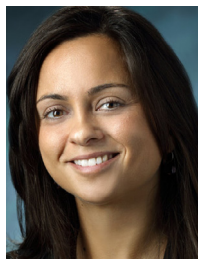


Endometriosis and the diagnosis of different forms of migraine: an association with dysmenorrhoea



BIOGRAPHY

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KEY MESSAGE

The prevalence of migraine among women with endometriosis is high, with menstrually related migraine being the most common type. In addition, dysmenorrhoea is more frequent when the two conditions coexist. Patients with endometriosis should be screened for migraine, using a multidisciplinary approach to improve the overall health outcomes.

ABSTRACT

Research question: Women with endometriosis are frequently affected by headache. How many of these have a clear diagnosis of migraine? Are the different forms of migraine related to the phenotypes and/or characteristics of endometriosis?

Design: This was a prospective nested case-control study. A consecutive series of 131 women with endometriosis who attended the endometriosis clinic were enrolled and examined for the presence of headache. A headache questionnaire was used to determine the characteristics of the headaches, and the diagnosis of migraine was confirmed by a specialist. The case group included women with endometriosis and a diagnosis of migraine, while the control group included women with only endometriosis. History, symptoms and other comorbidities were collected. A pelvic pain score and associated symptoms were assessed using a visual analogue scale.

Results: A diagnosis of migraine was made in 53.4% (70/131) of participants. Pure menstrual migraine was reported by 18.6% (13/70), menstrually related migraine by 45.7% (32/70) and non-menstrual migraine by 35.7% (25/70). Dysmenorrhoea and dysuria were significantly more frequent in patients with endometriosis and migraine than in those without migraine ($P = 0.03$ and $P = 0.01$). No difference was found for other variables, including age at diagnosis and duration of endometriosis, endometriosis phenotype, the presence of other autoimmune comorbidities or heavy menstrual bleeding. In most patients with migraine (85.7%) the headache symptoms had started years before the diagnosis of endometriosis.

Conclusion: The occurrence of headache in many patients with endometriosis is associated with the presence of different forms of migraine, is related to pain symptoms and often precedes the diagnosis of endometriosis.

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KEYWORDS

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Migraine
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INTRODUCTION

Endometriosis is a benign chronic inflammatory and sex hormone-dependent disease affecting up to 10–15% of women in their reproductive years ([Bulun et al., 2019](#); [Chapron et al., 2019](#)). Clinical features include dysmenorrhoea, dyspareunia, dyschezia, dysuria, non-cyclical pelvic pain, heavy menstrual bleeding, irregular menstrual cycles and infertility ([Vannuccini et al., 2022](#); [Zondervan et al., 2020](#)). Three major phenotypes are recognized: superficial, ovarian endometrioma and deep infiltrating endometriosis ([Chapron et al., 2019](#)).

Migraine is a complex disorder in which disabling headaches, lasting 4–72 h and variably accompanied by sensory alterations, nausea and vomiting, recur with low to high frequency ([Ashina, 2020](#)). The third edition of the International Classification of Headache Disorders (ICHD-3) distinguishes three types of migraine based on the relationship with the menstrual cycle: (i) pure menstrual migraine, which is defined as the occurrence of migraine attacks exclusively on day 1 ± 2 of menstruation in at least 2 out of 3 menstrual cycles, (ii) menstrually related migraine, when attacks occur during this window but also at other times of the cycle, and (iii) non-menstrual migraine.

Endometriosis and migraine share similarities in terms of pathogenesis ([Tietjen et al., 2006](#); [Vercellini et al., 2014](#)), with pain being the main common symptom in both conditions. Both conditions have a high prevalence in women of childbearing age, and the pathogenetic mechanisms involve a hormonal influence and chronic inflammation phenomena.

Observational studies suggest that migraine and endometriosis often coexist ([Balci BK, 2019](#); [Ferrero et al., 2004](#); [Jenabi ad Khazaei, 2020](#); [Maitrot-Mantelet et al., 2020](#); [Miller et al., 2018](#); [Wu et al., 2021](#)) and that migraine is associated with more severe endometriosis and the presence of adenomyosis ([Maitrot-Mantelet et al., 2020](#); [Wu et al., 2021](#)). Interestingly, a recent genome-wide association study found a positive and highly significant genetic association between endometriosis and migraine ([Adewuyi et al., 2020](#)).

This study investigated which forms of migraine are present in patients with

endometriosis with complaints of headache, evaluating the possible association with the phenotype of endometriosis, clinical symptoms and comorbidities. In addition, the timing of the onset of migraine compared with the diagnosis of endometriosis was evaluated.

MATERIAL AND METHODS

A prospective, nested case-control study was conducted. The initial cohort consisted of patients with endometriosis ($n = 131$) attending the authors' endometriosis clinic between September 2019 and March 2022. Within this cohort, women with endometriosis who also had migraine were considered cases, and women with endometriosis but without migraine were regarded as controls.

The diagnosis of endometriosis was based either on a previous surgical evaluation or on the combination of clinical symptoms and imaging (transvaginal ultrasound and/or magnetic resonance). Patients reporting headache were administered an *ad hoc* questionnaire (Supplementary Information) with standardized questions on headache including onset and diagnosis, timing of the headache attacks in relation to menstruation, and treatment. All participants were evaluated by a gynaecologist who recorded their characteristics, medical history and symptoms, and the results of physical examination.

The following data were collected: age, body mass index (BMI), smoking habit, family history of endometriosis, gynaecological and obstetric history, history of infertility, characteristics of the menstrual cycles and presence of endometriosis-associated symptoms (i.e. dysmenorrhoea, dyspareunia, chronic pelvic pain, dysuria or dyschezia). The presence of stress-related, inflammatory or autoimmune comorbidities, which included systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, autoimmune thyroid disorder, coeliac disease, multiple sclerosis, inflammatory bowel disease and Addison disease was also evaluated. Pelvic pain scores and associated symptoms were assessed using a visual analogue scale (VAS). Clinically, three phenotypes were distinguished: ovarian endometriosis, peritoneal superficial and deep infiltrating endometriosis, or mixed phenotypes ([Chapron et al., 2019](#)).

All participants with headache were also evaluated by a specialist at the authors' headache centre, to confirm the diagnosis of migraine; the diagnosis of aura was based on the presence of focal neurological symptoms reported by the patient. The prevalence of migraine and menstrually related migraine subtypes (i.e. pure menstrual, menstrually related and non-menstrual migraine) according to the ICHD-3 ("[Headache Classification Committee of the International Headache Society \(IHS\) The International Classification of Headache Disorders, 3rd edition, 2018](#)") was evaluated. The types of medication used by the patients were recorded. In the cohort of participants with endometriosis, those meeting the diagnostic criteria for migraine, independent of the type (with or without aura, episodic or chronic), were considered cases, and compared with those without migraine, as controls.

A migraine day was defined as a day with a headache meeting the criteria for migraine (with or without aura) or a day when an acute migraine-specific medication (triptan or ergot) was used. Consecutive migraine/headache days were considered as one single attack. The study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study was approved by the local Ethics Committee (no. 15211, 8 October 2019) and each participant signed the informed consent form.

Statistical analysis

The sample size was not based on any statistical considerations, and all consecutive outpatients with a diagnosis of endometriosis were included in the initial cohort. Demographic and baseline characteristics were summarized descriptively, namely using the mean \pm standard deviation (SD) or median and interquartile range (IQR; 25th, 75th percentile) for continuous variables, and number (percentage) for categorical data. Assumption of normality was assessed using the Shapiro–Wilk test. The chi-squared test or Fisher's exact test was used to compare categorical variables between the two groups, and the Student's *t*-test or Mann–Whitney test was used for continuous variables. Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY), and a *P*-value of <0.05 was considered significant.

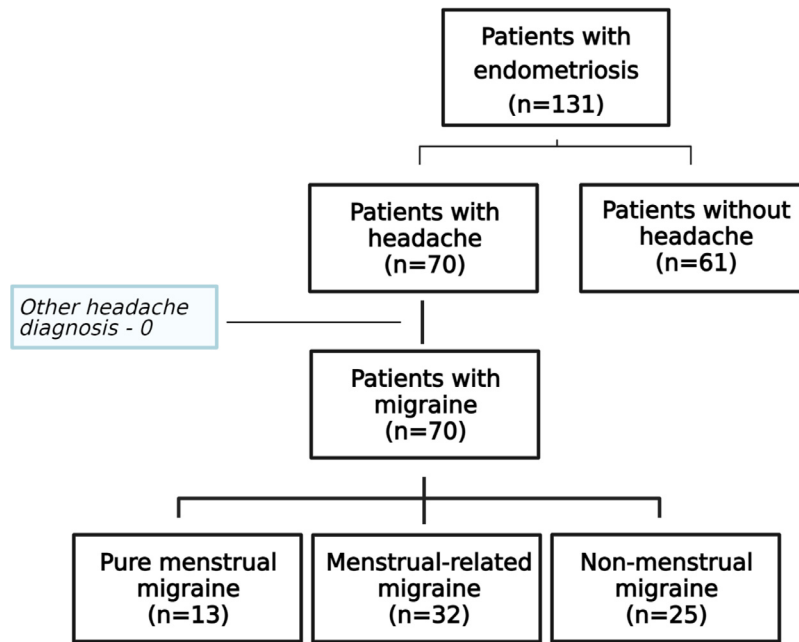


FIGURE 1 Flow chart of patient inclusion in the study.

RESULTS

The initial cohort consisted of 131 women with endometriosis with a median age of 33 years (IQR 28, 38 years) and a median BMI of 21 kg/m² (IQR 19, 24 kg/m²). Of these, headache was present in 70/131 patients (53.4%) and in all cases the diagnostic criteria for migraine with or without aura were met. Considering the menstrually related migraine subtypes according to the ICHD-3, the patients were categorized as having pure menstrual migraine (13/70, 18.6%; defined as migraine occurring exclusively on day 1 ± 2 of menstruation) or menstrually related migraine (32/70, 45.7%; defined as migraine occurring on day 1 ± 2 of menstruation, and additionally at other times of the cycle). The remaining 25 (35.7%) patients had non-menstrual migraine. The flowchart of participants is shown in [FIGURE 1](#).

No difference was found in terms of the characteristics of endometriosis such as the different phenotypes, dysmenorrhoea or chronic pelvic pain when comparing non-menstrual migraine with combined pure menstrual and menstrually related migraine (data not shown). The migraine features of these patients are summarized in [TABLE 1](#). The median age at onset of headache was 15 years (IQR 12, 18 years), and in most patients (85.7%) the migraine attacks had started years before the diagnosis of endometriosis, with a mean

time lag of 12 years. Aura was present in 10/70 patients (14.3%).

On average, participants with migraine reported a VAS pain intensity of 8 (IQR 7, 9) and most cases (84.3%) were classified as low-frequency episodic migraine, with a mean headache frequency of 3 days (±2.9 days SD) per month. According to the well-known sex preference of migraine, the most frequently reported family member who also had a history of headache was the mother (36.2%). Only 13/70 patients (18.6%) reported having seen a headache specialist before.

Ninety per cent of the patients reported current analgesic use, mostly with over-the-counter non-steroidal anti-inflammatory drugs (NSAID), as acute medication. The type and dosage of the NSAID were often self-chosen by the woman without medical advice and could substantially differ from the use recommended for migraine. Triptans, either alone or in combination with NSAID, were used by 8/70 (11.4%) participants, who corresponded to those who had received a prescription on their previous visit to the headache centre. No patient reported the use of monoclonal antibodies that block the calcitonin gene related peptide or its receptor. Only 8/70 (11.4%) patients reported an exclusive use of non-pharmacological treatments such as acupuncture, while 7/70 (10%) patients refused medication.

The phenotype of endometriosis and the comparison of the clinical history and symptoms between the participants with and without migraine are reported in [TABLE 2](#). Ovarian endometriosis and deep infiltrating endometriosis were the most frequent phenotypes; the incidence of each phenotype of endometriosis was similar between women with and without migraine. Dysmenorrhoea was the most frequently reported symptom and occurred more frequently in women with migraine (94.3%) than in those without migraine (82%) ($P = 0.03$; [TABLE 2](#)). The case group also more frequently reported a history of dysmenorrhoea in adolescence than did the control group ($P = 0.003$). Dysuria was more frequent in cases than controls (27.1% and 9.8%, respectively; $P = 0.01$). No difference was found for other variables, such as age at diagnosis and years since the diagnosis of endometriosis, presence of adenomyosis or autoimmune comorbidities, or heavy menstrual bleeding ([TABLE 2](#)).

DISCUSSION

Using the ICHD-3 criteria the present study provides novel data on which forms of migraine occur in patients with endometriosis. Migraine was diagnosed in the cohort of patients reporting headache, and in about one-third of the case group it was not related to menstruation. Dysmenorrhoea and dysuria, as well as a history of dysmenorrhoea in adolescence, were significantly more frequent in participants with migraine than in those without migraine, which could be related to some pain and inflammatory pathways common to these two conditions or an overall altered pain sensitivity in patients affected by migraine ([Brawn et al., 2014](#); [Clemenza et al., 2021](#); [Morotti et al., 2014](#); [Stovner et al., 2011](#)).

The current data confirm the high occurrence of migraine in patients with endometriosis ([Ferrero et al., 2004](#); [Jenabi and Khazaei, 2020](#); [Maitrot-Mantelet et al., 2020](#)), although with a prevalence that is slightly higher than that previously reported, spanning from 30% to 45% ([Balci BK, 2019](#); [Maitrot-Mantelet et al., 2020](#); [Wu et al., 2021](#)). However, this is the first study to detail headache characteristics and to compare the clinical features of women with endometriosis with and without migraine.

TABLE 1 HEADACHE CHARACTERISTICS REPORTED BY PATIENTS WITH A DIAGNOSIS OF MIGRAINE

Parameter	Patients with migraine (n = 70)
Age at onset (years), median (IQR)	15 (12, 18)
Headache starting in adolescence, n (%)	45 (64.3)
Pain intensity (0–10 scale), median (IQR)	8 (7, 9)
Migraine with aura, n (%)	10 (14.3)
Laterality of pain, n (%)	
Bilateral headache	32 (45.7)
Unilateral/alternating headache	38 (54.3)
Only left side	14 (20.0)
Only right side	12 (17.1)
Pain location, n (%)	
Temporal region	32 (45.7)
Frontal region	21 (30)
Ocular region	19 (27.1)
Neck region	9 (12.9)
Vertex region	3 (4.3)
Quality of pain, n (%)	
Pulsating pain	45 (64.3)
Dull/aching	19 (27.1)
Others	6 (8.6)
Associated symptoms, n (%)	
Nausea	47 (67.1)
Vomiting	20 (28.6)
Photophobia	47 (67.1)
Phonophobia	35 (50.0)
Osmophobia	18 (25.7)
Frequency of attacks, n (%)	
Episodic migraine	59 (84.3)
Chronic migraine	11 (15.7)
Timing of onset of migraine in relation to endometriosis, n (%)	
Migraine started before the diagnosis of endometriosis	60 (85.7)
Migraine and endometriosis diagnosed at the same age	4 (5.7)
Migraine started after the diagnosis of endometriosis	6 (8.6)

Percentages are calculated from the column total.

IQR, interquartile range (25th, 75th percentile).

Previous studies have shown that adolescents with endometriosis are more likely to experience migraine than adolescents without endometriosis (OR 1.22, 95% CI 1.03–1.44; *Miller et al., 2018*). The present findings showed that the diagnosis of migraine preceded that of endometriosis, and by several years, and that a history of adolescent dysmenorrhoea occurs more frequently in patients with an association of endometriosis and migraine. Therefore, dysmenorrhoea is a symptom that links

endometriosis and migraine and suggests that adolescents with either condition should be carefully evaluated, in order to receive appropriate diagnosis and comprehensive care.

Indeed, the diagnosis of both migraine and endometriosis is usually delayed by several years, with negative consequences on patients (*Nnoaham et al., 2011; Viticchi et al., 2011*). Increasing awareness and early diagnosis of migraine and endometriosis (and of their coexistence) could

significantly improve the clinical management of both. The alteration of pain sensitivity may represent a common substrate leading to a tendency for the person to perceive more pain. Pain threshold is altered in both endometriosis (*Poli-Neto et al., 2020*) and migraine, and by hormonal influences (*Helpfenstein et al., 2022*). Finally, a sensitization phenomenon is also relevant to both migraine and endometriosis (*Cromeens et al., 2021*), where the delay in treatment may cause a dysregulation of the peripheral and central nervous systems (*Stratton and Berkley, 2011*) and result in chronic pain. A shared mechanism more than a cause-and-effect relationship links endometriosis and migraine. Genetic studies on the relationship between endometriosis and migraine support a possible shared genetic background (*Adewuyi et al., 2020; Nyholt et al., 2009; Stratton and Berkley, 2011*). Furthermore, as in migraine, endometriosis has a high rate of recurrence within the same family (*Nyholt et al., 2009*).

An observation from the present study is that only 18% of women with endometriosis and migraine had seen a headache specialist for their migraine, a result that could partially explain the observed very low rates of appropriate diagnosis and treatment. This finding is consistent with a previous study reporting that a large proportion of individuals with weekly headache never consulted a specialist; the reason was not a poor or disorganized provision of headache services, but patients' reluctance to seek healthcare (*Do et al., 2022*).

The fact that most of the current study patients reported self-medication of headache, which could lead to an inappropriate acute use of analgesics, highlights the importance of a multidisciplinary approach to patients with endometriosis-related headache, who should receive appropriate diagnosis and treatment when a form of migraine is detected.

The strength of the present study is that this is the first study to detail headache characteristics and to compare the clinical features of patients with endometriosis with and without migraine. A questionnaire was used to determine the occurrence and the type of headache to collect detailed characteristics of the attacks. The Consensus Statement of Migraine (*Eigenbrodt et al., 2021*) recommends the

TABLE 2 COMPARISON OF CLINICAL HISTORY AND SYMPTOMS OF PATIENTS WITH ENDOMETRIOSIS WITH OR WITHOUT MIGRAINE

Parameter	Migraine (n = 70)	Controls (n = 61)	P-value
Endometriosis phenotype			
Ovarian	42 (60.0)	38 (62.3)	0.79
Peritoneal superficial	19 (27.1)	15 (25.0)	0.78
Deep infiltrating	42 (60.0)	33(54.1)	0.50
Age at menarche (years), median (IQR)	12.0 (11.8, 13.3)	12.0 (11.5, 14.0)	0.99
Age at diagnosis of endometriosis (years), mean \pm SD	27.9 \pm 5.7	29.4 \pm 7.2	0.15
Years since the diagnosis of endometriosis, median (IQR)	3 (2, 8)	4 (2, 7)	0.89
Dysmenorrhoea	66 (94.3)	50 (82.0)	0.03
Severe dysmenorrhoea (VAS \geq 7)	54 (81.8)	41 (82.0)	0.98
Dysmenorrhoea in adolescence	62 (88.6)	41 (67.2)	0.003
Dyspareunia	55 (78.6)	43 (70.5)	0.29
Dyschezia	30 (42.9)	24 (39.3)	0.63
Dysuria	19 (27.1)	6 (9.8)	0.01
Chronic pelvic pain	45 (64.3)	38 (62.3)	0.81
Heavy menstrual bleeding	32 (45.7)	23 (37.7)	0.29
Irregular menstrual cycle	25 (35.7)	23 (37.7)	0.81
Adenomyosis	51 (72.9)	41 (67.2)	0.48
Autoimmune comorbidities	10 (14.3)	8 (13.1)	0.85
Hormonal therapy	44 (62.9)	39 (63.9)	0.90
Surgery for endometriosis	22 (31.4)	25 (41.0)	0.26

Data are presented as n (%) unless otherwise specified. Percentages are calculated from the column total.

IQR, interquartile range (25th, 75th percentile); VAS, visual analogue scale.

use of diagnostic aids or screening tools to facilitate the diagnosis of migraine by evaluating patients' clinical features that suggest migraine. In particular, a questionnaire is considered a reliable and easy-to-use tool to screen patients for migraine (Verhagen et al., 2022). In addition, following the use of the questionnaire for the initial risk assessment for migraine, a medical evaluation was relevant to define the diagnosis. This procedure may become a relevant step in the diagnostic process of patients with endometriosis.

Possible limitations of the present study include the relatively small sample size and the risk of recall bias. Indeed, although headache diaries are not mandatory for a clinical diagnosis of menstrual migraine according to the ICHD-3 criteria, a prospective diary (for at least three cycles) is recommended for research purposes, as many women over-report the association between attacks and menstruation. However, the occurrence of migraine in relation to the menstrual cycle has been closely investigated by clinicians in the present study.

CONCLUSION

In conclusion, among women with endometriosis who have been screened for headache and been examined by a headache specialist, menstrually related migraine is the most common type of migraine diagnosed. Typical endometriosis-related pain symptoms, such as dysmenorrhoea and dysuria, occur more frequently in patients with endometriosis and migraine compared with those without migraine. In patients with endometriosis the co-presence of migraine, and vice versa, should be carefully investigated, to improve the overall health outcomes.

DATA AVAILABILITY

Data will be made available on request.

FUNDING

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AUTHOR CONTRIBUTIONS

All the authors contributed to the interpretation of the results, discussed the results and contributed to the final version of the manuscript. All the authors read and approved the final manuscript.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.rbmo.2023.03.020](https://doi.org/10.1016/j.rbmo.2023.03.020).

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