

Pain, Depression, and Quality of Life in Neuromyelitis Optica Spectrum Disorder

A Cross-Sectional Study of 166 AQP4 Antibody–Seropositive Patients

Ilya Aizenberg, MD, Daniel Richter, MD, Eugenia Henke, MD, Susanna Asseyer, MD, Friedemann Paul, MD, Corinna Trebst, MD, Martin W. Hümmert, MD, Joachim Havla, MD, Tania Kümpfel, MD, Marius Ringelstein, MD, Orhan Aktas, MD, Brigitte Wildemann, MD, Sven Jarius, MD, Vivien Häußler, MD, Jan-Patrick Stellmann, MD, Makbule Senel, MD, Luisa Klotz, MD, Hannah L. Pellkofer, MD, Martin S. Weber, MD, Marc Pawlitzki, MD, Paulus S. Rommer, MD, Achim Berthele, MD, Klaus-Dieter Wernecke, MD, PhD, Kerstin Hellwig, MD, Ralf Gold, MD, and Ingo Kleiter, MD, on behalf of the NEMOS (Neuromyelitis Optica Study Group)

Correspondence
Dr. Kleiter
ingo.kleiter@rub.de

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Abstract

Objectives

To evaluate prevalence, clinical characteristics, and predictors of pain, depression, and their impact on the quality of life (QoL) in a large neuromyelitis optica spectrum disorder (NMOSD) cohort.

Methods

We included 166 patients with aquaporin-4–seropositive NMOSD from 13 tertiary referral centers. Patients received questionnaires on demographic and clinical characteristics, Pain-Detect, short form of Brief Pain Inventory, Beck Depression Inventory–II, and Short Form 36 Health Survey.

Results

One hundred twenty-five (75.3%) patients suffered from chronic NMOSD-associated pain. Of these, 65.9% had neuropathic pain, 68.8% reported spasticity-associated pain and 26.4% painful tonic spasms. Number of previous myelitis attacks (OR = 1.27, $p = 0.018$) and involved upper thoracic segments (OR = 1.31, $p = 0.018$) were the only predictive factors for chronic pain. The latter was specifically associated with spasticity-associated pain (OR = 1.36, $p = 0.002$). More than a third (39.8%) suffered from depression, which was moderate to severe in 51.5%. Pain severity (OR = 1.81, $p < 0.001$) and especially neuropathic character (OR = 3.44, $p < 0.001$) were associated with depression. Pain severity and walking impairment explained 53.9% of the physical QoL variability, while depression and walking impairment 39.7% of the mental QoL variability. No specific medication was given to 70.6% of patients with moderate or severe depression and 42.5% of those with neuropathic pain. Two-thirds (64.2%) of patients with symptomatic treatment still reported moderate to severe pain.

From the Department of Neurology (I.A., D.R., E.H., K.H., R.G., I.K.), St. Josef-Hospital, Ruhr-University Bochum, Germany; Department of Neurology (I.A.), Sechenov First Moscow State Medical University, Russia; NeuroCure Clinical Research Center (S.A., F.P.), Charité Universitätsmedizin Berlin, Berlin Institute of Health, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Germany; Department of Neurology (C.T., M.W.H.), Hannover Medical School, Germany; Institute of Clinical Neuroimmunology (J.H., T.K., H.L.P.), University Hospital and Biomedical Center, Ludwig-Maximilians University Munich, Germany; Department of Neurology (M.R., O.A.), Medical Faculty, Heinrich Heine University Düsseldorf, Germany; Department of Neurology (M.R.), Center for Neurology and Neuropsychiatry, LVR-Klinikum Düsseldorf, Germany; Molecular Neuroimmunology Group (B.W., S.J.), Department of Neurology, University of Heidelberg, Germany; Institut für Neuroimmunologie und Multiple Sklerose (INIMS) (V.H., J.-P.S.), Zentrum für Molekulare Neurobiologie, Hamburg, Germany; Klinik und Poliklinik für Neurologie (V.H., J.-P.S.), Universitätsklinikum Hamburg-Eppendorf, Germany; APHM (J.-P.S.), Hopital de la Timone, CEMEREM, Marseille, France; Aix Marseille Université (J.-P.S.), CRMBM, CNRS UMR 7339, Marseille, France; Department of Neurology (M.S.), University of Ulm, Germany; Münster Department of Neurology with Institute of Translational Neurology (L.K., M.P.), University Hospital Münster, Germany; Department of Neurology (H.L.P., M.S.W.), University Medical Center, Göttingen, Germany; Department of Neurology (M.P.), Otto-von-Guericke University, Magdeburg, Germany; Department of Neurology (P.S.R.), Medical University of Vienna, Austria; Neuroimmunology Section (P.S.R.), Department of Neurology, University of Rostock, Germany; Department of Neurology (A.B.), School of Medicine, Technical University of Munich, Germany; Charité-Universitätsmedizin Berlin, CRO SOSTANA GmbH Berlin (K.-D.W.), Germany; and Marianne-Strauß-Klinik (I.K.), Behandlungszentrum Kempfenhausen für Multiple Sklerose Kranke gGmbH, Berg, Germany.

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Coinvestigators are listed in Appendix 2.

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Glossary

ADL = activity of daily living; BDI = Beck Depression Inventory; EDSS = Expanded Disability Status Scale; MCS = mental component summary; MPQ-SF = McGill Pain Questionnaire Short Form; NMOSD = neuromyelitis optica spectrum disorder; PDQ = PainDetect questionnaire; PTS = painful tonic spasm.

Conclusions

Myelitis episodes involving upper thoracic segments are main drivers of pain in NMOSD. Although pain intensity was lower than in previous studies, pain and depression remain undertreated and strongly affect QoL. Interventional studies on targeted treatment strategies for pain are urgently needed in NMOSD.

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disorder that primarily affects the visual pathway, brain, and spinal cord.^{1,2} Autoantibodies targeting aquaporin-4 (AQP4) are present in the majority of patients and proved to be pathogenic in animal models.^{3,4} NMOSD attacks often do not fully recover and residual clinical deficits remain in >75% of attacks.^{5,6} Beside severe physical impairments, NMOSD can go along with symptoms like chronic pain, cognitive deficits, and depression.^{7,8}

Spinal pain, girdle-like dysesthesia, and painful spasms were noted already in earliest disease descriptions in the 18th century.⁹ Nowadays, it has become clear that pain is a frequent and one of the most disabling symptoms of NMOSD.^{8,10-15} Chronic NMOSD-associated pain affects quality of life (QoL), with pain severity being the most important predictive factor.^{10,12,13,15} Possible underlying mechanisms include damage of the central nociceptive and antinociceptive pathways, particularly the dorsal horn of the spinal cord and the dorsal root entry zone, autonomic thoracolumbar nuclei, the periaqueductal gray, and hypothalamus. Excessive levels of extracellular glutamate and increase of proinflammatory factors, such as interleukin (IL)-6, IL-17, and C5a, can additionally facilitate nociceptive processing.¹⁶ Glutamate excitotoxicity can cause an imbalance between excitation and inhibition in nociceptive system, resulting in spontaneous neuropathic pain.

Because of the rarity of NMOSD, most previous studies of pain were relatively small.^{10,11,17} Moreover, several studies included a mixed population of AQP4-IgG-seropositive and -seronegative patients,^{10-13,15} whereas recent clinical trials clearly indicate that pathogenetic mechanisms are different in these forms.¹⁸ Accordingly, data on clinical and paraclinical predictors of pain as well as its association with depression and effects on QoL remain limited.

We sought to investigate clinical characteristics, risk factors, and impact of pain syndromes and depression in a Central European cohort of patients with AQP4-IgG-seropositive NMOSD. Furthermore, we wanted to evaluate the efficacy of immunotherapies and symptomatic treatment for both conditions and search for a short screening question to detect patients with disabling pain.

Methods

Patients

We performed an exploratory, questionnaire-based, cross-sectional study in the years 2017–2019. Patients with AQP4-IgG-seropositive NMOSD according to IPND criteria¹⁹ were identified through the registry of the German Neuromyelitis Optica Study Group (NEMOS, nemos-net.de). Details on the registry, participating centers, and data collection, quality and processing can be found in previous publications.^{5,6} Inclusion criteria were (1) age over 18 years and (2) positive AQP4-IgG, confirmed in a cell-based assay. Patients with known relevant cognitive deficits were excluded. All patients were in remission during the study. Clinical data, including Expanded Disability Status Scale (EDSS), therapies, and localization of spinal lesions in cervical and thoracic segments on MRI, were retrieved from the NEMOS database or local patient records. Data on current pain, depression, walking, and visual impairment and QoL were captured by self-reporting questionnaires. Patients were instructed to report on NMOSD-associated pain syndromes only.

Questionnaires

Current pain was assessed using the PainDetect questionnaire (PDQ),²⁰ the short form of the Brief Pain Inventory (SF-BPI), and the McGill Pain Questionnaire Short Form (MPQ-SF).²¹ The questions of the SF-BPI consist of 2 categories: (1) pain severity (present, highest, least, and average pain) based on a Numeric Rating Scale (NRS) from 0 (no pain) to 10 (worst pain imaginable) within the last week. The pain severity index score represents the average score of these 4 pain intensity scores. (2) Seven domains of pain-related interference in activity of daily living (ADL), rated from 0 (no interference) to 10 (complete interference): general activity, mood, walking ability, working ability, relations with other people, sleep, and enjoyment of life. The PDQ was administered to evaluate pain localization and discriminate between definite neuropathic (PDQ score >18), probable neuropathic (PDQ score 13–18), and nociceptive pain (PDQ score <13). The MPQ-SF consists of 15 words, describing sensory (11 words) and affective (4 words) components of pain. Patients rate their intensity as 0 = none, 1 = mild, 2 = moderate, or 3 =

severe. Three pain scores are derived from the sum of the rank values: (1) sensory, (2) affective, and (3) total descriptors. Painful tonic spasms (PTSs) were assessed asking the patient whether they experienced recurrent attacks or short episodes (duration <1 minute) of localized muscle spasms, accompanied by severe pain.

Depression was evaluated using Beck Depression Inventory II (BDI-II), scored from 0 (best) to 63 (worst) (<9: no depressive affect; 9–13: minimal mood disturbance; 14–20: mild depression, 21–28: moderate depression; and ≥29: severe depression). Clinically relevant depression was defined by a score of ≥14. Health-related QoL was measured with the SF-36 questionnaire, consisting of 36 items in 8 subscales. A Physical

Component Summary (PCS) and a Mental Component Summary (MCS) were calculated using norm-based attaining values from 0 (worst) to 100 (best).

Standard Protocol Approvals, Registrations, and Patient Consents

Ethics approval was obtained from the Institutional Review Board of the Ruhr-University Bochum (#15-5534). Ethics approval of the NEMOS registry was obtained in participating centers locally. Patients provided written informed consent. The study was performed according to International Conference on Harmonization/Good Clinical Practice and current legal requirements.

Statistical Analysis

Descriptive statistics were used to describe sample data. Comparisons of interval-scaled variables were performed using the 2-sample *t* test for normally distributed variables, the Mann-Whitney-Wilcoxon rank-sum test for nonparametric or ordinal-scaled variables, and the χ^2 test for categorical variables. We used binary logistic regression to evaluate factors associated with overall pain (yes vs no) as well as neuropathic (neuropathic vs nociceptive pain) and spasticity-related pain (spasticity-associated vs other [non-spasticity-associated] pain) as dependent variables. The following independent variables were included into the logistic model: sex, age, EDSS, disease duration, AQP4-IgG titer, overall number of previous relapses, number of myelitis attacks, and number of involved spinal segments. Concerning depressive state, sex, age, disease duration, walking, and visual impairment were included into analysis. A multiple robust regression model with backward feature selection was used to determine predictors for hrQoL, with PCS and MCS composites as dependent variables and age, sex, disease duration, walking and visual impairment, pain severity, and Beck depression index as independent variables.²² To check for correlations between pain intensity and different aspects of ADL, we performed the Spearman correlation test. This study was an exploratory pilot study, with no a priori sample size calculation. For the same reason, statistical significance was set at $p < 0.05$ without adjustment for multiple testing. Numerical calculations were performed by SPSS Statistics, Version 25, SPSS Inc., an IBM Company, and The R Project for Statistical Computing, Version 3.4.0 (2017-04-21), The R Foundation for Statistical Computing.

Data Availability

Anonymized data not published within this article are available on reasonable request from any qualified investigator within 5 years after publication.

Results

Demographic and Clinical Characteristics

Thirteen tertiary referral NEMOS centers participated in the study, and 172 questionnaires were sent back to the reading center in Bochum for analysis. The response rate was 83.1% (data on response rate available for 7 centers, addressing

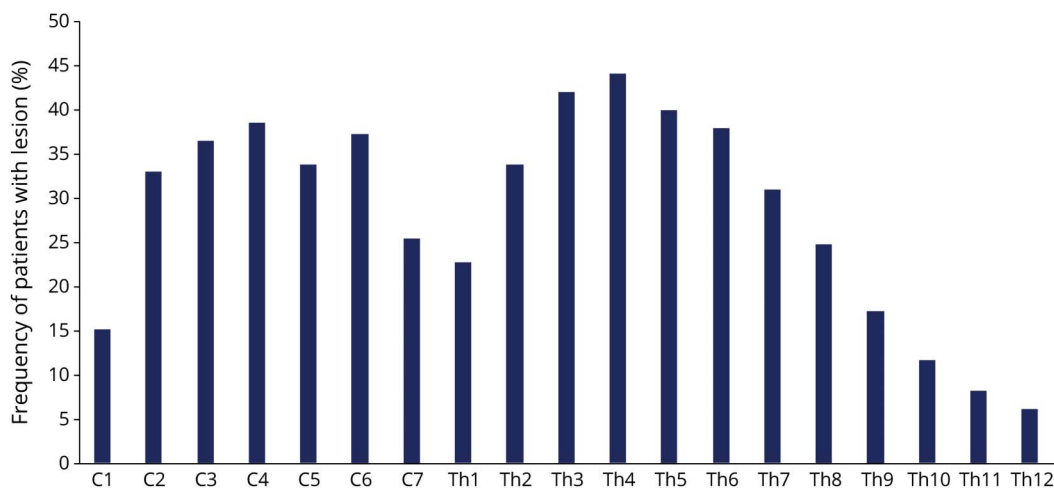
Table 1 Demographic Characteristics and Immunotherapy

	Mean (SD)/Median (min-max.)
Total number of patients (all AQP4-IgG seropositive)	166
F:M ratio	8.2:1
EDSS	3.5 (0.0–9.0)
Age, y	51.7 (13.4)
Disease duration, y	9.1 (8.1)
ARR	1.1 (1.6)
Total number of ON episodes since onset	2.2 (4.1)
Total number of myelitis episodes since onset	4.6 (7.4)
Total number of involved spinal segments	5.3 (4.1)
No. of involved cervical segments	2.2 (2.1)
No. of involved thoracic segments	3.2 (3.3)
AQP4-IgG titer (CBA)	1:100 (1:10–1:25,600)
Current immunotherapy	% , N
Rituximab	62.7%, 104 ^a
Azathioprine	12.0%, 20
Anti-IL6 therapy (tocilizumab N = 11, SA237 N = 1)	7.2%, 12
Mycophenolate mofetil	4.8%, 8
Other therapies (methotrexate N = 2, prednisone N = 2, mitoxantrone N = 2, IVIg N = 1, glatiramer acetate N = 1, cyclosporin N = 1)	5.4%, 9
Prednisone as add-on therapy	10.2%, 17
No immunotherapy	7.8%, 13

Abbreviations: ARR = annualized relapse rate; AQP4 = aquaporin-4; CBA = cell-based assay; EDSS = Expanded Disability Status Scale; F:M = female:male; ON = optic neuritis.

^a Five in combination with oral immunosuppressive agents.

Figure 1 Distribution of Persistent Spinal Lesions in Cervical and Thoracic Segments



Shown is the frequency (%) of patients (total $n = 143$) with a spinal lesion on MRI at the appropriate level.

71.1% of respondents). Data of 6 questionnaires were insufficient and had to be excluded. In total, 166 patients with AQP4-IgG-seropositive NMOSD (148 female and 18 male) were included. Main demographic and clinical characteristics are described in table 1. Most patients in the cohort had a history of myelitis (152; 91.6%) or optic neuritis (114; 68.7%), 95 (57.2%) of both myelitis and optic neuritis. Data on the last available spinal MRI were available for 143 of 166 patients (130 of 152 with a history of myelitis) and demonstrated a 2-peak distribution (C2-C6 and Th2-Th7) of lesion location (figure 1). Eleven of 21 patients without visible spinal lesions had a history of myelitis. Six patients only had a relapse in the previous 6 months.

Overall Pain Prevalence and Main Characteristics

Overall, 125 (75.3%) patients suffered from chronic NMOSD-associated pain. The intensity of NMOSD-associated chronic pain was moderate to severe in 55.2% of pain sufferers (figure 2A). Pain was mainly described as aching (90.4%), tender (76.8%), stabbing (68.8%), or burning (66.4%) on sensory dimensions and tiring-exhausting (68.0%) on affective dimension. Most prevalent were chronic pain without painless periods ($n = 77$, 61.6%). Isolated or overlapping pain attacks reported 48 (38.4%) and 40 (32.0%) patients accordingly (figure 2B). Every second patient ($n = 88$, 53%) reported pain as a symptom of the last relapse.

Prevalence of Different Types of Pain

One-third of pain sufferers had nociceptive ($n = 39$, 30.7%), probable neuropathic ($n = 43$, 33.9%), or definite neuropathic pain ($n = 40$, 31.5%) each; in 3 patients, the type of pain could not be identified (figure 2C). Pain was most often localized in legs (72.8%, in two-thirds of cases bilateral), followed by arms (48.8%, in half of cases bilateral), trunk (34.4%), and neck/head region (27.2%). Most intense pain were reported by patients with pain localization in the trunk (4.9 ± 1.7 vs 3.3 ± 2.2 , $p < 0.05$) or legs (4.1 ± 2.2 vs 3.2 ± 2.0 , $p < 0.05$). Trunk

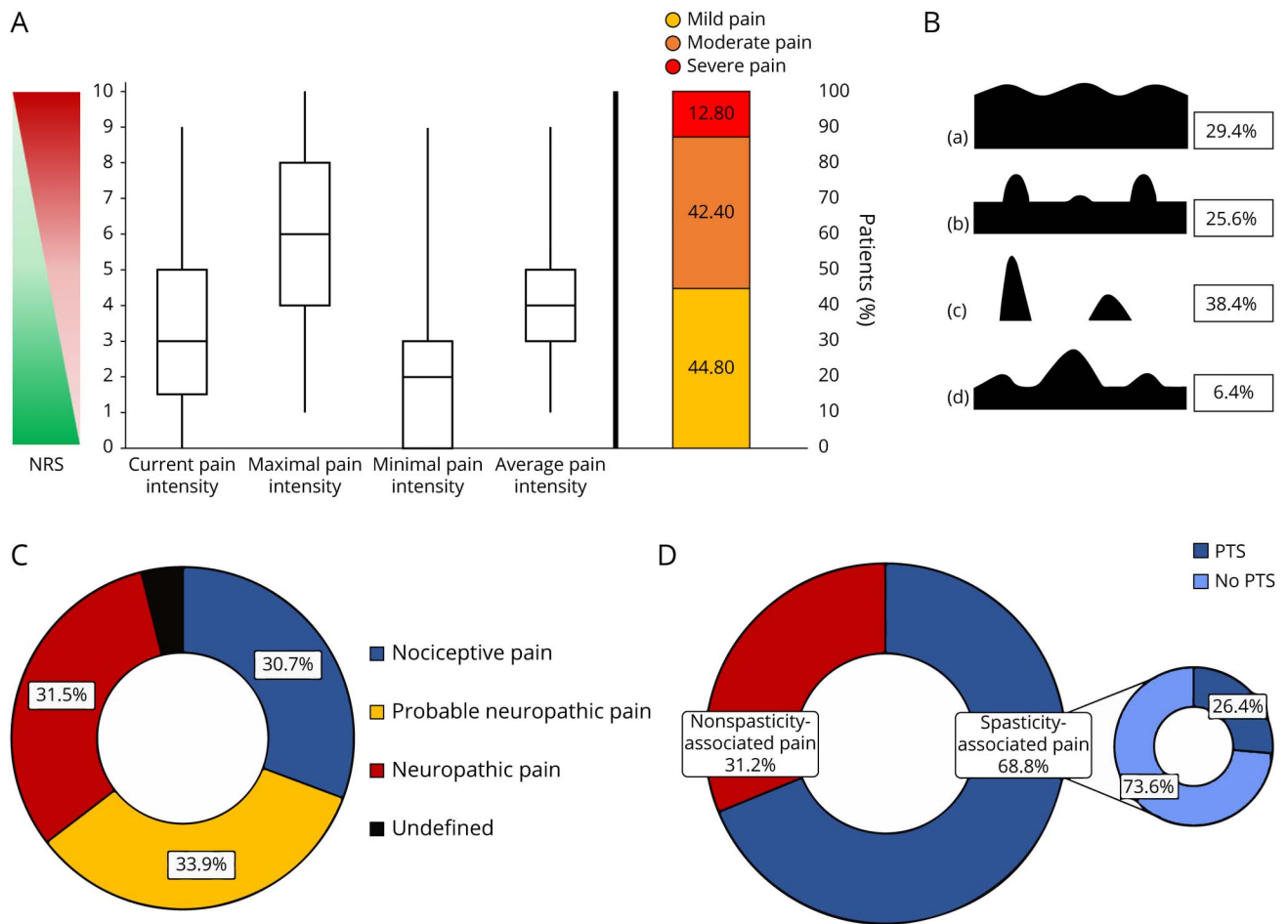
pains were more often of definite neuropathic than of probable neuropathic or nociceptive character (55.8% vs 27.9% vs 16.3%; $p < 0.05$), whereas no changes were found for pains in other regions of the body.

Two-thirds of the pain sufferers reported spasticity-associated pain ($n = 86$, 68.8%) (figure 2D). It was significantly more prevalent in patients with nociceptive than neuropathic pain (87.8% vs 55.8%, $p = 0.02$). Thirty-three patients (26.4%) had short-lasting PTS, mostly in the legs ($n = 28$, 84.8%) and rarely in the arms ($n = 6$, 18.2%). These patients reported approximately 5 PTS episodes a day (4.9 ± 6.4), with a range of 26 attacks per day to 1 per week.

Episodes of Myelitis Involving Upper Thoracic Segments Are Associated With Chronic Pain

Chronic pain was not associated with age, sex, AQP4-IgG titer, disease duration, overall disability (EDSS), or depressive state (BDI > 14). However, the number of previous attacks was significantly associated with the occurrence of pain (OR 1.12 [1.02–1.21], $p = 0.020$). More detailed analysis revealed that the total number of episodes of myelitis (OR 1.27 [1.05–1.57], $p = 0.018$), but not the number of optic neuritis (OR 1.02 [0.92–1.13], $p = 0.716$), was relevant. There was no association of pain prevalence or severity with the presence or any specific localization of persistent spinal lesions (table 2). However, we found an association of the number of involved spinal segments with pain (OR 1.14 [1.03–1.28], $p = 0.024$). Moreover, the number of lesions in the upper 6 thoracic segments only (but not in cervical or lower thoracic lesions) was associated with the risk of having pain in general (OR 1.31 [1.01–1.63], $p = 0.018$) and was the only specific factor increasing the risk of spasticity-associated pain among pain sufferers (OR 1.36 [1.10–1.67], $p = 0.002$). We could not find any specific factors associated with short-lasting PTS. Depressive state was the only factor strongly associated with neuropathic pain (OR 3.44 [1.35–8.80], $p = 0.001$).

Figure 2 Main Characteristics of the NMOSD-Associated Pain



(A) Intensity, (B) temporal patterns (a. continuous pain with slight fluctuations; b. continuous pain with pain attacks; c. pain attacks with painless periods; d. pain attacks without painless periods), and (C and D) character of pain. Values of pain intensity are given in median, interquartile range, and minimal and maximal values. Prevalence is given in (%). NMOSD = neuromyelitis optica spectrum disorder. NRS = Numeric Rating Scale, PTS = painful tonic spasm.

Pain Severity Strongly Correlates With Reduction of Activities of Daily Living

Effects of pain on ADL are given in table 3. Correlation analysis revealed a strong correlation of pain severity with general activity ($\rho = 0.69, p < 0.001$) and sleep ($\rho = 0.61, p < 0.001$), followed by mood ($\rho = 0.55, p < 0.001$), walking ability ($\rho = 0.54, p < 0.001$), normal work ($\rho = 0.52, p < 0.001$), enjoyment of life ($\rho = 0.50, p < 0.001$), and relations

($\rho = 0.46, p < 0.001$). We observed an even stronger negative effect of definite neuropathic pain on all evaluated ADL aspects compared with nociceptive pain.

Chronic Pain But Not Physical Impairment Is Associated With Depression in NMOSD

Sixty-six (39.8%) patients suffered from depression: mild in 32 (19.3%), moderate in 21 (11.6%), and severe in 13 (7.8%)

Table 2 Prevalence and Severity of Pain in 143 Patients With Spinal Lesions of Different Localizations

Localization of spinal lesions	Prevalence of pain	BPI-PSI	PainDetect score
No persistent lesions (N = 21)	68.2% (N = 15) ^a	3.6 ± 2.4	13.5 ± 5.1
Isolated cervical lesions (N = 27)	66.7% (N = 18)	3.4 ± 1.9	15.0 ± 7.5
Isolated thoracic lesions (N = 33)	81.8% (N = 27)	4.3 ± 2.2	17.4 ± 6.7
Cervicothoracic lesions (N = 62)	77.0% (N = 47)	3.7 ± 2.2	16.2 ± 6.6

Abbreviation: BPI-PSI = Pain Severity Index of Brief Pain Inventory.

BPI-PSI and PainDetect Score values are given in mean ± SD for pain sufferers. No significant differences were found.

^a Seven of 15 patients had at least 1 myelitis episode in the history.

Table 3 Effects of Neuropathic and Nociceptive Pain on ADL

	All pain sufferers (N = 125)	Patients with definite neuropathic pain (N = 40)	Patients with definite nociceptive pain (N = 39)
General activity	4.6 ± 2.6	5.7 ± 2.3 ^a	3.6 ± 2.6
Mood	4.0 ± 3.1	5.4 ± 2.9 ^a	3.0 ± 2.7
Walking ability	4.7 ± 3.4	5.8 ± 3.2 ^a	3.2 ± 3.1
Normal work	5.0 ± 3.2	6.6 ± 2.7 ^a	3.9 ± 3.1
Relations	3.4 ± 3.3	5.0 ± 3.2 ^a	2.4 ± 2.8
Sleep	4.1 ± 3.2	5.8 ± 3.0 ^a	2.8 ± 2.7
Enjoyment of life	3.7 ± 3.3	5.1 ± 3.2 ^a	2.8 ± 2.9

Abbreviation: ADL = activity of daily living. Values are given in mean ± SD. ^a $p < 0.001$, t test.

cases. There was no association between a depressive state (BDI > 14) and age, sex, or disease duration. Univariate regression analyses revealed pain severity as well as walking and visual impairment to be associated with depressive state. In the multiple logistic regression analysis, pain intensity (OR 1.53 [1.22–1.91], $p < 0.001$) remained the only factor independently associated with a depressive state.

Pain, Depression, and Walking Impairment Are 3 Main QoL Predictors

The physical but not the mental composite subscale was significantly lower in pain sufferers (table 4). Among pain sufferers, patients with definite neuropathic pain had significantly lower scores in both SF-36 composites comparing to those with nociceptive pain. Multivariate regression analysis identified pain severity ($p < 0.001$) and walking impairment ($p < 0.001$) as 2 independent predictors explaining 53.9% of the physical QoL composite variability. Depression measured by the BDI score ($p < 0.001$) and to a lesser extent walking impairment ($p = 0.043$) determined 39.7% of the mental QoL composite variability.

Symptomatic Pain Treatment Is Insufficiently Effective in Real-Life Practice

Two-thirds ($n = 81$, 64.8%) of the 125 pain sufferers took pain medications, antidepressants, or both. Most of them took 1 ($n = 44$, 35.2%) or 2 ($n = 25$, 20.0%) pain medications. Nine patients (7.2%) had 3 different pain medications, and 3 patients had 4, 5, and 6 medications each. Pain medication included nonopioid analgesics (including nonsteroidal anti-inflammatory drugs) ($n = 47$, 37.6%), antiepileptic medications for neuropathic pain (including gabapentin, pregabalin, carbamazepine, and oxcarbazepine)

($n = 51$, 40.8%), and opioids ($n = 13$, 10.4%). Antidepressants were taken by 21 (16.8%) pain sufferers. Surprisingly, only one-third ($n = 10$, 29.4%) of those with at least moderate depression (BDI > 20) took antidepressants. Seven of 10 suffered from pain with a median pain intensity of 5.0 (2.0–8.0), so that antidepressant medication could be a component of pain therapy.

Patients with definite neuropathic pain took symptomatic therapy significantly more often compared with those with nociceptive pain (85.0% vs 51.3%, $p = 0.002$, table 5). However, among the 40 patients with neuropathic pain, only 23 (57.5%) took specific medications. Retrospectively, patients reported a substantial reduction of the pain intensity through pain medications; median 60% (range 0–100) in all patients, 50% (0–100) in those with definite neuropathic pain, 65% (0–100) in those with nociceptive pain. Only 4 patients (4.9%) were pain-free, and 25 patients (30.9%) reported mild pain. Most patients still reported moderate ($n = 41$, 50.6%) or severe ($n = 11$, 13.6%) pain despite symptomatic treatment. Only 28.8% of those with spasticity-associated pain received antispastic medications.

Effects of Immunotherapies on Pain Experience

There was no difference in terms of pain prevalence or intensity in patients with different immunotherapies. Retrospectively, 39.5% of pain sufferers reported improvement of pain after start of immunotherapy: 28 of 75 (37.3%) under rituximab, 6 of 15 (40.0%) under azathioprine, 2 of 6 (33.3%) under mycophenolate mofetil, and 6 of 9 (66.7%) under tocilizumab.

Pain Pattern Question Can Be an Effective Screening Tool

Finally, we searched for a short screening question allowing identification of those patients most affected by pain in NMOSD. We used the 4 pain patterns from the PDQ (table 6). Patients suffering from pain attacks without painless intervals (patterns 2 and 4) had significantly more intense pains and a significantly lower physical QoL component. Moreover, the majority of those with pattern 4 suffered from moderate or severe depression (87.5%) and neuropathic pain (62.5%) and had lower mental QoL.

Discussion

We evaluated a large cohort of patients with AQP4-IgG-seropositive NMOSD for pain and comorbid depression. As much as 75.3% of all patients suffered from NMOSD-associated chronic pain, in line with previously reported 80%–86% in smaller studies from other geographic areas.^{10–12,14,23} The majority of patients reported continuous pain, often superimposed by pain attacks. Pain localization was in the legs in 3/4 and around the trunk and in arms in 1/2 each. Overall pain intensity was lower in our cohort compared with previous studies conducted a decade ago,^{10–12} and only 10%

Table 4 Quality of Life in Patients With and Without NMOSD-Associated Pain

SF-36 domain	All patients (N = 166)	Patients without pain (N = 41)	Patients with pain (N = 125)	Patients with definite nociceptive pain (N = 39)	Patients with definite neuropathic pain (N = 40)	Patients with BDI 0–14 (N = 99)	Patients with BDI >14 (N = 66)
SF-36 PF	47.7 ± 36.0	63.3 ± 39.1	43.4 ± 33.7 ^a	52.1 ± 36.9	36.1 ± 28.6 ^b	59.6 ± 35.2	30.7 ± 29.5 ^c
SF-36 RP	41.0 ± 41.3	44.7 ± 24.3	36.9 ± 38.8 ^a	39.1 ± 37.1	28.9 ± 38.7	53.6 ± 41.6	22.2 ± 33.0 ^c
SF-36 BP	52.2 ± 30.1	78.1 ± 32.9	44.7 ± 24.3 ^a	54.1 ± 23.6	33.9 ± 20.1 ^b	59.9 ± 27.2	41.6 ± 30.6 ^c
SF-36 GH	44.1 ± 20.4	51.7 ± 19.5	41.8 ± 20.2 ^a	46.5 ± 20.1	36.6 ± 15.8 ^b	51.3 ± 20.2	33.1 ± 15.3 ^c
SF-36 VT	43.1 ± 21.9	52.3 ± 20.6	40.3 ± 21.7 ^a	45.7 ± 21.3	31.2 ± 18.7 ^b	53.8 ± 18.6	27.0 ± 15.8 ^c
SF-36 SF	66.6 ± 29.7	77.3 ± 25.8	63.6 ± 30.1 ^a	68.3 ± 27.6	57.8 ± 30.2	77.7 ± 25.7	50.5 ± 27.5 ^c
SF-36 RE	68.5 ± 42.0	81.9 ± 34.6	65.3 ± 43.0 ^a	76.9 ± 37.6	52.1 ± 45.8 ^b	82.3 ± 35.2	47.9 ± 43.2 ^c
SF-36 MH	65.5 ± 20.9	68.0 ± 18.5	64.7 ± 21.7	70.7 ± 20.9	56.7 ± 24.3 ^b	76.8 ± 13.6	48.6 ± 18.5 ^c
SF-36 PCS	34.7 ± 12.2	43.9 ± 12.5	32.2 ± 10.8 ^a	34.4 ± 10.9	29.6 ± 9.3 ^b	38.1 ± 12.0	29.6 ± 10.7 ^c
SF-36 MCS	48.0 ± 11.6	49.2 ± 10.2	47.6 ± 12.0	50.5 ± 12.2	43.1 ± 11.6 ^b	53.2 ± 8.0	40.0 ± 11.6 ^c

Abbreviations: BP = bodily pain; GH = general health; MCS = mental component summary; NMOSD = neuromyelitis optica spectrum disorder; PF = physical functioning; QOL = quality of life; RE = role-emotional; RP = role-physical; SF = social functioning; SF-36 = short form 36 and its different domains; VT = vitality. Values are given in mean ± SD.

^a Significant lower comparing to patients without pain.

^b Significant lower comparing to patients with a nociceptive pain.

^c Significant lower comparing to patients without a depressive state, *t* test.

suffered from severe pain. Both median EDSS and the total number of involved spinal segments were lower than in previous studies. Less aggressive disease course, probably due to earlier diagnosis and/or more effective immunotherapy, could explain these differences. Indeed, two-thirds of our patients received rituximab, and about 40% reported reduction of pain under current immunotherapy. A positive selection bias could be another possible explanation. No data on questionnaire response rates have been reported in 2 of 3 abovementioned smaller surveys.^{11,12} Of interest, similar to one of the previous studies, we achieved a relative high response rate and pain severity was very similar in both studies (3.6 ± 2.8 other study; 3.8 ± 2.1 our cohort).¹⁰

Using the PDQ, 24% of our patients had definite neuropathic pain and further 26% signs of possible neuropathic pain. Two previous studies reported a significantly higher prevalence of neuropathic pain, 62% and 86%, respectively, based on the Douleur Neuropathique 4 questionnaire and less clearly defined clinical criteria.^{12,23} In a recent PainDetect-based small study, definite neuropathic pain was present in 7% only.¹⁴

We were able to identify several predictors of pain in our cohort. The number of myelitis episodes and the extent of spinal cord lesions independently contributed to the risk of NMOSD-associated pain. Previous smaller studies

demonstrated contradictory results.^{11,12,23} Although a correlation between pain intensity and an overall length of the spinal lesions was reported, this could not be confirmed in another study.^{11,12} It is likely that different severity and location (both sagittal and axial) of injuries have different effects on pain perception. In contrast to a recent UK study,²³ we could not confirm a protective effect of persistent cervical lesions; however, injuries in the upper thoracic (but not cervical or lower thoracic) segments were critical for development of chronic pain. Previously, a causative relationship between upper thoracic lesions and neuropathic pain was postulated.²³ As known, patients with spinal lesions develop both neuropathic and nociceptive pain.²⁴ To evaluate a link between spinal lesions and neuropathic pain, we compared patients with a definite nociceptive and definite neuropathic pain. We could not confirm a specific association of the latter with any extent or any precise sagittal lesions location. In contrast, the number of involved upper thoracic segments was significantly associated with the risk of spasticity-associated pain, observed in two-thirds of pain sufferers. Spasticity was one of the main mechanisms underlying nociceptive NMOSD-associated pain in our cohort, being present in almost 90% of these patients.

Similar to previous studies, we found that approximately 20% of all respondents suffered from short-lasting PTSs.¹⁷ Despite a previously supported association of PTS to incompletely

Table 5 Prevalence and Efficacy of Symptomatic Therapy in Pain Sufferers

	All pain sufferers (N = 125)	Patients with definite nociceptive pain (N = 39)	Patients with definite neuropathic pain (N = 40)
Symptomatic therapy	63.8% (81)	51.3% (20)	85% (34)
Pain reduction by symptomatic therapy in the last week (median, min-max)	60% (0-100)	65% (0-100)	50% (0-100)
Mean pain intensity	4.3 ± 2.0	3.3 ± 1.6	5.0 ± 2.0 ^a
Pain-free	4 (4.9%)	1 (5.0%)	0
Mild pain (1-3 NRS)	25 (30.9%)	10 (50.0%)	9 (26.5%)
Moderate pain (4-6 NRS)	41 (50.6%)	9 (45.0%)	15 (44.1%)
Severe pain (>6 NRS)	11 (13.6%)	0	10 (29.4%)

Abbreviation: NRS = Numeric Rating Scale.

If not otherwise specified, values are given in mean ± SD. Patients with ambiguous pain character (probable neuropathic or nociceptive) were excluded from this analysis.

^a $p < 0.001$, t test.

remyelinated spinal lesions, we could not confirm this finding either. In MS, PTs are supposed to be associated with thalamocortical lesions.^{25,26}

The 19% prevalence of moderate to severe depression in our cohort was lower compared with an earlier reported 28% in NMOSD.²⁷ Similar to previous studies, only pain severity but not disability, disease activity, or any other demographic parameter was associated with depression. Depression was the only factor associated with neuropathic but not nociceptive pain; however, identification of causative relationships between these conditions is impossible in a cross-sectional study. Bidirectional relationships between depression and neuropathic pain are well known and especially in inflammatory diseases share common underlying mechanisms.²⁸ It is noteworthy that a specific direct link between NMOSD and depression has been supposed in experimental studies: AQP4 deficiency itself results in a decreased hippocampal neurogenesis, which could contribute to the pathogenesis of depression.²⁹

Despite being mild to moderate, pain and depression can have enormous negative effects on patient's life. Pain markedly reduced all aspects of ADL. Pain intensity and walking impairment were 2 main factors independently associated with lower physical QoL, whereas the latter and depression had an impact on the mental QoL. Comparing patients with nociceptive and neuropathic pain, the latter had significantly lower ADL as well as both lower physical and mental composites of QoL. Of interest, 2 temporal pain patterns (persistent pain with pain attacks and pain attacks with pain between them) were associated with a markedly higher pain intensity, depression prevalence, and lower QoL. This simple image-based question allowing prompt identification of most disabled patients might be useful for pain screening in NMOSD.

In previous NMOSD studies, an insufficient symptomatic therapy has been reported.¹⁵ In our cohort, 65% received pain medications, and two-thirds of them reported a significant pain relief. Despite multiple medications, pain intensity mostly remained moderate, and only a minority of patients

Table 6 Association of 4 Pain Patterns With Pain Characteristics, Depression, and QoL

Pain pattern	Average pain intensity	Prevalence of definitive neuropathic pain	Prevalence of depression (BDI > 14)	Physical QoL	Mental QoL
Continuous pain with slight fluctuations	3.9 ± 2.0	22.2%	40.5%	33.2 ± 9.6	47.9 ± 11.7
Continuous pain with pain attacks	4.8 ± 2.0 ^a	35.5%	43.8%	27.9 ± 9.3 ^a	48.7 ± 10.9
Pain attacks with painless periods	3.0 ± 2.0	35.4%	33.3%	34.0 ± 11.1	47.9 ± 12.4
Pain attacks without painless periods	5.6 ± 1.8 ^a	62.5% ^b	87.5% ^b	24.9 ± 9.8 ^a	38.6 ± 13.4 ^b

Abbreviations: QoL = quality of life; BDI = Beck Depression Inventory II.

Values are given in mean ± SD.

^a Significant difference vs patterns 1 and 3; ANOVA

^b Significant difference vs patterns 1, 2, and 3; ANOVA or Fisher exact test, respectively.

was pain-free. Insufficient on-target medication could be one of the reasons: antispastic medications were administered in only 29% of those with a spasticity-associated pain and only 58% of patients with neuropathic pain had specific treatment.

Compared with pain, depression was less often adequately treated. Twenty-nine percent of those with moderate to severe depression received antidepressants. The actual number of patients receiving adequate antidepressant pharmacotherapy is probably even lower, as at least in some of them, antidepressants were administered as a part of pain therapy.

The strengths of our study are inclusion of a relatively large cohort of purely AQP4-IgG-seropositive NMOSD patients and the definition of clinical and paraclinical predictors of pain as well as its association with depression and effects on QoL. There are also limitations. Because we only asked for pharmacologic treatments, no information about nonpharmacologic pain therapies and psychotherapy is available. Transcutaneous electric nerve stimulation was recently reported to reduce persistent central neuropathic pain in NMOSD.³⁰ Because MRI data were retrieved by record review, we could not perform a precise analysis of transverse localization and size of the spinal lesions. In addition, no brain MRI was performed to evaluate central nociceptive pathways. There were no sufficient data on lumbar MRI, rarely involved by seropositive NMOSD. The analysis of lesion extension in the acute phase of myelitis could be also promising, as some injured foci become invisible afterward. Moreover, prospective evaluation of the type and severity of pain in the first 6 months after acute myelitis could be helpful for precise analysis of possible underlying mechanisms. A relatively high proportion of pain sufferers (35%) took no pain medications during the study. It remains unclear whether the medications have not been administered due to low pain intensity or stopped due to low efficacy and side effects. It would be important to address this point in further studies. Finally, we did not perform an analysis of fatigue, an important factor influencing depression and QoL.

In conclusion, chronic pain and depression are highly prevalent and strongly affect QoL and ADL in AQP4-IgG-seropositive NMOSD. Both conditions remain undertreated and therefore should be asked for in the diagnostic workup. Pain attacks without painless periods are typical for NMOSD and have the most severe impact. Episodes of myelitis involving upper thoracic segments are main drivers of pain in NMOSD and should be prevented and aggressively treated. Adequate immunotherapy has a beneficial effect on pain experience. Higher awareness and interventional studies on targeted symptomatic treatment of neuropathic and spasticity-associated pain, including characteristic and very intense short-lasting PTs, are warranted and could change a real-life clinical practice in NMOSD.

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Disclosure

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Teva, and Zambon, outside of the submitted work. S. Jarius reports no conflicts of interest. B. Wildemann received grants from the German Ministry of Education and Research, German Research Foundation, Dietmar Hopp Foundation, Klaus Tschira Foundation; grants and personal fees from Merck, Novartis, and Sanofi Genzyme; and personal fees from Bayer, Biogen, Roche, and Teva, none related to this work. V. Häußler has no conflict of interest. J.-P. Stellmann receives research funding from Deutsche Forschungsgemeinschaft and reports a grant from Biogen that partially funded the submitted work. A further grant is reported from Genzyme outside the submitted work. J.-P. Stellmann also received travel support and personal fees from Alexion, Biogen, and Genzyme outside the submitted work. M. Senel has received consulting and/or speaker honoraria from Alexion, Bayer, Biogen, Merck, Roche, and Sanofi Genzyme. She has received travel funding from Celgene and Teva. She has received research funding from the Hertha-Nathorff-Program. L. Klotz received compensation for serving on scientific advisory boards (Alexion, Janssen, Novartis, Merck Serono, Sanofi Genzyme, and Roche); speaker honoraria and travel support (Biogen, Novartis, Merck Serono, Sanofi Genzyme, Roche, and Teva); and research support (Biogen Idec, Merck Serono, Novartis, and Sanofi Genzyme). H.L. Pellkofer received honoraria for lectures from Bayer HealthCare, Biogen Idec, and Teva Pharma and travel reimbursement from Novartis. M.S. Weber receives research support from the Deutsche Forschungsgemeinschaft (DFG; WE 3547/5-1) and from Novartis, Teva, Biogen Idec, Roche, Merck, and the ProFutura Programm of the Universitätsmedizin Göttingen. M.S. Weber is serving as an editor for *PLoS One*. He received travel funding and/or speaker honoraria from Biogen Idec, Merck Serono, Novartis, Roche, Teva, Bayer, and Genzyme. M. Pawlitzki received travel accommodation and meeting reimbursement from Novartis. P.S. Rommer has received honoraria for lectures or consultancy from Alexion, Almirall, Biogen, Merck, Novartis, Roche, Sandoz, and Sanofi Genzyme. He has received research grants from Amicus, Biogen, Merck, and Roche, none related to this manuscript. A. Berthele has received personal compensations, speaker honoraria, and funding for travel from Alexion, Bayer HealthCare, Biogen, Celgene, Merck Serono, Mylan, Novartis, Roche, Sanofi Genzyme, and Teva. K.-D. Wernecke reports no disclosures. K. Hellwig received consultant and speaker honoraria and grant support from Bayer, Biogen, Merck, Novartis, Sanofi Genzyme, Roche, and Teva. R. Gold received speaker's and board honoraria from Baxter, Bayer Schering, Biogen Idec, CLB Behring, Genzyme, Merck Serono, Novartis, Stendhal, Talecris, and Teva. His department received grant support from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, and Teva, all not related to the content of this manuscript. I. Kleiter has received speaker honoraria and travel funding from Alexion, Bayer, Biogen, Novartis, Merck, Sanofi Genzyme, and Roche; speaker honoraria from Mylan; travel funding from the Guthy-Jackson Charitable Foundation; consulted for Alexion, Bayer, Biogen, Celgene, Chugai, IQVIA, Novartis, Merck, and Roche; and received research support from Chugai and Diamed. Go to [Neurology.org/NN](https://www.neurology.org/NN) for full disclosures.

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Appendix 1 Authors

Name	Location	Contribution
Ilya Ayzenberg, MD	Ruhr-University Bochum, Bochum, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Daniel Richter, MD	Ruhr-University Bochum, Bochum, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Eugenia Henke, MD	Ruhr-University Bochum, Bochum, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Susanna Asseyer, MD	Berlin Institute of Health, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Friedemann Paul, MD	Berlin Institute of Health, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Corinna Trebst, MD	Hannover Medical School, Hannover, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Martin W. Hümmert, MD	Ludwig-Maximilians University Munich, Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Joachim Havla, MD	Ludwig-Maximilians University Munich, Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Tania Kümpfel, MD	Ludwig-Maximilians University Munich, Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Marius Ringelstein, MD	Heinrich Heine University Düsseldorf, Düsseldorf, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Orhan Aktas, MD	Heinrich Heine University Düsseldorf, Düsseldorf, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data

Appendix 1 (continued)

Name	Location	Contribution
Brigitte Wildemann, MD	University of Heidelberg, Heidelberg, Germany;	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Sven Jarius, MD	University of Heidelberg, Heidelberg, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Vivien Häußler, MD	Zentrum für Molekulare Neurobiologie, Hamburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Jan-Patrick Stellmann, MD	Zentrum für Molekulare Neurobiologie, Hamburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Makbule Senel, MD	University of Ulm, Ulm, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Luisa Klotz, MD	University Hospital Münster, Münster, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Hannah L. Pellkofer, MD	Ludwig-Maximilians University Munich, Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Martin S. Weber, MD	University Medical Center, Göttingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Marc Pawlitzki, MD	University Hospital Münster, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Paulus S. Rommer, MD	Medical University of Vienna, Vienna, Austria	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Achim Berthele, MD	Technical University of Munich, Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Klaus-Dieter Wernecke, MD	CRO SOSTANA GmbH Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data

Appendix 1 (continued)

Name	Location	Contribution
Kerstin Hellwig, MD	Ruhr-University Bochum, Bochum, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Ralf Gold, MD	Ruhr-University Bochum, Bochum, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Ingo Kleiter, MD	Ruhr-University Bochum, Bochum, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

Appendix 2 Coinvestigators

Members of the Neuromyelitis Optica Study Group (NEMOS) are listed below in alphabetical order.

Name	Location	Role	Contribution
Philipp Albrecht	Heinrich Heine University, Düsseldorf, Germany	Co-investigator	Organizational Support
Klemens Angstwurm, MD	University Hospital, Regensburg, Germany	Co-investigator	Organizational Support
Antonios Bayas, MD	University Hospital, Augsburg, Germany	Co-investigator	Organizational Support
Judith Bellmann-Strobl, MD	Charité-Universitätsmedizin Berlin, Germany	Co-investigator	Organizational Support
Felix Bischof, MD	University Hospital, Tübingen, Germany	Co-investigator	Organizational Support
Stefan Bittner, MD	University Medical Center of the Johannes Gutenberg University, Mainz, Germany	Co-investigator	Organizational Support
Tobias Böttcher, MD	Johanna-Odebrecht-Stiftung, Greifswald, Germany	Co-investigator	Organizational Support
Buttmann Mathias, MD	University of Würzburg, Germany	Co-investigator	Organizational Support
Ankelien Duchow	Universitätsmedizin Berlin, Germany	Co-investigator	Organizational Support
Barbara Etrich, MD	University Hospital, Leipzig, Germany	Co-investigator	Organizational Support
Jürgen Faiss, MD	Asklepios Klinik, Teupitz, Germany	Co-investigator	Organizational Support

Continued

Appendix 2 (continued)

Members of the Neuromyelitis Optica Study Group (NEMOS) are listed below in alphabetical order.

Name	Location	Role	Contribution
Benedikt Frank, MD	University Hospital, Essen, Germany	Co-investigator	Organizational Support
Anna Gahlen, MD	Ruhr-University Bochum, Germany	Co-investigator	Organizational Support
Achim Gass, MD	University Hospital, Mannheim, Germany	Co-investigator	Organizational Support
Christian Geis	Department of Neurology, Jena University Hospital, Germany	Co-investigator	Organizational Support
Matthias Grothe, MD	University Hospital, Greifswald, Germany	Co-investigator	Organizational Support
Kerstin Guthke, MD	Klinikum Görlitz, Germany	Co-investigator	Organizational Support
Axel Haarmann, MD	University of Würzburg, Germany	Co-investigator	Organizational Support
Hans-Peter Hartung, MD	Heinrich Heine University, Düsseldorf, Germany	Co-investigator	Organizational Support
Bernhard Hemmer, MD	Technical University, Munich, Germany	Co-investigator	Organizational Support
Frank Hoffmann, MD	Krankenhaus Martha-Maria, Halle, Germany	Co-investigator	Organizational Support
Olaf Hoffmann, MD	St. Josefs-Krankenhaus, Potsdam, Germany	Co-investigator	Organizational Support
Ulrich Hofstadt-van Oy, MD	Klinikum Westfalen, Dortmund, Germany	Co-investigator	Organizational Support
Jutta Junghans, MD	Krankenhaus Martha-Maria, Halle, Germany	Co-investigator	Organizational Support
Matthias Kaste, MD	Nordwest Hospital Sanderbusch, Sande, Germany	Co-investigator	Organizational Support
Barbara Kaulen, MD	University Hospital, Hamburg, Germany	Co-investigator	Organizational Support
Peter Kern, MD	Asklepios Klinik, Teupitz, Germany	Co-investigator	Organizational Support
Pawel Kermer, MD	Nordwest Hospital Sanderbusch, Sande, Germany	Co-investigator	Organizational Support
Christoph Kleinschnitz, MD	University Hospital, Essen, Germany	Co-investigator	Organizational Support
Wolfgang Köhler, MD	University Hospital, Leipzig, Germany	Co-investigator	Organizational Support
Markus Kowarik, MD	University Hospital, Tübingen, Germany	Co-investigator	Organizational Support

Appendix 2 (continued)

Members of the Neuromyelitis Optica Study Group (NEMOS) are listed below in alphabetical order.

Name	Location	Role	Contribution
Markus Kraemer	Alfried-Krupp-Krankenhaus, Essen, Germany	Co-investigator	Organizational Support
Markus Krumbholz, MD	University Hospital, Tübingen, Germany	Co-investigator	Organizational Support
Stefan Langel, MD	Landeskrankenhaus Rheinhessen, Germany	Co-investigator	Organizational Support
Martin Liebetau, MD	St. Josefs-Hospital, Wiesbaden, Germany	Co-investigator	Organizational Support
Ralf Linker, MD	University Hospital, Regensburg, Germany	Co-investigator	Organizational Support
De-Hyung Lee, MD	University Hospital, Regensburg, Germany	Co-investigator	Organizational Support
Felix Luessi, MD	University Medical Center of the Johannes Gutenberg University, Mainz, Germany	Co-investigator	Organizational Support
Martin Marziniak, MD	Isar-Amper Klinik Ost, Munich, Germany	Co-investigator	Organizational Support
Christoph Mayer, MD	Neurologischen Gemeinschaftspraxis im Bienenkorbhaus, Frankfurt, Germany	Co-investigator	Organizational Support
Stefanie Meister, MD	University Hospital, Rostock, Germany	Co-investigator	Organizational Support
Arthur Melms, MD	Facharztpraxis für Neurologie und Psychiatrie, Stuttgart, Germany	Co-investigator	Organizational Support
Imke Metz, MD	University Hospital, Göttingen, Germany	Co-investigator	Organizational Support
Oliver Neuhaus, MD	SRH Krankenhaus, Sigmaringen, Germany	Co-investigator	Organizational Support
Sabine Niehaus, MD	Klinikum Dortmund, Germany	Co-investigator	Organizational Support
Florence Pache, MD	Charité University Medicine, Berlin, Germany	Co-investigator	Organizational Support
Hans-Ulrich Puhmann, MD	Schlosspark-Klinik, Berlin, Germany	Co-investigator	Organizational Support
Refik Pul, MD	University Hospital, Essen, Germany	Co-investigator	Organizational Support
Paulus Rommer, MD	Medical University of Wien, Austria	Co-investigator	Organizational Support

Appendix 2 (continued)

Members of the Neuromyelitis Optica Study Group (NEMOS) are listed below in alphabetical order.

Name	Location	Role	Contribution
Kevin Rostásy, MD	Vestische Caritas-Kliniken GmbH, Datteln, Germany	Co-investigator	Organizational Support
Lioba Rückriem, MD	MediClin Hedon-Klinik, Lingen (Ems), Germany	Co-investigator	Organizational Support
Klemens Ruprecht, MD	Charité-Universitätsmedizin Berlin, Germany	Co-investigator	Organizational Support
Christoph Ruschil, MD	University Hospital, Tübingen, Germany	Co-investigator	Organizational Support
Sven Schippling, MD	University Hospital, Zürich, Switzerland	Co-investigator	Organizational Support
Matthias Schwab, MD	University Hospital, Jena, Germany	Co-investigator	Organizational Support
Jörn Peter Sieb, MD	Helios Hansekllinikum, Stralsund, Germany	Co-investigator	Organizational Support
Nadja Siebert, MD	Charité-Universitätsmedizin Berlin, Germany	Co-investigator	Organizational Support
Claudia Sommer, MD	University Hospital, Würzburg, Germany	Co-investigator	Organizational Support
Annette Spreer, MD	University Medical Center of the Johannes Gutenberg University, Mainz, Germany	Co-investigator	Organizational Support
Martin Stangel, MD	Hannover Medical School, Hannover, Germany	Co-investigator	Organizational Support
Andrea Steinbrecher, MD	Helios Klinikum, Erfurt, Germany	Co-investigator	Organizational Support
Heike Stephanik, MD	University Hospital, Magdeburg, Germany	Co-investigator	Organizational Support
Muriel Stoppe, MD	University Hospital, Leipzig, Germany	Co-investigator	Organizational Support
Marie Süße, MD	University Hospital, Greifswald, Germany	Co-investigator	Organizational Support
Björn Tackenberg, MD	University Hospital, Marburg, Germany	Co-investigator	Organizational Support
Florian Then-Bergh, MD	University Hospital, Leipzig, Germany	Co-investigator	Organizational Support
Johannes Tünnerhoff, MD	University Hospital, Tübingen, Germany	Co-investigator	Organizational Support
Hayrrettin Tumani, MD	University Hospital, Ulm, Germany	Co-investigator	Organizational Support
Annette Walter, MD	Klinikum Herford, Herford, Germany	Co-investigator	Organizational Support

Appendix 2 (continued)

Members of the Neuromyelitis Optica Study Group (NEMOS) are listed below in alphabetical order.

Name	Location	Role	Contribution
Klaus-Peter Wandinger, MD	University Medical Center Schleswig-Holstein Campus, Lübeck, Germany	Co-investigator	Organizational Support
Clemens Warnke, MD	University Hospital, Köln, Germany	Co-investigator	Organizational Support
Robert Weissert, MD	University Hospital, Regensburg, Germany	Co-investigator	Organizational Support
Heinz Wiendl, MD	University Hospital, Münster, Germany	Co-investigator	Organizational Support
Christian Wilke, MD	Nervenzentrum, Potsdam, Germany	Co-investigator	Organizational Support
Alexander Winkelmann, MD	University Hospital, Rostock, Germany	Co-investigator	Organizational Support
Yavor Yalachkov, MD	University Hospital, Frankfurt, Germany	Co-investigator	Organizational Support
Lena Zeltner, MD	University Hospital, Tübingen, Germany	Co-investigator	Organizational Support
Uwe Zettl	University Hospital, Rostock, Germany	Co-investigator	Organizational Support
Ulf Ziemann, MD	University Hospital, Tübingen, Germany	Co-investigator	Organizational Support
Frauke Zipp, MD	University Medical Center of the Johannes Gutenberg University, Mainz, Germany	Co-investigator	Organizational Support

References

- Weinshenker BG, Wingerchuk DM. Neuromyelitis spectrum disorders. *Mayo Clin Proc* 2017;92(4):663–679.
- Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. *Curr Opin Neurol* 2019;32(3):385–394.
- Paul F, Jarius S, Aktas O, et al. Antibody to aquaporin 4 in the diagnosis of neuromyelitis optica. *PLoS Med* 2007;4(4):e133.
- Hillebrand S, Schanda K, Nigritinou M, et al. Circulating AQP4-specific auto-antibodies alone can induce neuromyelitis optica spectrum disorder in the rat. *Acta Neuropathol* 2019;137(3):467–485.
- Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation* 2012;9:14.
- Kleiter I, Gahlen A, Borisow N, et al. Neuromyelitis optica: evaluation of 871 attacks and 1153 treatment courses. *Ann Neurol* 2016;79(2):206–216.
- Moore P, Methley A, Pollard C, et al. Cognitive and psychiatric comorbidities in neuromyelitis optica. *J Neurol Sci* 2016;360:4–9.
- Beekman J, Keisler A, Pedraza O, et al. Neuromyelitis optica spectrum disorder: patient experience and quality of life. *Neuro Neuroimmunol Neuroinflamm* 2019; 6(4):e580.
- Jarius S, Wildemann B. The history of neuromyelitis optica. Part 2: 'Spinal amaurosis', or how it all began. *J Neuroinflammation* 2019;16(1):280.
- Kanamori Y, Nakashima I, Takai Y, et al. Pain in neuromyelitis optica and its effect on quality of life: a cross-sectional study. *Neurology* 2011;77(7):652–658.
- Qian P, Lancia S, Alvarez E, et al. Association of neuromyelitis optica with severe and intractable pain. *Arch Neurol* 2012;69(11):1482–1487.
- Zhao S, Mutch K, Elson L, et al. Neuropathic pain in neuromyelitis optica affects activities of daily living and quality of life. *Mult Scler* 2014;20(12):1658–1661.
- Kong Y, Okoruwa H, Revis J, et al. Pain in patients with transverse myelitis and its relationship to aquaporin 4 antibody status. *J Neurol Sci* 2016;368:84–88.

14. Asseyer S, Schmidt F, Chien C, et al. Pain in AQP4-IgG-positive and MOG-IgG-positive neuromyelitis optica spectrum disorders. *Mult Scler J Exp Transl Clin* 2018;4(3):2055217318796684.
15. Hyun JW, Jang H, Yu J, et al. Comparison of neuropathic pain in neuromyelitis optica spectrum disorder and multiple sclerosis. *J Clin Neurol* 2020;16(1):124–130.
16. Bradl M, Kanamori Y, Nakashima I, et al. Pain in neuromyelitis optica—prevalence, pathogenesis and therapy. *Nat Rev Neurol* 2014;10(9):529–536.
17. Kim SM, Go MJ, Sung JJ, et al. Painful tonic spasm in neuromyelitis optica: incidence, diagnostic utility, and clinical characteristics. *Arch Neurol* 2012;69(8):1026–1031.
18. Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med* 2019;381(22):2114–2124.
19. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015;85(2):177–189.
20. Freynhagen R, Baron R, Gockel U, et al. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006;22(10):1911–1920.
21. Melzack R. The short-form McGill pain questionnaire. *Pain* 1987;30(2):191–197.
22. Fox J, Weisberg A. *An R Companion to Applied Regression*. 3rd ed. SAGE Publications Inc.; 2018.
23. Tackley G, Vecchio D, Hamid S, et al. Chronic neuropathic pain severity is determined by lesion level in aquaporin 4-antibody-positive myelitis. *J Neurol Neurosurg Psychiatry* 2017;88(2):165–169.
24. Muller R, Brinkhof MW, Arnet U, et al. Prevalence and associated factors of pain in the Swiss spinal cord injury population. *Spinal Cord* 2017;55(4):346–354.
25. Tuzun E, Akman-Demir G, Eraksoy M. Paroxysmal attacks in multiple sclerosis. *Mult Scler* 2001;7(6):402–404.
26. Spissu A, Cannas A, Ferrigno P, et al. Anatomic correlates of painful tonic spasms in multiple sclerosis. *Mov Disord* 1999;14(2):331–335.
27. Chavarro VS, Mealy MA, Simpson A, et al. Insufficient treatment of severe depression in neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm* 2016;3(6):e286.
28. Walker AK, Kavelaars A, Heijnen CJ, et al. Neuroinflammation and comorbidity of pain and depression. *Pharmacol Rev* 2014;66(1):80–101.
29. Skucas VA, Mathews IB, Yang J, et al. Impairment of select forms of spatial memory and neurotrophin-dependent synaptic plasticity by deletion of glial aquaporin-4. *J Neurosci* 2011;31(17):6392–6397.
30. Mealy MA, Kozachik SL, Cook LJ, et al. Scrambler therapy improves pain in neuromyelitis optica: a randomized controlled trial. *Neurology* 2020;94(18):e1900–e07.