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Characterization of pain syndromes in patients with neuromyelitis optica

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Abstract

Background: Pain is common and refractory in spinal cord injury (SCI). Currently, most studies evaluated pain in male-predominant traumatic-SCI. Also, concomitant secondary pain syndromes and its temporal evolution were seldom reported.

Methods: We aimed to prospectively describe the main and secondary pain and its associated factors in inflammatory-SCI evaluating neuromyelitis optica (NMO) patients. In-remission NMO patients underwent neurological, imaging and autoantibody evaluations. Questionnaires detailing main and secondary pains, functional state, mood, catastrophizing, quality of life (QoL) and "non-motor symptoms" were used at two time points.

Results: Pain was present in 53 (73.6%) of the 72 patients included. At-level neuropathic pain was the most common main pain syndrome, affecting 32 subjects (60.4% of those with pain). Over 70% (n = 38) of this cohort reported two pain syndromes. Those without pain were significantly younger (26.1 ± 12.7 y.o. in those without pain and 40.1 ± 12.5, 37.2 ± 11.4 y.o. in those whose main pain was neuropathic and non-neuropathic, respectively, p = .001), and no differences in the inflammatory status were observed between groups. On follow-up, one-fifth (n = 11) had a different main pain syndrome from the first visit. Pain impacted QoL as much as disability and motor strength.

Conclusion: Pain is a prevalent and disabling non-motor symptom in NMO-SCI. Most patients experience more than one pain syndrome which can change in time even in the absence of clinical relapse. Age of the inflammatory-SCI was a major determinant of pain. Acknowledging temporal changes and multiplicity of pain syndromes in NMO-SCI may give insights into more precise designs of clinical trials and general management of pain in SCI.

Significance: In this longitudinal study with NMO-related SCI, pain affected almost three-quarters of patients with NMO. Over 70% have more than one pain syndrome and at-level neuropathic pain is the most common type of pain syndrome. Patients without pain were significantly younger but had the same burden of inflammatory lesions than those with pain. During follow-up, up to one fifth of patients presented with changes in the main pain syndromes, which can occur even in the absence of

clinical activity of the inflammatory disease. In this cohort, Pain affected quality of life as much as disability or motor strength.

1 | INTRODUCTION

Central neuropathic pain is defined as pain caused by a lesion or disease of the central somatosensory nervous system (Finnerup, Haroutounian, et al., 2016; Treede et al., 2019). It is a common condition after a spinal cord injury (SCI), affecting more than half of patients with SCI-related chronic pain (Siddall, McClelland, Rutkowski, & Cousins, 2003). Neuropathic pain in SCI is divided into "at-level," placed anywhere between the dermatome of the neurological level of injury (NLI) and three dermatomes below this level; and "below-level" located caudally to three dermatomes below the NLI (Bryce et al., 2011). Typically, patients with SCI present with more than one pain syndrome (i.e. one nociceptive and one neuropathic pain) with different pathophysiological mechanisms (Finnerup & Baastrup, 2012) and pain can impair quality of life to a greater extent than motor deficits (Rintala, Loubser, Castro, Hart, & Fuhrer, 1998; Widerström-Noga, Felipe-Cuervo, & Yezierski, 2001). Despite the recent research advances in SCI-related pain, its management has proved challenging and marked by absent or low analgesic effect treatments (Galhardoni et al., 2019). Part of this therapeutic failure is secondary to a paucity of human models to investigate the mechanisms of pain in SCI patients. To date, most studies provided cross-sectional information on pain characteristics in SCI patients, which fails to capture clinically relevant temporal changes in pain in these patients (Finnerup, Jensen, et al., 2016; Finnerup et al., 2014; Mordillo-Mateos et al., 2019; Richardson, Samaranayaka, Sullivan, & Derrett, 2019; Siddall et al., 2003; Zeilig, Enosh, Rubin-Asher, Lehr, & Defrin, 2012). Additionally, most studies were performed in traumatic SCI, a specific aetiology of SCI, with a massive male preponderance.

Neuromyelitis optica (NMO) is a severe autoimmune inflammatory and demyelinating disease of the central nervous system (Wingerchuk et al., 2015), associated with anti-aquaporin 4 autoantibody (AQP4-Ab) in 70%–75% of patients, with anti-myelin oligodendrocyte (MOG) antibody positive in around 10%, while 15% of cases are negative to both (Akaishi, Nakashima, Sato, Takahashi, and Fujihara (2017); Asgari, 2013; Chen et al., 2018; de Seze, 2019; Fabis-Pedrini et al., 2018; Flanagan et al., 2016; Jarius et al., 2016; Kitley et al., 2014; Kitley et al., 2012; Sepulveda et al., 2018; Weinshenker & Wingerchuk, 2017). The typical clinical presentation of NMO includes severe episodes of a painful optic neuritis (ON), causing significant visual loss; longitudinally extensive transverse myelitis (LETM), leading to symmetric paraparesis or quadriparesis, sensory loss, bladder dysfunction and occasionally brainstem lesions which are known to cause intractable nausea, vomiting and hiccups. It has a relapsing course in most cases. The term Neuromyelitis optica spectrum disorders (NMOSD) was introduced to encompass limited forms of NMO which included subjects with either LETM or ON and AQP4-Ab-seropositivity, those with encephalic lesions and subjects with coexisting autoimmune disorders (Wingerchuk et al., 2015; Wingerchuk, Lennon, Lucchinetti, Pittock, & Weinshenker, 2007). Pain is one of the most frequent symptoms and is known to affect up to 85% of subjects with NMO (Kanamori et al., 2011; Kim, Go, Sung, Park, & Lee, 2012; Muto et al., 2015; Qian et al., 2012). Unlike traumatic-SCI, NMO affects predominantly women.

With the present study, we performed the first prospective study in a cohort of patients with inactive NMO-related spinal cord lesions in order to describe the quality and temporal profile of pain syndromes in inflammatory SCI, considering both the patients' primary and secondary pains.

2 | METHODS

The study was performed at the Hospital das Clínicas of the University of São Paulo, from July 2013 to August 2015. Our Ethics Review Board approved the protocol, and all patients provided written informed consent before inclusion in the study (#690.455).

2.1 | Patients

Patients with suspected neuromyelitis optica spectrum disorder (NMOSD) from our institution's neuroimmunology outpatient clinic and partner hospitals were consecutively assessed for eligibility in the study. The diagnosis of myelitis was confirmed by a neuroinflammatory diseases specialist using the revised diagnostic criteria for neuromyelitis optica (Wingerchuk, Lennon, Pittock, Lucchinetti, & Weinshenker, 2006). We only included patients who were in remission of their inflammatory disease. Patients with relapses of transverse myelitis within 12 months preceding screening were excluded. Transverse myelitis relapse was defined as the acute onset of a neurological deficit (with motor, sensory or bladder involvement) attributed to an inflammatory lesion visualised in the spinal cord MRI. Other exclusion criteria included: extensive previous or current encephalic lesions, undetermined diagnosis of transverse myelitis, inability to answer questions because of difficulty with verbal and written communication, presence of functional impairment secondary

to cognitive decline or known major psychiatric illness. Prior to study enrolment, all patients included were in regular follow-up with the neuroinflammatory diseases specialist, which includes regular assessment of the cognitive function via screening during the consultation and neuropsychological assessment if any alteration of the Brazilian Version of the "Mini Mental State Examination" (MMSE) was detected (Bertolucci et al., 1994; Brucki, Nitrini, Caramelli, Bertolucci, & Okamoto, 2003; Folstein, Folstein, & McHugh, 1975). Likewise, psychiatric comorbidities were assessed during the regular follow-up consultation with the attending physician and referred to psychiatric evaluation if deemed necessary.

2.2 | Study design

The study was a prospective observational study, consisting of a first-entry visit in-person assessment (cross-sectional) and a second visit (follow-up), 6 to 18 months after the entry visit (longitudinal; Figure 1). Motor and non-motor function were systematically assessed in patients with NMO, including pain, sensory thresholds, disability, catastrophizing, anxiety, depression and quality of life. Patients were questioned regarding the presence or absence of chronic pain (pain present more than 50% of the time in the last three months; Treede et al., 2019). Patients with pain were further classified as having "neuropathic pain" or "non-neuropathic" pain, according to their main pain syndrome, as evaluated by a neurologist with further training in pain assessment and treatment. Pain syndromes were defined according to the International Association for the Study of Pain (IASP) criteria for neuropathic pain (Cruccu et al., 2010; Finnerup, Haroutounian, et al., 2016; Haanpaa et al., 2011; Treede et al., 2008), which is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" and neuropathic pain was considered when the grading system provided the diagnosis of "definite" neuropathic pain. This division was adopted as the presence of neuropathic and non-neuropathic pain derive from different mechanisms associated with chronic pain, and we aimed to study this distinction further. Central neuropathic pain was classified according to the neurological level of injury (NLI), and subdivided into "at-level" (which is located anywhere between the dermatome of the NLI and/or within the three dermatomes below this level), "below-level" (more than three dermatomes below the dermatome of the NLI) and "above-level" (above the dermatome of the NLI; Bryce et al., 2012a; Bryce et al., 2012b; Finnerup, 2013; Finnerup & Jensen, 2004). The sensory level (defined as the most caudal spinal cord dermatome with a normal pinprick, thermal and touch sensation) was also used for this division.

All information collected was systematically recorded in a dedicated record file. Patients with pain were offered free perpetual clinical follow-up with a pain specialist and both pharmacological and non-pharmacological pain treatment at this study's Institution. Those who accepted the referral were assisted at the spinal cord outpatient's clinic and had their pain drugs adjusted according to first-, second- and third-line medications described in the last consensus for the treatment of neuropathic pain (Finnerup et al., 2015). As this was a solely observational and not interventional study we only collected data regarding possible modifications and adjustments made in pain drugs and its dosage between the first and second evaluation.

2.2.1 | First visit (study entry) evaluation

Clinical assessment was performed during a routine medical visit to our outpatients' clinic. All patients underwent a full standardized neurological examination by a pain specialist, in order to determine the pain syndrome according to its mechanism and level (Bryce et al., 2011; Hulsebosch, Hains, Crown, & Carlton, 2009). All participants were assessed by the same researcher (FV), the syndromic pain diagnosis and NMOSD characteristics of every patient's case was presented in pre-planned meetings with a NMOSD and a pain specialist (SLAP and DCA, respectively) during data collection for confirmation purposes (total of five meetings). Subjects were questioned regarding all the pain syndromes they had and asked to classify it as their main and

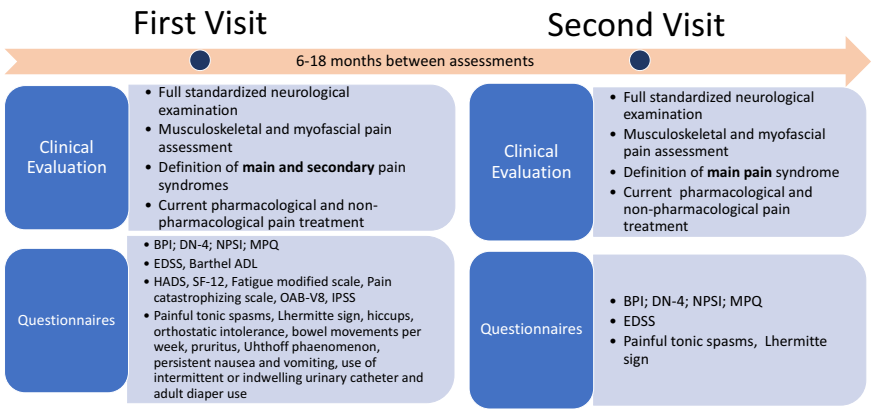

FIGURE 1 Summary of patient's evaluation on the first (study entry) and second visits. Barthel ADL, Barthel activity of daily life score; BPI, brief pain inventory; DN-4, Douleur neuropathique- 4; EDSS, expanded disability status scale; HADS, hospital anxiety and depression scale; IPSS, international prostatic symptoms score; MPQ, Short-form McGill pain questionnaire; NPSI, neuropathic pain symptom inventory; OAB-V8, overactive bladder 8-item questionnaire

secondary pain syndromes, according to their severity or impact in their lives. If more than one pain syndrome was present, both were assessed. They were requested to fill in questionnaires directed to their main pain syndrome, unless otherwise specified. They evaluated pain (brief pain inventory [BPI], neuropathic pain symptoms inventory [NPSI], *Douleur Neuropathique-4* [DN-4], Short-form McGill pain questionnaire [MPQ]), painful tonic spasms, and presence of Lhermitte sign, hiccups, orthostatic intolerance, persistent nausea, pruritus, Uhthoff phenomenon, quality of life (SF-12 health survey), disability (expanded disability status scale [EDSS], Barthel activities of daily life), fatigue (modified fatigue scale), anxiety and depression (hospital anxiety and depression scale [HADS]), catastrophizing thoughts scale (PCTS), urinary (overactive bladder 8 item [OAB-V8] and international prostatic symptoms score [IPSS]) and faecal dysfunction were also assessed.

2.2.2 | Second visit (follow-up) assessment

All subjects were invited to return to the hospital for a second evaluation 6 to 18 months after the first visit. A new clinical evaluation was performed in which pain (BPI, NPSI, DN-4, MPQ) and disability (EDSS) scales were filled in order to characterize changes in the pain syndromes. Data regarding activity of the inflammatory disease, pharmacological and non-pharmacological pain treatment was recorded. Those who could not return to the hospital were questioned via telephone or postal contact.

2.3 | Pain history and sociodemographic assessment

The sociodemographic assessment included questions about their current age, age of first and last relapse, self-declared sex, educational level, current marital status, presence of a partner, religion, current and previous use of alcohol, tobacco and illicit drugs, employment status and both individual and familiar income. Their pain characteristics, history, duration, quality, magnitude, localization and temporal relation to the inflammatory disease were assessed. All medications in use had their names and dosage registered. Analgesic and psychotropic drugs and doses were also detailed according to the brief pain inventory and the third version of the medication quantification scale (MQS-III; Harden et al., 2005).

2.4 | Inflammatory disease, imaging and functional status

Data regarding subjects' inflammatory auto-immune disease was collected from their electronic and paper notes, including onset symptoms, the number of relapses, treatment for the acute and chronic phase, lesion type and time elapsed since the last relapse. We assessed patients' functional status according to the Kurtzke EDSS (Kurtzke, 1983). We systematically reviewed spinal cord MRIs during the acute (the one closest to the last relapse) and chronic (the control image after at least six months of their last relapse) phases. We recorded the number of vertebral segments affected, type and site of lesions. Data regarding lesions with gadolinium-enhancement of lesions, presence of atrophy, lesion topography in the axial view and tumefaction was also documented. Previous and the most recent brain MRIs were both assessed to exclude prior cortical extensive lesions. The acute phase brain MRI was reviewed in order to assess the following aspects: diencephalic lesions surrounding the third ventricles and cerebral aqueduct, periependymal lesions surrounding the lateral ventricles, dorsal brainstem lesions adjacent to the fourth ventricle, corpus callosum, cerebellum and subcortical or deep white matter lesions. Extensive cortical lesions included those defined as “extensive and confluent hemispheric lesions with increased diffusivity on ADC map,” and “tumefactive hemispheric white matter lesions" (Kim et al., 2010, 2015). All the images were initially assessed by the radiology team from our institution who was blinded to clinical outcomes related to pain and functional status. Upon study entry, one of the authors reassessed those images to provide a deeper evaluation from a senior neuro radiologist with extensive experience in demyelinating diseases (LTL). They had no other role in data collection and were unaware of the pain status of patients.

2.5 | Serological evaluation

Samples were analysed for the presence of MOG- IgG and AQP4-IgG using in-house cell-based assays (CBAs) in live HEK-293 cells (Akaishi et al., 2016; Sato et al., 2013, 2014). Patients had their blood collected via peripheral venous puncture during a regular visit to the neuroimmunology outpatients clinic, and after centrifugation, the serum was stored at −80°C. Afterwards, the samples were analysed at Tohoku University, Sendai, Japan (further details provided as a Supplementary Material).

2.6 | General neurological evaluation

We performed a clinical evaluation and structured physical and neurological examination in all patients. It included (further details provided as a Supplementary Material):

a. Motor strength evaluation: given by a sum score of four muscles for each side of the body, distal and proximal

in upper and lower limbs. Score range: 0–40. Higher scores denote a better function.

b. Myotatic reflexes score: sum score of two reflexes in the upper limbs and two reflexes in the lower limbs using a Babinski percussion hammer (©2014 GF Health Products, Inc.; Hallett, 1993). Score range 0–32.
c. Deep mechanical hyperalgesia: evaluated in the muscle groups more frequently affected by myofascial pain syndrome (MPS; Teixeira, Figueró, Yeng, & Ciampi de Andrade, 2018). Trigger points (TP) were assessed with circa 4 kg/cm^2 of pressure, using the thumb (just enough to blanch the examiner's thumb; Moisset & Ciampi de Andrade, 2017; Okifuji, Turk, Sinclair, Starz, & Marcus, 1997). Trigger points were deemed active (meaning that the pain referred by the patient was myofascial in origin) if the patient reported similarity of at least 50% of his or her current pain complaint with the pain evoked by pressure on the tender nodule. Trigger points were deemed latent if the patient described pain upon pressure on the tender nodule, but it was not similar to their current pain depiction. We also evaluated the presence of deep mechanical hyperalgesia in twelve pre-established limb and axial muscle groups (Cury et al., 2014) using a pressure algometer (Pain Diagnostics & Thermograph Inc®). and the onset of pain was determined as the pressure pain threshold (PPT) by providing a continuously increasingly pressure at 0.3 kgf/cm^2/s (Ge, Madeleine, & Arendt-Nielsen, 2004), measured bilaterally (up to a maximum of 10 kgf/cm^2). Subsequently, in a new measurement, constant pressure was delivered to each point at 2 kgf/cm^2 above the measured PPT for three seconds to evoke pain and subjects rated their pain using a 100 mm visual analogue scale (0 = no pain; 100 = maximal pain imaginable). Measurements were taken bilaterally per muscular group and calculated as the average of both sides per muscular group (Rosier, Iadarola, & Coghill, 2002).
d. Sensory level: was defined using a safety pin, and light touch stimulus (Bryce et al., 2011).
e. Tactile touch sensitivity: using von Frey monofilament of 10 g (68.3 g/mm^2). The light touch sum score of three sites in the upper limbs and three sites in the lower limbs. It was scored from 0 to 3:0- no sensation, 1- diminished sensation, 2-normal sensation, 3- increased sensation. Score range: 0–36.
f. Mechanical nociceptive perception: using a safety pin. The pinprick sum score of three sites was calculated for the upper limbs and three sites in the lower limbs. Its score and range are the same of the "Tactile touch sensitivity."
g. Thermal sensitivity to non-painful cold: using the contact of the metal tuning fork at room temperature (23°C–25°C; Campbell, 2005). The thermal sum score of three sites in the upper limbs and three sites in the lower limbs. Its score and range are the same of the "Tactile touch sensitivity."
h. Proprioception: with the evaluation of vibration threshold of three sites in the upper limbs and three sites in the lower limbs. Average bilateral value is presented for upper limbs, lower limbs and all limbs. We used a Ryedel-Seiffer tuning fork of 128 Hz. Score 0–8, higher scores denote a better discriminative function. Limb kinaesthesia was evaluated in the extremities upper and lower limbs and classified as normal or abnormal.
i. Spasticity: assessed with the modified Ashworth spasticity scale (AS) and the sum of scores for each limb (upper and lower) provided a spasticity score (summed) for the upper, lower and four limbs. Score 0–20. Higher values indicate more severe spasticity (Katz, Rovai, Brait, & Rymer, 1992).
j. Abnormal sensory phenomena: the presence of hyperpathia, allodynia (to cold, brush and pressure), dysaesthesia was evaluated, and the number of dermatomes affected bilaterally was recorded. (Merskey, 1994). We have searched for hyperpathia using "suprathreshold repetitive punctate stimulation at 2 Hz for up to 60 s," as defined by Helme, Finnerup, and Jensen, (2018).We created a score that reflects the number of right and left dermatomes affected (Ducreux, Attal, Parker, & Bouhassira, 2006).
k. Visual acuity in both eyes: was assessed with the use of Rosenbaum visual acuity card. If it was not possible, we recorded whether patients could count the examiner's digits, perceive hands movement, perceive light, or if they could not see even light. Patients were requested to use their best corrective lens.
l. Direct Ophthalmoscopy: the optic nerve was classified as normal or atrophic.

2.7 | Questionnaires

2.7.1 | Pain questionnaires

The following questionnaires were used for pain assessment in all patients:

a. McGill pain questionnaire (MPQ) short-form (Ferreira, de Andrade, & Teixeira, 2013; Melzack, 1987): subdivided in sensory, affective and evaluative dimensions. Total score 0–15.
b. Brief pain inventory (BPI) short-form, subdivided in BPI Intensity BPI Interference. Score 0–10 (Daut, Cleeland, & Flanery, 1983; Ferreira, Teixeira, Mendonza, & Cleeland, 2011).
c. *Douleur Neuropathique*-4 Questionnaire (DN-4; Bouhassira et al., 2004; Santos et al., 2010): positive for scores ≥4. Score 0–10.

d. Pain catastrophising thoughts scale (PCTS): translated and validated to Portuguese (Flor, Behle, & Birbaumer, 1993; Sardá Junior et al., 2008; Sullivan, Bishop, & Pivik, 1995), further divided in rumination and helplessness subscores. Score 0–5 for each subscore and standardized in the same range for the total score.
e. Neuropathic pain symptom inventory (NPSI; de Andrade et al., 2011; Bouhassira et al., 2004): total score and the following subscores: continuous ongoing deep pain, continuous ongoing superficial pain, evoked pain, paroxysmal pain, paraesthesia/dysaesthesia. Total score 0–100.
f. Presence of painful tonic spasms and Lhermitte sign: patients were questioned regarding their current and past occurrence, and the Lhermitte sign was assessed during clinical assessment.

2.7.2 | Quality of life and disability assessment

a. SF-12 Health survey (Jenkinson et al., 1997; Ware, Kosinski, & Keller, 1996): 12-item questionnaire whose results are subdivided in physical (PCS) and mental (MCS) health composite scores. Score 0–100 for each composite score. Non-commercial license agreement obtained from Optuminsight Life Sciences, Inc. License number QM038812.
b. Barthel activities of daily living index (Barthel ADL; Anderson et al., 2008; Mahoney & Barthel, 1965): measures functional independence and mobility in activities of daily life. Score 0–100.
c. Expanded disability questionnaire scale (EDSS; Kurtzke, 1983): the composite score is given by multiple systems dysfunction. Higher values translate into a more significant burden of the disease.

2.7.3 | "Non-motor" symptoms assessments

By "non-motor" symptoms, we refer to symptoms present in this population but not usually described as part of its classical symptoms related to ON, TM and typical brainstem lesions.

a. Modified fatigue impact scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989; Mendes, Moreira, Tilbery, & Felipe, 1998): 9-item questionnaire. Higher values denote greater impairment of activities of daily life by fatigue. Score 7–63.
b. Overactive Bladder V8 score (OAB-V8; Acquadro et al., 2006): score ≥8 suggests overactive bladder. Score 0–42.
c. International prostate symptom score (IPSS; Barry et al., 1992): evaluates obstructive urinary symptoms. Score 0–35.
d. Hospital anxiety and depression scale (HADS; Botega, Bio, Zomignani, Garcia, & Pereira, 1995; Zigmond & Snaith, 1983): cut-off of 8 for anxiety and depression. Total score 0–42.

We inquired about the presence of hiccups, pruritus, Uhthoff phaenomenon (transient neurologic deficit related to increased body temperature), orthostatic intolerance, persistent nausea and vomiting, use of an intermittent or indwelling urinary catheter and adult diaper use. We assessed the presence of Uhthoff phaenomenon and asked patients to grade it in an 11-point Likert scale (0–11) of ascending intensity. We also scrutinized subjects' report of pruritus: localization (above, at or below sensitive level, in or out of the pain area and scalp area) and intensity (11-point Likert scale of increasing intensity). Patients were asked to report the number of average bowel movements per week, in order to assess faecal dysfunction and divided in those with chronic constipation (≤3 bowel movements/week; Bharucha, Dorn, Lembo, & Pressman, 2013), normal intestinal function and chronic incontinence (Paquette, Varma, Kaiser, Steele, & Rafferty, 2015).

2.8 | Statistical analyses

Results were expressed as the average ± standard deviation (minimum-maximum values). Descriptive statistics were used in the clinical characterization of the sample; χ^2 test was used to assess the associations between dichotomous variables, with a Bonferroni correction for post hoc analysis. The variables were assessed for normality using the Shapiro–Wilk normality test and after inspection of the values of kurtosis and skewness. Continuous variables with a normal distribution were analysed using a *t* test or one-way ANOVA with post hoc analysis using Tukey HSD procedure. Non-normal distributions implied the use of the Wilcoxon signed-rank test or Kruskal–Wallis test. Post hoc analysis of Kruskal–Wallis tests were performed using Dunn's procedure with Bonferroni correction. Spearman coefficients and multiple regression were used to assess the correlation between the continuous variables, aiming to understand the correlation between pain scores and other "non-motor" and motor symptoms. We also explored how those scores predicted the quality of life score in its physical component (SF12-PCS). For the model, the assumptions of normality of residuals, linearity and homoscedasticity were confirmed. Multicollinearity was rejected. The level of statistical significance was set at $p < .05$. All statistical calculations were performed using the software Statistical Package for the Social Sciences (SPSS, version 20.0.0; SPSS Inc.).

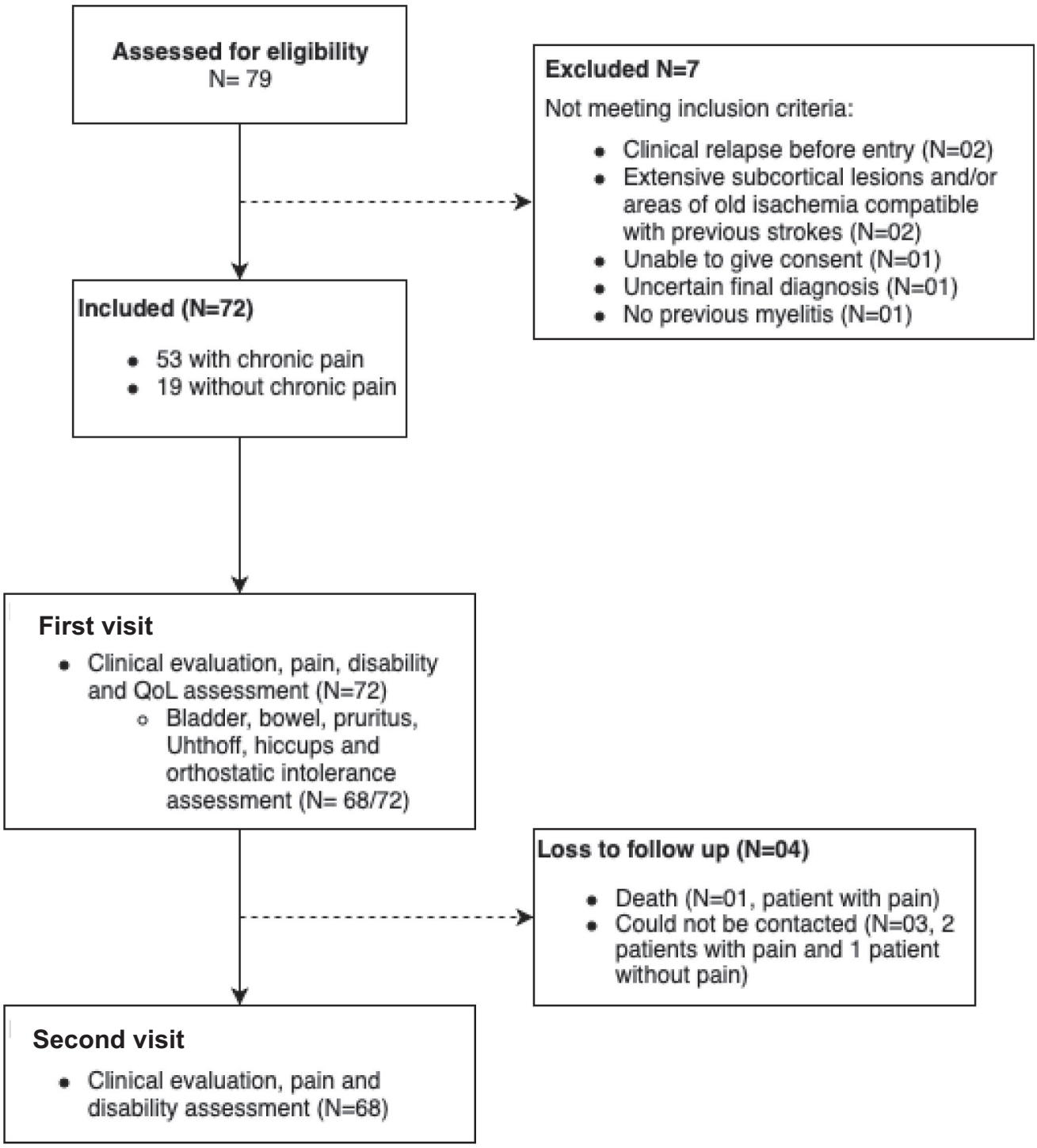

FIGURE 2 Strobe flowchart diagram. QoL, quality of life

3 | RESULTS

3.1 | First visit (study entry) evaluation

3.1.1 | Patients

Amongst the 79 patients initially assessed to be enrolled in the study, 72 were included (Figure 2). All patients were previously evaluated by the neuroinflammatory and demyelinating diseases unit in order to have the diagnosis of their myelitis established. We identified 53 (73.6%) patients with and 19 (26.3%) without chronic pain. Patients with chronic pain were subdivided according to the underlying main pain syndrome: 40 (55.6%) in neuropathic pain and 13 (18.1%) in non-neuropathic pain subgroups. Among those 53 subjects with chronic pain, 38 (71.7%) had more than one pain

syndrome. Women accounted for over 60% of patients in all groups, comprising 70.8% of the whole sample (Table S1- supplementary file).

Importantly, both groups of chronic pain patients were substantially older at the time of the assessment and had their first and last relapses at an older age when compared to those without pain. Mean age of disease onset was 40.1 ± 12.5 and 37.2 ± 11.4 y.o. in those whose main pain was neuropathic and non-neuropathic, respectively, compared to 26.1 ± 12.7 y.o. in those without pain ($p = .001$). Mean age of the last relapse followed the same trend: 43.3 ± 10.8, 41.2 ± 9.2, 27.6 ± 12.4 y.o. in those with neuropathic pain, non-neuropathic pain as their main pain syndromes and in those without any pain, respectively ($p < .001$). Notably, the time elapsed between disease onset and between the last relapse until study entry was not different between the three groups, neither was the number of relapses (Table S2- supplementary file).

3.1.2 | Inflammatory and imaging features

Patients of the three groups did not differ in inflammatory biomarkers of the disease as measured by clinical measurements of disease activity, laboratory findings and characteristics of their central nervous system MRI (spinal cord during the acute and chronic phase and brain MRI during the acute phase). Autoantibody status (anti-aquaporin-4 and anti-MOG antibodies), clinical presentation at the onset, number of relapses, current and acute phase immunosuppressant treatment was not statistically significant between those with neuropathic, non-neuropathic and no pain. Disability, as measured by the EDSS, was also similar between all the three groups (Table S2- supplementary file).

The number of vertebral segments affected by inflammatory lesions in the spinal cord during the acute phase and for a long-term follow-up MRI was also similar between the three groups and the analysis showed a decrease of affected segments during the chronic phase compared to the acute MRI in all groups (Tables S3 and S4- supplementary file). Subjects did not differ in the characteristics of the Brain MRI as well. No patient presented with large supratentorial brain lesions (Table S5- supplementary file).

3.1.3 | Neurological examination

All patients underwent a standardized neurological examination (Table 1): there were no differences in the motor strength, myotatic reflex, Ashworth spasticity, light touch, pinprick and thermal sensibility scores regardless of the presence of pain. The group with neuropathic pain showed the most affected vibration thresholds compared to the others. Analysis of deep mechanical hyperalgesia showed statistically significant differences between groups in the frequencies of active trigger points of quadratus lumborum and gluteus medius muscles, determined mostly by a higher prevalence among patients with non-neuropathic pain: 38.5%(5) had active trigger points in the quadratus lumborum and 30.8% (4) in the gluteus medius, compared to 10% (4) and 7.5% (3), respectively, for those with neuropathic as main pain ($p = .006$ and .017, respectively). None of those without pain had active trigger points in those muscles. Besides, those whose main pain was non-neuropathic presented with statistically significant lower PPT for the gluteus medius when compared to those with neuropathic pain and no pain (4.0 ± 1.5 for the non-neuropathic pain group and 6.2 ± 5.1 and 5.4 ± 2.9 for those with neuropathic pain and no pain, respectively, $p = .038$; Table S6- supplementary file).

3.1.4 | Abnormal sensory phaenomena

Only patients with neuropathic as their main pain syndrome were affected by mechanical dynamic allodynia (i.e. to brush), which was present in 27.5% ($n = 11$). Allodynia to brush was found in one patient without pain (5.3%) and in none of those with non-neuropathic pain. At-level hyperpathia affected more than half of patients in all groups, but in a significantly higher proportion of those with neuropathic pain: 39 (97.5%), versus 10 (76.9%) and 12 (68.4%) in the non-neuropathic pain and no pain groups ($p = .013$; Table 2).

Painful tonic spasms affected 14 (35%), 2 (15.4%) and 2 (10.5%) patients in the neuropathic pain, non-neuropathic pain and no pain groups, respectively ($p = .104$).

3.1.5 | Characteristics of the primary and secondary pain syndromes

Chronic pain was observed in 53 (73.6%) patients during the first evaluation, and 38 (71.7%) of them had more than one pain syndrome. Neuropathic pain at the sensory level ("at-level") was the most prevalent main pain syndrome, being observed in 32 patients (80% of those with neuropathic pain and in 59.3% of the total of patients with pain). Among those with non-neuropathic pain as their main pain, low back pain was the most common, affecting 8 (61.5%) subjects. As a secondary pain syndrome, low back pain affected 11 (27.5%) of those patients with a neuropathic pain as a main syndrome, whereas distal lower extremities neuropathic pain was the most prevalent secondary pain in those who had a non-neuropathic pain as their primary pain syndrome, affecting 4 (30.4%) of them (Figure 3a). Migraine affected 5

TABLE 1 Summary of neurological examination performed in all patients

	Neuropathic pain	Non-neuropathic pain	No pain	*p*
Sensory level, *n* (%)				.180
Cervical	22 (55)	4 (30.8)	12 (63.2)	
Thoracic	18 (45)	9 (69.2)	7 (36.8)	
Motor total score, mean ± *SD* (min-max) (0–40)	31.3 ± 4.7 (20–37)	33.6 ± 3.3 (26–37)	30.7 ± 5.6 (16–38)	.094
Upper limbs (0–20)	17.7 ± 2.1 (13–20)	18.7 ± 1.7 (16–20)	17.3 ± 2.5 (10–20)	.264
Lower limbs (0–20)	13.6 ± 4.3 (0–17)	14.9 ± 2.1 (10–17)	13.4 ± 5.6 (0–18)	.459
Myotatic reflex scale total score, mean ± *SD* (min-max) (0–32)	23 ± 7.5 (4–32)	24.1 ± 8.3 (8–32)	22.1 ± 7.8 (1–32)	.719
Upper limbs (0–16)	9.9 ± 4.7 (0–16)	11.8 ± 3.8 (4–16)	9.1 ± 4.8 (1–16)	.302
Lower limbs (0–16)	13.2 ± 4.4 (0–16)	12.2 ± 5.2 (2–16)	12.9 ± 4.7 (0–16)	.849
Ashworth Spasticity total score, mean ± *SD* (min-max) (0–20)	3.5 ± 2.2 (0–8)	2.6 ± 2.2 (0–6)	2.4 ± 2.4 (0–8)	.100
Upper limbs (0–10)	0.08 ± 0.3 (0–1)	0.08 ± 0.3 (0–1)	0.16 ± 0.5 (0–2)	.977
Lower limbs (0–10)	3.4 ± 2.1 (0–8)	2.5 ± 2 (0–6)	2.2 ± 2.2 (0–6)	.098
Light touch total score, mean ± *SD* (min-max) (0–36)	14.3 ± 3.7 (6–24)	15.8 ± 4.6 (8–24)	15.4 ± 3.8 (7–24)	.468
Upper limbs (0–18)	9 ± 2.7 (5–12)	9.9 ± 2.7 (6–12)	9.8 ± 2.4 (6–12)	.458
Lower limbs (0–18)	5.7 ± 3.1 (0–14)	5.9 ± 2.7 (0–12)	5.6 ± 3 (0–12)	.832
Pinprick total score, mean ± *SD* (min-max) (0–36)	16.5 ± 7.7 (0–33)	18.2 ± 4 (12–24)	17.6 ± 6.6 (6–30)	.478
Upper limbs (0–18)	8.6 ± 3.5 (0–15)	11.1 ± 3 (6–18)	9.9 ± 2.5 (6–12)	.156
Lower limbs (0–18)	8 ± 6.2 (0–18)	8.2 ± 4.3 (0–18)	7.4 ± 5.4 (0–18)	.813
Thermal sensibility total score, mean ± *SD* (min-max) (0–36)	12.3 ± 4.2 (3–19)	14.4 ± 6 (6–26)	14.3 ± 5.3 (6–24)	.237
Upper limbs (0–18)	8.9 ± 3.1 (3–13)	8.9 ± 3.7 (2–12)	8.7 ± 2.9 (3–12)	.931
Lower limbs (0–18)	3.6 ± 2.7 (0–7)	5.5 ± 3.7 (0–14)	5.6 ± 4.1 (0–12)	.15
Vibration threshold, mean ± *SD* (min-max) (0–8)	5.3 ± 1.4 (1.5–7.5)	6 ± 0.7 (4.6–6.9)	6.2 ± 1.2 (4–7.8)	**.044**[a]
Upper limbs (0–8)	7.1 ± 1.1 (3–8)	7.2 ± 0.6 (5.8–7.7)	7.5 ± 0.6 (6.5–8)	.236
Lower limbs (0–8)	3.5 ± 2.1 (0–7)	4.8 ± 1.5 (1.7–6.7)	4.9 ± 2.4 (0–7.5)	**.039**[b]
Limb kinaesthesia impairment, *n* (%)				
Distal interphalangeal joint of the index finger	3 (7.5)	1 (7.7)	0	.501
Hallux	17 (42.5)	3 (23.1)	6 (31.6)	.424

Note: Values are presented as mean ± standard deviation (minimum-maximum), except for the frequency of Limb kinaesthesia impairment which is presented as number of patients (*n*) and its percentage within groups (%), as indicated. Patients are divided as neuropathic and non-neuropathic pain groups according to their main pain syndrome. Score range is given for each questionnaire item or subitem. Only Pinprick and Thermal sensibility total score were analysed using one-way ANOVA. The remainder of the parameters were analysed using Kruskal–Wallis test with pairwise comparisons using Dunn's procedure with a Bonferroni correction for multiple comparisons. Post-hoc analysis: [a]Neuropathic pain versus no pain $p = .051$; Non-neuropathic pain versus no pain $p = 1.000$; Neuropathic pain versus Non-neuropathic pain $p = .563$. [b]Neuropathic pain versus no pain $p = .03$; Non-neuropathic pain versus no pain $p = 1.000$; Neuropathic pain versus non-neuropathic pain $p = .20$. Significance $p < .05$. A $p < .05$ was marked in bold numbers.

individuals (6.9%), but only one person reported it as its main pain syndrome.

Main pain intensity, measured by the BPI, was similar in those whose main pain was neuropathic pain and non-neuropathic pain (5.7 ± 1.9 and 5.1 ± 1.3, respectively, $p = .338$). DN-4 questionnaire was positive for neuropathic pain in 38 (95%) of those who met IASP criteria for this condition and in 7 (53.8%) of those who did not, showing a high sensibility of 95% but a low specificity of 46.2% (Table 3). As expected, patients whose main pain was neuropathic had a significantly higher

TABLE 2 Characterization of abnormal sensory phenomena amongst the three different groups

	Neuropathic pain	Non-neuropathic pain	No pain	*p*
Abnormal sensory phaenomena, *N* (%)				
Hyperpathia	39 (97.5)	12 (92.3)	14 (73.7)	**.015**[a]
At level	39 (97.5)	10 (76.9)	12 (68.4)	**.006**[b]
Extremities of the lower limbs	21 (52.5)	7 (53.8)	7 (36.8)	.487
Dysesthesia	4 (10)	1 (7.7)	1 (5.3)	.824
Allodynia to brush	11 (27.5)	0	0	**.006**[c]
Allodynia to pressure	11 (27.5)	0	1 (5.3)	**.021**[d]
Allodynia to cold	6 (15)	0	2 (10.5)	.326
Number of dermatomes with abnormal sensory phaenomena, mean ± *SD* (min-max)				
Hyperpathia	7.3 ± 5.6 (0–23)	6.1 ± 4.7 (0–12)	5.1 ± 4.9 (0–14)	.213
Dysesthesia	0.2 ± 1 (0–6)	0.5 ± 1.7 (0–6)	0.7 ± 2.4 (0–10)	.963
Allodynia to brush	0.8 ± 1.6 (0–8)	0	0	**.004**[e]
Allodynia to pressure	0.7 ± 1.3 (0–4)	0	0.1 ± 0.5 (0–2)	**.022**[f]
Allodynia to cold	0.3 ± 0.8 (0–4)	0	0.1 ± 0.5 (0–2)	.221

Note: Values are presented as mean ± standard deviation (minimum-maximum), except for the frequency of abnormal sensory phaenomena and Paroxystic pain phaenomena, which are presented as number of patients (*n*) and its percentage within groups (%), as indicated. Patients are divided as neuropathic and non-neuropathic pain groups according to their main pain syndrome. All the continuous variables were analysed using Kruskal–Wallis with pairwise comparisons using Dunn's procedure and the dichotomous variables were analysed using thee-way Chi Square. Bonferroni correction for multiple comparisons was applied in all cases.

Significance $p < .05$. A $p < .05$ was marked in bold numbers.

[a]Neuropathic pain versus no pain $p = .011$; Non-neuropathic pain versus no pain $p = .361$; Neuropathic pain versus non-neuropathic pain $p = .434$.

[b]Neuropathic pain versus no pain $p = .003$; Non-neuropathic pain versus no pain $p = .704$; Neuropathic pain versus non-neuropathic pain $p = .042$.

[c]Neuropathic pain versus no pain $p = .011$; Non-neuropathic pain versus no pain p = (no valid cases); Neuropathic pain versus non-neuropathic pain $p = .047$.

[d]Neuropathic pain versus no pain $p = .081$; Non-neuropathic pain versus no pain $p = 1.000$; Neuropathic pain versus non-neuropathic pain $p = .047$.

[e]Neuropathic pain versus no pain $p = .013$; Non-neuropathic pain versus no pain $p = 1.000$; Neuropathic pain versus non-neuropathic pain $p = .038$.

[f]Neuropathic pain versus no pain $p = .098$; Non-neuropathic pain versus no pain $p = 1.000$; Neuropathic pain versus non-neuropathic pain $p = .066$.

NPSI score when compared to those with main pain as non-neuropathic (31.8 ± 17.7 and 20.4 ± 12.8, respectively, $p = .032$), and 32 (80%) of them described continuous deep and superficial ongoing pain and paraesthesia and or dysaesthesia with sensations of pins and needles and tingling. The following neuropathic pain domains, as assessed by the NPSI, were significantly higher among those whose main pain was neuropathic when compared to non-neuropathic: continuous ongoing superficial pain (burning, the score for question 1) and paraesthesia/dysaesthesia (tingling, pins and needles; Figure 4). We could not find any association between the level of lesion (thoracic, cervical or cervicothoracic) and pain intensity (Table S16, supplementary file).

According to its very definition, secondary pain had an overall lower intensity in both groups when compared to the primary pain, as assessed by the BPI: 4.2 ± 1.9 and 3.9 ± 1.4 in those whose main pain was neuropathic and non-neuropathic, respectively ($p < .001$ and $p = .007$, respectively; Table S12, supplementary file).

As expected, patients with neuropathic and non-neuropathic pain as their main pain had higher MQS-III and used more drugs than patients with no pain. Twenty-eight (70%) of those patients whose main pain was neuropathic were under anticonvulsants drugs. More than half of subjects with a non-neuropathic syndrome as their main pain were under tricyclic antidepressant drug ($n = 7$, 53.8%; Table S7-supplementary file). During follow-up, there was no evidence of an increase in MQS-III within groups, when compared both visits ($p = .248$, $p = .445$, $p = .917$, in the neuropathic, non-neuropathic and no

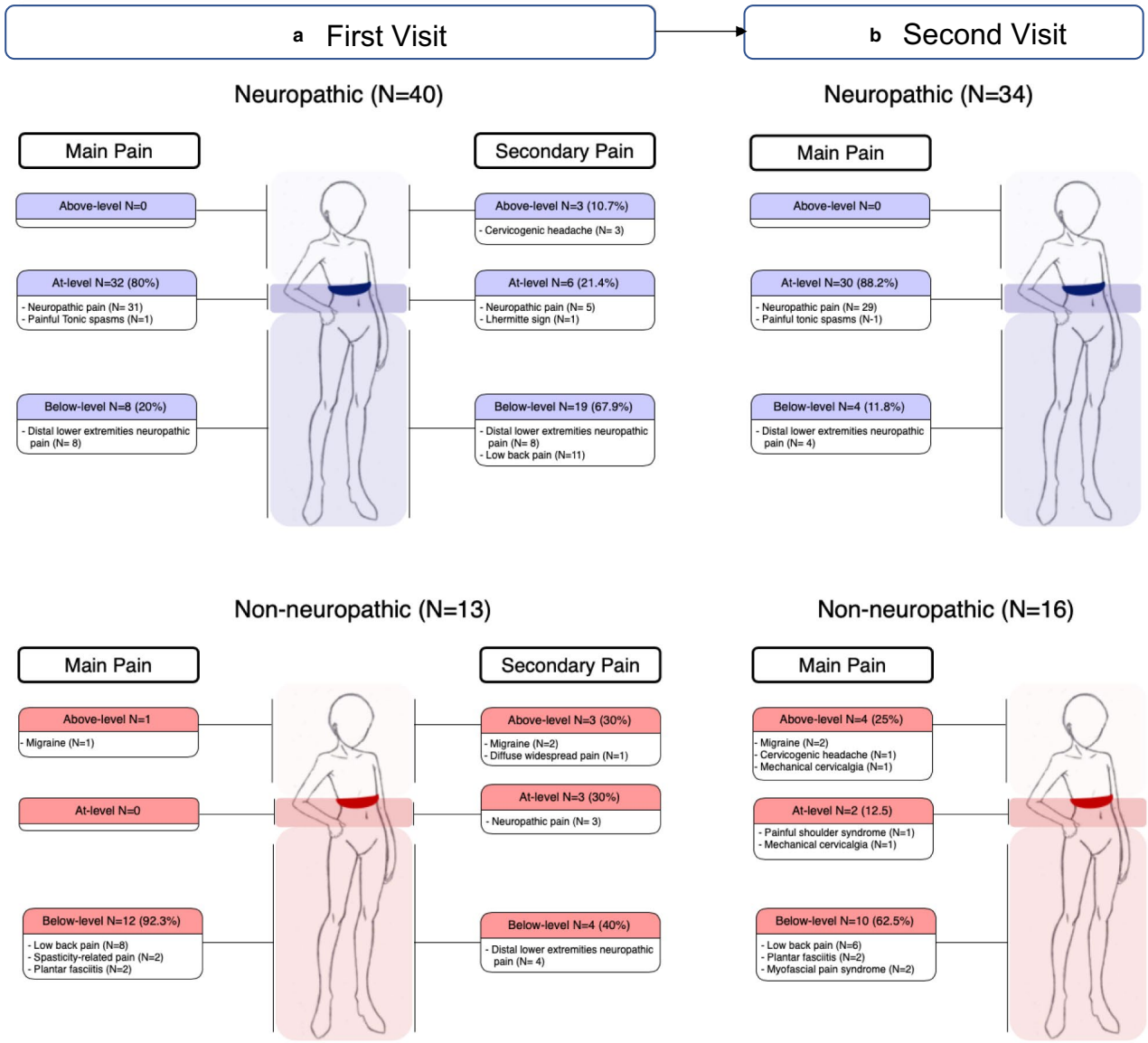

FIGURE 3 Pain syndromes divided according to the main pain syndrome during the first (a) and second visits (b). Values expressed as number of patients (n) and percentage within groups (%). Secondary pain is divided according to syndromic groups of the main pain

pain groups, respectively). A higher proportion of those whose main pain was neuropathic pain was under anticonvulsants when compared to the first visit ($n = 32$, 82.4%), while the same number was using tricyclic antidepressant drug and anticonvulsants in those whose main pain was non-neuropathic pain group ($n = 7$, 58.3%; Table S8- supplementary file).

3.1.6 | Quality of life, disability and psychological aspects

Patients whose main pain was neuropathic had significantly worse performance when compared to those without pain in the PCS-12 (physical composite scale of the SF-12), (32.5 ± 8 and 43.3 ± 11, respectively). They were not statistically different from those whose main pain was non-neuropathic, however (37.8 ± 11.3; Table 4). Assessment of anxiety and depression on the HAD scale showed no statistical difference between the groups. Groups were not statistically different in the scores of Barthel ADL and Fatigue Impact scales. Predictably, patients whose main pains were neuropathic and non-neuropathic had higher scores in the pain catastrophizing thoughts scale when compared to those without pain (17.6 ± 13.3, 16.5 ± 10.8 and 3.2 ± 5.3, respectively, $p < 000.1$), but did not differ between each other (Table 4).

3.1.7 | Non-motor symptoms

Sixty-eight patients (94.4% of the original sample) were questioned about the presence of pruritus, Uhthoff phaenomenon,

TABLE 3 General description of the main pain syndrome amid the 53 patients with chronic pain: 40 patients with neuropathic pain and 13 patients with non-neuropathic pain, during the baseline (first) evaluation

	Neuropathic pain	Non-neuropathic pain	*p*
BPI pain intensity, mean ± *SD* (min-max) (0–10)	5.7 ± 1.9 (1.8–10)	5.1 ± 1.3 (3.5–7.5)	.338
BPI pain interference, mean ± *SD* (min-max) (0–10)	4.6 ± 2.5 (0–9.9)	4.7 ± 2.7 (1.3–9.6)	.878
DN4, mean ± *SD* (min-max) (0–10)	5.8 ± 1.4 (2–9)	3.6 ± 1.9 (0–6)	**.001**
DN4 positive for neuropathic pain (≥4 affirmative answers), *n* (%)	38 (95)	7 (53.8)	**.002**
Quality of neuropathic pain (NPSI)			
Continuous ongoing deep pain (pressure/squeezing), *n* (%)	32 (80)	10 (76.9)	1.000
Intensity, mean ± *SD* (min-max) (0–10)	4.4 ± 3.2 (0–10)	3.8 ± 3.3 (0–10)	.435
Continuous ongoing superficial pain (burning), *n* (%)	32 (80)	6 (46.2)	**.019**
Intensity, mean ± *SD* (min-max) (0–10)	5.4 ± 3.3 (0–10)	2.4 ± 3 (0–8)	**.008**
Evoked pain (allodynia to brush, cold and pressure), *n* (%)	30 (75)	11 (84.6)	.707
Intensity, mean ± *SD* (min-max) (0–10)	2.9 ± 2.6 (0–10)	2 ± 1.2 (0– 4.3)	.278
Paroxysmal pain (electric shocks/stabbing), *n* (%)	12 (30)	4 (30.8)	1.000
Intensity, mean ± *SD* (min-max) (0–10)	1.3 ± 2.5 (0–10)	0.9 ± 1.5 (0–4)	.899
Paraesthesia/Dysaesthesia (tingling, pins and needles), *n* (%)	32 (80)	5 (38.5)	**.005**
Intensity, mean ± *SD* (min-max) (0–10)	3.2 ± 2.6 (0–9)	1.3 ± 2.1 (0–6.5)	**.011**
NPSI- total score, mean ± *SD* (min-max) (0–100)	31.8 ± 17.7 (8–90)	20.4 ± 12.8 (7–46)	**.032**
MPQ, mean ± *SD* (min-max)			
Sensory (0–8)	4.4 ± 1.8 (1–8)	4 ± 1.9 (1–7)	.503
Affective (0–5)	3.4 ± 1.1 (0–5)	3.6 ± 1 (2–5)	.620
Evaluative (0–2)	1.5 ± 0.5 (1–2)	1.3 ± 0.5 (1–2)	.231
Total (0–15)	9.2 ± 2.5 (4–14)	8.9 ± 2.6 (7.4–10.5)	.709

Note: Values expressed as mean ± standard deviation (maximum–minimum) or number of patients (*n*) and percentage within group (%), as indicated. Patients are divided as neuropathic and non-neuropathic pain groups according to their main pain syndrome. Score range is given for each questionnaire item or subitem.

Independent samples *t* test was used to analyse BPI VAS and BPI interference. The remainder of the variables were analysed using Wilcoxon test for the continuous variables and Chi-Square for the dichotomous variables. Significance $p < .05$. A $p < .05$ was marked in bold numbers.

Abbreviations: BPI, brief pain inventory; DN-4, *Douleur neuropathique*- 4; MPQ, Short-form McGill pain questionnaire; NPSI, neuropathic pain symptom inventory.

hiccups, dizziness upon standing, persistent nausea, urinary and faecal dysfunction. Pruritus was present in 20 (52.6%), 3 (25%) and 8 (44.4%) of those patients whose main pain was neuropathic, non-neuropathic and no pain, respectively ($p = .252$). Within the group with neuropathic pain as main pain, 16 (80%) out of 20 subjects who reported any pruritus, had this symptom on the pain area, whereas 1 (33.3%) out of 3 patients whose main pain was non-neuropathic reported the same ($p < .001$). Peculiarly, a total of 8 (25.8%) patients reported an unpleasant pruritus on their lower scalp, close to the C2 dermatome: in 5 of them (62.5%) it was above the current sensory level, but all of them had had previous inflammatory lesions in the upper cervical spinal cord and or medulla.

Importantly, symptoms compatible with overactive bladder were pervasive in all groups (78.9%, 83.3% and 77.8% of those whose main pain was neuropathic, non-neuropathic and no pain, respectively) as was the report of constipation (81.6, 66.7% and 55.6% in those whose main pain was neuropathic, non-neuropathic and who had no pain, respectively; Table S9-supplementary file).

3.2 | Follow-up and incidence of pain

Patients were re-evaluated between 6 and 18 months (9.9 ± 3.6 months) after the first visit: total follow-up of 59.3 persons-year. Sixty-eight patients (94.4% of the original sample) were reassessed by the same neurologist of the first evaluation (three patients lost follow-up, and one patient died). Two patients had a relapse of the inflammatory disease between the two visits, one of them as optic neuritis and the other as myelitis.

Fifty patients (73.5%) reported chronic pain in the follow-up (i.e. second) assessment. At-level neuropathic pain was again the most prevalent syndrome, affecting 29 (58% of the total cohort of patients with pain) subjects (Figure 3b). Three patients initially free from pain developed it after the first evaluation, one of them as an at-level neuropathic pain three months after

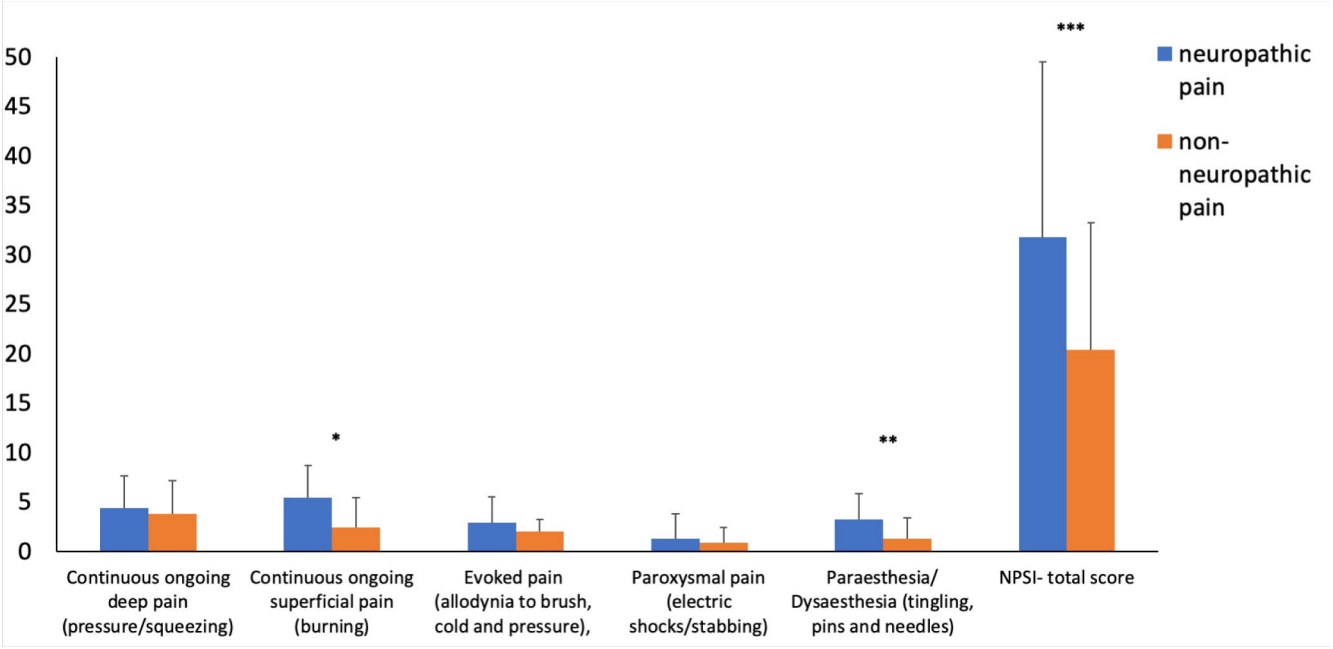

FIGURE 4 NPSI dimensions subscores for patients whose main pain was neuropathic and non-neuropathic. Values expressed as mean and standard deviation. Comparison between groups analysed using Wilcoxon test. Statistically significant differences highlighted as $*p = .008$, $**p = .011$, $***p = .032$

a new myelitis relapse, another as cervicogenic headache and a third as plantar fasciitis. The incidence rate of "new-pain" was 17.7per 100 persons-year. Thus, no patient had de novo neuropathic pain in the absence of new disease relapse, while de novo pain occurred due to musculoskeletal aetiologies in two.

Three patients who reported pain in the first visit were pain-free on the follow-up assessment. Interestingly, eleven patients who had reported pain upon study entry had a different pain syndrome on the second evaluation (20.8% of the original cohort of 53 subjects with pain; Figure 5).

During this follow-up there was no difference between patients with neuropathic and non-neuropathic as their main pain in BPI intensity, BPI interference and McGill short pain questionnaire total score, although NPSI scores were predictably higher among those whose main pain was neuropathic (Table S10-supplementary file).

3.3 | Correlation analysis

Pain intensity, as measured by the BPI intensity score, was tested for correlation with the following variables: (a) quality of life (12-Item Short-Form Health Survey, physical component—PCS—subscore), (b) anxiety and depression scores (HADS), (c) disability score (EDSS), (d) fatigue severity score. There was a moderate negative correlation between pain intensity and PCS ($\rho = -0.488$, $p < .001$). Pain also correlated moderately with anxiety and depression ($\rho = 0.497$, $p < .001$) and with fatigue severity scores ($\rho = 0.377$, $p = .006$; Tables S13 and S14, supplementary file).

Multiple regression analysis was performed to evaluate the influence of pain, fatigue, motor disability, anxiety and depression (as measured by their respective scores) in determining the variation in the physical component of quality of life. The multiple regression model predicted the physical component of quality of life, $F(4,66) = 14.56$, $p < .001$, $R^2 = 0.47$. The variables EDSS, BPI and fatigue scores showed strong evidence of adding to the equation, influencing the model in a similar proportion: standardized beta coefficients of -0.375 ($p < .001$), -0.320 ($p = .003$), -0.309 ($p = .006$), respectively. This indicates that pain influences in the physical component of quality of life almost as much as motor disability or fatigue (Table S15, supplementary file).

4 | DISCUSSION

In this prospective analysis of in-remission NMO patients, 74% experienced chronic pain. At-level neuropathic pain was the most common main pain syndrome, present in 60% of those who had any pain, followed by musculoskeletal pain, which affected 22%. Over 70% of patients had more than one pain syndrome. Importantly, even without a clinical relapse, one-fifth of patients reported a different main pain on follow-up. The presence of pain was not associated with lesion burden (measured by the brain and spinal cord MRI), previous inflammatory activity or prevalence of autoantibodies and it was as important as disability and motor strength when analysing quality of life in NMO, following previous studies (Burke, Lennon, & Fullen, 2018; Kong

TABLE 4 Baseline evaluation: quality of life, disability and psychological aspects

Psychological aspects	Neuropathic pain	Non-neuropathic pain	No pain	*p*
HADS, mean ± *SD* (min-max)				
Anxiety (0–21)	7.6 ± 4 (0–16)	7.4 ± 4.4 (1–16)	5.3 ± 3.3 (0–12)	.098
Depression (0–21)	5.5 ± 3.8 (0–15)	6.6 ± 4.6 (0–15)	3.9 ± 3.5 (0–13)	.145
Total (0–42)	13.1 ± 7 (1–28)	14 ± 7.9 (2–31)	9.2 ± 6.3 (0–25)	.089
Pain catastrophising scale, mean ± *SD* (min-max)				
Rumination (0–5)	2.2 ± 1.5 (0.2–5)	2 ± 1.2 (0.2–4.4)	0.3 ± 0.6 (0–2)	**<.001**[a]
Helplessness (0–5)	1.7 ± 1.6 (0–5)	1.6 ± 1.4 (0–4.5)	0.5 ± 0.8 (0–2.7)	**.003**[b]
Total (0–5)	2 ± 1.5 (0.1–4.9)	1.8 ± 1.2 (0.4–4.4)	0.4 ± 0.6 (0–2.3)	**<.001**[c]
Quality of life and disability				
SF−12, mean ± *SD* (min-max)				
PCS (0–100)	32.5 ± 8 (16.6–52.7)	37.8 ± 11.3 (19.8–53.2)	43.3 ± 11 (22.7–58.1)	**<.001**[d]
MCS (0–100)	46.9 ± 12.3 (20.1–70.9)	48.8 ± 9.9 (29.9–62.9)	50.7 ± 13.9 (21.4 – 66.8)	.307
Barthel ADL index, mean ± *SD* (min-max) (0–100)	72.4 ± 26.5 (10–100)	82.3 ± 23.4 (25–100)	75.8 ± 25.7 (20–100)	.235
Modified fatigue impact scale, mean ± *SD* (min-max) (7–63)	33.9 ± 16.4 (9–63)	32.2 ± 15.4 (10–60)	24.9 ± 17.9 (9–63)	.160

Note: Values expressed in mean ± standard deviation (minimum-maximum). Patients are divided as neuropathic and non-neuropathic pain groups according to their main pain syndrome. Score range is given for each questionnaire item or subitem.

One-way ANOVA with Tukey HSD procedure for post hoc analysis was used to compare Fatigue impact scale, HADS and PCS of SF-12. The remainder of the variables were compared using Kruskal–Wallis with pairwise comparisons using Dunn's procedure. Dichotomous variables were analysed using three-way chi square test. Bonferroni correction for multiple comparisons was applied in all cases.

Significance $p < .05$. A $p < .05$ was marked in bold numbers.

Abbreviations: Barthel ADL index, Barthel activities of daily life index; HADS, hospital anxiety and depression scale; MCS, mental health summary of the SF-12 health survey; PCS, physical health summary of the SF-12 health survey; SF-12, short form 12-item health survey.

[a]Neuropathic pain versus no pain $p < .001$; Non-neuropathic pain versus no pain $p < .001$; Neuropathic pain versus non-neuropathic pain $p = .874$.

[b]Neuropathic pain versus no pain $p = .004$; Non-neuropathic pain versus no pain $p = .020$; Neuropathic pain versus non-neuropathic pain $p = 1.000$.

[c]Neuropathic pain versus no pain $p < .001$; Non-neuropathic pain versus no pain $p < .001$; Neuropathic pain versus non-neuropathic pain $p = 1.000$.

[d]Neuropathic pain versus no pain $p < .001$; Non-neuropathic pain versus no pain $p = .246$; Neuropathic pain versus non-neuropathic pain $p = .196$.

et al., 2016). Few studies evaluated SCI-pain prospectively (Finnerup, Jensen, et al., 2016; Finnerup et al., 2014; Mordillo-Mateos et al., 2019; Richardson et al., 2019; Siddall et al., 2003; Zeilig et al., 2012), and to the best of our knowledge, this is the first to do so in inflammatory-SCI. In our cohort, pain was highly prevalent, and this compares to previous studies with non-inflammatory SCI (Bryce et al., 2012b; Dijkers, Bryce, & Zanca, 2009). Also, neuropathic pain was the most prevalent syndrome, while earlier traumatic-SCI cohorts reported a preponderance of nociceptive pain (Burke, Fullen, Stokes, & Lennon, 2017; Finnerup, Jensen, et al., 2016; Finnerup et al., 2014; Siddall et al., 2003). Perhaps inflammatory-SCI have worse functional status for upper limbs when compared to traumatic-SCI, increasing the odds of neuropathic pain. Acknowledging the multiplicity of pain syndromes and its mechanisms allows for different concomitant treatments, and may be one of the reasons why pain control in SCI is so difficult (Freynhagen et al., 2019). It has implications for clinical trials, as the evaluation of pain scores could be biased by the improvement of one type of pain but not the other. It could also jeopardize phenotype-based approaches to pain treatment.

The bedside examination can be a useful tool in differentiating pain syndromes: none of those with non-neuropathic pain presented with allodynia in the main pain area. It wasn't a frequent symptom, though: allodynia to brush and pressure affected 28% of those with neuropathic pain while allodynia to cold affected 15%. At-level hyperpathia affected most patients in all groups, but was significantly more prevalent in those whose main pain was neuropathic, affecting 98% of them. Both hyperpathia and allodynia are described for the first time in NMO, and it may have a role in a more accurate pain diagnosis (Vierck et al., 2015).

Another novelty of our study is informing the incidence of pain in NMO. We reported changes in pain syndromes throughout the follow-up and an incidence of pain of 17.7 per 100 persons-year. Amid those initially pain-free who developed pain in the second evaluation, only one subject developed new neuropathic pain after a relapse of myelitis. This information may have surveillance implications if replicated in future studies: the onset of a new neuropathic

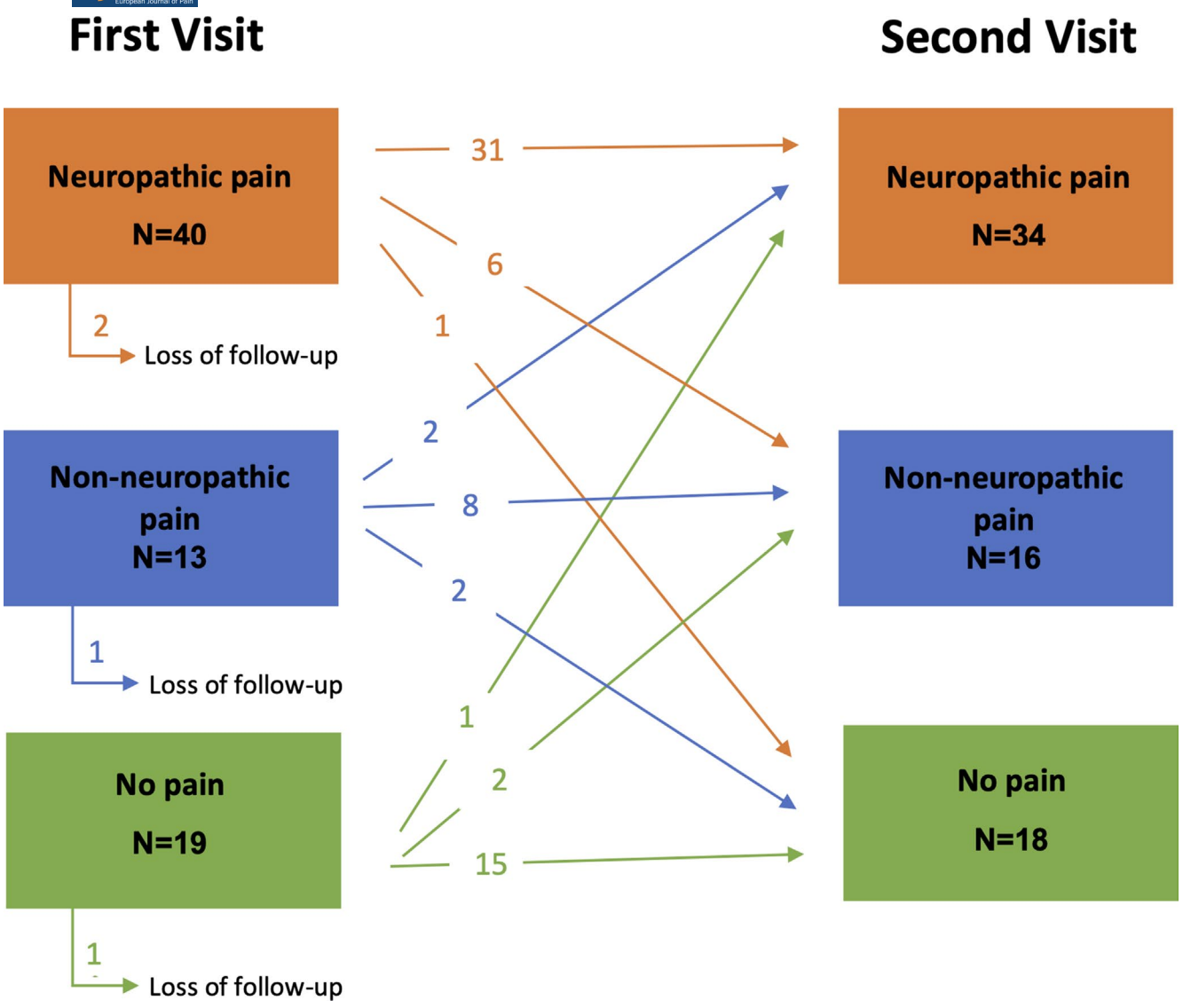

FIGURE 5 Description of changes in the main pain syndromes between the first and second visits

pain in an otherwise in-remission NMO patient may serve as a red flag to investigate new spinal cord inflammatory lesions. On follow-up, pain prevalence was as high as upon study entry, and at-level neuropathic pain was still the most prevalent syndrome. Interestingly, 21% of patients changed their main pain syndrome in the second evaluation. Two patients had a change of pain syndrome even without new inflammatory activity, which demonstrates non-neuropathic pain can occur solely due to previous structural lesions and associated secondary neuroplasticity (Bryce et al., 2007; Siddall et al., 2003). Although this is not a novelty in other types of SCI (Ducreux et al., 2006; Finnerup, Jensen, et al., 2016), it is a concept not previously explored in demyelinating diseases, where new pain is often associated to a potentially unrevealed inflammatory activity of the disease.

The DN4-Questionnaire had high sensibility but low specificity as a neuropathic pain screening tool when compared to the gold standard of a pain-neurologist diagnosis. This was expected, as most patients have either cervical or thoracic sensory levels and any pain below the NLI can be screened as positive DN-4 due to the lengthy somatosensory deafferentation. Our study highlights the challenge of diagnosing the pain syndrome below the NLI in SCI patients using the neuropathic pain grading system proposed by IASP (Finnerup, Haroutounian, et al., 2016). Finnerup and Baastrup had already recognized this difficulty and added further criteria for its diagnosis (Finnerup & Baastrup, 2012). This discussion is helpful but better specificity is needed in screening tools for neuropathic pain in this population. The use of NPSI may help in this task: sensations of "burning" and "tingling, pins and needles" were significantly more common among those with neuropathic pain and might be useful to distinguish between pain syndromes, particularly below the NLI. A study with traumatic-SCI (Putzke et al., 2002) reported similar findings. It remains to be established to which extent this

pain phenotype has any implication in its treatment, as it may translates different underlying mechanisms.

An original feature in our cohort is the striking age differences according to pain status: those with chronic pain were significantly older than those without at the time of study entry, disease onset and last clinical relapse. Age was already described as an important variable for chronic pain (Boogaard et al., 2015; Fitzgerald & McKelvey, 2016). There are multiple interacting neurobiological and behavioural factors that explain different responses to the somatosensory system with ageing. Older individuals have decreased thermal perceptions (as evidenced by increases in thermal thresholds; Gagliese, 2009), changes in the characteristics of the nociceptors (Gibson & Farrell, 2004), decreased density of Pacinian corpuscles and sensory epidermal nerve fibres density, decreased function of A- δ and C fibres (Da Silva et al., 2014; Guergova & Dufour, 2011) and altered neuroimmunological response to tissue injury (Ashcroft, Mills, & Ashworth, 2002). Animal models suggested that older rats with lesions of the somatosensory system have more pain and evidence of reduced neuroplasticity throughout the central nervous system (Crutcher, 2002). When compared to younger people, older subjects have altered temporal summation (Edwards, Fillingim, & Keefe, 2001; Fillingim, Loeser, Baron, & Edwards, 2016), impaired descending noxious inhibitory control (Lariviere, Goffaux, Marchand, & Julien, 2007) and slower or absent resolution of postinjury hyperalgesia after somatosensory system lesions (Zheng, Gibson, Khalil, Helme, & McMeeken, 2000). Also, older individuals demonstrate smaller cortical responses to peripheral thermal stimulation and significant structural brain changes when compared to controls without pain (Buckalew, Haut, Morrow, & Weiner, 2008). There is enough evidence that widespread modifications in the structure and function of peripheral and central nociceptive pathways may increase the risk of older subjects developing chronic pain when compared to younger ones with comparable lesions. Since NMO has a peak of incidence in the fourth decade of life, those biological mechanisms have implications in pain prevalence and response to treatment. Notwithstanding, we could not detect any impact of ageing on the plasticity of the pyramidal tract: there was no correlation between age and the degree of disability as measured by the EDSS or motor strength total score.

The prevalence of pain of in our cohort of NMO patients (73%) is comparable to previous studies which evaluated it in multiple sclerosis (MS; Foley et al., 2013; Moisset et al., 2013; O'Connor, Schwid, Herrmann, Markman, & Dworkin, 2008). While in our sample at-level neuropathic pain was the most common type of syndrome, previous studies have reported high prevalence of headaches and extremities neuropathic pain. Is it noteworthy that migraines were found in only 6.9% of our cohort, while it affected around half of patients with MS in previous studies (Moisset et al., 2013). The prevalence of migraine in our sample is smaller than previously reported in the general population, between 11% and 15% (Lantéri-Minet, Valade, Geraud, Chautard, & Lucas, 2005; Lipton et al., 2007), including studies in the Brazilian population (Peres et al., 2019; Queiroz et al., 2009). Comorbid primary headache prevalence in NMO is still not known in the literature, this is an original report. We also could not find differences in pain syndromes and its prevalence regardless of the antibody seropositivity. Nevertheless, our cohort had a higher prevalence of individuals with negative auto antibodies (both AQP4-Ab and MOG) than previously reported in the literature (35% vs. 15% in the study by Sepulveda et al., [2018]). We could not find any relationship between the level of injury and the prevalence of pain, as previously reported (Tackley et al., 2017), perhaps because we found more appropriate to consider the whole extension of the lesion rather than the midpoint.

One of the limitations of this longitudinal study is the short time of follow-up the fact that the changes in the pain syndromes might have been influenced by the treatment offered after the first assessment, despite no significant changes in MQS-III between evaluations within any group. Another limitation is the conduction of the study in a single tertiary hospital, though patients with a complex and somewhat rare disease such as NMO will be seen mainly in referral centres. There could also be a selection bias in our sample, in that only those free of inflammatory activity for at least one year were included: patients with a highly active disease could have different patterns and prevalence of pain syndromes. As most patients were invited during routine clinical appointments and none of them refused to participate, it's unlikely that those with less severe disease or pain were selected for this cohort. Since most patients had more than one pain and were classified according to the main pain syndrome, it may be argued that there was an underassessment of neuropathic pain, particularly when it was not the main pain syndrome. Since there is no standardized way to assess or report data from patients with more than one pain syndrome, we opted to proceed as most studies assessing pain in NMO, who focused on the main pain syndrome. Future studies and society recommendations on chronic pain assessment will probably better adapt clinical classification protocols for patients with multiple pain syndromes. A final point is that pain is a prevalent symptom, present in up to 28% of the Brazilian population (Leão Ferreira et al., 2016; de Souza, Grossmann, Perissinotti, & de Oliveira Junior, 2017), and our study was not designed to detail pre-existing pain syndromes, prone to memory bias. Although all patients reporting low back pain reported its onset after the first relapse of the inflammatory disease, it could be already present in a minor degree before. We also believe the lack of a specific questionnaire for migraines influenced in the report of this disease.

In conclusion, this original prospective study in NMO showed that pain is a significant problem in those patients, it is hard to identify based on screening tools, it has a functional impact similar to that of motor impairment, and that it can occur even in the absence of clinical inflammatory activity. Furthermore, the age of onset of the inflammatory disease in the spinal cord was a major determinant of the presence of pain.

Future prospective studies evaluating the progression of sensory disturbances and pain from the acute to the chronic phase of the inflammation in the spinal cord should contribute to the better understanding of the mechanisms of pain and future treatment for this symptom in SCI.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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