

## ORIGINAL ARTICLE

# Pain, depression, and quality of life in adults with MOG-antibody-associated disease

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## Abstract

**Background and purpose:** Myelin oligodendrocyte glycoprotein-antibody-associated disease (MOGAD) is an inflammatory autoimmune condition of the central nervous system. However, data on pain and depression have remained scarce. The aim of this study

**Abbreviations:** ADL, activities of daily living; AQP4-ab, aquaporin-4-antibody; BDI-II, Beck Depression Inventory II; EDSS, Expanded Disability Status Scale; hr-QoL, health-related quality of life; IgG, immunoglobulin G; MCS, mental component summary; MOG, myelin oligodendrocyte glycoprotein; MOG-ab, myelin oligodendrocyte glycoprotein-antibody; MOGAD, myelin oligodendrocyte glycoprotein-antibody-associated disease; MPQ-SF, McGill Pain Questionnaire Short Form; MS, multiple sclerosis; n, number; NEMOS, Neuromyelitis Optica Study Group; NMOSD, neuromyelitis spectrum disorder; ON, optic neuritis; PCS, physical component summary; PDQ, PainDetect Questionnaire; PSI, pain severity index; PTS, painful tonic spasms; QoL, quality of life; SAP, spasticity-associated pain; SF-36, Short Form 36 Health Survey; SF-BPI, Short Form of the Brief Pain Inventory.

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was to assess features of chronic pain and depression as well as their impact on health-related quality of life (hr-QoL) in MOGAD.

**Methods:** Patients with MOGAD were identified in the Neuromyelitis Optica Study Group registry. Data were acquired by a questionnaire, including clinical, demographic, pain (PainDetect, Brief Pain Inventory–Short Form, McGill Pain Questionnaire–Short Form), depression (Beck Depression Inventory-II), and hr-QoL (Short Form-36 Health Survey) items.

**Results:** Twenty-two of 43 patients suffered from MOGAD-related pain (11 nociceptive, eight definite neuropathic, three possible neuropathic) and 18 from depression. Patients with neuropathic pain had the highest pain intensity and most profound activities of daily living (ADL) impairment. Fifteen patients reported spasticity-associated pain, including four with short-lasting painful tonic spasms. Later disease onset, profound physical impairment, and depression were associated with chronic pain. Physical QoL was more affected in pain sufferers ( $p < 0.001$ ) than in pain-free patients, being most severely reduced by neuropathic pain ( $p = 0.016$ ). Pain severity, visual impairment, and gait impairment independently predicted lower physical QoL. Depression was the only factor reducing mental QoL. Twelve patients still suffering from moderate pain (pain severity  $4.6 \pm 2.3$ ) received pain medication. Only four out of 10 patients with moderate to severe depression took antidepressants.

**Conclusions:** Being highly prevalent, pain and depression strongly affect QoL and ADL in MOGAD. Both conditions remain insufficiently controlled in real-life clinical practice.

**KEYWORDS**

depression, MOG-antibody-associated disease, pain, quality of life, spasticity

**INTRODUCTION**

Myelin oligodendrocyte glycoprotein-antibody (MOG-ab)-associated disease (MOGAD) is an inflammatory autoimmune condition of the central nervous system [1,2]. MOG-abs bind conformationally intact myelin oligodendrocyte glycoprotein (MOG) and induce an inflammatory demyelination [3]. MOGAD patients may develop any combination of monophasic or relapsing optic neuritis (ON), transverse myelitis, acute disseminated encephalomyelitis, brain-stem symptoms, and less frequently, cortical involvement with seizures [1,4–6]. The clinical phenotype in adults is partly similar to aquaporin-4-antibody (AQP4-ab)-positive neuromyelitis spectrum disorder (NMOSD) [4]. However, based on a distinct immunopathogenesis, MOGAD is now considered a disease entity on its own [7–9].

In NMOSD, severe pain is one of the most frequent and disabling symptoms. Pain has a prevalence of over 80% and severely reduces the quality of life (QoL) [10–12]. Pain syndromes embrace neuropathic pain, nociceptive pain, and mixed pain, and can emerge in acute relapse or become chronic within the disease course [10–12]. Characteristic painful tonic spasms (PTS) occur in approximately 20% of patients with AQP4-ab-related NMOSD [13].

In MOGAD, data on pain are scarce, and clinical case reports and series often ignore pain as a severe symptom. However, ON-related headache or periorbital pain, neuropathic pain, including radiculopathy-like pain, and musculoskeletal pain have all been described anecdotally and can severely affect the patient's well-being [4,12,14–17].

In the current study we performed a systematic analysis of neuropathic and nociceptive pain syndromes, as well as depression, and their impact on QoL and activities of daily living (ADL) in adults with MOGAD in Germany.

**METHODS AND MATERIALS**

We performed an exploratory cross-sectional study in the years 2017 to 2019. MOG-ab-positive patients were identified through the registry of the German Neuromyelitis Optica Study Group (NEMOS; [www.nemos-net.de](http://www.nemos-net.de)) and through local electronic databases. A semistructured questionnaire, which was given to the patients by the local staff of the 11 participating tertiary referral centers, was sent back to the Bochum or Berlin centers in a pseudonymized fashion.

Inclusion criteria were: (i) age over 18 years, (ii) diagnosis of MOGAD [2] with positive cell-based assay detecting

MOG-immunoglobulin G (IgG). Exclusion criteria comprised (i) other diseases with relevant pain syndromes and (ii) severe cognitive deficits.

## Clinical data and assessment

The questionnaire comprised questions on demographics, disease course, previous relapses (history of ON and myelitis), current therapy, spasticity, as well as pain, depression, and health-related quality of life (hr-QoL) assessment scores (PainDetect Questionnaire [PDQ], Short Form of the Brief Pain Inventory [SF-BPI], McGill Pain Questionnaire Short Form [MPQ-SF], Beck Depression Inventory II [BDI-II], and Short Form 36 Health Survey [SF-36]).

Spasticity was assessed by asking if the patient experienced attacks or short episodes (<1 min) of intensive pain, accompanied by an increased tone (increased muscular tension) and cramps in the arms/legs.

The questions of the SF-BPI consist of two categories: (i) pain severity (present, highest, least, and average pain intensity) based on a numeric rating scale from 0 (no pain) to 10 (worst pain imaginable) within the last week. The pain severity index (PSI) represents the average score of the four pain intensity scores; (ii) seven domains of pain-related interference with daily life, 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 ask about pain localization and to discriminate between neuropathic (PDQ score, 19–38) and nociceptive pain (PDQ score, 0–12). PDQ score from 13 to 18 is considered to be possibly neuropathic [18]. We performed comparative analysis between patients with definitive neuropathic and nociceptive pain.

The MPQ-SF consists of 15 words describing sensory ( $n = 11$ ) and affective ( $n = 4$ ) components of pain. Patients rate the intensity of the respective pain quality as 0 = none, 1 = mild, 2 = moderate, or 3 = severe [19].

The BDI-II ranges from 0 (best) to 63 (worst) (<9: no depressive affect; 9–13: minimal mood disturbance; 14–20: mild depression, 21–28: moderate depression;  $\geq 29$ : severe depression). Clinically relevant depression was defined by a BDI score  $\geq 14$  [20].

SF-36 measures hr-QoL. It consists of 36 items in eight subscales with components of mental and physical health. A physical component summary (PCS) and a mental component summary (MCS) were calculated using norm-based attaining values from 0 (worst) to 100 (best) [21].

Patient-reported gait function (scored from 0 [best] to 3 [worst]; 0: no restriction; 1: >500 m without rest, 2: <500 m without rest, 3: inability to walk) and visual function (scored from 0 [best] to 4 [worst]; 0: no restriction; 1: restricted when reading, writing, or working on a PC only; 2: restricted during simple activities of daily life at home; 3: very bad vision, no orientation in a

foreign environment; 4: shadow vision, blindness) were assessed corresponding to the questionnaires' relapse history (ON: visual function; myelitis: gait function).

In addition to the patient-reported questionnaire, the Expanded Disability Status Scale (EDSS) was evaluated if available at the respective study center. The EDSS was assessed within 12 months relative to the questionnaire. Therefore, the analysis was focused on self-reported gait and visual function at the time of assessment.

Testing for serum MOG-abs was performed per local protocols using established cell-based assays [2,8].

## Statistics

Statistical analysis was performed using R (version 3.4.0; The R Foundation for Statistical Computing) [22]. To investigate group differences, we used the Fisher exact test for categorical variables (attack history, BDI-II score categories, sex, group comparisons of patients with intermittent vs. permanent pain), Mann-Whitney-Wilcoxon rank sum test for not normally distributed continuous variables (age, disease duration, self-reported gait and visual function, McGill Pain Questionnaire [MPQ] scores, measures of pain intensity, number of attacks, SF-36 scores, SF-BPI scores).

To check for correlations between measures of pain intensity and depression scores and for correlations between measures of pain intensity, depression scores, self-reported physical impairment, and PCS and MCS, respectively, we performed a Spearman correlation test. We performed an additional correlation analysis of PCS and MCS with the EDSS as an objective impairment score. A robust regression model [23] was used to determine predictors of hr-QoL with SF-36 PCS and MCS score.

For all models and corresponding statistical tests, statistical significance was set at  $p < 0.05$ . This study was exploratory, without an a priori sample size calculation and adjustments for multiple testing.

## RESULTS

### Description of cohort

Forty-three adult patients with MOGAD were included in the analysis. Table 1 provides the main demographic and clinical characteristics of the study participants. Current immunotherapy comprised azathioprine ( $n = 5$ ), glatiramer acetate ( $n = 1$ ), intravenous or subcutaneous immunoglobulin ( $n = 3$ ), methotrexate ( $n = 2$ ), mitoxantrone ( $n = 1$ ), mycophenolate mofetil ( $n = 1$ ), prednisolone ( $n = 1$ ), and rituximab ( $n = 19$ ).

### Prevalence of pain in MOGAD

Pain was a frequent symptom in our cohort. Overall, 22 of 43 (51%) patients suffered from chronic MOGAD-related pain. Eighteen patients

**TABLE 1** Demographic and clinical characteristics of patients included in this study

	MOG-ab-positive patients, <i>n</i> = 43
Sex, female/male (female %)	29/14 (67.4%)
Age, years, mean±SD	39.2 ± 14.7
Age at disease onset, years, mean±SD	33.5 ± 14.0
Disease duration, years, median (min-max)	3 (0–43.7)
Total number of previous attacks, median (min-max) <sup>a</sup>	3 (1–16)
Patients with a history of myelitis, <i>n</i> (%) <sup>b</sup>	34 (81%)
Patients with a history of ON, <i>n</i> (%) <sup>a</sup>	31 (77.5%)
Total number of ON attacks, median (min-max) <sup>c</sup>	1 (0–10)
Total number of myelitis attacks, median (min-max) <sup>d</sup>	1 (0–11)
EDSS, median (min-max) <sup>e</sup>	2.5 (0–8)
Patients on current immunosuppressive treatment, <i>n</i> (%) <sup>a</sup>	33 (82.5%)

Note: Relapse history included only previous attacks of ON and myelitis but no other possible manifestations. Percentages refer to the number of available data. Data available for <sup>a</sup>*n* = 40, <sup>b</sup>*n* = 42, <sup>c</sup>*n* = 38, <sup>d</sup>*n* = 37, <sup>e</sup>*n* = 33.

Abbreviations: EDSS, Expanded Disability Status Scale; min-max, minimum–maximum; MOG-ab, myelin oligodendrocyte glycoprotein-antibody; *n*, number; ON, optic neuritis; SD, standard deviation.

(42%) reported painful symptoms as part of their previous attacks. Of these, nine patients had transient pain only, and nine patients had persistent pain. Attack-related pain comprised myelitis-associated pain (*n* = 6), ON-associated pain (*n* = 7), and nonspecific pain like headache (*n* = 4), neck pain (*n* = 1), and generalized body pain (*n* = 1).

### Pain quality, intensity, and localization of relapse-independent pain

The following analysis of pain syndromes was performed in patients with relapse-independent MOGAD-related pain (*n* = 22). Pain was mainly described as cramping (*n* = 11), stabbing (*n* = 15), tender (*n* = 17), aching (*n* = 19) (sensory dimensions), and tiring/exhausting (*n* = 20) (affective dimension). Median present pain intensity was 3/10 (minimum–maximum: 0–9), median maximum and average pain intensity in the previous week were 6/10 (minimum–maximum: 1–9) and 3.5/10 (minimum–maximum: 1–9), respectively.

Of 22 patients with MOGAD-related pain, 12 suffered from permanent pain and nine from intermittent pain attacks. For one patient, no information was available. Six patients suffered from both permanent pain and pain attacks. Patients with pain attacks had the most severe pain: median PSI 4.4 (minimum–maximum: 2.5–9) in those with additional permanent pain and 4.3 (minimum–maximum: 1.5–6.5) in those without. Patients with persistent pain without attacks had the lowest median PSI: 2.1 (minimum–maximum: 1–4). Pain was localized mostly in the legs (*n* = 14, *n* = 11 bilaterally), following by

back pain (*n* = 12), arm pain (*n* = 8, *n* = 4 bilaterally), head/neck pain (*n* = 6), and anterior trunk pain (*n* = 3).

### Pain-associated factors

Demographics were similar in patients with and without pain (Table 2). However, patients with MOGAD-related pain were older at disease onset (*p* = 0.039) and clinically more impaired than patients without pain (self-reported gait function: *p* = 0.005). Moreover, clinically relevant depression was more frequent in pain sufferers (*p* = 0.034).

### Neuropathic and nociceptive pain

Eight of 22 patients with MOGAD-related pain fulfilled the PDQ criteria for definite neuropathic pain, three patients had a possible neuropathic pain component, and 11 patients had nociceptive pain.

As expected, patients with definite neuropathic pain had higher pain intensity scores than those with nociceptive pain (Table 3). They described their pain experience more often as shooting (*p* < 0.001), sharp (0.014), hot-burning (*p* = 0.018) (sensory dimensions), and fearful (*p* = 0.032) (affective dimension). Sensory and affective pain scores were also higher in patients with neuropathic pain. The groups did not differ with respect to age, sex, disease duration, number of relapses, annualized relapse rate, number with ON, and number with myelitis. However, patients with definite neuropathic pain had more severe gait restriction (*p* = 0.032) than patients with nociceptive pain.

### Spasticity-associated pain

Fifteen patients reported spasticity-associated pain (SAP). SAP was located in one (*n* = 6) or both legs (*n* = 9), or in both arms and in the back for one patient, respectively. Four patients (18.2%) presented short-lasting PTS. Patients with SAP had a trend toward higher numbers of previous relapses (*p* = 0.051) and surprisingly shorter disease duration (*p* = 0.048) than patients without SAP (Table 4). Patients with and without SAP did not differ with respect to demographics and depression prevalence.

### Depression is more prevalent in pain sufferers

Eighteen patients (41.9%) had signs of clinically relevant depression that was at least moderate (BDI ≥ 21) in 10 (23.3%) cases. Clinically relevant depression was more prevalent in pain sufferers than in patients without disease-related pain (59.1% vs. 25%, *p* = 0.034; Table 2). Demographics, disease duration, and relapse activity did not differ between patients with and without clinically relevant depression (Table 5). The depression score did not differ between patients with nociceptive versus neuropathic pain (Table 3) or between

**TABLE 2** Demographics, clinical characteristics, BDI-II, and SF-36 in patients with and without pain

	Patients with MOGAD-related pain, n = 22	Patients without MOGAD-related pain, n = 21	p value
Sex, female/male (female %)	16/6 (72.7%)	13/8 (61.9%)	0.526
Age, years, mean $\pm$ SD	42.4 $\pm$ 12.8	35.9 $\pm$ 16.1	0.101
Age at disease onset, years, mean $\pm$ SD	37.6 $\pm$ 12.0	29.3 $\pm$ 15.0	<b>0.039</b>
Disease duration, years, median (min-max)	3 (0-21)	3 (0-43.7)	0.961
Total number of previous attacks, median (min-max) <sup>a</sup>	3.5 (1-11)	3 (1-16)	0.409
Patients with a history of myelitis, n (%) <sup>b</sup>	19 (86.4%)	15 (75.0%)	0.444
Patients with a history of ON, n (%) <sup>c</sup>	15 (75.0%)	15 (80.0%)	>0.999
Total number of ON, median (min-max) <sup>d</sup>	2 (0-5)	1 (0-10)	0.881
Total number of myelitis, median (min-max) <sup>e</sup>	2 (0-11)	1 (0-4)	0.253
Self-reported visual function, median (min-max) <sup>f</sup>	1 (0-4)	0 (0-4)	0.557
Self-reported gait function, median (min-max) <sup>g</sup>	1 (0-3)	0 (0-1)	<b>0.005</b>
BDI-II, clinically relevant depression, n (%)	13 (59.1%)	5 (25.0%)	<b>0.034</b>
PCS, median (min-max) <sup>h</sup>	31.5 (9.4-53.8)	51.0 (21.9-65.8)	<b>&lt;0.001</b>
MCS, median (min-max) <sup>h</sup>	41.9 (27.3-63.9)	50.0 (21.1-63.3)	0.332

Note: These group comparisons were performed with the Fisher exact test for sex, BDI-II score categories, patients with ON/myelitis/both; and Wilcoxon test for age, disease duration, number of prior attacks, prior ON, and prior myelitis episodes, visual and gait function, PCS, and MCS (not normally distributed variables). Data available for <sup>a</sup>n = 19 pain patients and n = 21 pain-free patients, <sup>b</sup>n = 22 pain patients and n = 20 pain-free patients, <sup>c</sup>n = 20 pain patients and n = 20 pain-free patients, <sup>d</sup>n = 19 pain patients and n = 19 pain-free patients, <sup>e</sup>n = 20 pain patients and n = 17 pain-free patients, <sup>f</sup>n = 21 pain patients and n = 17 pain-free patients, <sup>g</sup>n = 18 pain patients and n = 21 pain-free patients, <sup>h</sup>n = 20 pain patients and n = 21 pain-free patients. All bold p-values are significant (<0.05).

Abbreviations: BDI-II, Beck Depression Inventory II (clinically relevant depression was defined by scores  $\geq$ 140); MCS, mental component summary (SF-36); min-max, minimum-maximum; MOGAD, myelin oligodendrocyte glycoprotein-antibody-associated disease; n, number; ON, optic neuritis; PCS, physical component summary; SD, standard deviation; SF-36, Short Form 36 Health Survey.

patients with permanent and intermittent pain (odds ratio: 1.1; 95% confidence interval: 0.1-8.8;  $p = 1.0$ ). However, depression severity correlated with a visual ( $\rho = 0.401$ ,  $p = 0.009$ ) and gait ( $\rho = 0.333$ ,  $p = 0.041$ ) impairment as well as pain intensity (PSI:  $\rho = 0.392$ ,  $p = 0.010$ ).

### Pain and depression strongly affect hr-QoL and ADL in MOGAD

Both physical and mental components of the QoL were altered in patients with MOGAD, with a median MCS of 43.2 (minimum-maximum: 21.1-63.9) and a PCS of 42.4 (minimum-maximum: 9.4-65.8) compared to the general population [21]. The physical component score was lower in patients with pain than in pain-free patients (Table 2). Moreover, this score was lower in patients with neuropathic pain than in patients with nociceptive pain (Table 3). Also, patients with depression had significantly lower MCS and PCS scores than patients without depression (Table 5).

Pain strongly affected all aspects of ADL: general activity, 5.5/10 (minimum-maximum: 1.5-10); walking ability, 5.5/10 (minimum-maximum: 0-10); mood, 5/10 (minimum-maximum: 1-10); working ability, 5/10 (minimum-maximum: 1-10); sleep 4/10 (minimum-maximum: 0-9); enjoyment of life, 3.5/10 (minimum-maximum: 0-8); and relations with other people 3/10 (minimum-maximum: 0-10).

Pain severity ( $\rho = -0.798$ ,  $p < 0.001$ ), gait ( $\rho = -0.690$ ,  $p < 0.001$ ), and visual impairment ( $\rho = -0.370$ ,  $p = 0.024$ ), as well as depression score ( $\rho = -0.361$ ,  $p = 0.022$ ) correlated with PCS. In a regression model including these four factors, pain severity (B = -5.455, SE = 0.810,  $p < 0.001$ ), visual function (B = -8.163, SE = 1.742,  $p < 0.001$ ), and gait function (B = -5.756, SE = 1.875,  $p = 0.005$ ), but not depression severity (B = 1.029, SE = 0.963,  $p = 0.294$ ), were significant predictors for physical QoL. The EDSS correlated with PCS ( $\rho = -0.720$ ,  $p < 0.001$ ) but not with MCS ( $\rho = -0.223$ ,  $p = 0.220$ ).

Clinically relevant depression (B = -15.484, SE = 2.896,  $p < 0.001$ ) was the only significant predictor for low mental QoL.

### Symptomatic pain medication

Only 12 (54.5%) patients with MOGAD-related pain received pain medications. Treatment comprised nonsteroidal anti-inflammatory drugs and paracetamol (acetaminophen) (n = 10), anticonvulsants and/or antidepressants (n = 7), opioids (n = 2), and antispastic medication (n = 4). Five of 11 patients only retrospectively reported more than 50% reduction of pain intensity. Patients with nociceptive pain received no (n = 6), one (n = 3), or two (n = 1) different pain medications. Six of 11 patients with definite or possible neuropathic pain received three to six different types of pain medication.

**TABLE 3** Comparison of measures of SF-BPI, MPQ-SF, BDI-II, and SF-36 between patients with and without neuropathic pain

	Patients with definite neuropathic pain, n = 8	Patients with definite nociceptive pain, n = 11	p value
Age, years, mean±SD	46.4 ± 9.0	41.3 ± 15.4	0.321
Sex, female/male (female %)	5/3 (62.5%)	9/2 (81.8%)	0.603
Disease duration, years, median (min-max)	3 (0-13)	3 (0-21)	0.921
Total number of previous attacks, median (min-max) <sup>a</sup>	3 (2-8)	4 (1-11)	0.725
Total number of ON, median (min-max) <sup>a</sup>	0.5 (0-4)	1.5 (0-5)	0.258
Total number of myelitis, median (min-max) <sup>b</sup>	2 (1-8)	1 (0-11)	0.352
Self-reported visual function, median (min-max) <sup>c</sup>	0.5 (0-4) 8	1 (0-3) 10	0.671
Self-reported gait function, median (min-max) <sup>d</sup>	2 (0-3)	0.5 (0-1)	<b>0.032</b>
Present pain intensity, median (min-max)	6 (3-9)	2 (0-5)	<b>0.002</b>
Minimal pain intensity	3 (2-9)	1 (0-4)	<b>0.003</b>
Maximal pain intensity	8 (5-9)	5 (1-9)	<b>0.027</b>
Average pain intensity	5 (3-9)	2 (1-6)	<b>0.010</b>
Pain severity index	5.1 (3.8-9)	2.8 (1-4.8)	<b>0.003</b>
Activity of daily living			
General activity	7 (5-10)	4 (2-8)	<b>0.020</b>
Mood	6.5 (3-10)	4 (2-8)	0.143
Walking ability	8.5 (3-10)	3 (0-10)	<b>0.020</b>
Working ability	9 (5-10)	3 (2-10)	<b>0.008</b>
Relations with other people	5.5 (2-10)	2 (0-9)	<b>0.020</b>
Sleep	6 (0-9)	3 (0-8)	0.183
Enjoyment of life	5 (0-8)	2 (0-7)	0.080
MPQ-SF, sensory category, median (min-max)	16.5 (6-25)	5.5 (0-12)	<b>0.002</b>
MPQ-SF, affective category, median (min-max)	5.0 (3-12)	2.0 (0-4)	<b>0.004</b>
BDI-II, clinically relevant depression, n (%)	6 (75.0%)	5 (45.5%)	0.352
PCS, median (min-max) <sup>c</sup>	20.5 (14.2-34.8)	40 (9.4-48.9)	<b>0.016</b>
MCS, median (min-max) <sup>c</sup>	36.5 (27.3-53.5)	44.5 (31.2-63.9)	0.122

Note: These group comparisons were performed using the Fisher exact test for sex and Wilcoxon test for all other (not normally distributed) variables. Data available for <sup>a</sup>n = 8 patients with neuropathic pain and n = 8 patients with nociceptive pain, <sup>b</sup>n = 6 patients with neuropathic pain and n = 9 patients with nociceptive pain, <sup>c</sup>n = 8 patients with neuropathic pain and n = 10 patients with nociceptive pain, <sup>d</sup>n = 7 patients with neuropathic pain and n = 8 patients with nociceptive pain. All bold p-values are significant (<0.05).

Abbreviations: BDI-II, Beck Depression Inventory II (clinically relevant depression was defined by scores ≥14); MCS, mental component summary (SF-36); min-max, minimum-maximum; MPQ-SF, McGill Pain Questionnaire Short Form; n, number; ON, optic neuritis; PCS, physical component summary; SD, standard deviation; SF-36, Short Form 36 Health Survey; SF-BPI, Short Form-Brief Pain Inventory.

The PSI correlated with the number of analgesic drugs ( $\rho = 0.536$ ;  $p = 0.012$ ).

Four of 15 patients with SAP received an antispastic medication. All of them still reported spasticity-associated pain attacks four, 10, 12, and 60 times a month.

## DISCUSSION

The present study highlights the importance of pain and depression in MOGAD. Over 40% of patients from this German multicenter cohort suffered from depression, and over 50% had nociceptive or

neuropathic pain. Both comorbidities severely affected the patients' QoL and were often untreated or resistant to treatment.

Recently, MOGAD has been acknowledged as a disease entity on its own, distinct from multiple sclerosis (MS) and NMOSD [5,7,8]. Underlying pathogenetic mechanisms, clinical presentation, attack severity, and remission rate are partly different in these diseases [5,7]. Differences on pain characteristics have also been supposed; however, specific data on pain in MOGAD are scarce [4,12,16,24,25]. Previous research mentioned pain mainly as part of acute symptoms in MOGAD attacks and focused on ON-related pain and neuropathic pain during relapses [2,4,14,24-27]. In our cohort, 18 patients (42%) mentioned painful symptoms as part of their previous attacks. Most

**TABLE 4** Comparison of demographics and clinical characteristics between patients with and without spasticity-associated pain

	Patients with spasticity-associated pain, n = 15	Patients without spasticity-associated pain, n = 7	p value
Age, years, mean±SD	41.2 ± 13.3	44.9 ± 12.3	0.548
Sex, female/male (female %)	12/3 (80.0%)	4/3 (75.0%)	0.330
Disease duration, years, median (min-max)	2.6 (0–13)	5 (2–21)	<b>0.048</b>
Total number of previous attacks, median (min-max) <sup>a</sup>	4 (2–11)	2.3 (1–5)	0.087
Patients with history of myelitis, n (%)	14 (93.3%)	5 (71.4%)	0.227
Total number of myelitis, median (min-max) <sup>b</sup>	2 (0–11)	1 (0–10)	0.142
Self-reported gait function, median (min-max) <sup>c</sup>	1.0 (0–2)	1.0 (0–3)	0.881
BDI-II, clinically relevant depression, n (%)	10 (66.7%)	3 (42.9%)	0.376
PCS, median (min-max) <sup>d</sup>	23.2 (9.4–53.8)	41.9 (14.2–48.9)	0.091
MCS, median (min-max) <sup>d</sup>	41.4 (27.3–63.9)	42.5 (39.8–53.5)	0.547

Note: These group comparisons were performed using the Fisher exact test for sex and BDI-II, and Wilcoxon test for all other (not normally distributed) variables. Data available for <sup>a</sup>n = 13 patients with and n = 6 patients without SAP, <sup>b</sup>n = 13 patients with and n = 7 patients without SAP, <sup>c</sup>n = 12 patients with and n = 6 patients without SAP, <sup>d</sup>n = 14 patients with and n = 6 patients without SAP. All bold p-values are significant (<0.05).

Abbreviations: BDI-II, Beck Depression Inventory II (clinically relevant depression was defined by scores ≥14); MCS, mental component summary (SF-36); min-max, minimum–maximum; n, number; PCS, physical component summary; SD, standard deviation; SF-36, Short Form 36 Health Survey.

**TABLE 5** Comparison of demographics and clinical characteristics between patients with and without clinically relevant depression

	Patients with depression, n = 18	Patients without depression, n = 24	p value
Age, years, mean±SD	38.4 ± 12.7	38.0 ± 14.1	0.980
Sex, female/male (female %)	12/6 (66.7%)	16/8 (66.7%)	>0.999
Disease duration, years, median (min-max)	2.5 (0–9)	3.5 (0–43.7)	0.160
Total number of previous attacks, median (min-max) <sup>a</sup>	4 (1–11)	2.5 (1–16)	0.334
Total number of ON, median (min-max) <sup>b</sup>	1 (0–10)	1 (0–10)	0.880
Total number of myelitis, median (min-max) <sup>c</sup>	2 (0–11)	1 (0–10)	0.410
Self-reported visual function, median (min-max) <sup>d</sup>	1.0 (0–4)	0.0 (0–3)	0.078
Self-reported gait function, median (min-max) <sup>e</sup>	1.0 (0–2)	0.0 n	<b>0.001</b>
Pain, n (%)	13 (72.2%)	9 (37.5%)	<b>0.040</b>
PCS, median (min-max) <sup>f</sup>	37.2 (9.4–51.0)	48.0 (14.2–65.8)	<b>0.020</b>
MCS, median (min-max) <sup>f</sup>	36.5 (25.7–49.7)	50.1 (21.1–63.9)	<b>&lt;0.001</b>

Note: These group comparisons were performed using the Fisher exact test for sex and Wilcoxon test for all other (not normally distributed) variables. Clinically relevant depression was defined by scores ≥14. Data available for <sup>a</sup>n = 17 patients with and n = 22 patients without depression, <sup>b</sup>n = 17 patients with and n = 20 patients without depression, <sup>c</sup>n = 17 patients with and n = 19 patients without depression, <sup>d</sup>n = 17 patients with and n = 22 patients without depression, <sup>e</sup>n = 12 patients with and n = 15 patients without depression, <sup>f</sup>n = 16 patients with and n = 24 patients without depression. All bold p-values are significant (<0.05).

Abbreviations: MCS, mental component summary (SF-36); min-max, minimum–maximum; n, number; ON, optic neuritis; PCS, physical component summary; SD, standard deviation; SF-36, Short Form 36 Health Survey.

importantly, even more patients (51%) suffer from chronic MOGAD-related pain. Consequently, pain prevalence in MOGAD is similar to those in MS (estimated as 50%) and lower than in NMOSD, where pain prevalence has been reported to be as high as 80% to 86% [10–12,28]. However, estimates can differ in small studies, most likely due to heterogeneities of patient cohorts, screening instruments, and diverging pain classifications.

The prevalence of neuropathic pain in MOGAD probably exceeds that in MS [12,29]. About 26% of our patients suffered from

neuropathic pain. In patients with MS, a prevalence of 29% has been reported in a meta-analysis, but a lower prevalence of 15% was found when more specific diagnostic criteria were used [30]. A recent study using the PDQ reported a prevalence of only 5% (compared to 18% in our cohort) of definite neuropathic pain in MS after a disease duration of 4 years [30]. In our cohort, patients with neuropathic pain were particularly disabled. Although average pain intensity in the whole cohort was mild, patients with neuropathic pain suffered from more severe pains, similar to those reported in

NMOSD [12,29]. Neuropathic pain was significantly stronger and affected the patients' general activity, walking, and working capacities as well as relations to other people, compared to nociceptive pain.

Thirty-five percent of our MOGAD cohort suffered from SAP, and PTS occurred in about 9% of the patients. These numbers are lower than in NMOSD, where PTS occurs with a prevalence of 25% to 40% [13,31–33].

Both neuropathic pain and SAP are most likely a consequence of a spinal cord damage. Although spinal cord lesions in NMOSD are typically long and extensive [34,35], spinal cord lesions in MOGAD can be smaller and less destructive. Still, due to the highly prevalent central lesions location, they may frequently involve relevant structures of the pro- and antinociceptive system, resulting in chronic therapy-refractory pain and/or dysesthesia [4]. As reported for patients with AQP4-IgG positive NMOSD [36], the number of previous myelitis attacks did not differ between patients with and without pain. Probably not a number of relapses, but precise axial lesion location, extension, and extent of tissue damage are decisive for chronic neuropathic and spasticity-associated pain. It has been shown that central neuropathic pain can be induced by oligodendrocyte death and axonal pathology in the spinothalamic tract [37]. Moreover, brainstem lesions can also facilitate the development of neuropathic pain by affection of ascending somatosensory fibers or descending inhibitory pathways [38,39].

A lower overall prevalence of pain in MOGAD may be linked to a better recovery of lesions compared to NMOSD [35]. We show that patients who were older at disease onset had a higher prevalence of pain, probably due to an age-dependent decrease of neuronal plasticity.

In addition to pain, depression was a relevant factor affecting the patients' well-being. Similar to NMOSD [12,40], clinically relevant depression occurred in 42% of the whole cohort and was significantly more prevalent in pain sufferers (60%). Vice versa, pain was more prevalent in patients with depression. Both conditions are known to intensify each other and can worsen independently from relapses enhanced by central mechanisms [41].

Although pain severity was one of the strongest predictors of low physical QoL, clinically relevant depression predicted reduced mental QoL. Our data support the need for adequate prevention and prompt treatment of severe MOGAD relapses [5,9], as physical impairment was directly associated with both depression and persistent—especially refractory neuropathic—pain. Of note, the relapse activity seems to also be associated with spasticity-associated pain.

We show the need of a systematic pain assessment in MOGAD, particularly as commonly used clinical assessment tools such as the EDSS do not cover pain. Moreover, our data indicate that pain is often undertreated or treated inadequately. In our cohort, patients with several pain medications still had higher pain intensity scores, highlighting the importance of a targeted specific and/or multimodal pain therapy.

## Limitations

The main limitation of our study is that information was based on a self-administered questionnaire without availability of clinical

interview and neurological examination. Therefore, we cannot provide a definite diagnosis of specific pain syndromes, and our results do not allow for pathophysiological conclusions. We also had no specific data on possible medication-associated pain syndromes (e.g., due to steroid-induced osteonecrosis). However, only three patients received steroids at the time of assessment, and none of them indicated having joint pain, corresponding to femoral head necrosis.

Only history of ON and myelitis were recorded, but no other possible syndromes (e.g., brainstem, cerebral). Therefore, our data on the respective type of previous attacks are incomplete. Moreover, we are aware that the questionnaire might be prone to selection bias, with patients suffering from pain having higher response rates. However, in three centers addressing 74% of the cohort, the response rate was over 75%. Last, our study remains explorative, as we could not perform an a priori sample size calculation and adjustments for multiple testing.

## CONCLUSIONS

Overall, we show that chronic pain and depression are substantial issues in MOGAD. Both conditions strongly reduce QoL and ADL, and are insufficiently controlled in clinical practice. Higher awareness of severely disabling neuropathic pain is of particular importance. Future research is needed to investigate precise underlying mechanisms and elaborate specific pain treatment strategies.

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## CONFLICT OF INTEREST

S.A. received travel grants from Celgene and speaker's honoraria from Roche and Bayer. E.H. reports no conflicts of interest. C.T. received honoraria for consultation and expert testimony from Biogen Idec/GmbH, Genzyme GmbH, Novartis Pharma GmbH, Merck, Chugai Pharma Germany GmbH, and Roche Pharma GmbH, none related to this work. M.W.H. reports no conflicts of interest. B.W. 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, Sanofi Genzyme; and personal fees from Bayer, Biogen, Roche, Teva, none related to this work. S.J. reports no conflicts of interest. M.R. received

speaker honoraria from Novartis, Bayer Vital GmbH, Roche, Alexion, and Ipsen, and travel reimbursement from Bayer Schering, Biogen Idec, Merz, Genzyme, Teva, Roche, and Merck, none related to this work. O.A. received personal fees from Alexion, Bayer Healthcare, Biogen, Celgene, Merck Serono, MedImmune, Novartis, Roche, Teva, and Zambon, none related to this work. M.P. received travel/accommodation/meeting reimbursement from Novartis. M.K. received travel grants from Merck Serono and Biogen. N.S. received travel funding from Sanofi-Aventis/Genzyme and speaker honoraria from Bayer AG. L.K. received compensation for serving on scientific advisory boards from Alexion, Janssen, Novartis, Merck Serono, Sanofi Genzyme, and Roche; speaker honoraria and travel support from Biogen, Novartis, Merck Serono, Sanofi Genzyme, Roche, and Teva; and research support from Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme). She receives research funding from the Deutsche Forschungsgemeinschaft, the German Ministry for Education and Research, the Interdisciplinary Center for Clinical Studies (IZKF) Muenster, and Innovative Medical Research Muenster. K.R. received research support from Novartis, Merck Serono, German Ministry of Education and Research, European Union (821283-2), Stiftung Charité (BIH Clinical Fellow Program), and Arthur Arnstein Foundation; speaker honoraria and travel grants from Bayer, Biogen Idec, Merck Serono, Sanofi-Aventis/Genzyme, Teva, Roche, Novartis, and the Guthy Jackson Charitable Foundation. J.B.-S. received travel grants and speaking honoraria from Bayer Healthcare, Biogen Idec, Merck Serono, Sanofi Genzyme, Teva, Roche, and Novartis, none related to this work. K.-D.W. reports no conflicts of interest. V.H. reports no conflict of interest. J.H. reports a grant for optical coherence tomography research from Friedrich-Baur-Stiftung and Merck; personal fees and nonfinancial support from Merck, Alexion, Novartis, Roche, Santhera, Biogen, Heidelberg Engineering, Sanofi Genzyme; and nonfinancial support of the Guthy-Jackson Charitable Foundation, none related to this work. A.G. reports no conflicts of interest. R.G. 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, none related to this work. F.P. serves as an academic editor for PLoS One, Associate Editor for *Neurology: Neuroimmunology and Neuroinflammation*; is a member of the Novartis OCTIMS study steering committee and MedImmune/Viela Bio steering committee; reports speaker honoraria and travel grants from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, Shire, Roche, Actelion, Celgene; and consultancies for Sanofi Genzyme, BiogenIdec, MedImmune, Shire, and Alexion; received research support from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Alexion, Merck Serono, German Research Council (DFG Exc 257), Werth Stiftung of the City of Cologne, German Ministry of Education and Research (BMBF Competence Network Multiple Sclerosis), Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program (combims.eu), Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis Society (USA). I.K. received speaker honoraria and travel funding from Alexion, Bayer, Biogen, Novartis, Merck, Sanofi Genzyme, 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; received research support from Chugai and Diamed. I.A. received travel grants from Biogen Idec and the Guthy-Jackson Charitable Foundation, served on scientific advisory boards for Roche and Alexion, and received research support from Diamed, none related to this work.

## AUTHOR CONTRIBUTIONS

**Susanna Asseyer:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing—original draft (equal); writing—review and editing (equal). **Eugenia Henke:** Data curation (equal); validation (equal); writing—review and editing (equal). **Corinna Trebst:** Data curation (equal); validation (equal); writing—review and editing (equal). **Martin Huemmert:** Investigation (equal); validation (equal); writing—review and editing (equal). **Brigitte Wildemann:** Investigation (equal); validation (equal); writing—review and editing (equal). **Sven Jarius:** Investigation (equal); validation (equal); writing—review and editing (equal). **Marius Ringelstein:** Investigation (equal); validation (equal); writing—review and editing (equal). **Orhan Aktas:** Investigation (equal); validation (equal); writing—review and editing (equal). **Marc Pawlitzki:** Investigation (equal); validation (equal); writing—review and editing (equal). **Melanie Korsen:** Investigation (equal); validation (equal); writing—review and editing (equal). **Luisa Klotz:** Investigation (equal); validation (equal); writing—review and editing (equal). **Nadja Siebert:** Investigation (equal); validation (equal); writing—review and editing (equal). **Klemens Ruprecht:** Investigation (equal); validation (equal); writing—review and editing (equal). **Judith Bellmann-Strobl:** Investigation (equal); validation (equal); writing—review and editing (equal). **Klaus-Dieter Wernecke:** Formal analysis (equal); methodology (equal); validation (equal); writing—review and editing (equal). **Vivien Haeussler:** Investigation (equal); validation (equal); writing—review and editing (equal). **Joachim Havla:** Investigation (equal); validation (equal); writing—review and editing (equal). **Anna Gahlen:** Investigation (equal); validation (equal); writing—review and editing (equal). **Ralf Gold:** Investigation (equal); validation (equal); writing—review and editing (equal). **Friedemann Paul:** Supervision (equal); validation (equal); writing—review and editing (equal). **Ingo Kleiter:** Conceptualization (equal); data curation (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal); writing—original draft (equal); writing—review and editing (equal). **Ilya Ayzenberg:** Conceptualization (equal); data curation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); validation (equal); writing—original draft (equal); writing—review and editing (equal).

## ETHICAL APPROVAL

Ethical approval was obtained from the institutional review board of Ruhr University Bochum (#15-5534) and of the participating centers. Patients provided written informed consent. The study was performed according to International Conference on Harmonization/Good Clinical Practice and current German legal requirements.

## DATA AVAILABILITY STATEMENT

Data are available upon reasonable request from any qualified investigator within 5 years after publication.

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## APPENDIX 1

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