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Migraine in women with chronic pelvic pain with and without endometriosis

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Abstract

Objective—To examine the prevalence of migraine in women with chronic pelvic pain with and without endometriosis.

Design—Prospective study of headache, pelvic pain, and quality of life before laparoscopic surgery for pelvic pain. Endometriosis was diagnosed pathologically. Headaches were classified as migraine or non-migraine using International Headache Society criteria.

Setting—Clinical research hospital.

Patient(s)—108 women in a clinical trial for chronic pelvic pain (NCT00001848).

Intervention(s)—Laparoscopy to diagnose endometriosis, assessment by neurologist to assess headaches.

Main Outcome Measure(s)—Prevalence of migraine and other headaches in women with chronic pelvic pain with or without endometriosis. Headache frequency, severity and relationship to pelvic pain and endometriosis.

Result(s)—Lifetime prevalence of definite or possible migraine was 67% of women with chronic pelvic pain. An additional 8% met criteria for possible migraine. Migraine was no more likely in women with endometriosis than those without. Women with the most severe headaches had a lower quality of life compared with those with pelvic pain alone.

Conclusion(s)—Migraine headache is common in women with chronic pelvic pain, regardless of endometriosis, and contributes to disability in those with both conditions. The strong association suggests a common pathophysiology.

Keywords

Chronic pelvic pain; endometriosis; headache; migraine; quality of life; regional pain syndrome

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Migraine is an episodic headache disorder with neurologic, gastrointestinal, and autonomic changes (1). In the United States, 18% of women and 6% of men had at least one migraine episode in the previous year (2). Before puberty, migraine prevalence is approximately 4%. After puberty, prevalence increases rapidly in girls, reaching a peak 1-year prevalence of approximately 23% in women aged 40 to 49 years (3, 4).

Chronic pelvic pain is similarly common, affecting 15% to 24% of reproductive-aged women and accounting for 10% of gynecologic outpatient visits (5–7). Endometriosis, a condition in which endometrial tissue grows outside of the uterus on the reproductive organs, pelvic viscera, and peritoneum, is commonly associated with chronic pelvic pain. Endometriosis is present in about 10% of reproductive-aged women (8).

There is emerging evidence of a relationship between migraine and endometriosis. In 1975, Tervila and Marttila (9) reported that 84% of women with menstrual pelvic pain and surgically documented endometriosis had recurrent menstrual headaches, compared with only 60% of those with dysmenorrhea without endometriosis. Twenty-eight percent of patients with endometriosis had nausea and “flashing in the eyes” with their headaches, consistent with migraine, while only 18% of those without endometriosis had migrainous features. In a large population-based survey by the Endometriosis Association, 65% of women with endometriosis reported having menstrual headaches (10). A study of women undergoing laparoscopy found migraine was more frequent in women with endometriosis compared to those without endometriosis (11). Tietjen et al. (12, 13) reported an increased frequency of menorrhagia and endometriosis in women with migraine, and Nyholt et al. (14) found common genetic influences on the co-occurrence of migraine and endometriosis.

However, none of these studies included women with chronic pelvic pain without endometriosis. Such patients are an important control group for understanding the relationship between these common conditions and shared pathogenetic mechanisms. Our study evaluated headache in women with chronic pelvic pain with and without endometriosis.

MATERIALS AND METHODS

Women participated in a placebo-controlled therapeutic trial of the safety and effectiveness of surgical excision of endometriosis combined with raloxifene or placebo in women with chronic pelvic pain (NCT00001848). All women had at least a 6-month history of chronic pelvic pain and met the inclusion and exclusion criteria listed in Table 1.

The participants provided a detailed medical and reproductive health history, including completion of standardized questionnaires on pelvic pain, headache, depression, and quality of life(15). Ambiguous or incomplete information was clarified by personal interview, and affected patients were evaluated by the study neurologist. Headache and pelvic pain severity were rated on a visual analog scale between 0 (no pain) and 10 (most intense pain). Laboratory tests included complete blood count (CBC), serum lipids, liver function test (LFT), blood urea nitrogen (BUN), creatinine, electrolytes, glucose, thyroid panel, antinuclear antibody (ANA), rheumatoid factor, erythrocyte antisedimentation rate (ESR), and creatinine kinase (CK).

Study participants underwent laparoscopic surgery to establish or exclude endometriosis and to resect endometriosis lesions, if present. Random biopsy samples of normal appearing peritoneum were not obtained. Excised tissue was examined histologically.

Women reporting recurrent headaches were classified using International Headache Society (IHS) criteria (16). Migraine was considered definite if all five major IHS criteria for

migraine were met (ICHD-2 1.1 and 1.2) and probable if four criteria were met (ICHD-2 1.6). Those with “definite” and “probable” migraine formed the migraine headache cohort. Women with headaches meeting 0 to 3 migraine criteria constituted the non-migraine headache cohort, and those without headache were placed in the third, no headache cohort.

The cohorts were compared on headache frequency and severity, use of analgesics, relationship of headaches to pelvic pain and endometriosis, and presence of comorbid conditions. Results were calculated as frequencies, percents, and mean ± standard error of the mean (SE). Group frequencies were compared by chi-square or Fisher’s exact tests, as appropriate. The *t* tests were performed for two-group and analysis of variance (ANOVA) for three group comparisons. The Jonckheere-Terpstrat test was used to assess trends between headache frequency and duration. Comparisons of the published population prevalence for chronic fatigue, asthma, and allergies to that in this study population were carried out using *Z*-tests for proportions, and the corresponding 95% confidence intervals of the differences were computed. $P \leq .05$ was considered statistically significant. Data were analyzed using SAS system software (SAS Institute Inc., Carey, NC).

The study was approved by the institutional review board of the National Institute of Child Health and Human Development. All participants gave written consent for participation.

RESULTS

One hundred and eight women met study criteria. Their mean age was 31 ± 0.7 (range: 17 to 46) years. Although only a 6-month history of pelvic pain was required for inclusion, most women had a longer history, with a mean duration of pelvic pain of 10.3 ± 0.7 years. The mean menstrual pelvic pain severity was 6.6 ± 0.3; non-menstrual pain severity was 5.2 ± 0.2. The race and ethnicity profile, 75% white, 18% African American, 2% Asian, 4% Hispanic, and 1% other, closely reflected that of the general U.S. population. Most of the women had never been pregnant (66%) and had no children (78%).

Recurrent headaches at any time were reported by 85 women (79%), 64 (59%) of whom had had a headache within the previous year. Only 23 women (21%) had never had recurrent headaches.

Of those reporting ever having recurrent headaches, 45 and 27 met criteria for definite and probable migraine, respectively. Nine (11%) met two or three migraine criteria, and four women (5%) met fewer than two. No woman had another disorder that could account for her headaches. Thus, 72 of 108 women (67%) with chronic pelvic pain had definite or probable migraine by IHS criteria (lifetime prevalence). Fifty-seven (53%) had at least one migraine attack in the previous year (1-year prevalence).

Endometriosis was diagnosed by pathologic examination of tissue resected at laparoscopy. Eighty-one women (75%) had endometriosis confirmed. Women with and without endometriosis were of similar age, gravidity, and parity. Those without endometriosis were more likely non-white and had a higher body mass index (BMI) (Table 2). Migraine was present in 54 (67%) of 81 women with endometriosis and 18 (67%) of 27 women without endometriosis ($P=1.0$). Similarly, endometriosis was documented in 54 (75%) of 72 patients with migraine and 27 (75%) of 36 patients without migraine ($P=1.0$; see Table 2).

All of the women had normal menstrual cycles. Fifty-three percent of those with headaches reported a temporal relationship between headaches and menses; headaches were most likely at the beginning of menses. The relation of headache to menses did not differ between headache cohorts.

At study entry, 84 (78%) participants reported using chronic pain medications. Analgesic use was not associated with the severity of headache or pelvic pain, or with headache frequency. Seventy-seven percent of those with migraine headaches, 100% of those with non-migraine headaches, and 75% of those without headaches used analgesics chronically.

Migraine was frequently undiagnosed and misdiagnosed. Only 49 of 72 women (68%) with migraine by IHS criteria stated that she had “migraine.” Four of 13 women (31%) with non-migraine headaches gave a history of migraine. Professional evaluation and prescription medication were underused. Among the 72 women with migraine, only 30 (42%) had ever sought medical attention for headaches. Among the 13 with non-migraine headaches, only 3 (23%) had sought treatment even though their headaches were as severe as those with migraine. For both headache groups combined, those who saw physicians had more severe headaches (6.6 ± 0.3) than those who did not (5.1 ± 0.3, P=.0007). Only 10 patients (33%) of those seeking medical treatment received triptans; 6 patients (18%) were prescribed isometheptene. Others received only non-migraine–specific analgesics or other medications.

Headaches were frequent in both headache cohorts, recurring between 1 and 16 times a month. Those with migraine reported the most frequent headaches. Ten headache patients, all with migraine, had at least 15 headache days per month. Seven of those 10 patients used analgesics during menses only and thus did not have medication overuse headache (ICH-2 8.2). The remaining three who used analgesics less frequently met criteria for chronic migraine (ICH-2 1.5.1).

Headache duration was not significantly different between migraine and non-migraine headache groups, lasting less than 2 to more than 24 hours in both. Similarly, reported average headache severity did not differ: 5.8 ± 0.2 migraine versus 4.9 ± 0.6 non-migraine headaches (P=.2329). Migraine patients (56%) were statistically significantly more likely than non-migraine headache patients (23%) to have family members with headaches (P=.0311).

Self-reported diagnoses of chronic fatigue syndrome, asthma, and allergies were statistically significantly more common in study patients than the general female population (Table 3). However, the frequencies of these conditions and fibromyalgia did not differ between cohorts. Depression tended to be more common in women with migraine (33%) than those with non-migraine headaches (23%) and those without headaches (17%) (P=.1047). Laboratory test results did not differ between the groups.

Women with pelvic pain had low quality-of-life scores for pain, disability, general health, and depression, regardless of whether they had endometriosis (see Table 2). Those without endometriosis had statistically significantly lower general health than those with endometriosis. Migraine did not further diminish quality of life except in women with the most frequent headaches who had higher disability scores than those with no headaches or less frequent headaches (P<.03).

DISCUSSION

In this study, 1-year migraine prevalence was 53% and lifetime prevalence was 67% in women between the ages of 17 and 45 years with chronic pelvic pain, a rate approximately 3 times the 18% 1-year prevalence in the general U.S. female population and more than double the 23% peak prevalence among similarly aged women (2, 3, 17, 18). Migraine headache frequency, duration, severity, and familial association were typical of cohorts with migraine and were not influenced by the presence of endometriosis. Unlike the finding of Tiedjen et al. (12, 13), biopsy-confirmed endometriosis was not more common in women with migraine than in those without migraine.

A limitation of our study is that we used published migraine prevalence reports rather than a matched control group. In addition, women volunteering for research studies on pain may be more likely to report pain elsewhere in the body. Although many women in our study population used analgesics for either pelvic pain or headaches, medication-overuse headaches were not found. Migraine is more frequent in those of lower socioeconomic status and in white women (10). These factors were unlikely to have affected our results because our participants were largely of middle socioeconomic status and their racial and ethnic distribution reflected that of the U.S. population.

We did not find differences in age, gravidity, parity, race, or severity of menstrual or non-menstrual pelvic pain between the women with migraine compared with those with non-migraine headaches or those without headaches. Although depression is reportedly associated with both migraine (19–22) and endometriosis (10, 23, 24), we found only a trend for self-reported depression to be more common in women with both migraine and pelvic pain compared with those without migraine, which may be because pain itself is a risk factor for depression (25, 26). Tietjen et al. (13) similarly failed to find an increased incidence of depression in those with comorbid migraine and endometriosis compared with migraineurs without endometriosis.

Endometriosis and migraine share comorbidities in addition to depression. Women with endometriosis have high rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome, and atopic disease (10). Migraine has similar associations with systemic lupus erythematosus (27), asthma and allergies (28, 29), and fibromyalgia (30–32). Tietjen et al. (13) reported that women with migraine and laparoscopy-confirmed endometriosis were more likely to report interstitial cystitis, chronic fatigue syndrome, and anxiety than women with migraine but no endometriosis. Although our participants were more likely to report chronic fatigue syndrome, asthma, and allergies than women in the general population, these comorbidities or fibromyalgia did not differ between the migraine, non-migraine headache, and no headache cohorts.

Endometriosis (33) and chronic pelvic pain (6) diminish quality of life; 81% of women with endometriosis miss work because of pain (10). Migraine sufferers also have a lower quality of life compared with the general population (20, 34). Similar to Terwindt et al. (28), who reported a decline in quality of life with increased headache frequency, we found that the women with most frequent headaches had higher disability scores than those with less frequent headaches. Thus, migraine did not appear to lessen quality of life beyond pelvic pain alone, except in the women with the most frequent headaches.

When two conditions occur in the same person, there are a number of alternative causal explanations (35). The apparent association may arise by coincidence or because of the method of participant ascertainment. One condition may cause the other. For example, it has been suggested that depression may cause migraine-like headaches as a form of masked depression. Shared environmental factors may also account for co-occurrence. For example, head injury is a risk factor for both migraine and epilepsy, and may account for part of the relationship between those disorders. Shared genetic risk factors may similarly account for the association between comorbid disorders (14). Finally, independent genetic or environmental risk factors may produce a brain state that gives rise to both migraine and a comorbid conditions (36).

Ferrero et al. (11) reported that among women undergoing laparoscopy those with endometriosis were statistically significantly more likely to have migraine (38%) than those without endometriosis (15%), supporting a specific relationship between endometriosis and

migraine. Their results differ from ours, in which migraine was as likely in women with endometriosis as in those with chronic pelvic pain without endometriosis.

A likely explanation for this difference is that Ferrero's endometriosis and nonendometriosis cohorts were not matched for the occurrence of pelvic pain. Their population encompassed women undergoing laparoscopy for a wide variety of indications. Post hoc analysis showed that pelvic pain and dysmenorrhea were statistically significantly more frequently the indication for surgery in the endometriosis cohort (44%) than the nonendometriosis cohort (24%; $P<.001$). Thus, in the Ferraro study as well as in ours, migraine might be more closely associated with chronic pelvic pain than with endometriosis itself.

Seeking a common pathophysiology uniting migraine and endometriosis, Ferrero et al. (11) noted that prostaglandins play a role in pathogenesis of migraine and that endometriosis is associated with elevated circulatory levels of prostaglandins. Dysregulation of nitric oxide synthesis has similarly been implicated in both migraine and endometriosis (37, 38). Although these might suffice as an explanation for migraine in those with endometriosis or associated with dysmenorrhea, our findings relate migraine to chronic pelvic pain rather than endometriosis per se.

Migrainous pain is initiated and sustained by trigeminal activation involving peripheral and central structures (39, 40). A similar, unifying pathophysiology may be impossible to identify for chronic pelvic pain, which can arise from the muscles, skin, blood vessels, and fascia of the abdominal wall and pelvic floor as well as the reproductive organs, bladder, bowel, and peritoneum (41). Absence of identifiable triggers, clear temporal patterns, and structural pathology also hamper our understanding of pelvic pain.

Central sensitization is a form of neural plasticity in which repeated painful stimulation leads to allodynia, hyperalgesia, and an increase in the territory of referred pain in absence of the initial precipitant. Spontaneous pain and pain in response to non-noxious stimuli can ensue. Central sensitization has been reported in migraine (36, 42), has been demonstrated in women with endometriosis (43), and can occur with other visceral pain (44). Because pain pathways converge on nociceptive brainstem structures, central sensitization could render women with chronic pain in one body area more liable to recurrent pain elsewhere.

We have demonstrated a strong association between chronic pelvic pain and migraine headaches. In migraine, prevention of sensitization with early treatment may be key to managing acute headache pain, whereas the use of drugs acting on enhanced central nervous system excitability is the key to preventing migraine (45). Similar concepts could be important in the development of treatment for chronic pelvic pain, apart from treatment of endometriosis. Further investigations into associations between these chronic pain conditions in women should control for the presence of pelvic pain in the absence of endometriosis, which may lead to better understanding and management of migraine, endometriosis, and chronic pelvic pain.

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TABLE 1

Inclusion and exclusion criteria of migraine study.

Criteria
Study inclusion
Age 17–45 y
Intact reproductive organs
Excellent health other than pelvic pain
At least a 3-mo history of pelvic pain
Less than grade III overweight or body mass index <40 kg/m^2
Regular, cyclic menses
No desire for pregnancy for the duration of the study
Study exclusion
Known cause of pelvic pain other than endometriosis
Significant laboratory abnormalities
Hysterectomy or bilateral salpingo-oophorectomy
Pregnancy or lactation
Use of hormonal contraception, selective estrogen receptor modulators, progestins, estrogens, steroids, or ovulation induction in the last 3 months
Other medical or surgical treatment for endometriosis in the prior 6 months
Untreated abnormal Papanicolaou smear or other gynecologic condition
History of stroke, complicated migraine, or documented transient ischemic attack
History of venous thrombosis, pulmonary embolism, or retinal vein thrombosis

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TABLE 2

Demographics and other characteristics of women with chronic pelvic pain, with and without endometriosis.

Characteristic	Endometriosis[a] (N = 81)	No endometriosis[a] (N = 27)	*P* value
Age, y	31.2 ± 0.8	31.5 ± 1.4	.86
Body mass index[b]	25.1 ± 0.6	28.4 ± 1.2	.01
Race, n (%)[b]			.02
White	65 (80.3)	16 (59.3)	
Black	13 (16.1)	7 (25.9)	
Hispanic	1 (1.2)	3 (11.1)	
Asian	2 (2.5)	0	
Other	0	1 (3.7)	
Gravida	0.9 ± 0.2	1.3 ± 0.4	.30
Parity	0.4 ± 0.1	0.8 ± 0.3	.23
Headache type, n (%)			
Migraine	54 (66.7)	18 (66.7)	1.0
Non-migraine headache	11 (13.6)	2 (7.4)	
No headaches	16 (19.8)	7 (25.9)	
Quality of life scores			
Pain	61.5 ± 4.1	63.0 ± 6.3	.86
Disability	18.0 ± 2.9	22.2 ± 6.2	.48
General health[b]	71.2 ± 1.8	62.9 ± 3.4	.02
Depression	27.1 ± 2.1	34.2 ± 4.0	.10

[a] Values are mean ± standard error of the mean.

[b] Statistically significant.

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TABLE 3

Rates per 100 of conditions comorbid with chronic pelvic pain.

Condition	Study population	U.S. female population[a]	95% Confidence interval of the difference	*P* value
Chronic fatigue syndrome	1.85	0.03	−0.012, 0.048	<.0001
Asthma	12.04	5.19	0.002, 0.135	.004
Allergies	70.37	18.41	0.430, 0.614	<.0001

[a]Sources of information: Idler et al. (46) and Reyes et al. (47).

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