

Migraine headaches and pain with neuropathic characteristics: Comorbid conditions in patients with multiple sclerosis



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ABSTRACT

We conducted a postal survey to assess the prevalence and characteristics of neuropathic pain and migraine in a cohort of multiple sclerosis (MS) patients. Of the 1300 questionnaires sent, 673 could be used for statistical analysis. Among the respondents, the overall pain prevalence in the previous month was 79%, with 51% experiencing pain with neuropathic characteristics (NCs) and 46% migraine. MS patients with both migraine and NC pain (32% of the respondents) reported more severe pain and had lower health-related quality of life than MS patients with either migraine or NC pain. Pain intensity in MS patients with migraine was moderate (6.0 ± 0.1). Migraine was mostly episodic, but headaches were occurring on ≥ 15 days per month in 15% of those with migraine. MS patients with migraine were younger and had shorter disease durations than those with NC pain. NC pain was most often located in the extremities, back and head, and was frequently described as tingling and pins-and-needles. The intensity of NC pain was low to moderate (4.9 ± 0.1), but positively correlated with the number of painful body sites. Nonetheless, patients with NC pain were more disabled (with a higher Expanded Disability Status Scale and pain interference index) than patients with migraine. Migraine, but not NC pain, was associated with age, disease duration, relapsing–remitting course, and interferon-beta treatment. This suggests that NC pain and migraine are mediated by different mechanisms. Therefore, pain mechanisms that specifically operate in MS patients need to be characterized to design optimal treatments for these individuals.

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1. Introduction

Multiple sclerosis (MS) is the most frequent chronic disease generating neurological disability in young adults. Among the many symptoms and types of disabilities associated with MS, chronic pain seems to be frequent, with an estimated prevalence of pain at any point during the course of the patients' MS, which ranges from 40% to 92%, depending of the selection method of patients and the type of data collection [20,35,36,43]. A recent meta-analysis calculated an overall pain prevalence of 63% [15].

Pain associated with MS can be classified into 3 main categories: neuropathic pain (that can be constant or intermittent), musculoskeletal pain (ie, painful tonic spasms, pain secondary to

spasticity, pain related to being wheelchair bound), and headaches [35]. The prevalence and importance of these 3 categories of pain vary from 1 study to another. Among specific pain syndromes in MS patients, pain with neuropathic characteristics (NCs) and headaches are the most prevalent according to the literature [15]. Nonetheless, the co-occurrence of these 2 entities has never been studied properly in a single study. The prevalence of headache in general and of migraine in particular is higher among MS patients compared with the general population, with several authors reporting $\sim 50\%$ of MS patients experiencing headaches [11,15,34,38]. The estimated prevalence of strict migraine in MS patients is between 21% and 35%, which is 2.6 times higher than in the general population [35,37]. Concerning central neuropathic pain, its prevalence among MS patients has been estimated to be $\sim 30\%$, including neuropathic extremity pain (7.1%–52.8%), Lhermitte's sign (9.7%–25.0%), and trigeminal neuralgia (2.0%–6.0%) [15]. Thus, the prevalence of pain with NCs is again higher (5 times

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higher) in MS patients than in the general population [6]. Different pain symptoms/syndromes [26,32] can be present in >1 body area in individual MS patients [1,36,39,46]. However, how these different pain symptoms/syndromes are related, how they evolve during the course of disease, and what the impact of their association is on MS patients is not known.

Limited information is available regarding the epidemiology and characteristics of pain in MS patients in France [7]. The purpose of this study was to characterize, by using a postal survey, the prevalence and clinical characteristics of pain, with a particular focus on headache and pain with NCs, in a large French group of well-defined MS patients. The main hypothesis was that migraine and pain with NC were not independent. The final goal was to assess the relationship between these 2 types of pain and their impact on the quality of life and examine the factors associated with their presence and severity in MS patients.

2. Methods

2.1. Subjects

The survey was conducted among the members of the MS patients' network in Auvergne, Auvergne being an administrative area in the center of France. The association was created in 2003, and the database was set up in 2004. Patients can join this association only if their MS diagnosis has been made by a neurologist (no patient's relative or self-report of the diagnosis). When the survey was done (February 2011), patients with a clinically isolated syndrome were not able to join the association. The patients' association database includes demographic characteristics, date of diagnosis, and date of the first symptoms (MS onset). It is reviewed annually to check whether patients are still alive and their postal address and phone numbers are still correct. The European Database for Multiple Sclerosis was created in 1990 and has been used in Auvergne since 2003. This database is completed by clinicians only and is used for the clinical follow-up of patients. It is used to collect Expanded Disability Status Scale (EDSS) data concerning disease-modifying therapy and disease course. The data are reviewed for each patient during each follow-up consultation. We have taken for the analysis in this study the most recent available data for each patient. The 2 databases are independent, and both are approved by the National Commission of Data Processing and Civil Liberties, in accordance with French law. The current study was approved by the local ethics committee.

2.2. Survey questionnaire

A questionnaire was sent to all 1300 members of the association in February 2011. A cover letter inviting patients to participate in the study accompanied each questionnaire.

To ensure a maximal response rate, the questionnaire was deliberately simple and designed to be completed in <10 minutes. The first question was "Are you suffering or have you suffered during the last month from pain or headache?" The remainder of the questionnaire only applied to participants who responded positively to this question. Each questionnaire was sent with a postage-paid return envelope, and it was clearly stated that those answering "no" to the first question should return the questionnaire, without completing the following pages. There was only 1 postal survey sent to each patient (no reminders).

The first part of the questionnaire was about the identification of migraine and repeated the second edition of the International Classification of Headache Disorders (ICHD-2), diagnostic criteria for strict migraine (category 1.1 for migraine without aura) [47]. This questionnaire is similar to the self-administered questionnaire already used in previous French surveys that had been validated

against face-to-face interviews performed by senior neurologists for the diagnosis of strict and probable migraine (formerly "migrainous disorders") [29]. Probable migraine (category 1.6.1 for probable migraine without aura) was identified as migraine attacks fulfilling all but 1 of the 4 diagnostic criteria for migraine without aura. In the 2006 revision of the ICHD-2 (ICHD-2R), new criteria were proposed in the appendix [21]. Chronic migraine (A1.5.1) is characterized by the presence of ≥ 15 days of headache per month for at least 3 months, with headache having the same clinical features of migraine without aura for at least 8 of those 15 days in the absence of medication overuse [41]. In the present study, those with migraine (1.1) who experienced headache ≥ 15 days per month were considered to have chronic migraine.

The subjects answered the 2 questions (including seven items) from the DN4 interview questionnaire regarding the characteristics of their pain [5]. A score of 1 was given to each positive item and a score of 0 to each negative item. The total score was calculated as the sum of the 7 items. Respondents with a total score at ≥ 3 were considered to have neuropathic pain characteristics [5]. Initially, the DN4 interview questionnaire was validated as a clinician-administered questionnaire. A complementary validation was made, and the results of the self-reported and clinician-administered questions for each of the 7 items showed excellent consistency (κ coefficients with a 95% confidence interval [CI] of 0.82–0.95; $P < .001$). The self-administered DN4 questionnaire had a sensitivity of 81.6% and a specificity of 85.7% for an optimal cutoff score of 3 out of 7, being similar to those observed in the initial study using a clinician-administered version of the questionnaire [6]. Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs and the 7-item DN-4 are the most commonly used questionnaires for diagnosis of neuropathic pain. They have similar sensitivity and specificity and are both validated for self-administration. We chose the DN-4 because it is validated in French and because we use it in our daily practice. Moreover, a large study was conducted in France using the same questionnaire, allowing comparison [6]. We have used the results of the study by Bouhassira et al. [6] assessing the prevalence of pain with NCs in the general population as historical controls. We have compared, among patients with NCs, the use of the 7 pain descriptors using a χ^2 test (comparison of a theoretical and an observed proportion, bilateral formulation). We consider as significant for this test P values $< .001$.

To assess the severity of pain and the impact on daily functions, the short form of the Brief Pain Inventory was used [8]. The results of the 4 pain intensity scores were pooled together in the Pain Severity Index (PSI) and the seven items concerning interference of pain were pooled together in the Pain Interference Index (PII). The Sullivan Pain Catastrophizing Scale score was also used [44].

2.3. Statistical analysis

Statistical analysis was performed using Pearson χ^2 test (or Fisher exact test if needed) testing for relationships between qualitative variables, whereas the Pearson correlation coefficient was used to assess relationships between quantitative variables. Comparing binary characteristics regarding quantitative variables, we performed a Student t test or, if needed, a Welch test (taking into account heterogeneity of variances). Regarding some binary variables of particular interest as the presence/absence of pain or NC, simple logistic models were performed using these variables as response variables and allowing the estimation of the odds ratio (OR) and their 95% CI toward binary characteristics (including dichotomized originally continuous variables). For the 95% CI, the normal distribution was assumed as sample sizes were considered large enough (Np and $N(1-p) \gg 5$) [14]. Furthermore, multiple logistic regressions were performed to adjust simultaneously for several explanatory variables (age, sex, age at MS onset, time from MS on-

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