Cephalalgia in Multiple Sclerosis

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ABSTRACT

Background.—From published figures, we know that pain has a significant impact on quality of life in patients with multiple sclerosis (18-21). In these patients, more pain, in addition to greater pain intensities are reported (19). Several studies also show a greater prevalence of both primary headache, i.e. migraine, cluster headache, and tension-type headache, in addition to secondary headache (35-39). Nonetheless, a very limited amount of data exists on the matter.

Purpose.—The aim of this paper is to further explore the association between self-reported headache among multiple sclerosis patients, as well as migraine in particular.

Methods.—We performed a questionnaire-based case-control study of 903 MS patients from the Oslo MS Registry, and used 1100 participants from the Norwegian Bone Marrow Registry as controls. Selected questions from two questionnaires per patient were used in this paper. Hypotheses have been tested using Pearson’s chi-squared test, and for several variables, an odds ratio with a 95% confidence interval have been given instead.

Results and Conclusion.— We found no significant difference in prevalence of headache and migraine between the total MS group and controls, but a lower prevalence of headache and migraine among PP-MS patients. Furthermore, we found a significantly lower prevalence in male MS patients compared to male controls with regard to self-reported headache in general, and of migraine exclusively (p = 0.015). MS patients also had a significantly higher headache symptom frequency (p < 0.001); moreover, we observed a higher proportion of MS patients with moderate headache pain intensity (OR = 1.59 [95% CI = 1.16-2.18]), along with a higher usage of prescription-free drugs in these patients (daily: OR = 6.35 [95% CI = 2.29-17.57]). Thus, MS patients with headache are more affected by this than controls.
I. A. Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disorder of unknown etiology, causing inflammatory demyelination in the central nervous system (CNS)(1). Together with its complications, it is the leading cause of mortality in patients with advanced neurological disability(2). The disorder is generally agreed to be autoimmune in nature(1;3-6), caused by a combination of both genetic and environmental factors, leading to inflammation and neurodegeneration(1;3). A distinctive feature of chronic multiple sclerosis is the hypocellular and demyelinated plaque(1); these well-demarcated lesions have a predilection for CNS white matter, brain stem, cerebellum, and the optic nerves(1). The lesion pathogenesis is location-dependent(7;8), and our knowledge of it remains fractional(1).

Symptoms in the early onset of multiple sclerosis are attributed to the slowing, or even complete impediment, of the conduction of action potentials, caused by inflammation, and the resulting damage that manifests itself as axonal demyelination(1). Partial remyelination and subsiding edema are believed to be the cause of the regression of symptoms(1). The symptoms of multiple sclerosis are many, both sensoric and motoric, such as spasticity, fatigue, tremor, depression, dysphagia, and dysarthria, in addition to neuropathic and non-neuropathic pain(9).

In 1996, Lublin et al.(10) suggested classification of the disease depending on the clinical course. There is an international consensus concerning the definition of three types of multiple sclerosis, namely primary progressive (PP) multiple sclerosis, secondary progressive (SP) multiple sclerosis, and relapsing-remitting (RR) multiple sclerosis. Primary progressive multiple sclerosis describes a continuously advancing disease progress, where minor improvements are allowed. In contrast, relapsing-remitting multiple sclerosis describes a clinical course with well-defined relapses – either with full recovery or sequelae. The consensus definition for secondary progressive multiple sclerosis includes a progressive course developed from a relapsing-remitting disease. Approximately 85% of new multiple sclerosis cases are relapsing-remitting, with 50-60% eventually progressing to secondary progressive(11). Diagnosis today is based on the McDonald criteria, a revision of the criteria proposed by Poser et al. in 1983 intended for use in research(12). The McDonald criteria
integrates MRI findings, which defines each case as either “MS”, “possible MS” or “not MS”(13).

Due to substantial geographical variations with regard to the prevalence of multiple sclerosis(14;15), Kurtzke divided the world into three areas, namely high frequency areas, medium frequency areas, and low frequency areas(15). The prevalence in Europe alone ranges from an estimated 4 per 100 000 (1978) to 193 per 100 000 (1983) in the Orkney Islands(14). In general, the prevalence is higher in northern US, Canada, northern Europe, southern Australia, and New Zealand, while being lower in Asia (except for eastern Russia), Africa and northern South America(14;15). In Oslo, Norway, the prevalence was 148 per 100 000 in 2005, with a marked variation between different ethnic groups(16). The peak age of onset is between 20 and 45 years(17), and females are more than twice as likely to develop multiple sclerosis compared to males(18).

The Norwegian Directorate of Health’s guidelines for management of multiple sclerosis (2011) are divided into relapse treatment and disease-modifying treatment(19). The latter is further subdivided into first-line, second-line, and third-line treatment. The guidelines do not cover the management of symptoms. Relapses are treated with corticosteroids if infections have been excluded. First-line treatment consists of glatiramer acetate (Copaxone®) and the interferon beta-drugs Avonex®, Betaferon®, Extavia®, Copaxone®, and Rebif®(19), which all lower the rate of clinical relapse by about 30%, and reduce the development of lesions on MRI(1). Patients with high disease activity should be offered natalizumab or fingolimod(19), which both reduce the rate of relapse by 60-70%, albeit these drugs have a higher risk of giving rise to serious adverse events(1). Mitoxantrone may be considered for treating cases of relapsing-remitting multiple sclerosis with persistently high disease activity, or cases of secondary progressive multiple sclerosis with persistently high disease activity and rapid progression(19).
I. B. Headache in Multiple Sclerosis

Until the early 1980s, pain was not regarded as part of the clinical picture of multiple sclerosis (20). From published figures, we know now that pain affects 29% - 86% of patients with multiple sclerosis, having a significant influence on the quality of life (20-23). While Svendsen et al. (21) in a Danish study found no difference in pain prevalence in the past month between MS patients and a sex- and age-stratified control group (498 of 627 [79.4%] vs. 364 of 487 [74.7%], respectively), MS patients reported more severe pain, measured using a visual analog scale, as well as a higher usage of analgesics. The MS patients also reported that pain interfered with daily life to a greater extent than the control group.

The International Classification of Headache Disorders (ICHD), published by the International Headache Society, adopted by the World Health Organization, and incorporated into the International Classification of Diseases, 10th Edition (ICD-10), recognizes three types of primary headache, i.e. headache symptoms that are not attributed to other disorders: Migraine, tension-type headache, and cluster headache and other trigeminal autonomic cephalalgias, including their subtypes (24).

Migraine affects about 18% of women and 6% of men in the United States (25-27), with similar numbers in Europe, and generally lower in the rest of the world (28), although one study found that the majority of migraine-affected in the United States have gone undiagnosed (29). In a large Norwegian study, Linde et al. reported a self-considered migraine prevalence of 8.0% (p = 0.10); 10.2% for women and 4.6% for men (30). This study found that actual migraine prevalence in the same population was 13.2% (p = 0.001); 16.5% for women and 8.0% for men (30). According to the ICHD-II’s migraine criteria (31), pain is usually moderate or severe, unilateral, has a pulsating quality, and is aggravated by routine physical activity. When untreated or unsuccessfully treated, pain lasts 4 to 72 hours. Either nausea and/or vomiting, or photophobia and phonophobia is present. If one or more aura symptoms are present, the headache begins within 60 minutes of aural onset. There is a high degree of comorbidity with other illnesses, such as cardiovascular, neurologic, psychiatric, and disorders associated with pain (28). Treatment includes avoiding known triggers, the
migraine specific drugs triptans and dihydroergotamine, as well as NSAIDs, paracetamol and opioid analgesics(32).

Tension-type headache (TTH) is the most common of the primary headaches; the largest European study based on 33,763 Danish twins revealed a 1-year-prevalence of 78.9% among men, and 92.5% among women(33). Other studies show great variation, with the largest American study of its kind reporting a 1-year prevalence of episodic tension-type headache of 38.3%(34). In contrast to migraine, pain associated with tension-type headache is usually of mild or moderate intensity, bilateral, has a pressing or tightening and non-pulsating quality, and lasts anywhere from 30 minutes to 7 days(31). Furthermore, there is no nausea or vomiting, and either photophobia, phonophobia, or both are not present(31). Treatment consists of avoiding known triggers, NSAIDs, paracetamol, and in more severe cases, combination drugs containing analgesics and caffeine(35). Tricyclic antidepressants, in particular amitriptiline, are recommended as the prophylactic drug of choice(35).

Cluster headache is the most prevalent of the trigeminal autonomic cephalalgias (TACs)(28), with a variation of prevalence in five studies from 56 to 326 cases per 100,000 persons(36). In conformity with the ICHD-II(31), the disorder is characterized by trigeminally distributed pain together with ipsilateral autonomic symptoms: Severe or very severe unilateral pain in the orbital or temporal region, lasting 15-180 minutes if left untreated, in addition to a sense of restlessness or agitation, or at least one of the following ipsilateral phenomena: Conjunctival injection/lacrimation, nasal congestion/rhinorrhea, eyelid edema, forehead and facial swelling and miosis/ptosis. Frequency of attacks is anywhere from one every other day, to 8 per day(31). Acute attacks of cluster headache can be treated by a variety of drugs, including, but not limited to, the triptans sumatriptan and zolmitriptan, oxygen inhalation, and dihydroergotamine(37). A subcutaneous injection of sumatriptan is the first choice, but if not tolerated, sumatriptan for nasal administration is available(37). Verapamil is the drug of choice for prophylaxis(37).

Several Italian studies have found a greater prevalence of headache among MS patients than controls(38-42). In a study of 137 patients with MS, D’Amico et al.(38) found that, after
excluding 21 cases in which headache developed only after the initiation of therapy, 67 [57.8%] suffered from headache as per IHS-criteria. 37 [31.9%] patients had tension-type headache, 29 [25.0%] had migraine, and 1 [0.9%] patient was diagnosed with cluster headache(38). Comparing the patients with and without headache, no difference was evident with regard to MS type, illness duration or disability(38). Similar numbers have been reported by Vacca et al., where 122 of 238 [51.3%] of MS patients had primary headache, versus 57 of 238 [23.9%] for the control group without MS(40). There was, however, no difference in the rates of headache types among the two groups(40). In contrast, a high prevalence of migraine among MS patients was observed by Villani et al.(39) Among 205 patients with relapsing-remitting MS, 102 [49.8%] had migraine(39). Interestingly, compared with a control group of 63 patients without MS, a lower proportion of the 102 MS patients with comorbid migraine used prophylactic drugs (p < 0.0001)(39). This was also true for the use of triptans (p < 0.0001)(39). Nicoletti et al. compared 101 MS patients with 101 controls, and found that 58 [57.5%] in the MS group, against 38 [37.6%] in the control group, had headache(41). One Italian study also assessed neuropathic and somatic pain, in addition to tension-type headache and migraine, in MS patients(42). 39.8% of MS patients had experiences at least one type of neuropathic or somatic pain (trigeminal neuralgia, L’Hermitte’s sign, dysesthetic pain, painful muscle spasms or lower back pain) at some point in their life; this number reached 58.5%, were the mentioned headache types also included(42). For the aforementioned symptoms at the time of examination, the numbers were 23.8% and 39.9%, respectively(42).

As already stated, D’Amico et al. found that, among the 137 patients with MS, 21 [15.3%] developed secondary headache after initiation of interferon(38), used to treat and control MS. Several other studies exist, documenting a positive correlation between disease-modifying therapies, interferon-beta drugs in particular, and either the exacerbation of, or the increased incidence of comorbid headache(43-47). One study reported an increase of headache frequency and duration in 18% of all 65 patients after initiation of interferon-beta therapy, and in 35% of patients already suffering from headache before the introduction of interferon-beta medication(44). Another study conducted by Villani et al. demonstrated a significant reduction of migraine frequency in a group of 33 patients, after switching from interferon-beta to natalizumab(43). A group of 30 patients continuing interferon-beta therapy were used as
controls(43). Furthermore, adverse effects other than headache have been linked to the use of interferon-beta, such as muscle ache, fatigue, fever, chills, nausea(45); this could explain any increase in the consumption of analgesics among MS patients.

The aim of this paper is to further explore the association between self-reported migraine and self-reported headache in general, and the different types of multiple sclerosis, in accordance with the classification of multiple sclerosis mentioned in section I. A. Emphasis is placed on headache prevalence between multiple sclerosis patients and controls.
II. Methods

PubMed searches were performed, combining multiple sclerosis AND review. Information and data from the articles found to be relevant to the topic were used in part A of the introduction about multiple sclerosis. The Norwegian Directorate of Health’s guidelines were used for up-to-date management of the disorder. Part B of the introduction is heavily based on the International Headache Society’s 2nd Edition of The International Headache Classification. These criteria have been adopted by the World Health Organization in their International Classification of Diseases. The headache types and their criteria are therefore listed as they appear in ICHD-2 and ICD-10. Additional searches were also performed for part B, combining multiple sclerosis AND cephalalgia or cephalgia or headache or pain. The articles were reviewed by title and abstract for relevance to the topic. A limited number of articles were found to exist on the relationship between multiple sclerosis and headache, or between multiple sclerosis and pain in general.

A questionnaire containing 13 questions (see appendix 1) based on the Norwegian “Helseundersøkelsen i Nord-Trøndelag 3” (The Nord-Trøndelag Health Study 3), a longitudinal population health study completed in June 2008, in which 48,289 of 93,210 people participated, was sent to 720 multiple sclerosis patients from the Oslo MS Registry. The study is designed as a case-control study, and 1,100 healthy individuals from the Norwegian Bone Marrow Registry were used as controls. Out of 720 MS patients, 690 received the headache questionnaire, and out of these 690, 526 patients returned the questionnaire, yielding a response rate of 526/690 = 76.2%. 454 patients responded to the questionnaire, yielding a cooperation rate of 444/690 = 64.3%. Of 1,100 controls, 1,097 received the same questionnaire. A total of 903 returned and responded to the questionnaire, yielding both response and cooperation rates of 903/1,097 = 82.3%.

This paper uses data from the aforementioned questionnaire, in addition to data from demographical questions in a questionnaire containing 40 demographical and environmental questions. In total, 444 patients and 903 controls responded to both the headache and demographical questionnaires, thus providing the basis for statistical calculations in this study.
The variables collected in the headache questionnaire include self-reported headache, headache duration and intensity, concomitant symptoms, and medication usage. Variables in the demographic questionnaire include sex, age, smoking habits, alcohol consumption, occupation, and other diseases. The scope of this paper, however, is confined to the relationship between headache and multiple sclerosis, thus only a selected few variables from the questionnaires were used in this paper.

The prevalence of self-reported headache and self-reported migraine were investigated in both the group with multiple sclerosis and the control group. The former group was further divided into groups consisting of patients with primary progressive, secondary progressive, and relapsing-remitting disease. Asymmetry among the groups with regard to duration was also examined. Differences were tested for statistical significance using Pearson’s chi-squared test. Furthermore, several single-variable dissimilarities were explored using odds ratio with a 95% confidence interval.

For the Pearson’s chi-squared test, P-values less than 0.05 (2-sided) were considered significant. Where applicable, a lower 95% confidence interval value of above 1 for the odds ratio was otherwise considered significant. All analyses were carried out using PC versions of Statistical Package for the Social Sciences (SPSS) version 20, and Microsoft Excel 2007.
III. Results

There were 444 patients from the Norwegian MS Registry and 903 controls from the Norwegian Bone Marrow Registry that responded to both questionnaires. Sex and age distributions are reported in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th></th>
<th>Control</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=444</td>
<td>%</td>
<td>n=903</td>
<td>%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>120</td>
<td>27.0%</td>
<td>374</td>
<td>41.4%</td>
</tr>
<tr>
<td>Women</td>
<td>324</td>
<td>73.0%</td>
<td>529</td>
<td>58.6%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29 years</td>
<td>4</td>
<td>0.9%</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>30-39 years</td>
<td>65</td>
<td>14.6%</td>
<td>257</td>
<td>28.5%</td>
</tr>
<tr>
<td>40-49 years</td>
<td>110</td>
<td>24.8%</td>
<td>429</td>
<td>47.5%</td>
</tr>
<tr>
<td>50-59 years</td>
<td>131</td>
<td>29.5%</td>
<td>213</td>
<td>23.6%</td>
</tr>
<tr>
<td>60-69 years</td>
<td>102</td>
<td>23.0%</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>70-79 years</td>
<td>25</td>
<td>5.6%</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>7</td>
<td>1.6%</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

There are more men in the control group, as well as a preponderance of individuals aged 49 and below. The F:M ratio in the MS group is 1:2.7 compared to almost 1:1.4 in the control group. In the MS group, there are more people aged 60 and above. 386 patients had either relapsing-remitting or secondary progressive multiple sclerosis, as shown in Table 2.
Table 2. Distribution of multiple sclerosis type among the 444 patients, and sex and age at onset of multiple sclerosis in relation to type.

<table>
<thead>
<tr>
<th>Type of MS</th>
<th>RR/SP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>n=386</td>
<td>n=55</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Women</td>
<td>94</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>78.3%</td>
<td>21.7%</td>
</tr>
<tr>
<td></td>
<td>91.0%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at MS onset</th>
<th>RR/SP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=386</td>
<td>n=55</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>10-19 years</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>7.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>20-29 years</td>
<td>157</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>40.7%</td>
<td>21.8%</td>
</tr>
<tr>
<td>30-39 years</td>
<td>129</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>33.4%</td>
<td>27.3%</td>
</tr>
<tr>
<td>40-49 years</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>15.3%</td>
<td>30.9%</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2.6%</td>
<td>18.2%</td>
</tr>
<tr>
<td>Missing data</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0.8%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Only 9% of the women suffer from primary progressive disease, compared to 21.7% for men. There is also a predominance of younger patients, aged 29 and below in the group with RR/SP, where 40.7% are in the age group of 20-29 years, in contrast to 21.8% of PP patients.

Table 3 shows the distribution of self-reported headache and migraine in particular for all participants.

Table 3. Distribution of self-reported headache and migraine among all participants with MS, relapsing-remitting or secondary progressive MS, primary progressive MS, and in the control group.

<table>
<thead>
<tr>
<th></th>
<th>All MS</th>
<th>RR/SP</th>
<th>PP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=444</td>
<td>n=386</td>
<td>n=55</td>
<td>n=903</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Headache</td>
<td>222</td>
<td>202</td>
<td>20</td>
<td>494</td>
</tr>
<tr>
<td></td>
<td>50.0%</td>
<td>52.3%</td>
<td>36.4%</td>
<td>54.7%</td>
</tr>
<tr>
<td>Migraine</td>
<td>44</td>
<td>39</td>
<td>5</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>9.9%</td>
<td>10.1%</td>
<td>9.1%</td>
<td>13.6%</td>
</tr>
</tbody>
</table>

For self-reported headache in general, the prevalences were 54.7% and 52.3% for the control group and the group with RR/SP, respectively, whereas only 36.4% of the participants in the PP group reported suffering from headache. These numbers result in $\chi^2 (3)$ value of 14.370, $p = 0.002$, that is, statistically significant that the prevalences are not equal in the three groups.
For the prevalences of self-reported headache in the MS group in general, i.e. all patients with either RR/SP and PP, versus the control group, no significant difference can be demonstrated, $\chi^2 (1) = 2.269, p = 0.132$, and between patients with RR/SP and PP, $\chi^2 (1) = 4.910, p = 0.027$.

Of the controls, 13.6% reported having migraine, compared to 10.1% of the participants within the RR/SP group, and 9.1% of the participants within the PP group. There is significant difference in the prevalences between all groups with regard to migraine, $\chi^2 (3) = 10.361, p = 0.016$. No significance is, in particular, found in the prevalence difference of migraine between participants with MS in general, and the control group, $\chi^2 (1) = 3.616, p = 0.057$, nor is the difference between the two groups of MS patients significant, $\chi^2 (1) = 0.055, p = 0.815$.

Table 4 shows the distribution of self-reported headache in the various groups.

**Table 4.** Distribution of self-reported headache among men and women with MS, and in relapsing-remitting or secondary progressive MS, primary progressive MS, and the control groups in relation to sex.[1]

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>RR/SP</th>
<th>PP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=222</td>
<td>n=202</td>
<td>n=20</td>
<td>n=494</td>
</tr>
<tr>
<td>Headache</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Men</td>
<td>44</td>
<td>36.7%</td>
<td>38</td>
<td>40.4%</td>
</tr>
<tr>
<td>Women</td>
<td>178</td>
<td>55.5%</td>
<td>164</td>
<td>56.2%</td>
</tr>
</tbody>
</table>

[1] Percentages show proportion of same-sex participants within that group with headache.

In the control group, 55.6% of men reported suffering from headache, versus 40.4% of men in the group with RR/SP, and only 23.1% of men in the group with PP. In contrast, self-reported headache was almost as prevalent among women in the control group as in the two other groups. There is a significant difference between men and women in this regard, $\chi^2 (3) = 14.370, p = 0.002$. A difference between all male MS patients and all male controls can be demonstrated, $\chi^2 (1) = 13.053, p < 0.001$, but no difference is found for female MS patients compared to female controls, $\chi^2 (1) = 0.155, p = 0.694$.

Similarly, Table 5 shows the distribution of self-reported migraine.
Table 5. Distribution of self-reported migraine among men and women with MS, and in relapsing-remitting or secondary progressive MS, primary progressive MS, and the control groups in relation to sex.[1]

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>RR/SP</th>
<th>PP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=44</td>
<td>n=39</td>
<td>n=5</td>
<td>n=123</td>
</tr>
<tr>
<td>Migraine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>5.8%</td>
<td>6.4%</td>
<td>3.8%</td>
<td>14.2%</td>
</tr>
<tr>
<td>Women</td>
<td>37</td>
<td>33</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>11.5%</td>
<td>11.3%</td>
<td>13.8%</td>
<td>13.2%</td>
</tr>
</tbody>
</table>

[1] Percentages show proportion of same-sex participants within that group with migraine.

Male controls report a prevalence of self-reported migraine of 14.2%, compared to 6.4% in the RR/SP group, and 3.8% in the PP group. Among women, migraine was almost equally prevalent in all three groups, with 13.2% of the controls reported suffering from migraine. In the RR/SP and PP groups, these numbers were 11.3% and 13.8%, respectively. This results in a significant difference among men and women, $\chi^2 (3) = 10.361$, $p = 0.016$. A significant difference between male MS patients and male controls is observed, $\chi^2 (1) = 5.919$, $p = 0.015$. No similar difference, however, is found for women, $\chi^2 (1) = 0.528$, $p = 0.467$.

Table 6 presents how many days per month the participants suffer from headache, and the distribution among the groups.

Table 6. Distribution of days per month with headache among all participants with MS, relapsing-remitting or secondary progressive MS, primary progressive MS, and in the control group.

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>RR/SP</th>
<th>PP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=243</td>
<td>n=222</td>
<td>n=21</td>
<td>n=538</td>
</tr>
<tr>
<td>Days per month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 day</td>
<td>55</td>
<td>49</td>
<td>6</td>
<td>184</td>
</tr>
<tr>
<td></td>
<td>22.6%</td>
<td>22.1%</td>
<td>28.6%</td>
<td>34.2%</td>
</tr>
<tr>
<td>1-6 days</td>
<td>120</td>
<td>113</td>
<td>7</td>
<td>290</td>
</tr>
<tr>
<td></td>
<td>49.4%</td>
<td>50.9%</td>
<td>33.3%</td>
<td>53.9%</td>
</tr>
<tr>
<td>7-14 days</td>
<td>37</td>
<td>31</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>15.2%</td>
<td>14.0%</td>
<td>28.6%</td>
<td>7.4%</td>
</tr>
<tr>
<td>&gt;14 days</td>
<td>31</td>
<td>29</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>12.8%</td>
<td>13.1%</td>
<td>9.5%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Most participants in all three groups have headache on average 1-6 days per month; this is true for 50.9% of the participants in the RR/SP group, 33.3% of the PP group, and 53.9% of the controls. However, among the participants with RR/SP, this number is 13.1% for more than 14 days, compared to only 9.5% and 4.5% in the PP group, and the control group.
respectively. The PP group has an even distribution of participants suffering from headache on average less than 1 day per month, 1-6 days per month, and 7-14 days per month. The highest prevalence of participants suffering from headache on average less than 1 day per month can be found in the control group; this is true for 34.2%. There is a statistically significant difference in the distribution of frequency between the three groups, $\chi^2 (9) = 43.861$, $p < 0.001$. There is also a significant difference between all the participants with MS and all the controls, $\chi^2 (3) = 34.637$, $p < 0.001$.

Table 7 shows the distribution of headache pain intensity between MS patients and controls.

<table>
<thead>
<tr>
<th>Pain intensity</th>
<th>MS n=224</th>
<th>%</th>
<th>Control n=492</th>
<th>%</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild:</td>
<td>70</td>
<td>31.4%</td>
<td>229</td>
<td>46.5%</td>
<td>0.53</td>
</tr>
<tr>
<td>Moderate:</td>
<td>126</td>
<td>56.2%</td>
<td>220</td>
<td>44.9%</td>
<td>1.59</td>
</tr>
<tr>
<td>Severe:</td>
<td>27</td>
<td>11.9%</td>
<td>43</td>
<td>8.7%</td>
<td>1.43</td>
</tr>
<tr>
<td>Missing data:</td>
<td>1</td>
<td>0.4%</td>
<td>0</td>
<td>0.0%</td>
<td></td>
</tr>
</tbody>
</table>

Fewer MS patients than controls report mild headache pain intensity, 31.4% versus 46.5%, $OR = 0.53$ (95% CI = 0.38-0.73). In contrast, more MS patients report moderate or severe pain intensity, $OR = 1.59$ (95% CI = 1.16-2.18), and $OR = 1.43$ (95% CI = 0.86-2.38), respectively. The difference between the groups with regard to severe pain intensity is, nonetheless, nonsignificant.

Table 8 shows how often all MS patients and all controls take prescription-free drugs due to headache.
Table 8. Distribution of usage frequency of prescription-free drugs due to headache among all MS patients and all controls.

<table>
<thead>
<tr>
<th>Usage frequency</th>
<th>MS</th>
<th>%</th>
<th>Control</th>
<th>%</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seldom/never:</td>
<td>295</td>
<td>66.6%</td>
<td>605</td>
<td>67.4%</td>
<td>1.01</td>
</tr>
<tr>
<td>1-3 times per mnth.:</td>
<td>96</td>
<td>21.6%</td>
<td>252</td>
<td>27.6%</td>
<td>0.72</td>
</tr>
<tr>
<td>1-3 times per week:</td>
<td>38</td>
<td>8.5%</td>
<td>41</td>
<td>4.4%</td>
<td>1.99</td>
</tr>
<tr>
<td>Daily:</td>
<td>15</td>
<td>3.3%</td>
<td>5</td>
<td>0.5%</td>
<td>6.35</td>
</tr>
</tbody>
</table>

As a group, 66.6% of MS patients and 67.4% of controls take prescription-free drugs for headache, OR = 1.01 (95% CI = 0.79-1.28). Even though more participants in the control group take prescription-free drugs 1-3 times per month, 27.6% versus 21.6%, OR = 0.72 (95% CI = 0.55-0.95), the reverse is true for 1-3 times per week, and daily, OR = 1.99 (95% CI = 1.26-3.14) and OR = 6.35 (95% CI = 2.29-17.57), respectively.
IV. A. Discussion

This paper is based on the largest case-control study performed on multiple sclerosis and cephalalgia. Questionnaires were sent to 970 multiple sclerosis patients, in addition to 1100 controls. Data is based on 444 patients and 903 controls that responded. Out of 444 MS patients, 324 were women, and out of the 903 controls, 529 women responded. The high female: male ratio in the group with multiple sclerosis reflects the nature of the disease, as women are more than twice as likely to develop MS(18). Almost all of the controls are in the 30-59 age group, with the majority being in their 40s. On the other hand, the majority of the patients are in the 40-69 age group. This naturally affects the reported headache prevalence in this study, as headache prevalence decreases with age(48;49). Furthermore, the lower response rate for the group with multiple sclerosis may similarly result in a lower observed prevalence of headache, lower observed pain intensity, and also lower observed usage of prescription-free drugs, as we cannot rule out that the patients with the most severe symptoms are the least likely to respond. Conversely, the higher female: male ratio of the patients could lead to a falsely high prevalence, as primary headache is more common in women(25-27;33;48).

Previous studies have reported a higher prevalence of headache in patients with multiple sclerosis(38-42), although a limited number of studies exist. In our study, we found no significant association between the prevalence of self-reported headache, migraine included, and multiple sclerosis in general. However, we found that the distribution of self-reported headache differed from that of the participants with relapsing-remitting disease or secondary progressive disease, and that of the participants with primary progressive disease. The prevalence was significantly lower among multiple sclerosis patients suffering from primary progressive disease than among patients with relapsing-remitting or secondary-progressive disease. This is in contrast to what was found by Martinelli Boneschi et al., who reported a higher prevalence of at least one type of pain, including headache, among 43 patients with primary progressive disease, than among 320 patients with relapsing-remitting disease (p = 0.02)(42). In addition, the same study reported a higher prevalence of tension-type headache in the group with primary progressive disease, compared to the group with relapsing-remitting disease, although not significant; 18.6% and 14.1%, respectively, and 10.8% in a group of 65
patients with secondary progressive disease (p value missing). We have merged the participants with RR and SP into one group in our study for this comparison.

Comparably, for migraine exclusively, we found no significant difference between MS patients and controls with regard to prevalence. Neither was, however, any significant difference found between the group with RR or SP, and the group with PP. Taken into account that all participants with self-reported migraine are included in the group of participants reportedly suffering from headache, this indicates that the higher number of self-reported headache in patients with PP can be ascribed to headache types other than migraine, namely tension-type headache, cluster headache, as well as secondary headache types. For both self-reported migraine and self-reported headache in general, the smaller sample size of the PP group must be taken into consideration, possibly impacting negatively upon the validity.

While no significant difference can be observed between MS patients and controls, this only applies to the two groups as a whole. For both self-reported headache and migraine, there is a significant difference between these groups when only observing male participants. That no significant difference can be observed in the groups as a whole is attributable to there being no demonstrable significant difference between the groups with regard to the female participants. The prevalence of self-reported migraine among controls in this study is, however, higher than expected: The largest Norwegian study reports prevalences of 10.2% and 4.6% for women and men, respectively(30), which are lower than the values observed in our study; 13.2% for women and 14.2% for men. One could perhaps expect bone marrow donators to be healthier than the average individual. We theorize that part of the explanation for our findings could be that the healthier control group in our study has a lower threshold of reporting pain and other headache symptoms. Given the considerably lower female:male ratio in the control group than in the MS group, the significant differences in self-reported headache and self-reported migraine between the male groups are conceivable. This theory is also supported by comparison of the prevalences of self-reported headache in our control group to what should be expected: Linde et al. reports headache prevalences of 42.6% in women and 29.6% in men, while the same numbers in our study are 54.1% and 55.6%,
respectively. One could therefore assume that, had we used a different control group, no significant difference would have been observed, or even that the headache prevalence in the MS group would have been significantly higher than among the controls.

We have found uneven distribution between the groups with reference to how many days per month the participants suffer from headache. MS patients with self-reported headache are observed to have symptoms a significantly greater number of days per month than the rest of the participants. We know that interferon-beta can increase both the frequency and pain intensity of headache(44), and while this study does not outline the usage of these drugs, first-line treatment in Norway is comprised of interferon-beta drugs(19). This should not be neglected, owing to the fact that the increased frequency of headache symptoms in MS patients could be ascribed to side effects of drug usage.

The single-variable factors examined in tables 6 through 8 detail headache pain intensity, and the usage of prescription-free drugs for headache. We observed that a significantly smaller proportion of MS patients had mild symptoms, whereas a significantly larger proportion had moderate symptoms, when compared to controls. Also, a nonsignificant larger proportion had severe symptoms. In addition, regarding prescription-free drug usage for headache, no significant difference was found between the groups when it comes to the participants that never or seldom take prescription-free drugs. A significantly smaller proportion of the MS patients take prescription-free medications for headache 1-3 times per month, while the reverse holds true for the proportion of MS patients taking such medications 1-3 times per week or daily. These variables were chosen in addition to headache and migraine prevalences and symptom frequency, due to the fact that little data exist on the matter. We know that interferon-beta may have adverse effects, e.g. muscle ache and fever(44). These effects alone could explain a portion of the higher prescription-free drug numbers. At least one study found that a lower proportion of MS patients with comorbid migraine used prophylactic drugs compared with controls(39), and several studies show that MS patients suffer from more somatic pain, as well as a higher intensity(21;42). There was, however, a misprint in the questionnaire connected to the questions on prescription-free drug usage in this study. Both “1-3 times per week” and “1-3 times per month” stated “1-3 times per week”, which could
have affected values for both of the variables, most likely leading to a falsely high proportion picking the true option stating “1-3 times per week”.

Omitting the limitations mentioned above, this study has one other plausible shortcomings: The 1100 controls have been taken from the Norwegian Bone Marrow Registry. These participants are all from Norway, but nonetheless geographically dispersed. In contrast, most MS patients live in eastern Norway, mainly in Oslo. This constitutes a biased sample, which could affect all variables in this study.
V. Conclusion

The major findings of this study are: i) A significantly lower prevalence in male MS patients compared to male controls with regard to self-reported headache in general, and to migraine. A similar prevalence in female MS patients as controls was observed, as well as between the control group and the MS group as a whole. ii) A significantly higher number of days per month of headache symptoms in MS patients compared to controls. iii) A significantly higher headache pain intensity and prescription-free drug usage for headache among patients with MS. Thus, MS patients who do have headache are more affected by this than controls.

No conflicts of interests have been declared for this study.
Reference List


Ref Type: Online Source


Ref Type: Online Source


Kjære deltaker.

Dette skjemaet inneholder spørsmål om hodepine, smørter, musker og ledd og bruk av reseptfrie medisiner.

Vi takker på forhånd for ditt verdifulle bidrag!

Hodepine og smørter

1. Har du vært plaget av hodepine det siste året?  □ Ja   □ Nei

   Hvis nei, gå til spørsmål 8

   Hvis ja, hva slags hodepine?
   □ Migréne
   □ Annen hodepine

2. Omtrent antall dager pr. måned med hodepine?
   □ Mindre enn 1 dag
   □ 1-6 dager
   □ 7-14 dager
   □ Mer enn 14 dager

3. Hvor sterk er hodepinen vanligvis?
   □ Mild (hemmer ikke aktivitet)
   □ Moderat (hemmer aktivitet)
   □ Sterk (forhinder aktivitet)

4. Hvor lenge varer hodepinen vanligvis?
   □ Mindre enn 4 timer
   □ 4 timer - 1 døgn
   □ 1 - 3 døgn
   □ Mer enn 3 døgn
5. Er hodepine vanligvis preget av/eller ledsaget av:  
(Sett ett kryss pr. linje)

- Bankelde/dunkende smerte?  
  □ Ja  □ Nei
- Pressende smerte?  
  □ Ja  □ Nei
- Ensidig smerte (høyre eller venstre)?  
  □ Ja  □ Nei
- Forverring ved moderat fysisk aktivitet?  
  □ Ja  □ Nei
- Kvalme og/eller oppkast?  
  □ Ja  □ Nei
- Lys og lydskyhet?  
  □ Ja  □ Nei

6. Før eller under hodepine; kan du ha forbigående:  
(Sett ett kryss pr. linje)

- Synsforstyrrelse? (takkede linjer/flimring/tåkesyn/lysglimt)  
  □ Ja  □ Nei
- Nummenhet i halve ansiktet eller i hånden?  
  □ Ja  □ Nei

7. Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine:  
□ □ Dager

---

Muskler og ledd

8. Har du i løpet av det siste året vært plaget med smertesmerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?  
□ Ja  □ Nei

Hvis nei, gå til spørsmål 11

Hvis ja, har du hatt plager i disse områdene? (Sett ett eller flere kryss)

□ Nakke
□ Skuldre
□ Øvre del av rygg
□ Albuer
□ Korsrygg
□ Håndledd/hender
□ Hofter
□ Knær
□ Ankler/fötter
9. Har du vært plaget i både i høyre og venstre kroppshalvdel?  □ Ja  □ Nei

10. Har plagene hindret deg i å utføre daglige aktiviteter?

   I arbeid?  □ Ja  □ Nei
   På fritiden?  □ Ja  □ Nei

11. Er du operert for ryggplager?

   Hvis ja, hvilken type operasjon?
   □ Prolaps/ischias-operasjon
   □ Avstivning
   □ Annet
   □ Ja  □ Nei

---

**Bruk av reseptfrie medisiner**

12. Hvor ofte har du brukt reseptfrie medisiner mot følgende plager i løpet av den siste måneden? (Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th>Plage</th>
<th>Sjelden/aldri</th>
<th>1-3 g/uke</th>
<th>1-3 g/uke</th>
<th>Daglig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halsbrann/sure oppstøt</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Treg mage</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Hodepine</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Smerter i muskler/ledd</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

13. Har du brukt noen av disse reseptfrie medisinene minst en gang i uka i løpet av den siste måneden? (Sett ett kryss pr. linje)

Paracetamol, Paracet, Panodil, Pamol, Pinex, Perfalgan  □ Ja  □ Nei
Albyl E (500 mg), Aspirin, Globoïd, Dispril  □ Ja  □ Nei
Ibuprofen, Ibux, Ibupro, Ibumetin, Brufen  □ Ja  □ Nei
Naproxen, Naprosyn, Ledox  □ Ja  □ Nei
Andre  □ Ja  □ Nei