FERNANDA VALERIO DA SILVA

Caracterização do perfil de síndromes dolorosas, psicofísica e medidas de excitabilidade cortical em doentes com neuromielite óptica controlada

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Programa de Neurologia

Orientador: Prof. Dr. Daniel Ciampi Araújo de Andrade

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FERNANDA VALERIO DA SILVA

Characterization of pain, psychophysics and cortical excitability profile in patients with controlled neuromyelitis optica spectrum disorders

Thesis presented to the Faculdade de Medicina, Universidade de São Paulo to obtain the degree of Doctor in Science

Graduate Program in Neurology

Advisor: Prof. Dr. Daniel Ciampi Araújo de Andrade

SÃO PAULO
2019

“Unlearning is not forgetting, it is neither deletion, cancellation nor burning off. It is writing bolder and writing anew. It is commenting and questioning. It is giving new footnotes to old and other narratives. It is the wiping off of the dust, clearing of the grass, and cracking off the plaster that lays above the erased. Unlearning is flipping the coin and awakening the ghosts. Unlearning is looking in the mirror and seeing the world (…).”

Bonaventure Soh Bejeng Ndikung

Long Night of Ideas, 14 April 2016, SAVVY Contemporary
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LIST OF ABBREVIATIONS AND ACRONYMS

2-AG	-	2-arachidonoylglycerole
ADEM	-	Acute disseminated encephalomyelitis
ADL	-	Activities of daily life
AQP4-Ab	-	Aquaporin-4 antibodies
Barthel ADL	-	Barthel activity of daily life scale
BPI	-	Brief pain inventory
CBA	-	Cell-based assay
CDT	-	Cold detection threshold
CEPESQ	-	Comissão de Ética em Pesquisa
CI	-	Confidence interval
CNS	-	Central nervous system
CONEP	-	Comissão Nacional de Ética em Pesquisa
CPM	-	Conditioned pain modulation
CPT	-	Cold pain threshold
CSF	-	Cerebrospinal fluid
DN-4	-	Douleur neuropathique-4
EDSS	-	Expanded Disability Status Scale
F:M	-	Female: male ratio
FMUSP	-	Faculdade de Medicina da Universidade de São Paulo
GABA	-	Gama amino butyric acid
HADs	-	Hospitalar Anxiety and Depression Scale
HC	-	Hospital das Clínicas
HEK 293	-	Human embryonic kidney 293 cells
HPT	-	Heat pain threshold
HRQOL	-	Health related quality of life or quality of life
IASP	-	International Association for the Study of Pain
ICF	-	Intracortical facilitation

IgG	-	Immunoglobulin G
INC	-	Infrathrelshold cold stimulation
IPND	-	International Panel for NMO Diagnosis
IPSS	-	International Prostate Symptom Score
LETM	-	Longitudinally extensive transverse myelitis
MCS	-	Mental Health Composite Scale
MEP	-	Motor evoked potentials
MOG	-	Myelin oligodendrocyte glycoprotein
MPQ	-	Short form McGIll Questionnaire
MPS	-	Myofascial pain syndrome
MPT	-	Mechanical detection thresholds
MQS	-	Medication quantification scale
MRC	-	Medical Research Council
MRI	-	Magnetic ressonance image
MS	-	Multiple Sclerosis
NINDS	-	National Institute of Neurological Disorders and Stroke
NLI	-	Neurological level of injury
NMO	-	Neuromyelitis optica
NMOSD	-	Neuromyelitis optica spectrum disorders
NP	-	Neuropathic pain
NPSI	-	Neuropathic pain symptom inventory
OAB-V8	-	Overactive bladder-8 item
ON	-	Optic Neuritis
PCS	-	Physical Health Composite Scale
PPT	-	Pain pressure threshold.
PRCTS	-	Pain Related Catastrophizing Thoughts scale
PTS	-	Painful tonic spasms
QST	-	Quantitative sensory test
RCT	-	Randomised Clinical Trial
RMT	-	Rest motor threshold
SCI	-	Spinal cord injury
SF12	-	Short Form--12 Health survey

SICI	-	Short inhibitory cortical inhibition
SLE	-	Systemic erythematous lupus
SS	-	Sjögren syndrome
SUH	-	Suprathreshold heat stimulation
TCLE	-	Termo de Consentimento Livre e Esclarecido (Consent form)
TM	-	Transverse myelitis
TP	-	Trigger point
UK	-	United Kingdom
USA	-	United States of America
VAS	-	Visual analogue scale
WDT	-	Warm detection threshold
y.o/yo	-	Years-old

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RESUMO (in Brazilian Portuguese)

Valerio-da-Silva F. *Caracterização do perfil de síndromes dolorosas, psicofísica e medidas de excitabilidade cortical em doentes com neuromielite óptica controlada* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2019.

Introdução: Neuromielite óptica (NMO) é uma doença inflamatória desmielinizante do sistema nervoso central associado com auto anticorpo anti-aquaporina 4 (AQP4-Ab) em até 90% dos casos e com anticorpo anti glicoproteína de mielina oligodendrocítica (MOG-IgG) em cerca de 20% dos indivíduos negativos para AQP4-Ab. A apresentação clínica típica do NMO inclui neurite óptica grave (ON), mielite transversa longitudinalmente extensa (MTLE) e lesões do tronco encefálico conhecidas por causar náuseas, vômitos e soluços intratáveis. A dor é um dos sintomas mais frequentes e incapacitantes dessa síndrome. Sabe-se que afeta até 85% dos indivíduos, que é mais intensa e responde menos aos tratamentos usuais quando comparados aos pacientes com esclerose múltipla. O objetivo deste estudo foi caracterizar as síndromes dolorosas em indivíduos na fase crônica livre de recidiva da NMO. A doença também foi considerada um bom modelo para estudar os mecanismos de dor após lesão medular. **Métodos**: Trata-se de um estudo longitudinal, composto por duas avaliações. A avaliação para entrada no estudo consistiu em um exame neurológico complete padronizado, a fim de determinar as síndromes dolorosas principal e secundária de acordo com seu mecanismo e nível. Os pacientes foram convidados a preencher questionários avaliando a dor (Inventário breve de dor [BPI], Questionário de dor McGill [MPQ], inventário de sintomas de dor neuropática [NPSI]), espasmos tônicos dolorosos, sinal de Lhermitte, incapacidade (EDSS, Barthel ADL), ansiedade e depressão (escala hospitalar de ansiedade e depressão [HADS]), catastrofização (escala de pensamentos catastróficos na dor [PCTS]), disfunção urinária e fecal (questionário de bexiga hiperativa [OAB-V8], escore de sintomas prostáticos internacionais [IPSS]). Também foram realizados teste quantitativo sensitivo (QST) em área controle (com sensibilidade normal) e área de maior dor e medidas de excitabilidade cortical bilaterais (CE). Imagens prévias de ressonância magnética de encéfalo e medula espinhal foram revistos. Foi realizada uma consulta de acompanhamento entre 6 e 18 meses após a primeira visita, na qual a

síndrome dolorosa principal foi reavaliada e os pacientes foram solicitados a preencher questionários (DN-4, BPI, MPQ, BPI, NPSI) sobre a dor. **Resultados**: Setenta e dois pacientes foram incluídos. Foram identificados 53 (73,6%) indivíduos com dor crônica e 19 (26,3%) sem dor. Quarenta (55,6%) pacientes apresentaram dor neuropática (NP) e 13 (18,1%) dor não neuropática (não-NP). Entre os 53 indivíduos com dor crônica, 38 (71,7%) tinham mais de uma síndrome dolorosa. Dor neuropática no nível sensitivo foi a síndrome dolorosa mais prevalente, sendo observada em 31 doentes (58,5% do total de pacientes com dor). O grupo com dor não-neuropática teve dor lombar como a síndrome mais comum, afetando 8 (61,5%) indivíduos. O grupo com dor neuropática teve um número significativamente maior de dermátomos afetados por alodínea dinâmica (0,8 ± 1,6, comparado a zero dermátomos nos outros 2 grupos, p = 0,004) e estática (0,7 ± 1,3 comparado a 0 no grupo com dor não-neuropática e 0,1 ± 0,5 dermátomos no grupo sem dor). A hiperpatia em nível foi significativamente mais prevalente no grupo com dor neuropática: 39 (97,5%) nesse grupo, contra 10 (76,9%) e 12 (68,4%) nos grupos dor não-neuropática e sem dor (p = 0,013). Os pacientes com dor neuropática apresentaram desempenho significativamente pior quando comparados aos sem dor, no PCS-12 (componente físico do SF-12), (32,5 ± 8 e 43,3 ± 11, respectivamente). O PCS-12 correlacionou-se com a intensidade da dor no BPI nos grupos dor neuropática (r = -0,387, p = 0,014) e não-neuropática (r = -0,734, p = 0,004). Dentro do grupo com dor neuropática, 16 (80%) pacientes relataram prurido na área de dor, enquanto apenas 1 (33,3%) paciente com dor não neuropática relatou o mesmo (p <0,001). O QST apresentou maiores limiares para a detecção de estímulos quentes dentre aqueles com dor neuropática, quando comparado ao grupo com dor não-neuropática (41,3 ± 5,6 e 36,9 ± 3, respectivamente, p = 0,045). As amplitudes do potencial evocado motor a 120 e 140% foram significativamente menores nos dois grupos com dor quando comparados aos pacientes sem dor. A avaliação de acompanhamento foi realizada em 68 pacientes e 50 (73,5%) relataram dor. A dor neuropática do nível foi novamente a síndrome dolorosa mais prevalente, afetando 29 (58%) indivíduos. Três pacientes inicialmente sem dor relataram na o sintoma na segunda visita. A taxa de incidência de dor foi de 17,7 por 100 pessoas-ano. Onze pacientes que haviam relatado dor na entrada do estudo tinham uma síndrome de dor diferente na segunda avaliação (20,8% da amostra original). O grupo com dor neuropática teve uma diminuição significativa na intensidade do BPI (de 5,6 ± 1,9 para 4,8 ± 2, p = 0,039). O escore total do MPQ diminuiu significativamente em ambos os grupos com dor neuropática (de 9 ± 2,4 para 8 ± 3,1, p = 0,014) e naqueles com dor não-neuropática (9,2 ± 2,5 a 7 ± 4, p = 0,031). **Conclusão**: A dor é prevalente em pacientes com NMO e a dor neuropática de nível é a síndrome mais comum. A incidência de novas dores

e alterações nas síndromes dolorosas não está relacionada à nova atividade inflamatória, mas ao dano estrutural permanente crônico na medula espinhal e tronco cerebral secundário à atividade autoimune prévia. A avaliação das síndromes dolorosas é importante para o tratamento correto desse sintoma e deve ser reavaliada regularmente, mesmo em pacientes sem novas recidivas clínicas.

Descritores: neuromielite óptica; neuralgia; traumatismos da medula espinal; dor; limiares sensoriais; dor musculoesquelética; doenças auto-imunes desmielinizantes do sistema nervoso central; excitabilidade cortical

ABSTRACT

Valerio-da-Silva F. *Characterization of pain, psychophysics and cortical excitability profile in patients with controlled neuromyelitis optica spectrum disorders* [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2019.

Introduction: Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the central nervous system. It is associated with anti-aquaporin 4 autoantibody (AQP4-Ab) in up to 90% of cases and with anti-myelin oligodendrocyte glycoprotein (MOG-IgG) in around 20% of subjects negative to AQP4-Ab. The typical clinical presentation of NMOSD includes severe optic neuritis (ON), longitudinally extensive transverse myelitis (LETM) and brainstem lesions known to cause intractable nausea, vomiting and hiccups. Pain is one of the most frequent and disabling symptoms in this syndrome. It is known to affect up to 85% of subjects with NMO which is more intense and less responsive to usual treatments when compared to multiple sclerosis patients. The aim of this study was to fully characterise all pain syndromes in individuals in the chronic relapse-free phase of NMO. The disease was also deemed a good model to study pain mechanisms in spinal cord injuries. **Methods**: This is a longitudinal study, comprised by 2 evaluations. The Baseline study entry visit consisted of a full standardized neurological examination, in order to determine the main and secondary pain syndrome according to its mechanism and level. Patients were requested to fill questionnaires evaluating pain (*Douleur Neuropathique-4* [DN-4], brief pain inventory [BPI], Short-form McGill Pain Questionnaire [MPQ], Neuropathic pain symptoms inventory [NPSI]), painful tonic spasms, Lhermitte sign, hiccups, orthostatic intolerance, persistent nausea, pruritus, fatigue (modified fatigue scale), Uhthoff phaenomenon, quality of life (SF-12), disability (EDSS, Barthel ADL), anxiety and depression (Hospital anxiety and depression scale [HADS]), catastrophizing (PCTS), urinary and faecal dysfunction(OAB-V8,IPSS). Quantitative sensory test (QST) and measures of cortical excitability (CE) were performed. Previous brain and spinal cord MRIs were reviewed. A follow up visit was done between 6 and 18 months after the first visit, in which the main pain syndrome was reassessed and patients again were requested to fill pain questionnaires (DN-4, BPI, MPQ, BPI, NPSI) and report painful tonic spasms and Lhermitte sign. **Results**: Seventy-two patients were included. We identified 53 (73.6%) patients with chronic pain and 19 (26.3%) without any chronic pain

syndrome. Forty (55.6%) patients had neuropathic pain (NP) and 13 (18.1%) had non-neuropathic pain (non-NP). Amongst those 53 subjects with chronic pain, 38 (71.7%) had more than one pain syndrome. NP at the sensory level was the most prevalent pain syndrome, being observed in 31 patients (58.5% of the total pain patients). Amid the non-NP patients, low back pain was the most common pain syndrome, affecting 8 (61.5%) subjects. NP group had a significantly higher number of dermatomes affected by allodynia to brush (0.8 ± 1.6, compared to zero dermatomes in the other 2 groups, p = 0.004) and to pressure (0.7 ± 1.3 compared to no 0 in the non-NP group and 0.1 ± 0.5 dermatomes in the no pain group). At-level hyperpathia affected a significantly proportion of patients with NP: 39 (97.5%) in this group, versus 10 (76.9%) and 12 (68.4%) in the non-NP and no pain groups (p= 0.013). Patients with NP had significantly worse performance when compared to those without pain, in the PCS-12 (physical component of the SF-12), (32.5 ± 8 and 43.3 ± 11, respectively). PCS-12 correlated with BPI intensity pain amid NP (r= -0.387, p= 0.014) and non-NP (r= -0.734, p= 0.004) groups. Within the group with neuropathic pain, 16 (80%) of patients reported itching on the pain area, whereas only 1 (33.3%) patient with non-neuropathic pain reported the same (p<0.001). QST showed higher thresholds for warm stimuli detection within NP group, when compared to non-NP (41.3 ± 5.6 and 36.9 ± 3, respectively, p= 0.045) group. Motor evoked potential amplitudes at 120 and 140% were significantly lower in both groups with pain when compared to those without pain. The follow up assessment was done in 68 patients and 50 (73.5%) reported pain. At-level NP was the most prevalent syndrome, affecting 29 (58%) subjects. Three patients initially without pain reported it in the follow up visit. Incidence rate of pain was 17.7per 100 persons-year. Eleven patients who had reported pain upon study entry had a different pain syndrome on the second evaluation (20.8% of the original sample). NP group had a significant decrease in BPI intensity (from 5.6± 1.9 to 4.8±2, p= 0.039). MPQ total score significantly decreased in both groups with NP (from 9±2.4 to 8±3.1, p=0.014) and in those with non-NP (9.2±2.5 to 7±4, p=0.031). **Conclusion**: Pain is prevalent in patients with NMO and at-level NP is the most common syndrome. The incidence of new pain and changes in its syndromes is not related to new inflammatory activity but to the permanent chronic structural damage in the spinal cord and brainstem secondary to previous autoimmune activity. Assessment of pain syndromes is important for its treatment and they should be re-evaluated regularly even in patients without new clinical relapses.

Descriptors: neuromyelitis optica; neuralgia; spinal cord Injuries; pain; sensory thresholds; musculoskeletal pain; demyelinating autoimmune diseases, CNS; cortical excitability

1 INTRODUCTION

Neuromyelitis optica (NMO) or Devic's disease, is an inflammatory demyelinating disease of the central nervous system (CNS). It was first described in 1804 by Antoine Portal when portraying the case of the *Marquis de Causan* (Portal, 1804; Jarius and Wildemann, 2012). Although many other authors described similar cases throughout the 19th century, it was the classical description of a case series with optic neuritis and acute myelitis by Devic and Gault that coined the name “Neuromyelitis optica acuta” (Devic, 1895a, 1895b and 1894; Gault 1894). The ground-breaking description of the anti-aquaporin 4 antibody (AQP4-Ab) as a biomarker in NMO defined it as a separate and autonomous entity, rather than a subtype of multiple sclerosis (MS). It was an important advance towards its better clinical and laboratory characterization and allowed for the elucidation of its Immunopathogenesis (Lennon *et al*., 2004 and 2005; Jarius and Wildemann, 2013). Aquaporin 4 is the main channel that regulates water homoeostasis in the central nervous system. Recently, other biomarkers have been described in NMO patients, such as the antibody anti myelin oligodendrocyte glycoprotein (MOG) (Kitley *et al*., 2012b; Kitley *et al*., 2014; Jarius *et al*., 2016; Ogawa *et al*., 2017). Nevertheless, a parcel of NMO patients is currently seronegative for any antibody known in this disease.

The typical clinical presentation of NMO includes severe episodes of a painful optic neuritis (ON), causing significant visual loss; transverse myelitis

(TM) leading to symmetric paraparesis or quadriparesis, sensory loss and bladder dysfunction. NMO brainstem lesions are known to cause intractable nausea and vomiting, hiccups (Misu *et al*., 2005), ataxia, narcolepsy and even acute neurogenic respiratory failure (Wingerchuk *et al*., 1999; 2006 and 2007; Popescu *et al*., 2011; Kremer *et al*., 2014; Wingerchuk *et al*., 2015). The disease has a relapsing course in up to 90 percent of cases (Ghezzi *et al*., 2004; Mealy *et al*., 2012). Optic neuritis and transverse myelitis can occur simultaneously, although the interim between disease-defining attacks of optic neuritis and myelitis can be of years or decades (O'Riordan *et al*., 1996).

1.1 Pain in NMO

The extensive involvement of the spinal cord due to inflammatory lesions leads to significant motor, sensory and neurovegetative involvement, whose recovery varies among patients. Pain in demyelinating diseases of the central nervous system had already been described as a factor that contributes to worsening of quality of life, resulting in increased costs for the health system (Clifford and Trotter 1984; Moulin, 1988; Solaro *et al*.. 2004).

The first report on prevalence of pain and its characteristics in this disease dates from 2011. Kanamori *et al*, (2011) described some patterns, characteristics and impact on quality of life and functionality of NMO patients.

Patients with NMO can develop several pain syndromes. Up to the present time, a high prevalence of pain has been reported in this population, which is described as more intense and less responsive to usual treatments when compared to those patients with multiple sclerosis (Kanamori *et al*.,

2011; Qian *et al*., 2012; Kim *et al*., 2012; Muto *et al*., 2015). The most frequently described pain syndrome is neuropathic, although scarce studies have made use of a validated screening instrument for its diagnosis (Zhao *et al*., 2014; Asseyer *et al*., 2018). Also, the majority of published studies have deliberately excluded seemingly non-neuropathic pain syndromes from the analysis of pain in NMO.

Pain syndromes are frequent after spinal cord structural damage and there may be influence of inflammatory mediators of the acute demyelinating disease for the onset of pain in NMO (Bradl *et al*., 2014). As in patients with spinal cord injury of other aetiologies (as traumatic), diverse mechanisms of pain as well as several painful syndromes occur (Finnerup and Jensen, 2004; Bryce *et al*., 2007; Finnerup, 2013). Those include non-neuropathic pain syndromes, as musculoskeletal or nociceptive pain, probably coexisting with neuropathic pain syndromes. Moreover, brain lesions after the acute phase of NMO are not extensive and pervasive cognitive deficits are not an incapacitating feature in this disease. On the other hand, traumatic spinal cord injuries (SCI) frequently concur with brain injuries due to high-energy impacts involved in this pathology and can affect as many as 60% of subjects with spinal cord injury (Wecht *et al*., 2018). Therefore, NMO is an interesting model to study mechanisms of pain in spinal cord injuries due to lesser contributing factors of brain lesions.

The correct clinical diagnosis of the pain syndrome is important for the adequate treatment of pain, which has a dynamic character and can be modified with the course of inflammatory diseases. This dynamism is

characteristic of recurrent autoimmune inflammatory and demyelinating lesions and has a huge impact on the course of pain treatment.

In addition to pain, other non-motor symptoms have been described. These include fatigue, depression, urinary dysfunction, Uhthoff's phenomenon, cognitive dysfunction, pruritus, vomiting and intractable hiccups, restless legs syndrome and other sleep disorders (Chanson *et al*., 2011; Akaishi *et al*., 2015; Muto *et al*., 2015; Song *et al*., 2015; Shi *et al*., 2016). Those symptoms also impact in the quality of life and long-term outcome of NMO patients.

1.2 Study Rationale

To date, few prospective studies have assessed patients with inflammatory lesions of the spinal cord with a focus on pain and its mechanisms. Changes in sensory thresholds are limited to a single study (Pellkofer *et al*., 2013) and there is no information on cortical excitability in NMO. It is also unknown whether pain syndromes can change during the course of the disease. Furthermore, neurologists and pain specialists are oblivious to which medications have greatest potential to improve pain symptomatology in NMO.

With the present study, we aimed to deepen the current knowledge about pain and its mechanisms in inflammatory myelopathies and characterize, through validated scales, the various dimensions and associated pain syndromes and non-motor symptoms (such as disability, Uhthoff's phenomenon, pruritus, urinary and faecal dysfunction, depression, anxiety and

catastrophism). In addition, we sought to prospectively assess the influence of disease progression on pain, and how it correlates with motor changes and inflammatory activity. Furthermore. neuromyelitis optica was chosen as a model of spinal cord injury of non-traumatic aetiology free of widespread cortical lesions that could bias patient's assessment.

Since the last published consensus on the diagnosis of NMO (Wingerchuk *et al*., 2015) the terms "neuromyelitis optica" and "neuromyelitis optica spectrum disorders" were merged and the unified nomenclature "neuromyelitis optica spectrum disorders" (NMOSD) was adopted. For the purposes of this thesis, the term "NMO" was chosen to refer to the disease throughout the sessions.

2 OBJECTIVES

a) Characterize and determine the prevalence of major and secondary pain syndromes in patients diagnosed with NMO and their correlation with data on psychophysics and cortical excitability.

b) Investigate the presence of other non-motor symptoms of the disease: mood, pruritus, Uhthoff's phenomenon, urinary and faecal dysfunction, catastrophism and fatigue.

c) Evaluate the evolution of pain syndromes longitudinally, with the progression and activity of the inflammatory disease.

d) Determine the correlation between the pain syndromes and inflammatory lesion load of the disease.

e) Clarify pain mechanisms in patients with NMO, as a model for SCI without extensive brain lesions or outstanding cognitive deficits.

3 LITERATURE REVIEW

3.1 History of Neuromyelitis Optica

The earliest description of a patient with a sensory deficit, paralysis and visual loss dates back from 1804, by Antoine Portal (Portal, 1804). In this book he describes the clinical history of the “Marquis de Causan", who evolves with a recurrent paralysis and sudden loss of vision. The autopsy revealed a “hardened”, cartilaginous spinal cord at the cervical level with red, inflamed surrounding membranes. The brain and the remainder of the body were fully healthy (Jarius and Wildemann, 2012). Twenty-five years later John Abercrombie described a case of “neuroencephalitis optica”, in 1829, in the second edition of “Pathological and Practical Researches on Diseases of the Brain and Spinal Cord”. A patient with spinal pain, recurrent visual loss and persistent nausea and vomiting is portrayed (Abercrombie, 1828). Edward Hocken gives the account of a paediatric case of sudden onset fever followed by pain in the cervical spine, spasticity and bilateral amaurosis. The author uses the term “spinal amaurosis: for the first time in this report of 1841 (Hocken, 1841; Jarius and Wildemann, 2014). In 1844 Giovanni Pescetto depicted the case of a woman who developed acute amaurosis and cervical myelitis (Pescetto, 1844). In the following years, multiple reports of cases with acute onset tetraparesis and bilateral optic neuritis are to be found in the literature (Durrant, 1850; Clarke, 1865; Allbutt, 1870; Charcot, 1877; Erb,

1880; Schanz, 1893) The term “Neuromyelitis optica acuta” is a translation of the French term ‘neuro-myélite optique aiguë’. It was coined by Eugène Devic in a paper presented on the “Congrès Français de Médecine” in 1894 (Devic,1894a and 1895a). Devic described a singular syndrome characterized by acute myelitis and optic neuritis. Later on the same year, Fernand Gault published his PhD thesis, which reviewed the previous medical literature and described clinicopathological features of 16 cases who presented with sudden visual loss followed in weeks by motor, sensory and neurovegetative symptoms of acute spinal cord injury (Gault, 1894). Peppo Acchioté (Akşiyote) was the first to suggest the eponym *“maladie de Devic*” in 1907 (Acchiote, 1907). Multiple reports and descriptions of the disease followed during the 19th and 20th century (Katz, 1986; Weill and Gallavardin, 1903; Brissaud and Brecy, 1904; Acchiote, 1907; De Lapersonne, 1911; Bouchut and Dechaume, 1927; Salvati, 1928; Marinesco *et al*., 1930; Sager and Grigorescu, 1933; Stengel, 1935; McKee and McNaughton, 1937; Kennedy, 1938; Shone, 1940; Singh, 1944; De and Chatterjee, 1946; Robertson *et al*., 1946; Liu and Tao, 1948; de Gispert Cruz, 1949; Mascati, 1949; Sharma and Sahai, 1949; Stansbury, 1949; Lehoczky, 1952).

The definition and diagnostic criteria changed greatly throughout the 20th century. Earlier studies by Kuroiwa *et al*. in the 70’s and 80’s considered that NMO did not have relapses or long gaps between the myelitis and neuritis. It also excluded cases with mild paresis and unilateral optic neuritis (Shibasaki and Kuroiwa, 1969; Kuroiwa *et al*., 1975 and 1977). In 1996, studies still considered that incomplete myelitis was not a part of the syndrome (O'Riordan

et al., 1996). Although Abercrombie, Devic and Gault described brainstem symptoms in those patients with NMO, it was not until the 21st century that they were definitely considered part of the disease (Samart and Phanthumchinda, 2010; Popescu, *et al*., 2011; Kremer, *et al*., 2014; Lana-Peixoto, *et al*., 2014; Lemos, *et al*., 2015). Interestingly, seminal papers that defined the disease as an entity apart fromMS) proposed diagnostic criteria that excluded patients with symptoms other than neuritis and myelitis (Wingerchuk *et al*., 1999). Brain lesions were thought to be atypical in NMO. Nowadays, it is known that up to 60% of patients do have encephalic lesions, most of them asymptomatic (Wingerchuk *et al*., 2007; Ito *et al*., 2009; Samart and Phanthumchinda, 2010; Collongues *et al*., 2010a; Kim *et al*., 2010; Popescu *et al*., 2010 and 2011; Pires *et al*., 2012; Sato *et al*., 2013; Papadopoulos and Verkman, 2013; Kremer *et al*., 2014; Lana-Peixoto *et al*., 2014; Kimura *et al*., 2014; Wingerchuk *et al*., 2015; Song *et al*., 2015; Lemos *et al*., 2015; Kim *et al*., 2015). Even the classical criteria of 3-or-more-vertebral-segments-LETM to diagnose NMO was challenged recently, with the acknowledgement of shorter and discontinuous lesions in this syndrome (Flanagan *et al*., 2015). In the last years the co-existence of NMO with other autoimmune was also described, such as myasthenia gravis, Hashimoto thyroiditis (Kister *et al*., 2006; Kay *et al*., 2008; Leite *et al*., 2012; Jarius *et al*., 2012a; Spillane *et al*., 2013; Wang and Yan, 2017), and connective tissue disorders, such as systemic erythematous lupus (SLE) and Sjögren syndrome (SS) (Pittock *et al*., 2008; Chanson *et al*., 2013; Carvalho *et al*., 2014; Iyer *et al*., 2014; Freitas and Guimaraes, 2015; Shahmohammadi *et al*., 2018).

The breakthrough discovery of a specific pathogenic autoantibody in 2004 finally defined NMO as an inflammatory demyelinating disease in its own right, distinct from MS (Lennon *et al*., 2004 and 2005; Tanaka *et al*., 2007; Roemer *et al*., 2007). Until recently, NMO was still considered a subtype of MS (Kalman and Lublin, 2001; Lucchinetti *et al*., 2002; de Seze *et al*., 2003; Tanaka *et al*., 2007). The description of the antibody AQP4-Ab, also known as Neuromyelitis optica- Imunoglobulin G (NMO-IgG), revolutionized its diagnostic criteria (Wingerchuk *et al*., 2006). Another autoantibody associated with NMO was described in 2011 and defined as anti-myelin-oligodendrocyte-glycoprotein (MGO-Ab) (Mader *et al*., 2011; Kitley *et al*., 2012b). Notwithstanding, a parcel of those subjects with NMO is still seronegative, and clinicians must rely on clinical and radiologic features to differentiate those from other conditions such as MS.

The recognition that the clinical manifestations of NMO is more heterogeneous than previously thought led to the term “Neuromyelitis optica spectrum disorders”, definitely coined in 2007 (Wingerchuk *et al*., 2007; Jacob *et al*., 2007; Wingerchuk, 2007a and 2007b). The term initially applied to limited forms of NMO, such as isolated LETM, isolated recurrent optic neuritis and exclusive brainstem manifestations. Typically, but not necessarily, those conditions occur in the presence of AQP4-Ab.

Finally, the need of a better characterization of subjects with NMO and the discovery of new pathological, clinical and laboratory markers led to the last clinical consensus on the disease, published in 2015 (Wingerchuk *et al*., 2015). The 2015 International Panel for NMO Diagnosis (IPND) criteria

combined the 2006 and 2007 definitions by including all AQP4-Ab seropositive patients. It also defined different criteria based on seropositivity to AQP4-Ab. A broader array of clinical and magnetic ressonance image (MRI) phenotypes was defined. Posterior revaluation of the consensus reported that it led to a 76% increase in the diagnosis of NMO (Hamid *et al*., 2017).

3.2 Immunopathogenesis of NMO

The pathophysiology of NMO is primarily mediated by the humoral immune system, while MS is mostly a cell-mediated disorder. In NMO, profuse demyelination and inflammation affects multiple spinal cord segments and the optic nerves with associated axonal loss, perivascular lymphocytic infiltration, and vascular proliferation. Prominent vasculocentric complement activation and immunoglobulin deposition are seen in a distinctive rosette and rim pattern surrounding thickened and hyalinised blood vessels (Wingerchuk *et al*., 2007). Large numbers of eosinophils, neutrophils, macrophages and a small number of T cells are found in those active lesions. This vasculocentric distribution of immunocomplexes corresponds to the normal expression of aquaporin 4 in the endfeet of astrocytes and is accompanied by a marked loss of astrocytic Aquaporin-4 (AQP4). The neuropathologic features of NMO at autopsy are more compatible with necrotic lesions of the cord rather than demyelination. Brain lesions exhibit the same profile of the spinal cord ones (Pittock *et al*., 2006; Mandler *et al*., 1993; Lucchinetti *et al*., 2002). In the CNS, AQP4-ab binds selectively to the abluminal face of microvessels, pia, subpia, and Virchow-Robin sheaths.

The association with autoimmune diseases such as SLE, SS, thyroiditis, myasthenia gravis and the identification of the NMO disease-specific autoantibody, AQP4 autoantibody, provided further evidence for an autoimmune pathogenesis in this disease (Lennon *et al*., 2004 and 2005). AQP4-Ab belongs to the complement activating immunoglobulin G-1 (IgG1) subclass. A key feature of NMO is the presence of terminal membrane attack complex, indicating complement activation in sites of AQP4 loss.

Numerous proinflammatory cytokines are elevated in the serum and CSF of NMO patients. Serum IL-6 are increased and are involved with the continuance of AQP4-Ab-positive plasmablasts in the blood. In the CSF, IL-6 and B cell recruiting and activating factor (BAFF) levels are also high, providing a B-cell friendly environment within the CNS. Anaphylatoxin C5a levels are also elevated in the CSF of those patients. Eculizumab, a C5 inhibitor was demonstrated to reduce relapse rates in NMO (Jarius *et al.*, 2014).

The immunologic mechanisms of lesions in seropositive anti-myelin oligodendrocyte-glycoprotein IgG (MOG-IgG) patients are not fully understood. Not even the normal function of MOG is clarified. MOG is part of the immunoglobulin superfamily. It is one of the components of the CNS myelin sheath. It probably plays parts in the adhesion of myelin fibres, regulation of the stability of oligodendrocyte microtubule, and regulation of the interaction between myelin and the immune system by the complement pathway. MOG-IgG pathogenicity is related to alteration of oligodendrocyte cytoskeleton. It is also implicated in both complement-dependent and cell-based cytotoxicity. No evidence of astrocytopathy has been reported in MOG-IgG cases. In older

studies about animal models with rats, the injection of MOG peptides produced a paralytic relapsing-remitting neurological disease with extensive plaque-like demyelination via T-cell response (Bernard *et al*., 1997; Dale *et al*., 2014; Spadaro *et al*., 2015; Bar-Or *et al*., 2016; Dos Passos *et al*., 2018).

3.3 Epidemiology of Neuromyelitis Optica

Since NMO was considered a subtype of MS until recently, reliable epidemiological studies were not available until the last decade. It is probable that historically many NMO cases were misdiagnosed as MS, infectious myelitis or spinal cord tumours. Prevalence and incidence rate in many countries have not yet been reported and there are few population-based studies.

NMO is considered a rare disease worldwide: the prevalence rate ranges between $0.52/10^5$ (95% CI 0.39–0.67) (Cabrera-Gomez *et al*., 2009) and $10/10^5$ in Martinica (Flanagan *et al*., 2016).

In European countries with predominantly Caucasian populations, NMO prevalence rates ranges from 0.72 in Merseyside, United Kingdom (UK) (Jacob *et al*., 2013), 0.77 in Austria (Aboul-Enein *et al*., 2013), 0.89 in Catalonia (Sepulveda *et al*., 2017), 1.96 in Wales (Cossburn *et al*., 2012) to 4.4 per 10^5 in Denmark (Asgari *et al*., 2011). In Caribbean islands (Cuba and Martinica) with black, mixed and Caucasian (Spanish) populations, prevalence rates vary from 0.54 to 2.53 per 10^5 (Cabre *et al*., 2009). A Cuban study reported a higher prevalence of $0.8/10^5$ amid blacks and mixed individuals and $0.43/ 10^5$ amid white ones. In Asia, there was also a great range of prevalence values: in Japan, it varied from 0.9 to $4.1/ 10^5$ (Houzen *et al*., 2012 and 2017),

in Southern India it was 2.7/10^5 (Pandit and Kundapur, 2014), in Penang Island, Malaysia, it was 1.99/10^5 (3.3/10^5 in Chineses and only 0.43/10^5 in Malays) (Hor *et al*., 2018). In Iran, three different studies reported prevalences between 0.81 and 1.9 per 10^5 (Etemadifar *et al*., 2014; Kashipazha *et al*., 2015; Eskandarieh *et al*., 2017). In Australia and New Zealand, prevalence was 0.7 per 10^5: 1.57/10^5 in Asians and 0,57/10^5 in whites (Bukhari *et al*., 2017). In the United States, prevalence in a predominantly white population was set at 3.9/10^5. The same study set the prevalence rate at 10/10^5 in a predominantly black population in Martinica, the highest ever reported (Flanagan *et al*., 2016). One study in Brazil reported a cross sectional prevalence of NMO of 0.37 per 10^5 inhabitants, in a single city (Alvarenga *et al*. 2017).

Similarly, incidence rates differ according to geographic area and predominant local ethnicity. It is also heavily affected by changes in diagnostic criteria of NMO throughout the years. In predominantly white populations in the UK and Austria it was 0.08 (Jacob *et al*., 2013) and 0.05 per 10^5 (Aboul-Enein *et al*., 2013), respectively. In Denmark, incidence varied from 0.08 (Dale *et al*., 2018) to 0.40 per 10^5 (Asgari *et al*., 2011), a disparity certainly attributable to different diagnostic criteria used in each study. In Cuba it was as low as 0.05/ 10^5, and was similar across ethnic groups. In the United States of America (USA), it was 0.07/10^5 in a white population. The same study described an incidence rate ten times higher in a population of Martinica (Flanagan *et al*., 2016).

Overall, these studies suggest a relatively broad range of prevalence rates, including differences in geographic and ethnic cohorts. Cases of NMO have been described throughout the world, although there seems to be a higher prevalence among non-Caucasian populations: Black and Asians.

Remarkably, ethnicity is a prominent element in prognosis of NMO. In Cuba, black subjects developed onset symptoms older, had more relapses and more lesions on brain MRI when compared to white ones (Cabrera-Gomez *et al*., 2009). The same pattern of greater brainstem MRI abnormalities was shown amongst African-Americans in the USA (Flanagan *et al*., 2016). A comprehensive 2012 study about prognostic factors in AQP4-Ab positive patients in the UK and Japan demonstrated that age of onset and ethnicity were associated with outcome: young white patients presented more optic neuritis, but visual impairment was more severe in non-white patients. Older patients in all ethnicities presented with myelitis and greater motor disability and white patients had a later age of onset, therefore worse motor outcomes. In contrast, white patients had a later age of onset and worse motor outcomes. Only 20.3% of the British sample in this study was black of Caribbean origin and it was significantly younger at onset than white and Japanese patients combined (mean 28.0 ± 13.1 years and 44.9 ± 17.2 years, respectively). Again, brain and brainstem onset symptoms were more common in Afro-Caribbean patients and all of them had a relapsing course, whereas 20% of the Japanese and white subjects had a monophasic course. Relapse rates were higher in black when compared to Japanese patients (Kitley *et al*., 2012a). It is not fully clear whether ethnic differences are also related to social factors. However, it is noteworthy that universal health care is guaranteed in the UK and Japan.

All studies have reported a higher prevalence of NMO in women rather than men, with a female predominance usually higher than observed in MS, ranging from 66–88% in the studied cohorts (Cabre *et al*., 2009; Cabre, 2009;

Collongues *et al*., 2010a; Asgari *et al*., 2011). A more even distribution between men and women was reported in monophasic cases, although there might be a misdiagnosis bias in those studies. A relapsing course was reported in 81-91% of those with positive AQP4-Ab (Jarius, *et al*., 2012b; Collongues *et al*., 2014).

Women also represent most of seropositive AQP4-Ab patients, around 85%, when compared to only 44% amid the seronegative ones (Kitley *et al*., 2013). There are some subtle gender variations in different ethnicities: women represented 82% of patients in whites from the UK, 87% in Austria (only whites and positive AQP4-Ab), 75%-100% in Afro-Caribbeans, and 98% in a Japanese cohort (Siritho *et al*., 2011).

The lowest female: male (F:M) ratio reported was in India 1.2:1 (Pandit and Kundapur, 2014). In Iran, it varied from 2.3:1 (Etemadifar *et al*., 2014) to 7.5:1 (Kashipazha *et al*., 2015; Eskandarieh *et al*., 2017). In Japan, F:M ratio was 5.7:1 (Houzen *et al*., 2017), Australia 6:1(Bukhari *et al*., 2017). In Europe, it varied from 2.8:1 (Asgari *et al*., 2011) in Southern Denmark to 7:1 in Austria (Aboul-Enein *et al*., 2013). In the Caribbean it ranged from 7.3:1 to 8.8:1 (Cabrera-Gomez *et al*., 2009; Flanagan *et al*., 2016). In Minnesota, USA, and Brazil it was 5:1 (Papais-Alvarenga *et al*., 2002; Flanagan *et al*., 2016).

Seropositivity to AQP4-Ab was high in all studies, except for a Southern Indian which reported only 27% of seropositive patients. Interestingly, it was also the study with the higher prevalence of men amid all the previous ones. Within the American continent studies informed seropositivity between 58.6 and 73.5% in Brazil (Papais-Alvarenga *et al*., 2015; Alvarenga *et al.*, 2017; Adoni *et al*., 2008); 79% in Martinica and 83% in the USA (Flanagan *et al*., 2016). In Europe, it was

also high: from 62% in the South Denmark to 88% in the UK (Asgari *et al*., 2011; Jacob *et al*., 2013). In Japan, the most recent study in Hokkaido reported 79% of positive AQP4-Ab patients. In Iran, it ranged from 51 to 66%.

The other antibody implicated in the pathology of NMO is the MOG-IgG. Most studies have found MOG-IgG exclusively in AQP4-IgG-negative patients. Patients with MOG antibodies represent around 20% of the patients negative for AQP4-Ab in different studies. There seems to be a higher prevalence of men amid seropositive MOG-IgG individuals when compared to AQP4-Ab positive population (Sato *et al*., 2014; Jarius *et al*., 2016). Median age of onset in those patients does not differ from those with AQP4-Ab: between 31 and 37.5 years-old (y.o.) in different studies (Sato *et al*., 2014; Oliveira *et al*., 2018; de Seze, 2019).

When compared to MS, age of onset is usually higher in NMO. A compilation of 226 NMO patients in South America showed mean age of onset of 31.2±13.5 y.o. (Alvarenga *et al.*, 2017), similar to a median age of 30.2 y.o. in Cuba (Cabrera-Gomez *et al*., 2009). Adoni *et al*. (2010) reported the youngest median age of onset of all samples: 26 y.o. (range 7-55 yo). The oldest median age of onset was reported in Austria, of 55.2 y.o. (Aboul-Enein *et al*., 2013). The mean age of onset of NMO ranged from 32.6-45.7 y.o. in most cohorts (Pandit *et al*., 2015). Wingerchuk *et al*. (1999) and Jarius *et al*. (2012b) described peak of onset between 35 and 45 y.o. Late-onset NMO (onset age > 50 y.o.) is not rare. In a large European multicentre cohort study, it comprised 25% of cases and onset age ranged from 50 to 82.5 y.o. Eighty percent of this cohort was female, 93% were Caucasians and 85% were seropositive for AQP4-Ab. In this age group, outcome was characterized by

motor impairment and comparatively good visual function. Both EDSS and death were predicted by older age at onset (Collongues *et al*., 2014). Two previous studies showed that the proportion of seropositive females increased with age, and was highest in those older than 65 y.o. (Jarius *et al*., 2012b; Quek *et al*., 2012). Paediatric onset is rare: less than 5% of cases have their first relapse before 18 y.o. (Collongues *et al*., 2010b; Kitley *et al*., 2012a).

The disorder is sporadic in the great majority of cases. Familial cases have been reported in a frequency of up to 3% of total cases and are indistinguishable from sporadic ones in age, sex and clinical presentation features (Matiello *et al*., 2010).

Up to 90 percent of cases have a relapsing course (Ghezzi *et al*., 2004; Mealy *et al*., 2012). If untreated, 60% of patients will have a relapse in 12 months and 90% will have a relapse within 3 years of the onset event (Wingerchuk *et al*., 1999; Wingerchuk and Weinshenker, 2003; Adoni *et al*., 2010; Asgari *et al*., 2011). Different studies described median time to second attack between 8 and 12 if the disease is left untreated (range 1-216 months). Mortality ranged from 2.9-25% and was related to the autoimmune-inflammatory disease in most cases (Pandit *et al*., 2015). Nowadays, five-year survival rates are higher than 90% (Ghezzi *et al*., 2004).

A study comparing AQP4-Ab seropositive and seronegative patients failed to show differences in age of onset, time to relapse, relapse rates, rate of EDSS progression, and mortality rate. Predictors of outcome were tetraparesis during the first attack of TM and multiple attacks of TM in the first year of the disease (Jarius, *et al*., 2012b). AQP4-Ab positive subjects were

reported as having a higher frequency of lesions in the periaqueductal grey matter, hypothalamic, and area postrema (areas with greater density of Aquaporin 4) (Marignier *et al*., 2013).

More than half of patients with NMO develop both ON and longitudinally extensive transverse myelitis (LETM) (Akaishi *et al*., 2017).

Between 30 and 50% of patients with NMO have laboratory or clinical findings of systemic or organ-specific autoimmunity. The most commonly reported are SS, SLE, Myasthenia gravis (MG) and autoimmune thyroid disorders (Shahmohammadi *et al*., 2018; Jarius *et al.*, 2014).

3.4 Clinical Presentations, Disease Course and Prognosis

The classical acute clinical presentation of NMO consists of severe bilateral or unilateral ON and LETM. The 2015 consensus recognized symptoms resulting from NMO characteristic brain lesions as important for its diagnosis. Some clinical presentations are especially suggestive of NMO: simultaneously bilateral optic neuritis which involves the optic chiasm, causes an altitudinal visual field defect or leads to serious visual disability (acuity 20/200 or worse); complete spinal cord syndrome, particularly in the context of painful tonic spasms; and an area postrema syndrome, comprising intractable hiccups or nausea and vomiting (Wingerchuk *et al*., 2015).

Brain lesions were reported to cause different symptoms. The most cited are intractable hiccups nausea and vomiting, which can affect up to 46% of NMO patients (Kim *et al*., 2015). Other less common manifestations include: nystagmus, ophthalmoplegia, dysarthria, dysphagia, ataxia, narcolepsy,

syndrome of inappropriate antidiuretic hormone secretion, hypothermia, hypotension, hypersomnia, hyperphagia, hypothyroidism, hyperprolactinemia, galactorrhoea and behavioural changes (Baez *et al*., 2012; Samart and Phanthumchinda, 2010; Wingerchuk, 2007b; Kremer *et al*., 2014; Adoni *et al*., 2010). Hemispheric lesions can cause hemiparesis and encephalopathy. Some dramatic cases may present with acute respiratory failure due to wide-ranging cervical and medulla lesions.

A small subgroup of patients was reported to have a more benign outcome, with minor disability after 10 years (Collongues *et al*., 2011).

Most cases follow a relapsing course (80- 90%) (Mealy *et al*., 2012; Ghezzi *et al*., 2004). Although optic neuritis and transverse myelitis can occur simultaneously, the interval between the events can vary greatly (from some months to decades).

Older studies describe severely impaired patients after 7-8 years of disease: 60% of patients with EDSS $\geq$ 6 and blindness in one eye (Wingerchuk *et al*., 1999). This figure is changing rapidly with more awareness about the disease and more effective treatments.

Other laboratory features typical of this disease include conspicuous cerebrospinal fluid (CSF) pleocytosis (> 50×10^6 leucocytes/L) with a high proportion of neutrophils in 35% of patients (Jarius *et al*., 2011). Oligoclonal bands in the CSF are present in less than 20% of subjects with NMO (Wingerchuk *et al*., 2015).

Compared to patients with seropositive AQP4-Ab or all-autoantibody seronegative patients, subjects seropositive for MOG-IgG antibodies were

more frequently male, had a more restricted phenotype (optic nerve involvement more than spinal cord), more frequently had bilateral simultaneous optic neuritis, more often had a single attack, had spinal cord lesions distributed in the lower portion of the spinal cord, and usually demonstrated better functional recovery after an attack. Some studies reported them as younger, but the full characterization of those subjects is still in development (Sato *et al*., 2014; Jarius *et al*., 2016; Chen *et al*., 2018; Oliveira *et al*., 2018; de Seze, 2019).

To date, there is no definite known cure for NMO. Acute attacks are treated with IV Methylprednisolone and/or Plasma exchange. No Randomised Clinical Trial (RCT) was performed to assess efficacy of these treatments. Data on intravenous immunoglobulin are still scarce (Marignier *et al.*, 2017). Maintenance therapy include use of azathioprine, mycophenolate mofetil and rituximab (Sellner *et al*., 2010; Trebst *et al*., 2014).

3.5 MRI Findings

In the acute phase, the spinal cord lesions are traditionally described as LETM that affects 3 or more vertebral bodies, usually in the cervical and/or thoracic segments. Such lesions normally comprise the central grey matter and are accompanied by cord swelling, gadolinium-enhancement, hyperintensity on T2-weighted and hypointensity on T1-weighted sequences on the MRI (Kim *et al*., 2010). They are more frequently localised in the cervical and upper thoracic spinal cord segments, rather than lower thoracic and lumbar regions (Kim *et al*., 2015). One study of spinal cord MRI NMO reported

that over 60% of them had cervical cord involvement (Cassinotto *et al*., 2009). Another study showed that 70% of patients who had LETM had cervical cord involvement (27% of which with extension to the brainstem) (Asgari *et al*., 2013). Notwithstanding, shorter and more caudal myelitis have been described in recent years (Flanagan *et al*., 2015). During the chronic phase and specially after multiple relapses, the cord may evolve with atrophy and cavitations at the sites of previous inflammation.

Optic neuritis lesions in NMO regularly comprise more than half of the optic nerve length and may involve the optic chiasmal. During the acute phase there may be a marked swelling and contrast enhancement. During the chronic phase of previously affect optic nerves atrophy with high signal on T2-weighted images may occur (Akaishi *et al*., 2016; Kim *et al*., 2015).

Brain abnormalities are found in up to 85% of patients with NMO and can be subdivided in:

a) Dorsal brainstem lesions adjacent to the fourth ventricle (very specific of patients with NMO) including the area postrema and the nucleus tracts solitarius. The area postrema has a more permeable brain blood barrier and is more easily targeted by AQP4-Ab. They often continue to cervical lesions.
b) Diencephalic lesions surrounding the third ventricles and cerebral aqueduct, which include the thalamus, hypothalamus, and anterior border of the midbrain.
c) Periependymal lesions surrounding the lateral ventricles- NMO lesions are located immediately next to the lateral ventricles. Acute

lesions in the corpus callosum are often oedematous and heterogeneous, creating a “marbled pattern”. In the chronic phase those lesions can evolve with atrophy, cystic changes or may simply disappear (Nakamura *et al*., 2009).

d) Hemispheric white matter lesions (> 3cm dimeter)- usually broad and confluent, with tumefactive aspect or long radial-shape following white matter tracts. They tend to shrink or disappear. Some lesions can mimic acute disseminated encephalomyelitis (ADEM) or neoplasias.

e) Lesions involving the corticospinal tracts, which can be unilateral or bilateral.

f) “Cloud-enhancing lesions, with enhancement after administration of gadolinium intravenously (IV) and blurred margins on the MRI (Ito *et al*., 2009; Pires *et al*., 2012; Kim *et al*., 2015). Other laboratory features typical of this disease include conspicuous CSF pleocytosis (> 50×10^6 leucocytes/L) with a high proportion of neutrophils (Jarius *et al*., 2011). Oligoclonal bands in the CSF are present in less than 20% of subjects with NMO.

3.6 Diagnostic Criteria

Different diagnostic criteria have been used. The last consensus on NMO diagnosis dates back from 2015. For the purposes of this thesis, Wingerchuk *et al.* (2006 e 2007) criteria were considered (Boxes 1 and 2).

Box 1 - Proposed diagnostic criteria for neuromyelitis optica (NMO) (Wingerchuk *et al*., 2006)

Definite NMO
Optic neuritis
Acute myelitis
With at least two of three supportive criteria:
1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments 2. Brain MRI not meeting diagnostic criteria for multiple sclerosis 3. AQP4-Ab seropositive status

Abbreviations: NMO - Neuromyelitis optica; MRI - magnetic resonance image
Adapted from the "Revised diagnostic criteria for neuromyelitis optica", Wingerchuk *et al*, 2006.

Box 2 - Proposed diagnostic criteria for Neuromyelitis spectrum disorders (NMOSD) (Wingerchuk *et al*., 2007)

Limited forms of neuromyelitis optica
Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord lesion seen on MRI)
Optic neuritis: recurrent or simultaneous bilateral
Asian optic-spinal multiple sclerosis
Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease
Optic neuritis or myelitis associated with brain lesions typical of neuromyelitis optica (hypothalamic, corpus callosal, periventricular, or brainstem)

Abbreviations: MRI - magnetic resonance image
Adapted from the "The spectrum of neuromyelitis optica", Wingerchuk *et al*, 2007.

In 2015 the terms NMO definite and NMOSD were united into the NMOSD nomenclature witinh the "International consensus diagnostic criteria for neuromyelitis optica spectrum disorders". Serologic status for AQP4-Ab was acknowledged as an important watershed for the different possible clinical presentations in this context (Box 3).

Box 3 - NMO diagnostic criteria for adult patients (Wingerchuk *et al.*, 2015)

Diagnostic criteria for <u>POSITIVE</u> AQP4-IgG NMO

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

Diagnostic criteria for <u>NEGATIVE OR UNKNOWN STATUS</u> AQP4-IgG NMO

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfilment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable

Core clinical characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMO-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMO-typical brain lesions

Additional MRI requirements for NMO without AQP4-IgG and NMO with unknown AQP4-IgG status

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium- enhancing lesion extending over half of the optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending over $\geq$3 contiguous segments (LETM) OR $\geq$3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

Abbreviations: AQP4: aquaporin-4; IgG: immunoglobulin; LETM: longitudinally extensive transverse myelitis lesions; NMO: neuromyelitis optica
Adapted from the "International consensus diagnostic criteria for neuromyelitis optica spectrum disorders", Wingerchuk *et al.* (2015).

The last consensus cautions against radiographic lesions in the MRI more compatible with MS, like cortical involvement, Dawson's fingers, incomplete lesions involving predominantly the periphery of the spinal cord. It

also highlights that sarcoidosis, neoplasias, paraneoplastic syndromes and infectious diseases can cause lesions that mimic NMO.

Unlike some forms of MS, NMO does not have a progressive course.

3.7 "Non-Motor" Symptoms in NMO

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. These include: pain, pruritus, bowel and bladder dysfunction, fatigue, cognitive dysfunction, mood disorders (mainly anxiety and depression), Uhthoff phaenomenon, sleep disorders and pruritus.

Blanc *et al.* (2008) was the first to describe subtle cognitive dysfunctions in patients with NMO when compared to healthy subjects, with poorer performance in tests of attention, short-term memory, executive functions and language. Those patients did not perform worse than MS, nevertheless and the impact of mood was not evaluated. He *et al*. (2011) described memory and attention impairment and decreased information processing speed in patients with NMO without current brain lesions and found a correlation with fatigue and depression. He concluded that fatigue and depression may affect cognitive function in those patients with NMO. The same pattern of cognitive impairment was found in another sample of NMO patients, in which 67% of subjects presented with some dysfunction in one of the cognitive domains (Moore *et al*., 2016).

In 2011 Chanson *et al*. reported lower quality of life scores (HRQOL) in patients with NMO when compared to normal subjects. He found that the

HRQOL dimension related to cognitive function was better in NMO than in MS, and the sphincter dysfunction worse in NMO than in MS. Fatigue as seemed to be milder in NMO when compared to MS and he ascertained disability as the main predictive factor of an unfavorable evolution. Shi *et al*. (2016) demonstrated that lower HRQOL scores was predicted by anxiety, disability, fatigue and depression in NMO. Depression and fatigue were again described as equally prevalent in MS and NMO patients by Akaishi *et al*. (2015), and the oral administration of levocarnitine in patients with low serum carnitine levels was not beneficial.

Depression seems to be insufficiently treated and correlate with neuropathic pain and fatigue. Chavarro *et al.* (2016) described a NMO cohort in which 28% of patients had moderate or severe depression and that 48% had neuropathic pain, as screened by the “PainDetect questionnaire”. Severity of depression was mildly associated with neuropathic pain, but this relationship was confounded by levels of fatigue. Only 40% of patients with moderate or severe depressive symptoms received antidepressant medical treatment and yet, 50% of those treated reported persistent moderate to severe depressive symptoms even under treatment. Cognitive impairments were observed in 67% of NMO patients. The prevalence and profile of cognitive impairments and lifetime prevalence of depression was similar between NMO and MS groups. However, significantly higher rates of recurrent depression and suicidality were observed in NMO patients.

Bowel and bladder dysfunction was reported in almost 80% of patients with NMO. Urinary symptoms reported included urgency, hesitancy,

incontinence, interrupted stream and nocturia. Over 23% of patients were constipated and 23% had become incontinent. Disease duration was 6.5 years (range 4 -468 months). A study with video urodynamics and bladder ultrasonography made in 2016 found that 80% of patients with NMO had lower tract urinary symptoms (LUTS) and voiding dysfunction: detrusor-sphincter dyssynergia in 23.3%, detrusor overactivity in 20% and both in 36.6% of subjects this cohort. Mean disease duration was 33.8±30.8 months. It also found a correlation between voiding dysfunction the degree of neurological impairment (de Carvalho *et al*., 2016).

Uhthoff phaenomenon was investigated in 2014 and found to be present in 48.1% of the subjects with NMO, compared to 54.1% of those with MS. Concomitant sensory and motor symptoms were the most frequent symptoms, followed by visual disturbances (Park *et al*., 2014). Another study described that 27.1% of the NMO subgroup presented this phaenomenon (Muto *et al*., 2015).

Disruption of sleep architecture was described in NMO: decrease in sleep efficiency, greater number of arousals per night, sleep apnea and a much higher frequency of periodic leg movements when compared to healthy subjects, especially in those patients with infratentorial lesions. Another study decribed hypoxemia, sleep disturbances and depression in these patients (Song *et al*., 2015; Pan *et al*., 2015; Hyun *et al*., 2016).

Pruritus was noted to be common in patients with NMO, and described in frequencies between 26.3 and 64.4% of the cohorts (Elsone *et al*., 2013; Xiao *et al*., 2016Netravathi *et al*., 2017; He *et al*., 2017). Elsone *et al*. (2013) was the first to describe it in 2013, with a prevalence of 27.3% within a week

of other symptoms of TM: 25% of this sample had the symptom as their first manifestation of myelitis (first or relapses). An Indian study reported prevalence of pruritus in 28.1% of patiens. All of them reported it as their onset symptom of TM (Netravathi *et al*., 2017). A Chinese cohort informed pruritus during the course of their illness in 64.4% of subjects. Of those, 42.1% had it as their initial symptom, followed by limb weakness (He *et al*., 2017).

3.7.1 Pain in NMO

Pain was not fully recognized as a frequent and significant symptom in NMO until 2011, when a high prevalence of refractory pain was reported in these patients with a great impact on quality of life. In a cross-sectional study, Kanamori *et al*. (2011) evaluated 37 patients with NMO and encountered chronic pain in 83.8% of them. When compared to MS, patients with NMO had higher scores on Brief Pain Inventory (BPI). They also found that HRQOL scores were lower in those patients. The author describe pain involving “trunk and both legs” as the most frequent in those subjects with NMO, but no other neuropathic pain screening tool was used. In 2012, two studies evaluated the frequency of painful (or paroxystic) tonic spasms. Kim *et al*. (2012) described a much higher frequency of Painful tonic spasms (PTS) in NMO when compared to MS and idiopathic acute transverse myelitis without anti-aquaporin 4 antibody (25%, 2.9 and 2.4% respectively). In this study patients had a mean interval of 48.1 days from the onset of the first myelitis episode and the beginning of PTS. Usmani *et al*. (2012) informed the prevalence of PTS in 8 (14% of their cohort) of patients with NMO. Onset of PTS was

between 0 and 91 months after the onset of disease (mean of 24.6 months). The authors inform 87.5% of patients had a good response to carbamazepine. Another Brazilian paper describes prevalence of 94.7% of tonic spasms in NMO, at some stage of the evolution of the disease (Abaroa *et al*., 2013). Two other studies reported prevalence of PTS between 22.6 and 26.7% in NMO (Carnero Contentti *et al*., 2016; Liu *et al*., 2017) and included patients in any phase of the disease. All those studies reiterate a good response to sodium-channel blocking antiepileptic drugs for PTS (Carbamazepine or Oxcarbazepine).

In 2012, the first study that attempts to group pain syndromes in NMO patients is published. Qian *et al*. (2012) establishes a prevalence of 86.2% of pain in NMO patients, and informs the following pain syndromes: “Tonic spasms” (89.7%); “Dysesthetic pain" (pain associated with neuropathic phaenomenon such as tingling, numbness, burning) (82.8%), “Banding/girdle” (69%), “Lhermitte sign” (65.5%), and retro orbital pain (55.2%). The paper also informs that most patients with NMO still had pain scores greater than 4, despite the use of analgesic medication. Pain syndromes considered to be “non-neuropathic” were excluded from those analysis and time between the last relapse and the study entry evaluation is not clear.

The first and only study to perform quantitative sensory test in NMO patients dates from 2013. Pellkofer *et al*. (2013) reported that 10 out of 11 patients with NMO (90.9%) presented with neuropathic pain, ascertained by the report of descriptors associated with neuropathic pain, such as burning, tingling, pins and needles and pruritus. The study mixed patients in chronic

and acute phase of the disease (last relapse between 2.5 and 27 months). Although DN-4 Questionnaire is described as being used, its final scores are not reported. Pain located in an area corresponding to CNS lesion was considered to be neuropathic, and it was the case of all patients. QST was conducted on both hands and both feet of patients, regardless of their pain area. When compared to healthy controls, QST profile of NMO patients presented mechanical and thermal sensory loss, dynamic mechanical allodynia and paradoxical heat sensation. Abnormal mechanical hypoalgesia or hyperalgesia VAS scores were found to correlate with plasma levels of the endogenous cannabinoid 2-arachidonoylglycerole (2-AG). The authors conclude that the degree of mechanical hyperalgesia reflects central sensitization of nociceptive pathways which seem to be controlled by the major brain endocannabinoid 2-AG.

DN-4 Questionnaire was used as a screening tool for neuropathic pain for the first time in a British 2014 study. Among 50 NMO patients, DN-4 was positive for neuropathic pain (NP) in 62% (31/50) of patients. Three subjects denied pain. Pain was more often localized on back and legs. Over half of patients presented a BPI (Brief pain inventory) severity index greater than 7. Possible non-neuropathic syndromes are not described and pain was associated with a lower physical composite score (PCS) of SF-36. (Zhao *et al*., 2014).

In 2016 Kong *et al*. investigate the relationship between NMO and AQP4-Ab status. In a cross-sectional study with 44 patients, pain scores correlated strongly with quality of life, as previously reported in other studies. Nevertheless, pain was only correlated with disability in the subgroup

seropositive for AQP4-Ab. Data from both groups showed a correlation between pain and pain catastrophizing thoughts scales (PCTS), which is hardly surprising. However, patients with AQP4-Ab negative showed a greater correlation between pain and PCTS.

Tackley *et al*. (2017) evaluated 76 individuals seropositive for AQP4-Ab. The BPI pain severity subscore was used to assess individuals and pain assessment was made only once: individuals were deliberately instructed to report only “myelitis-related pain”. Whereas all subjects had their previous spinal cord MRI assessed, a subset of 26 of them had another spinal cord MRI performed at the time of the study entry. The authors concluded that persistent thoracic lesions associated with higher chronic pain scores, unrelatedly to number of myelitis relapses, lesion length and lesion burden.

Different types of headaches have been reported in NMO, although it is probably even more underreported than the other types of pain. Pain upon the acute optic neuritis is well recognized and it is the first symptom in up to 67% of patients (Morrow and Wingerchuk, 2012). Trigeminal neuralgia was reported in 3 out of 258 NMO patients (Kremer *et al*., 2014) but another study focusing on the images of patients with this diagnosis and trigeminal neuralgia complains did not find trigeminal root entry zone abnormalities on MRI (Sugiyama *et al*., 2015). Whether trigeminal neuralgia was a comorbidity or a symptomatic presentation of the disease (as seen in circa 5% of MS patients) remains to be investigated. Case reports describe trigeminal autonomic cephalalgia (Mathew *et al*., 2016) and cervicogenic headache(Choi *et al*., 2014) as initial (and frequently misleading) presentations of NMO. The

prevalence of comorbid primary headache in NMO is not known. A Japanese study reported higher prevalence of migraine with aura amid AQP4-Ab-positive “optospinal MS” when compared to seronegative ones (Doi *et al*., 2009; Masters-Israilov and Robbins, 2017).

Recently, a cross-sectional study reported pain in MOG patients and informed different its different syndromes. It used painDETECT Questionnaire as a screening tool for NP. Chronic pain was present in 86% (12/14) MOG-IgG-positive (86%), 83% (24/29) AQP4-IgG-positive and 100% (6/6) of AQP4 and MOG-IgG-negative. Neuropathic pain was found in 41.7% of patients with positive MOG-IgG, an only in those with myelitis (which comprised 50% of those with neuropathic pain). Headache/neck pain was found in 41.7% of subjects in this group. Among the 29 patients seropositive for AQP4-Ab, 27 had previous myelitis, and neuropathic pain was described in 79.1% of them. Headache and neck pain were found in other 20.8%. Those negative for all antibodies presented with neuropathic pain in 83.3% and headache in 33.3% of cases. Pain associated with arthralgias and spasticity was described in a minority of all 3 groups. Only 36% of them received analgesic medications and pain relief was neglectable (Asseyer *et al*., 2018).

3.8 Pain in Other Spinal Cord Injuries

Pain in non-inflammatory spinal cord injuries has been extensively studied and is reported to be highly prevalent, with most studies describing pain in over 2/3 of patients. The estimates do vary greatly between studies, mainly due to different classifications for pain in SCI. The overall prevalence

of pain after SCI ranges from 25 to 96%(Dijkers *et al.*, 2009),whereas for severe pain, the prevalence ranges from 30 to 51%.9 (Bryce *et al*., 2012a).

A study from Siddall *et al*. (2003) found that after 5 years of SCI the most prevalent pain syndrome was musculoskeletal, affecting 58% of subjects. It was followed by “at level” neuropathic pain (present in 42% of sample) and “below level” neuropathic pain (prevalent in 34% of subjects).

Factors associated with the onset of pain have been studied but results are conflicting. Observational studies have suggested that neuropathic pain is more common in those with incomplete lesions (Davidoff *et al*., 1987), although it was not confirmed by other authors (Summers *et al*., 1991). The lesion of the spinothalamic tract is considered necessary to the onset of neuropathic pain in SCI subjects but it is certainly not enough (Finnerup and Jensen, 2004). Psychosocial factors such as disturbed mood and acceptance of disability seem to be related to the presence and severity of pain in SCI patients (Stormer *et al*., 1997).

Interestengly, all studies with SCI patients have considered mainly spinal cord lesions secondary to traumas and aggressions (gunshot wounds and stabbing). Most studies exclude those with SCI secondary to inflammatory lesions.

In 2012 a unified pain taxonomy for SCI was developed by an expert panel (Bryce *et al*., 2012a and 2012b). It recognizes different pain mechanisms for patients with SCI (nociceptive and neuropathic) and subdivides as shown in Figure 1 below:

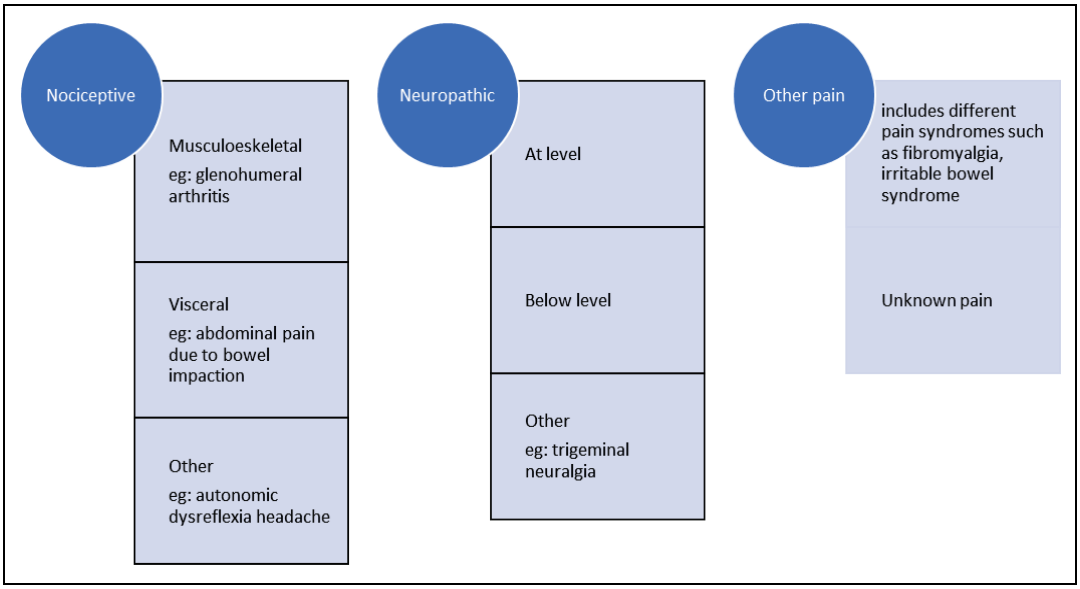


Figure 1 - International Spinal Cord Injury Pain (ISCIP) Classification

The most common clinical pain presentation in SCI are two or more simultaneous pain types (e.g. musculoskeletal shoulder pain and “at-level” neuropathic pain) (Yezierski, 2009; Finnerup, Baastrup, 2012). As the treatment of pain depends on the current diagnosis of its mechanisms, acknowledging this multiplicity allows for different concomitant approaches and may be one of the reasons why pain control is so difficult in this population. The International Association for the Study of Pain Taxonomy (http://www.iasp-pain.org/ Taxonomy) defines neuropathic pain as ‘‘pain caused by a lesion or disease of the somatosensory nervous system’’. A proposed grading system further subdivides neuropathic pain in “definite”, “probable”, and “possible” neuropathic pain (Finnerup *et al*., 2016). Because abnormal sensory signs below the level of SCI are common, irrespective of the nature of pain (neuropathic or nociceptive), much confusion arises when evaluating those patients. In 2012 Finnerup and Baastrup added further criteria to help identifying the underlying mechanism of pain syndromes below the

neurological level of injury: (1) onset of pain within 1 year following SCI; (2) no primary relation to movement, inflammation or other local tissue damage; and (3) the descriptive adjectives typical of neuropathic pain such as ‘hot-burning’, ‘tingling’, ‘pricking’, ‘pins-and-needles’, ‘sharp’, ‘shooting’, ‘squeezing’, ‘cold’, ‘electric’ or ‘shock-like’.

4 METHODS

The study was executed at the “Hospital das Clínicas da Universidade de 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 (#195.401). All participating patients were informed about the research via oral presentation and reading of the consent form (deemed *“Termo de Consentimento Livre Esclarecido”* [TCLE], in Portuguese). All of them signed this document in order to authorize the use of their data, anonymously, and grant their participation in the study.

4.1 Patients

Patients attending the demyelinating diseases outpatients’ clinic were consecutively assessed for eligibility in the study. Amongst the 79 patients initially assessed to be enrolled in the study, 72 were included. The diagnosis of inflammatory myelitis was confirmed by a neuroinflammatory diseases specialist using the Revised diagnostic criteria for neuromyelitis optica (Wingerchuk *et al*., 2006), The spectrum of neuromyelitis optica (Wingerchuk *et al*., 2007) and the Revised diagnostic criteria for neuromyelitis optica (Wingerchuk *et al*., 2015). We only included patients who were in remission of their inflammatory disease. Patients with attacks of transverse myelitis less than 12 months before the study

entry visit were excluded. Transverse myelitis attack was defined as the acute onset of a neurological deficit (with motor, sensory and/or bladder involvement) attributable 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 and refusal to sign the TCLE.

All subjects were questioned regarding the presence of pain anywhere and included in the groups with and without chronic pain according to the following criteria:

Inclusion criteria in group "with chronic pain":

- Complaint of pain anywhere in the last 3 months, more than 50% of the days.
- Diagnosis of NMO or NMOSD, according to Wingerchuck *et al*., 2006 e 2007 criteria(Wingerchuk *et al*., 2006 and 2007b) with previous inflammatory myelitis.
- Patient's willing to grant consent to the use of their data and participation in the study, via the signature of the TCLE.

Inclusion criteria in group "without chronic pain":

- Diagnosis of NMO or NMOSD, according to Wingerchuk *et al*. (2006 and 2007) criteria with previous inflammatory myelitis.
- Patient's willing to grant consent to the use of their data and participation in the study, via the signature of the TCLE.

4.2 Study Design

The study was a prospective observational study, consisting of a baseline (first entry visit) in-person assessment (cross-sectional) and a follow-up (second) evaluation, 6 to 18 months after the entry visit (longitudinal). Motor and non-motor function were systematically assessed in patients with NMO including pain, sensory thresholds, disability, catastrophising, 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 3 months). In the presence of chronic pain, patients were subdivided in “Neuropathic pain” group, and “Non-neuropathic” group, according to their main pain syndrome, as evaluated by a fully qualified 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 (Treede *et al*., 2008; Cruccu *et al*., 2010; Haanpaa *et al*., 2011; Finnerup *et al*., 2016), which is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”. This division was adopted as the presence of neuropathic and non-neuropathic derive from different mechanisms associated with chronic pain, and we aimed to study this distinction further. Pain was also classified according to the neurological level of injury (NLI), and subdivided into “At-level” (which is located anywhere between the dermatome of the neurological level of injury 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 and 2012b; Finnerup, 2013;

Finnerup and Jensen, 2004). The sensory level (defined as the lowest spinal cord dermatome that still has normal pinprick, thermal and touch sensation) was also used for this division.

All information acquired 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 in the same hospital where they were enrolled. Those who accepted the referral were seen at the spinal cord outpatient's clinic of the "Pain Centre of the University of Sao Paulo" and had their pain drugs adjusted according to 1st and 2nd line medications described in the last consensus for the treatment of neuropathic pain (Finnerup *et al*., 2015a). 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

4.1.1 Baseline (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 (Hulsebosch *et al*., 2009; Bryce *et al*., 2011). Subjects were questioned regarding all the pain syndromes they had and asked to classify it as their main and secondary pain syndromes, according to their severity and/or impact in their lives. If more than one pain syndrome was present, both were assessed. They were requested to fill

questionnaires evaluating pain (BPI, neuropathic pain symptoms inventory [NPSI], *Douleur Neuropathique-4* [DN-4], Short form McGill pain questionnaire [MPQ]), painful tonic spasms, Lhermitte sign, hiccups, orthostatic intolerance, persistent nausea, pruritus, Uhthoff phaenomenon, 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]), PCTS) urinary (overactive bladder 8 item [OAB-V8] and international prostatic symptoms sore [IPSS]) and faecal dysfunction. Quantitative sensory test (QST), conditioned pain modulation test (CPM) and cortical excitability (CE) measurements were performed in this visit (Figure 2).

4.1.2 Follow up assessment

All subjects were invited to return to the hospital for a new evaluation 6 to 18 months after the first visit. A new clinical evaluation was performed and pain (BPI, NPSI, DN-4, MPQ), 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 and postal contact (Figure 2).

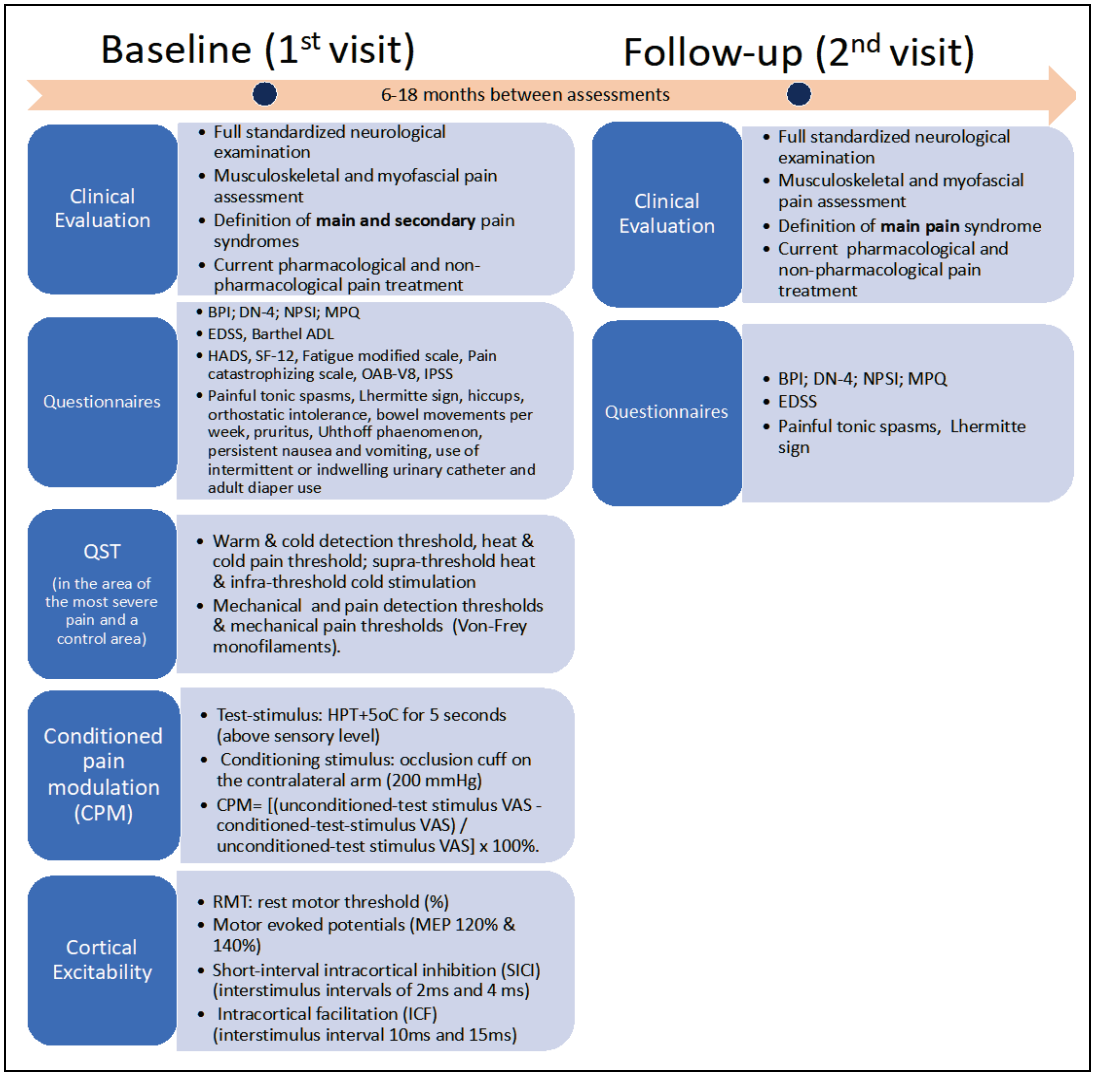


Figure 2 - Summary of assessments

4.3 Pain History and Socio Demographic Assessment

Subjects were enquired regarding their individual clinical history, previous diseases or noteworthy traumas and events in their lives and habits relevant to the current study and pain syndrome evaluation. Their pain characteristics, history, duration, quality, magnitude, localisation 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 3rd

version of the medication quantification scale (MQS-III) (Harden *et al*., 2005).

The Socio Demographic assessment included questions about their current age, age of first and last relapse, self-declared sex, years of schooling, educational level, current marital status, presence of a partner, religion, current and previous use of alcohol, tobacco and illicit drugs, employment status, individual and familiar income.

4.4 Inflammatory Disease, Imaging and Functional Status Assessments

Data regarding subjects' inflammatory auto-immune disease was collected from their electronic and paper notes, including: onset symptoms, 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 3 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 discard prior cortical extensive lesions. The most recent brain MRI was reviewed in order to assess the following aspects: Diencephalic lesions surrounding the third ventricles and cerebral aqueduct, peri ependymal lesions surrounding the lateral ventricles, dorsal brainstem lesions adjacent to the fourth ventricle, corpus callosum, cerebellum and subcortical or deep white matter lesions.

4.5 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 (Sato *et al*., 2013 e 2014; Akaishi *et al*., 2016). For AQP4- IgG detection, HEK-293 cells were transiently transfected with the M23 isoform of AQP4, and the samples were tested at an antibody dilution of 1:4. Two investigators scored the assays. The presence of MOG antibodies was analysed using a CBA with live HEK-293 cells transiently transfected with a plasmid containing full-length human MOG cDNA (cDNA; pIRES2-Dsred2 vector, BD Biosciences, San Jose, CA, USA) using the FUGENE6 transfection agent (Promega Corp., Madison, WI). Goat anti-human IgG labelled with Alexa488 (Invitrogen, Carlsbad, CA) was used as a secondary antibody after the transfected cells were exposed to the patients' diluted serum. The samples were tested for MOG antibodies at a dilution rate of 1:128, and only patients whose samples were judged to be positive by two observers were considered positive with high titers. The antibody titres from both assays were calculated semi-quantitatively using serial twofold dilutions.

Patients had their blood collected via peripheral venous puncture during a regular visit to the neuroimmunology clinic and after centrifugation the serum was stored at −80°C. Afterwards, the samples were shipped to the Tohoku University, Sendai, Japan, where they were stored at −80°C until analysis. They were then processed by Dr Douglas Kazutoshi Sato, MD, PhD. Samples were sent to Japan for analysis due to an international research collaboration between the Department of Neurology Tohoku University Graduate School of Medicine,

Sendai, Japan and the Department of Neurology, School of Medicine of the University of Sao Paulo. The result of the analysis was kindly informed to the main author or this study (FVS) by Dr. Samira Apostolos-Pereira.

4.6 General Neurological Evaluation

We performed a clinical evaluation and structured physical and neurological examination in all patients. It included:

a) **Motor strength evaluation:** given by a sum score of 4 muscles for each side of the body: elbow flexion, wrist extension, knee extension and ankle dorsiflexion. The manual muscle strength was scored according to the six-point Likert Medical Research Council scale (ranges from 0- no muscle power to 5 normal muscle power) for each muscle (Council, 1942). Minimum score of 0 and maximum of 40. Higher scores denote a better function.

b) **Myotatic reflexes score:** given by a sum score of 2 reflexes in the upper limbs and 2 reflexes in the lower limbs: bicipital, brachioradialis, patellar, achilles tendon for each side of the body, using a Babinski percussion hammer (©2014 GF Health Products, Inc., Atlanta, GA, USA). The National Institute of Neurological Disorders and Stroke (NINDS) myotatic reflex score (Hallett, 1993) was used for grading. It ranges from 0 to 4: 0- absent, 1- small, less than normal, 2- lower half of normal range, 3- upper half of normal range, 4- enhanced, more than normal. Minimum score of 0 and maximum of 32.

c) **Sensory level:** was defined using safety pin, cold stimuli and 10-g Von Frey monofilament.

d) **Tactile touch sensitivity**: using von Frey monofilament of 10 g (68.3 g/mm^2). Light touch sum score of 3 sites in the upper limbs and 3 sites in the lower limbs: lateral upper arm, lateral wrist, distal interphalangeal joint of the second finger, proximal pretibial area, lateral malleolus and hallux for each site of the body. The light touch sensibility was scored from 0-3: 0- no sensation, 1- diminished sensation, 2- normal sensation, 3- increased sensation. Minimum score of 0 and maximum score of 36.

e) **Mechanical nociceptive perception**: using a safety pin. Pinprick sum score of 3 sites was created in the upper limbs and 3 sites in the lower limbs: lateral upper arm, Lateral wrist, distal interphalangeal joint of the second finger, proximal pretibial area, lateral malleolus and hallux for each site of the body. The pinprick sensibility is scored from 0-3: 0- no sensation, 1- diminished sensation, 2- normal sensation, 3- increased sensation. Minimum score of 0 and maximum score of 36.

f) **Thermal sensitivity to non-painful cold:** using the contact of the metal tuning fork at room temperature (Campbell, 2005). Thermal sum score of 3 sites in the upper limbs and 3 sites in the lower limbs: lateral upper arm, lateral wrist, distal interphalangeal joint of the second finger, proximal pretibial area, lateral malleolus and hallux for each site of the body. The thermal sensibility to a metal at room

temperature (25ºC) is scored from 0-3: 0- no sensation, 1- diminished sensation, 2- normal sensation, 3- increased sensation. Minimum score of 0 and maximum score of 36.

g) **Proprioception:** with the evaluation of vibration threshold of 3 sites in the upper limbs and 3 sites in the lower limbs: elbow, styloid process of ulna, distal interphalangeal joint of the third finger, iliac crest, tibial tuberosity and lateral malleolus for each site of the body. No difference between both sides of the body was found, using non-parametric paired tests, hence the average bilateral value is presented. Vibration thresholds were measured using a Ryedel Seiffer diapason of 128 Hz and vary from 0 to 8 Hz per site. Higher scores denote a better function. Limb kinaesthesia was evaluated in the extremities upper and lower limbs (thumbs and halluces, bilaterally) and classified as normal or abnormal.

h) **Neurovegetative evaluation of trophic, vasomotor and sudomotor dysfunction**: in two sites in the upper limbs and two sites in the lower limbs: arm, second finger, leg and foot, for each side of the body. The dysfunction is either absent (0) or present (1), for each site in each site of the body. A sum score was generated per subitem (0-8). Overall minimum score of 0 and maximum score of 24. Higher scores indicate greater burden of neurovegetative dysfunction.

i) **Spasticity in all limbs**: 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 four limbs (0-16), where the higher values indicate more severe spasticity (Katz *et al*., 1992).

j) **Abnormal sensory phaenomena:** the presence of hyperpathia, allodynia (to cold, brush and pressure), dysaesthesia was evaluated and the number of dermatomes affected bilaterally was recorded.

k) **Visual acuity in both eyes:** 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.

4.7 Musculoskeletal and Myofascial Pain Assessment

All patients were systematically evaluated for the presence of myofascial pain syndrome (MPS) (Teixeira *et al*., 2018). A trained pain specialist examined the muscle groups that were more frequently affected by MPS on the site of pain referred by the patient. Trigger points (TP) were pressured with circa 4 kg/cm^2 of pressure, using the thumb (just enough to blanch the examiner's thumb) (Okifuji *et al.*, 1997; Chakrabarty and Zoorob, 2007). The presence of tout bands and referred pain were evaluated. Trigger points were deemed active (meaning that the pain referred by the patient was myofascial in origin) if the patient reported a similarity of at least 50% of his

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 12 pre-established limb and axial muscle groups (Cury *et al*., 2014). The potential trigger point areas were examined with the use of a pressure algometer (Pain Diagnostics & Thermograph Inc®, Great Neck, NY) (Figure 3) and the level of tenderness was quantified evaluating the pressure pain threshold (PPT): the pressure algometer tip was held still and pressure was steadily increased from zero until a PPT was elicited (up to a maximum of 10 kg/cm^2). Subsequently, a constant pressure 2 kg/cm^2 above the established threshold for each muscle was applied for 3 seconds to provoke pain (that was limited by each patient's tolerance). The subjects were then asked to rate their pain using a visual analogue scale from 0-100 in a 100mm- ruler. Measurements were taken bilaterally per muscular group and calculated as the average of both sides per muscular group (Rosier *et al*, 2002).

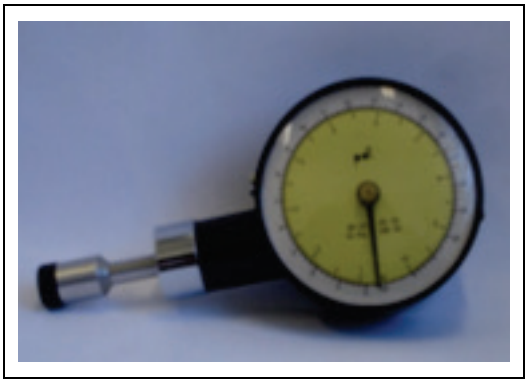


Figure 3 - Algometer Pain Diagnostics & Thermograph Inc®, Great Neck, NY

4.8 Questionnaires

4.8.1 Pain questionnaires

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

a) **Short-form McGill Pain Questionnaire** (Melzack, 1987; Ferreira *et al.*,2013). It was subdivided in the Sensory (sum of questions 1-8. Range 0-8), Affective (sum of scores for questions 9 to 13, range 0-5) and Evaluative (sum of scores for questions 14 and 15, range 0-2) dimensions. Total values are also presented (sum of sensory, affective and evaluative subscores, range 0-15).

b) **Brief Pain Inventory) short form,** including pain severity index (mean of scores for questions 3–6, range 0-10), and pain interference in daily activities (mean of scores for questions 9A to 9G, range 0-10) (Daut *et al.*, 1983; Ferreira *et al*., 2011).

c) ***Douleur Neuropathique*-4** (Bouhassira *et al*., 2004; Santos *et al*., 2010), developed to screen and assess possible neuropathic component of the pain. The screening is positive for scores ≥ 4. Total number of positive answers are also presented.

d) **Pain catastrophising thoughts scale (PCTS):** the current version has 9-questions, and was translated and validated to Portuguese (Flor *et al*., 1993; Sullivan *et al.*, 1995; Sardá Junior, 2008). It measures pain intensity, emotional distress, pain related disability and pain behaviour. It is further divided into two subscores: rumination and helplessness. The results for each question ranges from 0 to 5 and the final result is given by the sum of the scores per

individual question divided by the total number of questions. The highest possible overall score is 5, and higher values indicate higher levels of catastrophising. We reported the rumination, helplessness and total scores.

e) **Neuropathic Pain Symptom Inventory** (Bouhassira *et al*., 2004; de Andrade *et al*., 2011a): designed specifically to assess the different symptoms of neuropathic pain. We evaluated the NPSI- total score (0-100, higher values indicate more intense symptoms) and segmented the questionnaire in the following sub scores (range from 0 to 10, composed by the mean score for the questions that compose each subitem, higher values denote higher intensity of symptoms): Continuous ongoing deep pain (pressure/ squeezing, mean score for questions 2 and 3), Continuous ongoing superficial pain (burning, score for question 1), Evoked pain (allodynia to brush, cold and pressure, mean score for questions 8,9 and 10), Paroxysmal pain (electric shocks/stabbing, mean score for questions 5 and 6), Paraesthesia/Dysaesthesia (tingling, pins and needles, mean score for questions 11 and 12).

f) Presence of painful tonic spasms and Lhermitte sign: patients were questioned regarding their current and past occurrence.

4.8.2 Quality of life, mood, fatigue, disability and urinary dysfunction assessment scales

a) **Hospital Anxiety and Depression Scale** (Zigmond and Snaith, 1983; Botega *et al.*, 1995). In this tool, anxiety and depression subscales range from 0 to 21 and scores of 8 for anxiety and depression are currently used as cut-offs.

b) **SF-12 Health survey** (Ware *et al.*, 1996; Jenkinson *et al*., 1997) – 12-item questionnaire whose results are subdivided in the PCS and Mental Health Composite Scale (MCS) scores. Range from 0-100: higher scores indicate better health status. Non-commercial license agreement obtained from Optuminsight Life Sciences, Inc. License number QM038812.

c) **Modified fatigue impact scale** (Mendes *et al.*, 1998; Krupp *et al*., 1989) - 9-item questionnaire which ranges from 7-63. Higher values denote greater impairment of activities of daily life by fatigue.

d) **Barthel Activities of Daily Living index (Barthel ADL)** (Mahoney and Barthel, 1965; Anderson *et al*., 2008) - measures functional independence and mobility in activities of daily life. Ranges from 0-100 and higher values indicate better performance.

e) **Expanded disability questionnaire scale** (Kurtzke, 1983) - ranges from 0 to10, in which a composite score is given by multiple systems dysfunction. Greater values translate into greater burden of the disease.

f) **Overactive Bladder V8 score** (Acquadro *et al*., 2006) - consisting of 8 questions inquiring about the degree of disturbance caused by overactive bladder symptoms, graded from 0 (no distress) to 5

(extremely distressed). Scores ≥ 8 suggest overactive bladder. Ranges from 0-42.

g) **International prostate symptom score** (Barry *et al*., 1992) - score consisting of 7 questions to evaluate urinary obstructive symptoms. Total scores between 0 and 7 suggest none or mild symptoms; 8-19 moderate symptoms; 20-35 severe symptoms.

4.8.3 Other "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.

Patients were questioned regarding the presence of hiccups, pruritus, Uhthoff phaenomenon, orthostatic intolerance, persistent nausea and vomiting, use of 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 scrutinised 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 *et al*., 2013), normal intestinal function and chronic incontinence (Paquette *et al*., 2015).

4.9 Psychophysics Testing

4.9.1 Quantitative Sensory Testing

The quantitative analysis of the sensitive phaenomena with the QST is a psychophysic method which quantifies the positive and negative phaenomena of the exteroceptive sensibility transmitted by the small and large fibres of the peripheral nervous system. It determinates pain and non-nociceptive thresholds, and generates painful stimuli which makes the diagnosis of hyperalgesia and hyperpathia (Arendt-Nielsen and Yarnitsky, 2009).

The QST device was developed by Fruhstofer (Fruhstorfer *et al.*, 1976) and complemented by Dyck *et al.* (1978). It is composed by a computerized system and a thermoelectrical stimulator deemed Marstock Testing System. This stimulator is connected to a digital-analog converter which translates the intensity of the stimuli in graphs. The thermode which evaluate the thermal thresholds use the “Peltier principle”: the passage of the electric current through two semiconductors determines heating or cooling according to the current direction. When at the beginning of the test, the temperature of the stimulator is maintained in the thermal adaptation range (31° to 36° C). The perception of the hot or cold stimulus and pain to the hot or cold stimuli is determined by the increase or decrease in the temperature of the stimulator that activates the skin receptors. Those skin receptors are the free nerve endings that trigger action potentials in the A-σ and or myelinated C small fibres that are conducted to the long tracts of the spinal cord (Verdugo and Ochoa, 1992).

Patients underwent a QST battery intended to assess the integrity of the large (Aβ) and small-fibres (A-σ, C) mediated sensory inputs. Patients with pain were evaluated at the site of the most severe pain (main pain) and at a "control area" above each individual sensory level (Figure 4. Patients without pain were matched with another subject with pain and similar sensory level and were tested in the same "main pain" area of the matched subject and in their own control area above their own sensory level. The control area was chosen in a site up to 5 dermatomes above the sensory level but below the dermatome supplied by the sensitive spinal nerve originated in the second cervical vertebra (C2).

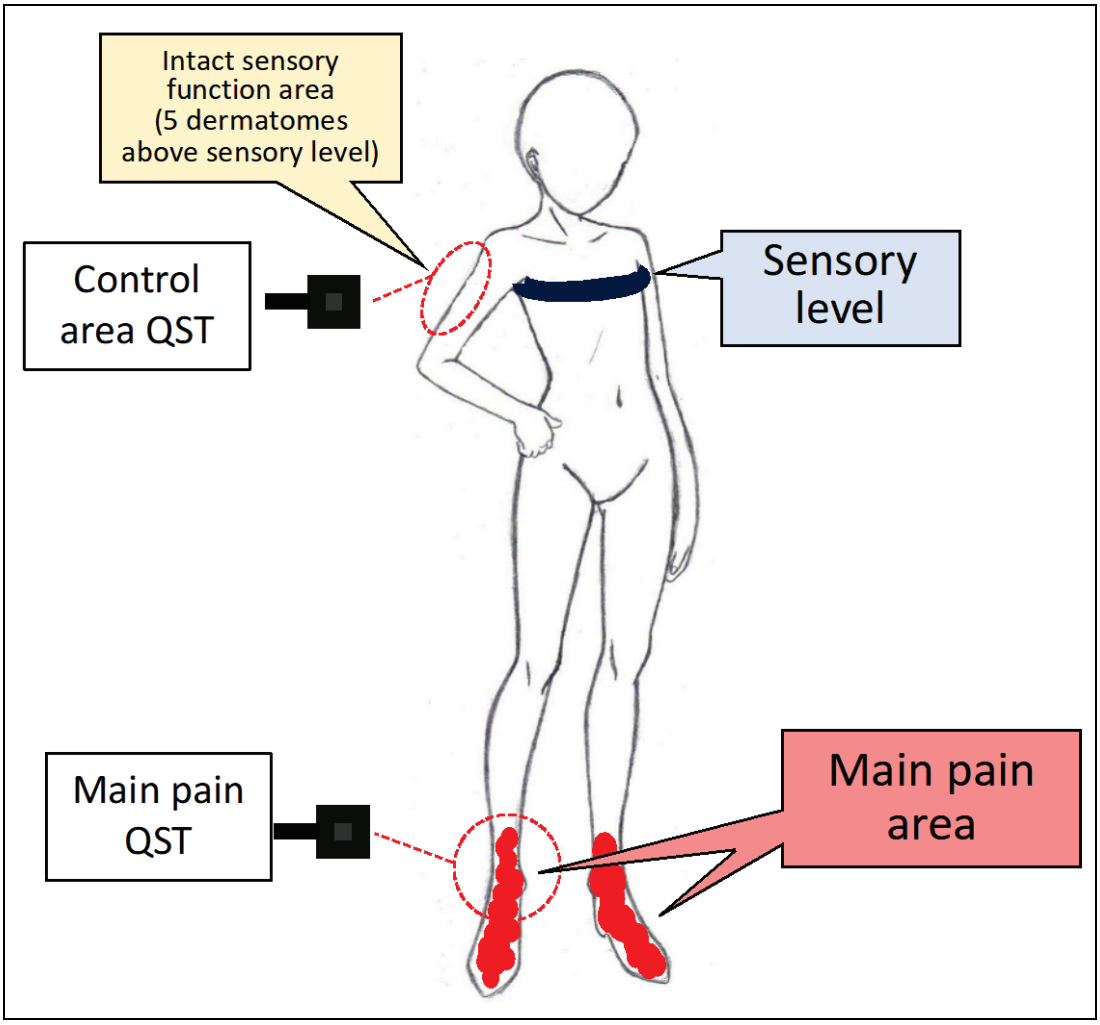


Figure 4 - Areas where QST was performed

Thermal thresholds were measured using a TSA-2001 device (Medoc, Ramat Yshai, Israel) (Figure 5). For thermal detection thresholds (warm detection threshold [WDT], cold detection threshold [CDT]), the method of limits was used by employing use of a contact-thermode (30x30 mm). Cooling and heating were produced at a linear rate of 1°C/sec. from a starting neutral temperature of 32°C. Cold pain and heat pain thresholds (CPT) and heat pain threshold (HPT); respectively were also determined by the methods of limits with temperature changes at 1°C/sec. Inter-stimuli intervals were 6 to 8 seconds for detection thresholds, 15 to 20 seconds for heat pain thresholds,

and 20 to 30 seconds for cold pain thresholds. During tests, the thermode was gently moved around the test area after each trial to prevent unintended habituation. Temperatures did not exceed 50°C for heat and 0 °C for cold to avoid tissue damage. All thermal thresholds were expressed as absolute temperature values.

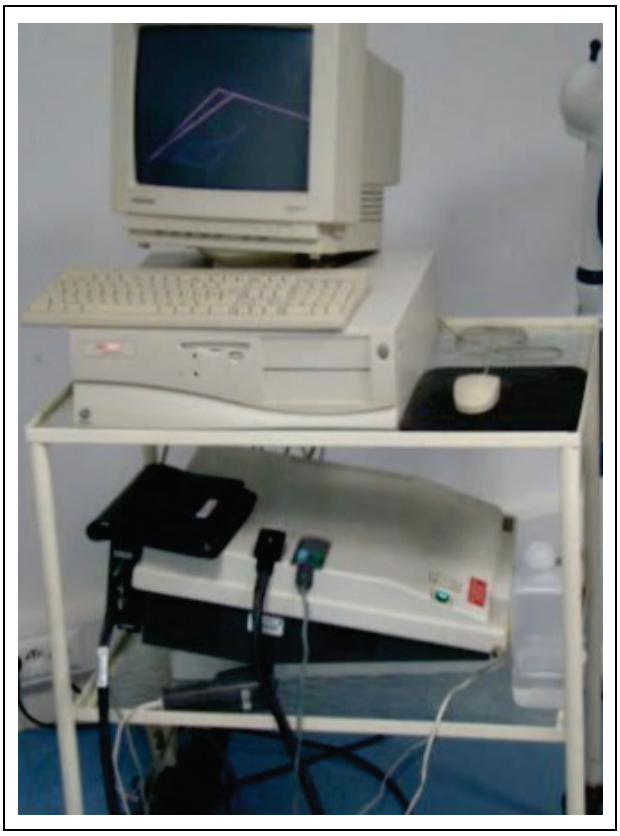


Figure 5 - Device used for the QST tests (VSA- 3000/TSA-2001, Medoc©, Ramat Yshai, Israel)

Mechanical detection thresholds (MDT) and mechanical pain thresholds (MPT) were measured using von Frey hairs ranging from 0.008 to 300 g (NC 17775; Bioseb, France) (Figure 6). MPT was defined as the lowest pressure that was considered painful by the patient in 50% of six trials in ascending and descending orders.

Figure 6 - Von Frey monofilaments calibrated from 0.008 to 300 g (NC17775, Bioseb©, France)

Suprathreshold heat stimulations (SuH) were also performed, with temperature increasing at a linear rate of 2°C/s from a starting neutral temperature of 32°C and kept constant for2 s at two different target temperatures (46 and 48°C, in random order, provided HPT was < 46°C). Evoked pain intensity was scored on a visual analogue scale (VAS, 0–100 mm) and averaged. Infrathreshold cold stimulation (InC) was performed by decreasing the temperature from 32 to 10°C and 5°C (provided CPT was<5°C). The two SuH VAS scores obtained (for 46 and 48°C), and the InC VAS scores (for 10 and 5°C) were, respectively, averaged to obtain a single value of SuH and InC.

4.9.2 Conditioned pain modulation

CPM is studied experimentally by measuring the pain intensity after a painful 'test' stimulus delivered alone and right after the application of a second noxious 'conditioning' stimulus. A reduction in the magnitude of the 'unconditioned-pain' in response to the 'conditioned-pain" is considered as the CPM (Yarnitsky *et al*., 2015).

The 'test-stimulus' was applied by a thermode (TSA-2001, Medoc, Ramat-Yishai, Israel) with a 30x30 mm Peltier surface, which was applied alone over a chosen control area above the sensory level. Temperature was increased by 1o C/sec starting from 32ºC and the HPT was determined as described above in the QST section. Unconditioned painful stimulation was performed by a constant stimulus set at HPT+5ºC for five seconds and pain intensity was determined via a written 100-mm visual analogue scale (VAS, 0-100). It was recorded as the "unconditioned test-stimulus VAS" (Figure 7). After a five-minute interval, the conditioning stimulus was applied in an adjacent area, also above the sensory level. For the conditioning stimulus, a single, 8-cm-wide chamber, occlusion cuff was adjusted on the contralateral arm, 2 cm superior to the cubital fossa (Fujii *et al.*, 2006; Cathcart *et al*., 2009). The cuff was inflated by the researcher via hand gripping of the bulb up to 200 mmHg. Inflation continued for the time necessary until the patient verbally rated their arm pain as 6-7/10 in a verbal numeric pain rating scale, in a stable trend for 5 seconds. Extra care was taken in order not to produce harmful arm ischaemia with cuff inflation. Immediately after a stable pain intensity was reached, a second test-stimulation, identical to the first one, was repeated and

the “conditioned test-stimulus VAS” recorded (Figure 8). The CPM was calculated as [(unconditioned-test stimulus VAS - conditioned-test-stimulus VAS)/unconditioned-test stimulus VAS] x 100%.

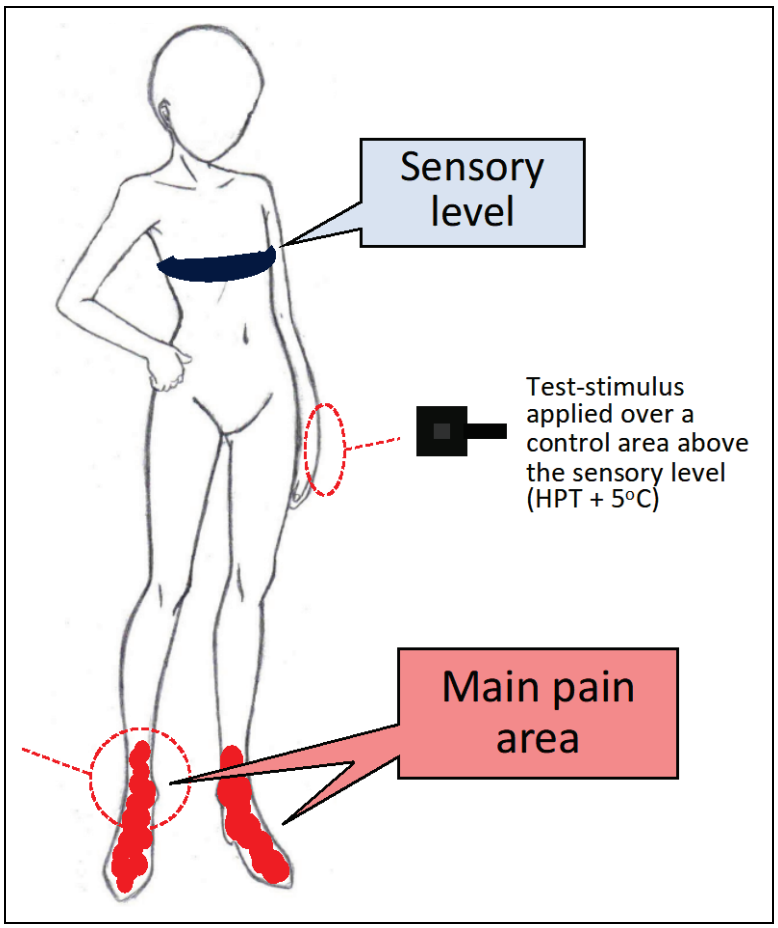


Figure 7 - CPM: 1st Test-stimulus is applied and unconditioned test-stimulus VAS is recorded (0-100)

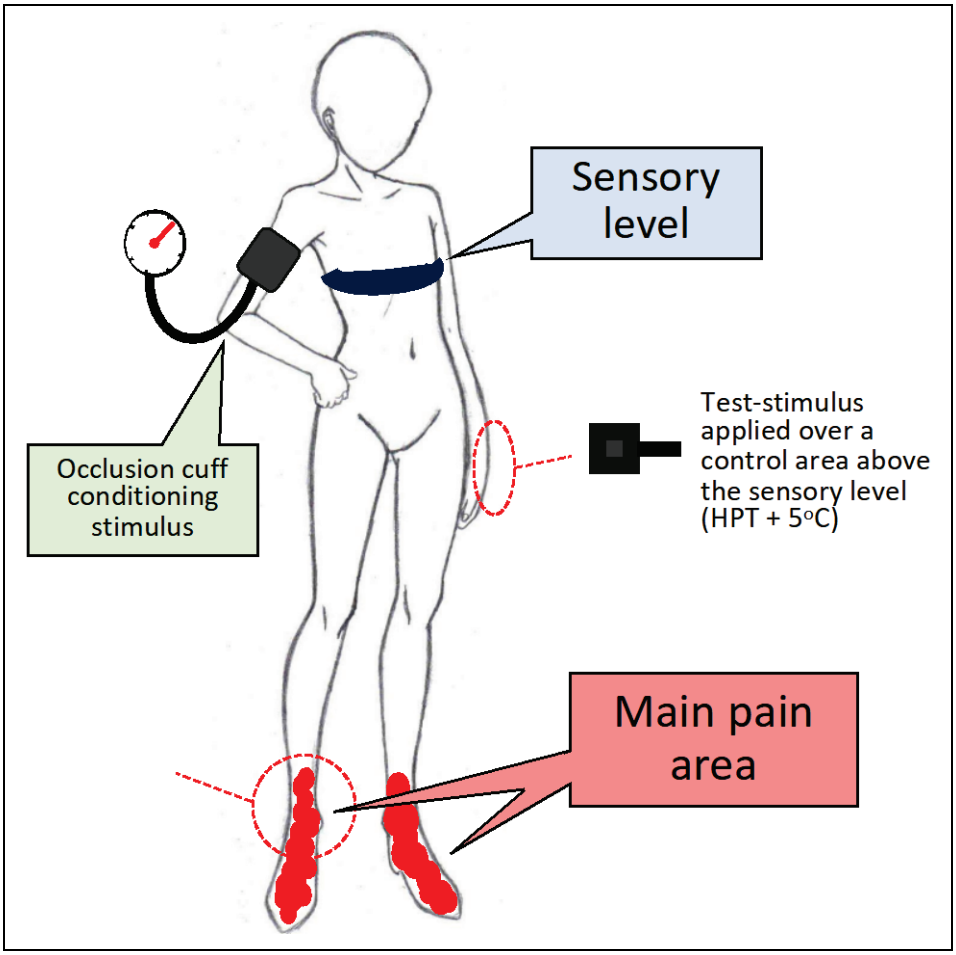


Figure 8 - CPM: 2nd test-stimulus is applied while the occlusion cuff is playing the role of "conditioning stimulus" on the contralateral arm, causing local pain. Conditioned test-stimulus VAS is recorded (0-100): patients are required to grade the pain cause by the test-stimulus (thermode over a control area heated 5ºC above the individual HPT)

4.10 Neurophysiological Assessment: Cortical excitability Measurements

The transcranial magnetic stimulation (TMS) equipment was developed by the British engineer Anthony Barker (Barker *et al.*, 1985) to generate transcutaneous motor evoked potentials in the cerebral cortex. It modifies cortical activity using an electric field induced by a magnetic field, which is generated by a coil placed on the surface of the skull. Transcranial magnetic

stimulation is based on the principle of Faraday (1831) and consists of the passage of electric current by a coil to generate electromagnetic field capable of producing difference of potential and electric current induced at some distance from it. This current is able to depolarise neurons.

Participants underwent a 30-minute session for CE measurements. They were seated in a comfortable reclining chair in a lab at room temperature and were asked to keep as relaxed as possible. Transcranial magnetic stimulation was performed with a MagPROX100 machine (Magventure Tonika Elektronic, Farum, Denmark), using a circular shaped coil (C-100 Magventure Tonika Elektronic, Farum) (Figure 9).

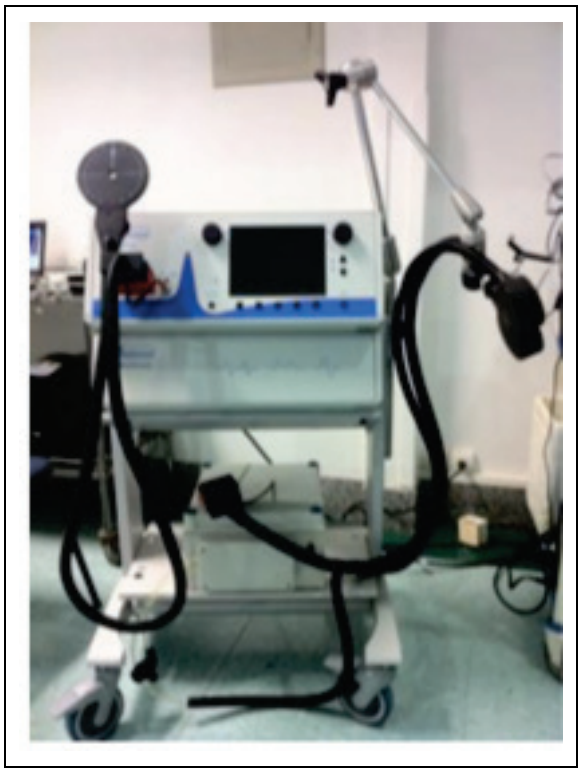


Figure 9 - TMS machine used in the study. MagProX100® (MagVenture®- Tonika Elektronic, Farum, Dinamarca)

During stimulation, surface electromyography (EMG) was recorded and monitored continuously online using pre-gelled, disposable Ag/AgCl electrodes (10 mm diameter). Active electrodes were placed on the skin above the first dorsal interosseous muscle and reference electrodes were placed over the metacarpophalangeal joints. Motor cortical excitability testing included the determination of rest motor threshold (RMT); motor evoked potentials (MEP's), short-interval intracortical inhibition (SICI) at interstimulus intervals (ISI) of 2ms and 4 ms and intracortical facilitation (ICF) at ISI 10ms and 15ms, in both hemispheres as previously reported (Mhalla *et al*., 2010; de Andrade *et al*., 2011b; Ciampi de Andrade *et al*., 2014; Cueva *et al*., 2016). The resting motor threshold corresponds to the lowest stimulus intensity capable of evoking MEP's with a minimum amplitude of 50 mV, after at least five of ten magnetic pulses administered when the target muscle is in rest. It is increased by drugs that inhibit voltage-dependent sodium channels and is not influenced by drugs that modulate NMDA or gama amino butyric acid (GABA) receptors (Rossini *et al*., 2015). The RMT was measured as A/msec and expressed as a % of the maximum power of the TMS machine. The relationship between the intensity of the stimuli and the amplitude of the MEP, that is, the response curve of the stimuli, was evaluated by measuring the MEP (mV), stimuli with 120% and 140% of the evoked resting potential, and the ratio between the MEP amplitude obtained with 140% of the RMT and 120% of the RMT (140/120). This recruitment curve refers to the increase in MEP amplitude by increasing the intensity of the stimulation with TMS in order to activate neurons less excitable or spatially distanced from the centre of activation with TMS. This curve gets steeper with adrenergic drugs and flatter with ionic channels blockers and GABA agonist drugs (Hallett *et al*., 1999) .The

SICI consists of applying subliminal conditioning stimuli (below RMT) administered 2 and 4 ms before the supraliminal (above RMT) stimuli. It increases with the use of GABA-A, antiglutamatergic and dopaminergic agonists, is not influenced by ion channel blockers and is reduced in patients with neuropathic pain (Kujirai *et al*., 1993; Mhalla *et al*., 2010;). The measurement of ICF consists of the application of infra-threshold conditioning stimuli followed by supra-threshold stimuli after 10 and 15 ms. It causes increased motor evoked potential and depends on the activation of NMDA receptors (Ziemann *et al.*, 1996). MEPs were recorded for over cortical representation of the contralateral M1 representation of the first dorsal interosseous muscle, with an electromyography amplifier module (Magventure Tonika Elecktronic, Denmark) and surface electrodes (Alpine Biom, Skovlunde, Denmark). Paired pulses were delivered, with the intensity of the conditioning stimulus set at 80% of the RMT, and the intensity of the test stimulus at 120% of the RMT. Conditioned stimuli were randomly applied and intermixed with control non-conditioned test stimuli. For each ISI, the results of four trials were averaged and the changes in test MEP amplitude induced by conditioning stimuli were expressed as a MEP amplitude. The mean inhibition at ISI 2 and 4 ms and facilitation at ISI 10 and 15 ms are used for statistical comparisons, thus providing a final ICI and ICF for each hemisphere. Additionally, each single CE parameter was classified for each individual according to published normative data as normal, high (above 95%CI) or low (below 95%CI), and the corresponding percentages of these three possible outcomes were compared between groups according to the presence of neuropathic pain, non-neuropathic or no pain (Cueva *et al*., 2016).

4.11 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. 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 Wilcoxon signed rank test or Kruskal Wallis test. For QST and Cortical Excitability measurements, the Kruskal-Wallis test with Dunn's procedure for multiple comparisons between the groups was applied. For QST and CPM, the Kruskal-Wallis test with Dunn's procedure for multiple comparisons between the groups was used. For RMT, One-way ANOVA was used, whereas Cortical Excitability measurements were analysed using Kruskal-Wallis test with Dunn's procedure for multiple comparisons between the groups. Spearman coefficients were used to assess correlation between the dichotomous variables and Bonferroni correction for multiple comparisons was used to low p-values if necessary. Mixed Anova was used to analyse the difference between and within groups between the 1st and 2nd assessment. The level of statistical significance was set at $p<0.05$. All statistical calculations were performed using the software Statistical Package for the Social Sciences (SPSS, version 20.0.0; SPSS Inc., Chicago, IL, USA).

5 RESULTS

5.1 Baseline (Study Entry) Evaluation

5.1.1 Patients

Seventy-nine subjects diagnosed with NMO were evaluated to participate in the study. Two subjects were excluded due to a clinical relapse in the 12 months preceding the inclusion in the study. Two subjects were excluded after we reviewed their brain MRI and noted extensive subcortical lesions and areas of old ischaemia compatible with previous strokes. One subject was excluded as the final diagnosis was not of NMO. One subject was excluded as he had only previous optic neuritis without myelitis. One subject was excluded due to cognitive impairment secondary to vascular dementia. Seventy-two patients with inflammatory transverse myelitis were included and assessed (Figure 10). 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 chronic pain and 19 (26.3%) without any chronic pain syndrome. Patients with chronic pain were subdivided according to the underlying mechanism of their main pain syndrome: 40 (55.6%) in Neuropathic pain and 13 (18.1%) in non-neuropathic pain. Amongst those 53 subjects with chronic pain, 38 (71.7%) had more than 1 pain syndrome. They were classified according to their primary pain syndrome.

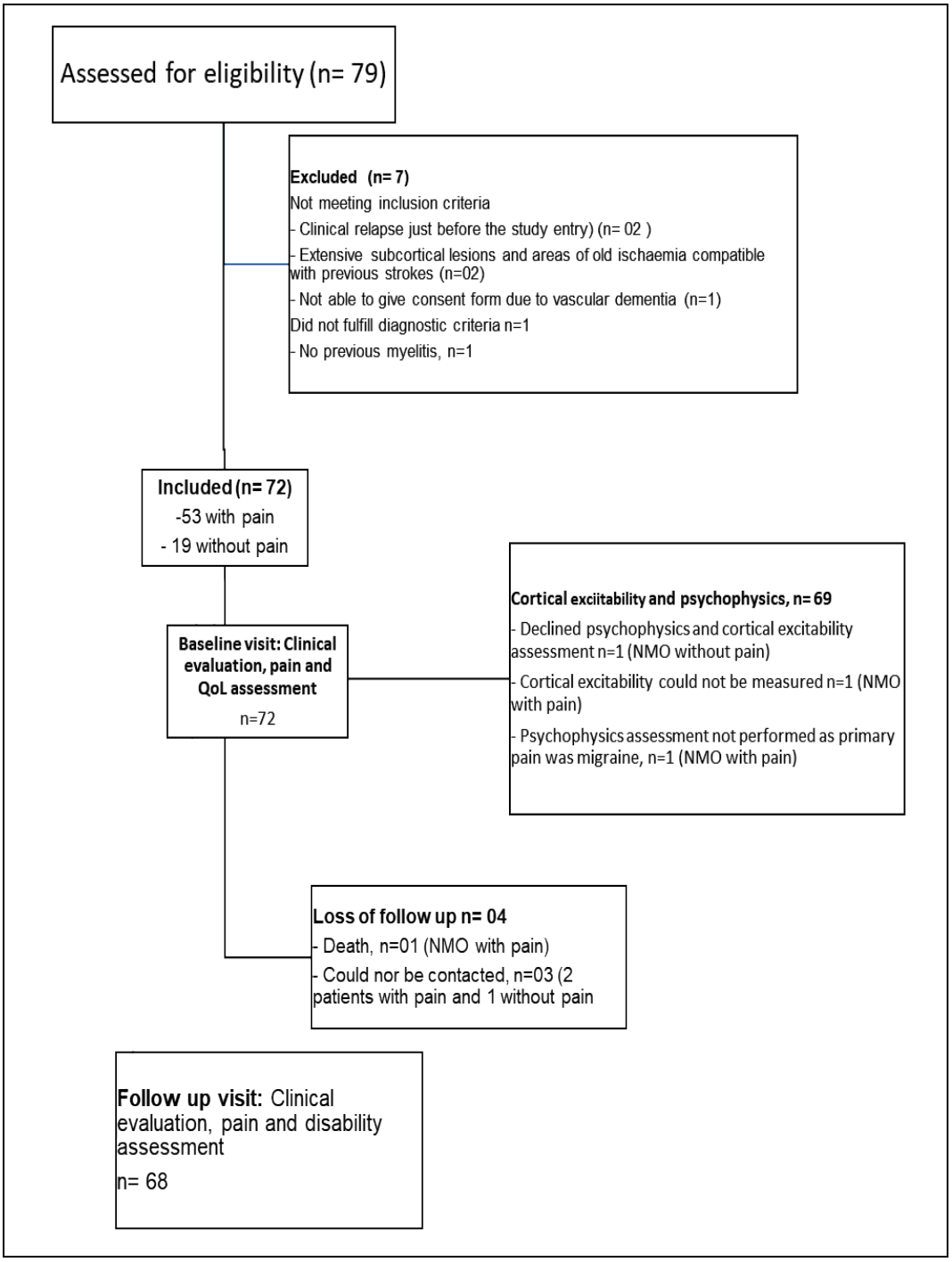


Figure 10 - Strobe flow diagram

5.1.2 Socio Demographic Features

The demographic profile of these patients is detailed in Table 1. Both groups of chronic pain patients were significantly older at the time of evaluation, when compared to those without pain. Women composed the majority of patients in all groups, in similar proportions. There was a statistic difference in marital status between groups (p=0.003) mainly driven by a higher proportion of single individuals in the group with no pain (63.2% vs 17.5% and 15.4% in those with neuropathic and non-neuropathic pain respectively). Similarly, most patients with neuropathic (72.5%) and non-neuropathic pain (76.9%) had in-house partners, compared to only 36.8% of those without pain. Those marital and relationship differences certainly reflect the younger age of those without pain.

All patients declared having a religion or being spiritualized. There was no difference between groups.

Less than 50% of patients were currently working in all groups, and there was no difference between them. All patients who did not have income themselves were provided by their families.

Table 1 - Baseline socio-demographic features

	Neuropathic Pain	Non-Neuropathic Pain	No Pain	p
Number of patients n, (%)	**40 (55.6)**	**13 (18.1)**	**19 (26.3)**	
Age at evaluation, years-old, mean ± SD (min-max)	48.2 ± 11.1 (24-71)	46.5 ± 8.3 (32-57)	31.4 ± 11.8 (15-59)	**<0.001**[1]
Schooling, years, mean ± SD, (min-max)	9.7 ± 3.2 (0-15)	8.5 ± 3.4 (0-15)	11 ± 3.1 (7-17)	0.105
Female, n (%)	27 (67.5)	10 (76.9)	14 (73.7)	0.770
Marital status, n (%)				**0.003**
Single	7 (17.5)	2 (15.4)	12 (63.2)	
Married	25 (62.5)	10 (76.9)	3 (15.8)	
Domestic partnership	1 (2.5)	0	2 (10.5)	
Separated/ Divorced	5 (12.5)	1 (7.7)	1 (5.3)	
Widowed	2 (5)	0	1 (5.3)	
In-house partner n (%)	29 (72.5)	10 (76.9)	7 (36.8)	**0.020**[2]
Religion, n (%)				0.672
Protestant	13 (32.5)	2 (15.4)	7 (36.8)	
Catholic	20 (50)	10 (76.9)	10 (52.6)	
Spiritist	4 (10)	1 (7.7)	2 (10.5)	
Other	3 (7.5)	0	0	
Active practicing religious rituals	24 (60)	8 (61.5)	9 (47.4)	0.614
Employment status, n (%)				0.752
Employed	9 (22.5)	4 (30.8)	7 (36.8)	
Unemployed	5 (12.5)	1 (7.7)	4 (21.1)	
Retired	15 (12.5)	3 (23.1)	5 (25.3)	
Housekeeper	2 (5)	1 (7.7)	1 (5.3)	
On sickness benefit	9 (22.5)	4 (30.8)	2 (10.5)	
Currently working, n (%)	9 (22.5)	4 (30.8)	7 (36.8)	0.487
Provides most of family income	17 (42.5)	5 (38.5)	6 (31.6)	0.723
Individual income, mean ± SD, (min-max) (R$-Brazilian reals)	1407.08 ± 1239.28 (0-6000)	1123.23 ± 737.74 (0-2300)	1093.26 ± 1063.59 (0-4000)	0.487
Family income, mean ± SD, (min-max) (R$-Brazilian reals)	3885.03 ± 4857.26 (1000-30000)	3177.31 ± 2358.45 (900-8000)	3642.11 ± 6567.46 (700-30000)	0.394
Number of persons who live with current family income, mean ± SD, (min-max)	3.43 ± 1.5 (1-7)	3.1 ± 1 (1-5)	3.2 ± 1.2 (1-5)	0.723

Abbreviations: The values are presented as mean ± standard deviation (minimum-maximum). Continuous variables were analysed using One-way Anova with Tukey HSD procedure for post hoc analysis, except for individual and family income and number of people under the same family income who were analysed using Kruskal-Wallis test. Dichotomous variables were analysed using three-way chi square test.

[1] Neuropathic pain versus No Pain p<0.001; Non-Neuropathic pain versus No Pain p= 0.001; Neuropathic pain versus Non-Neuropathic pain p= 0.877. [2] Neuropathic pain versus No Pain p=0.012; Non-Neuropathic pain versus No Pain p= 0.036; Neuropathic pain versus Non-Neuropathic pain p= 1.000.

Significance $p < 0.05$.

5.1.3 Non- prescription drugs use

Regarding the use of tobacco and alcohol, a minority of patients in both groups reported current or previous use and there was no statistical difference of consumption between groups (Table 2). Only 2 patients within “neuropathic pain" group reported current and regular use of smoked marijuana for analgesic purposes. One patient without pain reported previous use of crack cocaine and one patient in the neuropathic pain group reported previous use of intranasal cocaine.

Table 2 - Previous and current tobacco and alcohol consumption

	Neuropathic Pain	Non-Neuropathic Pain	No Pain	p
Tobacco consumption, n (%)				
Previous	17 (42.5)	3 (23.1)	3 (15.8)	0.108
Current	8 (20)	2 (15.4)	4 (21.1)	1.000
Smoking load, mean ± SD (min-max) (packs-years)	8.8 ± 14.6 (0-60)	3.8 ± 7.8 (0-25)	1.9 ± 4.3 (0-15)	0.080
Alcohol consumption, n (%)				
Previous	7 (17.5)	2 (15.4)	0	0.135
Current	2 (5)	1 (7.7)	1 (5.3)	1.000

Abbreviations: The values are presented as mean ± standard deviation (minimum-maximum). Continuous variables were analysed using using Kruskal-Wallis test. Dichotomous variables were analysed using three-way chi square test.

Significance $p < 0.05$.

5.1.4 Other previous chronic diseases

There was a significant difference between groups (p=0.024) in the prevalence of hypertension, mainly driven by higher proportion of patients with this condition in the group with neuropathic pain. There was no statistical difference in the prevalence of the most common chronic diseases between the groups. Only one subject within “Neuropathic pain” group reported previous malignant cancer- an oral espinocelular carcinoma, surgically removed and cured.

Two subjects in the group with Neuropathic pain had rheumatologic diseases: one with Churg-Strauss vasculitis and the other with connective tissue mixed disease.

Two subjects in the group without chronic pain reported the diagnosis of migraine. However, upon study entry both reported migraine crisis less than once a month. Two individuals in the non-neuropathic pain group reported migraine, one of them labelled it as their current main pain syndrome. Only one subject within the neuropathic pain group reported migraine, and it was classified as its secondary pain (Table 3).

Table 3 - Prevalence of previous chronic diseases

	Neuropathic Pain	Non-Neuropathic Pain	No Pain	p
Diabetes mellitus, n (%)	6 (15)	2 (15.4)	2 (10.5)	0.348
Hypertension, n (%)	13 (32.5)	1 (7.7)	1 (5.3)	**0.024**[1]
Cardiopathy, n (%)	2 (5)	1 (7.7)	1 (5.3)	1.000
Chronic Hepatitis C (no cirrhosis), n (%)	2 (5)	0	0	1.000
Depression, n (%)	10 (25)	4 (30.8)	2 (10.5)	0.345
Rheumatologic disease, n (%)	2 (5)	0	0	1.000
Hypothyroidism, n (%)	3 (7.5)	1 (7.7)	0	0.501
Migraine, n (%)	1 (2.5)	2 (15.4)	2 (10.5)	0.133

Abbreviations: The values are presented as mean ± standard deviation (minimum-maximum). All variables were analysed using three-way chi square test.

[1] Neuropathic pain versus No Pain p=0.024; Non-Neuropathic pain versus No Pain p= 1.000; Neuropathic pain versus Non-Neuropathic pain p= 0.145.

Significance $p < 0.05$.

5.1.5 Clinical history and treatment of NMO

Subjects without chronic not only were younger upon study entry (Table 1), but also significantly younger upon first (p=0.001) and last relapse (p<0.001). This finding was not associated with auto antibody status, clinical presentation at onset, number of relapses and current immunosuppressant treatment. Only one subject in the group with neuropathic pain used methotrexate as their chronic immunosuppressant drug, due to previous bone marrow suppression after the introduction of Azathioprine. Subjects also didn't differ in their degree of disability between groups, as measured by the EDSS (p=0.073) (Table 4).

Table 4 - Characteristics of the inflammatory disease, its current treatment, degrees of disability and sequelae related to myelitis and optic neuritis

	Neuropathic Pain	Non-Neuropathic Pain	No Pain	p
Age at presentation (years-old), mean ± SD, (min-max)	40.1 ± 12.5 (15-67)	37.2 ± 11.4 (12-52)	26.1 ± 12.7 (10-56)	**0.001** [1]
Time from first relapse until inclusion in the study (months), mean ± SD, (min-max)	98.1 ± 69.3 (15-292)	111.5 ± 112.1 (15-452)	63.7 ± 44.6 (14-198)	0.119
Age at the last relapse (years-old), mean ± SD, (min-max)	43.3 ± 10.8 (19-67)	41.2 ± 9.2 (26-54)	27.6 ± 12.4 (10-56)	**<0.001** [2]
Time from last relapse until inclusion in the study (months), mean ± SD, (min-max)	59.3 ± 46.2 (12-205)	64.5 ± 36 (13-128)	46.4 ± 33 (13-148)	0.290
Relapses, mean ± SD, (min-max)	3±3.4 (1-20)	2.2±1.5 (1-6)	2.5±2.7 (1-10)	0.691
AQP4ab + ve, n (%)[α]	24 (60)	7 (53.8)	11 (57.9)	0.925
MOG-IgG + ve, n (%)	2 (5.1)	2 (15.4)	1 (5.3)	0.429
Concomitant rheumatologic disease, n (%)	2 (5)	0	0	-
Optic Neuritis, n (%)	17 (42.5)	4 (30.8)	7 (36.8)	0.736
Legally blind [β] , n (%)	5 (12.5)	2 (15.4)	2 (10.5)	1.000
Ability to stand, n (%)	31 (77.5)	10 (76.9)	13 (68.4)	0.742
EDSS, mean ± SD, (min-max) (0-10)	5.5 ± 1.9 (2-8.5)	4.7 ± 2.4 (2-8)	4.3 ± 2.4 (1.5-8)	0.073
Onset symptoms, n (%)				
Motor dysfunction	8 (20)	2 (15.4)	6 (31.6)	0.544
Sensory disturbances (tingling and numbness)	16 (40)	2 (15.4)	9 (47.4)	0.191
Pain	17 (42.5)	9 (69.2)	8 (42.1)	0.224
Bladder dysfunction	1 (2.5)	0	0	1.000
Optic neuritis	7 (17.5)	3 (23.1)	2 (10.5)	0.573
Nausea and vomiting	4 (10)	1 (7.7)	1 (5.3)	1.000
Current immunosuppressant drug				
Azathioprine, n (%)	28 (70)	11 (84.6)	14 (73.7)	0.583
Daily dosage, mg, mean ± SD (min-max)	115.3±73.5 (0-250)	115.4±59.1 (0-150)	131.3±57.4 (0-200)	0.739
Prednisone, n (%)	15 (37.5)	3 (23.1)	7 (36.8)	0.621
Daily dosage, mg, mean ± SD (min-max)	13.6±12.9 (0-50)	7±8.4 (0-20)	10.3±8.5 (0-20)	0.579

[α] One patient with Neuropathic pain refused to have his blood collected to test for anti-Aquaporin-4 Antibody.

[β] Visual acuity of the better eye ≥ 20/200

Abbreviations: AQP4ab: Antibody Anti Aquaporin-4; MOG-IgG: Antibodies against myelin oligodendrocyte glycoprotein; EDSS: expanded disability status scale.

The values are presented as mean ± standard deviation (minimum-maximum) or number of patients (n) and its percentage within group (%). Continuous variables were analysed using One-way Anova with Tukey HSD procedure for post hoc analysis, except for dosage of Azathioprine and Prednisone which were individually analysed with Kruskal-Wallis test. Dichotomous variables were analysed using three-way chi square test.

[1] Neuropathic pain versus No Pain p<0.001; Non-Neuropathic pain versus No Pain p= 0.039; Neuropathic pain versus Non-Neuropathic pain p= 0.759.[2] Neuropathic pain versus No Pain p<0.001; Non-Neuropathic pain versus No Pain p= 0.003; Neuropathic pain versus Non-Neuropathic pain p= 0.818.

Significance p < 0.05.

Upon the beginning of the study, patients were classified in Neuromyelitis optica according to the consensus criteria of 2006 and 2007. (Wingerchuk *et al*., 2006 and 2007). During recruitment, new criteria were published in 2015 (Wingerchuk *et al*., 2015). We show the classification of patients according to groups (Table 5).

Table 5 - Diagnostic classification of patients according to Neuromyelitis optica consensus 2006/2007 and 2015

	Neuropathic Pain	Non-Neuropathic Pain	No Pain	p
Diagnostic criteria Consensus 2006 and 2007, N (%)				1.000
NMO defined	26 (65)	9 (69.2)	12 (63.2)	
NMOSD	14 (35)	4 (30.8)	7 (36.8)	
Diagnostic criteria Consensus 2015, N (%)				0.847
NMO AQP4ab +ve	24 (60)	7 (53.8)	11 (57.9)	
NMO AQP4ab -ve	5 (12.5)	3 (23.1)	4 (21.1)	
NMO MOG-IgG +ve	2 (5)	2 (15.4)	1 (5.3)	
NMO + rheumatologic disorder	2 (5)	0	0	
LETM	7 (17.5)	1 (7.7)	3 (15.8)	

Values are presented as number of patients (n) and its percentage within group (%). All variables were analysed using three-way chi square test.

Significance $p < 0.05$.

There was no difference between groups regarding their treatment received during the acute phase of the NMO relapse (Table 6).

Table 6 - Description of the t reatment received for the inflammatory disease during the acute phase

	Neuropathic Pain	Non-Neuropathic Pain	No Pain	p
Corticosteroid pulse therapy, N (%)	**39 (97.5)**	**13 (100)**	**19 (100)**	**1.000**
0	1 (2.5)	0	0	0.380
1	9 (22.5)	3 (23.1)	5 (26.3)	
2-5	12 (30)	8 (61.5)	6 (31.6)	
> 5	18 (45)	2 (15.4)	8 (42.1)	
Intravenous immunoglobulin (IVIG) therapy, N (%)	2 (5)	0	2 (10.5)	0.630
Plasmapheresis, N (%)	11 (27.5)	1 (7.7)	5 (26.3)	0.389

Values expressed as number of patients (n) and percentage within group (%).

* 3-way chi-square.

Significance $p < 0.05$.

5.1.6 Imaging Features

Patients did not differ in the extension or severity of their inflammatory lesion in the spinal cord during the acute phase, except for a higher prevalence of gadolinium enhancement in the group with neuropathic pain and no pain, when compared to those with non-neuropathic pain (p=0.009) (Table 7). Fourteen patients did not have the acute phase spinal cord MRI available: 7 (17.5%), 3 (23%), 4 (21.5%) in the Neuropathic pain, Non-Neuropathic pain and No pain groups, respectively. The proportion of patients with missing acute-phase MRI was not different between groups (p=0.851, Fisher's Exact Test).

Table 7 - Spinal cord MRI findings during the acute phase of their last clinical relapse

Acute phase Spinal cord MRI	Neuropathic Pain	Non-Neuropathic Pain	No Pain	p
Vertebral segments*, mean ± SD (min-max)	9.6 ± 4.9 (2-22)	10 ± 4.7 (5-18)	10.6 ± 4.4 (6-22)	0.745
Characteristics, n (%)				
Gadolinium enhancement	29 (87.9)	4 (40)	12 (80)	**0.009**[1]
Tumefactive	25 (75.8)	5 (50)	11 (73.3)	0.354
Atrophy	6 (18.2)	1 (10)	4 (26.7)	0.726
Cavitation	5 (15.2)	1 (10)	2 (13.3)	1.000
Medulla involvement	10 (30.3)	3 (30)	5 (33.3)	1.000
Discontinuous lesions	8 (24.2)	2 (20)	1 (6.7)	0.414
Sagittal involvement, n (%)				
Holocord (longitudinal)	2 (6.1)	1 (10)	2 (13.3)	0.562
Cervical	5 (15.2)	2 (20)	2 (13.3)	0.891
Cervicothoracic	17 (51.5)	4 (40)	8 (53.3)	0.874
Thoracic	9 (27.3)	2 (20)	3 (20)	0.916
Thoracolumbar	3 (9.1)	1(10)	0	0.490
Axial involvement, n (%)				
Holocord (axial)	26 (78.8)	5 (50)	11 (73.3)	0.200
Central grey matter	4 (12.1)	5 (50)	3 (20)	0.052
Lateral white matter	1(3)	0	0	1.000
Posterior columns	2 (6.1)	0	1 (6.7)	1.000

*number of vertebral segments with increased signal intensity on T2-weighted sequences. Discontinuous lesions had all their levels reported. Only valid cases are reported in the frequencies. Number of vertebral segments was analysed using Kruskal Wallis test. The remainder of the data was analysed using 3-way chi-square with Bonferroni comparison for multiple comparisons. [1] Neuropathic pain versus No Pain p=0.662; Non-Neuropathic pain versus No Pain p=0.087; Neuropathic pain versus Non-Neuropathic pain p= 0.005. Significance $p < 0.05$. Bonferroni correction for multiple comparisons P=0.0125.

The long-term follow-up MRI (over 6 months after the last clinical relapse) revealed that all groups of patients had a smaller number of vertebral segments with increased signal intensity on T2-weighted sequences, but no significant difference was detected between the groups, as exposed in Table 8. Sixteen patients did not have the chronic phase spinal cord MRI available: 10 (25%), 1 (7.7%), 4 (21.5%) in the Neuropathic pain, Non-Neuropathic pain and No pain groups, respectively. The proportion of patients with missing follow up MRI was not different between groups (p=0.432, Fisher's Exact Test).

Table 8 - Spinal Cord MRI findings during the long-term follow up (6 or more months after the last clinical relapse)

Chronic phase Spinal cord MRI	Neuropathic Pain	Non-Neuropathic Pain	No Pain	p
Vertebral segments*, mean ± SD (min-max)	6.2 ± 4.2 (0-16)	5.8 ± 6.5 (0-21)	7 ± 5.1 (0-21)	0.462
Characteristics, n (%)				
Gadolinium enhancement	3 (10)	1 (8.3)	0	0.646
Tumefactive	3 (10)	0	1 (7.1)	0.801
Atrophy	19 (63.3)	6 (50)	10 (71.4)	0.503
Cavitation	4 (13.3)	2 (16.7)	3 (21.4)	0.887
Medulla involvement	5 (16.7)	3 (25)	4 (28.6)	0.621
Discontinuous lesions	9 (30)	0	2 (14.3)	0.088
Sagittal involvement, n (%)				
Holocord (longitudinal)	0	1 (8.3)	1 (7.1)	0.211
Cervical	6 (20)	2 (16.7)	1 (7.1)	0.632
Cervicothoracic	12 (40)	4 (33.3)	7 (50)	0.674
Thoracic	8 (26.7)	3 (25)	4 (28.6)	1.000
Thoracolumbar	3 (10)	1 (8.3)	0	0.646
Axial involvement, n (%)				
Holocord (axial)	3 (10)	0	1 (7.1)	0.801
Central grey matter	17 (56.7)	9 (75)	10 (71.4)	0.497
Lateral white matter	9 (30)	0	1 (7.1)	**0.039**[1]
Posterior columns	8 (26.7)	1 (8.3)	3 (21.4)	0.471
Anterior columns	1 (3.3)	0	0	1.000

*number of vertebral segments with increased signal intensity on T2-weighted sequences.

Values expressed as mean ± standard deviation (maximum-minimum) or number of patients (n) and percentage within group (%), as indicated.

Discontinuous lesions had all their levels reported. Only valid cases are reported in the frequencies. Number of vertebral segments was analysed using Kruskal Wallis test. The remainder of the data was analysed using 3-way chi-square with Bonferroni comparison for multiple comparisons. [1] Neuropathic pain versus No Pain p=0.132; Non-Neuropathic pain versus No Pain p=1.000; Neuropathic pain versus Non-Neuropathic pain p= 0.041. Significance $p < 0.05$. Bonferroni correction for multiple comparisons P=0.0125.

The groups also did not differ in the characteristics of the Brain MRI. No patient presented with cloud-like enhancing brain lesions (Table 9).

Table 9 - Brain MRI findings per group

Brain MRI, n (%)	Neuropathic Pain	Non-Neuropathic Pain	No Pain	P*
Normal	10 (25)	2 (15.4)	6 (31.6)	0.657
Site of lesions (hyperintensities on T2-weighted sequences)				
Subcortical or deep white matter	27 (67.5)	10 (76.9)	9 (47.4)	0.200
Diencephalic lesions surrounding the third ventricles and cerebral aqueduct	4 (10)	1 (7.7)	1 (5.3)	1.000
Peri ependymal lesions surrounding the lateral ventricles	12 (30)	6 (46.2)	6 (31.6)	0.585
Dorsal brainstem lesions adjacent to the fourth ventricle (area postrema and nucleus tracts soltarius)	10 (25)	3 (23.1)	6 (31.6)	0.875
Corpus callosum lesions	3 (7.5)	2 (15.4)	2 (10.5)	0.660
Cerebellum lesions	1 (2.5)	1 (7.7)	0	0.397

Values expressed as number of patients (n) and percentage within group (%).

* 3-way chi-square. Significance $p < 0.05$.

5.1.7 Neurological Examination

All patients underwent a standardised neurological examination, as described in the previous session. The results are shown in the Table 10. There were no differences in the motor, myotatic reflex, Ashworth spasticity, light touch, pinprick and thermal sensibility scores. The group with neuropathic pain showed worst vibration thresholds, when compared to the others. Patients with non-neuropathic pain had significantly lower neurovegetative dysfunction scores, due to less impaired trophic function.

Table 10 - Summary of neurological examination performed in all patients

	Neuropathic Pain	Non-Neuropathic Pain	No Pain	p
Sensory level, n (%)				
Cervical	22 (55)	4 (30.8)	12 (63.2)	0.180
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)	0.094
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)	0.719
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)	0.100
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)	0.468
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)	0.478
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)	0.237
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)	**0.044**[1]
Neurovegetative dysfunction total score, mean ± SD (min-max) (0-24)	9.2 ± 5.4 (0-24)	4.9 ± 4.2 (0-12)	9.1 ± 6.5 (0-24)	**0.048**[2]
Trophic dysfunction, mean ± SD (0-8)	1.9 ± 2.1 (0-8)	0.3 ± 1.1 (0-4)	2.5 ± 3 (0-8)	**0.016**[3]
Vasomotor dysfunction, mean ± SD (0-8)	2.4 ± 2.6 (0-8)	1 ± 1.9 (0-5)	1.9 ± 2.8 (0-8)	0.215
Sudomotor dysfunction, mean ± SD (0-8)	4.9 ± 2.6 (0-8)	3.6 ± 3.4 (0-8)	4.7 ± 3.5 (0-8)	0.431
Limb kinestesia impairment, n (%)				
Distal interphalangeal joint of the index finger	3 (7.5)	1 (7.7)	0	0.501
Hallux	17 (42.5)	3 (23.1)	6 (31.6)	0.424

Values are presented as mean ± standard deviation (minimum-maximum), except for the frequency of Limb kinestesia impairment which is presented as number of patients (n) and its percentage withing groups (%), as indicated. 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: [1] Neuropathic pain versus No Pain p=0.051; Non-Neuropathic pain versus No Pain p=1.000; Neuropathic pain versus Non-Neuropathic pain p= 0.563. [2] Neuropathic pain versus No Pain p=1.000; Non-Neuropathic pain versus No Pain p=0.193; Neuropathic pain versus Non-Neuropathic pain p= 0.043. [3] Neuropathic pain versus No Pain p=1.000; Non-Neuropathic pain versus No Pain p=0.021; Neuropathic pain versus Non-Neuropathic pain p= 0.031.

Significance $p < 0.05$.

5.1.8 Abnormal Sensory Phaenomena

The Extension of abnormal sensory phaenomena per group is presented in Table 11. The score reflects the number of right and left dermatomes affected. Patients with neuropathic pain have a significantly higher number of dermatomes affected by Allodynia to brush (0.8 ± 1.6, compared to zero dermatomes in the other 2 groups, p = 0.004) and to pressure (0.7 ± 1.3 compared to no 0 in the non-neuropathic pain group and 0.1 ± 0.5 dermatomes in the no pain group). Nevertheless, allodynia to brush and pressure affected only 11 (27.5%) of those patients with neuropathic pain (Figure 1). Hyperpathia affected the greatest number of dermatomes in all groups (7.3 ± 5.6 in the neuropathic pain group, 6.1 ± 4.7 in the non-neuropathic pain group and 5.1 ± 4.9 dermatomes in the group with no pain, p= 0.213). At-level Hyperpathia affected a significantly proportion of patients with Neuropathic pain: 39 (97.5%) in this group, versus 10 (76.9%) and 12 (68.4%) in the non-neuropathic pain and no pain groups (p= 0.013). Notwithstanding, it was a prevalent phaenomenon in all groups. Paroxystic painful sensory phenomena of 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= 0.104), as shown in Graphic 1.

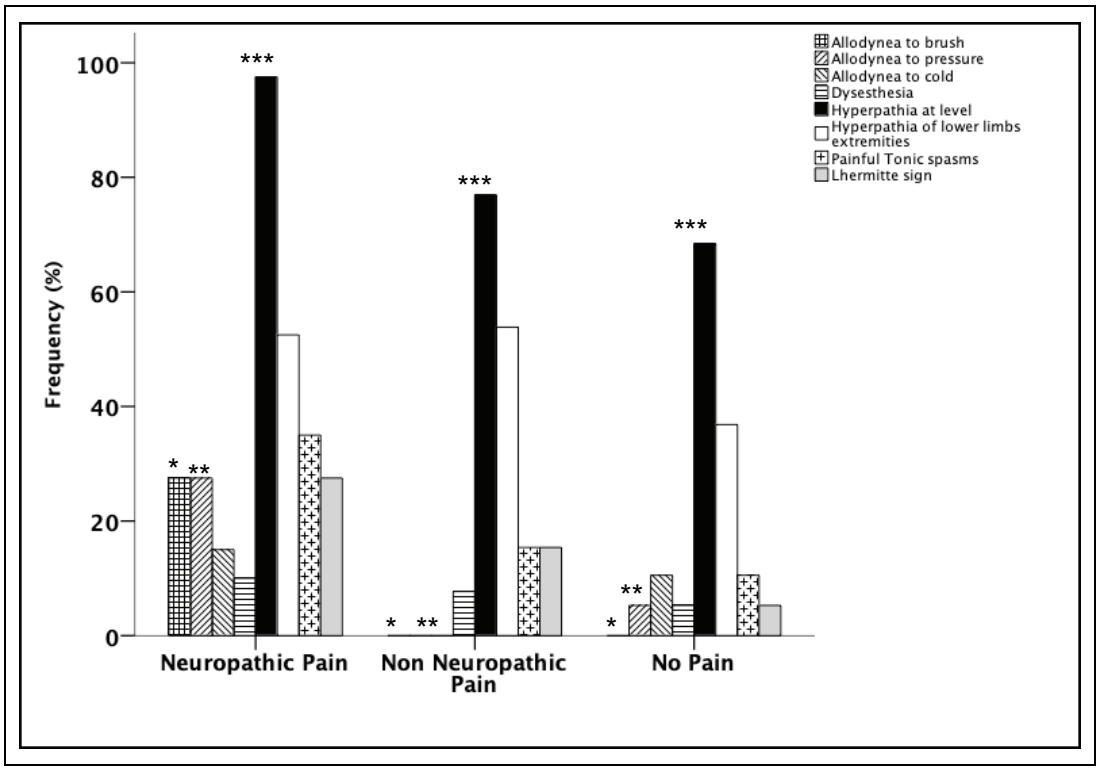
Table 11 - Characterization of abnormal sensory phaenomena amongst the three different groups

	Neuropathic Pain	Non-Neuropathic Pain	No Pain	p
Abnormal sensory phaenomena, N (%)				
Hyperpathia	39 (97.5)	12 (92.3)	14 (73.7)	**0.015**[1]
At level	39 (97.5)	10 (76.9)	12 (68.4)	**0.006**[2]
Extremities of the lower limbs	21 (52.5)	7 (53.8)	7 (36.8)	0.487
Dysesthesia	4 (10)	1 (7.7)	1 (5.3)	0.824
Allodynia to brush	11 (27.5)	0	0	**0.006**[3]
Allodynia to pressure	11 (27.5)	0	1 (5.3)	**0.021**[4]
Allodynia to cold	6 (15)	0	2 (10.5)	0.326
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)	0.213
Dysesthesia	0.2 ± 1 (0-6)	0.5 ± 1.7 (0-6)	0.7 ± 2.4 (0-10)	0.963
Allodynia to brush	0.8 ± 1.6 (0-8)	0	0	**0.004**[5]
Allodynia to pressure	0.7 ± 1.3 (0-4)	0	0.1 ± 0.5 (0-2)	**0.022**[6]
Allodynia to cold	0.3 ± 0.8 (0-4)	0	0.1 ± 0.5 (0-2)	0.221

The 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. 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. [1] Neuropathic pain versus No Pain p=0.011; Non-Neuropathic pain versus No Pain p=0.361; Neuropathic pain versus Non-Neuropathic pain p= 0.434; [2] Neuropathic pain versus No Pain p=0.003 ; Non-Neuropathic pain versus No Pain p=0.704; Neuropathic pain versus Non-Neuropathic pain p= 0.042; [3] Neuropathic pain versus No Pain p=0.011; Non-Neuropathic pain versus No Pain p= (no valid cases) ; Neuropathic pain versus Non-Neuropathic pain p= 0.047; [4] Neuropathic pain versus No Pain p=0.081 ; Non-Neuropathic pain versus No Pain p=1.000; Neuropathic pain versus Non-Neuropathic pain p= 0.047. [5] Neuropathic pain versus No Pain p=0.013; Non-Neuropathic pain versus No Pain p=1.000; Neuropathic pain versus Non-Neuropathic pain p= 0.038; [6] Neuropathic pain versus No Pain p=0.098; Non-Neuropathic pain versus No Pain p=1.000; Neuropathic pain versus Non-Neuropathic pain p= 0.066.

Significance $p < 0.05$.

Graphic 1 - Frequency of abnormal sensory phaenomena



Significantly higher frequency of allodynia to brush (* p = 0.003), allodynia to pressure (**p= 0.012) and hyperpathia at level (*** p= 0.003) in the group with neuropathic pain. Significance p < 0.05.

5.1.9 Pain pressure thresholds and myofascial pain evaluation

Analysis of PPT per muscular group trigger point and the degree of elicited pain in a visual analogue scale (VAS) is shown in Table 12. It is noteworthy that the statistically significant difference 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. In this group, the dominant pain syndrome is indeed low back pain. Those patients also present with lower PPT for gluteus medius.

Table 12 - Pressure pain thresholds (PPT) measured on the trigger points of each muscular group. Values are bilateral average

Muscular groups, mean ± SD (min-max)	Neuropathic pain	Non-Neuropathic pain	No Pain	p
Glabela PPT (0-10)	1.9±0.6 (1-4)	1.7±0.6 (0.5-3)	1.5±0.6 (0-2.7)	0.174
Sternocleidomastoideus				
PPT (0-10)	1.6±0.5 (5-3.2)	1.6±0.8 (0.5-2.9)	1.7±1 (0.8-5)	0.992
VAS (0-100)	57.6±19.1 (15-92.5)	56.8±17.3 (29-82.5)	64.6±20.8 (30-100)	0.381
Active, n(%)	1 (2.5)	0	0	1.000
Latent, n(%)	3 (7.5)	1 (7.7)	0	0.570
Trapezius				
PPT (0-10)	3.2±1.2 (1.5-6.9)	3.1±1.1 (1.3-5.3)	3.1±1.7 (1.1-7.9)	0.826
VAS (0-100)	58.7±18.9 (12- 85)	56.8±16.6 (30- 81.5)	58.7±19.7 (26.5-91)	0.948
Active, n(%)	2 (5)	2 (15.4)	0	0.201
Latent, n(%)	4 (10)	2 (15.4)	2 (10.5)	0.878
Pectoralis major				
PPT (0-10)	3±1.1 (1.5-5.9)	2.74±1.1 (1.6-5.8)	2.9±1.6 (0.6-8.4)	0.804
VAS (0-100)	55.6± 20.3 (11-87)	55.3±22.5 (10-90.5	55.2±19.5 (15-90)	0.998
Active, n(%)	0	0	0	-
Latent, n(%)	2 (5)	0	2 (10.5)	0.630
Supraspinatus				
PPT (0-10)	3.7±1.3 (1.5-7.2)	3.7±1.5 (2-7.1)	3.8±1.7 (0.6-7.8)	0.847
VAS (0-100)	54.9± 20.7 (13-100)	61.2±11.4 (45-80.5)	58.2±20.6 (21.5-90)	0.578
Active, n(%)	3 (7.5)	0	0	0.581
Latent, n(%)	1 (2.5)	1 (7.7)	4 (21.1)	**0.042**[1]
Biceps brachii				
PPT (0-10)	4±1.7 (0.5- 8.5)	3.5±1.6 (1.8-7.1)	3.9± 1.9 (1.3-9.5)	0.430
VAS (0-100)	49.6±20.9 (9-96)	53.1±19.1 (25-80)	55± 20.5 (10-90)	0.627
Active, n(%)	1 (2.5)	0	0	1.000
Latent, n(%)	4 (10)	0	1 (5.3)	0.826

Continue

Continuation

Muscular groups, mean ± SD (min-max)	Neuropathic pain	Non-Neuropathic pain	No Pain	p
Triceps brachii				
PPT (0-10)	4.2±1.6 (1.5-8.1)	3.6±1.7 (1.6-8.1)	4.2±1.8 (2.4-8.8)	0.303
VAS (0-100)	47.1±20.5 (9-79)	53±20.4 (15-79.5)	47.3± 21.1 (4.5-85)	0.657
Active, n(%)	1 (2.5)	0	0	1.000
Latent, n(%)	2 (5)	0	1 (5.3)	1.000
Quadratus lumborum				
PPT (0-10)	4.8±2.4 (1.2-10)	3.8±1.2 (2.5-7.3)	4.9± 3 (0.5-10)	0.481
VAS (0-100)	47.7±27 (0-100)	53.±18.4 (23.5-80)	37.9±26.4 (0.0-84)	0.222
Active, n(%)	4 (10)	5 (38.5)	0	**0.006**[2]
Latent, n(%)	0	0	3 (15.8)	**0.021**[3]
Gluteus medius				
PPT (0-10)	6.2±5.1 (1.2- 10)	4.0±1.5 (2.3-8)	5.4±2.9 (0-10)	**0.038**[4]
VAS (0-100)	41.9±23.7 (0-90)	53.7±20.2 (22.5-80.5)	42.4±30.7 (0-95)	0.265
Active, n(%)	3 (7.5)	4 (30.8)	0	**0.017**[5]
Latent, n(%)	0	2 (15.4)	1 (5.3)	**0.046**[6]
Piriformis				
PPT (0-10)	9.3±10.7 (2.8-10)	5.5±2 (2-7.9)	6.7±2.3 (3.3-10)	0.066
VAS (0-100)	34.±25.8 (0-89.5)	46.7±22.7 (11-89.5)	43.5±28.5 (0-80)	0.238
Active, n(%)	1 (2.5)	1 (7.7)	0	0.397
Latent, n(%)	0	1 (7.7)	1 (5.3)	0.194
Vastus lateralis				
PPT (0-10)	5.8±2.5 (0.5-10)	4.5±1.3 (2.9-7.3)	5.5±2.9 (0-10)	0.288
VAS (0-100)	42.1±25.2 (0-86.5)	48.5±22.3 (10-79.5)	45±29.2 (0-95)	0.721
Active, n(%)	1 (2.5)	0	0	1.000
Latent, n(%)	2 (5)	0	1 (5.3)	1.000

Continue

Conclusion

Muscular groups, mean ± SD (min-max)	Neuropathic pain	Non-Neuropathic pain	No Pain	p
Gastrocnemius				
PPT (0-10)	6.2±4.1 (2.3-10)	4.5±1.4 (2.5-8.2)	6±2.6 (1.8-10)	0.228
VAS (0-100)	41.6±26.4 (0-81)	46.7±24.1 (10-91.5)	43.7±27.6 (0-78.5)	0.871
Active, n(%)	0	0	0	-
Latent, n(%)	1 (2.5)	1 (7.7)	2 (10.5)	0.287

Values are presented as mean ± standard deviation (minimum-maximum), except for the frequency of active and latent trigger points, which are presented as number of patients (n) and its percentage within groups (%), as indicated.

Abbreviations: PPT- pressure pain threshold (0-10 kg/cm); VAS- visual analogue scale (0-100 mm)

All frequencies were analysed using 3-Way Chi-Square with Bonferroni correction for multiple comparisons.

PPTs of all muscles, piriformis and gastrocnemius VAS were analysed using Kruskal Wallis test with pairwise comparisons using Dunn's procedure with a Bonferroni correction for multiple comparisons. The remainder of VAS were analysed using One-way ANOVA. Post-hoc analysis: [1] Neuropathic pain versus No Pain p= 0.033; Non-Neuropathic pain versus No Pain p= 0.625; Neuropathic pain versus Non-Neuropathic pain p=0.434 [2] Neuropathic pain versus No Pain p= 0.294; Non-Neuropathic pain versus No Pain p= 0.006; Neuropathic pain versus Non-Neuropathic pain p= 0.031 [3] Neuropathic pain versus No Pain p= 0.030 ; Non-Neuropathic pain versus No Pain p= 0.253 ; Neuropathic pain versus Non-Neuropathic pain p= - [4] Neuropathic pain versus No Pain p=1.000 ; Non-Neuropathic pain versus No Pain p=0.223; Neuropathic pain versus Non-Neuropathic pain p= 0.032 [5] Neuropathic pain versus No Pain p= 0.544; Non-Neuropathic pain versus No Pain p= 0.020 ; Neuropathic pain versus Non-Neuropathic pain p= 0.053 [6] Neuropathic pain versus No Pain p= 0.322; Non-Neuropathic pain versus No Pain p=0.552; Neuropathic pain versus Non-Neuropathic pain p= 0.057.

Significance <0.05. Bonferroni correction for multiple comparisons P=0.0125.

5.1.10 Characteristics and treatment of 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. Patients indicated what was their main and secondary pain syndrome. The findings are summarized in Table 13. Neuropathic pain at the sensory level ("At-level) was the most prevalent pain syndrome, being observed in 31 patients (77.5% of those with neuropathic pain and 58.5% 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. All patients were offered free continuous treatment for their chronic pain.

Table 13 - Localisation (according to neurological level of injury): at level, below level and above level), and pain syndromes of the main (n=53) and secondary pain, found in this casuistic

	Neuropathic pain	Non-Neuropathic pain	P
Main Pain, n=53	40	13	
Localisation, n (%)			<0.001
At level	32 (80)	0	
Below level	8 (20)	12 (92.3)	
Above level	0	1 (7.7)	
Pain syndromes, n (%)			<0.001
At level Neuropathic pain	31 (77.5)	0	
Low back pain	0	8 (61.5)	
Distal lower extremities Neuropathic pain	8 (20)	0	
Spasticity-related pain	0	2 (15.4)	
Plantar fasciitis	0	2 (15.4)	
Painful tonic spasms	1 (2.5)	0	
Migraine	0	1 (7.7)	
Secondary Pain, n=38		10	
Pain syndromes			**<0.001**
Low back pain	11 (27.5)	0	
Distal lower extremities Neuropathic pain	8 (20)	4 (30.8)	
At level Neuropathic pain	5 (12.5)	3 (23.1)	
Cervicogenic headache	3 (7.5)	0	
Migraine	0	2 (15.4)	
Diffuse widespread pain	0	1 (7.7)	

Values expressed as number of patients (n) and percentage within groups (%), as indicated.
Secondary pain is divided according to the syndromic groups of the main pain.
All variables were analised using Fisher's exact test. Significance $p < 0.05$.

The mean pain intensity according to the BPI was similar in the group with neuropathic pain and non-neuropathic pain as their main pain syndrome (5.7± 1.9 and 5.1±1.3, respectively, p= 0.338). DN-4 questionnaire was positive for neuropathic pain in 38 (95%) of those who met IASP criteria for this condition, applied by a pain specialist neurologist and in 7 (53.8%) of those who didn't, showing a high sensibility of 95% but a low specificity of 46.2%. As expected, patients with neuropathic pain had a significantly higher NPSI score when compared to those with non-neuropathic pain (31.8 ± 17.7 and 20.4 ± 12.8, respectively, p= 0.032), 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 (Table 14).

Table 14 - 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)	0.338
BPI Pain interference, mean ± SD (min-max) (0-10)	4.6±2.5 (0-9.9)	4.7±2.7 (1.3-9.6)	0.878
DN4, mean ± SD (min-max) (0-10)	5.8±1.4 (2-9)	3.6±1.9 (0-6)	**0.001**
DN4 positive for Neuropathic pain (≥ 4 affirmative answers), n (%)	38 (95)	7 (53.8)	**0.002**
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)	0.435
Continuous ongoing superficial pain (burning), n (%)	32 (80)	6 (46.2)	**0.019**
Intensity, mean ± SD (min-max) (0-10)	5.4±3.3 (0-10)	2.4±3 (0-8)	**0.008**
Evoked pain (allodynia to brush, cold and pressure), n (%)	30 (75)	11 (84.6)	0.707
Intensity, mean ± SD (min-max) (0-10)	2.9±2.6 (0-10)	2±1.2 (0- 4.3)	0.278
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)	0.899
Paraesthesia/ Dysaesthesia (tingling, pins and needles), n (%)	32 (80)	5 (38.5)	**0.005**
Intensity, mean ± SD (min-max) (0-10)	3.2±2.6 (0-9)	1.3±2.1 (0-6.5)	**0.011**
NPSI- total score, mean ± SD (min-max) (0-100)	31.8±17.7 (8-90)	20.4±12.8 (7-46)	**0.032**
MPQ, mean ± SD (min-max)			
Sensory (0-8)	4.4±1.8 (1-8)	4±1.9 (1-7)	0.503
Affective (0-5)	3.4±1.1 (0-5)	3.6±1 (2-5)	0.620
Evaluative (0-2)	1.5±0.5 (1-2)	1.3±0.5 (1-2)	0.231
Total (0-15)	9.2±2.5 (4-14)	8.9±2.6 (7.4-10.5)	0.709

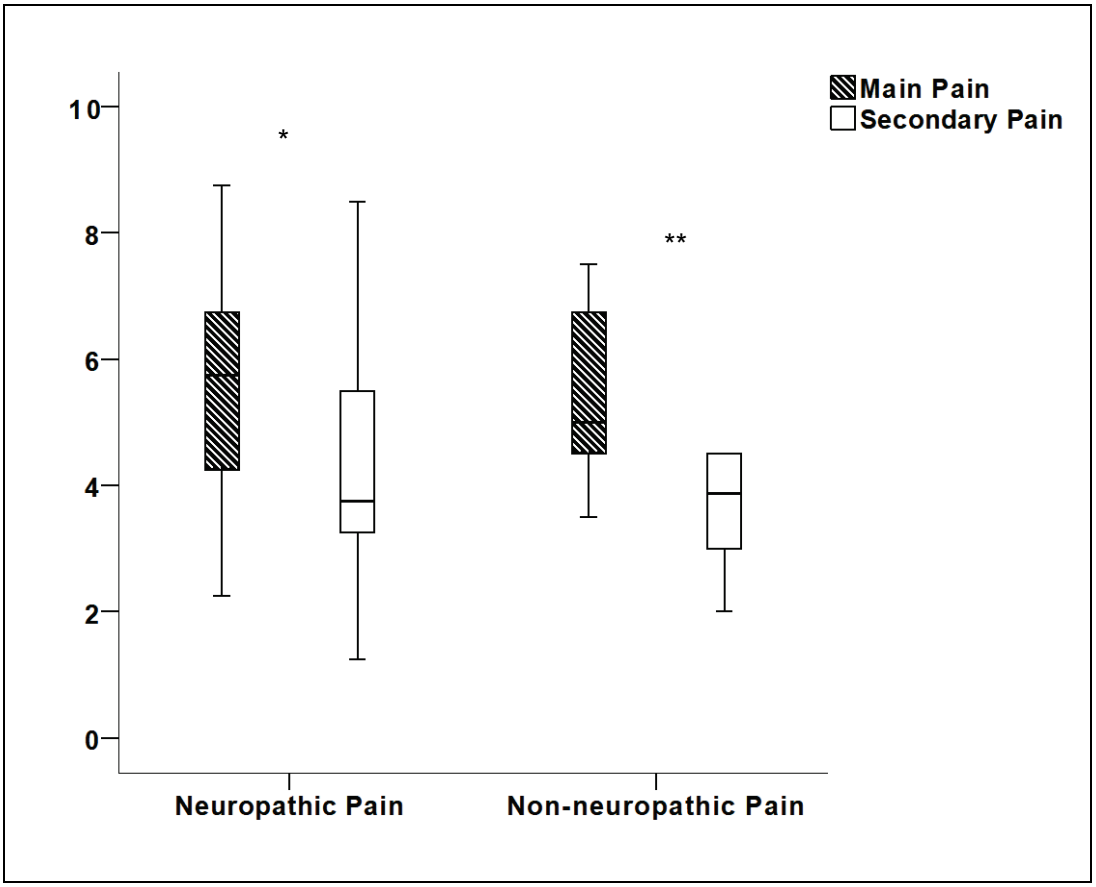
Values expressed as mean ± standard deviation (maximum-minimum) or number of patients (n) and percentage within group (%), as indicated.

Abbreviations: BPI: Brief Pain Inventory; DN-4: *douleur neuropathique*- 4; NPSI: neuropathic pain symptom inventory; MPQ: Short-form McGill Pain Questionnaire. 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 $p < 0.05$.

Secondary pain was neuropathic in 21 (55.3%) and non-neuropathic in

17 (44.7%) of cases. DN-4 Questionnaire showed a sensitivity of 90.5% and specificity of 76.5%, when compared to the examination of the pain specialist using IASP criteria for neuropathic pain. It had an overall lower intensity in both groups, as assessed by the BPI intensity score, shown in Graphic 2.

Graphic 2 - BPI intensity of the main and secondary pain in the two groups, according to the primary pain syndrome



Abbreviations: BPI: brief pain inventory. Independent t-test: *p<0.001; **p=0.001. significance p < 0.05.

We performed an analysis according to the pain localisation distribution in those 38 (71.7%) patients with more than one pain syndrome, in order to define whether they were in the same area (mixed pain syndromes) or in two spatially distant areas (coexistent pain syndromes). Only 4 (10.5%) of those patients with two pain syndromes had mixed pain syndromes, and 34 (89.5%) had coexistent pain syndromes (Table 15).

Table 15 - General description of pain in those 38 patients with two pain syndromes, subdivided in mixed and coexistent pain

	Mixed pain	Coexistent pain	p
Number of patients, n (%)	4 (10.5)	34 (89.5)	
Neuropathic as main pain syndrome, n (%)	2 (50)	26 (76.5)	0.279
BPI Pain intensity, mean ± SD (min-max) (0-10)	6.1±1.3 (4.5-7.5)	5.5±1.6 (2.3-8.8)	0.476
BPI Pain interference, mean ± SD (min-max) (0-10)	6.4±2.7 (3.7-9.6)	5.0±2.6 (1.1-9.9)	0.343
DN4, mean ± SD (min-max) (0-10)	5 ±1.4 (3-6)	5.2±1.9 (0-9)	0.801
DN4 positive for Neuropathic pain (≥ 4 affirmative answers), n (%)	3 (75)	28 (82.4)	0.574
Quality of neuropathic pain (NPSI)			
Continuous deep ongoing deep pain (pressure/ squeezing), n (%)	3 (75)	29 (85.3)	0.513
Intensity, mean ± SD (min-max) (0-10)	3.1±2.3 (0-5.5)	5.3±3.4 (0-10)	0.297
Continuous superficial ongoing deep pain (burning), n (%)	3 (75)	25 (73.5)	1.000
Intensity, mean ± SD (min-max) (0-10)	5.4±3.3 (0-10)	2.4±3 (0-8)	0.801
Evoked pain (allodynia to brush, cold and pressure), n (%)	4 (100)	25 (73.5)	0.322
Intensity, mean ± SD (min-max) (0-10)	3.1±1.1 (1.7-4.3)	2.6 ± 2.5 (0-10)	0.394
Paroxysmal pain (electric shocks/stabbing), n (%)	3 (75)	10 (29.4)	0.107
Intensity, mean ± SD (min-max) (0-10)	3.0 ± 2.0 (0-4.5)	1.2 ±2.5 (0-10)	0.102
Paraesthesia/ Dysaesthesia (tingling, pins and needles), n (%)	3 (75)	22 (64.7)	1.000
Intensity, mean ± SD (min-max) (0-10)	3.0±2.7 (0-6.5)	2.7±2.9(0-9)	0.801
NPSI- total score, mean ± SD (min-max) (0-100)	32.5±14.0 (16-46)	30.8±18.6 (7-90)	0.766
MPQ, mean ± SD (min-max)			
Sensory (0-8)	5.5±1.7 (3-7)	4.4±1.8 (1-8)	0.217
Affective (0-5)	3.3±1.7 (1-5)	3.6±0.9 (2-5)	0.801
Evaluative (0-2)	1.3±0.5 (1-2)	1.5±0.5 (1-2)	0.447
Total (0-15)	10±3.7 (5-14)	9.5±2.4 (4-14)	0.630
SF-12 , mean ± SD (min-max)			
MCS (0-100)	36.8±5.6 (29.9-42.4)	46.5±11.4 (20.1-70.9)	0.092
PCS (0-100)	36.3±9.4 (29.6-49.9)	31.6±8.7 (16.6-49.8)	0.320

Values expressed as mean ± standard deviation (maximum-minimum) or number of patients (n) and percentage within group (%), as indicated.

Abbreviations: BPI: Brief Pain Inventory, intensity measured in a 0-10-point scale, interference in a 0-10 (minimal to maximal) point scale; DN-4: *douleur neuropathique*- 4; NPSI: neuropathic pain symptom inventory; MPQ (Short-form McGill Pain Questionnaire); SF-12: Short form 12-item health survey; PCS: Physical health summary of the SF-12 health survey; MCS: Mental health summary of the SF-12 health survey.

Continuous variables were analysed using Mann-Whitney test. Dichotomous variables were analysed using Chi square or Fisher exact test.

As expected, patients with neuropathic and non-neuropathic pain had higher MQS-III and used more drugs than patients with no pain. Twenty-eight (70%) of those patients with neuropathic pain were under anticonvulsants drugs. More than half of subjects with non-neuropathic pain were under Tricyclic Antidepressant drug (7, 53.8%) (Table 16).

Table 16 - Baseline pain and psychotropic drugs

	Neuropathic pain	Non-Neuropathic pain	No Pain	p
MQS-III , mean ± SD (min-max)	12.6±7.8 (0-26.5)	8.5±7.6 (0-24.4)	3.8±5.8 (0-18.2)	**<0.001[1]**
Number of drugs per patient, mean ± SD (min-max)	2.4 ± 1.5 (0-6)	1.8 ± 1.5 (0-5)	0.7 ± 0.9 (0-3)	**<0.001[2]**
Anticonvulsants, n (%)	28 (70)	6 (46.2)	5 (26.3)	**0.006[3]**
Gababentin, n(%)	16 (40)	5 (38.5)	2 (10.5)	0.060
Dosage (mg/day), mean±SD (max-min)	1968.8±1132.4 (300-3600)	1160±750.3 (400-2400)	450±212.1 (300-600)	0.066
Carbamazepine, n (%)	14 (35)	2 (15.4)	3 (15.8)	0.239
Dosage (mg/day), mean±SD (max-min)	450±244.2 (200-1200)	500±141.4 (400-600)	333.3±115.5 (200-400)	0.404
Pregabaline, n (%)	3 (7.5)	0	0	0.581
Dosage (mg/day), mean±SD (max-min)	250±86.6 (150-300)	0	0	-
Lamotrigine, n (%)	4 (10)	0	0	0.376
Dosage (mg/day), mean±SD (max-min)	118.8±68.8 (50-200)	0	0	-
Tricyclic Antidepressants, n (%)	11 (27.5)	7 (53.8)	1 (5.3)	**0.006[4]**
Amitriptyline, n (%)	9 (22.5)	7 (53.8)	1 (5.3)	**0.009[5]**
Dosage (mg/day), mean±SD (max-min)	37.5±23.4 (12.5-75)	46.4 ± 17.3 (25-75)	25	0.397
Imipramine, n (%)	2 (5)	0	0	1.000
Dosage (mg/day), mean±SD (max-min)	75± 35.3 (50-100)	0	0	-

Continue

Continuation

	Neuropathic pain	Non-Neuropathic pain	No Pain	p
Selective serotonin and/or noradrenaline reuptake inhibitors, n (%)	13 (32.5)	3 (23.1)	1 (5.3)	0.066
Venlafaxine, n (%)	5 (12.5)	1 (7.7)	0	0.250
Dosage (mg/day), mean±SD (max-min)	135 ± 62.8 (75-225)	75		0.343
Fluoxetine, n (%)	4 (10)	2 (15.4)	0	0.196
Dosage (mg/day), mean±SD (max-min)	25±10 (20-40)	20 ± 0 (20-20)	0	0.480
Sertraline, n (%)	4 (10)	0	1 (5.3)	0.826
Dosage (mg/day), mean±SD (max-min)	75 ± 28.9 (50-100)	0	50	0.414
Anti-spasticity, n (%)	13 (32.5)	4 (30.8)	5 (26.3)	0.939
Baclofen, n (%)	13 (32.5)	4 (30.8)	5 (26.3)	0.939
Dosage (mg/day), mean±SD (max-min)	40 ± 14.7 (20-60)	45 ±12.9 (30-60)	32±28.6 (10-80)	0.350
Opioids, n (%)	6 (15)	0	0	0.123
Methadone, n (%)	2 (5)	0	0	1.000
Dosage (mg/day), mean±SD (max-min)	20±14.1 (10-30)	0	0	-
Tramadol, n(%)	3 (7.5)	0	0	0.581
Dosage (mg/day), mean±SD (max-min)	133.3 ± 28.9 (100-150)	0	0	-
Oxycodone, n (%)	1 (2.5)	0	0	1.000
Dosage (mg/day), mean±SD (max-min)	30	0	0	-
Muscle relaxants, n (%)	2 (5)	1 (7.7)	0	0.752
Cyclobenzaprine, n (%)	0	1 (7.7)	0	0.181
Dosage (mg/day), mean±SD (max-min)	0	10	0	-
Orphenadrine, n (%)	1 (2.5)	0	0	1.000
Dosage (mg/day), mean±SD (max-min)	50	0	0	-
Carisoprodol, n (%)	1 (2.5)	0	0	1.000
Dosage (mg/day), mean±SD (max-min)	100	0	0	-

Continue

Conclusion

	Neuropathic pain	Non-Neuropathic pain	No Pain	p
Simple analgesics, n (%)	6 (15)	0	0	0.123
Dipyrone, n (%)	2 (5)	0	0	1.000
Dosage (mg/day), mean±SD (max-min)	400±141.4 (300-500)	0	0	-
Paracetamol, n (%)	4 (10)	0	0	0.376
Dosage (mg/day), mean±SD (max-min)	1065±826 (500-2250)	0	0	-
Non-steroidal Anti-inflammatory, n (%)	3 (7.5)	0	0	0.581
Nimesulide, n (%)	3 (7.5)	0	0	0.581
Dosage (mg/day), mean±SD (max-min)	300±0 (300-300)	0	0	-
Benzodiazepine, n (%)	1 (2.5)	1 (7.7)	2 (10.5)	0.287
Diazepam, n (%)	1 (2.5)	1 (7.7)	2 (10.5)	0.287
Dosage (mg/day), mean±SD (max-min)	5	10	10±0 (10-10)	0.632
Neuroleptic, n (%)	3 (7.5)	0	0	0.581
Chlorpromazine, n (%)	3 (7.5)	0	0	0.581
Dosage (mg/day), mean±SD (max-min)	50±25 (25-75)	0	0	-
Smoked cannabis, n (%)	2 (5)	0	0	1.000

Abbreviations: MQS-III: medication quantification score, 3rd version, 2005.

Values expressed as mean ± standard deviation (maximum-minimum) or number of patients (n) and percentage within group (%), as indicated.

The continuous variables were analysed using Kruskal Wallis with pairwise comparisons using Dunn procedure. Dichotomous variables were analysed using three-way chi square test. Bonferroni correction for multiple comparisons was applied in all cases. [1] Neuropathic pain versus No Pain p< 0.001; Non-Neuropathic pain versus No Pain p=0.192; Neuropathic pain versus Non-Neuropathic pain p= 0.311. [2] Neuropathic pain versus No Pain p< 0.001; Non-Neuropathic pain versus No Pain p=0.144; Neuropathic pain versus Non-Neuropathic pain p= 0.450. [3] Neuropathic pain versus No Pain p=0.002; Non-Neuropathic pain versus No Pain p=0.283; Neuropathic pain versus Non-Neuropathic pain p= 0.183.[4]Neuropathic pain versus No Pain p= 0.081; Non-Neuropathic pain versus No Pain p=0.003; Neuropathic pain versus Non-Neuropathic pain p= 0.081. [5] Neuropathic pain versus No Pain p= 0.145; Non-Neuropathic pain versus No Pain p=0.003; Neuropathic pain versus Non-Neuropathic pain p= 0.032

Significance p < 0.05. Bonferroni correction for multiple comparisons P=0.0125.

5.1.11 Quality of life, disability and psychological aspects

Patients with Neuropathic pain 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 with non-neuropathic pain, however (37.8 ± 11.3). The PCS-12 correlated with pain intensity scores as measured by the BPI, in the group with neuropathic pain (r= -0.387, p= 0.014) and in the group with non-neuropathic pain (r= -0.734, p= 0.004). The MCS-12 (mental composite scale of the SF-12) did not show statistical difference between the groups and did not correlate with the pain scores.

Assessment of anxiety and depression on the HADS showed no statistical difference between the groups. HAD-Depression sub score ≥ 8 was found in 13 (32.5%), 5 (38.5%) and 3 (15.8%) of those with neuropathic pain, non-neuropathic pain and no pain, respectively (p=0.298). HAD-Anxiety sub score ≥ 8 was found in 18 (45%), 5 (38.5%) and 3 (15.8%) of those with neuropathic pain, non-neuropathic pain and no pain, respectively (p=0.092).

BPI Intensity scores had a moderate correlation with HADS score in the neuropathic pain group (rs=0.477, p = 0.002) and in the non-neuropathic pain group (rs=0.599, p=0.031). Similarly, BPI Interference scores showed a moderate correlation with HADS scores in the group with neuropathic pain (rs=0.558 p<0.001) and a strong correlation in the non-neuropathic pain group (rs= 0.710 p=0.007).

The groups were not statistically different in the scores of Barthel ADL and Fatigue Impact scales. Predictably, patients with neuropathic pain and

non-neuropathic pain had higher scores in the pain catastrophizing 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 17). BPI interference had a moderate correlation with fatigue scores in those with neuropathic pain (rs=0.450, p = 0.004) and a strong correlation in those with non-neuropathic pain (rs= 0.653 p=0.016).

Table 17 - 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)	0.098
	Depression (0-21)	5.5 ± 3.8 (0-15)	6.6 ± 4.6 (0-15)	3.9 ± 3.5 (0-13)	0.145
	Total (0-42)	13.1 ± 7 (1-28)	14 ± 7.9 (2-31)	9.2 ± 6.3 (0-25)	0.089
Pain catastrophizing 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)	**<0.001**[1]
	Helplessness (0-5)	1.7 ± 1.6 (0-5)	1.6 ± 1.4 (0-4.5)	0.5 ± 0.8 (0-2.7)	**0.003**[2]
	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)	**<0.001**[3]
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)	**<0.001**[4]
	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)	0.307
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)	0.235
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)	0.160

Values expressed in mean ± standard deviation (minimum-maximum).

Abbreviations: HADS: Hospital Anxiety and Depression Scale; Barthel ADL index: Barthel activities of daily life index; SF-12: Short form 12-item health survey; PCS: Physical health summary of the SF-12 health survey; MCS: Mental health summary of the SF-12 health survey. 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.

[1] Neuropathic pain versus No Pain p<0.001; Non-Neuropathic pain versus No Pain p< 0.001; Neuropathic pain versus Non-Neuropathic pain p= 0.874. [2] Neuropathic pain versus No Pain p=0.004; Non-Neuropathic pain versus No Pain p= 0.020; Neuropathic pain versus Non-Neuropathic pain p= 1.000.[3] Neuropathic pain versus No Pain p<0.001; Non-Neuropathic pain versus No Pain p< 0.001; Neuropathic pain versus Non-Neuropathic pain p= 1.000. [4] Neuropathic pain versus No Pain p<0.001; Non-Neuropathic pain versus No Pain p= 0.246; Neuropathic pain versus Non-Neuropathic pain p= 0.196.

Significance p < 0.05.

5.1.12 Other non-motor symptoms

Sixty-eight patients (94.4%) were questioned about the presence of pruritus, Uhthoff phaenomenon, 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 with neuropathic pain, non-neuropathic pain and no pain, respectively (p=0.252). Within the group with neuropathic pain, 16 (80%) of patients reported itching on the pain area, whereas only 1 (33.3%) patient with non-neuropathic pain reported the same. 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. Results are summarized in Table 18.

Table 18 - Baseline evaluation: other Non-motor symptoms

			Neuropathic pain	Non-Neuropathic pain	No Pain	p
Pruritus	**N (%)**		20 (52.6)	3 (25)	8 (44.4)	0.252
	mean ± SD	**Grading (0-10)**	2.8 ± 3.1 (0-10)	1.4 ± 2.8 (0-8)	2.3 ± 3.2 (0-8)	0.315
	Localization, n (%)	**At-level**	17 (85)	2 (66.7)	4 (50)	0.171
		Below-level	1 (5)	0	2 (25)	
		Above-level	2 (10)	1 (33.3)	2 (25)	
		C2 dermatome	5 (13.2)	1 (8.3)	2 (11.1)	1.000
		In one of the pain areas	16 (80)	1 (33.3)	-	**<0.001**
Uhthoff phaenomena	**N (%)**		18 (47.4)	5 (41.7)	11 (61.1)	0.602
	mean ± SD	**Grading (0-10)**	7.4 ± 2.7 (0-10)	5.7 ± 3.2 (0-8)	5.8 ± 2.7 (0-9)	0.106
Hiccups	**N (%)**		2 (5.3)	1 (8.3)	1 (5.6)	1.000
Dizziness upon standing	**N (%)**		17 (44.7)	2 (16.7)	6 (33.3)	0.204
Persistent nausea and vomiting	**N (%)**		7 (18.4)	1 (8.3)	1 (5.6)	0.547
Urinary dysfunction						
Overactive bladder	**N (%)**		30 (78.9)	10 (83.3)	14 (77.8)	1.000
OAB-V8 (0-42)	**mean ± SD**		18.4 ± 11.8 (0-42)	16.7 ± 11.3 (3-40)	19.2 ± 14.3 (1-42)	0.886
IPSS: Voiding/ Obstructive classification	**N (%)**	**Mild symptoms**	10 (26.3)	7 (58.3)	7 (38.9)	0.099
		Moderate symptoms	9 (23.7)	1 (8.3)	7 (38.9)	
		Severe symptoms	19 (50)	4 (33.3)	4 (22.2)	
IPSS score (0-35)	**mean ± SD**		15.6 ± 9.7 (0-30)	12 ± 11.7 (0-35)	12.2 ± 10.1 (0-32)	0.372
Intermittent catheterization	**N (%)**		6 (15.8)	3 (25)	2 (11.1)	0.607
Indwelling catheterization	**N (%)**		0	0	0	
Faecal dysfunction						
None	**N (%)**		5 (13.2)	3 (25)	6 (33.3)	0.243
Constipation	**N (%)**		31 (81.6)	8 (66.7)	10 (55.6)	
Incontinence	**N (%)**		2 (5.3)	1 (8.3)	2 (11.1)	
Bowel movements per week	**mean ± SD**		3.9 ± 2.6 (0.5-14)	4.8 ± 3.6 (1-13)	4.4 ± 2.5 (1-7)	0.628
Adult diaper use	**N (%)**		9 (23.7)	1 (8.3)	3 (16.7)	0.541

Values expressed as mean ± standard deviation (maximum-minimum) or number of patients (n) and percentage within group (%), as indicated.

Abbreviations: OAB-V8: Overactive bladder 8-item questionnaire, IPSS: International Prostate Symptom Score. One-way Anova was use to compare continuous data and three-way Fisher exact test was used to compare frequencies between groups.
Significance $p < 0.05$.

5.1.13 Psychophysics assessment: QST and CPM

Seventy patients underwent QST: one patient in the group without pain refused the test and another in the non-neuropathic pain reported migraine as main pain syndrome, hence she was not evaluated with this instrument. There was no difference in any QST parameter in the control area of patients with neuropathic pain, non-neuropathic pain and no pain (Table 19).

Table 19 - Mean values of all QST parameters in the control area. Subjects without pain were matched with those with pain for the same area

	Neuropathic pain	Non-Neuropathic pain	No Pain	p
Cold Detection Threshold (ºC)	29.5 ± 1.7 (20.8-31.3)	29.8 ± 0.9 (27.7-31)	29.6 ± 1.3 (26.2-31.2)	0.995
Warm Detection Threshold (ºC)	34.4 ± 1 (31.3-36.6)	34.8 ± 0.9 (33.6-36.5)	34.4 ± 0.8 (33.4-36.5)	0.484
Cold Pain Threshold (ºC)	17.6 ± 5.4 (2.2-26)	17.7 ± 3.8 (12.9-25.4)	17.9 ± 6.6 (5-27.8)	0.769
Heat Pain Threshold (ºC)	41.8 ± 2.8 (37.6-46.1)	41.4 ± 2.3 (37.6-46.5)	42.5 ± 3.4 (36.1-46.8)	0.509
Suprathreshold heat pain stimuli (pain rating 0–100)	50.8 ± 23.1 (10-91)	47.3 ± 25.6 (10-90)	43.1 ± 20 (20-90)	0.441
Suprathreshold cold pain stimuli (pain rating 0–100)	39.3 ± 23.5 (0-97)	36.2 ± 23.2 (9-70)	27.7 ± 16.5 (0-70)	0.191
Mechanical detection threshold (mN)	3.3 ± 4 (2.53-27.9)	2.5 ± 0.0 (2.53-2.53)	2.9 ± 0.9 (2.53-5.53)	0.271
Mechanical pain threshold (mN)	171.2 ± 72.6 (40.3-292)	125.6 ± 80.8 (4.93-292)	177.3 ± 83.1 (52.6-292)	0.174
Mechanical pain sensitivity (pain rating 0–100)	24.6 ± 17.4 (0-80)	19 ± 16.4 (3-60)	23.2 ± 16.8 (0-50)	0.551
Dynamic mechanical allodynia (pain rating 0–100)	0	0	0	1.000
Wind-up ratio	1.6 ± 5.1 (0-30)	0.6 ± 0.7 (0-2)	0.3 ± 1.2 (0-5)	0.167

The values are presented as mean ± standard deviation (minimum-maximum)

Kruskal Wallis test was used to analyse all parameters. Significance $p < 0.05$.

In the most painful area, individuals with Neuropathic pain had higher thresholds for warm stimuli detection, when compared to those with non-neuropathic pain (41.3 ± 5.6 and 36.9 ± 3, respectively, p= 0.045). They were also the only individuals to display any degree of dynamic mechanical allodynia (Table 20).

Table 20 - Mean values of all QST parameters in the most painful area. Subjects without pain were matched with those with pain for the same area

Patients	Neuropathic pain	Non-Neuropathic pain	No Pain	p
	40	13	19	
Cold Detection Threshold (ºC)	20 ± 10.1 (0-30.7)	26.8 ± 2.6 (23.4-30.2)	21.2 ± 12.2 (0-30.8)	0.078
Warm Detection Threshold (ºC)	41.3 ± 5.6 (33.9-50)	36.9 ± 3 (33.6-42.2)	39.9 ± 6.1 (33.6-50)	**0.048**[1]
Cold Pain Threshold (ºC)	5.6 ± 7.9 (0-26.6)	8.7 ± 8.1 (0-23.7)	10.1 ± 9.8 (0-27.7)	0.173
Heat Pain Threshold (ºC)	46.8 ± 3.5 (38.6-50)	43.6 ± 4.3 (37.4-49.9)	44.7 ± 4.6 (37.1-50)	**0.048**[2]
Suprathreshold heat pain stimuli (pain rating 0–100)	33.8 ± 25.1 (0-92)	43.6 ± 29.4 (5-90)	35.5±24.2 (0-85)	0.525
Suprathreshold cold pain stimuli (pain rating 0–100)	18.6 ± 23 (0-76)	33.2 ± 27 (0-74)	17.3 ± 18.8 (0-56)	0.117
Mechanical detection threshold (mN)	11.7 ± 14.6 (2.53-61.7)	6.2 ± 4.6 (2.53-18.4	12.8 ± 21.8 (2.53-82)	0.085
Mechanical pain threshold (mN)	186.4 ± 96.1 (27.9-292)	155.6 ± 86.2 (52.6-292)	185.9 ± 87.6 (52.6-292)	0.555
Mechanical pain sensitivity (pain rating 0–100)	18.8 ± 21.1 (0-80)	20.8 ± 13.5 (0-45)	17.4 ± 18.8 (0-70)	0.483
Dynamic mechanical allodynia (pain rating 0–100)	9.9 ± 18.3 (0-61)	0	0	**0.008**[3]
Wind-up ratio	4.7 ± 11.3 (0-52)	5 ± 9.5 (0-32)	1.2 ± 3.3 (0-14)	0.382

The values are presented as mean ± standard deviation (minimum-maximum). Kruskal Wallis test with pairwise comparisons using Dunn's procedure with a Bonferroni correction for multiple comparisons was used to analyse all parameters. [1] Neuropathic pain versus No Pain p=0.931; Non-Neuropathic pain versus No Pain p=0.505; Neuropathic pain versus Non-Neuropathic pain p= 0.045. [2] Neuropathic pain versus No Pain p=0.427; Non-Neuropathic pain versus No Pain p=1.000; Neuropathic pain versus Non-Neuropathic pain p= 0.064

[3] Neuropathic pain versus No Pain p=0.026; Non-Neuropathic pain versus No Pain p=1.000; Neuropathic pain versus Non-Neuropathic pain p= 0.070. Significance $p < 0.05$.

We analysed the difference in the different parameters between the control area and the most painful of each subject, and the results are shown in Table 21: Individuals with pain had a statistically significant difference in the warm detection threshold when compared to those with non-neuropathic pain (-6.8 ± 5.5 and -2.1 ± 3.6, respectively, p= 0.025) and also in the heat pain thresholds, when compared to those with no pain (-4.5 ± 4.6 and --2.2 ± 3.6, respectively, p= 0.021). EDSS correlated with the differences of cold detection threshold between the control and the pain area in those with neuropathic pain (rs=0.335 p=0.035) and without pain (0.551, p=0.018), but not in those with non-neuropathic pain (rs= 0.018 p=0.956). Only in those with neuropathic pain, we also found a moderate correlation between NPSI total scores and the difference of VAS associated to dynamic allodynia in the control area (rs=-0.375 p=0.017).

Table 21 - Difference between control and pain area amid the 3 groups (control minus most painful area)

	Neuropathic pain	Non-Neuropathic pain	No Pain	p
Cold Detection Threshold (ºC)	9.6 ± 10.2 (-4-30.8)	3 ± 3.2 (-1.2-7.6)	8.4 ± 12.5 (-1.8-30.8)	0.116
Warm Detection Threshold (ºC)	-6.8 ± 5.5 (-15.4-1.2)	-2.1 ± 3.6 (-8.5-1.7)	-5.5 ± 6.3 (-15.8-2.2)	**0.030**[1]
Cold Pain Threshold (ºC)	12 ± 8.5 (-8.5-24.4)	9 ± 7.3 (-2.4-19.2)	7.8 ± 7.9 (-5.7-22)	0.128
Heat Pain Threshold (ºC)	-4.5 ± 4.6 (-11.8-3.8)	-2.2 ± 5.6 (-10.3-6.1)	-2.2 ± 3.6 (-12.1-3)	**0.019**[2]
Suprathreshold heat pain stimuli (pain rating 0–100)	17 ± 27.9 (-37-91)	3.8 ± 18.1 (-30-38)	12.3 ± 24.5 (-25-40)	0.345
Suprathreshold cold pain stimuli (pain rating 0–100)	20.7 ± 24.5 (-23-87)	3 ± 23.4 (-50-47)	10.4 ± 19.4 (-38-48)	0.066
Mechanical detection threshold (mN)	-8.4 ± 13.3 (-59.2-0)	-3.6 ± 4.6 (-15.9-0)	-9.8 ± 21.9 (-79.5-0)	0.052
Mechanical pain threshold (mN)	-15.2 ± 116.2 (-230.3-186)	-30 ± 49.3 (-116-35)	-15.3 ± 71.2 (-186-70)	0.783
Mechanical pain sensitivity (pain rating 0–100)	5.7 ± 22.9 (-50-52)	-1.8 ± 15.1 (-28-30)	5.8 ± 17.6 (-30-43)	0.327
Dynamic mechanical allodynia (pain rating 0–100)	-9.9 ± 18.3 (-61-0)	0	0	**0.008**[3]
Wind-up ratio	-3 ± 12.4 (-52-28.9)	-4.5 ± 9.7 (-32-2)	-0.9 ± 3.6 (-14-5)	0.739

The values are presented as mean ± standard deviation (minimum-maximum)

Kruskal Wallis test with pairwise comparisons using Dunn's procedure with a Bonferroni correction for multiple comparisons was used to analyse all parameters

[1] Neuropathic pain versus No Pain p=1.000; Non-Neuropathic pain versus No Pain p=0.291; Neuropathic pain versus Non-Neuropathic pain p= 0.025. [2] Neuropathic pain versus No Pain p=0.021; Non-Neuropathic pain versus No Pain p=1.000; Neuropathic pain versus Non-Neuropathic pain p= 0.398. [3] Neuropathic pain versus No Pain p=0.026; Non-Neuropathic pain versus No Pain p=1.000; Neuropathic pain versus Non-Neuropathic pain p= 0.070. Significance $p < 0.05$.

Conditioned Pain Modulation scores were not statistically different between groups with Neuropathic Pain, non-Neuropathic pain and no pain: -12.3 ± 46.5, -7.7 ± 23.5 and -3.6 ± 25.6 % respectively (p= 0.853).

5.1.14 Neurophysiological assessment: Cortical excitability

Rest motor threshold was measured bilaterally, and a paired t-test showed no difference between the two sides. Therefore, an average of both sides was considered the individual measure of RMT (%) and it showed no difference between the three groups. MEP amplitudes at 120 and 140% were significantly lower in both groups with pain when compared to those without pain (Table 22).

Table 22 - Cortical excitability parameters per group

Parameters	Neuropathic pain	Non-Neuropathic pain	No Pain	p
RMT (%)	52.9 ± 10.6 (37.5-83)	56.9 ± 10.7 (40.5-76.5)	50.9 ± 6.4 (37.5-62)	0.239
MEP 120% (µV)	489.9 ± 549.6 (9.54-1982.9)	438.7 ± 418.5 (84.5-1339.4)	1170.7 ± 1212.4 (94.3-4555.7)	**0.009**[1]
MEP 140% (µV)	1026 ± 1038.1 (27.4-3900)	1000.1 ± 798.1 (178.6-2850)	2217.8 ± 2120.9 (363.5-9200)	**0.008**[2]
Ratio MEP140%/ MEP120%	2.7 ± 1.6 (0.8-7.5)	2.8 ± 1.3 (1.4-5.1)	2.5 ± 1.5 (0.42-6.9)	0.785
SICI (µV)	0.8 ± 0.8 (0.1-3.7)	0.61 ± 0.6 (0.2-2.4)	0.5 ± 0.2 (0.1-0.8)	0.098
ICF (µV)	2.7 ± 2.5 (0.4-11.7)	1.5 ± 0.9 (0.8-4.1)	2.2 ± 1.7 (0.2- 6.6)	0.314

Abbreviations: The values are presented as mean ± standard deviation (minimum-maximum). RMT: rest motor threshold; MEP: Motor evoked potentials; SICI: Short Inhibitory Cortical Inhibition; ICF: Intracortical Facilitation. One way Anova was use to compare RMT between groups. The remainder of the data was analysed using Kruskal-Wallis test with pairwise comparisons using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons; significance p<0.05. [1] Neuropathic pain versus No Pain p=0.008; Non-Neuropathic pain versus No Pain p=0.088; Neuropathic pain versus Non-Neuropathic pain p= 1.000.[2] Neuropathic pain versus No Pain p=0.006; Non-Neuropathic pain versus No Pain p=0.124; Neuropathic pain versus Non-Neuropathic pain p= 1.000. Significance p< 0.05.

Normative data from healthy controls in the same population (Cueva *et al.*, 2016) enabled the classification of each cortical excitability parameter as normal, high or low (Table 23). Most patients with neuropathic and non-neuropathic pain had low MEP 120 and 140, compared to just over one third of those with no pain. Short inhibitory cortical inhibition was High in 17 (43.6%)

of those with neuropathic pain, compared to only 1 (7.7%) with non-neuropathic pain and 6 (33.3%) with no pain, demonstrating defective intracortical inhibition in the neuropathic pain group.

Table 23 - Classification of individual results for cortical excitability based on normative data (Cueva *et al.*, 2016)

Parameters		Neuropathic pain	Non-Neuropathic pain	No Pain	p
RMT (%)	Low	11 (28.2)	1 (7.7)	5 (27.8)	
	Normal	6 (15.4)	3 (23.1)	4 (22.2)	0.593
	High	22 (56.4)	9 (69.2)	9 (50)	
MEP 120 (µV)	Low	25 (64.1)	9 (69.2)	7 (38.9)	
	Normal	4 (10.3)	1 (7.7)	2 (11.1)	0.352
	High	10 (25.6)	3 (23.1)	9 (50)	
MEP 140 (µV)	Low	26 (66.7)	7 (53.8)	6 (33.3)	
	Normal	3 (7.7)	3 (23.1)	2 (11.1)	0.081
	High	10 (25.6)	3 (23.1)	10 (55.6)	
SICI (µV)	Low	12 (30.8)	6 (46.2)	10 (55.6)	
	Normal	10 (25.6)	6 (46.2)	2 (11.1)	0.054
	High	17 (43.6)	1 (7.7)	6 (33.3)	
ICF (µV)	Low	16 (41)	8 (61.5)	7 (38.9)	
	Normal	9 (23.1)	3 (23.1)	3 (16.7)	0.514
	High	14 (35.9)	2 (15.4)	8 (44.4)	

Abbreviations: The values are presented as N (%). RMT: rest motor threshold; MEP: Motor evoked potentials; SICI: Short Inhibitory Cortical Inhibition; ICF: Intracortical Facilitation. Three-way chi square was used to compare frequencies between groups; significance $p< 0.05$.

There was a significant moderate positive correlation between the amplitude of the MEP at 120% of the RMT and the BPI Intensity score, in those patients with Neuropathic pain ($p=0.016$, $rs=0.382$). Among those patients with non-neuropathic pain, we also found a positive correlation between the amplitude of the MEP at 140% of the RMT and NPSI total score ($p=0.039$, $rs=0.576$) (Table 24).

Table 24 - Multiple bivariate correlation with Spearman Rank Analysis

	Neuropathic pain		Non-Neuropathic pain		No Pain	
	P-value	rs	P-value	rs	P-value	rs
MEP 120% vs BPI Intensity	**0.016**	**0.382**	0.214	-0.370	-	-
MEP 120% vs BPI Interference	0.556	0.097	0.152	-0.421	-	-
MEP 120% vs NPSI total score	0.841	-0.033	0.241	0.350	-	-
MEP 120% vs SF12-MCS	0.843	-0.033	0.668	-0.132	0.669	-0.108
MEP 120% vs SF12-PCS	0.177	-0.221	0.390	0.188	0.938	0.020
MEP 120% vs MQS-III	0.785	0.045	0.692	-0.122	0.914	-0.028
MEP 140% vs BPI Intensity	0.060	0.304	0.491	-0.210	-	-
MEP 140% vs BPI Interference	0.909	0.019	0.370	-0.271	-	-
MEP 140% vs NPSI total score	0.777	-0.047	**0.039**	**0.576**	-	-
MEP 140% vs SF12-MCS	0.811	-0.039	0.571	-0.173	0.639	-0.119
MEP 140% vs SF12-PCS	0.133	-0.166	0.908	0.124	0.804	-0.063
MEP 140% vs MQS-III	0.509	0.109	0.103	0.739	0.129	0.610
Ratio MEP 140/120 vs BPI Intensity	0.169	-0.225	0.154	0.419	-	-
Ratio MEP 140/120 vs BPI Interference	0.419	-0.133	0.177	0.399	-	-
Ratio MEP 140/120 vs NPSI total score	0.953	0.010	0.452	0.229	-	-
Ratio MEP 140/120 vs SF12-MCS	0.478	0.117	0.482	-0.214	0.711	-0.094
Ratio MEP 140/120 vs SF12-PCS	0.471	0.119	**0.031**	**-0.599**	0.276	-0.271
Ratio MEP 140/120 vs MQS-III	0.679	0.069	0.350	0.283	0.610	0.129

Abbreviations: MEP: Motor evoked potentials; SICI: Short Inhibitory Cortical Inhibition; ICF: Intracortical Facilitation ; MQS-III: medication quantification score, version III, 2005; SF-12: Short form 12-item health survey; PCS: Physical health summary of the SF-12 health survey; MCS: Mental health summary of the SF-12 health survey; BPI: brief pain inventory; NPSI: neuropathic pain symptoms inventory

Data analysed using Spearman's rank correlation coefficient.

Significance $p < 0.05$.

Bivariate correlation between pain scores and the different cortical excitability parameters are shown below. There was a moderate negative correlation between BPI interference scores and MEP 120% and 140% (rs=-0.294, p=0.013 and rs=-0.305, p= 0.010, respectively), NPSI total scores and MEP 120% and 140% (rs= -0.263, rs= 0.028 and rs = -0.249, p=0.038, respectively) and between BPI total score and MEP 140% (rs=-0.240, p= 0.045) (Table 25).

Table 25 - Multiple bivariate correlation with Spearman Rank Analysis between cortical excitability measurements and pain scores of the whole cohort

	BPI total score		BPI Intensity		BPI Interference		NPSI total	
	P-value	rs	P-value	rs	P-value	rs	p-value	rs
RMT (%)	0.776	0.035	0.916	-0.013	0.503	0.081	0.735	0.041
MEP 120% (µV)	0.060	-0.226	0.231	-0.145	**0.013**	**-0.294**	**0.028**	**-0.263**
MEP 140 (µV)	**0.045**	**-0.240**	0.167	-0.167	**0.010**	**-0.305**	**0.038**	**-0.249**
Ratio MEP 140/120	0.947	-0.008	0.778	-0.034	0.916	0.013	0.664	0.053
SICI (µV)	0.687	0.049	0.504	0.081	0.759	0.037	0.348	0.114
ICF (µV)	0.529	-0.077	0.512	-0.080	0.540	-0.074	0.983	0.003

Abbreviations: RMT: rest motor threshold; MEP: Motor evoked potentials; SICI: Short Inhibitory Cortical Inhibition; ICF: Intracortical Facilitation BPI: brief pain inventory; NPSI: neuropathic pain symptoms.
Data analysed using Spearman's rank correlation coefficient.
Significance p< 0.05.

There was no correlation between any of the CE measurements with total motor scores (sum of all four limbs, distal and proximal. Greater values denote better function) and EDSS, demonstrating no relationship between cortical excitability parameters and disability (Table 26).

Table 26 - Multiple bivariate correlation with Spearman Rank Analysis between cortical excitability measurements and EDSS and motor strenght total score of the whole cohort.

	EDSS		Motor Strength total score	
	P-value	rs	P-value	rs
RMT (%)	0.466	0.089	0.174	-0.165
MEP 120% (µV)	0.970	0.005	0.816	-0.028
MEP 140 (µV)	0.830	0.026	0.683	0.050
Ratio MEP 140/120	0.983	-0.003	0.197	0.156
SICI (µV)	0.265	0.135	0.359	0.111
ICF (µV)	0.655	-0.054	0.700	0.047

Abbreviations: RMT: rest motor threshold; MEP: Motor evoked potentials; SICI: Short Inhibitory Cortical Inhibition; ICF: Intracortical Facilitation EDSS: expanded disability status scale.
Data analysed using Spearman's rank correlation coefficient.
Significance p< 0.05.

We decided to perform analysis of cortical excitability measurements divided in groups according to the use of drugs reported to cause alterations in its values according to the most recent literature in TMS (Ziemann *et al*., 2015).

Carbamazepine and lamotrigine, voltage-gated sodium channels blockers anti-epileptic drugs, cause increase in RMT and decrease in SICI/ in increase ICF. There was no difference in any of the CE measurements when comparing users of any of them or each of them (Table 27).

As Gabapentin (voltage-gate calcium channel blocker) and diazepam (positive allosteric modulator of the GABA-A receptor) cause increase in SICI and decrease in ICF, we also analysed CE parameters according to their use. Similarly, there were no differences between groups (Table 28).

Finally, we divided patients in those who used baclofen (GABA-B receptor agonist), a drug reported to decrease SICI and increase ICF. And again there were no differences between users and non-users of this drug in any of the CE measurements (Table 29).

Table 27 - Comparison of cortical excitability measurements between groups divided according to the use of lamotrigine, carbamazepine or any of those drugs. Those drugs are known increase RMT and decrease SICI/increase ICF. Comparisons are made only within groups

Using the drug	Carbamazepine (CBZ)		p	Lamotrigine (LTG)		p	CBZ or LTG		p
	yes	no		yes	no		yes	no	
N	19	51		4	66		22	48	
RMT (%)	50.1± 8.5	54.3± 10.1	0.121	59.8±13	59.7±9.6	0.344	50.9±9.2	54.1±10	0.174
MEP 120% (µV)	640.7±569.8	660.9± 885.2	0.797	165.1±149	685.2 ± 822.2	0.065	581±551.6	689.6±904.6	0.800
MEP 140% (µV)	1411.3± 1225.4	1296.4± 1530.1	0.456	498.4±535.7	1377.9 ± 1470	0.078	1305.4± 1179.8	1337.8±1564.4	0.800
Ratio MEP140%/ MEP120%	2.89± 1.7	2.6±1.4	0.611	2.7±1.1	2.7±1.5	0.617	2.9±1.6	2.5±1.4	0.376
SICI (µV)	0.61±0.33	0.71±0.72	0.736	0.9±0.62	0.67±0.64	0.319	0.68±0.4	0.69±0.72	0.343
ICF (µV)	1.6±0.86	2.6±2.4	0.156	3±3.5	2.3±2.1	0.990	1.9±1.6	2.6±2.3	0.153

Abbreviations: The values are presented as N (%). RMT: rest motor threshold; MEP: Motor evoked potentials; SICI: Short Inhibitory Cortical Inhibition; ICF: Intracortical Facilitation. Mann-Whitney U test was used to compare values between groups; significance p< 0.05.

Table 28 - Comparison of cortical excitability measurements between groups divided according to the use of gabapentin, diazepam or any of those drugs. These drugs are known to increase SICI/ decrease ICF. Comparisons are made only within groups

Using the drug	Gabapentin		p	Diazepam		p	Either drugs		p
	yes	no		yes	no		yes	no	
N	22	48		4	66		24	46	
RMT (%)	54.4±11.7	52.5±8.9	0.800	52±5.9	53.2±10	0.932	54.2±11.2	52.6±9.1	0.785
MEP 120% (µV)	632.5±722.6	666±851.1	0.467	1047.7±1141.6	631.7±789	0.779	649.9±727.1	658.4±854.6	0.492
MEP 140% (µV)	1312.6±1275.7	1334.5±1530.5	0.681	1712±1451.1	1304.3±1453.5	0.397	1317.8±1237.7	1332.7±1556.6	0.833
Ratio MEP140%/ MEP120%	2.5±1.0	2.7±1.7	0.879	3.6±2.7	2.6±1.4	0.723	2.7±1.3	2.7±1.6	0.824
SICI (µV)	0.59±0.39	0.73±0.7	0.676	0.68±0.3	0.69±0.72	0.501	0.61±0.4	0.73±0.74	0.990
ICF (µV)	2.32±1.9	2.4±2.2	0.939	2.5±2.8	2.6±2.3	0.600	2.5±2.0	2.3±2.2	0.720

Abbreviations: The values are presented as N (%). RMT: rest motor threshold; MEP: Motor evoked potentials; SICI: Short Inhibitory Cortical Inhibition; ICF: Intracortical Facilitation. Mann-Whitney U test was used to compare values between groups; significance $p < 0.05$.

Table 29 - Comparison of cortical excitability measurements between groups divided according to the use of baclofen. This drug is known to decrease SICI/ increase ICF

Using the drug	Baclofen		p
	yes	no	
Number of patients	21	49	
RMT (%)	54.3±9.9	52.6±9.8	0.663
MEP 120% (µV)	723.8±738.9	626.1±841.2	0.813
MEP 140% (µV)	1349.1±1162.5	1318.1±1562.8	0.744
Ratio MEP140%/ MEP120%	2.6±1.7	2.7±1.4	0.763
SICI (µV)	0.57±0.3	0.74±0.7	0.985
ICF (µV)	1.9±1.5	2.5±2.3	0.380

Abbreviations: The values are presented as N (%). RMT: rest motor threshold; MEP: Motor evoked potentials; SICI: Short Inhibitory Cortical Inhibition; ICF: Intracortical Facilitation. Mann-Whitney U test was used to compare values between groups; significance $p < 0.05$.

5.2 Follow Up Assessment

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 1 patient died): 58 (85.3%) via in-person examination and 10 (14.7%) via telephonic contact. Only two patients had had a relapse of the inflammatory disease between the two visits, one of them as optic neuritis and the other as myelitis.

Patients with pain in the first appraisal were offered treatment for their pain between the two evaluations and had pain drugs introduced and its dosages adjusted by a pain specialist in an outpatients' clinic. Fifty patients (73.5%) reported feeling pain in the follow up assessment. At-level Neuropathic pain was the most prevalent syndrome, affecting 29 (58% of the total cohort of patients with pain) subjects. Low back pain was the second most

common pain syndrome, affecting 6 (12% of the total of patients with pain) subjects (Table 30).

Table 30 - Follow up assessment: Localisation of the main pain syndrome according to sensory level (at-level, below-level and above-level), and their general description, divided according to the pain syndromes in this assessment (19 patients, 27.5% of the sample, do not have pain)

Main Pain	Neuropathic pain	Non-Neuropathic pain	P*
Number of subjects n, (%)	34 (49.3)	16 (23.2)	
Localisation			**<0.001**
At-level	29 (85.3)	2 (12.5)	
Below-level	5 (14.7)	10 (62.5)	
Above-level	0	4 (25)	
Pain syndromes, n (%)			**<0.001**
At-level Neuropathic pain	29 (85.3)	0	
Low back pain	0	6 (37.5)	
Distal lower extremities Neuropathic pain	4 (11.8)	0	
Myofascial syndrome (limbs)	0	2 (12.5)	
Mechanical cervicalgia	0	1 (6.2)	
Plantar fasciitis	0	2 (12.5)	
Painful tonic spasms	1 (2.9)	0	
Migraine	0	2 (12.5)	
Painful shoulder syndrome	0	1 (6.2)	

Values expressed in number of subjects (n) and its percentage within its group (%), as indicated. 3-way Chi-square test was used to analyse all variables.

Significance $p < 0.05$

Three patients initially free from pain, developed this symptom after the first evaluation, one of them as a at level neuropathic pain 3 months after a new myelitis relapse, another as cervicogenic headache and a third as plantar fasciitis. Incidence rate of pain was 17.7per 100 persons-year.

Three patients who reported pain in the baseline visit denied it on the follow-up assessment. 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), 6 (54.5%) of which had an improvement in their neuropathic pain, but reported musculoskeletal pain. Figure 11 presents the changes in syndromic diagnosis of the main pain throughout the study. Pain syndromes divided by neurologic injury level and in the first (baseline) and second (follow-up) evaluations are summarized in Graphic 3.

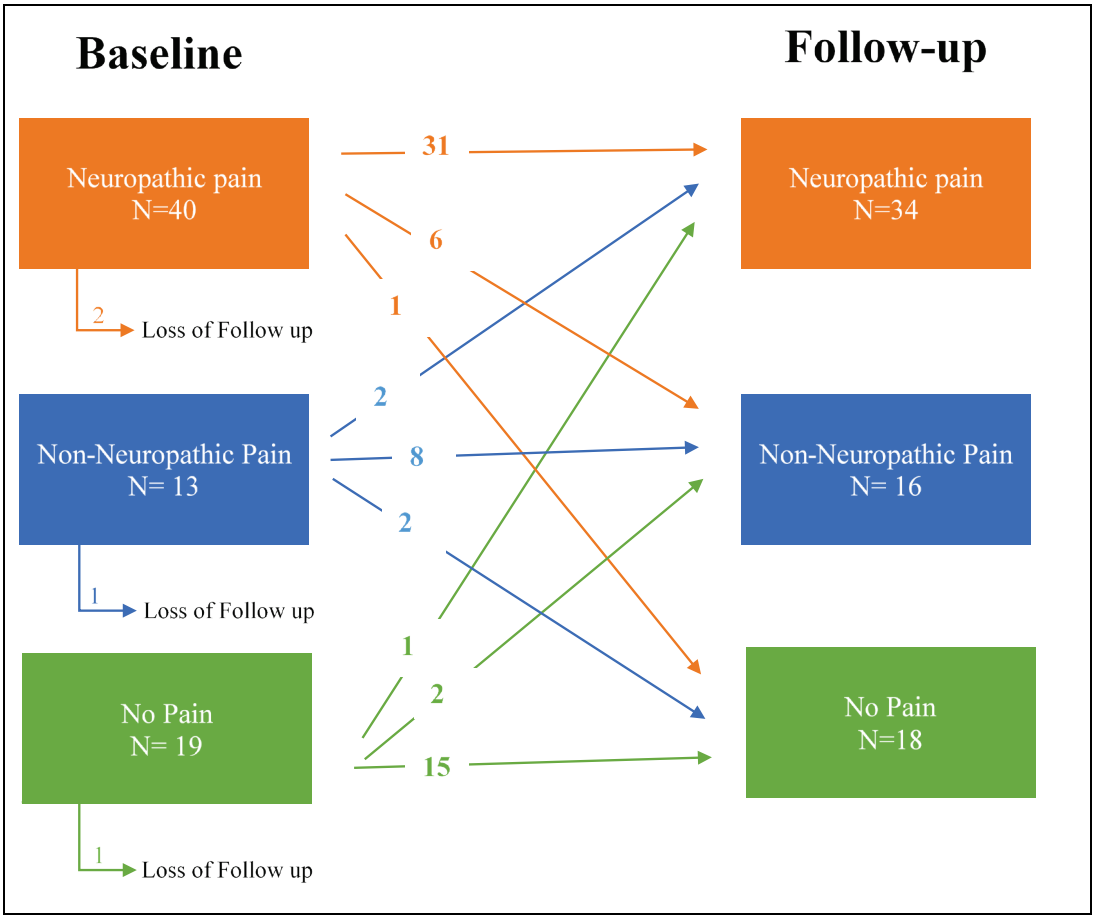
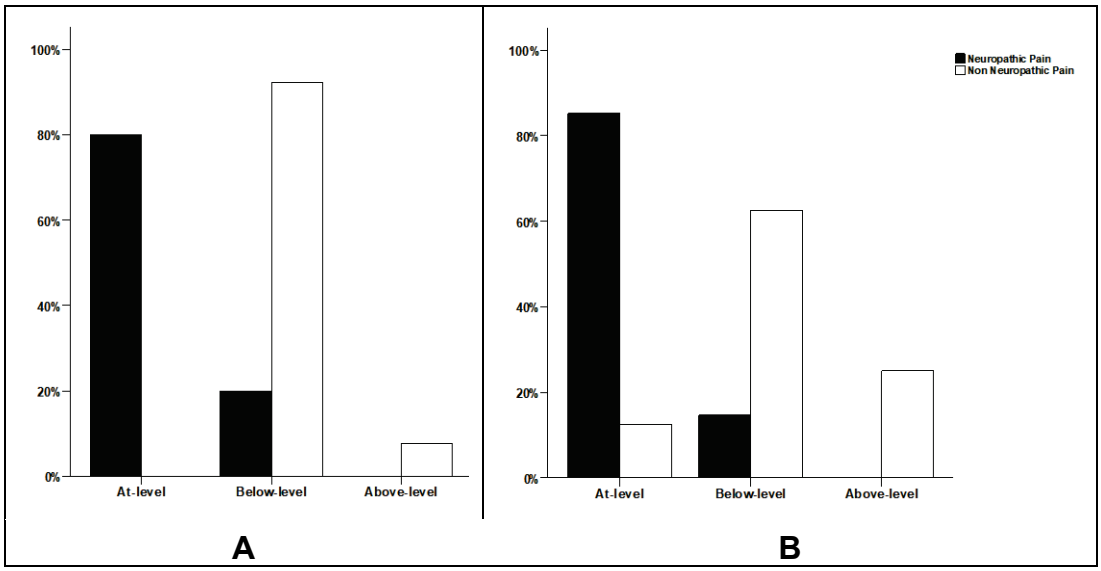


Figure 11 - Description of the changes in pain syndromes per group between the Baseline and Follow-up assessment of the current study (only main pain was assessed in both occasions)

Graphic 3 - Localisation of neuropathic and non-neuropathic pain syndromes, according to the neurological level of injury. A: Baseline; B: Follow up



A significantly greater proportion of patients with Neuropathic pain during the baseline evaluation were using anticonvulsants on the follow up analysis (82.4%), when compared to those with non-neuropathic and no pain (58.3% and 33.3%, respectively, p=0.001). Gabapentin was the most frequently used drug. The majority of those with non-neuropathic pain were using amitriptyline (58.3%) and/or Gabapentin (58.3%) (Table 31).

Table 31 - Pain drugs per patient during the follow-up (second) evaluation. (Patients are classified according to their main pain syndrome in the baseline assessment, as they were medicated accordingly)

	Neuropathic pain	Non-Neuropathic pain	No Pain	p
Number of drugs per patient, mean ± SD (min-max)	2.3±1.3 (0-5)	2.2±1.6 (0-5)	0.7±1.1 (0-4)	**< 0.001[1]**
Anticonvulsants, n (%)	32 (82.4)	7 (58.3)	6 (33.3)	**0.001[2]**
Gababentin, n (%)	23 (60.5)	7 (58.3)	4 (22.2)	**0.023[3]**
Dosage (mg/day), mean±SD (max-min)	2108.7±946.2 (300-3600)	1114.3±481.1 (300-1800)	675±450 (300-1200)	**0.003[4]**
Carbamazepine, n (%)	10 (26.3)	0	2 (11.1)	0.086
Dosage (mg/day), mean±SD (max-min)	400±294.4 (200-1200)	0	400±0 (400-400)	0.354
Pregabaline, n (%)	5 (13.2)	0	0	0.177
Dosage (mg/day), mean±SD (max-min)	330 ±113.7 (225-450)	0	0	-
Lamotrigine, n (%)	5 (13.2)	1 (8.3)	0	0.245
Dosage (mg/day), mean±SD (max-min)	170±67.1 (100-250)	50	0	0.132
Tricyclic Antidepressants, n (%)	9 (23.7)	7 (58.3)	1 (5.6)	**0.006[5]**
Amitriptyline, n (%)	8 (21.1)	7 (58.3)	1 (5.6)	**0.004[6]**
Dosage (mg/day), mean±SD (max-min)	34.4±18.6 (25-75)	42.9 ± 23.8 (25-75)	25	0.594
Imipramine, n (%)	1 (2.6)	0	0	1.000
Dosage (mg/day), mean±SD (max-min)	50	0	0	-

Continue

Continuation

	Neuropathic pain	Non-Neuropathic pain	No Pain	p
Selective serotonin and/or noradrenaline reuptake inhibitors, n (%)	8 (21.1)	3 (25)	1 (5.6)	0.284
Venlafaxine, n (%)	8 (21.1)	2 (16.7)	0	0.081
Dosage (mg/day), mean±SD (max-min)	159.4 ± 48.1 (75-225)	112.5±53 (75-150)	0	0.236
Fluoxetine, n (%)	0	1 (8.3)	0	0.176
Dosage (mg/day), mean±SD (max-min)	0	20	0	-
Sertraline, n (%)	0	0	1 (5.6)	0.441
Dosage (mg/day), mean±SD (max-min)	0	0	50	-
Anti-spasticity, n (%)	11 (28.9)	3 (25)	3 (16.7)	0.692
Baclofen, n (%)	11 (28.9)	3 (25)	3 (16.7)	0.692
Dosage (mg/day), mean±SD (max-min)	38.2±11.7 (30-60)	43.3 ±15.3 (30-60)	16.7±5.8 (10-20)	**0.019**[7]
Opioids, n (%)	8 (21.1)	1 (8.3)	1 (5.6)	0.331
Methadone, n (%)	2 (5.3)	0	0	1.000
Dosage (mg/day), mean±SD (max-min)	30±14.1 (20-40)	0	0	-
Tramadol, n(%)	6 (15.8)	1 (8.3)	1 (5.6)	0.677
Dosage (mg/day), mean±SD (max-min)	133.3 ± 40.8 (50-150)	150	50	0.211
Oxycodone	0	0	0	-
Muscle relaxants, n (%)	1 (2.6)	2 (16.7)	0	0.131
Cyclobenzaprine, n (%)	1 (2.6)	0	0	1.000
Dosage (mg/day), mean±SD (max-min)	5	0	0	-
Orphenadrine, n (%)	0	1 (8.3)	0	0.176
Dosage (mg/day), mean±SD (max-min)		25	0	-
Carisoprodol, n (%)	0	1 (8.3)	0	0.176
Dosage (mg/day), mean±SD (max-min)	0	300	0	-

Continue

Conclusion

	Neuropathic pain	Non-Neuropathic pain	No Pain	p
Simple analgesics, n (%)	1 (2.6)	1 (8.3)	0	0.391
Dipyrone, n (%)	1 (2.6)	1 (8.3)	0	0.391
Dosage (mg/day), mean±SD (max-min)	3000	1000	0	0.317
Paracetamol, n (%)	0	0	0	-
Non-steroidal Anti-inflammatory drug, n (%)	1 (2.6)	1 (8.3)	0	0.391
Nimesulide, n (%)	1 (2.6)	1 (8.3)	0	0.391
Dosage (mg/day), mean±SD (max-min)	50	50	0	1.00
Benzodiazepine, n (%)	1 (2.6)	0	1 (5.6)	0.691
Diazepam, n (%)	1 (2.6)	0	1 (5.6)	0.691
Dosage (mg/day), mean±SD (max-min)	10	0	10	1.000
Neuroleptics, n (%)	3 (7.9)	1 (8.3)	0	0.495
Chlorpromazine, n (%)	3 (7.9)	1 (8.3)	0	0.495
Dosage (mg/day), mean±SD (max-min)	41.7±28.9 (25-75)	14	0	0.157
Smoked cannabis, n (%)	1 (2.6)	0	0	1.000

Values expressed in mean ± standard deviation (minimum-maximum) or number of subjects (n) and its percentage within its group (%), as indicated. All continuous variables were analysed using Kruskal Wallis with pairwise comparisons using Dunn procedure. Dichotomous variables were analysed using three-way chi square test. Bonferroni correction for multiple comparisons was applied in all cases.

[1] **Neuropathic pain versus No Pain p< 0.001; Non-Neuropathic pain versus No Pain p=0.012**; Neuropathic pain versus Non-Neuropathic pain p= 1.000. [2]**Neuropathic pain versus No Pain p<0.001** ; Non-Neuropathic pain versus No Pain p=0.176; Neuropathic pain versus Non-Neuropathic pain p= 0.059; [3] **Neuropathic pain versus No Pain p=0.010** ; Non-Neuropathic pain versus No Pain p=0.063; Neuropathic pain versus Non-Neuropathic pain p=1.000; [4] **Neuropathic pain versus No Pain p=0.014;** Non-Neuropathic pain versus No Pain p=1.000; **Neuropathic pain versus Non-Neuropathic pain p= 0.049;** [5]Neuropathic pain versus No Pain p= 0.143; **Non-Neuropathic pain versus No Pain p=0.003**; Neuropathic pain versus Non-Neuropathic pain p= 0.025; [6]Neuropathic pain versus No Pain p= 0.111; **Non-Neuropathic pain versus No Pain p=0.003;** Neuropathic pain versus Non-Neuropathic pain p= 0.014; [7]**Neuropathic pain versus No Pain p= 0.029; Non-Neuropathic pain versus No Pain p=0.038**; Neuropathic pain versus Non-Neuropathic pain p= 1.000.

Significance p< 0.05. Bonferroni correction for multiple comparisons of frequency variables P=0.0125.

During the follow up assessment, patients with Neuropathic and non-neuropathic pain didn't display statistically significant differences between themselves in BPI intensity (5.1±1.9 vs 4.4±1.8, respectively p=0.207), BPI interference (4±2.5 vs 4.1±2.7, respectively p=0.914), and McGill Short Pain Questionnaire total score (8.3±2.6 vs 8±2.7, respectively p=0.950). Predictably, NPSI scores were higher in those with neuropathic pain (29.4±15.8) in comparison with non-neuropathic pain (19.1±12.7, p= 0.028). DN-4 Questionnaire sensitivity for neuropathic pain was 91.2% and its specificity was 56.2% (Table 32).

Table 32 - Follow up assessment: General description of the main pain syndrome and EDSS of the 50 patients with chronic pain, divided between the neuropathic and non-neuropathic pain syndromes of the second evaluation (19 patients, 27.5% of the total sample, do not have pain)

	Neuropathic pain	Non-Neuropathic pain	p
Number of subjects, n (%)	34 (68)	16 (32)	
BPI Pain intensity, mean ± SD (min-max) (0-10)	5.1±1.9 (1.5-8.8)	4.4±1.8 (1.5-8.5)	0.207
BPI Pain interference, mean ± SD (min-max) (0-10)	4±2.5 (0-9.7)	4.1±2.7 (0-9.9)	0.914
DN4, mean ± SD (min-max) (0-10)	5.8±1.9 (2-10)	3.3±2.1 (0-7)	**<0.001**
DN4 positive for Neuropathic pain (≥ 4 affirmative answers), n (%)	31 (91.2)	7 (43.8)	**0.001**
Quality of neuropathic pain (NPSI)			
Continuous deep ongoing pain (pressure/ squeezing), n (%)	25 (73.5)	11 (68.8)	0.726
Intensity, mean ± SD (min-max) (0-10)	3.8±3.2 (0-10)	2.9±2.9 (0-10)	0.387

Continue

Conclusion

	Neuropathic pain	Non-Neuropathic pain	p
Continuous superficial ongoing pain (burning), n (%)	25 (73.5)	11 (68.8)	0.726
Intensity, mean ± SD (min-max) (0-10)	4.9±3.4 (0-10)	3.5±3 (0-8)	0.163
Evoked pain (allodynia to brush, cold and pressure), n (%)	25 (73.5)	14 (87.5)	0.466
Intensity, mean ± SD (min-max) (0-10)	2.9±2.3 (0-8.7)	1.9±1.6 (0-6)	0.233
Paroxysmal pain (electric shocks/stabbing), n (%)	9 (26.5)	4 (25)	1.000
Intensity, mean ± SD (min-max) (0-10)	1±2 (0-9)	0.9±1.7 (0-4.5)	0.968
Paraesthesia/ Dysaesthesia (tingling, pins and needles), n (%)	26 (76.5)	5 (31.2)	**0.002**
Intensity, mean ± SD (min-max) (0-10)	3.3±2.4 (0-8.5)	1.1±2.1 (0-7.5)	**0.002**
NPSI- total score, mean ± SD (min-max) (0-10)	29.4±15.8 (5-78)	19.1±12.7 (5-46)	**0.028**
McGill Pain Questionnaire, mean ± SD (min-max)			
Sensory (0-8)	4±2 (1-8)	3.9±1.8 (1-7)	0.883
Affective (0-5)	3.2±1.1 (0-5)	2.9±1.1 (1-4)	0.439
Evaluative (0-2)	1.1±0.3 (1-2)	1.2±0.4 (1-2)	0.511
Total (0-15)	8.3±2.6 (3-15)	8±2.7 (3-12)	0.950
EDSS (0-10)	5.5±1.9 (2.5-8)	5.1±2 (2-8.5)	0.564

Values are presented as mean ± standard deviation (minimum-maximum), or number of subjects (n) and its percentage (%) within groups, as indicated.

Abbreviations: BPI: Brief Pain Inventory; DN-4: *douleur neuropathique*- 4; NPSI: neuropathic pain symptom inventory; MPQ: Short-form McGill Pain Questionnaire; EDSS: expanded disability status scale.

BPI intensity, BPI interference, NPSI total score and MPQ total score were analysed using t-test. The remainder of the continuous variables were analysed using Mann Whitney U test. Dichotomous variables were analysed using Fisher exact test.

Significance $p < 0.05$.

Patients were also analysed throughout the study (baseline and follow up assessment), according to its original baseline pain category. We performed this statistical analysis in order to assess changes of scores in the same individuals.

There was a statistically significant interaction between the pain category (neuropathic, non-neuropathic or no pain) and time on BPI Intensity ($p=0.047$, $F(2, 65) = 3.213$, partial $\eta 2 = 0.090$); BPI Interference ($p=0.033$, F

(2,65), partial η2 = 0.100), MPQ Affective dimension (p= 0.015, F (2,65)= 4.495, partial η2 = 0.121), MPQ, Evaluative dimension,(p= 0.008, F(2,65)= 5.245, partial η2 = 0.139) and MPQ, Total score (p=0.002 F (2,65)= 6.790, partial η2 = 0.173) (Table 33). Patients with Neuropathic pain had a statistically significant decrease in BPI intensity (from 5.6± 1.9 to 4.8±2, p= 0.039), between the baseline and follow up assessment (Graphic 4B). MPQ total score significantly decreased in both groups with neuropathic pain (from 9±2.4 to 8±3.1, p=0.014) and in those with non-neuropathic pain (9.2±2.5 to 7±4, p=0.031) (Graphic 4E).

On the other hand, NPSI total score showed only a statistically significant main effect of group between the different groups (p< 0.001, F (2,65)= 27.966, partial η2=0.591). It was higher in those with Neuropathic pain when compared to non-neuropathic pain and no pain groups in the baseline evaluation (31±17.3 versus 21.2±13.8 and zero; Tukey Post Hoc analysis p=0.045 neuropathic pain vs non-neuropathic pain and p<0.001 in neuropathic pain vs no pain). During the follow up, it was not statistically higher when compared to those with non-neuropathic pain (27.8±16 vs 22.3±14.4, Tukey post hoc analysis, p=0.245). There was no difference in NPSI scores between the two time points in any group (main time effect: p=0.564 F (1,65) = 0.336, partial η2=0.005). EDSS was stable in all groups thru the study (Graphic 4A).

Table 33- General description of the main pain syndrome and EDSS of the 69 patients who were re-evaluated, divided according to baseline pain syndromes

	Neuropathic pain (n=38)		P[1]	Non-Neuropathic pain (n=12)		P[2]	No Pain (n=18)		P[3]	P[4]	P[5]	P[6]
	1st	2nd		1st	2nd		1st	2nd				
BPI Pain intensity, mean ± SD	5.6± 1.9	4.8±2	**0.039**	5.2±1.4	3.7±2.6	0.065	0	0.9±2.2	0.106	**<0.001[α]**	**<0.001[β]**	**0.047[a]**
BPI Pain interference, mean ± SD	4.6±2.5	3.8±2.7	0.074	4.8±2.8	3.3±2.7	0.141	0	0.9±2.1	0.091	**<0.001[ε]**	**0.001[δ]**	**0.033[b]**
NPSI- total score, mean ± SD	31±17.3	27.8±16	0.147	21.2±13.8	22.3±14.4	0.508	0	3.1±7.6	0.108	**<0.001[γ]**	**<0.001[φ]**	0.204[c]
McGill Pain Questionnaire (MPQ), mean ± SD												
Sensory	4.2±1.6	3.8±2.1	0.207	4.2±1.8	3.5±2.5	**0.043**	0	0.6±1.5	0.102	**<0.001[λ]**	**<0.001[μ]**	0.059[d]
Affective	3.3±1.1	3±1.3	0.136	3.6±1.1	2.7±1.5	0.074	0	0.4±1	0.088	**<0.001[θ]**	**<0.001[σ]**	**0.015[e]**
Evaluative	1.5±0.5	1.2±0.4	**0.003**	1.3±0.5	0.8±0.4	0.054	0	0.2±0.4	0.083	**<0.001[ν]**	**<0.001[ρ]**	**0.008[f]**
Total	9±2.4	8±3.1	**0.014**	9.2±2.5	7±4	**0.031**	0	1.2±2.8	0.085	**<0.001[τ]**	**<0.001[ω]**	**0.002[g]**
EDSS (0-10)	5.4±1.8	5.5±1.7	0.324	4.5±2.2	4.4±2.3	0.586	4.4±2.3	4.6±2.3	0.310	0.096	0.167	0.617[h]

Values expressed in mean ± standard deviation (minimum-maximum) or number of subjects (n) and its percentage within its group (%), as indicated. All variables were analysed using 2-way Mixed ANOVA.

Abbreviations: BPI: Brief Pain Inventory, intensity measured in a 0-10-point scale, interference in a 0-10 (minimal to maximal) point scale; NPSI: neuropathic pain symptom inventory; "1st "refers to the baseline assessment; "2nd" refers to the follow up assessment.

[1] P-value of the analysis within Neuropathic Pain group, between the first and second evaluation. [2] P-value of the analysis within Non-Neuropathic Pain group, between the first and second evaluation. [3] P-value of the analysis within No Pain group, between the first and second evaluation. [4] P-value of the analysis between groups, during the first (baseline) evaluation. [5] P-value of the analysis between groups, during the second (follow-up) evaluation. [6] P-value of the analysis of the interaction between the interventions and time (1st and 2nd assessments), across all groups.

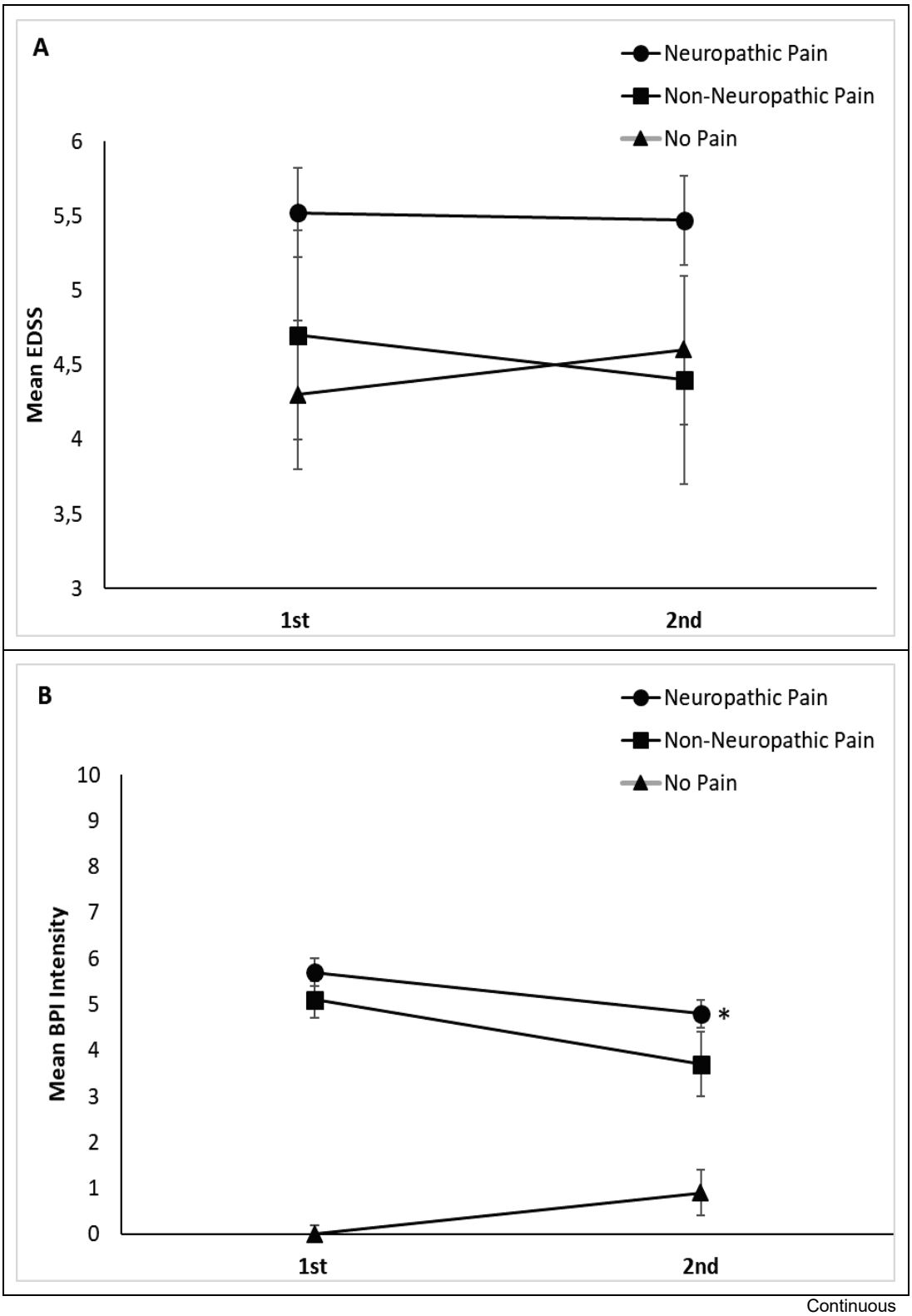
There was a statistically significant interaction between the interventions and time on [a]BPI Intensity, F(2, 65) = 3.213, partial η2 = 0.090; [b] BPI Interference F(2,65), partial η2 = 0.100; [e] MPQ, Affective dimension, F (2,65)= 4.495, partial η2 = 0.121; [f] MPQ, Evaluative dimension, F(2,65)= 5.245, partial η2 = 0.139; [e] MPQ, Total score, F (2,65)= 6.790, partial η2 = 0.173.

There was not a statistically significant interaction between the interventions and time on [c] NPSI total score, F(2,65)= 1.631, partial η2=0.048 (the main effect of time showed no statistically significant difference in NPSI score at different time points, p=0.564 F (1,65)= 0.336, partial η2=0.005. The main effect of group showed statistically significant difference in NPSI score between different groups, p< 0.001, F (2,65)= 27.966, partial η2=0.591); [d] MPQ, Sensory dimension, F (2,65)= 2.961, partial η2 = 0.083 (the main effect of time showed no statistically significant difference in MPQ Sensory score at different time points, p=0.440 F (1,65)= 0.604, partial η2=0.009. The main effect of group showed statistically significant difference in MPQ Sensory score between different groups, p< 0.001, F (2,65)= 38.151, partial η2=0.540); [h] EDSS, F(2,65)= 0.486, partial η2=0.015.

[α] Neuropathic pain versus No Pain p< 0.001; Non-Neuropathic pain versus No Pain p< 0.001; Neuropathic pain versus Non-Neuropathic pain p= 0.502.[β] Neuropathic pain versus No Pain p<0.001 ; Non-Neuropathic pain versus No Pain p=0.002; Neuropathic pain versus Non-Neuropathic pain p= 0.265[δ] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p=0.037; Neuropathic pain versus Non-Neuropathic pain p= 0.815.[ε] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p <0.001; Neuropathic pain versus Non-Neuropathic pain p= 0.982.[γ] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p =0.001; Neuropathic pain versus Non-Neuropathic pain p= 0.045.[φ] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p =0.016; Neuropathic pain versus Non-Neuropathic pain p= 0.245.[λ] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p <0.001; Neuropathic pain versus Non-Neuropathic pain p= 0.729. [μ] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p =0.001; Neuropathic pain versus Non-Neuropathic pain p= 1.000.[θ] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p <0.001; Neuropathic pain versus Non-Neuropathic pain p= 1.000.[σ] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p <0.001; Neuropathic pain versus Non-Neuropathic pain p= 1.000.[ν] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p <0.001; Neuropathic pain versus Non-Neuropathic pain p= 0.498.[ρ] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p <0.001; Neuropathic pain versus Non-Neuropathic pain p= 0.064. [τ] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p <0.001; Neuropathic pain versus Non-Neuropathic pain p= 1.000. [ω] Neuropathic pain versus No Pain p <0.001; Non-Neuropathic pain versus No Pain p <0.001; Neuropathic pain versus Non-Neuropathic pain p= 1.000.

Significance p< 0.05.

Graphic 4 - Changes in EDSS (A), BPI Intensity (B), BPI Interference (C), NPSI score (D) and MPQ total score (E) between the 1st (baseline) and 2nd (follow-up) assessments



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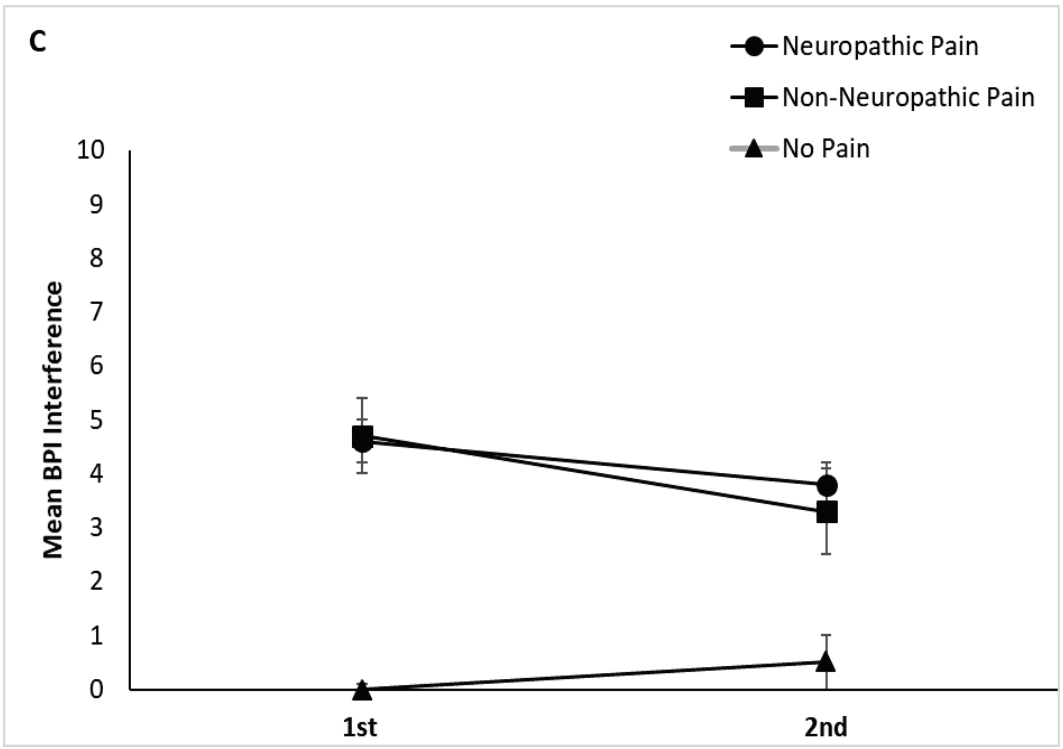
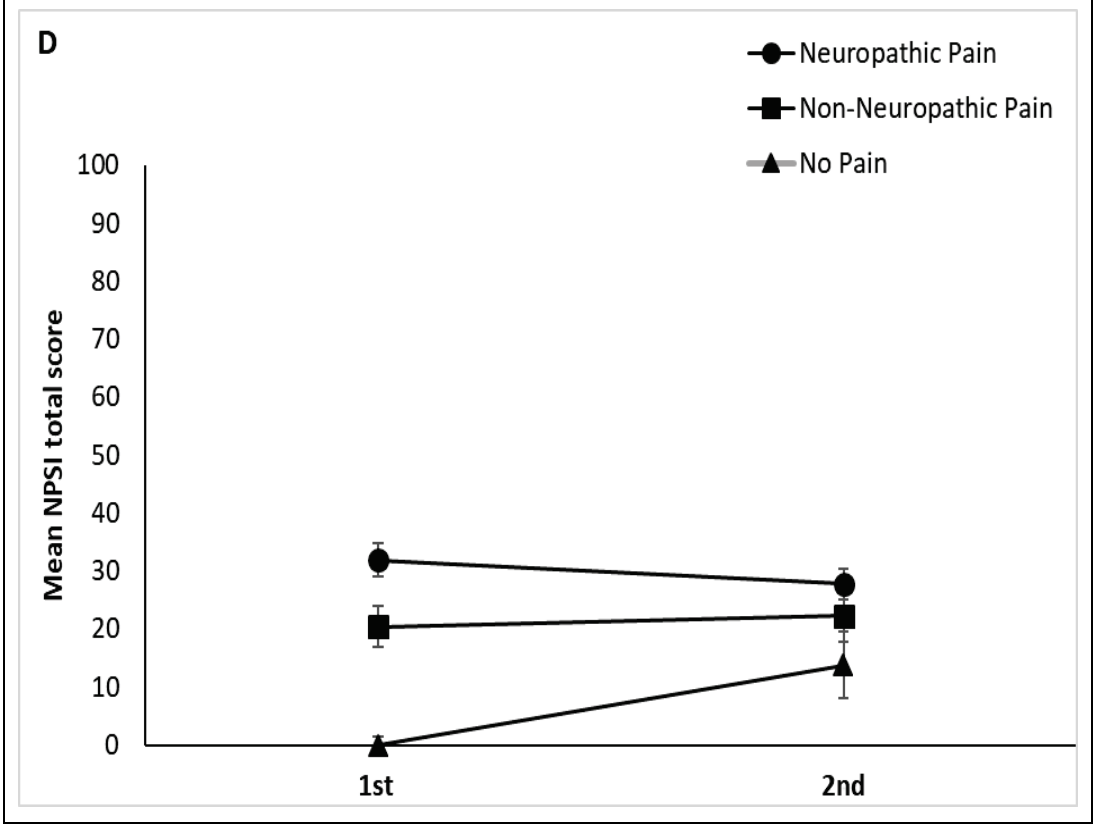
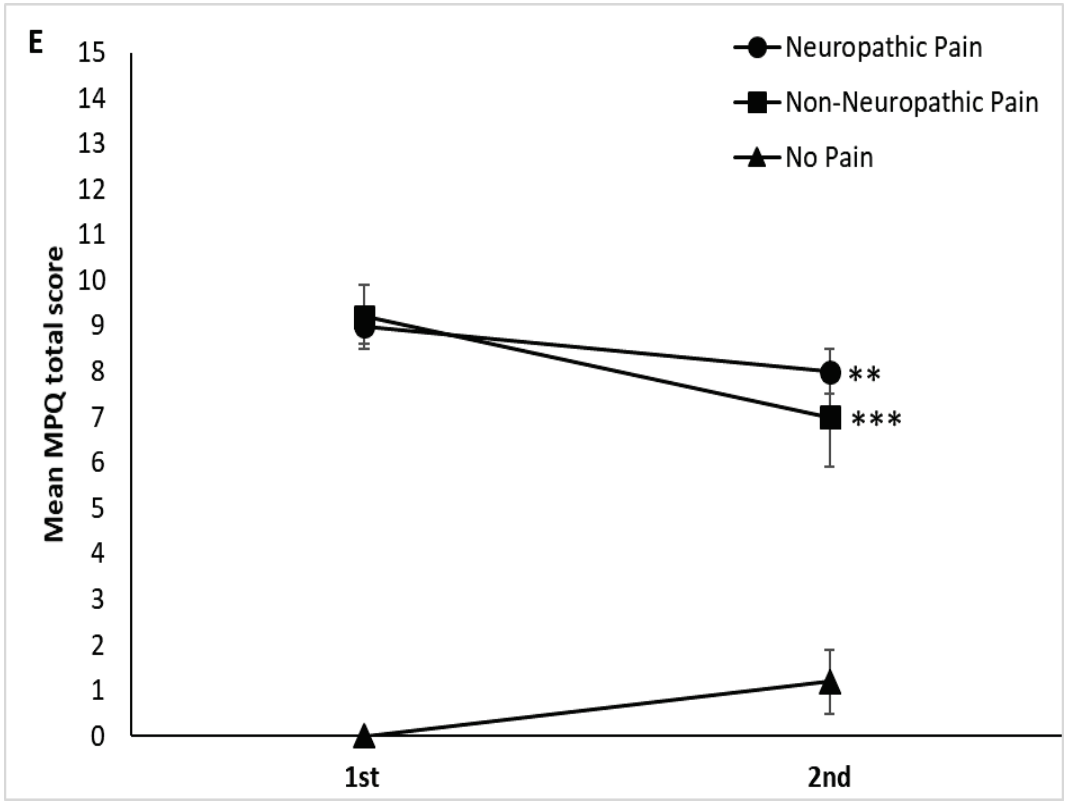
Continuation





Continuous

Conclusion



Values are presented as mean ± standard error of the mean.

Abbreviations: EDSS: expanded disability status scale, BPI: Brief Pain Inventory; DN-4: *douleur neuropathique*- 4; NPSI: neuropathic pain symptom inventory; MPQ: Short-form McGill Pain Questionnaire. "1st " refers to baseline assessment. "2nd " refers to follow-up assessment.

* p= 0.039, patients with Neuropathic pain had a statistically significant decrease in BPI intensity (from 5.6± 1.9 to 4.8±2)

** p= 0.014, patients with Neuropathic pain had a statistically significant decrease in MPQ total score (from 9±2.4 to 8±3.1)

***p= 0.031, patients with non-neuropathic pain had a statistically significant decrease in MPQ total score non-neuropathic pain (from 9.2±2.5 to 7±4)

6 DISCUSSION

The main aim of this study was evaluating pain, psychophysics and cortical excitability measures in NMO patients and understand the impact of an inflammatory disease in its quiescent phase on symptoms, with a focus on pain. We also analysed how pain syndromes can alter with the course of the inflammatory disease and as a result of previous lesions, even in patients without any signs of new activity. Furthermore, we collected data regarding symptoms described in this population: pruritus, fatigue, orthostatic intolerance, hiccups, Uhthoff phaenomena, urinary and faecal symptoms.

We found a high prevalence of chronic pain in this cohort of NMO patients free from relapses for at least 12 months. Chronic pain affected 73.6% of our patients during baseline (first) evaluation. This is line with the limited literature in chronic pain amid NMO patients. So far, different studies described pain in 70-80% of NMO cohorts studied (Kanamori *et al*. 2011; Qian et al. 2012; Kong *et al*., 2016). And until 2018, no study had reported pain syndromes other than neuropathic ones (Asseyer *et al*. 2018) and yet, the prevalence of concomitant pain syndromes is yet to be described. The majority of patients with pain (71.7%) had more than one pain syndrome: typically, but not always patients had one neuropathic pain syndrome and one non-neuropathic pain syndrome. As main pain syndrome, the most prevalent pain syndromes in our cohort was “at-level neuropathic”, observed in 58.5% of those with pain. The second most prevalent

pain syndrome was low back pain, affecting 15.1% of our sample. Low back pain was also the most common secondary pain syndrome: it affected 28.9% of those with 2 pain syndromes (40% of those with neuropathic pain as their primary pain syndrome and 2 different pains). Likewise, amid those with a non-neuropathic pain syndrome as their main pain, 40% had low back pain as their secondary pain. These results demonstrate for the first time in NMO patients the complexity of care necessary to understand pain in this population. Although widely recognized amid other spinal cord injury patients (Finnerup, 2013; Widerström-Noga, 2017), this multiplicity was not described in NMO yet.

This study brings the new knowledge that non-neuropathic pain is fairly common and that most patients have more than one pain syndrome: it's essential to acknowledge this multiplicity, as failing to do so will result in unsatisfactory pain treatments, as demonstrated in traumatic SCI patients (Cruz-Almeida *et al*., 2005). Most patients with traumatic SCI consider pain management a significant unmet need (Widerström-Noga et al., 2001; Rubinelli *et al.*, 2016). All studies which evaluated pain in NMO reported their "intractable" feature despite the use of analgesics, including those for neuropathic pain. Report of dosages is not available, though, neither combination of drugs(Kanamori *et al*., 2011; Qian *et al*., 2012; Zhao *et al*., 2014). It is fair to suppose that part of this "resistance" to their current pain drugs in NMO patients is due to incorrect or insufficient diagnosis of all pain syndromes present in those patients.

Kanamori *et al*. (2011) described that most NMO patients reported a "pain involving "trunk and both legs", but unfortunately, this study did not use

any neuropathic pain screening tool. It is feasible to assume that the authors were describing the two most common pain syndromes in NMO: “at-level” neuropathic pain and distal extremities “below-level” neuropathic pain. A figure presented in this paper also reports that patients presented with pain on the low back area, which is line with our findings.

Qian *et al*. (2012) also reports high frequencies of neuropathic pain (“Tonic spasms” [89.7%], “Dysesthetic pain" [82.8%], “Banding/girdle” [69%], “Lhermitte sign” [65.5%], and retro orbital pain [55.2%]). It is noteworthy that this study and many others with NMO deliberately excluded any pain that could be classified as “non-neuropathic pain”(Tackley *et al*., 2017; Kong *et al*., 2016). This methodological exclusion of non-neuropathic pain in NMO is important especially when comparing with other types of SCI patients. A prospective study with non-inflammatory SCI reported musculoskeletal pain as the most frequent, affecting almost 60% of that cohort (especially on shoulders, above level), followed by “at level” neuropathic pain (41% of subjects) and “below-level” neuropathic pain (34%) (Siddall *et al*., 2003). It also reported visceral pain, a type of pain that was not found in our cohort or any other previous study.

A tool for screening of neuropathic pain was included in only two studies so far: Zhao *et al*. (2014) used DN-4 Questionnaire and based on this tool reported a prevalence of 62% in neuropathic pain among patients with NMO. No analysis against a “gold standard” was made, i.e., evaluation by a pain specialist. Asseyer *et. al*. (2018) used painDETECT (Freynhagen *et al*., 2006) questionnaire to screen for neuropathic pain in NMO patients. With this tool, it

reported a prevalence of neuropathic pain in 41.7% of patients with MOG-IgG+, 79.1% of those with AQP4-Ab and 83.3% of those negative for both antibodies. No gold standard is reported against this screening toll, hence, again, no information about is sensibility of specificity is provided.

Our study used DN4-Questionnaire as a screening tool in NMO patients and comparing with the pain syndrome diagnosis of neurologist specialized in pain, it showed a high sensibility of 95%, but a low specificity of 46.2% in this cohort. This result is not unexpected, as most patients have either cervical or thoracic sensory levels and any pain below this very extensive area can be considered positive by the DN-4 due to lengthy somatosensory deafferentation present in patients with spinal cord injuries. A previous study compared different neuropathic pain screening tools in non-inflammatory SCI patients and reported DN4 as the best tool, with a sensibility of 92.9% and specificity of 75% (Hallstrom and Norrbrink, 2011). It may be the case that neuropathic pain was overrepresented in this sample, affecting 70% of those patients, as according to literature, musculoskeletal pain is the most common pain type in patients with SCI, affecting shoulders (Siddall *et al*., 2003). Finnerup and Baastrup (2012) acknowledged this difficulty of correct diagnosis of neuropathic pain below the NLI in SCI patients and added further criteria for its diagnosis as an addition to the neuropathic pain grading system proposed by IASP: (1) onset of pain within 1 year following SCI; (2) no primary relation to movement, inflammation or other local tissue damage; and (3) the descriptive adjectives typical of neuropathic pain such as ‘hot-burning’, ‘tingling’, ‘pricking’, ‘pins-and-needles’, ‘sharp’, ‘shooting’, ‘squeezing’, ‘cold’,

‘electric’ or ‘shock-like’. This discussion is certainly helpful but specific screening tools for neuropathic pain in SCI must be developed in the future as better specificity is needed in screening tools for neuropathic pain in this population.

Another important and new information brought by our study is the similarity of BPI intensity scores (5.7± 1.9 and 5.1±1.3, in neuropathic and non-neuropathic patients, respectively, p= 0.338) and BPI interference scores (4.6±2.5 and 4.7±2.7, in neuropathic and non-neuropathic patients, respectively, p=0.878), between the two groups with pain. This data highlights the importance of recognizing all pain syndromes in NMO patients, as non-neuropathic pain is no less disturbing than neuropathic pain.

Our study was the first to use NPSI to describe pain in NMO and it showed that the descriptors “pressure/ squeezing” (for continuous ongoing deep pain) was present in 80% of those with neuropathic pain and 76.9% of those with non-neuropathic pain. “Burning” was equally prevalent in the neuropathic pain group (80%), and only 46.2% of those with non-neuropathic pain using this descriptor. Another very common descriptor in neuropathic pain was “tingling, pins and needles” (paraesthesia), in up to 80% of them, against only 38.5% of those with non-neuropathic pain. Although this is the first study to analyse those descriptors of pain in NMO, it suggests that the report of “burning” and “tingling, pins and needles” is more specific for neuropathic pain and might be useful to distinguish a neuropathic from a non-neuropathic pain specially in an area below the NLI. In accordance with our findings, a study with traumatic SCI patients described the descriptors “tingling” and “burning”

as more likely to be of neuropathic pain, whereas the words “dull” and “aching” (therefore continuous deep pain) were more common in non-neuropathic pain (Putzke *et al*., 2002).

We also found a prevalence of migraine of 6.9% in our cohort. One patient reported migraine as her primary pain syndromes and 5 patients(13.2% of those with 2 pain syndromes) reported headache as their secondary pain syndrome upon study entry: 2 as migraine and 3 as cervicogenic headache.The prevalence of migraine in our study compares to reported prevalences between 2.6 and 21.7% in the general population (Yeh *et al.*, 2018).There are scarce studies about the prevalence of headache in NMO. Asseyer *et al*. (2018) reported a prevalence of headache/neck pain of 24.5% in their cohort of NMO patients. Previously, a Japanese study reported higher prevalence of migraine with aura amid AQP4-Ab-positive “optospinal MS” when compared to seronegative ones (Doi *et al*., 2009; Masters-Israilov and Robbins, 2017). It is probable that headaches are even more underreported than the other types of pain in NMO patients. The prevalence of comorbid primary headache in NMO is stil not known in the literature and our study is the first to describe it. Headaches can be extremely distressing and it is important to treat them within the context of a multisymptomatic chronic disease.

Another novelty of our study is the unparalleled information of incidence of pain in NMO. Since this is the first study to perform a longitudinal evaluation of those patients, we could describe changes in pain syndromes throughout the follow-up period and an incidence of pain of 17.7 per 100 persons-year. Amid those patients initially pain-free who developed pain in the second

evaluation, only one had neuropathic pain and it was 3 months after a relapse of myelitis. During our second evaluation the prevalence of pain was stable in 73.5% of our cohort and again, at-level Neuropathic pain was the most prevalent syndrome, affecting 58% of those with pain. However, interestingly, 20.8% of the original cohort changed their primary pain syndrome in the second evaluation: this an information of vital importance, as it shows the need of re-evaluating and redefining patient's pain syndromes between consultations in order to adjust treatment. Only one patient had a new pain after a relapse: this information demonstrates that pain can develop and change its characteristics even in the absence of new inflammatory activity, but solely due to previous structural lesions because of the disease (Siddall *et al*., 2003; Bryce *et al*., 2007). Although this kind of information is not a novelty for those who study mainly traumatic and syringomyelic spinal cord injuries (Ducreux *et al*., 2006; Finnerup, *et al*., 2016), it is a new concept in this type of autoimmune demyelinating disease. And this study is the first to include only NMO subjects free from myelitis relapse in the last 12 months, therefore without new spinal cord lesions in this interim.

Most patients included in this study were female (51, 70.8%), and there were no gender-related differences in pain prevalence, regardless of its type. This is compatible with the epidemiological data available in NMO, which shows a predominance of females in this autoimmune disease (Alvarenga *et al.* 2017; Houzen *et al*., 2017; Bukhari *et al*., 2017; Sepulveda *et al*., 2017; Eskandarieh *et al*., 2017a and 2017b). It is also in accordance with the previous studies of pain in NMO.

Painful (or paroxystic) tonic spasms (PTS) were first described in 1958 in MS patients, and defined as “a paroxysmal episode of intense pain that accompanied tonic postures of the limbs with or without being precipitated by abrupt movement or sensory stimulation” (Matthews, 1958). This symptom has been extensively described in NMO and had their prevalence reported between 14 and 26% in most studies (Usmani *et al*., 2012; Kim *et al*., 2012; Carnero Contentti *et al*., 2016; Liu *et al*., 2017). One study described the onset of this symptom between 0 and 91 days after a myelitis relapse (Usmani *et al*., 2012) and another on average 48.1 days from the onset of myelitis symptoms (Kim *et al*., 2012). No study has ever evaluated whether those symptoms can disappear spontaneously and their prevalence in NMO patients long time after their last relapse. Similarly, we described a prevalence of 25% of PTS in our cohort. Only one patient reported it as her main pain syndrome and another with low back pain as primary pain described it as its secondary pain. Most patients reported frequency of PTS smaller than once a week and could remember having a greater number of events in the first months following the relapse. More studies are necessary to determine whether PTS can cease spontaneously and if it is more distressing and prevalent during the acute phase of the myelitis.

An important feature in our cohort, not analysed in previous studies about pain in NMO, is the striking age differences between those with and without pain: individuals with neuropathic and non-neuropathic pain were significantly older than those without pain at the time of study entry (48.2±11.1, 46.5±8.3 and 31.4±11.8 y.o., respectively, $p<0.001$), at the time of disease onset (40±12.5, 37.2±11.4 and 26.1±12.7 y.o., respectively, $p<0.001$) and at the time of last

clinical relapse (43.3±10.8, 41.2±9.2 and 27.6±12.4 y.o., $p < 0.001$). It demonstrates that age is an important factor in the occurrence of pain, which is compatible with previous studies in neuropathic pain and also in pain after spinal cord injuries (Boogaard *et al*., 2015; Fitzgerald and McKelvey, 2016). There are multiple interacting neurobiological and behavioural factors that explain different responses to the somatosensory system with aging. In the periphery, decrease in thermal perception (as evidenced by increase in thermal thresholds), and decrease in the vibration sensibility were described in older individuals (Gagliese, 2009). Studies have described changes in the characteristic of the nociceptors (Gibson and Farrell, 2004), decreased density of Pacinian corpuscles, sensory epidermal nerve fibres density and decreased function of A- δ and C fibres (Guergova and Dufour, 2011; Da Silva *et al*., 2014). Neuroimmunological response to tissue injury is also an important factor (Ashcroft *et al.*, 2002), as it decreases with age. Animal models have 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 *et al.*, 2001; Fillingim *et al*., 2016), impaired descending noxious inhibitory control (Lariviere *et al*., 2007) and slower resolution (or no resolution at all) of postinjury hyperalgesia after lesions of the somatosensory system (Zheng *et al*., 2000). Finally, older individuals demonstrate smaller cortical responses to peripheral thermal stimulation and significant structural brain changes when compared to controls without pain (Buckalew *et al*., 2008). The neurobiology of aging and its impact in pain states is still under science scrutiny. Notwithstanding,

there is enough evidence to show that widespread change in the structure and function of peripheral and CNS nociceptive pathways may place older subjects at a great risk of developing chronic pain when compared to younger ones with comparable lesions of the somatosensory pathways. As NMO has a peak of incidence in the fourth decade of life, those biological mechanisms will certainly have implications in pain prevalence and response to treatment in those individuals. Although age certainly has an impact on the plasticity of the somatosensory system, its impact on the plasticity of the pyramidal tract was not seen in our cohort: we have failed to find correlation between age and the degree of disability as measured by the EDSS (rs -0.112, p=0.491; rs= 0.336 p=0.262; rs=-0.339, p= 0.156, in those with neuropathic pain, non-neuropathic pain and no pain, respectively) or motor strength total score (rs=0.157, p= 0.332; rs=0.253 p=0.405; rs=0.452 p=0.052 in those with neuropathic pain, non-neuropathic pain and no pain, respectively) in any of the three groups on bivariate analysis using Spearman rank test. EDSS and motor strength total score was not different across groups with neuropathic pain, non-neuropathic pain and no pain. Previous studies characterizing NMO cohorts with late onset have described higher EDSS in those individuals (Collongues *et al*., 2014; Mao *et al*., 2015). This study's cohort had only 12 individuals who could be classified as late-onset NMO (age of onset $\geq$ 50 y.o) and the mean age of disease onset in our patients with pain was 39.4±12.2 y.o. Because of that the differences in EDSS with aging could not be found in our cohort.

Still regarding sociodemographic features, in this present study patients with pain were more likely to be married than those without pain. However, when

stratified by age, those differences between groups disappeared, showing that age was just a confounder in marital status. Associations with marital status and pain have not been described in the literature. We also described that around 1/3 of patients were working: 22.5%, 30.8% and 36.8% of those with neuropathic pain, non-neuropathic pain and no pain were working, respectively. This is certainly related to their previous or current disabilities. This social data was never reported in the literature before. Adapting functions and retraining individuals with NMO could increase their employment rates and decrease the burden of social care systems in different countries.

When analysing comorbidities, we could find a significantly higher proportion of patients with essential hypertension in patients with neuropathic pain (32.5%) versus those with non-neuropathic pain and no pain (7.7 and 5.5%, respectively, p=0.024). When analysing this data regarding hypertension in two age strata, older and younger or equal to 35 y.o., this statistically significant difference in proportion of individuals with hypertension is no longer seen, showing that age was a confounder for this relationship. A recent study described prevalence of cardiovascular diseases among demyelinating diseases (including MS, NMO and TM) and found no difference of comorbidities (such as diabetes mellitus, hypertension and hyperlipidaemia) in those diseases when compared to general population. It also described a prevalence of hypertension of 16.1% in NMO (mean age 46.1±12.2 y.o.) (Saroufim *et al*., 2018). This is close to the overall prevalence of hypertension in this cohort: 20.8% (15 subjects).

Use of tobacco has been related to increase of risk of MS onset and of the disease assuming a secondarily progressive course (Degelman and

Herman 2017), but but there is still inconsistent evidence in NMO patients (Kremer *et al*., 2015; Simon *et al*., 2015). Our cohort was composed of roughly 20% of current smokers and 32% of previous smokers. There was no difference between groups with pain and without. Due to the small number of smokers per group conclusions regarding this legal drug and the onset of pain in NMO are hard to reach.

Regarding data on the inflammatory activity of NMO, there were no differences between the three groups, except for those differences already described in age of first and last relapse between those with and without pain. Time from first and last relapse until study entry was equal among groups with neuropathic pain, non-neuropathic pain and no pain, as well as number of relapses and current and previous immunosuppressant therapy. Similarly, percentage of patients with previous optic neuritis was the same in all groups. Previous studies of pain in NMO have not addressed those differences between groups with and without pain, neither have selected those in acute or quiescent phase of NMO and our study is the first to compare those features. Previous studies in MS have suggested more pain in patients with higher EDSS and more relapses (Solaro *et al*., 2004). However, we could not find any differences in markers of clinical lesion load between our groups with and without pain: EDSS scores and frequency of legally blind patients did not show statistically significant disparities across all groups. This data suggests equality of lesion load and structural changes after NMO among those with pain and no pain and further data is presented ahead to corroborate this reality of our cohort.

Previous literature data have suggested some association between neuropathic pain as onset symptom and a relapsing course of NMO (Wingerchuk *et al*., 1999; Jarius *et al*., 2012b). Another recent study reported that 57% of their patients with NMO recalled an increase in intensity of pain as first indicator of a relapse (Zhao *et al*., 2014). In this present study we could not find any statistically significant differences regarding onset symptoms across groups, but similarly, pain was the most common first presentation. Forty-seven % of our patients had pain as their onset symptom and sensory disturbances (numbness and tingling) were the first symptom in 37.5% of them. We ascertained this information with patient's notes if possible, in order to dimish the risk of recall bias.

In our cohort, the prevalence of seropositive AQP4-ab individuals was of 60%, 53.8 % and 57.9% in those with neuropathic pain, non-neuropathic pain and no pain, respectively. The overall prevalence of 58.3% of seropositivity in our sample is not dissonant from studies which report seropositivity between 58.6 and 88% (Adoni *et al*., 2008; Asgari *et al*., 2011; Jacob *et al*., 2013; Papais-Alvarenga *et al*., 2015; Flanagan *et al*., 2016; Alvarenga *et al*., 2017). It must be said that the methodology to test for aquaporin-4 has changed throughout the years, and prevalence of this antibody may change with the new epidemiological studies. Currently the preferred method is CBA, whereas until 10 years ago ELISA was frequently used. Another antibody present in a very small number of patients in our sample is the MOG-IgG, and it did not show any statistically significant difference between groups. It was present in 5.1% (2), 15.4% (2) and 5.3% (1)

of those with neuropathic pain, non-neuropathic pain and no pain. The only study to analyse pain syndromes in an appreciable number of MOG-IgG positive patients dates from 2018 and presents a prevalence of pain in 86% of sample (12/14 individuals). The most frequent pain syndromes in those individuals were neuropathic pain and headache/neck pain, affecting 41.7% of the sample in both cases. As the present study has a very small number of MOG-IgG positive patients, conclusions regarding pain syndromes and patterns are difficult and may be misleading.

In the present study data comparing spinal cord imaging studies both in the acute and chronic phase of NMO did not differ between groups, demonstrating a similar structural lesion load due to inflammatory activity in all groups, regardless of the presence and type of pain. Over half of patients had cervical or cervico-thoracic lesions in all groups, both during the relapse and in the chronic phase. This contrasts with a recent study which concluded that persistent thoracic lesions predicted greater “myelitis-associated” chronic pain, unrelatedly to number of myelitis relapses, lesion length and lesion burden (Tackley *et al*., 2017). In this study the authors argue that upper mid thoracic lesions may impair afference of information regarding the body’s sensory state to autonomic areas, which would be important for well-being and motivating behaviour to maximise comfort or to minimise pain. The authors conclude that damage to exclusively thoracolumbar autonomic nuclei or their projections may have a dysregulative effect on pain information processing at the level of the spinal cord. Although an interesting hypothesis, it is hard to ignore that the mechanisms of pain in spinal cord injuries involve a much more complex

physiopathology of peripheral and central sensitization. It would be unlikely that an exclusive autonomic dysregulation would generate those differences. Furthermore, association between a thoracic level of spinal cord injuries and greater pain was not reported in traumatic SCI patients. Those individuals would be subjected to the same pathological processes described in this paper, regardless of the mechanism of spinal cord lesion.

In consistence with similar EDSS scores, our patients with pain did not show a greater burden of disease on most of their clinical scores when compared to those without pain. Motor, myotatic reflexes, Ashworth spasticity, light touch, pinprick and thermal sensibility scores did not display statistically significant differences across all groups. An important finding was diminished vibrarion threlsholds among those patients with neuropathic pain, when compared to non-neuropathic and no pain groups.

It is known that sensory nerve fibres terminate in the spinal dorsal horn in a modality specific pattern. Nociceptive A- δ fibres terminate in laminae I and V, C fibres terminate in laminae I and II (outer). Low threshold A β fibres terminate in lamina II inner and laminas III and IV. Dorsal horn nociceptive neurons are inhibited by A β afference. Animal models have shown that high frequency vibro-tactile stimulation of large diameter low threshold mechanoreceptive afferents inhibit responses of nociceptive dorsal horn neurons to noxious stimuli (Salter and Henry, 1990). Also, cutaneous vibro-tactile stimuli result in reduction in somatosensory cortical neurons in area 3B, with a decreased responsiveness to heat nociceptive input (Tommerdahl *et al*. 2005; Staud *et al*., 2011). It may be that a more severe lesion of the dorsal

horn due to previous inflammatory activity diminishes input of peripheral A- β fibres, therefore decreasing the inhibitory effect over nociceptive neurons. The clinical finding of decreased vibration thresholds only in those with neuropathic pain demonstrates the decreased A-β fibres afference and could be one of the spinal mechanisms of pain in this population.

Another interesting finding from the bedside neurological evaluation of those individuals is the high prevalence of hyperpathia in all groups, but significantly higher in those with neuropathic pain. The frequency of “at-level” hyperpathia was of 97.5% in those with neuropathic pain as their primary pain syndrome, compared to 76.9% and 68.4% of those with non-neuropathic pain and no pain, respectively. This is a difference statistically significant (p=0.006) driven by the higher prevalence in the first group. In the extremities of lower limbs, it affected more than half of those with pain and a bit more than one third of those without pain, showing no statistically significant difference between groups. Hyperpathia may be triggered partly by loss of inhibition on cord nociceptive neurons, due to loss of large fibres functions. In hyperpathic pain there is partial or complete deafferentation and that is shown by raised thresholds to pain, typical of the symptom. However, the configuration of the spatial, temporal, and the qualitative components of pain in those patients are compatible with central sensitization. Other mechanisms included diminished central inhibition and enhanced facilitation (Helme *et al.*, 2018). This phaenomenon has never been described in NMO patients, but is known to occur in peripheral and central pain.

Allodynia to brush and to pressure are present almost exclusively in patients with neuropathic pain. Each one affected 27.5% of this population an

no patients with non-neuropathic pain. Only one subject without pain reported allodynia to pressure. The term “allodynia” can be defined as a painful response to a non-nociceptive stimulus. Allodynia in the context of neuropathic conditions with sensory loss is described as an important marker of the activity of the nociceptive system. Stimulus- dependent pain can only be seen in areas with preserved ascending sensory pathways. Therefore, those patients with allodynia typically have less sensory deficits than those with only spontaneous pain. Large myelinated A-β fibres with low thresholds are present in allodynia to brush. However, it was demonstrated to occur in post stroke central pain with disturbances of thermal pathways, which may suggest that impaired thermal input is necessary in this pain state. The presence of this phaenomena on the area of pain can help differentiate neuropathic and non-neuropathic pain syndromes. Allodynia to pressure, on the other hand, depends on central changes in addition to peripheral input. It is mediated by A-δ fibres mostly (Jensen and Finnerup, 2014). Like hyperpathia, the present study id the first to describe allodynia in NMO patients. The presence of hyperpathia and/or allodynia may have a role in the correct diagnosis of neuropathic pain syndromes in those subjects.

As opposed to those frequent abnormal sensory phaenomena found in neuropathic pain patients, the musculoskeletal examination focused on myofascial pain syndromes revealed a significantly higher frequency of active trigger points of the muscles quadratus lumborum and gluteus medius in patients with non- neuropathic pain, when compared to the other two groups. Also, pressure pain thresholds measured with the use of an algometer were

significantly lower in the non-neuropathic pain group. Similarly, this specific feature of the bedside examination can help differentiate between neuropathic pain syndromes and non-neuropathic pain syndromes which occur in an area below the sensory level.

Consistent with several previous studies, we found that patients with neuropathic pain had significantly worse performance in the PCS-12 when compared to those without pain, (32.5 ± 8 and 43.3 ± 11, respectively. Lower scores denote worst performance) and were not statistically different from those with non-neuropathic pain, however (37.8 ± 11.3). The PCS-12 correlated with pain intensity scores as measured by the BPI, in the group with neuropathic pain (r= -0.387, p= 0.014) and in the group with non-neuropathic pain (r= -0.734, p= 0.004). Again, it shows the importance of recognizing non-neuropathic pain syndromes in NMO, as it has a strong negative correlation with BPI intensity. Kong *et al*. (2016) also reported that pain correlated strongly with quality of life. Most studies that evaluated quality of life report this same pattern of lower quality of life symptoms among those with higher pain scores. Other studies have shown that quality of life is affected by anxiety, disability, fatigue and depression in NMO patients (He *et al*., 2011; Shi *et al*., 2016).

In the present study we found a significant correlation between BPI intensity and interference scores with HADS scores, demonstrating the deleterious effect of pain on depression and anxiety. We could also demonstrate the association between BPI interference and fatigue in both groups with pain. BPI Intensity scores had a moderate correlation with HADS score in the neuropathic pain group (rs=0.477, p = 0.002) and in the non-neuropathic pain

group (rs=0.599, p=0.031). Similarly, BPI interference scores showed a moderate correlation with HADS scores in the group with neuropathic pain (rs=0.558 p<0.001) and a strong correlation in the non-neuropathic pain group (rs= 0.710 p=0.007). BPI Interference had a moderate correlation with fatigue scores in those with neuropathic pain (rs=0.450, p = 0.004) and a strong correlation in those with non-neuropathic pain (rs= 0.653 p=0.016).

Constant and recurrent pruritus in any specific area of the body was noted in 45.6% of our cohort of patients, with no statistically significant difference between groups (52.6%, 25 % and 44.4% in those with neuropathic pain, non-neuropathic pain and no pain). We specifically inquired patients about areas of consistent pruritus and not just random eventual itchiness related to dry skin, allergies of bug bites. Different studies have reported this symptom in NMO and described frequencies between 26.3 and 64.4% of the cohorts (Elsone *et al*., 2013; Xiao *et al*., 2016; Netravathi *et al*., 2017; He *et al*., 2017). Elsone *et al*. (2013) reported that one fourth of NMO patients had pruritus preceding any other motor or sensory disturbance as an onset symptom. What our study presents as novelty is the description that among those who have pruritus, it is present on the pain area in 80% of those patients with neuropathic pain and only in 33.3% of those with non-neuropathic pain. The symptom is not specific of neuropathic pain but can be used as an important one to screen for neuropathic pain in the forthcoming studies or in the clinical evaluation of pain.

We also evaluated the presence of Uhthoff phaenomenon in our cohort. It was present in 50% of our sample, with no difference between groups. This

prevalence is similar to another study which reported it in 48.1% of the subjects with NMO, compared to 54.1% of those with MS (Park e*t al*., 2014). A lower prevalence of Uhthoff was described in another study in 2015: only 27.1% of the NMO subgroup (Muto *et al*., 2015). Most patients in our cohort were not distressed by his symptom.

Orthostatic hypotension in SCI patients have long been described and is known to be a disabling symptom in this population. It can affect up to 74% of those patients (Phillips and Krassioukov, 2015; Krassioukov *et al*., 2009). It has not been properly described in NMO. However, 36.8% of the present study cohort reported dizziness upon standing. Although orthostatic and lying positions measurements of blood pressure were not carried out during this study, it is a symptom to be explored in the next studies.

Two previous studies have reported bladder and bowel symptoms in NMO patietnts. De Carvalho *et al*. (2016) reported that 80% of patients with NMO had LUTS and voiding dysfunction: detrusor-sphincter dyssynergia in 23.3%, detrusor overactivity in 20% and both in 36.6% of subjects this cohort. It also found a correlation between voiding dysfunction and the degree of neurological impairment measure by the EDSS. Similarly, our study found that the great majority of this cohort reported overactive bladder symptoms: 78.9%, 83.3% and 77.8% of those with neuropathic pain, non-neuropathic pain and no pain. Curiously, only 6 (8.3%) subjects were prescribed Oxybutynin, an anticholinergic medication used to overactive bladder symptoms demonstrating a probable high percentage of undertreatment of a distressing symptom. Moderate or severe obstructive and voiding symptoms were

reported in 67% of our cohort and 15.3% of patients were using intermittent urinary catheterization.

Regarding bowel symptoms, another study in NMO reported that over 23% of patients were constipated and 23% had faecal incontinence (Mutch *et al*., 2015). We found a much higher prevalence of constipation in NMO: 81.6% of those with neuropathic pain, 66.7% of those with non-neuropathic pain and 55.6% of those with no pain. Faecal incontinence affected only 5.3%, 8.3% and 11.1% of those with neuropathic pain, non-neuropathic pain and no pain respectively. There are no other studies about this symptom in the literature of NMO patients, although it is known to be prevalent and severe in traumatic SCI. Feces impaction in the bowel is a frequent cause of autonomic dysreflexia and visceral pain in SCI (Burns *et al*., 2015).

Only one study performed QST in individuals with NMO so far. (Pellkofer *et al*., 2013). It compared the sensory profile of 11 patients with NMO (10 of which reported pain upon evaluation) with heathy controls. Regardless of the pain syndromes, all subjects were tested in both hands and both feet. This study revealed pronounced mechanical and thermal sensory loss when compared to healthy controls. Also, patients with NMO exhibited dynamic mechanical allodynia and paradoxical heat sensation. In this limited study of only 10 individuals, the authors also found a relationship between the presence of abnormal mechanical hypoalgesia or hyperalgesia and plasma levels of the endogenous cannabinoid 2-arachidonoylglycerole (2-AG) and conclude that the degree of mechanical hyperalgesia, reflecting central sensitization of nociceptive pathways, is controlled by the major brain endocannabinoid 2-AG.

The present study is the first to perform QST in a large cohort of patients with NMO. In order to understand the sensitive profile of patients with pain and its differences to those without pain, we evaluated the thermal and mechanical thresholds of the area with the most severe pain and compared with one of normal sensory function, up to 5 dermatomes above the sensory level. Subject without pain were matched to those with pain. In the analysis of the differences in each parameter between the control area and the affected area (therefore, greater differences denote bigger disparities of function between the two areas) we found that subjects with neuropathic pain had a statistically significant difference in the warm detection threshold when compared to those with non-neuropathic pain (-6.8 ± 5.5 and -2.1 ± 3.6, respectively, p= 0.025) and also in the heat pain thresholds, when compared to those with no pain (-4.5 ± 4.6 and --2.2 ± 3.6, respectively, p= 0.021). Furthermore, only patients with neuropathic pain presented with dynamic mechanical allodynia: no other patient in the other two groups presented with this symptom. Although not a prevalent symptom, it seems to be highly associated with neuropathic pain, in relation with central sensitisation.

A Danish study compared traumatic SCI patients with and without pain to evaluate differences in the QST profile between those subjects. In accordance with our findings, the authors described a higher frequency of brush or cold evoked pain, dysaesthesia or pinprick hyperalgesia on the level of lesion of patients with pain when compared to those without pain in dermatomes corresponding to lesion level than SCI patients without pain. Interestingly, the authors did not find differences in at-level hyperpathia between groups. There

was a significant correlation between intensity of brush-evoked dysaesthesia at lesion level and spontaneous pain below lesion level of SCI (Finnerup *et al*., 2003). In a recent prospective study, patients with recent SCI were followed and changes in their sensory tests recorded. Those who developed pain were compared to those who did not have pain. And again, in line with our study, individuals who developed central pain had higher thermal thresholds than those who did not and displayed high rates of abnormal sensations (allodynia and hyperpathia) (Zeilig *et al*., 2012). As it is the case in our study, hyperexcitability of nociceptive neurons and central sensitization in the context of damage to spinothalamic tracts precedes central pain.

When it comes to cortical excitability measurements, both patients with neuropathic and non-neuropathic pain presented with decreased MEP 120 and 140% when compared to subjects without pain, despite similar RMT across all groups This supports that chronic pain leads to significant alterations in neurophysiological parameters of cortical excitability, even when compared with subjects with the same disease. It suggests that those patients have changes in neuronal membrane excitability related to ion channels.

When performing bivariate analysis of MEP 120% and 140% with other measures of disability, spasticity and motor function, we could not find any correlation, demonstrating that lesion of the pyramidal tract is not the cause of this difference in MEP parameters. Similarly, the comparison of CE measurements between those patients using drugs known to alter its values (carbamazepine, lamotrigine, gabapentin, baclofen and diazepam) did not show any differences, ruling out a possible effect of drugs in the differences found.

Furthermore, we found a modest negative correlation between BPI total score vand MEP 140% (rs=- 0.240 p= 0.045) and NPSI scores and MEP 140% (rs=-0.249 p=0.038). That indicates that higher values of pain scores are correlated with lower values of amplitudes of MEP 140%.

Our study is the first to show those differences in NMO patients. Other studies have assessed CE changes in fibromyalgia and chronic facial pain patients and found the same pattern of alterations (Mhalla *et al*., 2010; Galhardoni *et al*., 2018).

Pain is a common symptom in “NMO survivors”: patients who have already overcome the acute phase of the disease and now have to cope with the burden of the structural changes in the CNS. The analysis of clinical data, psychophysics and cortical excitability measurements suggests mechanisms of pain similar to those already reported in non-inflammatory SCI.

Future studies could evaluate patients during the acute phase of the disease and evaluate changes in the somatosensory system and pain profile with its progression towards the chronic phase.

Pain causes a great negative impact in patients with a chronic disabling disease. Multicenter larger studies would be ideal to understand better the mechanisms of pain in this population and the best treatment approach to both neuropathic and non-neuropathic syndromes.

7 CONCLUSIONS

a) Pain is a very prevalent symptom in patients with NMO and as rule, they have more than one pain syndrome, typically one neuropathic and one neuropathic. The most common main pain syndrome is “at-level” neuropathic pain and the second most common pain syndrome is low back pain. Psychophysics measurements suggests thatindividuals with neuropathic pain syndromes had higher thermal thresholds than those who did not and display high rates of abnormal sensations (allodynia and hyperpathia). Cortical excitability measurements suggest that subjects with chronic pain, regardless of its underlying mechanism, have smaller amplitude of MEP 120% and 140% when compared to subjects without pain regardless the current use of different drugs and changes in scores that denote the function of the pyramidal tract.

b) Other symptoms frequently underdiagnosed and undertreated in those patients include overactive bladder, constipation, pruritus (especially over the main pain area), dizziness upon standing and Uhthoff phaenomenon. Overactive bladder is especially prevalent and poorly medicated. Prutitus is very frequent on areas with neuropathic pain. There was a correlation between poorer physical scores in quality of life and higher pain scores and between higher scores of depression, anxiety and fatigue and higher pain scores, demonstating the deleterious effect of pain over quality of life, mood and fatigue in those patients.

c) Changes in pain syndromes are common in NMO patients even in the absence of relapses and this fact should prompt physicians to re-evaluate pain syndromes regularly.

d) The occurrence of pain in NMO patients is not necessarily associated with new inflammatory activity of the disease, but to accumulated lesion load on the somatosensory system.

e) The most important factor to determine chronic pain is age upon onset of disease and its last relapse, and it is probably related to aging-related plasticity changes in the somatosensory system. Psychophysics measurements suggests that hyperexcitability of nociceptive neurons and central sensitization after spinothalamic tracts damage is related to the onset of neuropathic pain in spinal cord injuries. Equally, motoked potentials decreased in pain patients irrespective of disability and use of psychothopic drugs evidence cortical. This supports that chronic pain leads to significant alterations in neurophysiological parameters of cortical excitability, and that those patients have changes.

8 ANNEXES

Annex A - Patient's Evaluation File (in Brazilian Portuguese)

Protocolo: Avaliação de pacientes com Mielite inflamatória

Nome:_____ N ° no Estudo_____

RGHC: _____ Telefones ( )_____

I.DADOS SÓCIODEMOGRAFICOS

SEXO	**IDADE**	**DATA DE NASCIMENTO**
1.fem ( ) 2.masc ( )	_____ anos	/ /

NÍVEL EDUCACIONAL:

1.Analfabeto( ) 2. Ensino fundamental ( ) 3. Ensino médio ( )
4.Superior ( ) 5.pós-graduação ( )

ESTADO CIVIL:

1.solteiro( ) 2.casado( ) 3.união consensual( ) 4.separado( ) 5.divorciado( ) 6.viúvo( )

SITUAÇÃO CONJUGAL: 1.Com companheiro( ) 2.sem companheiro( )

RELIGIÃO:	**PRATICANTE:**
1.ateu( ) 2.evangélico( ) 3.católico( ) 4.espírita ( ) 6. Judeu ( ) 5.Outro_____	0. não( ) 1. sim ( )

HABITOS E VICIOS

TABACO ( ) SIM ( ) NÃO Carga:_____m/a ( ) Prévio ( ) Atual

ÁLCOOL ( ) SIM ( ) NÃO ( ) Prévio ( ) Atual

OUTROS: ( ) crack ( ) cocaína ( ) outro

SITUAÇÃO DE TRABALHO:

1.empregado( ) 2.desempregado( ) 3.aposentado( ) 4.dona de casa( )
5.autônomo( ) 6.estudante( ) 7.Licença saúde( ) 8.informal( )

Você está trabalhando atualmente? 0.não ( ) 1.sim ( )

1.Diagnóstico: MTLE ( )_____ NMO ( ) Outros ( )_____

2.Primeiro surto: _____ meses Data _____ 1º sintoma: _____

3. Ultimo Surto: _____M Data: _____ Total Surtos: _____

4. Acometimento

a. Neurite Optica ( ) NAO ( ) uni ( ) bilateral

b. Lesão Medular ( )

DATA	NIVEL	EXTENSAO (CV)	Realce Gd	Atrofia	Lesão medula central	Lesão medula perif (A/P)	Tumefativa	Holo

c.Lesao encefálica ( ) ( ) não tem RM encéfalo

DATA	Bulbo	Ponte	Mesencefalo	NO	Periaq 3/4 VV	Area postrema	Microangiopatia

5. Anticorpo Anti aquaporina 4 : ( ) Positivo ( ) Negativo

Outro Anticorpo: _____

6. Tratamentos realizados:

a. Pulsoterapia_____ b. Plasmaferese: _____

c. Imunoglobulina: _____

Imunossupressao atual

Medicamento	Dose	Posologia

Outros Medicamentos em uso:

Medicamento	Dose	Posologia

Doenças previas:

	NAO	SIM
Diabetes Melitus		
Doença Cerebrovascular		
Hipertensão arterial		
Doença vascular periférica		
Doença renal crônica		
Neoplasia maligna		
Doença cardiocirculatíria		
Doença Hepática		
Depressão		
Doença Trato Gastrointestinal		
Doença Autoimune		
Outras: _____		

III. EXAME FISÍCO

Exame neurológico

1) Força Motora G 0-1-2-3-4-5

	DIREITO		ESQUERDO	
	Distal	Proximal	Distal	Proximal
MMSS				
MMII				

2) Reflexos osteotendíneos: ausente 0, diminuido1, normal 2, vivo 3, Exaltado 4

	DIREITO	ESQUERDO
BICIPITAL		
ESTILORRADIAL		
PATELAR		
AQUILEU		

2) Sensibilidade Superficial: ausente 0, diminuido1, normal 2 aumentado 3

TATIL

	DIREITO		ESQUERDO	
MMSS	Segundo Dedo			
	Punho			
	Braço			
MMII	Primeiro Dedo			
	Tornozelo			
	Perna			

NIVEL SENSITIVO: _____ HIPERPATIA NO NIVEL: SIM ( ) NAO ( )

Observações: _____

DOR A AGULHA:

	DIREITO		ESQUERDO	
MMSS	Segundo Dedo			
	Punho			
	Braço			
MMII	Primeiro Dedo			
	Tornozelo			
	Perna			

Observações: _____

TERMICA AO FRIO:

	DIREITO		ESQUERDO	
MMSS	Segundo Dedo			
	Punho			
	Braço			
MMII	Primeiro Dedo			
	Tornozelo			
	Perna			

Observações: _____

	DIREITO	ESQUERDO
DISESTESIA		
ALODINEA DINAMICA		
ALODINEA ESTATICA		
ALODINEA TERM FRIO		
HIPERPATIA		

3) Sensibilidade Profunda: normal 0, alterado 1
a) posição dedo média de 10x D: mão( ) pé ( )
E: mão( ) pé ( )

b) vibração 128Hz diapasão D: (Riddel Seifer)

		DIREITO	ESQUERDO
MMSS	FALANGE DISTAL 3o QD		
	PUNHO (ESTILOIDE)		
	COTOVELO		
MMII	MALEOLO MEDIAL		
	TIBIA		
	CRISTA		

4) Ataxia Nobile-Orazio: ( )
normal com olho fechado 0
discreta alteração 1
grave alteração2
não pode ficar de olho fechado 3

5) Disautonomia: normal 0, alterado 1

DIREITO	SEGUNDO DEDO	PUNHO	BRAÇO	PERNA	PÉ
TROFISMO					
VASOMOTOR					
SUDOMOTOR					
ESQUERDA					
TROFISMO					
VASOMOTOR					
SUDOMOTOR					

6) Acuidade visual (Rosenbaum):

OD: FO:

OE: FO:

7) Espasmos dolorosos: ( ) Sim ( )Nao

8) Sinal de Lhermitte : ( ) Sim ( ) Nao

Quadro 1 - Escala de Ashworth modificada

Grau	Observação clínica
0	Tônus normal.
1	Aumento do tônus no início ou no final do arco de movimento.
1+	Aumento do tônus em menos da metade do arco de movimento, manifestado por tensão abrupta e seguido por resistência mínima.
2	Aumento do tônus em mais da metade do arco de movimento.
3	Partes em flexão ou extensão e movidos com dificuldade.
4	Partes rígidas em flexão ou extensão.

Fonte: Dados da pesquisa.

FONTE: MODIFIED Ashworth scale (Katz et al. 1992)

	MSD	MSE	MID	MIE
Ashworth				

V DIAGNOSTICO DA DOR

1-DOR PRIMARIA: _____

DO nível 1 ( ) ABAIXO do Nível 2 ( ) ACIMA do Nível 3 ( )

2- DOR SECUNDARIA: _____

DO nível 1 ( ) ABAIXO do Nível 2 ( ) ACIMA do Nível 3 ( )

Annex B - CAPPesq Approval

Hospital das Clínicas da FMUSP
Comissão de Ética para Análise de Projetos de Pesquisa - CAPPesq

PROJETO DE PESQUISA

Título: ESTIMULAÇÃO MAGNÉTICA TRANSCRANIANA PARA DOR CENTRAL
Pesquisador Responsável: Dr. Daniel Ciampi de Andrade / Prof. Manoel J.Teixeira / Dr. Marco A. Marcolin **Versão:** 3
Pesquisador Executante: Ricardo Galhardoni **CAAE:** 05832812.6.0000.0068
Co-autores: Prof. Dr. Manoel Jacobsen Teixeira; Diego Toledo Reis Mendes Fernandes
Instituição: HCFMUSP
Departamento: NEUROLOGIA

NOTIFICAÇÃO

Tipo de Notificação: Outros
Detalhe: Inclusão de pesquisadora executante.
Justificativa: Inclusão do nome da Medica neurologista Fernanda Valério da Silva, Lattes numero.6381549417618636 ao projeto de
Data do envio: 19/05/2014

PARECER CONSUBSTANCIADO DO CEP

Registro on-line: 8685
Número do Parecer: 658.495
Data da Relatoria: 21/05/2014
Apresentação da Notificação: Em carta datada de 19 de maio de 2014, os autores solicitam a inclusão da doutoranda Fernanda Valério da Silva que fará a caracterização dos participantes da pesquisa com lesão medular, em seu projeto de doutorado. Informam ainda que até o momento já foram incluídos 39 pacientes.
Objetivo da Notificação: Idem ao parecer anterior.
Avaliação dos Riscos e Benefícios: Idem ao parecer anterior.
Comentários e Considerações sobre a Notificação: Inclusão de novo pesquisador executante, para realizar a caracterização dos participantes da pesquisa com lesão medular, em seu projeto de doutorado.
Considerações sobre os Termos de apresentação obrigatória: Idem ao parecer anterior
Conclusões ou Pendências e Lista de Inadequações: Aprovada a inclusão de novo pesquisador executante.
Situação do Parecer: Aprovado
Necessita Apreciação da CONEP: Não

São Paulo, 23 de Maio de 2014

Prof. Dr. Alfredo José Mansur
Coordenador
Comissão de Ética para Análise de Projetos de Pesquisa - CAPPesq

Rua Dr. Ovídio Pires de Campos, 225 - Prédio da Administração - 5º andar
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Annex C - Consent form (Termo de consentimento livre e esclarecido- TCLE)

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO- HCFMUSP

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

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DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU RESPONSÁVEL LEGAL

1. NOME: .:.....
.....

DOCUMENTO DE IDENTIDADE Nº : ..... SEXO : .M ☐ F ☐

DATA NASCIMENTO: ...../...../.....
ENDEREÇO ..... Nº ..... APTO: .....
BAIRRO: ..... CIDADE .....
CEP:..... TELEFONE: DDD (.....) .....

2.RESPONSÁVEL LEGAL .....
.....
NATUREZA (grau de parentesco, tutor, curador etc.) .....

DOCUMENTO DE IDENTIDADE :.....SEXO: M ☐ F ☐

DATA NASCIMENTO.: ...../...../.....
ENDEREÇO: ..... Nº ..... APTO: .....
BAIRRO: ..... CIDADE: .....
CEP: ..... TELEFONE: DDD (.....).....
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APPENDICES

Appendix A - Barthel Index of Activities of Daily Living (Brazilian Portuguese version)

ATIVIDADE	PONTUAÇÃO
ALIMENTAÇÃO 0 = incapacitado 5 = precisa de ajuda para cortar, passar manteiga, etc, ou dieta modificada 10 = independente	
BANHO 0 = dependente 5 = independente (ou no chuveiro)	
ATIVIDADES ROTINEIRAS 0 = precisa de ajuda com a higiene pessoal 5 = independente rosto/cabelo/dentes/barbear	
VESTIR-SE 0 = dependente 5 = precisa de ajuda, mas consegue fazer uma parte sozinho 10 = independente (incluindo botões, zipers, laços, etc	
INTESTINO 0 = incontinente (necessidade de enemas) 5 = acidente ocasional 10 = continente	
SISTEMA URINÁRIO 0 = incontinente, ou caracterizado e incapaz de manejo 5 = acidente ocasional 10 = continente	
USO DO TOILET 0 = dependente 5 = precisa de alguma ajuda parcial 10 = independente (pentear-se, limpar se)	
TRANSFERÊNCIA (DA CAMA P/ CADEIRA E VICE VERSA) 0 = incapacitado, sem equilíbrio para ficar sentado 5 = muita ajuda (uma ou duas pessoas, física), pode sentar 10 = pouca ajuda (verbal ou física) 15 = independente	
MOBILIDADE (EM SUPERFÍCIES PLANAS) 0 = imóvel ou < 50 metros 5 = cadeira de rodas independente, incluindo esquinas, > 50 metros 10 = caminha com ajuda de uma pessoa (verbal ou física) > 50 metros 15 = independente (mas pode precisar de alguma ajuda; ex.: bengala) > 50 metros	
ESCADAS 0 = incapacitado 5 = precisa de ajuda (verbal, física ou ser carregado) 10 = independente	
TOTAL:	

PONTUAÇÃO
TOTAL (0-100):
Orientações:

1. A pontuação na Escala de Barthel refere se ao que os sujeitos fazem e não ao que eles recordam ter feito um dia.
2. Seu principal objetivo é saber sobre o grau de independência em relação a qualquer tipo de ajuda (física ou verbal).
3. Se o sujeito não consegue ler o questionário, alguém pode ler o mesmo para ele. É permitido que algum amigo ou parente responda pelo sujeito (caso este esteja impossibilitado de responder).
4. Preferencialmente procure obter respostas relativas às últimas 48 horas, dependendo do caso, pode ser por períodos maiores.

Appendix B - DN-4 Questionnaire (Brazilian Portuguese version)

Por favor, nas quatro perguntas abaixo, complete o questionário marcando uma resposta para cada número:

ENTREVISTA DO PACIENTE

Questão 1: A sua dor tem uma ou mais das seguintes características?

	sim	não
1- Queimação		
2- Sensação de frio dolorosa		
3- Choque elétrico		

Questão 2: Há presença de um ou mais dos seguintes sintomas na mesma área da sua dor?

	sim	não
4- Formigamento		
5- Alfinetada e agulhada		
6- Adormecimento		
7- Coceira		

EXAME DO PACIENTE

Questão 3: A dor está localizada numa área onde o exame físico pode revelar uma ou mais das seguintes características?

	sim	não
8- Hipoestesia ao toque		
9- Hipoestesia a picada de agulha		

Questão 4: Na área dolorosa a dor pode ser causada ou aumentada por:

	sim	não
10- Escovação		

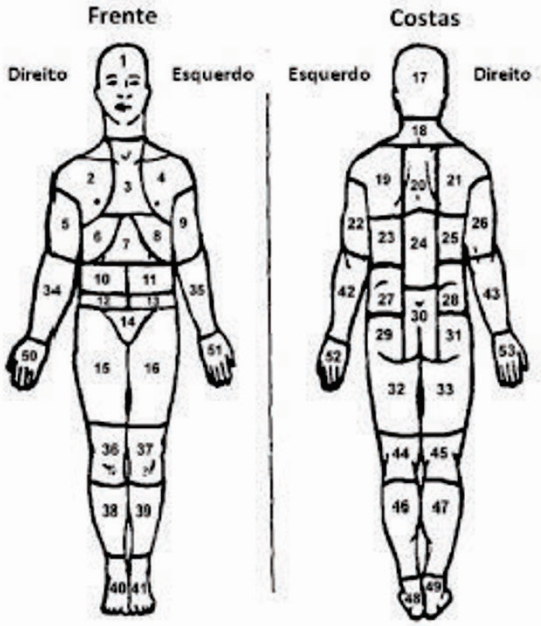
Retirado de SANTOS JG; BRITO JO; DE ANDRADE DC; KAZYIAMA VM; FERREIRA KA; SOUZA I; TEIXEIRA MJ; BOUHASSIRA D; BAPTISTA AF. **Translation to Portuguese and Validation of the Douleur Neuropathique 4 Questionnaire**. *The Journal of Pain*, 2009.

Appendix C - BPI- Brief Pain Inventory- (Brazilian Portuguese version)

1) Durante a vida, a maioria das pessoas apresenta dor de vez em quando (dor de cabeça, dor de dente, etc.). Você teve, hoje, dor diferente dessas?

1. Sim ☒ 2. Não ☒

2) Marque sobre o diagrama, com um X, as áreas onde você sente dor, e onde a dor é mais intensa.



3) Circule o número que melhor descreve a pior dor que você sentiu nas últimas 24 horas.

0 1 2 3 4 5 6 7 8 9 10

sem dor pior dor possível

4) Circule o número que melhor descreve a dor mais fraca que você sentiu nas últimas 24 horas.

0 1 2 3 4 5 6 7 8 9 10

sem dor pior dor possível

5) Circule o número que melhor descreve a média da sua dor.

0 1 2 3 4 5 6 7 8 9 10

sem dor pior dor possível

6) Circule o número que mostra quanta dor você está sentindo agora (neste momento).

0 1 2 3 4 5 6 7 8 9 10

sem dor — pior dor possível

7) Quais os tratamentos ou medicações você está recebendo para dor?

Nome	Dose/Frequência	Data de Início

8) Nas últimas 24 horas, qual a intensidade da melhora proporcionada pelos tratamentos ou medicações que você está usando?

Circule o percentual que melhor representa o alívio que você obteve.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

sem alívio ← → alívio completo

9) Circule o número que melhor descreve como, nas últimas 24 horas, a dor interferiu na sua:

Atividade geral

0 1 2 3 4 5 6 7 8 9 10

não interferiu ← → interferiu completamente

Humor

0 1 2 3 4 5 6 7 8 9 10

não interferiu ← → interferiu completamente

Habilidade de caminhar

0 1 2 3 4 5 6 7 8 9 10

não interferiu ← → interferiu completamente

Trabalho

0 1 2 3 4 5 6 7 8 9 10

não interferiu ← → interferiu completamente

Relacionamento com outras pessoas

0 1 2 3 4 5 6 7 8 9 10

não interferiu ← → interferiu completamente

Sono

0 1 2 3 4 5 6 7 8 9 10

não interferiu ← → interferiu completamente

Habilidade para apreciar a vida

0 1 2 3 4 5 6 7 8 9 10

não interferiu ← → interferiu completamente

Adaptado de: FERREIRA, KA; TEIXEIRA MJ; MENDONZA, TR; CLEELAND, CS. **Validation of Brief Pain Inventory to Brazilian patients with pain.** Support Care Cancer. 2010 Mar 10.

Appendix D- NPSI - Neuropathic Pain Symptom Inventory (Brazilian Portuguese version)

Você tem sofrido de dor devido a lesões ou doença do sistema nervoso. Esta dor pode ser de diversos tipos. Você pode ter dor espontânea, ex: dor na ausência de qualquer estímulo, que pode ser duradoura ou ocorrer em ataques breves. Você pode também ter dor provocada ou aumentada por um leve toque, pressão ou contato com o frio na área dolorosa. Você pode sentir um ou mais tipos de dor. Este questionário foi desenvolvido para ajudar o seu médico a melhor avaliar e tratar diferentes tipos de dor que possa sentir.

Nós queremos saber se você sente dor espontânea, isto é, dor sem qualquer estímulo. Para cada uma das seguintes questões, por favor, selecione o número que melhor descreve a sua **gravidade médida da dor espontânea durante as últimas 24 horas.** Selecione o número 0 se você não sentiu tal dor (circule um número apenas).

Q1. A sua dor dá a sensação de queimadura?											
Não queima	0	1	2	3	4	5	6	7	8	9	10	A pior queimadura imaginável
Q2. A sua dor dá a sensação de apertar?												
Não aperta	0	1	2	3	4	5	6	7	8	9	10	Aperta o pior imaginável
Q3. A sua dor dá a sensação de pressão?												
Sem pressão	0	1	2	3	4	5	6	7	8	9	10	A pior pressão imaginável

Q4. **Durante as últimas 24 horas**, a sua dor espontânea tem estado presente:
Seleciona a resposta que melhor descreve o seu caso.

Permanentemente		
Entre 8 e 12 horas		
Entre 4 e 7 horas		
Entre 1 e 3 horas		
Menos que 1 hora		

Nós queremos saber se você teve ataques breves de dor. Para cada uma das seguintes questões, por favor, selecione o número que melhor descreve a sua **gravidade medida da dor espontânea durante as últimas 24 horas.** Selecione o número 0 se você não sentiu tal dor (circule um número apenas).

Q5. A sua dor dá a sensação de choque elétrico?											
Sem choque elétrico	0	1	2	3	4	5	6	7	8	9	10	O pior choque elétrico imaginável
Q6. A sua dor dá a sensação de apunhalar?												
Sem punhalada	0	1	2	3	4	5	6	7	8	9	10	A pior punhalada imaginável

Q7. **Durante as últimas 24 horas**, quantos destes ataques de dor teve?
Seleciona a resposta que melhor descreve o seu caso.

Mais de 20		
Entre 11 e 20		
Entre 6 e 10		
Entre 1 e 5		
Sem ataques de dor		

Nós queremos saber se você sente dor provocada ou aumentada por leve toque, pressão, contato com o frio na área onde dói. Para cada uma das seguintes questões, por favor, selecione o número que melhor descreve a sua **gravidade medida da dor espontânea durante as últimas 24 horas.** Selecione o número 0 se você não sentiu tal dor (circule um número apenas).

Q8. A sua dor é provocada ou aumentada por um leve toque na área dolorosa?												
Sem dor	0	1	2	3	4	5	6	7	8	9	10	A pior dor imaginável
Q9. A sua dor é provocada ou aumentada por pressão na área dolorosa?												
Sem dor	0	1	2	3	4	5	6	7	8	9	10	A pior dor imaginável
Q10. A sua dor é provocada ou aumentada por contato com algo frio na área dolorosa?												
Sem dor	0	1	2	3	4	5	6	7	8	9	10	A pior dor imaginável

Nós queremos saber se você sente sensações anormais **na zona onde dói**. Para cada uma das seguintes questões, por favor, selecione o número que melhor descreve a sua **gravidade médida da dor espontânea durante as últimas 24 horas.** Selecione o número 0 se você não sentiu tal dor (circule um número apenas).

Q11. Sente alfinetes e agulhas?												
Sem alfinetes nem agulhas	0	1	2	3	4	5	6	7	8	9	10	Os piores alfinetes e agulhas imagináveis
Q12. Sente dormente?												
Sem dormência	0	1	2	3	4	5	6	7	8	9	10	O mais dormente imaginável

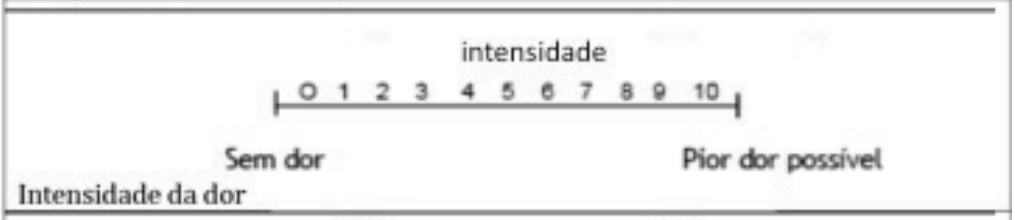
Baseado em ANDRADE DC; NISHIMURA CM; FERREIRA KSL; GALHARDONI R; ZAKKA, TM; TEIXEIRA, MJ. **Validação psicométrica do inventário de sintomas de dor neuropática para o português**. 2010. (Apresentação de trabalho/Comunicação)

Appendix E - Short Form McGill Questionnaire (Brazilian Portuguese version)

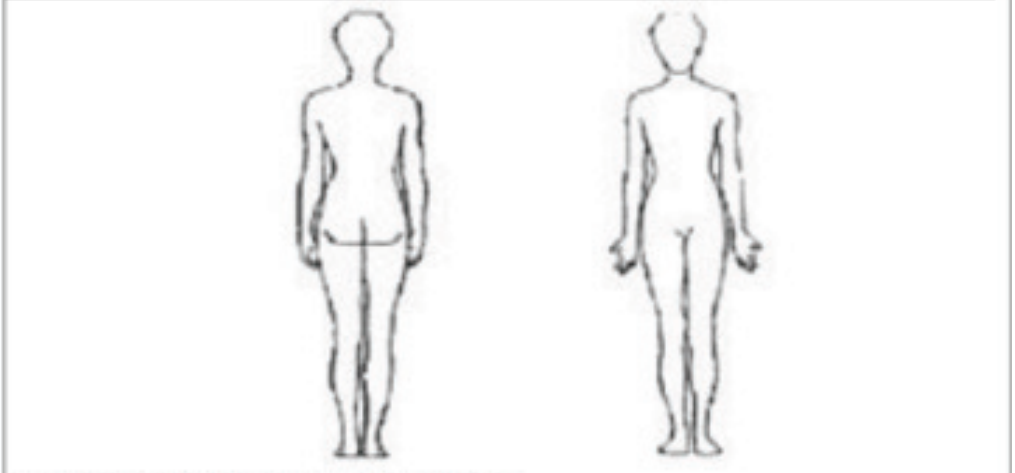
McGill forma breve

Marcar com "X" a presença ou ausência de cada característica da dor

Dimensão Sensitiva	Presente	Ausente
Latejante		
Pontada		
Choque		
Fina/agulhada		
Fisgada		
Queimação		
Espalha		
Dolorida		
Dimensão Afetiva		
Cansativa		
Enjoada		
Sufocante		
Apavorante		
Aborrecida		
Dimensão Avaliativa		
Que incomoda		
Insuportável		



Intensidade da dor



Localização da dor (marcar a localização)

Appendix F - HADS - Hospitalar Anxiety and Depression Scale (Brazilian Portuguese version)

Assinale com "X" a alternativa que melhor descreve a sua resposta a cada questão.

1. Eu me sinto tenso(a) ou contraído(a):			
( ) a maior parte do tempo [3]	( ) boa parte do tempo [2]	( ) de vez em quando [1]	( ) nunca [0]
2. Eu ainda sinto que gosto das mesmas coisas de antes:			
( ) sim, do mesmo jeito que antes [0]	( ) não tanto quanto antes [1]	( ) só um pouco [2]	( ) já não consigo ter prazer em nada [3]
3. Eu sinto uma espécie de medo, como se alguma coisa ruim fosse acontecer:			
( ) sim, de jeito muito forte [3]	( ) sim, mas não tão forte [2]	( ) um pouco, mas isso não me preocupa [1]	( ) não sinto nada disso [0]
4. Dou risada e me divirto quando vejo coisas engraçadas:			
( ) do mesmo jeito que antes [0]	( ) atualmente um pouco menos [1]	( ) atualmente bem menos [2]	( ) não consigo mais [3]
5. Estou com a cabeça cheia de preocupações:			
( ) a maior parte do tempo [3]	( ) boa parte do tempo [2]	( ) de vez em quando [1]	( ) raramente [0]
6. Eu me sinto alegre:			
( ) nunca [3]	( ) poucas vezes [2]	( ) muitas vezes [1]	( ) a maior parte do tempo [0]
7. Consigo ficar sentado à vontade e me sentir relaxado:			
( ) sim, quase sempre [0]	( ) muitas vezes [1]	( ) poucas vezes [2]	( ) nunca [3]
8. Eu estou lento(a) para pensar e fazer coisas:			
( ) quase sempre [3]	( ) muitas vezes [2]	( ) poucas vezes [1]	( ) nunca [0]
9. Tenho uma sensação ruim de medo como um frio na barriga ou um aperto no estômago:			
( ) nunca [0]	( ) de vez em quando [1]	( ) muitas vezes [2]	( ) quase sempre [3]
10. Eu perdi o interesse em cuidar de minha aparência:			
( ) completamente [3]	( ) não estou mais me cuidado como eu deveria [2]	( ) talvez não tanto quanto antes [1]	( ) me cuido do mesmo jeito que antes [0]
11. Eu me sinto inquieto(a), como se eu não pudesse ficar parado(a) em lugar nenhum:			
( ) sim, demais [3]	( ) bastante [2]	( ) um pouco [1]	( ) não me sinto assim [0]

12. Fico animado(a) esperando as coisas boas que estão por vir:			
( ) do mesmo jeito que antes [0]	( ) um pouco menos que antes [1]	( ) bem menos do que antes [2]	( ) quase nunca [3]
13. De repente, tenho a sensação de entrar em pânico:			
( ) a quase todo momento [3]	( ) várias vezes [2]	( ) de vez em quando [1]	( ) não senti isso [0]
14. Consigo sentir prazer quando assisto a um bom programa de televisão, de rádio ou quando leio alguma coisa:			
( ) quase sempre [0]	( ) várias vezes [1]	( ) poucas vezes [2]	( ) quase nunca [3]

Versão baseada em CASTRO MM; QUARANTINI L; BATISTA-NEVES S; KRAYCHETE DC; DALTRO C; MIRANDA-SCIPPA A. **Validade da Escala Hospitalar de Depressão e Ansiedade em Pacientes com Dor Crônica.** *Rev. Bras. Anestesiol.*, 56:5, 470-477, 2006.

Appendix G - SF-12- HEALTH SURVEY SCORE (Brazilian Portuguese version)

1. **Em geral, o (a) Sr (a) diria que sua saúde é:**

☐ Excelente ☐ Muito Boa ☐ Boa ☐Regular ☐Ruim

2. **O Sr. acha que sua saúde, agora, o dificulta de fazer algumas coisas do dia a dia, como por exemplo: atividades médias (como mover uma cadeira, fazer compras, limpar a casa, trocar de roupa)?**

☐Sim, dificulta muito ☐ Sim, dificulta um pouco ☐Não, não dificulta de modo algum

3. **O Sr. acha que sua saúde, agora, o dificulta de fazer algumas coisas do dia a dia, como por exemplo: subir três ou mais degraus de escada?**

☐Sim, dificulta muito ☐ Sim, dificulta um pouco ☐ Não, não dificulta de modo algum

4. **Durante as últimas 4 semanas, o(a) Sr.(a) teve algum dos seguintes problemas com seu trabalho ou em suas atividades do dia a dia: fez menos do que gostaria, por causa de sua saúde física ?**

☐Sim ☐Não

5. **Durante as últimas 4 semanas, o(a) Sr.(a) teve algum dos seguintes problemas com seu trabalho ou em suas atividades do dia a dia: sentiu-se com dificuldade no trabalho ou em outras atividades, por causa de sua saúde física?**

☐Sim ☐Não

6. **Durante as últimas 4 semanas, o(a) S.r(a) teve algum dos seguintes problemas: fez menos do que gostaria, por causa de problemas emocionais?**

☐Sim ☐Não

7. **Durante as últimas 4 semanas, o(a) Sr.(a) teve algum dos seguintes problemas: deixou de fazer seu trabalho ou outras atividades cuidadosamente, como de costume, por causa de problemas emocionais?**

☐Sim ☐Não

8. **Durante as últimas 4 semanas, alguma dor atrapalhou seu trabalho normal (tanto o trabalho de casa como o de fora de casa)?**

☐Não, nem um pouco ☐Um pouco ☐Moderadamente ☐ Bastante ☐Extremamente

9. **Quanto tempo durante as últimas 4 semanas: o(a) Sr(a) tem se sentido calmo e tranqüilo?**

☐ Todo o tempo ☐A maior parte do tempo ☐Boa parte do tempo ☐Alguma parte do tempo ☐ Uma pequena parte do tempo ☐ Nunca

10. **Quanto tempo durante as últimas 4 semanas: o(a) Sr(a) teve bastante energia?**

☐ Todo o tempo ☐A maior parte do tempo ☐Boa parte do tempo ☐Alguma parte do tempo ☐ Uma pequena parte do tempo ☐ Nunca

11. **Quanto tempo durante as últimas 4 semanas: o(a) sr(a) sentiu-se desanimado e deprimido ?**

☐ Todo o tempo ☐A maior parte do tempo ☐Boa parte do tempo ☐Alguma parte do tempo ☐ Uma pequena parte do tempo ☐Nunca

12. **Durante as últimas 4 semanas, em quanto do seu tempo a sua saúde ou problemas emocionais atrapalharam suas atividades sociais, tais como: visitar amigos, parentes, sair, etc. ?**

☐ Todo o tempo ☐A maior parte do tempo ☐Alguma parte do tempo ☐ Uma pequena parte do tempo ☐Nunca

Ware JE, Sherbourne DC. The MOS 35 item short form survey (SF-36) Conceptual Framework and item selection. Med Care 1992;30:473-83

Appendix H - Fatigue Severity Scale (Brazilian Portuguese version)

Farei agora nove afirmações. Você deverá dar uma nota de 1 a 7, onde 1 significa que você discorda completamente e 7 indica que você concorda plenamente com a afirmação. Lembre-se de que estas afirmações referem-se às suas duas últimas semanas."

1. Minha motivação é menor quando eu estou fatigado	1	2	3	4	5	6	7
2. Exercícios me deixam fatigado	1	2	3	4	5	6	7
3. Eu estou facilmente fatigado	1	2	3	4	5	6	7
4. A fadiga interfere com meu desempenho	1	2	3	4	5	6	7
5. A fadiga causa problemas freqüentes para mim.	1	2	3	4	5	6	7
6. Minha fadiga impede um desempenho físico constante	1	2	3	4	5	6	7
7. A fadiga interfere com a execução de certas obrigações e responsabilidades	1	2	3	4	5	6	7
8. A fadiga é um dos três sintomas mais incapacitantes que tenho.	1	2	3	4	5	6	7
9. A fadiga interfere no meu trabalho, na minha família ou na minha vida social.	1	2	3	4	5	6	7

Mendes MF et al. 1998

Appendix I - Pain Catastrophizing thoughts SCALE (PCTS) (Brazilian Portuguese version)

Na maior parte do tempo, nos dizemos coisas. Por exemplo: nos encorajamos a fazer coisas, nos culpamos quando cometemos um erro ou nos recompensamos por algo que fizemos com sucesso. Quando estamos com dor, frequentemente também nos dizemos coisas que são diferentes das coisas que nós dizemos quando estamos nos sentindo bem. Abaixo existe uma lista de pensamentos típicos de pessoas que estão com dor. Por favor, leia cada uma dessas frases e marque com que frequência você tem esses pensamentos quando sua dor está forte. Por favor, circule o número que melhor descreve a sua situação utilizado esta escala: 0 = quase nunca até 5 = quase sempre.

	quase nunca					quase sempre
1. Não posso mais suportar esta dor.	0	1	2	3	4	5
2. Não importa o que fizer minhas dores não mudarão.	0	1	2	3	4	5
3. Preciso tomar remédios para dor.	0	1	2	3	4	5
4. Isso nunca vai acabar.	0	1	2	3	4	5
5. Sou um caso sem esperança.	0	1	2	3	4	5
6. Quando ficarei pior novamente?	0	1	2	3	4	5
7. Essa dor está me matando.	0	1	2	3	4	5
8. Eu não consigo mais continuar.	0	1	2	3	4	5
9. Essa dor está me deixando maluco	0	1	2	3	4	5

Adaptado de SARDÁ J; NICHOLAS MK; PEREIRA IA; PIMENTA, CAM; ASHGARI A; CRUZ RM. ***Validação da Escala de Pensamentos Catastróficos sobre Dor.*** *Acta Fisiatr., 15 (1), 31-36, 2008.*

Appendix J - EDSS - Expanded DISABILITY status Scale (Brazilian Portuguese version)

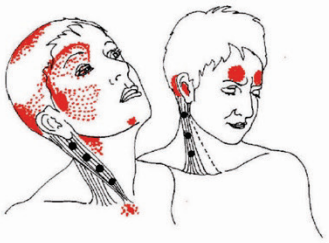
Escore	Característica	Score Total
0	Exame neurológico normal (todos os SF grau 0; cerebral grau 1 aceitável)	
1.0	Sem incapacidade (1 SF grau 1)	
1.5	Sem incapacidade (2 SF grau 1)	
2.0	Incapacidade mínima em 1 SF (1 SF grau 2, outros grau 0 ou 1)	
2.5	Incapacidade minima em 2 SF (2 SF grau 2, outros grau 0 ou 1)	
3.0	Incapacidade moderada em 1 SF (1 SF grau 3, outros grau 0 ou 1) ou incapacidade discreta em 3 ou 4 SF (3/4 SF grau 2, outros grau 0 ou 1). Deambulando plenamente.	
3.5	Deambulação plena, com incapacidade moderada em 1SF (1 SF grau 3) e 1 ou 2 SF grau 2; ou 2SF grau 3; ou 5 SF grau 2 (outros 0 ou 1)	
4.0	Deambulação plena, até 500 m sem ajuda ou descanso (1 SF grau 4, outros 0 ou 1)	
4.5	Deambulação plena, até 300 m sem ajuda ou descanso. Com alguma limitação da atividade ou requer assistência mínima (1 SF grau 4, outros 0 ou 1)	
5.0	Deambulação até 200 m sem ajuda ou descanso. Limitação nas atividades diárias (equivalentes são 1 SF grau 5, outros 0 ou 1; ou combinação de graus menores excedendo o escore 4.0)	
5.5	Deambulação até 100 m sem ajuda ou descanso. Incapacidade impedindo atividades plenas diárias (equivalentes são 1SF grau 5, outros 0 ou 1; ou combinações de graus menores excedendo o escore 4.0)	
6.0	Assistência intermitente ou com auxilio unilateral constante de bengala, muleta ou suporte (equivalentes são mais que 2 SF graus 3+)	
6.5	Assistência bilateral (equivalentes são mais que 2 SF graus 3+)	
7.0	Não anda 5 m mesmo com ajuda. Restrito a cadeira de rodas. Transfere da cadeira para cama (equivalentes são combinações com mais que 1 SF 4+, ou piramidal grau 5 isoladamente)	
7.5	Consegue apenas dar poucos passos. Restrito á cadeira de rodas. Necessita ajuda para transferir-se (equivalentes são combinações com mais que 1 SF grau 4+)	
8.0	Restrito ao leito, mas pode ficar fora da cama. Retém funções de autocuidado; bom uso dos braços (equivalentes são combinações de vários SF grau 4+)	
8.5	Restrito ao leito constantemente. Retém algumas funções de autocuidade e dos braços (equivalentes são combinações de vários SF grau 4+)	
9.0	Paciente incapacitado no leito. Pode comunicar, não come, não deglute (equivalentes é a maioria de SF grau 4+)	
9.5	Paciente totalmente incapacitado no leito. Não comunica, não come, não deglute (equivalentes são quase todos de SF grau 4+)	
10.0	Morte por esclerose múltipla	

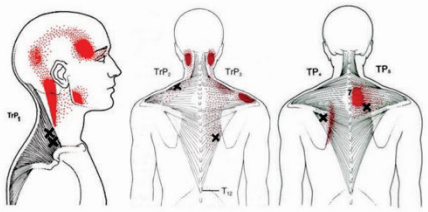
1. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: na expanded disability status scale (EDSS). Neurology 1983;33:1444-1452.

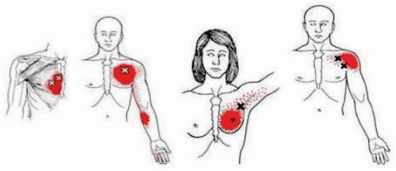
2. Goodkin DE, Cookfair D, Wende K, et al., and Multiple Sclerosis Collaborative Research Group. Inter- and Intrarater scoring agreement using grades 1.0 to 3.5 of the Kurtzke Expanded Disability Status Scale (EDSS). Neurology 1992;42:859-863.

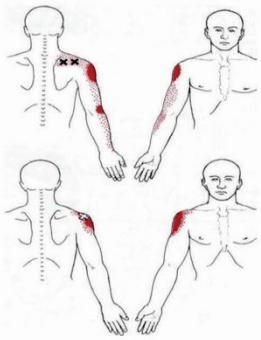
Appendix K - Muscle Trigger Points Evaluation: PPT (in Brazilian Portuguese)

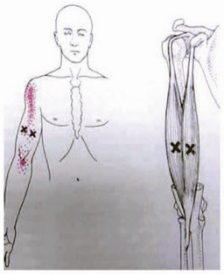
Ponto Zero: medir dolorimetria na glabela _____

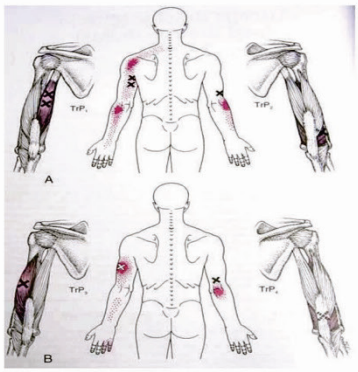
ECM **(n. acessorio** **XI par)** **PONTO MEDIO**	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Ao longo do ventre do músculo (do processo mastóide até esterno e clavícula)			Dor frontal, mastóidea (divisão clavicular) e Dor em forma de arco na bochecha, maxilar, crista supra- orbital , e pode descer até porção superior do esterno (divisão esternal)

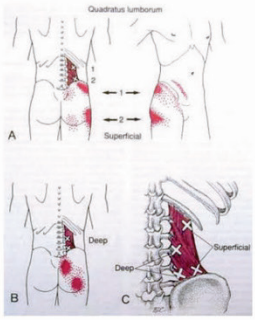
Trapézio **(n. acessorio –** **XI par** – Anterior para posterior	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
PG1:Porção média da borda anterior do trapézio superior PG2: caudal e levemente lateral ao PG1			PG1: Dor região postero-lateral do pescoço associado à dor em Hemi-crânio temporal ipsilateral até órbita ipsilateral PG2: occiptal e cervical posterior ipsilateral

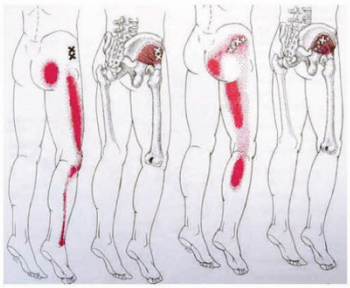
Peitoral maior **(peitoral – C5 a C7)**	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Palpação em pinça na região axilar. Palpação plana na região esternal e clavicular com o braço em abdução.			PG1 clavicular: dor sobre o músculo deltóide anterior e localmente para a seção clavicular do proprio peitoral maior. PG2 esternal: dor no torax e face interna do braço, antebraço e porção ulnar da mão.

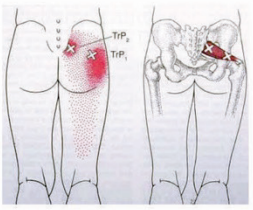
Supra-espinhal (supra-escapular – C5-C6)	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Ao longo da borda superior da espinha da escápula, principalmente ângulo da espinha			Dor profunda em aspecto posterior e profundo do deltóide, face radial do braço, epicôndilo lateral, antebraço e punho

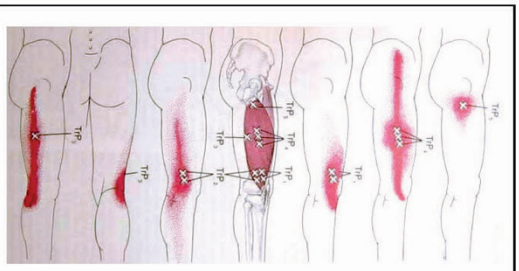
Biceps braquial	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Localização média e anterior do braço			Dor em região anterior do deltóide e fossa antecubital

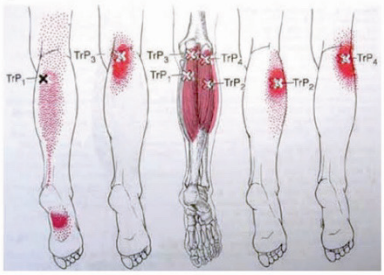
Triceps braquial **3 dedos acima cotovelo - posterior**	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
			TrP1: parte posterior do braço e ombro TrP2: dor em epicôndilo lateral TrP3:parte dorsal do braço e dedos anular e minimo TrP4: região olécrano

Quadrado Lombar	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Ponto médio da borda superior da porção posterior do ilíaco, paravertebral profundo de L3 a L5, borda inferior da 12° arco cost			Região sacro ilíaca, glútea inferior, ao longo da crista ilíaca posterior

Glúteo Mínimo	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Porção lateral e inferior da borda superior do ílio			Face lateral da coxa, joelho e tornozelo, face medial da região glútea e posterior da coxa e sura até maléolo lateral

Piriforme	DIREITO LDP: VAS (+2) : A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Entre porção média e lateral, quando dividimos o músculo em três partes do trocanter maior do fêmur até superfície interna do sacro.			Dor ciática, sacroiliaca, região glútea lateral, face posterior do quadril e 2/3 proximais da coxa

Vasto lateral	DIREITO LDP: VAS (+2): A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
			Face lateral da coxa e joelho

Gastroc-nêmios (medial)	DIREITO LDP: VAS (+2): A / L	ESQUERDO LDP: VAS (+2): A / L	
Localização PGs			Dor Referida
Ponto médio do ventre muscular da cabeça medial e da cabeça lateral, e porção inferior da fossa poplítea medial e lateral			Região sural, fossa poplítea, porção inferior da coxa e superfície plantar do pé, ao longo do tendão calcâneo