancement	New-onset MOGAD (encephalomyelitis), MOG-IgG: 1:1,000 (confirmed by 2 different cell-based assays; positive at follow-up: 1:320 1 y after initial attack and under immunotherapy with rituximab)	Lymphocytic pleocytosis (142/µL), elevated protein (51.4 mg/dL), lactate (2.4 mmol/L), Q-albumin (9.00×10^{-3}), OCBs negative (type 1), no bacterial or viral infection	IV ceftriaxone, ampicillin and acyclovir; IV methylprednisolone 1,000 mg/d for 5 d, Initiation of immunotherapy with rituximab due to early relapsing disease course	Partial recovery EDSS 3.5 and 1.5	none
64	m	COVID-19 vaccine (ChAdOx1-S [recombinant]) (Vaxzevria, AstraZeneca), 1st dose	7 d	Pain in the right eye (pressure sensitivity of the bulb, pain on movement), retro-orbital headache	Brain MRI: T2 hyperintense longitudinal lesion of the right optic nerve with Gd-enhancement (Figure 1C)	New-onset MOGAD (optic neuritis), MOG-IgG: 1:200 (confirmed by 2 different cell-based assays; positive at follow-up: 1:100 9 mo after initial attack)	Mild pleocytosis (5.7/µL, 45% lymphocytes, 55% monocytes), protein (47.3 mg/dL), lactate (2.67 mmol/L), Q-albumin (6.2×10^{-3}), OCBs negative (type 4), MRZ reaction negative	IV methylprednisolone 1,000 mg/d for 3 d, Initiation of immunotherapy with azathioprine for secondary prevention after positive MOG-IgG at follow-up	Complete recovery EDSS 1 and 0	none
36	f	COVID-19 mRNA vaccine (nucleoside-modified) (Comirnaty, BioNTech/Pfizer) 3rd dose, homologous	9 d	Nausea, dizziness, nystagmus, diplopia, hypesthesia (tongue, mouth, and palate on the right), discrete hypesthesia and hypoalgesia starting at Th7, and of the left hand, discrete fine motor disturbance of the left hand, and stance/gait ataxia	Brain MRI: Multiple large demyelinating supratentorial, infratentorial and brainstem lesions with Gd-enhancement (Figure 1D)	NMOSD relapse, disease duration 4 y, AQP4-IgG–negative, MOG-IgG–negative	not done	IV methylprednisolone 1,000 mg/d for 5 d, immunotherapy with rituximab	Partial recovery EDSS 3.5 and 2.5	none

Abbreviations: AQP4-IgG = aquaporin-4 immunoglobulin G; EDSS = Expanded Disability Status Scale; FLAIR = fluid-attenuated inversion recovery; Gd = gadolinium; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis; MOGAD = MOG-antibody–associated disease; MOG-IgG = myelin oligodendrocyte glycoprotein immunoglobulin G; mRNA = messenger RNA; MRZ reaction = intrathecal humoral immune response against measles (M), rubella (R) and/or varicella-zoster (Z) viruses (positive = at least in 2/3); NMOSD = neuromyelitis optica spectrum disorders; OCBs = oligoclonal bands.

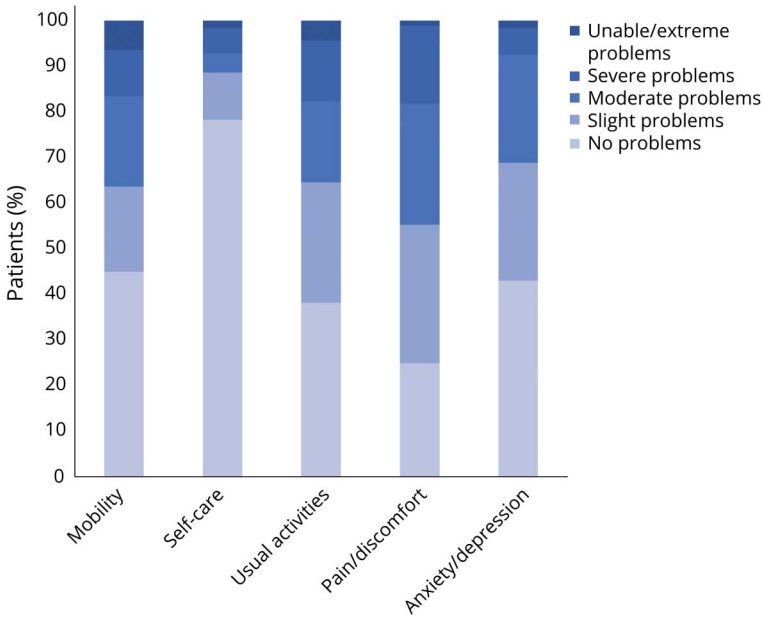
EQ-VAS were higher or stable in the COPANMO(G)-Study population ($p = 0.016$ and $p = 0.054$, respectively).

Discussion

The COVID-19 pandemic has affected many aspects of daily life, especially for those in need of medical care, because the healthcare system was faced with a major shift of resources to combat SARS-CoV-2 infections.[10] The insecurities and concerns from patients reaching us within the first year of the pandemic led us to initiate this study. The COPANMO(G)-Study assessed the effects of the COVID-19 pandemic on numerous aspects of patients' lives during the pandemic in a large German and Austrian study sample of patients with NMOSD and MOGAD.

In this study sample, the effects of the COVID-19 pandemic on patients' access to and use of healthcare services were less pronounced than one might have expected given their risk status[29] and previous studies from other contexts.[23,30] In most

Figure 2 Level of Problems Experienced by Patients



Patients were able to provide levels on a scale from 0 to 5 (0 = no problems, 5 = unable/extreme problems) for each of the 5 dimensions of the EuroQoL Group 5-Dimension 5-Level questionnaire.

of the patients who changed their appointments during the pandemic, this was performed because of the risk of infection. It is therefore reasonable to assume that patients with NMOSD and MOGAD in this study sample had good access to healthcare services, mirrored by a high and constant level of satisfaction with medical care. A relevant proportion of patients made changes to immunotherapy on their own or through the primarily treating neurologist. Accordingly, as the pandemic progresses, it is advisable to establish information programs for patients and healthcare providers to inform them about the higher risks of interrupting treatment compared with the risk of immunotherapy on the course of COVID-19.[11-14,31]

The 12% (n = 23/187) of patients who have knowingly been infected with SARS-CoV-2 contrast with 21%[32,33] of the German general population who had already contracted SARS-CoV-2 by March 15, 2022, at database closure. As patients reported the risk of infection being their main reason for changing their appointments, it is conceivable that patients avoided situations with high risk of contracting SARS-CoV-2. This could at least partly explain the lower infection rates among our study sample. The lower rate of infection in this study compared with the general population should thus not be taken as indication for an overall lower risk in patients with NMOSD/MOGAD, an assumption with no pathophysiologic rational existing in its favor, but rather as a result of risk-adopted behavior. Almost all patients in this study sample had a nonsevere disease course (96%), which contrasts with the results of a systematic review and meta-analysis of COVID-19 in patients with NMOSD[12] which found higher pooled rates of hospitalization (34% vs 17% in our study sample) and intensive care treatment (15% vs 0% in our study sample). Other multicenter studies about COVID-19 outcomes in patients with NMOSD, not included in this systematic review, presented higher rates of hospitalization (35%[13]; 23%[11]) and intensive care admission as well (12%[11]; 9%[13]). A fundamental difference between the samples in these studies and our sample was the exclusion of patients with MOGAD,[11,12] or the separate analysis of patients with NMOSD and MOGAD,[13] so comparability is limited. One Turkish multicenter study with 63 COVID-19 cases included patients with MOGAD in the analysis analogous to our study.[34] They described more similar outcomes (hospitalization: 22%; intensive care admission: 2%), which might indicate a milder course of COVID-19 in MOGAD but should be verified in larger studies. Owing to demographic and clinical differences, direct comparison again is not possible. Our COVID-19 study sample had a larger proportion of female patients and had a higher mean age. Although the proportion of patients with MOGAD was alike (21% vs 22% in our study), we had a higher proportion of AQP4-IgG–positive NMOSD (51% vs 65% in our study), and patients had a longer disease duration (median of 2.5 years vs median of 9 years in our study). Moreover, all the mentioned studies consist of patients infected before the presence of the omicron-variant and had their focus on outcome after COVID-19. In our study sample, 39% of infections occurred during the omicron-wave, with a lower risk of severe outcome for the omicron-variant compared with earlier variants.[35] In addition, as the vaccination campaign progressed, patients might have acquired better basic immunity against SARS-CoV-2 when they became infected later in the pandemic.

Most patients followed the public recommendations on vaccination against SARS-CoV-2. The vaccination rate among

our patients of 89% was even higher than in the general German population older than 18 years with 85,4%.[36] The association, albeit weak, of NEMOS center counseling and willingness to vaccinate emphasizes the importance of specialized centers for patients with NMOSD and MOGAD because lack of routine in the management of such rare diseases might lead to an overcautious attitude toward vaccination. Furthermore, through the networking of the NEMOS centers, there was a continuous exchange of experience with vaccination against SARS-CoV-2 in patients with NMOSD and MOGAD. This may have encouraged physicians at NEMOS centers to give a stronger recommendation for vaccination compared with others who are less familiar with these diseases and, in particular, vaccination against SARS-CoV-2 in patients with these rare diseases.

As an interim summary, the data from this study support that providing care for patients with NMOSD and MOGAD through specialized centers with years of experience in managing these rare diseases helps to ensure that care is available during a pandemic. Undoubtedly, we did not have a control group of patients who were not affiliated to specialized centers. However, we think that the high and constant satisfaction shown in our study makes it worth considering the introduction of similar care structures in other contexts.

In this study sample, 3 patients developed new-onset MOGAD, while 1 patient with double-seronegative NMOSD experienced a relapse temporally related to vaccination against SARS-CoV-2. Meanwhile, several cases of CNS demyelination after vaccination against SARS-CoV-2 have been published.[18] However, the number of corresponding NMOSD[17,18,37-39] and MOGAD[19,40] cases is very small, especially compared with more than 12 billion administered SARS-CoV-2 vaccination doses worldwide so far.[41] This study underlines that in the case of clinical signs compatible with NMOSD or MOGAD in temporal association with a vaccination against SARS-CoV-2, an appropriate diagnostic workup should be performed to establish a therapy as soon as possible to avoid long-term sequelae. It is important that a causal relationship between vaccination and MOGAD has not been established so far. Given the extremely high number of vaccinations performed, a temporal coincidence cannot be excluded. Moreover, the fact that SARS-CoV-2 vaccination has been reported in association with numerous (neurologic and nonneurologic) complications and the fact that "postvaccinal" MOGAD and NMOSD have been reported after a broad variety of vaccinations[42-45] argue more in favor of SARS-CoV-2 vaccination acting as an unspecific trigger causing exacerbation of preexisting and latent MOGAD or NMOSD than in favor of a specific pathomechanism such as molecular mimicry as recently discussed.[19] Moreover, a recent large population-based cohort study indicated no elevated risk of immune-mediated neurologic events after vaccination against COVID-19 but demonstrated a higher risk of such events in people who became infected with SARS-CoV-2.[46] Although we report additional cases with manifestation of NMOSD and MOGAD attacks in temporal association with SARS-CoV-2 vaccination, in the overview of the currently available data, there is no strong evidence that SARS-CoV-2 vaccination harbors relevant risks concerning NMOSD and MOGAD. This supports the current recommendations on vaccination because the benefits outweigh the risks. However, further studies are needed to determine the exact effects of SARS-CoV-2 infection and vaccination on disease manifestation or relapse in patients with NMOSD and MOGAD.

In 2 of the presented cases, acute disseminated encephalomyelitis (ADEM) cannot be excluded with certainty as a differential diagnosis because of the to date monophasic disease course and short follow-up times.[3] However, even in the absence of a new relapse event, in our opinion, immunotherapy should be initiated, particularly in the case of MOG-IgG persistence and/or MRI signs of temporal dissemination.[47] This highlights the need for intensive research on biomarkers to distinguish between ADEM and chronic MOGAD to make a valid decision in favor of or against permanent immunotherapy.

It is of interest that the patient-reported HRQoL in our study did not decrease compared with the prepandemic CHANCE-^{NMO} study sample from the same study group.[26] This may be explained by a higher proportion of comparatively less severely affected patients in the COPANMO(G) study. However, this might also be an effect caused by the pandemic: patients with chronic diseases might perceive their HRQoL to be better during the pandemic than before because they have not been affected as much by the pandemic-related restrictions compared with the healthy population. This may be supported by a study that assessed the HRQoL in relation to the stringency of government interventions in response to COVID-19: as more stringent government interventions were applied, there was a stronger increase in EQ-5D-5L values of chronically diseased patients compared with healthy people.[48] Since there was no improvement in HRQoL in the dimensions of pain/discomfort and anxiety/depression, these may be the domains that were most affected by the pandemic for the patients in our study sample. Particularly as those who had higher scores in these dimensions rated their personal risk of contracting SARS-CoV-2 to be higher, they might restrict their daily lives more than needed potentially lowering their HRQoL. Overall, data on HRQoL in patients with NMOSD or MOGAD during the COVID-19 era remain scarce, so it would be worthwhile to investigate this issue in more detail.

We count the multicenter study approach and, considering the rarity of NMOSD and MOGAD, the high number of patients as well as the robust quality of clinical data retrieved from the curated and validated NEMOS database, and provision of an extensive overview, because this study is not limited to a particular pandemic wave, among the strengths of this study. However, there are also limitations. First, data collection started after more than 1 pandemic year. At that time, the medical restrictions were not as pronounced as right at the beginning of the pandemic, vaccines were available, and physicians were better equipped to deal with COVID-19. This

might retrospectively have improved the patients' overall perception of their experience with health care during the pandemic. However, our questionnaire was designed to find out about patients' experience throughout all stages of the pandemic and put no focus on a specific time frame. Second, based on the study type, recall bias may have influenced the results. Third, there may be a relevant inclusion bias because more affected patients, by either their underlying disease or a particularly severe course of COVID-19, may be underrepresented in this study. Another limitation resulting from data collection based on self-reporting is possible response bias, particularly concerning satisfaction with medical care and HRQoL. Another minor limitation might be patients misleadingly reporting no change of their access to certain types of therapies, although they might not attend them previously.

However, the overall clinical experience of the different centers is consistent with the results presented, especially regarding the course of COVID-19.

In conclusion, the effects of the COVID-19 pandemic on patients with NMOSD or MOGAD affiliated with specialized centers were less substantial than expected. Our findings emphasize that established care structures for patients with serious rare diseases such as NMOSD or MOGAD can provide continuous health care and, as well, conduct a successful vaccination campaign, even under the stress implemented by an ongoing pandemic. Patients' satisfaction with medical care and HRQoL did not decline. Moreover, our study highlights the importance of further studies investigating the temporal association between vaccination against COVID-19 and either relapse or first manifestation of NMOSD or MOGAD.

Acknowledgment

The authors thank all patients for participating in the study and all contributors of the Neuromyelitis Optica Study Group (NEMOS) for their support. Special thanks also go to Sikinika Hache, Heike Miethke, Monika Höveler, Carolin Risau, Carolin Berning, and Carolin Schwake for excellent practical support.

Study Funding

There was no specific funding for this study. The NEMOS cohort/NationNMO was supported by the German Ministry for Education and Research (BMBF) as part of the German Competence Network Multiple Sclerosis (KKNMS).

Disclosure

M.W. Hümmert declares that he has no conflict of interest. F. Bütow declares that she has no conflict of interest. D. Tkachenko declares that she has no conflict of interest. I. Ayzenberg has received travel grants from Biogen Idec and Guthy-Jackson Charitable Foundation, served on scientific advisory boards for Roche and Alexion, and received research support from Diamed, none related to this manuscript. T. Pakeerathan declares that she has no conflict of interest. K. Hellwig received consultant and speaker honoraria from Bayer, Biogen, Merck, Novartis, Sanofi Genzyme, Roche, and Teva. L. Klotz received compensation for serving on Scientific Advisory Boards for Alexion, Genzyme, Janssen, Merck Serono, Novartis, and Roche. She received speaker honoraria and travel support from Bayer, Biogen, Genzyme, Grifols, Merck Serono, Novartis, Roche, Santhera, and Teva. She receives research support from the German Research Foundation, the IZKF Münster, IMF Münster, Biogen, Novartis, and Merck Serono. V. Häußler declares that she has no conflict of interest. J.-P. Stellmann received research grants and speaker honoraria from Biogen, Genzyme, and Alexion outside the submitted work. C. Warnke has received institutional honoraria and/or grant support from Novartis, Sanofi-Genzyme, Alexion, Janssen, Merck, Biogen, and Roche. Y. Goereci declares that she has no conflict of interest. T. Etgen declares that he has no conflict of interest. F. Luessi received consultancy fees from Roche and support with travel cost from Teva Pharma. P. Bronzlik declares that he has no conflict of interest. S. Gingele reports research support from Alnylam Pharmaceuticals, CSL Behring, Else Kröner Fresenius Foundation, Deutsche Forschungsgemeinschaft, and Hannover Biomedical Research School (HBRS) and honoraria for lectures from Alnylam and Merck all outside the submitted work. A.S. Lauenstein has received speaker honoraria from Novartis and Roche, as well as compensation for serving on an advisory board of Teva. I. Kleiter has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Alexion, Almirall, Biogen, Celgene, Hexal, Horizon, Merck, and Roche/Chugai. P.S. Rommer has received speaker honoraria including advisory boards speaker honoraria from Alexion, Allmiral, Amicus, Biogen, Merck, Novartis, Sandoz, Sanofi Genzyme, Roche, and Teva. F. Paul declares that he has no conflict of interest. J. Bellmann-Strobl has received travel grants and speaking honoraria from Bayer Healthcare, Sanofi Genzyme, in addition to received compensation for serving on a scientific advisory board of Roche, all unrelated to this work. A. Duchow declares that she has no conflict of interest. F. Then Bergh has received honoraria for speaking and advisory board consultation from Alexion, Roche, and Horizon Therapeutics, all unrelated to this work. R. Pul received honoraria for lectures from Alexion, Bayer Healthcare, Biogen, BMS/Celgene, Horizon, Novartis, Merck, Roche, Sanofi-Aventis, and Teva. He received research grants from HERZ Burgdorf, Novartis, and Merck. A. Walter received speaker honoraria and meeting expenses from Novartis, Bayer, Biogen, Sanofi Genzyme, Teva, Roche, and Merck. H. Pellkofer received honoraria for lectures from Bayer Health Care, Biogen Idec, and Teva Pharma and travel reimbursement from Novartis. T. Kümpfel has received speaker honoraria including advisory boards from Bayer Healthcare, Teva Pharma, Merck, Novartis Pharma, Sanofi-Aventis/Genzyme, Roche Pharma, and Biogen as well as grant support from Novartis and Chugai Pharma in the past. M. Pompsch Declares that he has no conflict of interest. M. Kraemer Received consulting and/or speaker honoraria

from Chugai Pharma and Roche Pharma. P. Albrecht Has received personal fees, travel support, and research grants from Abbvie, Allergan, Bristol Myers Squibb, Celgene, Ipsen, Janssen Cilag, Lilly, Merck, Merz, Novartis, Roche, and Teva outside the submitted work. O. Aktas has received personal fees from Alexion, Bayer Healthcare, Biogen, Celgene, Merck Serono, MedImmune, Novartis, Roche, Teva, and Zambon, outside of the submitted work. M. Ringelstein received speaker honoraria from Novartis, Bayer Vital GmbH, Roche, Alexion, and Ipsen and travel reimbursement from Bayer Schering, Biogen Idec, Merz, Genzyme, Teva, and Merck, none related to this study. M. Senel has received consulting and/or speaker honoraria from Alexion, Bayer, Biogen, Bristol-Myers-Squibb, Merck, Roche, and Sanofi Genzyme. She has received travel support from Celgene and TEVA. She has received research funding from the Hertha-Nathorff-Program. None of this related to the current study. K. Giglhuber declares that she has no conflict of interest. A. Berthele received speaker and consulting honoraria from Alexion, Biogen, Bayer Healthcare, Celgene, Merck, Novartis Pharma, and Roche, all outside the submitted work. S. Jarius declares that he has no conflict of interest. B. Wildemann received grants from the German Ministry of Education and Research, German Research Foundation, Dietmar Hopp Foundation, Klaus Tschira Foundation, and Merck Serono; grants and personal fees from Merck, Novartis, and Sanofi Genzyme; and personal fees from Bayer, Biogen, Roche, and TEVA, none related to this work. C. Trebst has received honoraria for consultation and expert testimony from Alexion Pharma Germany GmbH, Chugai Pharma Germany GmbH, and Roche Pharma GmbH. None of this interfered with the current report. Go to Neurology.org/NN for full disclosure.

Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* September 16, 2022. Accepted in final form November 16, 2022. Submitted and externally peer reviewed. The handling editor was Editor Josep O. Dalmau, MD, PhD, FAAN.

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Continued

Appendix 1 *(continued)*

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Appendix 2 *(continued)*

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Appendix 2 *(continued)*

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Effects of the COVID-19 Pandemic on Patients With NMO Spectrum Disorders and MOG-Antibody–Associated Diseases: COPANMO(G)-Study

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Neurol Neuroimmunol Neuroinflamm 2023;10;
DOI 10.1212/NXI.0000000000200082