Increased frequency of migraine among women with endometriosis

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BACKGROUND: Our aim is to assess the prevalence and characteristics of headache in patients with endometriosis compared with women without this disease. METHODS: One hundred and thirty-three women with histologically proven endometriosis and 166 controls were interviewed by a neurologist experienced in headache diagnosis; the headache disorders were classified according to the 1988 International Headache Society criteria. RESULTS: The prevalence of migraine was significantly higher among women with endometriosis [n = 51, 38.3%; 95% confidence interval (CI) 30.1–47.2%] than in controls (n = 25, 15.1%; 95% CI 10.0–21.4%) (P < 0.001). Migraine with aura was observed in 18 women with endometriosis (13.5%) and in two controls (1.2%; P < 0.001). The age at migraine onset was significantly lower in women with endometriosis than in controls (16.4 versus 21.9 years; P = 0.001). No significant difference was observed in pain intensity and attack frequency between the two groups; a trend for women with endometriosis to have longer unmedicated attacks was observed. No significant correlation was observed between attack frequency, unmedicated headache duration, migraine intensity and the severity of endometriosis. CONCLUSION: Migraine is more frequent in women with endometriosis than in controls, although its presence and characteristics are not related to the severity of endometriosis.

Key words: endometriosis/headache/migraine/migraine with aura

Introduction

Despite the fact that headache may seriously impair the quality of life in those who suffer from it, these patients often do not seek adequate diagnosis and treatment. In particular, several recent, large-scale studies documented failure of primary care physicians to identify migraine (Tepper et al., 2003) and suggested that the evaluation of the patients by headache experts is required for adequate diagnosis (Lipton et al., 2002, 2003). Correct diagnosis of migraine is important because inappropriate treatment can result in inadequate pain relief and poor patient outcomes.

Subjects with endometriosis are significantly more likely to have a number of additional distressing or disabling conditions than other women; these include a variety of autoimmune diseases, allergies, asthma, hypothyroidism, chronic fatigue syndrome and fibromyalgia (Sinaii et al., 2002). Clinical observations since the 1970s have suggested that women with endometriosis suffer headache significantly more often than those without endometriosis (Tervila and Marrtila, 1975); however, to the best of our knowledge, no previous study has examined the prevalence and characteristics of headache in women with endometriosis by using the 1988 International Headache Society (IHS) criteria (Headache Classification Committee of the International Headache Society, 1988). The IHS classification system is the standard clinical and research tool for categorizing headache disorders; this system has been found to be clinically applicable, exhaustive, reliable and valid (Iversen et al., 1990; Rasmussen et al., 1991a; Merikangas et al., 1993; Granella et al., 1994; Leone et al., 1994; Olesen, 1996).

In the current study, we sought to determine the prevalence and characteristics of headache in patients with endometriosis compared with women without this disease.

Materials and methods

This study included women of reproductive age undergoing laparoscopy because of infertility, ovarian cysts, uterine leiomyomas or pelvic pain in the period between June 2002 and April 2004. During the pre-operative clinic, all women examined by two investigators (F.S. and B.S.) were asked, ‘In the past year, have you had at least one headache?’ If this question was answered in the affirmative, the patients were referred to a neurologist experienced in headache diagnosis (P.S.) who performed a clinical interview. Headache disorders were classified according to the 1988 IHS criteria (Headache Classification Committee of the International Headache Society, 1988), which divides headaches into two broad categories: primary
and secondary headache disorders. Secondary headaches are attributed to another disorder, and can be caused by intracranial or extracranial structural abnormalities or by systemic or metabolic conditions. In primary headache disorders, the headache itself is the illness; primary headache disorders include migraine, tension-type headache and cluster headache.

Age at headache onset, headache frequency, relationship to the menstrual cycle, duration of headache (unmedicated), pain intensity (scored on a 10-point ranked ordinal scale, from 0 = absence of pain to 10 = the worst possible pain) and disability were investigated. Specific questions were asked about headache features including the location and quality of pain, and the occurrence of nausea, vomiting, photophobia, phonophobia, and visual or sensorimotor aura. Subjects suffering headache were asked about usual treatment for their headache; they were also asked if they had ever consulted a physician for headache and, if so, if the physician was a headache specialist. The interview included questions on demographic (age) and health characteristics/behaviours (height, weight, smoking status, use of oral contraception). The neurologist who performed the interview was not aware of the gynaecological problems of the patients; in all cases, the interview was performed before surgery.

Data on the patient’s primary gynaecological problem, full menstrual history, medical therapies and previous surgical treatments were collected. The presence of dysmenorrhoea, deep dyspareunia and chronic pelvic pain (>6 months) was investigated. The patients were asked to rate the intensity of the pain symptoms in the 3 months before surgery on a 10-point ranked ordinal scale (from 0 = absence of pain to 10 = the worst possible pain). During laparoscopy, the location and extension of endometriotic lesions were recorded. The extent of endometriosis was scored according to the revised classification of the American Fertility Society (rAFS) (American Fertility Society, 1985). The diagnosis of endometriosis was confirmed by the histological examination of specimens removed at surgery. All women who had used GnRH analogues in the year prior to surgery were excluded from the study. Thirty-nine women had mild endometriosis (rAFS, stage I–II) and 94 severe endometriosis (rAFS, stage III–IV).

None of the patients included in the study reported previous cerebrovascular events (haemorrhagic or ischaemic stroke). The prevalence of headache was significantly higher among women with endometriosis [n = 133; 36.1% (95% CI 28.8–44.0%)] than in the control group (n = 166; 22.3% (95% CI 15.7–30.1%); 95% CI 55.1–72.1%]. Accordingly, the final study population included 133 women with endometriosis and 166 controls.

Table I shows demographic characteristics, health behaviours and indication for surgery of the women included in the study. Thirty-nine women had mild endometriosis (rAFS, stage I–II) and 94 severe endometriosis (rAFS, stage III–IV). Among women with endometriosis, 117 (88.0%) subjects reported dysmenorrhoea, the mean (±SD) intensity of pain was 8.2 ± 2.1; 83 (62.4%) patients complained of deep dyspareunia, the mean (±SD) intensity of pain was 6.3 ± 2.0; and 58 (43.6%) women suffered chronic pelvic pain (>6 months), the mean (±SD) intensity of pain was 6.5 ± 2.4. None of the patients included in the study reported previous cerebrovascular events (haemorrhagic or ischaemic stroke).

**Statistical analysis**

Based on the results of a previous study investigating migraine prevalence in women (Lipton et al., 2001b), a power calculation indicated that ~280 patients in each group would be necessary to detect a 10% difference in migraine prevalence between the two groups with a power of at least 80% at a 5% level of significance. The study was ended pre-term based on the results of an interim analysis.

Data were analysed by using Student’s t-test, Mann–Whitney U-test, 2 × 2 χ² test, and Fisher’s exact test. The Spearman test was employed to evaluate the correlation between the intensity of migraine and the severity of pain symptoms. Statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) (version 10.0.5, SPSS Inc., Chicago, IL). A P-value < 0.05 was considered statistically significant.

**Results**

**Baseline characteristics of the study population**

Out of 304 women approached for the study, 299 patients gave their consent and were interviewed, yielding a response rate of 98.4%; accordingly, the final study population included 133 women with endometriosis and 166 controls.

Table I shows demographic characteristics, health behaviours and indication for surgery of the women included in the study. Thirty-nine women had mild endometriosis (rAFS, stage I–II) and 94 severe endometriosis (rAFS, stage III–IV). Among women with endometriosis, 117 (88.0%) subjects reported dysmenorrhoea, the mean (±SD) intensity of pain was 8.2 ± 2.1; 83 (62.4%) patients complained of deep dyspareunia, the mean (±SD) intensity of pain was 6.3 ± 2.0; and 58 (43.6%) women suffered chronic pelvic pain (>6 months), the mean (±SD) intensity of pain was 6.5 ± 2.4. None of the patients included in the study reported previous cerebrovascular events (haemorrhagic or ischaemic stroke).

**Prevalence of headache in women with and without endometriosis**

The prevalence of headache was significantly higher among women with endometriosis [n = 85, 63.9%; 95% confidence interval (CI) 55.1–72.1%] than in the control group (n = 60; 36.1%; 95% CI 28.8–44.0%) (P < 0.001). When the different types of headache were considered, only migraine (both with and without aura) was significantly more frequent among women with endometriosis (n = 51, 38.3%; 95% CI 30.1–47.2%) than in the control group (n = 25, 15.1%; 95%
CI 10.0–21.4%) \((P < 0.001)\) (Table II). In particular, migraine with aura was observed in 18 women with endometriosis (13.5%; 95% CI 8.2–20.5%) and in two control subjects (1.2%; 95% CI 0.1–4.3%) \((P < 0.001)\).

No significant difference was observed in the prevalence of migraine among women with mild (15 out of 39) and severe endometriosis (36 out of 94) \((P = 0.986)\). Among women with endometriosis, there was a trend for the prevalence of migraine to be higher in subjects with dysmenorrhoea, deep dyspareunia and/or chronic pelvic pain (39.5%, 47 out of 119) than in women without pain symptoms (28.6%, four out of 14), but the difference was not statistically significant \((P = 0.427)\).

**Characteristics of migraine in women with and without endometriosis**

Headache characteristics for the 51 women with endometriosis and 25 controls suffering migraine are displayed in Table III. The age at migraine onset was significantly lower in women with endometriosis than in controls \((P = 0.001)\); seven (13.7%) women with endometriosis and no control had experienced migraine onset before the age of 10 years; 30 (58.8%) women with endometriosis and 15 (60.0%) controls had experienced migraine onset between 10 and 20 years of age. The mean intensity of pain was similar in women with and without endometriosis; 41.2% \((n = 21)\) of women with endometriosis and 32.0% \((n = 8)\) of controls reported very high levels of pain (9–10 on a 10-point scale). No significant difference was observed in the migraine attack frequency between women with and without endometriosis; 64.7% \((n = 33)\) of women with endometriosis and 64.0% \((n = 16)\) of controls reported more than one migraine attack per month; 15.7% \((n = 8)\) of women with endometriosis and 16.0% \((n = 4)\) of controls reported one or more migraine attack per week.

Only 9.8% of women with endometriosis and 8.0% of controls reported exclusively menstrual-associated attacks (MacGregor, 1996), while 51.0% of women with endometriosis and 68.0% of controls were subjected to headache during menses and at other times as well. Both in women with endometriosis and in control subjects, menstrual migraine attacks and non-menstrually associated attacks were not significantly different in severity and duration (data not shown).

**Table II. Prevalence of primary and secondary headache among women with and without endometriosis**

<table>
<thead>
<tr>
<th>Endometriosis ((n = 133))</th>
<th>Control group ((n = 166))</th>
<th>(P)-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary headache</td>
<td>72 (54.1%; 45.3–62.8)</td>
<td>48 (28.9%; 22.2–36.4)</td>
</tr>
<tr>
<td>Secondary headache</td>
<td>13 (9.8%; 5.3–16.1)</td>
<td>12 (7.2%; 3.8–12.3)</td>
</tr>
<tr>
<td>Migraine</td>
<td>51 (38.3%; 30.1–47.2)</td>
<td>25 (15.1%; 10.0–21.4)</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>18 (13.5%; 8.2–20.5)</td>
<td>2 (1.2%; 0.1–4.3)</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>33 (24.8%; 17.7–33.0)</td>
<td>23 (13.9%; 9.0–20.1)</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>0 (0.0%)</td>
<td>1 (0.6%; 0.0–0.3)</td>
</tr>
<tr>
<td>Tension-type headache</td>
<td>21 (15.8%; 10.0–23.1)</td>
<td>22 (13.3; 8.5–19.4)</td>
</tr>
</tbody>
</table>

\(^a\)\(x^2\) test.

**Table III. Distribution of headache characteristics among women with and without endometriosis suffering migraine**

<table>
<thead>
<tr>
<th>Endometriosis ((n = 51))</th>
<th>Control group ((n = 25))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at headache onset (years) ((\text{mean} \pm \text{SD}))</td>
<td>16.4 \pm 7.0</td>
<td>21.9 \pm 6.1</td>
</tr>
<tr>
<td>Positive family history of migraine [(n / %)]</td>
<td>19 (37.3%)</td>
<td>8 (32.0%)</td>
</tr>
<tr>
<td>Pain intensity (mean \pm SD)</td>
<td>8.0 \pm 1.7</td>
<td>7.8 \pm 1.8</td>
</tr>
<tr>
<td>Frequency of headache (no./year) ((\text{mean} \pm \text{SD}))</td>
<td>44.2 \pm 57.6</td>
<td>39.9 \pm 42.6</td>
</tr>
<tr>
<td>Unmedicated headache duration (h) ((\text{mean} \pm SD))</td>
<td>28.1 \pm 30.8(^a)</td>
<td>21.6 \pm 14.9</td>
</tr>
<tr>
<td>Menstrual-associated attacks(^b) [(n / %)]</td>
<td>4 (9.8%)</td>
<td>2 (8.0%)</td>
</tr>
<tr>
<td>Attacks during menses and at other times as well [(n / %)]</td>
<td>26 (51.0%)</td>
<td>17 (68.0%)</td>
</tr>
<tr>
<td>Attacks unrelated to the menstrual cycle [(n / %)]</td>
<td>21 (41.2%)</td>
<td>6 (24.0%)</td>
</tr>
<tr>
<td>Ever referred to a physician for headache [(n / %)]</td>
<td>36 (70.6%)</td>
<td>15 (60.0%)</td>
</tr>
<tr>
<td>Ever referred to headache specialist [(n / %)]</td>
<td>14 (27.4%)</td>
<td>6 (24.0%)</td>
</tr>
<tr>
<td>Preventive treatment</td>
<td>3 (5.9%)</td>
<td>1 (4.0%)</td>
</tr>
<tr>
<td>Acute treatment</td>
<td>47 (92.2%)</td>
<td>23 (92.0%)</td>
</tr>
<tr>
<td>Analgesics and NSAIDs</td>
<td>36 (70.6%)</td>
<td>18 (72.0%)</td>
</tr>
<tr>
<td>Triptans</td>
<td>4 (7.8%)</td>
<td>1 (4.0%)</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>3 (5.9%)</td>
<td>2 (8.0%)</td>
</tr>
<tr>
<td>Other medications</td>
<td>4 (7.8%)</td>
<td>2 (8.0%)</td>
</tr>
<tr>
<td>No medications</td>
<td>1 (2.0%)</td>
<td>1 (4.0%)</td>
</tr>
</tbody>
</table>

\(^a\)Eleven women with endometriosis did not answer.

\(^b\)Attacks occurring regularly on or between days 2 or 2 of the menstrual cycle and at no other time (MacGregor, 1996).

Numerical data are expressed as the mean \((\pm \text{SD})\) and compared using Student’s \(t\)-test or the Mann–Whitney U-test. Categorical data are expressed as \(n / \%\) and compared using \(\chi^2\) analysis or Fisher’s exact test.

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There was a trend for women with endometriosis to have longer unmedicated attacks owing to a higher percentage of subjects experiencing attacks of \( \geq 48 \text{h} \) (10 out of 41, 24.4%) than in the control group (four out of 25, 16.0%).

**Medical consultation and medication use**

The majority (70.6% of women with endometriosis and 60.0% of controls) of migraine sufferers had consulted a physician at some time for headache; however, referral to a headache specialist was reported by only 27.4% of women with endometriosis and 24.0% of control subjects.

Preventive treatment was used by three women with endometriosis and one control. Analgesic (either alone or in combination) and non-steroidal anti-inflammatory drugs (NSAIDs) were the most frequently used medications for the acute treatment both among women with endometriosis (70.6%) and in the control group (72.0%). Only 7.8% of women with endometriosis and 4.0% of controls used triptans (Table III).

**Disability**

Of those who were employed (35 women with endometriosis and 22 controls), 51.4% of women with endometriosis and 22.7% of controls reported at least one missed day due to dysmenorrhoea or headache in the 3 months before surgery \((P < 0.032)\). When at work with migraine, the women with endometriosis and controls reported, respectively, a mean \((\pm SD)\) reduction in work effectiveness of 46.7% \((\pm 18.7\%)\) and 30.5% \((\pm 8.6\%)\) \((P < 0.001)\).

**Correlation between migraine characteristics and severity of endometriosis**

No significant difference was observed in attack frequency and unmedicated headache duration between women with mild and severe endometriosis. The mean \((\pm SD)\) migraine intensity was similar in women with mild \((7.9 \pm 1.5)\) and severe endometriosis \((8.1 \pm 1.8)\). No correlation was observed between the intensity of dysmenorrhoea and the intensity of migraine \((r = 0.035, P = 0.824, n = 43)\). Among women with endometriosis, no significant difference was observed in the mean \((\pm SD)\) intensity of dysmenorrhoea between subjects with and without migraine \((8.2 \pm 2.2\) and \(8.2 \pm 2.0)\). The intensity of deep dyspareunia and chronic pelvic pain did not correlate with the intensity of migraine.

**Discussion**

In our population of women with endometriosis, 33.8% of patients suffered migraine and 13.5% experienced aura preceding headache onset; this prevalence of migraine is significantly higher than that observed in the control group. This finding is strengthened by the fact that the prevalence of migraine observed in the control women (15.1%) is similar to that reported by other authors (range 15–19%) in Italy (D’Alessandro et al., 1988; Roncolato et al., 2000) and in other countries (Rasmussen et al., 1991b; Stewart et al., 1992, 1996; Lipton et al., 2001b; Lucas, 2004). Although a recall bias cannot be excluded, women with endometriosis reported a lower age at migraine onset than controls. Furthermore, our results indicate that migraine severity is similar in women with and without endometriosis and it is not related to the severity of endometriosis.

The findings of the current study raise some problems and concerns.

Headache classification depends on accurate diagnosis. Subjects suffering migraine often do not seek appropriate care and it has been reported that 82% of patients who consult a physician about their headaches do not visit a neurologist or headache specialist; instead, they consult their primary care practitioner, which, for many women is their gynaecologist (Lipton et al., 2001a; MacGregor et al., 2003). About 60% of women notice an increase in the frequency of migraine attacks during the menstrual cycle, and this relationship may be the reason why these patients consult gynaecologists regarding their headaches (MacGregor, 1996; Kornstein and Parker, 1997).

Only 27.4% of women with endometriosis and 24.0% of control subjects had seen a headache specialist for their migraine; this low rate of migraine assessment by a specialist resulted in low rates of specific treatment. Most (98.0% of women with endometriosis and 96.0% of controls) of our patients with migraine had used medications to treat their headache, but the majority of the patients used symptomatic drugs; 70.6% of women with endometriosis and 72.0% of controls used analgesics or NSAIDs. Other symptomatic drugs, such as triptans and ergot derivatives, were taken by only a minority of patients. With these elements in mind, it seems reasonable to conclude that the rate of specialized care and adequate treatment of migraine in our sample is low.

It is well known that the physical health and the emotional well-being of many women of reproductive age are significantly affected by endometriosis when dysmenorrhoea, deep dyspareunia and chronic pelvic pain are present. When endometriosis and migraine are co-morbid, each exerts a significant and independent negative influence on health-related quality of life. Among the employed subjects included in the current study, women with endometriosis reported missing more working days (because of dysmenorrhoea or migraine) and to have a more severe reduction in work effectiveness (when at work with dysmenorrhoea or migraine) than controls.

The strengths of the current study consist of the fact that, during the study period, all patients examined by two investigators during the pre-operative clinic were approached for the study and the participation was almost complete.

Over 70% of women with endometriosis included in the current study had severe disease (rAFS, stage III–IV). The high prevalence of severe endometriosis in our series can be explained by the fact that our institute represents a referral centre for the surgical treatment of endometriosis in our region, Liguria, in Northern Italy, and many cases of severe disease were referred to our institute from other centres. However, the high prevalence of severe endometriosis in the current series is unlikely to affect our findings because the prevalence and severity of migraine were similar among women with mild and severe endometriosis.
Previous studies showed that migraine prevalence declines after spontaneous menopause (Wang et al., 2003), while the sudden hormonal changes caused by surgical ovariectomy may worsen the migraine course (Neri et al., 1993). Considering that, to the best of our knowledge, no previous study has examined the effect of GnRH analogue treatment on migraine course, no woman who had used this treatment in the year prior to surgery was included in the study.

Among women of reproductive age, migraine, particularly with aura, is an independent risk factor for ischaemic stroke (Tzourio et al., 1993; Carolei et al., 1996; Donaghy et al., 2002; Nightingale and Farmer, 2004) and the relative risk is greatly reduced with adequate diagnosis and treatment.

A significant impairment, and their work performance may be significantly bid, the well-being of the patient may be significantly impaired, and their work performance may be significantly reduced. Although migraine cannot be cured or completely eliminated using currently available treatment, pain and associated symptoms can be controlled and disability can be greatly reduced with adequate diagnosis and treatment.

References


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