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► To cite this version:

Xavier Moisset, Lemlih Ouchchane, Nathalie Guy, Dimitri J. Bayle, Radhouane Dallel, et al.. Migraine headaches and pain with neuropathic characteristics: comorbid conditions in patients with multiple sclerosis.: Migraine and neuropathic pain in multiple sclerosis. *Pain*, 2013, 154 (12), pp.2691-9. 10.1016/j.pain.2013.07.050 . inserm-00854608

HAL Id: inserm-00854608

<https://inserm.hal.science/inserm-00854608>

Submitted on 27 Aug 2013

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MIGRAINE HEADACHES AND PAIN WITH NEUROPATHIC CHARACTERISTICS: COMORBID CONDITIONS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Text pages: 32, **Tables:** 6, **figure:** 2

Abstract: 244 words, **Introduction:** 439 words, **Discussion:** 1551 words (+ references),

References: 54

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Running title: Migraine and neuropathic pain in multiple sclerosis

Key words: pain, multiple sclerosis, migraine, headache, neuropathic pain

INTRODUCTION

Multiple sclerosis (MS) is the most frequent chronic disease generating neurologic 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 three main categories: neuropathic pain (that can be constant or intermittent), musculoskeletal pain (i.e., painful tonic spasms, pain secondary to spasticity, pain related to being wheelchair-bound), and headaches [35]. The prevalence and importance of these three categories of pain vary from one study to another. Among specific pain syndromes in MS patients, pain with neuropathic characteristics (NC) and headaches are the most prevalent according to the literature [15]. Nonetheless, the co-occurrence of these two 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 around 50% of MS patients suffering headache [11,15,34,38]. Estimated prevalence of strict migraine in MS patients is between 21 and 35%, that 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 around 30%, including neuropathic extremity pain (7.1% to 52.8%), Lhermitte's sign (9.7% to 25.0%) and trigeminal neuralgia (2.0% to 6.0%) [15]. Thus, the prevalence of pain with NC is again higher (five times higher) in MS patients than in the general population [6]. Different pain symptoms/syndromes [26,32] can be present in more than one 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 is the impact of their association in 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 neuropathic characteristics (NC), in a large French group of well-defined MS patients. The main hypothesis was that migraine headaches and pain with NC were not independent. The final goal was to assess the relations between these two types of pain, their impact on the quality of life and examined the factors associated with their presence and severity in MS patients.

METHODS

Subjects

The survey was conducted among the members of the “MS patients’ network in Auvergne”, Auvergne being an administrative area in the centre of France. The association was created in 2003 and the database 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 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 if patients are still alive and if their postal address and phone numbers are still correct. EDMUS (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 was used to collect data concerning EDSS, 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 two databases are independent and both are approved by the National Commission of Data Processing and Civil Liberties (CNIL), in accordance with French law. The current study was approved by the local ethics committee.

Survey questionnaire

A questionnaire was sent to all the 1,300 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 it was designed to be completed in less than 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 one 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 have been proposed in the appendix [21]. Chronic migraine (A1.5.1) is characterized by the presence of 15 or more 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, migraineurs (1.1) suffering from headache 15 or more days per month were considered to have chronic migraine.

The subjects answered the two 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 seven items. Respondents with a total score at 3 or more 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 seven items

showed excellent consistency (kappa coefficients with 95% CI of 0.82-0.95; $p < 0.001$). The self-administered DN4 questionnaire had a sensitivity of 81.6% and a specificity of 85.7% for an optimal cut-off score of 3 out of 7, being similar to those observed in the initial study using a clinician-administered version of the questionnaire [6]. “S-LANSS” and “7 items 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 have chosen 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., (2008) assessing the prevalence of pain with neuropathic characteristics in the general population, as historical controls [6]. We have compared, among patients with NC, the use of the 7 pain descriptors using a χ^2 test (comparison between a theoretical and an observed proportion, bilateral formulation). We consider as significant for this test p -values < 0.001 .

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 four 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].

Statistical analysis

Statistical analysis was performed using Pearson chi-square test (or Fisher exact test if needed) testing for relationships between qualitative variables while the Pearson correlation coefficient test was used to assess relationships between quantitative variables. Comparing binary characteristics regarding quantitative variables, we performed Student t -tests or, if needed, Welch’s tests (taking into account heterogeneity of variances). Regarding some binary

variables of particular interest as presence/absence of pain or NC, simple logistic models were performed using these variables as response variables and allowing the estimation of odds ratio (OR) and their 95% confidence interval (95%CI) towards 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]. Further, multiple logistic regressions were performed to adjust simultaneously for several explanatory variables (age, sex, age at MS onset, time from MS onset and EDSS). As proposed by some statisticians, we have chosen to report all the individual p-values and confidence intervals, without doing any mathematical correction for distinct tests comparing two modalities [40]. For comparisons concerning three modalities (Tables 5 and Figure 2), we have performed first a one way analysis of variance (ANOVA I) and, if ANOVA I was significant, we added a multiple comparisons procedure (Tukey honestly significant difference test) to detail differences between more than two modalities while keeping the family-wise type I error set at 5%. All statistical analyses were performed on SAS® (v9.3, SAS institute inc., Cary; NC, USA) with a type I error set at 5%.

RESULTS

Of the 1,300 questionnaires sent, 681 (52.4%; 95%CI: 49.7 – 55.1) were returned and 673 (i.e. 98.8% of those returned) could be assessed. Demographic characteristics were not different between respondents and non-respondents. A total of 529 subjects reported pain (Figure 1), which leads to a prevalence of 78.6% (95%CI: 75.5 – 81.7). Sex ratio, time from onset and mean EDSS were not significantly different between patients with or without pain. Patients with pain were significantly younger than patients without pain. Of these 529 patients with pain, 361 reported headache that is 53.6% (95% CI: 49.9 – 57.4) of the respondents. Four hundred and eighty-nine subjects reported extra-cephalic pain (i.e. pain other than headache); among whom 346 reported pain with neuropathic characteristics (51.4% of the respondents; 95%CI: 47.6 – 55.2). As patients with primary progressive or secondary progressive MS did not behave differently in terms of prevalence of pain, headaches, migraine and pain with NC, we present the whole results as relapsing-remitting MS (RR-MS) or not.

Pain with neuropathic characteristics

In this survey, we found that pain with neuropathic characteristics (NC) was not explained by sex, age or the time from disease onset (table 1). The mean pain intensity, as measured by the VAS score was 4.9 ± 0.1 , and 36.8% of the respondents had NC pain of moderate to severe intensity ($\geq 4/10$). Patients with NC reported pain that was more intense. Two out of the seven pain descriptors were particularly used by MS patients with NC: “pins and needles” and “tingling”. The number of pain locations was higher for patients presenting with NC. Among these patients with NC, 58% presented with three or more painful sites and 61% presented pain in both upper and lower limbs. The number of painful body sites was positively correlated with both the pain severity index (PSI) and pain interference index (PII) ($r=0.34$, $p<0.001$ and $r=0.22$, $p<0.001$ respectively). Moreover, the PSI and PII were positively

correlated ($r=0.58$, $p<0.001$). The number of pain sites was negatively correlated with age ($r=-0.12$, $p=0.008$).

The negative impact of pain on daily living activities was significantly higher for NC pain, particularly for mood and sleep ($p=0.01$). The pain catastrophizing score was higher in patients with NC ($p<0.001$). Finally, migraine was more frequent in patients with NC pain ($p<0.001$).

Interestingly, only 78 out of the 346 patients presenting pain with NC had a prescription for specific anti-neuropathic drugs (59 with antiepileptic drugs, 20 with tricyclic anti-depressants, 7 with venlafaxine and 5 with duloxetine, some of them receiving both antiepileptic and antidepressant drugs) whereas the others had prescriptions of analgesics from the three steps ladder of the World Health Organization, benzodiazepines or anti-spastic drugs (Table 2). Some patients were not taking any drugs but were using physiotherapy, relaxation or hypnosis. Two hundred and forty-eight of the patients presenting pain with NC had a $PSI \geq 4$. Out of them, 70 were receiving specific drugs, i.e. 28%.

Headaches

The 361 patients with headache (table 3) were significantly younger than the other respondents ($p<0.001$) and had a shorter time from onset ($p=0.004$). Among them, 179 subjects (26.6%; 95%CI: 23.3 – 29.9) fulfilled all IHS criteria for migraine, thus meeting the definition of strict migraine, and 130 (19.3%; 95%CI: 16.3 – 22.3) fulfilled all IHS criteria for migraine except 1, thus meeting the definition of probable migraine.

The sex ratio was not statistically different between migraineurs and non-migraineurs. Migraine patients were younger, had shorter disease duration and were more often presenting an RR-MS. Patients with migraine had a headache of moderate intensity (6.0 ± 0.1) and 15% of patients with strict migraine experienced headaches 15 or more days per month, that is 3.9%

of all the respondents. Headaches occurring 15 or more days per month are supposed to be chronic migraine provided that there is no medication overuse; medication overuse headache (MOH; 8.2 of the IHS classification) in the second case. What is crucial in the definition of MOH is that treatment occurs both frequently and regularly, i.e., on 2 or more days each week. The questionnaire included the type of medications (e.g., codeine or caffeine-containing ones) but unfortunately neither the frequency nor the quantity used by patients. Thus, we cannot know whether some patients actually fulfilled the criteria for MOH.

The number of pain locations was not different between migraineurs and non-migraineurs. The EDSS was significantly lower for migraineurs. NC pain was significantly more prevalent in patients with migraine. There was a trend for higher prevalence of migraine in patients receiving beta-interferon (table 3). Logistic regressions performed among all the respondents showed that younger age was associated with both the presence of headache ($OR_{1-2} = 4.98$; 95%CI: 2.44 – 10.10 and $OR_{1-3} = 5.85$; 95%CI: 2.87 – 11.90, comparing first and second and first and third terciles respectively) and migraine ($OR = 3.11$; 95%CI: 1.68 – 5.78). RR-MS disease course was only associated with migraine ($OR = 1.91$; 95%CI: 1.12 – 3.26).

Twenty-four out of the 309 patients (i.e. 7.8%) with strict migraine were taking preventive treatment (13 with amitriptyline, 4 with dihydroergotamine, 3 with propranolol, 3 with topiramate and 1 with indoramine). For the treatment of the attacks, very few patients had an optimal treatment. Only 59 had NSAID and 11 had a triptan (i.e. respectively 19.1% and 3.6%). All these patients were among the 274 patients with a headache pain above 4/10. Among the patients suffering probable migraine 15 or more days per week, some were possibly suffering from medication overuse headache. Analgesic drugs consumed are listed in table 2.

Comorbidities

Migraine and pain with NC were both found to be present in 32% of the patients (table 4). To ensure our sample size was sufficient, we performed a retrospective power calculation. In our survey, migraine prevalence is 46% and pain with NC is 51%. If these two entities were independent, the co-occurrence would be supposed to be present in only 23.5% of the patients. Nonetheless, the observed prevalence for the co-occurrence is 32%. To demonstrate, a statistically significant difference between this theoretical and this observed proportion with a power of 99% (type I error set at 5%, bilateral formulation), 510 subjects were needed. With our 673 respondents, this power is easily reached.

As described above, patients with migraine were younger, presented more frequently with a RR-MS and had a lower EDSS. Pain with neuropathic characteristics was associated with numerous pain locations. The proportion of migraine sufferers was higher in the group of patients affected by pain with NC, showing the high comorbidity of these two symptoms. In the sub-group of patients suffering from both migraine and pain with NC, the headache pain intensity and the pain severity index for other types of pain were higher. Moreover, the pain interference index and the catastrophizing were also higher in this sub-group.

Impact of time from MS onset and aging

As expected, the proportion of RR-MS decreased and EDSS increased with age. Global pain prevalence was not significantly different in the different disease duration or age groups, even if there was a trend toward lower prevalence among patients with longer MS duration or older patients (table 5). Longer disease duration and aging were both associated with lower headache and migraine risk. The peak prevalence for pain with NC and for the number of painful body sites was between 36 and 54 years old.

Disease modifying therapies

The status for disease modifying treatment was known for 399 patients among the respondents (table 6). Patients receiving beta-interferon therapy were younger and had lower EDSS. The risk of pain in general and of pain with NC was neither increased nor decreased by the disease modifying treatments (Figure 2). The patients undergoing beta-interferon treatments presented with a higher rate of headaches and migraine.

DISCUSSION

This study assessed the prevalence and co-occurrence of headaches and neuropathic pain in a large French group of well-studied MS patients. MS prevalence in our administrative area (Auvergne) is closed to the country-wide one, i.e. 95 per 100,000 inhabitants [17]. Given that there are 1,347,387 inhabitants in Auvergne [24], the number of MS patients in this area should be 1280, that is, very close to the 1,300 members of the MS patients' network. We speculate that as MS prevalence is similar to that of the country, the observed pain prevalence should also be representative of that in our country. Of the 1300 sent questionnaires, 673 could be used for statistical analysis. Study patients had a mean age of 50 years, were mostly female (80%), had a mean disease duration of almost 15 years and an EDSS of 3.7. A RR-MS disease course was present in 74%.

Pain

This study confirms that pain is very common in MS patients. Almost 80% of patients reported pain in the previous month, with 51% of them suffering NC pain and 46% migraine. Moreover NC pain and migraine were both reported by 32% of our MS patients. Such overall pain prevalence is in the upper range of those previously reported [15]. Patients with pain were younger than those without pain. On the other hand, neither sex ratio, nor mean disease duration, nor mean EDSS were significantly different between patients with or without pain.

Pain with neuropathic characteristics

In our survey, 51% of patients suffered NC pain. This prevalence is slightly above the 34 to 49% reported in several previous studies [3,18,46]. It has to be noted, however, that none of these studies used questionnaires specifically designed to detect the neuropathic characteristics of pain. This likely led to underestimating the actual prevalence of NC pain in MS patients. Moreover, most of these studies [3,23,27,31,42,54] used restrictive definitions,

some of them reporting only neuropathic extremity pain, leading to a mean prevalence of 27% for this symptom alone [15]. Using the very same DN4 questionnaire as here, Truini and collaborators [50] found only 14% of their patients suffering neuropathic pain and 5% ongoing neuropathic extremity pain. In this latter study, however, the overall pain prevalence was strikingly low (30%) and the mean age of patients 39 years. We noted here that the prevalence of NC pain significantly decreases in patients younger than 35-years old. It cannot be ruled out, however, that self-administration of the DN4 questionnaire, although validated, leads to a slight overestimation of NC pain prevalence.

NC pain was more intense than non-NC pain. NC pain was often located in the limbs and in more than one body region. Thus, 58% of NC pain patients reported pain in three or more body regions. The number of pain locations, pain intensity and pain interference were significantly and positively associated with the report of NC pain. In our study the words ‘pins and needles’ and ‘tingling’ were most frequently used by MS patients to describe their NC pain. In previous studies of patients with MS the adjectives most often used to describe NC pain were: aching, stabbing, cutting, shooting, pricking, tingling, heavy, dull, cramping, smarting and squeezing [36,45,46,51]. It is interesting to note that, compared with the general population suffering chronic neuropathic pain, MS patients were more likely to use the pain adjectives of ‘painful cold’, ‘tingling’, ‘itching’ and ‘numbness’ [6]. Such descriptors of neuropathic pain in MS patients could be related to central mechanisms, whereas in the general population, neuropathic pain is mostly due to peripheral mechanisms.

When compared to non-NC pain, NC pain was associated with a higher level of pain catastrophizing and stronger interference of pain with daily living activities, particularly for mood and sleep. NC pain is known to independently contribute to quality-of-life impairment [2]. Our data in this specific population thus confirm that NC pain has a more negative impact on quality-of-life than non NC pain. The pain catastrophizing scores in central neuropathic

pain are as elevated as in peripheral neuropathic pain [30]. As reported in most studies, no link between NC pain and EDSS was found ([25,27,31,36,46];but see [42]).

Consistent with most previous studies (for review see [35]), gender, age and disease duration were not correlated with NC pain. Two studies have reported associations between age or disease duration and pain [9,32]. But most cross-sectional studies failed to find any clear association between age [3,23] or disease duration [3,23,39,46] and pain. It has also been suggested that the prevalence of neuropathic pain increases when the disease has a progressive course [31,42,49]. But such a correlation could not be found in many other studies [18,19,25,36,46,54]. Disease modifying treatments were associated with the prevalence of neither general nor NC pain. Less than a quarter of patients suffering NC pain were receiving a specific treatment for neuropathic pain.

Headaches

The overall prevalence of headache was 54%, which is within the range of the previously reported prevalence [15]. The overall prevalence of migraine was 46%, thus, 2.2 times more than in a historical French cohort [29], but consistent with that in a recent meta-analysis [37]. As previously reported [53], these patients suffered migraine an average 8 days a month with a mean pain intensity of 6. Migraine was episodic in most patients (85%) but headaches were occurring 15 or more days per month in a large minority (15%) of them; that is, the overall prevalence of chronic migraine in our MS patients was 3.9%, thus, much higher than that in the general population (1.4 to 2.2%) [33]. Such a high prevalence has already been reported once [53]. Pain catastrophizing was higher in MS patients with migraine than in those with other headaches. There was no difference in pain interference between patients with migraine and those with other headaches. Migraine was, in addition, associated with younger age, shorter disease duration, lower EDSS and RR-MS compared with other headaches. Among

disease modifying treatments, patients receiving interferons were more prone to migraine. These results are consistent with previous reports [11,13,38,53]. It is noteworthy that only 11% of migraineurs received a preventive treatment and 21%, a specific treatment for migraine attacks. These data confirm the low rate of triptans prescription in MS-migraineurs [52].

In MS patients suffering from pain, NC was significantly associated with higher risk of migraine. When patients had both pain with NC and migraine, they reported higher pain severity, more pain interference on usual activities and a higher pain catastrophizing, than patients suffering either NC pain or migraine alone. To our knowledge, this is the first study showing a correlation between migraine and neuropathic pain, a previous publication having provided evidence for correlation between migraine and various other pain-related symptoms, such as Lhermitte's sign, cranial neuralgia and restless legs syndrome that are 2–5 times higher in MS patients with migraine compared with MS patients without headaches [28].

Possible mechanisms of NC pain and migraine in MS patients

The prevalence of migraine, higher in young patients, decreases with aging. On the other hand, the prevalence of NC pain is maximum between 36- and 54-years old, suggesting that NC pain appears early but not at the very beginning of the disease. Interestingly, such age-dependency of NC pain prevalence in MS patients appears to be different from that in the general population which simply increases with age. Thus, in a population-based survey, neuropathic pain prevalence is around 5% before the age of 50-years, and around 9% thereafter [6]. In addition, our MS patients with migraine had shorter disease duration and higher RR-MS than those with NC pain. Our study thus reveals that migraine, but not NC pain, is associated with young age, short disease duration, RR-MS and interferons treatment. Biondi [4] had hypothesized that migraine is a neuropathic pain syndrome. That risk factors

do not similarly affect migraine and NC pain suggests that, on the other hand, these two pain syndromes do not rely on the same mechanisms.

Limitations

One limitation of this survey is the relatively low response rate (52%), though this response rate is close to that of other epidemiological studies using the same methodology [12,16,20,22,48]. Nevertheless, the cohort is well-described and non-responders were not different from responders concerning demographic and clinical characteristics. The second limitation is the lack of information concerning the frequency of analgesics use, making it impossible to definitively separate chronic migraine from medication overuse headache. Another major limitation is the lack of information about pain duration. In accordance with previous studies, we classified patients with or without pain on the basis of self-reported pain during the last month [3,7,16,18,20,22,25,46]. Unfortunately, the duration of pain is rarely reported in other studies and we did not have this data either. Finally, it is perhaps regrettable that the patients did not undergo physical examination to confirm both diagnosis of migraine and neuropathic pain. However, the questionnaires used are well-validated, even if a slight overestimation is possible.

Conclusion

Migraine and NC pain are comorbid in MS and are associated with more intense pain and interference on normal activities. Both types of pain are present early in the disease course. Migraine seems to be associated with the inflammatory phase of the disease and would involve a dysfunctional mechanism, i.e. amplification of nociceptive signaling in the absence of either [peripheral tissue] inflammation or neural lesion [10]. Neuropathic pain could rather be due to early lesions in the CNS. The correlation between migraine and neuropathic pain

deserves further study. Specific therapeutic studies are needed, taking into consideration pain specificities associated with MS.

Acknowledgements

This survey was possible thanks to the collaboration of the association 'Réseau SEP Auvergne'. We thank Pr Alain Artola for critical reading of the manuscript and English editing and Dr Christian Dualé for administrative support.

Disclosures

Teva provided financial support for this survey. XM has benefited from travel to conference from Merk-Serono, Biogen-Idec and Genzyme. LO, NG, DJB and RD have no conflict of interest. PC benefited from honoraria, travel to conferences or consultancies from Teva, Merck-Serono, Novartis, Biogen-Idec, Pfizer, Sanofi-Aventis, Genzyme and Bayer-Schering.

All the authors took part to the conception of the questionnaire, discussed the results and commented on the manuscript. XM wrote the manuscript.

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TABLE CAPTIONS and LEGENDS

Table 1: Patients with extra-cephalic pain, with or without neuropathic characteristics

Table 2: Treatments used. NSAID: non steroidal anti inflammatory drug; SAID: steroidal anti inflammatory drug.

Table 3: Patients with pain, with or without migraine (strict or probable)

Table 4: Patients with pain: co-occurrence of migraine and pain with neuropathic characteristics (NC). Patients with both symptoms experienced more intense pain, a higher interference on activities of daily living and a higher catastrophizing score.

Table 5:

A: Prevalence of overall pain and pain subgroups according to time from disease onset.

B: Prevalence of overall pain and pain subgroups according to age at time of survey.

For statistical comparisons, first column is referenced as 'A', second column as 'B' and third column as 'C'. All significant differences (\neq) are reported ($p < 0.05$). NS = Non significant.

Table 6: Disease modifying treatments at time of survey

FIGURE LEGENDS.

Figure 1: Main characteristics of the cohort and the different sub-groups

NC: Neuropathic Characteristics. Continuous variables are displayed as mean \pm SEM (standard error of the mean).

Figure 2: Impact of disease modifying treatments

Blue: 120 patients undergoing beta-interferon therapy; Red: 133 patients undergoing other disease modifying treatment; Green: 146 patients without any disease modifying treatment

Continuous variables are displayed as mean \pm SEM (standard error of the mean). Binary variables are expressed as percent \pm IC95%. Statistical results are displayed when significant (** for $p < 0.01$ and *** for $p < 0.001$).