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Comprehensive review

Prevalence and natural history of pain in adults with multiple sclerosis: Systematic review and meta-analysis

Peter L. Foley [a,b,*], Hanna M. Vesterinen [a], Barry J. Laird [b,c], Emily S. Sena [a,d], Lesley A. Colvin [e], Siddharthan Chandran [a], Malcolm R. MacLeod [a], Marie T. Fallon [b]

[a] Division of Clinical Neurosciences, University of Edinburgh, Edinburgh, UK
[b] Department of Palliative Medicine, Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, UK
[c] European Palliative Care Research Centre (PRC), Norwegian University of Science and Technology, Trondheim, Norway
[d] The Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, University of Melbourne, Heidelberg, Australia
[e] Department of Anaesthesia and Pain Medicine, University of Edinburgh, Edinburgh, UK

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ABSTRACT

The prevalence, associations, and natural history of pain in multiple sclerosis (MS) are poorly understood. The objective of this work was to study the prevalence of pain syndromes in MS both cross-sectionally, and longitudinally during the MS disease course. We systematically identified prospective studies detailing pain prevalence in definite MS. We used pooled prevalence estimates, explored heterogeneity using meta-regression, and analysed prevalence during the disease course using both estimates at disease milestones and longitudinal studies. Twenty-eight articles (7101 subjects) describing overall pain, or pain syndromes, met inclusion criteria. Pooled overall pain prevalence (17 studies, 5319 subjects) was 63% (95% confidence interval [CI] 55–70%). Marked heterogeneity in this estimate was not significantly explained by selected study design variables (use of outpatient sample, timeframe prior to study over which pain was assessed) or sample demographic variables (mean Expanded Disability Status Scale, mean disease duration, proportion of female sex, and proportion with progressive MS). We quantified prevalence of headache (43%; 95% CI 33–52%), neuropathic extremity pain (26%; 95% CI 7–53%), back pain (20%; 95% CI 13–28%), painful spasms (15%; 95% CI 8.5–23%), Lhermitte sign (16%; 95% CI 10–25%), and trigeminal neuralgia (3.8%; 95% CI 2–6%) in included studies. Prevalence of pain at MS disease milestones (prior to onset, at onset, and at relapse) and during longitudinal follow-up was poorly described. Pain is common in MS, as are specific pain syndromes. The clinical associations and natural history of pain in MS require clarification. Future study could be enhanced by standardised study design.

1. Introduction

Pain is a key symptom in multiple sclerosis (MS). It has been rated by people with MS as one of their most important symptoms [17] and is often severe [20]. In addition, pain has frequently been linked to adverse disease outcomes including impaired quality of life [42] and disability [1], and is therefore potentially a highly important therapeutic target in MS [44].

Despite its clinical importance, however, many features of pain associated with MS remain poorly understood. Overall pain prevalence is unclear, with estimates ranging widely from 29% to 86% [6,41]. Studies examining relationships of pain prevalence to clinical variables use differing patient samples and study design, and report inconsistent conclusions. There is, therefore, limited understanding of which MS patient groups suffer most frequently from pain, or of the influence of study methodology on pain estimates. Lastly, the natural history of pain during the disease course is uncertain. One previous systematic review carried out in 2007 [31] usefully explored some of these issues. The authors did not, however, examine the literature published in languages other than English, and did not use weighted meta-analysis to calculate prevalence estimates. Therefore, confidence intervals for estimates are not available, and between-estimate heterogeneity has not been quantified nor formally explored.

Better understanding of the prevalence, and natural history, of MS-related pain could help to estimate the true extent of this problem, as well as to identify patient groups in which pain is most prevalent. Furthermore, better understanding of the epidemiology of pain in MS could improve understanding of symptom mechanisms,

* Corresponding author. Address: Bramwell Dott Building, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. Tel.: +44 131 537 2922; fax: +44 131 332 5150.
E-mail address: peterfoley@nhs.net (P.L. Foley).

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and potentially contribute to development of targeted treatment strategies. We therefore carried out a systematic review and meta-analysis of the prevalence, and natural history, of pain in MS. We firstly aimed to identify, assess, and synthesise cross-sectional studies of the prevalence of pain, and secondly to study longitudinal relationships of pain prevalence or incidence to disease course.

2. Methods

2.1. Literature search and selection criteria

We used a strategy based upon recent systematic reviews [19,25,28,29,50] (Appendix A, supplementary material) to search Medline (from 1977), EMBASE (from 1974), and the Cochrane Library (November 11, 2011). We used Cited Reference Search (Web of Science) to identify articles referencing identified publications (January 3, 2012). Searches were limited to only studies of humans. We hand-searched reference lists and contacted authors to identify unpublished data.

To achieve the most reliable ascertainment, we included only prospective studies characterising clearly defined pain in adults with definite MS. We considered the diagnosis of MS as definite where use of recognised contemporaneous criteria, including McDonald [27], revised McDonald [34], or Poser [35] was described, or, if diagnostic criteria were not specified, where the diagnosis was explicitly confirmed by a neurologist [1,9,33,46]. We excluded studies investigating pain attributed solely to a treatment or intervention, those where subjects were selected for symptoms including pain, those reporting insufficient data to calculate pain incidence or prevalence, studies of childhood-onset MS (because of possible epidemiological differences from MS with adult onset [37]), and re-published data (Appendix A). Where interventional trials described the presence of pain, we assessed baseline data only. We reviewed titles and abstracts of identified studies. Potentially relevant articles were then reviewed in full by two authors (P.F., B.L.) using a standardised data extraction form. Disagreements were resolved by consensus. Studies published in languages other than English were reviewed by fluent medically qualified volunteers.

2.2. Data extraction and analysis

We extracted methodological data including; pain types studied and excluded, assessment instruments used, and timeframe over which pain was assessed in relation to the study (termed here "pain timeframe"). We recorded demographic properties of the sample, the prevalence of pain overall, and, where available, prevalence of pain syndromes, including prevalence of "neuropathic" or "somatic" pain syndromes (after O'Connor and colleagues) [31] as reported by investigators. We selected pain syndromes according to availability of data, and clinical relevance. Headache subtypes could not be analysed because of overlapping groups [7].

We carried out quality assessment according to 4 criteria. We noted investigator blinding of any type (for instance clinical assessment blinded to pain status); use of, or reference to, externally available validated instruments (relevant to prevalence estimation); presence of control groups; and description of longitudinal follow-up (relevant to comparison with wider populations, and to longitudinal characterisation, respectively).

Ninety-five percent confidence intervals of proportions were calculated by the Clopper-Pearson method [30]. Pooled proportions were calculated by DerSimonian and Laird random-effects meta-analysis [8]. Where study numbers allowed, we stratified pooled proportions by pain timeframe into studies examining pain within 1 month prior to assessment, and studies examining pain over longer periods. We chose the threshold of 1 month to balance study numbers in each stratum. We used the I^2 statistic to estimate heterogeneity. We visually inspected funnel plots, and used Egger and Begg-Mazumdar tests to estimate risk of bias.

We used meta-regression – in the absence of individual patient data – to explore study and demographic variables that might influence estimate heterogeneity. Seventeen estimates of overall pain [1–3,5,9,11,13,14,18,20,21,32,39,41,43,47,51] and 17 estimates of overall headache [1,2,7,10,14,18,20–22,33,36,38,43,45,48,49] were analysed. Study numbers were insufficient to allow meta-regression for other pain syndromes. We selected specific methodological characteristics of studies (investigator blinding, outpatient population studied, and pain timeframe used); as well as demographic characteristics of the sample (mean Expanded Disability Status Scale [EDSS], proportion female, proportion progressive MS, and mean disease duration) as independent variables based on availability of data, and on previously reported associations [31]. We did not distinguish between primary progressive and secondary progressive MS [26] in the primary analysis given low numbers of studies using this classification. Given limited study numbers, we used univariate analyses with significance threshold of $P < 0.05$, and Bonferroni correction for multiple comparisons. We also studied relationships between pain prevalence or incidence and the MS disease course using estimates at disease milestones (prior to disease onset, at disease onset, and at relapse) and longitudinal cohort studies of overall pain. We used StatsDirect v2.7.8b (StatsDirect Ltd, Cheshire, UK), and Stata v10 (StataCorp LP, College Station, TX USA).

3. Results

From 3674 abstracts we identified 28 studies, including 7101 subjects, which met inclusion criteria (Fig. 1).

3.1. Characteristics and quality assessment of included studies

Seventeen studies (5319 subjects) described overall pain and 11 (1782 subjects) described specific pain subtypes. The majority of these assessed headache (10 studies, 1581 subjects, one of which [10] included 2 patient samples). Study methodology and quality assessment are summarised in Table 1. In each sample, between 55% [41] and 96% [22] of subjects were female, between 30% [32] and 100% [10] had relapsing remitting MS, mean age was between 30.8 [10] and 54 [32] years, mean EDSS score was between 1.1 [10] and 5.3 [13], and mean disease duration was between 2.5 [5] and 23 [32] years (Appendix A). On quality assessment using our 4 prespecified criteria, only 8 studies described any control population (6 contemporaneous [13,22,36,38,43,45], 2 historical [20,23]), 4 described any blinding procedure [23,38,45,49], and 5 described follow-up [5,22,33,38,41]. Seventeen used at least one externally available validated instrument, of which 9 [10,22,33,36,45,48,49] were headache studies referring to International Headache Society Criteria [15,16]. Of overall pain studies, 2 studies [41,51] met one criterion, 4 [5,13,20,43] met 2, and none met more than 2. Of pain subtype studies, 5 studies [7,10,46,48] met one criterion, 3 [33,36,49] met 2, 3 [22,23,45] met 3, and one [38] met all 4.

3.2. Prevalence of pain overall, and of specific pain syndromes

Pooled overall pain prevalence from 17 estimates [1–3,5,9,11,13,14,18,20,21,32,39,41,43,47,51] was 62.8% (95% confidence interval [CI] 55.1–70.3%). Pain prevalence stratified by study pain timeframe (for studies examining pain within the last month prior to assessment, and studies examining pain over longer periods) was 61.8% (95% CI 51.6–71.5%) and 64.7% (95% CI 51.7–76.7%), respectively (Fig. 2).