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Low back pain in patients with Multiple Sclerosis: a systematic review and the prevalence in a French Multiple Sclerosis population

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Low back pain in patients with multiple sclerosis: a systematic review and the prevalence in a French multiple sclerosis population

Purpose

The prevalence and management of back pain in MS patients was assessed by a systematic review, and the results of a survey on the characteristics of low back pain in a sample of French MS patients are reported.

Methods

A systematic search was conducted according to the PRISMA guidelines. The outcomes of interest included the prevalence of back pain, severity of pain and impact on daily activities. Moreover, the prevalence of low back pain and its consequences on daily living in a large French MS population were assessed.

Results

Fourteen studies were included in the systematic review. The prevalence of back pain in MS patients ranged from 8,6 to 50%, but that of low back pain in particular ranged from 41,6 to 52,4%.

Concerning the survey, 237 patients participated in the online questionnaire. The prevalence of low back pain in the French MS patients was 76,4%. The patients with chronic low back pain had more limitations in their daily life activities than those without chronic low back pain.

Conclusion

Patients with MS commonly suffer from low back pain, but it is still an underdiagnosed cause of pain that reduces one's ability to perform activities in daily life.

Keywords: Multiple Sclerosis; Low back pain; Pain; Musculoskeletal pain

Introduction

With a prevalence ranging from 5% to 22% [1], spinal pain is a common cause of pain in the general population and is one of the largest public health problems. Low back pain (LBP) is the most common cause of spinal pain and its occurrence was approximately 84% of the population during their lifetime. The types of LBP are defined by the duration of pain: acute, subacute and chronic. Acute LBP is pain lasting less than 4 weeks, and subacute pain is pain lasting 4 to 12 weeks. Chronic low back pain (CLBP) is defined as continuous pain in the low back region that persists for more than 12 weeks without significant improvement in the intensity of pain. Five to 10% of LBP patients develop CLBP[2]. The prevalence of CLBP varies from 4,2% to 23% in the general population [2]. CLBP is a leading cause of activity limitations and work absence, leading to a major cost burden for the society [3,4]. The causes of CLBP are multidimensional and complex. LBP is generally due to spinal instability [5]. Then, pain induces adaptative but altered muscle activation patterns [5], altered lumbosacral proprioceptive acuity [6], and restricted range of motion[7], which increase the risk of chronic or recurrent LBP [8,9]. These modifications in the neuromuscular activity and biomechanics of the spine affect an individual's postural stability and gait. For example, CLBP alone can induce a forward trunk inclination[10], which alters the kinetic and kinematic characteristics of an individual's gait and gait initiation pattern[11]. During a dynamic task or gait, CLBP patients reduce their trunk velocity and range of motion to decrease the forces applied on the lower back [10]. These changes in posture decrease an individual's adaptability during movement, leading to freezing-like behavior [10]. In addition, during a dynamic challenging task, CLBP patients do not adapt their base of support [10]. These changes in adaptative strategies increase an individual's risk of physical deconditioning.

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that induces motor and sensory deficits, visual impairments and gait and postural balance disorders. Pain is a common symptom in patients with MS, considering 29 to 86% of MS patients report pain [12] as one of the most distressing symptoms[13]. Several authors have proposed pain classification systems for individuals with MS [12,14]. Even though neuropathic pain is the most commonly reported type of pain in individuals with MS [12], the presence of the MS disease predisposes patients to develop nociceptive or musculoskeletal pain, especially back pain [15], which are less often reported. The prevalence of back pain and its predisposing factors in the MS population are not well known [16]. Nevertheless, muscle trunk weakness, somatosensory disorders, asymmetric posture and gait impairments

due to MS can induce back pain [16]. In addition to the presence of MS, the presence of LBP can exacerbate the functional difficulties of these patients, such as postural instability and gait impairments.

Independent of the assessment of MS-specific impairments, the functional evaluation of LBP involves several clinical tests, but there is no gold standard [17]. The use of motion capture systems allows the characterization of balance, gait and movement disorders in LBP patients, but there is limited and inconsistent evidence of kinematic/kinetic measures that can be used clinically [18]. For example, Delpierre et al. proposed an index based on 10 discrete variables extracted from the range of motion, but it is a complex and time-consuming assessment for clinical practice [19]. Alternatively, in daily practice, clinical questionnaires are often used to assess the impact of LBP, but they do not reflect the real capacity of patients in daily life [20]. To the best of our knowledge, the functional impact of LBP on daily life activities in the MS population has rarely been evaluated.

The first objective of this study was to conduct a systematic review of the literature to determine the impact of LBP on the functional outcomes of MS patients. To complete this review, the second objective was to record the types of LBP in a large sample of MS patients by administering a French national survey to examine the functional impact and specific care of LBP in MS patients.

Methods

1. Systematic review

The systematic review was performed in accordance with the PRISMA guidelines (<http://www.prisma-statement.org/>). A systematic search was conducted during December 2019 in the following databases: PubMed, Web of Science and the Cochrane Library. The following keywords and MeSH headings were used for the search: Multiple Sclerosis AND back pain OR musculoskeletal pain OR lumbar pain. To supplement the literature search, the reference lists of the selected articles were searched, and Google Scholar searches were conducted. Only articles in the English language were analyzed. There were no limitations regarding the year of publication.

The population of interest was MS patients with a definite diagnosis of MS or clinical isolated syndrome in addition to back pain, especially LBP. The outcomes of interest included the prevalence of back pain and LBP, severity of pain, type of pain, duration of pain and impact on quality of life or activities in daily life.

The eligibility assessment was performed by screening the titles and abstracts of the articles (Figure 1). Due to methodological heterogeneity in the studies, there was a lack of comparative data, and no meta-analyses could be performed. The data are reported descriptively. The following data were extracted: the study design, population characteristics, prevalence of back pain and LBP, severity of pain, pain score and impact on daily activities or quality of life (Tables 1 - 2).

The Newcastle-Ottawa Scale for case control studies was used to assess the quality of the case control studies [21,22]. Each study could obtain a maximum of nine stars: 4 stars for the selection of the study groups, 2 stars for the comparability of the groups, and 3 stars for the exposure or outcome of interest. Two reviewers used the Newcastle-Ottawa Scale checklist to rate the methodological quality of the studies. Any disagreements in the ratings were resolved through discussions.

2. Survey

The survey assessed the prevalence of LBP in a French MS population and identified limitations in daily living. MS patients were recruited online with social media applications, such as Carecity (Paris, France), and PARC SeP (Plateforme d'Accompagnement de Ressources et de Coordination pour la Sclérose en Plaques et la maladie de Parkinson; Lille, France) which is a regional care network for MS and Parkinson patients from January to May 2018. The recruitment with the PARC SeP was done in thanks to their Facebook homepage, with a link to the online questionnaire. There was no other approach to recruit patients. The inclusion criterion was MS patients older than 18 years old. The project was reviewed and approved by the local ethical committee.

The questionnaire took approximately 10 minutes to complete (Appendix 1). All data were self-reported. The first part of the questionnaire concerned the general assessment of the patient and his or her case of MS: sociodemographic data; information on the history of MS, rheumatologic disease or spine surgery; and whether the individual used a walking aid or wheelchair were recorded. Subsequently, if patients reported LBP during this first part of the questionnaire, supplementary questions about LBP were asked to distinguish current LBP from a history of LBP.

- For patients with current LBP, the questions concerned the duration of LBP (*i.e.*, < 4 weeks, 4-12 weeks and > 12 weeks), treatments (*i.e.*, physiotherapy, medical treatment, or none), type of emergence (*i.e.*, suddenly or progressively), radiculopathy (*i.e.*, if pain spread into the lower limbs), and pain occurrences (*i.e.*, at rest, during

sitting posture, standing position, at walk or at rest and during specific postures). Neuropathic pain was evaluated with the “Douleur Neuropathique 4” questionnaire (DN4). DN4 is the French questionnaire that has been validated to evaluate the symptoms of neuropathic pain in patients with LBP and MS [23,24]. The DN4 result is positive if the score is greater than or equal to 4, indicating the presence of neuropathic pain. A visual analog scale was used to assess the intensity of all types of pain (from 0 to 10). The EIFEL (Echelle d’Incapacité Fonctionnelle pour l’Evaluation des Lombalgies) questionnaire is the French adaptation of the Roland and Morris Disability Questionnaire. The EIFEL questionnaire was used to evaluate the influence of LBP, independently of the aspects of MS, on the patients’ quality of life and their limitations on daily activities [25]. The EIFEL questionnaire was self-administered.

- The patients with a history of LBP had specific questions on the duration of LBP, frequency of LBP episodes, and whether they received treatments.

The population was divided into the following 3 groups according their responses to the first part of the survey: no LBP MS patients, current LBP MS patients and history of LBP MS patients.

All data analyses were performed using R software (version 3.4.2). For each group, descriptive statistics were used to evaluate means, medians, and interquartile ranges for continuous variables and frequencies for noncontinuous measures. For group comparisons, the Chi-squared test with Fisher’s test correction and the Kruskal–Wallis test or Mann–Whitney test were used when the application compliance condition was not respected. The significance level was adjusted using the Bonferroni method where needed ($p < 0.016$) for the comparison of the 3 groups. Then, for all the tests, the significance level was set to be $p < 0.05$.

Results

1. Systematic review

After a systematic search of the databases, 924 articles were retrieved. Fourteen of the articles were included: 12 articles reported back pain in MS patients (transversal studies), and 2 articles evaluated the effect of transcutaneous electrical nerve stimulation on LBP in MS patients (case control studies). Figure 1 shows the process of study inclusion. The characteristics of the population, methods of pain evaluation, prevalence of back pain and LBP and the impact on daily living for the 12 transversal studies are reported in Table 1, and those for the 2 case control studies are reported in Table 2.

1.1. Characteristics of the MS population

These studies evaluated 5780 patients, including 4001 females and 1356 males. Three studies did not report the sex of the MS patients [21,26,27]. A total of 3565 patients had relapsing remitting MS, 682 had secondary progressive MS, and 224 patients had primary progressive MS. Only one study evaluated LBP in patients with clinical isolated syndrome [28]. Five studies did not report the form of MS [21,22,26,29,30]. The patients were between 18 and 80 years old. Three studies evaluated patients with a low EDSS score (EDSS<4) [24,28,31]. Two studies did not report the EDSS score of the MS patients[26,29].

1.2. Evaluation of back pain

Most of the studies evaluated back pain with interviews [16,24,26–29,31–35], clinical exams [16,27,28,32,33] or an online survey [30]. Back pain was evaluated by several different types of rating scales: a self-administered comorbidity questionnaire, a numeric rating scale, the Nordic Musculoskeletal Questionnaire, the painDETECT Questionnaire, the visual analog scale, the McGill pain questionnaire and the Brief Pain Inventory. When the quality of life of the MS patients was assessed, it was again assessed by several different scales: the health-related quality of life questionnaire, Multiple Sclerosis International Quality of Life, European Quality of Life-5 Dimensions. Only Marck et al. 2016 reported the specific impact of LBP on quality of life or on the ability to perform activities of daily living [30].

1.3. Prevalence, risk factors, type of back pain and LBP, duration of pain in MS patients and impact on the ability to perform activities of daily living

The prevalence of back pain in MS patients varied from 8,6 to 50% [24,26–32,34,35]. Back pain was the most common cause of comorbidities and the most limiting factor for daily activities in MS patients [30]. The prevalence of LBP varied from 41,6 to 52,4% [16,32,34]. Few studies have suggested that back pain and LBP are common in patients with an early stage of the disease [30,34]. Massot et al. suggested that female MS patients with progressive form, visual disorders or a high EDSS score are at risk of developing LBP. Only three studies assessed back pain intensity, and they reported the intensity to be moderate [29,32,35]. No studies evaluated the intensity or duration of pain in MS patients with LBP.

1.4. Treatment of LBP

Only transcutaneous electrical nerve stimulation treatment was evaluated[21,22]. This technique did not lead to significant improvement in the LBP of the MS patients (Table 2).

1.5. Quality assessment of studies

According to the Ottawa scale checklist, the 2 case-control studies were of moderate quality. A detailed overview of the quality of the studies is provided in Table 3. The total score was 6 stars out of a possible nine stars.

2. Results of the survey

2.1. Sociodemographic results

Two hundred thirty-seven MS patients participated in the study, and 234 questionnaires were completed (return rate of approximately 99%). The sociodemographic and medical data are shown in Table 4. One hundred and seventy-eight patients presented with LBP (*i.e.*, a prevalence of approximately 76.1%), 41 had a history of LBP (17.5%), and 15 patients did not report having LBP (6.4%).

2.2. Patients with current LBP

Regarding the duration, 69.6% of patients had chronic LBP, 19.9% suffered from subacute LBP and 17.4% had acute LBP. No difference in the sociodemographic factors was found between CLBP patients and subacute or acute LBP patients.

A total of 74.7% of patients reported that LBP began progressively, 11.2% disclaimed that the pain began suddenly, whereas 14% of patients did not know when the pain started. A total of 45.5% of patients reported a trigger factor for LBP, 33.7% reported no trigger factor and 20.8% did not know whether LBP began with a trigger factor.

Only 73.6% of patients reported having LBP to a doctor, and 63.3% of these patients had complementary exams. CLBP patients more often reported to their doctor than patients with acute LBP ($p=0.002$), and they also had more complementary exams than patients with subacute LBP ($p=0.006$) or with acute LBP ($p=0.028$). To treat their LBP, 52.7% of patients underwent medical treatments, 72.5% underwent physiotherapy treatment and 28.2% underwent osteopathy treatment. No difference was found between groups treated with physiotherapy.

The pain evaluation results are presented in Table 5. Regarding the type of pain, the intensity of pain in all MS patients with LBP (independent of the duration) was not different between patients with neuropathic pain and those with nonneuropathic pain. For all MS patients with LBP, a total of 48.3% of patients reported pain spreading into the lower limb. For these patients, 24.4% had neuropathic pain with a positive DN4 result. For 52.3% of patients, the pain occurred only during physical activity, such as walking or transfer to a wheelchair. A total of 32.7% of patients reported that pain occurred both during physical activity and at rest, whereas 14.9% declared that the pain appeared at rest only. Regarding the duration of LBP, the pain intensity was not significantly different among the 3 LBP groups (acute, subacute or CLBP). Particularly for the patients with the CLBP who were the most represented patients, patients with a positive DN4 result did not have more severe pain than those without a

positive DN4 result. Compared to the subacute and acute LBP patients, CLBP patients presented an increased intensity of pain during physical activity ($p<0.001$) and during the day ($p<0.001$).

The median EIFEL score was $5 \pm 4,7$ for the MS patients with LBP. Patients with CLBP had more limitations of activities in daily life than patients with acute LBP ($p=0.03$). LBP led to absence from work in 31% of MS patients, and there was no difference between the CLBP patients and patients with subacute or acute LBP in the rate of absence from work. Independent of the duration of LBP, 36,5% of patients used one or more walking aids for locomotion: 30.3% used a stick, 18% used a manual wheelchair, 8.4% used an electric wheelchair and 0.6% a walker.

2.3. Patients with a history of LBP.

Eighty-five percent of patients with a history of LBP claimed having more than one episode of LBP during the last year. A total of 65.8% of these patients had a consultation with a doctor for LBP, and 63% of them had complementary exams. Regarding the treatment, 43,9% of patients underwent physiotherapy treatment, 36,6% were administered drugs, and 24,4% underwent osteopathy treatment.

Discussion

This article is the first to review the literature and report the impacts of LBP on functional outcomes in MS patients. Finally, to address the lack of information in the literature, the sociodemographic data, characteristics, medical care and limitations in daily life activities in the French MS population were collected from the national survey. In MS patients, the prevalence of back pain and LBP varied from 8.6 to 50% [30,31,35] and from 41.6 to 52.4% [16,32], respectively. LBP is present even in patients with an EDSS score of < 4 [24,28,31], and its prevalence is at least twice as high as that in the general population [2]. The present survey reports a higher prevalence (76.1%), with 17.5% of patients suffering from recurrent episodes of LBP. This difference may be explained in part by the method of recruiting MS patients for the survey. Due to their own interest in the study, patients concerned about LBP or having had a history of LBP might be over-represented in this study. Although LBP is the leading cause of comorbidities and limitations in activities in daily life in MS patients, the etiologies, history, types, severities and treatments of LBP are only rarely evaluated [29,30]. No specific studies on back pain in MS patients were found in the systematic review, and LBP was only described in studies about pain in MS patients. Although several classifications of pain have been proposed, neuropathic and musculoskeletal

pains remain the most commonly evaluated types of pain. This dichotomic evaluation appears to be insufficiently relevant for LBP in MS patients and cannot explain the cause of LBP. Indeed, in our survey, 32.7% of MS patients with LBP presented with both neuropathic and nociceptive pain, whereas 24.4% of patients had only neuropathic pain with a positive DN4 result. This high prevalence of neuropathic pain in LBP patients is consistent with the high prevalence of neuropathic pain and low back lesions in the MS population[12,36]. Moreover, common causes of LBP, such as degenerated discs, the compression of nerve roots or inflammation, can also induce neuropathic pain.

The physiopathology of LBP related to MS is not known. Several risk factors have been suggested in a few studies [16,29], but none of them have been assessed. The authors suggested that lower limb weakness, spasticity, somatosensory disorders, asymmetric posture and walking impairments can induce LBP [12,24,37]. Nevertheless, these factors could not explain the high prevalence of LBP observed at the early stage of MS. However, the authors suggested that somatosensory disorders in MS patients induce altered balance control of the trunk, which can eventually lead to spine instability and LBP [38]. In addition, Ketelhut et al. (2015) reported modifications in trunk muscle activity during walking in MS patients with a low EDSS score [39]. Lateral flexor, external, and internal obliques and the rectus abdominis were less activated on the most affected side during walking, suggesting an early weakness in trunk muscles leading to compensation strategies. This trunk muscle weakness worsened with the EDSS score and led to an increase in trunk sway during upright standing or during walking [38,40]. This type of weakness can also affect the posture of the lumbar spine. Since lumbar lordosis plays an important role in shock attenuation during gait[41], the presence of both posture and lumbar lordosis disorders in MS patients decrease these individuals' capacities to attenuate shock. In addition, from the early stage of MS, patients are less able to absorb repetitive impacts at foot contact during gait [42], which can also worsen LBP.

In the general population, LBP, especially CLBP, reduces walking speed, stride length and coordination between trunk segments[43]. During gait, CLBP patients modify their pattern of trunk muscular activity and reduce the acceleration and movements of the trunk to decrease the forces applied to the lumbar spine and avoid painful sensations[10,43]. These modifications in trunk coordination impair the ability of patients to deal with unexpected perturbations [44]. Moreover, patients adopt a less adaptive posture, a freezing-like posture, during trunk movements[10]. For MS patients, these specific modifications due to LBP add

up to the MS symptoms and worsen these patients' general disability due to postural and gait disorders. The convergence between LBP and MS appears as a vicious circle since worsening of one's gait and the progression of postural disorders with the progression of the disease can increase the risk of LBP[10].

Regarding the modifications that LBP can induce in addition to MS impairments, the early diagnosis and treatment of LBP appears to be important but challenging for the care of MS patients. Concerning the diagnosis, this systematic review showed that a specific clinical test or tool to evaluate LBP in MS is missing. Concerning the clinical care of LBP in MS patients, according to the survey results, most patients talked about LBP with their doctor if the pain persisted for more than 12 weeks (73,6%), and most of them received physiotherapy (72,5%) or medical treatments (52,7%). These results were consistent with the European guidelines for the management of LBP [45]. Nevertheless, the present literature review and the subsequent survey suggested that LBP associated with MS depends on physiopathological mechanisms that are different than those reported in the general population. A better understanding of the physiopathological mechanisms may allow us to propose a prevention strategy and specific care for LBP in MS patients, especially at the early stage of the disease. Moreover, this article highlights the importance of developing specific tools to evaluate LBP and its specific impact on MS.

Study limitations

Several limitations were identified in our review and survey. Due to the limited number of articles in the literature, there were insufficient data to perform a meta-analysis, and the interpretation of the results is also limited. Only papers in the English language were included. Regarding the survey, a questionnaire was used for the French MS population, and it was available online only. All data were self-reported, and it is therefore not possible to assess the accuracy or reliability of the data. In addition, since patients who filled out our questionnaire were interested in LBP, there may be an overestimation of the prevalence of LBP. The survey did not address questions about the onset of LBP, about the timing or order of the diagnoses of MS and LBP, or about the efficiency of LBP management.

Conclusion

The prevalence of LBP is 2 or 3 times higher in MS patients, even in those at an early stage of the disease, than in the general population. Mixed types of LBP (neuropathic and nociceptive) and LBP of moderate intensity are present in these patients, but the limitations in the ability to

perform activities of daily living are significant. Altered muscle activation patterns and somatosensory deficits in the trunk can induce LBP, and LBP alone can induce balance and gait disorders, which worsen the patients' physical function. This vicious circle occurs even at the early stage of the disease. Specific management of LBP should be proposed to MS patients as soon as possible before the patients develop CLBP.

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Declaration of conflicting interests

The authors report no conflicts of interest.

Table 1: The prevalence, severity of pain, and limitations in activities in daily living due to back pain in MS patients that were reported in the included studies

Study	Population	Outcomes measures	Results for back pain
<p><i>Kahraman et al. 2019</i> [34]</p>	<p>223 MS patients: 150 females, 73 males 93% RRMS, 5.6% SPMS, 1.4% progressive-relapsing MS. 124 MS patients presented musculoskeletal pain: 88 females and 36 males, mean age 34 years [27-42], median EDSS score: 1.5 [1.0-2.5], mean disease duration: 5 [2.5-11]</p> <p>47 MS patients presented with neuropathic pain: 32 females and 15 males, mean age 35 [29-42], median EDSS score: 2.0 [1.5-2.75], mean disease duration: 4.25 [2-8.25]</p> <p>52 patients had no pain: 30 females and 22 males, mean age 34 [25.25-41.75], median EDSS score: 1.5 [0-2.5], mean disease duration: 4 [0.8-9.5]</p>	<p>Interviews and questionnaire. The Nordic Musculoskeletal Questionnaire was used to evaluate back pain. The painDETECT Questionnaire was used to evaluate neuropathic pain. The Modified Fatigue Impact Scale, the Beck Depression Inventory, the Epworth Sleepiness Scale and the Multiple Sclerosis International Quality of Life were used.</p>	<p>LBP was the most common type of pain: 52.4% MS patients with musculoskeletal pain had a lower EDSS score than did MS patients with neuropathic pain.</p>
<p><i>Labuz-Roszak et al. 2019</i> [35]</p>	<p>144 MS patients: 110 females, 34 males Mean age 41±12 Median EDSS score: 3.2±1.9 Mean disease duration: 10.3±8.6 79.2% RRMS 20.8% SPMS</p>	<p>Interviews and questionnaires Pain severity was measured with the Visual Analogic Scale Quality of life was assessed by the European Quality of life-5 Dimensions. The depressive symptoms were evaluated with the Hospital Anxiety and Depression Scale, and the EDSS</p>	<p>50% of patients presented with back pain. The intensity was moderate to severe, with a score of 5.6±2.4 for back pain.</p>

		score was noted.	
<i>Marck et al. 2016</i> [30]	<p>Participants were recruited online. Questionnaire assessed the comorbidities and quality of life in MS patients. 2399 MS patients were evaluated: 1892 females, 407 males</p> <p>Mean age: 45.5 ± 10.6</p> <p>Median disease duration was 6 years [3-12]</p> <p>61.6% RRMS</p> <p>55.6% none or mild disability</p> <p>44.4% moderate to severe disability</p>	The Self-Administered Comorbidity Questionnaire and Health-related quality of life questionnaire were used.	<p>36.2% of patients presented with back pain. 43.8% received treatment</p> <p>52.2% of patients reported that back pain limited their daily activity.</p> <p>Back pain was the leading cause of comorbidities and the leading cause of limitations in activities of daily living.</p>
<i>Massot et al. 2016</i> [16]	<p>190 MS patients: 138 females, 52 males</p> <p>Mean age 54.9±9.2</p> <p>Median EDSS score: 6</p> <p>Mean disease duration: 19.3±9.9</p> <p>48.9% SPMS, 27.4% RRMS, 23.7% PPMS</p> <p>27.9% used a walking stick, 53.7% used a wheelchair, a walker or more than one walking aid</p>	<p>Interviews and clinical exams were performed by a rehabilitation physician. The severity of pain was evaluated by the Numeric Rating Scale</p> <p>Clinical exams were performed to assess muscle testing, spasticity in the lower limbs, and the EDSS score.</p>	<p>41.6% of patients presented with low back pain at the exam, 2.1% had thoracic pain and 3.2% had cervical pain. Radiculopathy was present in 6.8% of the patients.</p> <p>Risk factors of low back pain in MS patients were a progressive form of MS, visual dysfunction according to the EDSS score, and the female sex.</p>
<i>ShayestehAzar et al. 2015</i> [29]	<p>115 MS patients, 88 females, 27 males,</p> <p>Mean age: 30.4 ± 5.9</p> <p>Mean disease duration: 2.2±2</p>	<p>Interview and questionnaires</p> <p>Pain severity was measured with the Numeric Rating Scale questionnaire, the Nordic musculoskeletal questionnaire was used to investigate the cases of musculoskeletal pain.</p>	<p>During last year, 38.3% of patients presented back pain, 30.4% had back pain 7 days before the exam, and 22.6% of patients reported that back pain interfered with daily activities.</p> <p>Women had a 5.16 times higher risk of having upper back pain than men. Patients with a recent diagnosis of MS presented a lower risk of having upper back pain. The mean pain severity was 3.75±2.25.</p>
<i>Vidovic et al.</i>	61 MS patients: 44 females, 17 males	Interviews and clinical exam were	52% had low back pain, and 31% had neck

2014 [32]	Mean age: 47.5 Mean disease duration: 10.9 57% RRMS, 36% SPMS, 7% PPMS Mean EDSS: 5.5	performed to assess pain severity with visual analog scale, and EDSS.	pain. Patients with low back pain had a VAS score of 6.75, and patients with neck pain had a VAS score of 5.68.
<i>Seixas et al.</i> 2011 [28]	85 MS patients 23 males, 62 females Mean age: 39.7±11.7 Mean disease duration: 10.9±7.1 years Median EDSS score: 2 RRMS: 71%, SPMS: 18%, PPMS: 1%, CIS: 11%	Interviews and clinical exam: EDSS score, The Brief Pain Inventory, The McGill Pain Questionnaire	34% of patients had pain during the day or the week before the exam. One of the most common sites of pain was the back (prevalence 27%)
<i>Martinelli et al.</i> 2008 [31]	428 MS patients : 267 females, 161 males, Mean age: 38.4±10.8 Mean disease duration 9.6 years EDSS 2 RRMS 74.7%, SPMS 15.2%, PPMS 10%	Interview: type of pain, location, EDSS score.	Actual back pain during the evaluation: 8.6% 13.8% of patients declared that they experienced back pain during his or her lifetime.
<i>Solaro et al.</i> 2004 [24]	1672 MS patients, 1152 females, 520 males, Mean age 40 (median 40 [14-74]) Disease duration 10.5 (median 8 [0-47]) RRMS : 74%, SPMS : 20,5%, PPMS : 5,5% Mean EDSS score 2.9 (median 2.5 [0-7])	Interviews using a face to face structured questionnaire: pain location, type of pain, EDSS score	16.4% reported having back pain, and 72.9% of women reported having back pain. Compared to the MS patients without back pain, the MS patients with back pain were significantly older, and a higher EDSS score and disease duration, and were more likely to have a secondary progressive form of MS.
<i>Svendsen et al.</i> 2003 [33]	150 patients: 50 MS patients with pain, 50 MS without pain, and 50 healthy controls. For the MS patients with pain: 21 males, 29 females,	Interviews and clinical exam: McGill pain questionnaire, pain location, pain intensity with visual analog scale, type of pain. Neurological exams were performed to	70% of MS patients with pain reported having back pain, 17.2% had central pain, and 40% of patients with back pain presented with musculoskeletal pain.

	Age 50.5±9.5 Mean disease duration : 12.1±5.9 years RRMS 28%, SPMS 48%, PPMS 24%; Mean EDSS score: 5.1 ±1.9 No significant difference was observed between groups in the age, sex, or EDSS score of the MS patients.	assess the EDSS score and spasticity in upper and lower limbs; quantitative sensory examinations were performed with Von Frey hairs, the Dixon up–down method and vibration.	
<i>Stenager et al. 1995 [46]</i>	49 MS patients RRMS 42.8%, 59.2% SPMS The mean deterioration score of the EDSS ranged from 3.4 to 4.5.	Interviews and clinical exams were performed in 1986 and five years later: EDSS score, pain location, pain type.	6 had back pain at the first evaluation 12 patients reported having back pain 5 years later
<i>De Moulin et al. 1988 [26]</i>	159 MS patients	Interviews: pain location, pain type, EDSS score	14% presented with back pain

Abbreviations: EDSS: Expanded Disability Status Scale; PPMS: primary progressive multiple sclerosis; RRMS: remittent recurrent multiple sclerosis; SPMS: secondary progressive multiple sclerosis

Table 2: The treatments for low back pain in MS patients that were reported in the studies

Study	Population	Protocols and Outcomes measures	Results
<i>Al-Smaid</i> 2003 [21]	15 MS patients with CLBP were allocated into 3 groups.	<p>Randomized placebo controlled study</p> <p>3 groups of patients :</p> <ul style="list-style-type: none"> - 5 patients with low frequency TENS (4 Hz,200 μs) - 5 patients with high frequency TENS (110 Hz, 200 μs) - 5 patients with placebo TENS <p>Patients were assessed at the beginning of the study, at 6 weeks, and at 10 weeks.</p> <p>Patients had to apply TENS on the lumbar spine at least twice daily for 45 minutes for 6 weeks.</p> <p>Outcome measures were the Roland Morris Disability Questionnaire, Short Form-36, McGill Questionnaire, and VAS scores.</p>	All groups showed a decrease in pain and a decrease in the impact of back pain on daily living after treatment. No significant difference was found between groups.
<i>Warke</i> 2006 [22]	90 MS patients (69 females, 21 males) with CLBP allocated into 3 groups. No significant differences were detected in the demographic data between groups.	<p>Randomized placebo controlled study</p> <p>3 groups of patients :</p> <ul style="list-style-type: none"> - 30 patients with low frequency TENS (4 Hz,200 μs) - 30 patients with high frequency TENS (110 Hz, 200 μs) - 30 patients with placebo TENS <p>Patients were assessed at the beginning of the study, at 6 weeks, at 10 weeks and at 32 weeks.</p> <p>Patients had to apply TENS on the lumbar spine at least twice daily for 45 minutes for 6 weeks.</p> <p>Outcome measures were the VAS for average LBP, McGill Questionnaire Visual analog scale for the worst LBP and back and leg spasms, the Roland Morris Disability Questionnaire, Barthel Index, Rivermead mobility Index, Multiple Sclerosis Quality of life-54 Instrument results.</p>	<p>VAS and McGill questionnaire scores decreased in the 3 groups during treatment period, but no significant difference was found across groups.</p> <p>The high frequency TENS group showed a decrease in the worst LBP and back and leg spasms, but the results were not significant.</p> <p>No significant differences were found in the other outcomes.</p>

Abbreviations: CLBP: chronic low back pain; MS: multiple sclerosis; TENS: transcutaneous electrical nerve stimulation; VAS: Visual Analog Scale

Table 3: Methodological evaluation of the studies performed with the Newcastle Ottawa Scale

	Selection				Comparability		Exposure			Total
	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 1	Criteria 2	Criteria 1	Criteria 2	Criteria 3	
<i>Warke et al. 2006 [22]</i>	X	X	X	X	X			X		6
<i>Al-Smaid et al. 2003 [21]</i>	X	X	X		X	X		X		6

Variables	Current LBP (n=178)	History of LBP (n=41)	No LBP (n=15)	<i>p</i>
Age (years)	48±11.4	48±11	50±8.7	0.58
Females/Males (%)	86/14	78/22	60/40	0.02
Weight (kg)	68±16.4	74±14.7	70±19.1	0.87
Tall (m)	1.66±0.1	1.68±0.1	1,67±0.2	0.37
Median EDSS score (%)	4.5±1.3	4±1.2	4 ±1.2	0.27
<4	24.7	29.3	26.7	
4-5.5	27	36.6	20	
6-7.5	38.8	29.2	40	
>7.5	9.5	4.9	13.3	
Disease duration (%)				
< 5 years	27	29.2	26.7	0.97
5 – 10 years	33	26.8	20	0.46
>10 years	40	43.9	53.3	0.90
MS form (%)				
Remittent Recurrent form	57.3	58.6	46.7	0.69
Progressive form	32.6	31.7	26.7	0.87
Unknow	10.1	9.7	26.7	0.18
History of rheumatology disease (%)	18.5	12.2	13.3	0.50
Ankylosing spondylitis	18.1	0	0	
Rheumatoid arthritis	3	0	25	
Rheumatoid psoriasis	6	20	25	
Others	72.7	80	50	
Visual disorders related to MS (%)	48.9	43.9	46.7	0.83
Smoker (%)	32.2	31.7	40	0.83
Consumes alcohol (%)	66.3	82.3	60	0.10
Work Activity (%)	48.3	61	53.3	0.36
Walking aids (%)	36.5	29.2	33.3	0.64

Table 4: Sociodemographic data of the MS patients

Note: the values are the mean ± SD, unless otherwise indicated

Abbreviations: LBP: low back pain; EDSS: Expanded Disability Status Scale, MS: Multiple Sclerosis

Table 5: Pain evaluation in patients with current LBP performed with the Visual Analog Scale

	Score
At the evaluation	5 \pm 2.2
During the day	5 \pm 1.9
Upon waking up	5 \pm 2.8
At night	4 \pm 2.7

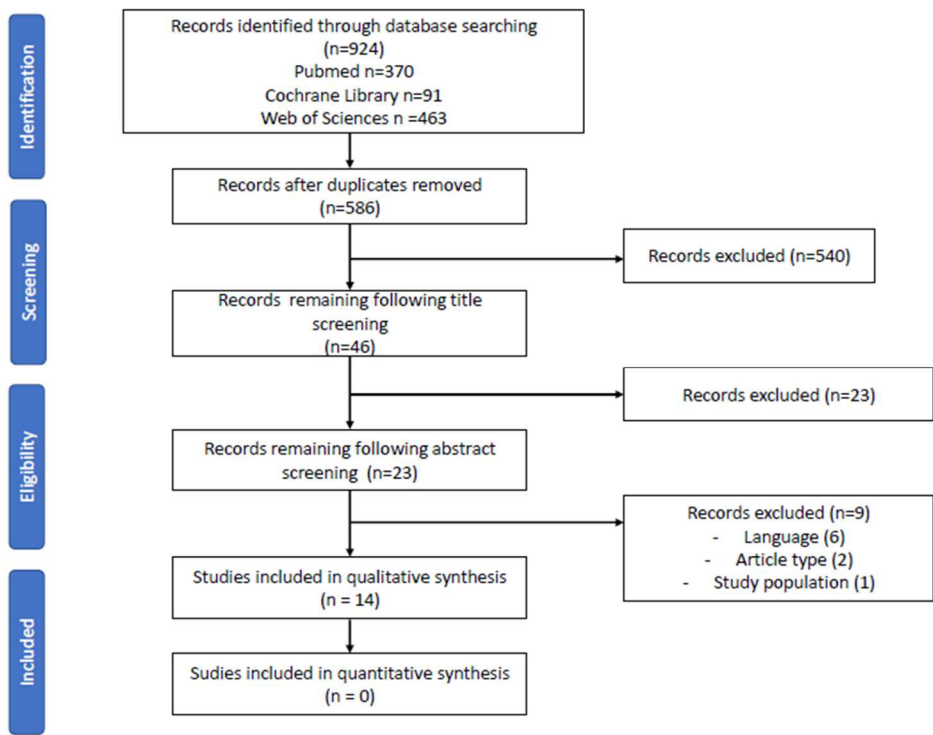


Figure 1: Flow chart

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