Pain in Patients With Multiple Sclerosis
A Population-Based Study

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Background: Pain is an important symptom in patients with multiple sclerosis (MS). The estimated pain prevalence varies between 30% and 90%. To our knowledge, previous studies do not include a whole population sample of patients with MS.

Objective: To assess pain prevalence and its clinical characteristics and impact on daily life in a population sample of MS patients and in a reference group.

Design: Postal survey.

Setting: Aarhus County, Denmark.

Participants: The population of patients with definite MS in Aarhus County (n=771) and a sex- and age-stratified reference group from the general population (n=769).

Main Outcome Measures: Pain prevalence, intensity, and treatment requirement; and the impact of pain on daily life.

Results: Response rates for MS patients and reference subjects were 81.3% and 63.3%, respectively. Pain in the month preceding assessment occurred in 79.4% of MS patients and in 74.7% of reference subjects (prevalence proportion ratio, 1.06; 95% confidence interval, 0.99-1.13). Patients with MS had a higher pain intensity (“when pain is at its least” median visual analog scale score, 20.0 vs 11.0 mm [P<.01]; and “when pain is at its worst” median visual analog scale score, 68.0 vs 55.0 mm [P<.01]). Daily intake of analgesics occurred in 24.4% of MS patients and 9.0% of reference subjects (prevalence proportion ratio, 2.7; 95% confidence interval, 2.0-3.6). Patients with MS more often reported that pain interfered with daily life “most of the time” or “all the time.”

Conclusions: The frequency of reported pain in MS patients was not higher than in the background population. However, pain intensity, the need for analgesic treatment, and the impact of pain on daily life were higher in MS patients.

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MULTIPLE SCLEROSIS (MS) is a chronic disease with no curative treatment. Accordingly, symptomatic treatment is important. Pain has not previously been considered an important element of MS, but in recent years, acute and chronic pain syndromes have been recognized as symptoms in patients with MS.1-11 The reported prevalence of pain in patients with MS differs considerably, with figures ranging from 30% to 90%.1,3,5,11 Previous studies differ in design and type of pain registered. To our knowledge, no study has been based on a representative sample of the whole population of MS patients.

The presence of pain may influence quality of life and daily activities. In a previous study,6 one third of the MS patients indicated that pain was the worst symptom of MS. Archibald et al1 evaluated the effect of pain on social performance, and found that pain affected the ability of a patient with MS to perform as a worker, partner, parent, and friend.

The present study (a) assesses the pain prevalence in the preceding month in a population sample of MS patients; (b) assesses pain prevalence in a sex- and age-stratified reference group from a background population; and (c) compares pain prevalence, characteristics, treatment, and impact on daily life in the 2 groups.

METHODS

A postal survey concerning pain in the preceding month was undertaken in the population of MS patients in Aarhus County, Denmark, and in a sex- and age-stratified reference group drawn from a general population. The population in Aarhus County includes 640 000 inhabitants. Invitations to participate, along with questionnaires, were mailed to potential participants between January 18, and April 26, 2001. Nonresponders received a reminder 1 month after the first mailing.

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Patients with MS living in Aarhus County were identified through the Danish Multiple Sclerosis Registry. Inclusion criteria were as follows: (a) living in Aarhus County, (b) definite MS (criteria of Poser et al\textsuperscript{15}), (c) 18 years or older, and (d) patient aware of the diagnosis. To ensure the correctness of the diagnosis and the patient’s awareness of the diagnosis, one of us (H.J.H.), from The MS Clinic, Aarhus, covering all inhabitants of the county, reviewed the medical records for all patients known in the clinic. In case the patient was unknown in the clinic, the diagnosis was uncertain, or the patient’s knowledge about the diagnosis could not be documented, the general practitioner was contacted. The general practitioner was asked whether she or he could confirm the diagnosis and the patient’s awareness about the diagnosis and approve the contact to the individual patient.

Reference subjects were randomly selected from the same general population as MS patients. They were identified through the Central Office of Civil Registration, in which all inhabitants in each area of Denmark are registered. We obtained information about birth date, name, and address from the register. Inclusion criteria were as follows: (a) sex and age stratified to patients with MS and (b) living in Aarhus County. The only exclusion criterion was a diagnosis of MS.

A questionnaire was developed (data available from the authors). Questions about pain focused on pain experienced in the month preceding the assessment. Acute and chronic pain syndromes were included. If needed, participants were contacted by telephone for clarifying responses. The local ethical committee and the Danish Data Protection Agency approved the study, which was performed according to the Declaration of Helsinki.

Comparisons regarding demographic characteristics were conducted using the \( \chi^2 \) test for categorical data and the non-parametric Mann-Whitney test comparing median age. For pain (including treatment and description) and abnormal sensations, prevalence proportion ratios (PPRs) with 95% confidence intervals (CIs) were calculated. Bivariate analyses (Mantel-Haenszel) were used to assess the impact of other pain treatment on analgesic drug consumption. Differences in median visual analog scale scores were analyzed using the Mann-Whitney test. \( \chi^2 \) Test statistics were used, comparing 2 or more frequencies (including pain treatment requirement and the impact of pain or physical health on daily life). Individuals with missing information from the questionnaire were excluded from the specific analysis.

RESULTS

At study start (December 12, 2000), 860 subjects in Aarhus County who were 18 years or older were registered in the Danish Multiple Sclerosis Registry with definite or probable MS (using the criteria of Poser et al\textsuperscript{15}). The inclusion and exclusion of patients is shown in Figure 1. Questionnaires were mailed to 771 MS patients and 769 reference subjects. After 1 written reminder, 627 (81.3%) of the MS patients and 487 (63.3%) of the reference subjects had returned the questionnaire. Nonresponders in the MS group were older than responders; no difference was found in sex distribution. Nonresponders in the reference group did not deviate from responders regarding sex and age.

DEMOGRAPHIC CHARACTERISTICS

No differences in sex distribution and age were found between MS patients and reference subjects (Table 1). The distribution in 10-year age groups was also equal in the 2 groups when splitting the groups according to sex. Patients with MS had a lower prevalence of reported muscle joint disorders than the reference subjects, while the prevalence of other diseases was similar (Table 1). The distribution of educational levels differed between the groups, with a lower educational level in the MS group (Table 1).

MS DISEASE

Of the 627 MS patients who responded to the questionnaire, 73 (11.6%) reported attacks in the preceding month (ie, an episode \([ \geq 24 \text{ hours}\) duration] with new neurological symptoms or aggravation of existing neurological symptoms not associated with fever). Of these 73 patients, 46 (63.0%) reported pain during the attack. Of the 627 responders, 356 (56.8%) reported muscle spasms. Of these 356 patients, 47.7% reported painful muscle spasms.

PAIN

Pain Prevalence

No difference in pain prevalence in the month preceding the assessment was found (498 [79.4%] of 627 responders in the MS group vs 364 [74.7%] of 487 responders in the reference group reported pain) (PPR, 1.06; 95% CI, 0.99-1.13). In the reference group, 74.0% (304/411) of subjects answering the first request had pain vs 78.9% (60/76) of subjects answering the second request (P=.36). The corresponding figures in the MS group were 78.7% (410/521) vs 83.0% (88/106) (P=.32).
In both groups, most subjects with pain assessed pain as mild on the Verbal Rating Scale (Table 2). However, the distribution of assessment in the 3 categories (mild, moderate, and severe) differed between the 2 groups ($\chi^2 = 26$, $P < .01$), with a higher prevalence of MS patients rating pain as moderate or severe than reference subjects. On the visual analog scale, MS patients reported a significantly higher pain intensity than reference subjects, “when pain is at its least” and “when pain is at its worst” (Table 2).

### Pain Treatment

More MS patients with pain than reference subjects with pain reported daily or constant treatment-requiring pain (Table 3). Patients with MS more often reported an intake of analgesic drugs for 4 days or longer (44.4% vs 24.4%) (PPR, 1.8; 95% CI, 1.5-2.2). Physiotherapeutic pain treatment was more frequent in the patient group as well (44.4% vs 8.7%) (PPR, 5.1; 95% CI, 3.6-7.3). Patients undergoing physiotherapeutic treatment had the same intake of analgesics as reference subjects undergoing physiotherapeutic treatment, while MS patients not treated with physiotherapy had a higher consumption of analgesics than reference subjects not treated with physiotherapy (41.3% vs 21.5%) (PPR, 1.9; 95% CI, 1.5-2.5). No differences were found for other types of pain management, including acupuncture and chiropractic care.

Of all MS patients, 24.4% (153/627) had a daily intake of analgesic drugs compared with 9.0% (44/487) of the reference subjects (PPR, 2.7; 95% CI, 2.0-3.6); of these patients and reference subjects, 37.3% and 29.9%, respectively, took more than 1 type of analgesic drug. Simple analgesics (aspirin and acetaminophen), tricyclic antidepressants, anticonvulsants, and opioids were more frequently taken by MS patients than by reference subjects (Table 3).

## Pain Location

More MS patients with pain than reference subjects with pain reported pain in more than 1 location (81.3% vs 70.3%) (PPR, 1.16; 95% CI, 1.07-1.25). Pain in the eyes,
The Impact of Pain on Daily Life

The words having, tingling/touching, heavy, cramping, shooting, and aching were more frequently used by the MS patients than the reference subjects (Table 5).

SENSORY SYMPTOMS

Of the MS patients vs the reference subjects, 33.3% vs 18.9% reported abnormal sensations (PPR, 2.00; 95% CI, 1.56-2.56). Of these groups, 36.5% of the MS patients and 12.7% of the reference subjects reported painful abnormal sensations. Dysesthesia (painful or unpleasant sensation evoked by touch) was reported by 38.1% of the MS patients and 12.9% of the reference subjects (PPR, 3.02; 95% CI, 2.35-3.92). Of these groups, 56.5% of the MS patients and 12.3% of the reference subjects reported painful abnormal sensations that occurred most frequently in the extremities in both groups.

Table 3. Data for Treatment-Requiring Pain

<table>
<thead>
<tr>
<th>Pain Location</th>
<th>Patients With MS</th>
<th>Reference Subjects</th>
<th>PPR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>121 (22.7)</td>
<td>79 (16.6)</td>
<td>1.51 (1.16-1.97)</td>
</tr>
<tr>
<td>Neck</td>
<td>190 (35.1)</td>
<td>141 (29.8)</td>
<td>1.28 (1.06-1.54)</td>
</tr>
<tr>
<td>Back</td>
<td>209 (39.3)</td>
<td>164 (34.3)</td>
<td>1.28 (1.06-1.55)</td>
</tr>
<tr>
<td>Joints</td>
<td>133 (25.5)</td>
<td>88 (18.4)</td>
<td>1.49 (1.22-1.83)</td>
</tr>
<tr>
<td>Muscles</td>
<td>144 (27.2)</td>
<td>105 (22.2)</td>
<td>1.37 (1.12-1.67)</td>
</tr>
<tr>
<td>Extremities</td>
<td>209 (40.8)</td>
<td>141 (29.8)</td>
<td>1.42 (1.17-1.73)</td>
</tr>
</tbody>
</table>

Table 4. Data for Medication Use

<table>
<thead>
<tr>
<th>Type of Medication</th>
<th>Patients With MS</th>
<th>Reference Subjects</th>
<th>PPR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple analgesics</td>
<td>66 (10.8)</td>
<td>28 (5.9)</td>
<td>1.84 (1.21-2.79)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>38 (6.2)</td>
<td>21 (4.4)</td>
<td>1.41 (0.84-2.36)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>9 (1.6)</td>
<td>4 (0.8)</td>
<td>1.37 (0.62-2.98)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>13 (2.3)</td>
<td>3 (0.6)</td>
<td>2.16 (0.91-5.10)</td>
</tr>
<tr>
<td>Interferon beta‡</td>
<td>96 (16.8)</td>
<td>0 NA</td>
<td>NA</td>
</tr>
<tr>
<td>Spasmolytics</td>
<td>125 (20.4)</td>
<td>0 †</td>
<td>NA</td>
</tr>
<tr>
<td>Opioids</td>
<td>42 (6.9)</td>
<td>9 (1.9)</td>
<td>3.64 (1.89-7.02)</td>
</tr>
<tr>
<td>TCA</td>
<td>38 (6.5)</td>
<td>21 (4.4)</td>
<td>1.71 (0.94-3.10)</td>
</tr>
<tr>
<td>Other</td>
<td>212 (36.1)</td>
<td>116 (24.4)</td>
<td>1.49 (1.21-1.82)</td>
</tr>
</tbody>
</table>

Table 5. Pain Description

<table>
<thead>
<tr>
<th>Words Chosen†</th>
<th>Patients With MS</th>
<th>Reference Subjects</th>
<th>PPR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No words</td>
<td>18 (3.6)</td>
<td>18 (4.9)</td>
<td>0.73 (0.39-1.38)</td>
</tr>
<tr>
<td>Other words</td>
<td>133 (25.6)</td>
<td>105 (22.2)</td>
<td>1.24 (0.90-1.70)</td>
</tr>
<tr>
<td>Tending</td>
<td>88 (16.3)</td>
<td>52 (10.9)</td>
<td>1.69 (1.20-2.40)</td>
</tr>
<tr>
<td>Tender</td>
<td>88 (17.7)</td>
<td>52 (14.3)</td>
<td>1.24 (0.90-1.70)</td>
</tr>
<tr>
<td>Aching</td>
<td>99 (19.9)</td>
<td>52 (14.3)</td>
<td>1.39 (1.03-1.88)</td>
</tr>
<tr>
<td>Pungent</td>
<td>14 (2.8)</td>
<td>4 (1.1)</td>
<td>2.53 (0.89-7.20)</td>
</tr>
<tr>
<td>Sharp</td>
<td>103 (20.7)</td>
<td>63 (17.3)</td>
<td>1.20 (0.90-1.60)</td>
</tr>
<tr>
<td>Stabbing</td>
<td>34 (6.8)</td>
<td>21 (5.8)</td>
<td>1.18 (0.70-1.98)</td>
</tr>
<tr>
<td>Shooting</td>
<td>181 (36.3)</td>
<td>103 (28.3)</td>
<td>1.28 (1.05-1.56)</td>
</tr>
<tr>
<td>Throbbing</td>
<td>75 (15.1)</td>
<td>42 (11.3)</td>
<td>1.78 (1.29-2.45)</td>
</tr>
<tr>
<td>Gnawing</td>
<td>81 (16.3)</td>
<td>50 (13.7)</td>
<td>1.18 (0.86-1.62)</td>
</tr>
<tr>
<td>Cramping</td>
<td>100 (20.0)</td>
<td>49 (13.5)</td>
<td>1.49 (1.10-2.03)</td>
</tr>
<tr>
<td>Sharp</td>
<td>103 (20.7)</td>
<td>63 (17.3)</td>
<td>1.20 (0.90-1.60)</td>
</tr>
<tr>
<td>Punishing</td>
<td>14 (2.8)</td>
<td>4 (1.1)</td>
<td>2.53 (0.89-7.20)</td>
</tr>
<tr>
<td>Sharp</td>
<td>103 (20.7)</td>
<td>63 (17.3)</td>
<td>1.20 (0.90-1.60)</td>
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</tr>
</tbody>
</table>
OTHER TREATMENT IN THE MS GROUP

Of the MS patients, 125 were treated with spasmyloytic agents. Interferon beta was taken by 96 of the patients. (Information about interferon beta comes from medical records at The MS Clinic.) No difference in total pain was found between patients taking and not taking interferon beta. However, patients treated with interferon beta more frequently reported a headache (52.1% vs 38.0%) (PPR, 1.4; 95% CI, 1.1-1.8).

THE IMPACT OF PHYSICAL HEALTH ON DAILY LIFE

Of the MS patients, 45.0% found that physical health interfered with daily life all the time; the corresponding figure in the reference group was 7.2%. The difference in the distribution of answers in the strata between the 2 groups was highly significant ($\chi^2 = 339$, $P<.001$).

COMMENT

To our knowledge, this is the first population-based study of pain in MS patients including a comparable reference group. No difference was found in the frequency of unspecific pain between the 2 groups, but treatment-requiring pain was more frequent among MS patients than in the sex- and age-stratified reference group. More than one quarter of the MS patients with pain reported daily treatment-requiring pain, and 41.6% reported that pain interfered with daily life most or all of the time.

Possible selection and information biases need to be considered: (a) Did the included MS patients in fact represent the population of MS patients in Aarhus County? (b) Was the reference group a representative sample from a background population? (c) Was the MS diagnosis correct? (d) Was the information about pain from the questionnaire reliable?

Patients in Denmark with a diagnosis of suspected MS are reported to the Danish Multiple Sclerosis Registry; in addition, the MS registry receives files from the National Registry of Patients (including all patient contacts to hospitals in Denmark). Each case is evaluated, and if the criteria of Poser et al15 (definite or probable MS) are not fulfilled, the patient is excluded from the MS registry. We cannot exclude that we missed a few patients with MS in Aarhus County. The diagnosis may have been new and not registered in the MS registry yet. Furthermore, we excluded 23 patients because they were considered unable to answer or the diagnosis was unknown to the patients and/or their relatives. The reference group was randomly sampled from the general population through the Central Office of Civil Registration (including all inhabitants in Denmark). The response rate was higher in the MS group than in the reference group. However, we found no significant difference in pain prevalence between subjects answering the first request and subjects answering the second request, neither in the reference group nor in the MS group. In a Danish population study,17 no difference in migraine prevalence between responders and nonresponders in the postal survey was found, indicating that nonresponders probably do not represent a group of subjects with no or fewer symptoms related to a pertinent disease. However, we acknowledge that the difference in response rates might have biased the results toward more patients with pain in the reference group.

We were able to confirm the diagnosis of definite MS (criteria of Poser et al13) for each patient included in the study by reviewing medical records and/or contacting patients’ general practitioners. In the questionnaire, the participants were asked about pain in the preceding month. The short period was chosen to avoid information bias due to memory problems. We assume that most of the responders were able to recall significant pain during the past month. However, we cannot exclude that more MS patients than reference subjects had cognitive problems with affected memory and problems recalling symptoms even within the past month.

Only few studies concerning pain in MS patients include a reference group. In a study7 of sensory symptoms in 387 MS patients, a reference group, sex and age matched with the patients but not randomly drawn from the general population, was included. The researchers reported that no differences in prevalence of pain some time in the past appeared between patients and control subjects, but MS patients more often reported active pain. In accordance with that information, we found no difference between patients and reference subjects in pain prevalence over time (1 month). We included chronic and acute pain syndromes, and cannot provide an exact estimate of the prevalence of active pain. In agreement with Rae-Grant et al,7 we found that MS patients more often reported pain in their extremities and face than reference subjects.

The 1-month prevalence of pain was estimated to be 53% in a previous study2 of 85 outpatients with MS. Of the patients with pain, 64% took analgesics during the past month. This is in agreement with our study, in which 20.9% of the patients reported analgesic consumption for fewer than 4 days and 44.4% reported analgesic consumption for 4 days or more in the past month (in total, 65.3%).

We did not find any association between disease duration and pain. This is in agreement with 2 previous studies,1,17 whereas other studies6,8,18 found an association between disease duration and the prevalence of pain. We defined disease duration as time since diagnosis, while other studies might have chosen duration of symptoms as the definition. We found a higher pain prevalence in MS patients aged 40 to 59 years compared with the youngest age group ($\geq$39 years), while pain in the older age groups was similar to that in the youngest age group. Other studies18 found a tendency toward higher pain prevalence in MS patients with increasing age. Because of the limitations of a postal survey, information about disease course and disability score was unavailable.

Patients with MS reported a lower prevalence of muscle/joint disease than reference subjects; otherwise, the groups were similar concerning other diseases. When other diseases were included as potential confounding variables in the analysis, the pain prevalence in the MS group was statistically higher than in the reference group. However, this difference disappeared if musculoskeletal disease was not included. We find it likely that musculoskeletal disease may be un-
derdiagnosed in MS patients because symptoms are wrongly connected to MS. Therefore, the information about musculoskeletal disease from the questionnaire may not be reliable. Based on this assumption, we suggest that the crude PPR of 1.06 (95% CI, 0.99-1.13) is the most correct expression of the relative prevalence of pain in MS patients compared with reference subjects.

A lesion in the somatosensory pathways in the central nervous system may cause central pain, but pain can also be due to musculoskeletal dysfunction as a consequence of disability. About one third of the MS patients have central pain.11,20 In the present study, 38.1% of the MS patients reported touch-evoked dysesthesia and 36.5% reported painful abnormal sensations, which are characteristic features of neuropathic pain.21 In addition, we found that 22.9% of MS patients choose the pain descriptor hot/burning, which has been claimed to be one of the most common qualities of central pain.20 However, 15.0% of the reference subjects also reported painful abnormal sensations and about 10.2% had hot/burning pain. In agreement with previous studies,5,7,24 we found that about 40.7% of the patients had back pain. The figure was not higher than in the reference group. Muscle/joint pain was more frequent in MS patients than in reference subjects. Of the MS patients, 39.6% had muscle pain and 41.9% had pain localized to the joints. Earlier, tendon-skeletal pain was reported in 20% of MS patients.10 Pain located at the muscle or joints may be compatible with musculoskeletal pain, but can also represent a central pain phenomenon. The data obtained in the present study are not sufficient to evaluate the prevalence of central vs nociceptive pain. Such a categorization will demand a supplementary examination with detailed sensory testing.

It has previously been reported that pain disables the social performance of MS patients.3 By including a reference group, we can add that pain and physical health interfere with daily life more often in MS patients than in reference subjects. Fatigue and weakness are common symptoms that may affect the physical and mental aspects of quality of life and social functioning in MS patients.22,23 More MS patients than reference subjects chose tiring/exhausting to describe their pain. However, no fatigue inventory was included in the present study and the association between fatigue and pain cannot be evaluated.

In conclusion, the frequency of reported pain in a Danish population sample of MS patients was similar to that reported by a sample from the general population. However, pain intensity, treatment requirement, number of pain sites, and the influence of pain on daily life were higher in MS patients than in reference subjects. This indicates that pain in MS patients is clinically important. We suggest that a careful analysis and classification of pain in MS patients, along with a mechanism-based treatment strategy, may improve the quality of life for MS patients.

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Author contributions: Study concept and design (Drs Svendsen, Jensen, Overvad, Hansen, Koch-Henriksen, and Bach); acquisition of data (Drs Svendsen, Hansen, Koch-Henriksen, and Bach); analysis and interpretation of data (Drs Svendsen, Overvad, Koch-Henriksen, and Bach); drafting of the manuscript (Dr Svendsen); critical revision of the manuscript for important intellectual content (Drs Svendsen, Jensen, Overvad, Hansen, Koch-Henriksen, and Bach); statistical expertise (Drs Svendsen, Overvad, and Koch-Henriksen); obtained funding (Drs Svendsen, Jensen, Hansen, and Bach); administrative, technical, and material support (Dr Bach); study supervision (Drs Jensen, Overvad, Hansen, Koch-Henriksen, and Bach).

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REFERENCES