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DOES LOCALIZATION OF DEMYELINATING LESIONS INFLUENCE THE INTENSITY OF BACK PAIN AND QUALITY OF LIFE IN PATIENTS WITH RELAPSING-REMITTENT MULTIPLE SCLEROSIS? A CROSS-SECTIONAL STUDY

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ABSTRACT – ***Objective:*** Pain is a frequently reported symptom in patients with Multiple Sclerosis (MS), often linked to demyelinating lesions seen on magnetic resonance imaging (MRI) in the brainstem or spinal cord. Individuals with MS may also experience nociceptive or musculoskeletal pain, particularly low back pain (LBP). This study sought to assess the impact of the location of demyelinating lesions on the severity of back pain and on the quality of life (QoL) in patients with relapsing-remitting MS.

Patients and Methods: Patients with relapsing-remitting MS who experienced low back pain were included in the study and divided into two groups based on the location of demyelinating lesions found on MRI scans: Group A (cerebral, cerebellar, and spinal lesions) and Group B (cerebral and spinal lesions). All participants underwent assessments for pressure pain threshold using Fisher's algometer, evaluations for pain intensity and interference with daily activities using the Brief Pain Inventory (BPI) Severity Index and Interference Index. Additionally, physical disability was measured using the Modified Barthel Index, and QoL was assessed using both the European Quality of Life-5 Dimensions-3 Levels index and European Quality of Life-Visual Analogue Scale.

Results: Ten multiple sclerosis patients were recruited, with 6 participants in Group A and 4 in Group B. A significant difference was observed in PPT scores using Fisher's algometer, revealing lower scores in the group with cerebellar lesions.

Conclusions: Our findings suggest that cerebellar demyelinating lesions may affect pain threshold intensity, though the effects on activities of daily living (ADLs) and perceived health-related quality of life (HRQoL) are still under debate.

KEYWORDS: Pain, Multiple sclerosis, Cerebellum, Demyelinating lesions, Magnetic resonance imaging.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that affects over 2.2 million people worldwide. In Europe, the age-standardized prevalence ranges from 60-120 per 100,000 individuals, with a higher incidence in females compared to males, with ratios ranging from 2.3-3 to 1[1,2]. Several environmental factors may increase the risk of developing MS, including infections (such as the Epstein Barr Virus), vitamin deficiencies (such as vitamin B12 and D), and smoking habits[1].

The pathogenic hallmark of multiple sclerosis (MS) is characterized by perivenular inflammation involving T-lymphocytes and macrophages infiltrating the white matter, leading to demyelinating lesions and neuro-axonal damage. This process triggers a progressive neurodegenerative process[3]. Clinically, patients may experience focal symptoms depending on the specific area of the central nervous system affected. These symptoms may resolve completely or partially in a relapsing-remitting pattern. Alternatively, patients may describe chronic symptoms resulting from widespread brain involvement, which worsen progressively in cases of primary or secondary progressive forms of the condition[4].

Pain has been recognized as a significant symptom of MS since Charcot first described the disease in 1872. The prevalence of pain in MS is estimated to be around 1% in the first year of diagnosis but can affect up to 70% of patients. It is often chronic, affecting about 60% of cases[5].

Risk factors for pain in MS include a variety of demographic characteristics such as age, female gender, and lower education level. Emotional conditions such as depression, fatigue, and sleepiness also play a role in the experience of pain in individuals with MS. Additionally, disease-related features such as a higher disease burden, increased disability, and a progressive disease course are contributing factors to the presence of pain in individuals with MS[6-8]. Individuals living with MS may experience various forms of pain over the course of their lives, such as musculoskeletal pain, persistent and sporadic central neuropathic pain, as well as a combination of neuropathic and non-neuropathic pain[6]. Individuals with MS appear to be particularly prone to experiencing back pain, whether it be nociceptive or musculoskeletal in nature, although it is less frequently reported. The prevalence and risk factors associated with back pain in this population remain poorly understood[9]. Regarding the onset and intensity of pain in multiple sclerosis from a pathogenetic standpoint, the lateral spinothalamic tract and medial lemniscus have been extensively researched. These pathways are known to be connected to the somatosensory cortex (SSC), leading to an association between hypo/hyperesthesia and pain[5,8]. Consisted with the distribution of ascending pain pathways, the SSC serves as the primary pathway for localizing pain, with the ventral posterior lateral thalamic nuclei and limbic circuit playing prominent roles in emotional and motivational responses[10].

Multiple brain regions are likely involved in the processing of pain signals and emotional responses to pain. The specific brain areas that are involved in this process depends on the type of pain being experienced. In general, the ascending pain processes separate signals into two primary pathways: one that is responsible for localization, which involves the somatosensory cortex, and another that is responsible for emotional and motivational responses, which includes the VPL thalamic nuclei, periaqueductal grey, and the limbic forebrain.

While the function of these cortical structures in pain processing in MS patients is well known, it is possible that other brain areas may also be involved[11]. In particular, it has been proposed a putative role of cerebellum as cognitive modulator of pain, through an accurate evaluation of its cortical and sub-cortical wide connectivity[12,13]. Although several neuroimaging studies discovered a possible association of some painful conditions with brainstem demyelinating lesions in MS[14], less is known about the potential association between back pain and specific lesions identified at magnetic resonance imaging (MRI) in people with MS. Hence, the purpose of this study is to examine how the radiological localization of demyelinating lesions impacts the intensity of pain and QoL in a group of MS patients experiencing back pain.

PATIENTS AND METHODS

Patients

In this cross-sectional study, we included patients with diagnosis of relapsing-remitting MS according to revised McDonald Criteria[15] affected by low back pain referred to our outpatient rehabilitation service. Based on the localization of demyelinating lesions at MRI, we divided our cohort in two groups: patients with cerebral, cerebellar, and spinal lesions (Group A) and patients with cerebral and spinal lesions (Group B).

Methods

All participants were evaluated with our experimental protocol assessing pressure pain threshold (PPT) through Fisher algometer on the perceived painful point at low back; both pain intensity and interference with the activities of daily living (ADL) through the Brief Pain Inventory (BPI) and its two indexes BPI Severity Index (BPI-SI) and BPI Interference Index (BPI-II); the physical disability using the Modified Barthel Index (MBI) and the Health-Related Quality of Life (HRQoL) through the European Quality of Life - 5 Dimensions - 3 Levels (EuroQol-5D-3L) index (EQ-5D-3L index) and EuroQol-Visual Analogue Scale (EQ-VAS). The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of University of Campania ''Luigi Vanvitelli'' (Protocol n. 5807/18). All participants signed informed consent and gave their consent for publication.

Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences 25 (SPSS 25 Inc., Armonk, NY, USA) software. Continuous variables are presented as means ± standard deviations (SD), categorical data as absolute values and percentages. Distribution of all variables was tested using Shapiro-Wilk test. Intergroup comparisons were made using *t*-test for independent variables, after applying Levene's test for variance. The Wilcoxon-Mann-Whitney test was used for data not normally distributed. We considered a significance threshold of $p<0.05$.

RESULTS

Ten MS patients (4 males and 6 females) with back pain were enrolled with a mean age of 43.60±15.94 and a mean Body Mass Index (BMI) of 26.53±5.64. The mean scores of Fisher's algometer, BPI-SI, BPI-II, MBI, EQ-5D-3L, EQ-VAS are shown Table 1.

Table 1. Scores of outcomes in our cohort of MS patients affected by back pain (n=10).

Variables	Mean (± SD)
Fisher's algometer (kg)	4.52 ± 1.91
BPI-SI	3.52 ± 2.29
BPI-II	4.47 ± 2.89
MBI	91.50 ± 8.51
EQ-5D-3L	0.69 ± 0.17
EQ-VAS	5.96 ± 1.45

Continuous variables are expressed as mean ± standard deviation.
Abbreviations: standard deviation, SD; BPI, Brief Pain Inventory; BPI-SI, BPI Severity Index; BPI-II, BPI Interference Index; MBI, Modified Barthel Index; EuroQol-5D-3L index, European Quality of Life - 5 Dimensions - 3 Levels index; EQ VAS, EuroQol-Visual Analogue Scale.

According to the localization of demyelinating lesions, 6 patients were included in Group A and 4 in Group B: a statistically significant between-group difference was found only for PPT at Fisher's algometer (Table 2).

Table 2. Statistical changes between groups based on the localization of demyelinating lesions (n=10).

Variables	Group A (n=6)	Group B (n=4)	*p*-value
Fisher's algometer (kg)	3.58 ± 1.1	5.93 ± 2.12	0.049*
BPI-SI	4.10 ± 2.32	2.66 ± 2.26	0.240
BPI-II	4.82 ± 3.28	3.94 ± 2.56	0.453
MBI	90.00 ± 8.37	93.75 ± 9.46	0.580
EQ-5D-3L	0.67 ± 0.11	0.71 ± 0.24	0.807
EQ-VAS	6.10 ± 1.75	5.78 ± 1.21	0.617

Continuous variables are expressed as mean ± standard deviation.
Abbreviations: BPI, Brief Pain Inventory; BPI-SI, BPI Severity Index; BPI-II, BPI Interference Index; MBI, Modified Barthel Index; EuroQol-5D-3L index, European Quality of Life - 5 Dimensions - 3 Levels index; EQ VAS, EuroQol-Visual Analogue Scale.

DISCUSSION

Our research indicates that demyelinating lesions located in the cerebellum may have an impact on the intensity of pain and QoL for MS patients experiencing lower back pain. Pain is often reported as one of the most prevalent and debilitating symptoms for individuals with MS[16]. In literature, few studies have evaluated the neuroradiological correlates of MS pain, most of them investigating neuropathic pain[10]. Patients with MS often experience musculoskeletal pain, particularly lower back pain (LBP), although the exact prevalence is not well documented[9,17]. In MS, the brainstem is commonly believed to be the primary location of demyelinating lesions associated with pain. However, several studies have found that spinal lesions may also play a significant role in causing limb or radicular pain. This may be due to their direct interference with sensory afferent pathways or their disruption of descending inhibitory pathways[18,19].

On the other hand, the relationship between cerebellar lesions and painful conditions in MS has not yet been thoroughly investigated. Our findings revealed a significant difference in pain pressure threshold (PPT) between groups, with MS patients experiencing back pain and cerebellar lesions scoring higher than those with just cerebral and spinal lesions. These results suggest that the location of cerebellar lesions may impact the perception of low back pain. It is possible that the cerebellum plays a role in pain perception by processing nociceptive inputs through the deep cerebellar nuclei, the anterior vermis, and bilaterally in cerebellar hemispheric lobule VI[20]. For what concerns pain severity, worse scores were showed in the group with cerebellum lesions, although the difference was not statistically significant. According to both the available literature and to our findings, we could speculate that the cerebellum may be involved in the perception of pain severity by modulating pain modulating circuits in the brainstem (i.e., periaqueductal gray, rostral ventromedial medulla, dorsolateral pontine tegmentum), supporting the difference found about LBP severity in our groups[21]. Considering the potential biomechanical causes of LBP in MS, they seem to be different from what observed in the general population[9]. Weakness in the lower limbs, spasticity, asymmetric posture, and balance and gait impairment are all considered potential triggers of lower back pain in patients with MS. In addition, somatosensory involvement can further contribute to impaired trunk balance, leading to progressive spine instability and the development of lower back pain. In terms of QoL, the group with cerebellum lesions exhibited lower scores, although the difference was not statistically significant when compared to the other group. It is widely recognized that LBP has a negative impact on QoL in both the general population[22] and individuals with MS[23]. Therefore, it is important to further investigate the potential influence of cerebellum lesions on quality of life in MS patients with LBP.

The occurrence of low back pain in MS patients may also be attributed to the aforementioned trigger factors. Additionally, lesions in the cerebellum could potentially serve as a predictive factor for this painful condition, affecting pain perception and potentially offering improved management and treatment options for these patients.

CONCLUSIONS

LBP is often underestimated and undertreated in individuals with MS, leading to a higher risk of chronicization. Demyelinating lesions located in the brainstem or spinal cord have been implicated in various painful conditions. Our research suggests that demyelinating lesions in the cerebellum may play a role in the perception of pain in MS patients with LBP.

Authors Contributions:

Conceptualization, G.I., A.M. and F.G.; methodology, S.L. and M.P.; writing-original draft preparation, S.L.; writing-review and editing, M.P. and G.B.; supervision, G.I., A.M. and F.G.; All authors have read and agreed to the published version of the manuscript.

Availability of data and material:

Available from the corresponding author on reasonable request.

Conflict of interests:

The authors declare that they have no conflict of interest to disclose.

Data availability statement:

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Committee approval:

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