Clinical perspective on pain in multiple sclerosis

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CLINICAL PERSPECTIVE ON PAIN IN MULTIPLE SCLEROSIS

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Abstract

Pain is an important and frequent symptom in multiple sclerosis [MS), which leads to a low quality of life, increased disability level, lack of employment and mental health. Recently, studies have shown increased interest in pain in MS and there is a growing evidence of its prevalence. However, the literature suffers from lack of experimental studies focusing on pain reduction. This topical review summarizes the current knowledge about pain in MS with its definitions, assessments, treatments and rehabilitation within a holistic perspective.

Introduction to pain

People with Multiple Sclerosis (pwMS) report their pain as one of the most annoying symptoms of their disease.[1, 2] While being a chronic unpleasant sensory experience, pain is an underestimated component of MS[3]. It also interferes with quality of life (QoL)[4], activity of daily living (ADL), sleep[5, 6] and work ability[7] in MS. This topical review aimed to provide an up-to-date overview of widespread definitions of pain, related outcome measurements, treatments and rehabilitation in MS.

In general, pain can be classified according to its duration and based on the underlying mechanisms. In the literature, pain lasting more than 12 weeks is accepted as chronic pain.[8, 9] Based on underlying mechanisms, pain is classified as nociceptive, neuropathic, nociplastic and mixed in the literature. The International Association for the Study of Pain (IASP) defines *nociceptive pain* as "*Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.*"[10] In nociceptive pain, a noxious insult to non-neural tissue stimulates nociceptors. The stimulation is carried by lateral and medial nociceptive pathways through the spinal cord to the thalamus and mainly to the somatosensory cortex. In *neuropathic pain*, there is a direct injury to the peripheral nervous system or central nervous system. Usually, burning and electrical sensations accompany.[11] It is defined as "*Pain caused by a lesion or disease of the somatosensory nervous system.*"[10]. Neuropathic pain can be divided into two types according to the location of the lesion or disease, *peripheral neuropathic* and *central neuropathic pain.*[10] After realizing that the binary classification (nociceptive and neuropathic) of pain does not cover all circumstances[12], the IASP defined nociplastic pain as *"Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain."*[10]. Lastly, *mixed pain* is the combination of multiple types of pain (nociceptive, neuropathic, nociplastic) and is

seen in the same body area.[13] However, it is noted that none of the pain classifications of the IASP have yet been employed in MS.

Types of pain in MS based on the underlying mechanisms

The underlying mechanisms of pain in MS is still unclear. However, O'Connor et. al. (2008) and Truini et. al. (2013) proposed pain classifications in MS according to the pathophysiology. Although the binary classification remains the same with the pain literature as neuropathic and nociceptive, both of the studies classified the pain in different ways. Figure. 1 shows a comparing overview of the current pain classifications in MS, suggested by O'Connor et. al. (2008) and Truini et. al. (2013).

O'Connor (2008) and Truini et. al. (2013) agreed that the most common neuropathic pain was continuous burning sensation in the lower limbs.[6, 14] O'Connor et. al. (2008) classified this common type of pain in MS as "dysesthesia"[6], however, Truini et. al. (2013) recommended to use "ongoing extremity pain".[14] PwMS with ongoing extremity pain is more likely to have greater disability levels compared to pwMS without pain. The underlying mechanisms of dysesthesia is still unclear, but MS lesions in the spinothalamic pathway are considered to be the reason of dyesthetic extremity pain.[6, 14] O' Connor et. al (2008) described intermittent central neuropathic pain as originating from demyelination of the nerve system, such as; trigeminal neuralgia (TN) and Lhermitte's sign. Lhermitte's sign thought to be associated with the lesions at the cervical spinal cord level and TN is more likely to be associated with the lesions at the trigeminal nuclei and nerve roots.[6]

Painful tonic spasm is specific to MS and is the spontaneous muscle contractions which might occur as a result of the lesions in the motor pathway (especially in internal capsule and cerebral peduncle). It can start from face, arm or leg and diffuse to the adjacent body area.[6, 14] However, the spasms may not be always painful. O'Connor et. al. (2008) classified painful tonic spasms as musculoskeletal pain since the demyelination does not

seem to affect somatosensory pathways.[6] Spasticity pain is separately defined by Truini et. al. (2013) in order to preclude the confusion between painful tonic spasms and spasticity originated pain.[14]

While O'Connor et. al. (2008) argued that back pain sometimes can centrally originate, MS back pain is currently considered as mechanical-originated pain which can be developed secondary to the disease symptoms.[6, 14] Inactivity, muscle weakness and spasticity are thought to engender postural anomalies which result in pain.[14]

Compared to the general population, headache is found to be more common in MS. However, it is unclear whether headache was present before MS. Headache in MS is thought to have neuropathic and nociceptive mechanisms, and therefore, O'Connor et. al (2008) classified headache as mixed pain.[6] Truini et. al. (2013) classified treatment induced pains which may be developed secondary to medications (flu-like myalgias, headache, pain at the injection areas and long-term use of corticosteroid). The fourth group of pain was other pains which included mainly visceral pains.[14]

(Insert Figure.1 here)

Types of pain in MS based on duration

Pain lasting more than 12 weeks is accepted as chronic pain in MS.[15] However, some studies described chronic pain as lasting more than one month.[16]

Types of pain in MS based on intensity

In chronic pain literature, mild pain classified as 0-4, moderate pain as 5-7, severe pain as 8-10, based on numeric rating scales ranging from 0-10.[17] However, the optimal cut-off scores of the pain intensity were not explicitly stated for MS pain. In 2012, Alschuler et. al. recommended two different cut-off scores for average pain (mild: 0-2, moderate: 3-5, severe: 6-10) and for the worst pain (mild: 0-4, moderate: 5-7, severe: 8-10)

measured by Numeric Rating Scale.[17] Some pwMS report fluctuating intensity of pain depending on the time of the day (increasing pain during the day or greater intensity in the morning) or increased pain intensity by physical activity.[18]

Prevalence and characteristics of pain in MS

MS comprises a wide variety of pains and has an overall prevalence of 63% (17 studies, 5319 participants; 95% CI= 55.1-70.3%)[19] with a range from 29% to 86%.[6] This wide-range prevalence has several reasons. For instance, most of the studies described pain in different ways. Excluding certain types of pain, different sample sizes, heterogeneity of the study cohorts in terms of disease duration and progression, evaluating pain with different outcome measures, the absence or presence of control groups, investigating the time of pain and recruiting in-/outpatients were the other reasons of wide prevalence interval.[6, 19]

A meta-analysis (28 studies, 7101 participants) reported that headache was the most prevalent pain with 42.5% prevalence. Followed by headache, neuropathic extremity pain was more prevalent than musculoskeletal pain with 26.6% prevalence. Back pain prevalence was 20% and painful spasms were common with 15% prevalence. TN prevalence was reported as 3.8%.[19] Lhermitte's sign prevalence was reported as 16.6%.[19] Longitudinal follow-up studies showed increased pain prevalence resulting in increased disability level and increased severity.[16, 20, 21] When pain prevalence compared to different courses of MS, it is found that relapsing-remitting type of MS (RRMS) had the lowest pain prevalence (RRMS: 50%, 5 studies, 2089 participants; secondary progressive MS: 70%, 5 studies, 673 participants and primary progressive MS: 70%, 5 studies, 393 participants).[19]

Another discrepancy in the literature is whether pain is one of the first symptoms of MS. Although one study did not mention pain as an onset symptom of MS[3], another study reported that pain was the first symptom, with 11%-23% prevalence.[6] Osterberg et. al.

reported that central neuropathic pain was the first symptom of the 5.5% pwMS.[18] Moreover, recent studies in the literature point pain out as one of the important prodromal frequent symptoms of MS. [22, 23] Location of MS pain can be alone in one body site or it can be experienced in many locations at the same time. PwMS with pain report 6.62 different locations.[8, 24] However, except headache, it is more commonly experienced in (bilateral) lower limbs, upper limbs and back.[2, 8, 18, 25] Sensory complaints have also been reported to accompany central neuropathic pain in MS. The underlying mechanisms of central pain are still unclear. However, the similarities between central post-stroke pain and central pain in MS provides some clues regarding the mechanisms. In stroke literature, it is argued that patients with altered temperature and pain sensibility develop central pain, indicating the lesions of the spinothalamic pathway.[25] Similarly, pwMS with pain have sensory hyperexcitability and spinothalamic dysfunctions which result in altered temperature sensation and allodynia.[6, 18] The qualities of central pain experience in pwMS are described as burning, aching and pricking.[4, 25] In addition, Scherder and colleagues found that 24% of pwMS with chronic pain had decreased touch sensibility, 26% of pwMS had decreased joint position sense indicating dorsal column-medial lemniscal pathway dysfunctioning.[26] However, they excluded participants with central pain.

Impacts of pain in MS

Compared to other neurological conditions, pain has greater interference in MS. It negatively affects health related QoL,[5, 27, 28] ADL,[5, 20, 29] mental health, social functioning, employment, sleep and life enjoyment.[6, 8] Pain is highly associated with fatigue, depression and anxiety. [23, 30, 31] In case the pain is neuropathic the degree of interference increases, especially in terms of depression.[26, 32] However, Day et. al. suggests that the association between pain and depression is exaggerated throughout the past studies,

because when the severity of MS symptoms reduced, the association between pain and depression become controlled.[33]

Possible risk factors for developing pain in MS

Several clinical and demographic risk factors of pain in MS have been reported. Having older age,[34-36] longer disease duration[37, 38] and greater severity of MS[8, 28, 35, 36, 38] were reported to be possible risk factors. Solaro et. al. claims that neuropathic pain is strongly associated with the disease severity[36] and people with musculoskeletal pain seems to have lower Expanded Disability Status Scale [39] scores.[32] In contrast, other studies reported no relationships between having older age[8, 27, 28, 40] and longer disease duration.[8, 18, 27, 41] Gender is a conflicting risk factor since some studies found no difference between females and males[8, 24, 28, 38, 41] while other studies found a difference.[3, 15, 27, 35, 36] However, females are more likely to report their pain[15] and to have more severe and neuropathic pain.[27, 29, 36] PwMS with mental health problems tend to report pain much more than the pwMS without mental health problems.[6, 8, 27, 28] Lower education level was mentioned as a risk factor of MS pain,[6, 33] however, this was not confirmed in another recent study.[32] In addition, an association betweeen lower socioeconomic and marital status and pain intensity is found.[33] In future, taking the type of pain (neuropathic or nociceptive) into account when reporting risk factors may be more indicative.

Outcome measures evaluating pain in MS

In MS literature, pain outcome measures are used to determine its intensity, to identify its type and to understand its impacts on the aspects of everyday life. Beyond several outcome measures, surveys are widely used, as well.[14, 19] However, this methodological discrepancy is one of the most important reasons of wide-range prevalence rates. Because of the subjective nature and individual aspects of pain, to precisely measure pain is difficult. Therefore, the self-reported pain measures have a prominent role.[42] Recently,

Burkill et. al. used prescription register data of pwMS, as an interesting approach, to objectively detect the pain profile in MS.[39] Yet, not only in MS, but also in all neurological conditions, there has not been a widely accepted assessment method for pain.[43]

To evaluate the severity of the pain, self-reported outcome measures such as; the Visual Analogue Scale [VAS] or Numeric Rating Scales are commonly used.[20] The severity is measured on a single-item scale, where "0" represents no pain, "10" or "100" represents great pain.[43] In today's world, the extensive usage of technology has leaded the research domain to deliver VAS electronically as smartphone or tablet application and electronic visual analogue scale (eVAS) are found to be reliable and useful for MS population.[44]

To determine the type of pain, the PainDETECT (a nine-item self-reported questionnaire), the Nordic Musculoskeletal Questionnaire (evaluates the frequency of musculoskeletal pain in different body areas with two sections), the Douleur Neuropathique en 4 questions (DN4, self-administered and clinician-administered versions exist) were used in the literature.[27, 32, 36, 38, 45] The PainDETECT and the DN4 are widely used screening tools. The DN4 has both self-reported evaluation and physical examination part. Therefore, it is more sensitive compared to generic screening tools.

To evaluate the features pain, the McGill Pain Questionnaire (short form and expanded and revised short form exist), the Neuropathic Pain Symptom Inventory (12 items, 10 description of different neuropathic pain symptoms and 2 items for assessing temporal aspects of pain) and the Neuropathic Pain Scale (with 9 items evaluating the intensity and description of pain)[46] are used. The McGill Pain Questionnaire evaluates various aspects (such as sensory, effects of pain) of pain as well as its intensity. The Short-Form McGill Pain Questionnaire consists of 2 subscales (sensory and affective) and rating scale for the intensity of pain.[47] The Neuropathic Pain Scale is validated for MS population,[43, 48] which is a strength compared to other measures.

The impact of pain is analyzed by the Pain Interference Scale of the Brief Pain Inventory (7-item, 10-item and 12-item versions exist evaluating the interference of pain),[8, 17] the Graded Chronic Pain Disability Score,[20] the two-item Bodily Pain Scale from SF-36 (The SF-36 BPS)[8, 27] and the Medical Outcomes Study Pain Effects Scale (PES- it is the part of the MS Quality of Life Inventory). The Graded Chronic Pain Disability Score is a 7-item scale which evaluates pain intensity and pain-related disability. The SF-36 BPS is a part of The SF-36 and evaluates the intensity and interference of the pain.[47] The Pain Interference Scale of the Brief Pain Inventory, The Graded Chronic Pain Disability Score[43, 49] and The PES are validated for MS.[50] The Pain Interference Scale of the Brief Pain Inventory includes several components, and seems sufficiently comprehensive to evaluate the interference of pain in MS. Algometer (evaluating thermal and pressure pain thresholds) usage in studies is scarce.[29, 51, 52] Several studies assessed co-existing sensory complaints of MS pain by Quantitative Sensory Testing (evaluating perception of vibration, touch, warm, cold and heat pain).[18, 25] In order to discriminate neuropathic pain and nociceptive pain, neurophysiological tests are recommended to use, such as; somatosensory evoked potentials and laser evoked potentials. However, they are not widely used in literature to characterize the MS pain.[53]

In order to identify the neuropathic pain, the IASP Special Interest Group on Neuropathic Pain recommends a grading system. According to this grading system, evaluating neuropathic pain by screening tools is highly recommended, but these tools may fail to identify neuropathic pain precisely. Therefore, clinical examination is also mandatory.[54]

Pharmacological treatments for pain in MS

The efficacy of the drugs on pain relief is limited and further experimental studies are needed in order to evaluate the effects of drugs.[15, 53]

In general, analgesics (anti-inflammatories and opioids), anti-epileptics, anti-depressants, cannabinoids, muscle relaxants (i.e. baclofen, diapezem, tizanidine, dantrolenc)[27] and

spasmolytic medications are prescribed for pain relief.[4, 15, 26] *Antidepressants* are sometimes preferred because of the neuromodulation capacity of these drugs in neuropathic pain. However, the efficacy of antidepressants is unclear.[55] Besides uncertain effectiveness, some side-effects are reported such as; gaining weight, cardiovascular effects, constipation, urinary retention, sexual dysfunction, orthostatic hypotension.[6, 15, 55] *Anti-epileptics* (lamotrigine, carbamazepine, gabapentin, pregabalin, levetiracetam) are mostly prescribed for trigeminal neuralgia, but because of the small sample sizes of the studies, the effectiveness of anti-epileptics in trigeminal neuralgia is inconclusive. For central pain in MS, antiepileptics are reported to have side-effects.[15, 53, 55, 56] *Cannabinoids* are reported to reduce neuropathic pain in MS,[53] with high-frequency side-effects.[6, 15] While it is found to be effective also for spasticity pain in MS, the severity of side-effects should be taken into account.[53, 56] *Analgesics* (anti-inflammatories and opioids) are the most commonly used drugs for low back pain in MS[28]. High dosage *morphine* reduced the neuropathic pain in a minority of patients , therefore, it is excluded being a routine treatment.[55] *Muscle relaxant drugs* and intrathecal continuous baclofen infusion have unconfirmed and limited effectiveness on MS pain reduction.[53, 55]

Despite the wide variety of side effects of the above mentioned medications, pwMS with pain tend to use daily medications and this usage increases over time.[21] Since the relief is not provided by drugs, pwMS seek alternative treatments.[21] In clinical practice, pwMS are prescribed by a combination of drugs. However, there is limited number of studies, with small sample sizes, investigating the effectiveness of combined drug therapy.[57] Therefore, not only medications but also non-pharmacological interventions should be considered combined with drugs in order to have optimal pain relief in MS.[53]

Rehabilitation interventions for pain in MS

Rehabilitation interventions have a noteworthy contribution to pain management. Table. 1 provides an overview of the different kinds of rehabilitation interventions targeting MS pain.

A meta-analysis (10 RCTs, 389 participants) of exercise interventions for pain reduction suggested that exercise interventions have small to moderate beneficial effect on pain reduction in MS.[58] Because of the high heterogeneity between the included studies (I^2= 77%), the results were inconclusive (Table 1). Different studies investigated the effects of reflexology[59, 60] and hydrotherapy[61] on pain reduction. They found significant beneficial effects on pain reduction. However, it is difficult to be conclusive about the effectiveness of these interventions. Therefore, further studies are needed analyzing the effects of reflexology and hydrotherapy on pain reduction.

Its clinical utility and having no side-effects may make Transcutaneous electrical nerve stimulation (TENS) one of the first-line rehabilitation interventions. However, the efficacy of TENS on chronic pain[62] or specifically on neuropathic pain is still unclear.[63] A systematic review (4 studies, 179 participants) investigated the effects of TENS on central pain in MS and found that TENS is safe and beneficial for central pain in MS.[64] The results of the review suggested that the frequency of the TENS did not show any difference on pain reduction.[64] (Table 1). Non-invasive brain stimulation techniques (repetitive transcranial magnetic stimulation-rTMS or transcranial direct current stimulation-tDCS) are shown to have analgesic effects on pain, however, transcranial random noise stimulation-tRNS, a new form of brain stimulation techniques, had no significant effect on pain modulation.[65-67] (Table 1).

Psychological treatments have a prominent role on pain in MS. A Cochrane review suggested that psychotherapy (3 RCTs of different psychotherapy approaches, 247 participants) had beneficial effects on pain reduction in MS, with very low level of

evidence.[68] Recently, neurofeedback and mindfulness enhanced hypnosis[69] and mindfulness-based stress reduction[70] were used to improve pain in MS and while neurofeedback and mindfulness enhanced hypnosis[69] had beneficial effects on pain, there was no significant effect of mindfulness-based stress reduction on pain in MS.[70]

(Insert Table 1. here)

Biopsychosocial aspect of pain in MS

Not only biomedical factors induce pain and result in greater severity and interference, but also the way of thinking about pain, feelings after pain and behaviors have immense effects. Therefore, considering pain within a biomedical perspective would provide limited perspective.[71] It is argued that in case pwMS experience pain, they develop coping strategies, pain emotions and beliefs, such as; pain catastrophizing[71], fear-avoidance, avoidance-endurance and pain acceptance.[72] Harrison et. al (2015) suggested that some factors have the potential for being helpful or unhelpful for pain experience of pwMS. For instance, catastrophic thoughts about experienced pain may increase pain severity and its interference. On the other hand, pain acceptance behavior might protect pwMS from greater interference on everyday life. All these interacted factors might result in increased anxiety, worry and depression. A worried pwMS with pain might avoid exercising or even participating to an ordinary social event with the fear of re-experiencing pain.[72, 73] It is argued that depression is a predictive factor of pain in MS and anxiety, fatigue and alexithymia is associated with depression.[30, 74]These comorbid symptoms of MS might restrict the efficacy of interventions since mental health is negatively affected.[30] As a result, considering pain in a biopsychosocial perspective is crucial for a successful pain management.

Conclusion

Different types of pain are present in MS with varying prevalence. Except headache dysesthesia is also thought to be the most prevalent pain in MS. The literature emphasizes the principal role of pain in low quality of life, increased disability level, sleep disturbances and employment capacity in the MS population. In order to reduce pain and support pwMS with pain, foremost, pain should be measured effectively. However, very few of the pain outcome measures are validated for MS population. Evaluating pain with various outcome measures result in inconsistent pain prevalence in MS. In addition, although pwMS use mostly drug combinations, pain relief is limited. There are various treatment and rehabilitation interventions with inconclusive results. Therefore, more controlled trials which evaluates the efficacy of the interventions and compare various treatment approaches should be conducted to improve pain with more conclusive results. While aiming to reduce the pain, researchers and clinicians should be aware of the biopsychosocial aspects of the pain and the planned approaches should consider the interaction between psychology, social environment and medical situation.

Conflict of interest

The authors have no conflict of interest.

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