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Endometriosis and Headache

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Abstract Headache and endometriosis show some similarities in their clinical and epidemiological features that are probably due to the influence of female sexual hormones on both disorders. Epidemiological studies indicate that they are comorbid disorders. However, the nature of the comorbidity is not known with certainty, but a likely explanation may be common susceptibility genes. Another possibility is that, because they both are related to pain, increased pain sensitivity induced by one of the disorders may lead to a higher likelihood of developing the other, possibly mediated by nitrogen oxide or prostaglandins. A common link to the widespread use of estroprogestins may seem less probable. For physicians dealing with women with either of these disorders, awareness of the comorbidity may be helpful in the treatment of the patient.

Keywords Comorbidity · Endometriosis · Genes · Headache · Menarche · Migraine · Perimenstrual Headache · Fertility · Prostaglandins · Nitric oxide

Introduction

From the point of view of headache science, the relation between headache and typical "women's" diseases like endometriosis is interesting because many features of headache, and migraine in particular, suggest a relation to female hormones. From a clinical perspective, it is important to know whether disorders are comorbid, and if so, to investigate the mechanisms for the comorbidity because this can have relevance for the choice of investigations to make and throw light on the pathophysiology and the etiology of both of them.

Endometriosis is a common health problem for women. Its exact prevalence is unknown because surgery is required for its diagnosis, but it is estimated to be present in 3% to 10% of women of reproductive age and 25% to 35% of infertile women. It often is accompanied by chronic pelvic pain, which occurs in 15% to 24% of fertile women, and active endometriosis is found in about 33% of women with chronic pelvic pain [1]. The prevailing theory for the pathogenesis of endometriosis (Sampson's theory) posits that viable endometrium can flow retrogradely through the uterine tubes into the peritoneum during menstruation. Accordant with this theory, it has been found that women with increased exposure to menses (early menarche, short cycle length, long menstrual bleeding, and low parity) are at risk. However, these findings are not consistent, and it has been objected that some of them may also be the results, rather than the cause, of endometriosis [2•]. A particular problem for this "auto-transplant theory" is that it fails to explain endometriosis in women who have never menstruated [3]. Another hypothesis, also compatible with extraperitoneal cysts (eg, in the lungs), is that endometriosis is caused by small defects of embryogenesis [4].

Among the headaches, it is particularly for migraine that a relation to sex hormones has been studied. Migraine is especially common among fertile women, often starting around the age of menarche and improving after menopause [5]. About half of all women with migraine report an

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association with menstruation (menstrually related headache), though attacks exclusively in relation to menstruation (pure menstrual migraine) occur in only 5% to 8% of women with migraine [6, 7]. Menstrual attacks seem to be precipitated by the abrupt fall of estrogen at the end of the luteal phase of the menstrual cycle. Although many factors may precipitate attacks, migraine now is mostly understood as a disorder of the brain, but vascular factors probably also play a role in the pathogenesis.

Similar Features of Endometriosis and Headache

Although migraine and endometriosis clearly affect different parts of the body, they share some clinical and epidemiological features, most of which probably can be accounted for by the influence of female sex hormones on both disorders.

Early menarche seems to be a risk factor for both headache [8•] and endometriosis [2•, 9•]. For headache, it is of interest that age of menarche seems to influence the prevalence of headache, not only among adolescents but throughout life [8•]. Both psychological factors related to early physical maturation, as well as physiological factors related to higher estrogen levels or to increased estrogen sensitivity, have been invoked to explain why headache is more prevalent in females with early menarche. In the case of endometriosis, if the theory of retrograde flow of menstrual blood is true, all conditions (including early menarche) that lead to more menstruations will give a higher prevalence of endometriosis.

The fact that both migraine and endometriosis are related to early menarche could indicate that one disorder causes the other, but more likely, early menarche is a factor that increases the risk of both. Because menstruation is almost a prerequisite for developing endometriosis and because the hormonal fluctuation related to menstruation is a strong trigger for migraine attacks in women, it would seem logical that the earlier menstruation starts, the more likely it is that one or both disorders will develop. The relation of both disorders to early menarche also could explain the finding that migraine seems to start earlier in women with endometriosis [10].

The common relation to sex hormones probably explains similarities in relation to treatment with gonadotropin-releasing hormone (GnRH) agonists (GnRH-a). A Cochrane report has assessed GnRH-a to be effective against pain associated with endometriosis [11•]. A case study has shown that migraine attacks abated during treatment with a GnRH-a for endometriosis [12]. In a small (n=5), noncontrolled, open study, treatment with GnRH-a tended to relieve menstrual headaches also in women without endometriosis [13]. In another study on migraineurs without endometriosis, in which medical menopause was first induced with a GnRH-a and the women then received either estrogen add-back or placebo in a blinded fashion, it was found that the GnRH-a with estrogen was superior to the GnRH-a with placebo on all headaches [14]. The estrogen levels were probably stable in all patients, but the effect was most marked in the estrogen add-back group. It may be objected that in this study, the effect may be caused by the estrogen as much as by the GnRH-a.

It also should be noted that headache is commonly listed as a side effect of GnRH-a for treatment of endometriosis, but there seems to be less headache with this treatment than with danazol [11•]. In general, when headache is reported as a side effect, one often may question whether it is caused by the drug or whether it occurs incidentally during the drug treatment.

Comorbidity

Several studies indicate a comorbidity between headache and endometriosis (ie, that they co-occur in the same individual more often than what would be expected from chance). The first study to suggest this was published in 1975. Before an operation for pelvic pain, 125 women were asked about headache in the menstrual period. Those who, during operation, proved to have endometriosis externa (ie, outside the uterine cavity) had significantly more headache than participants with pain from other causes, and headache was almost as common as pelvic pain [15].

This relation has been confirmed in later studies. In a case–control study, endometriosis was more common in migraineurs than in the control patients without headache (22 vs 9.6%, P<0.01). Among the women with migraine, headache on 15 days per month or more occurred significantly more often among those with than among those without comorbid endometriosis, and headache-related disability also was significantly higher in migraineurs with endometriosis [16]. The group with migraine and endometriosis had more comorbid conditions, not only those that may be directly caused by endometriosis (eg, dysmenorrhea, metrorrhagia, and infertility), but they also had more depression, anxiety, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and interstitial cystitis. Migraineurs more often had symptoms of premenstrual dysphoric disorder than control patients, but there was no significant difference between the migraineurs with or without endometriosis. This is in accordance with the results from a small treatment study [17] showing a significant positive correlation between the severity of headache and premenstrual syndrome (PMS), and the data indicated that PMS symptoms were worsened by the presence of headache.

Another case–control study [10] demonstrated a higher prevalence of headache among 133 women with endometriosis than among 166 control patients (63.9 vs 36.1%, $P<0.001$). This difference only concerned migraine (38.3 vs 15.2%, $P<0.01$), being most marked for migraine with aura (13.5% vs 1.2%, $P<0.001$). Virtually no difference was found with regard to tension-type headache (21 vs 22%) [10].

Mechanism for the Comorbidity

An epidemiological association between migraine and endometriosis may represent methodological artifacts, but there also are some potential natural and iatrogenic mechanisms that could explain the association, which will be consider here.

One possibility is that endometriosis may cause migraine, or vice versa. Looking at the first option, it has been demonstrated that the pain in endometriosis is related to endometrial implants in pelvic tissue [18]. However, many studies have failed to demonstrate a consistent relation between the pain and the anatomy and biochemistry of the implants. In a rat model of endometriosis, it has been shown that the ectopic implants develop both sensory and autonomic nerve supply, mediating the nerve impulses through splanchnic nerves and the vagal nerve to the central nervous system. It is suggested that the implants may lead to central sensitization, causing an increased reaction to afferent impulses also from healthy organs, which can explain the relative lack of association between the localization of implants and the pain. Conceivably, this also may apply to sensory input from the head, decreasing the threshold for developing head pain. This mechanism would not be specific for endometriosis, which would be in accordance with the findings of a prospective study of 108 women undergoing laparoscopy for pelvic pain that had lasted at least 6 months. The prevalence of migraine was not higher among women with endometriosis than among those with other pelvic pain [19••]. However, this theory may not be corroborated by the finding that among patients with endometriosis and headache, no difference was found with regard to headache duration or frequency among patients with mild endometriosis and patients with severe endometriosis [10].

If increased sensitivity constitutes the link between endometriosis and headache, this effect could be mediated by prostaglandins or nitric oxide (NO). Prostaglandins are thought to play a role in pain transmission and migraine headache by decreasing noradrenergic transmission, sensitizing nociceptors, and promoting neurogenic inflammation [20, 21]. Endometriosis is associated with a significant increase in prostaglandin production [22–24]. NO is an important molecule in the regulation of cerebral blood flow [25•], but it also is involved in angiogenesis and nociceptive processing, and several lines of evidence support its role in both primary headaches [25] and endometriosis [26•, 27]. However, no study has to date shown that there is a direct link between prostaglandins or NO produced by the endometrial implants and migraine attacks, so this would at present seem highly speculative.

The reverse possibility, that migraine may somehow cause endometriosis or at least make its detection more likely, also should be considered. Migraineurs have been shown to have a lower threshold for pain not only during attacks and in the pre-attack phase [28•], but also in the interictal phase [29•]. This could mean that those with headache will suffer from more pain if they develop endometriosis, and thus, increase the likelihood that endometriosis is diagnosed. However, the fact that the presence and severity of migraine does not seem to influence the intensity of dysmenorrhea experienced by the women with endometriosis is not in accord with this theory [10].

Interestingly, it also has been hypothesized that migraine may lead to endometriosis in a more direct way. This is based on a study of 50 female migraineurs and 52 age- and sex-matched control patients [30]. Surgically confirmed endometriosis occurred more often in the migraine group (30% vs 4%, $P<0.001$). In addition, the migraine group had more often a history of self-reported menorrhagia (63% vs 37%), bruising, rectal bleeding, and excessive bleeding after minor trauma ($P<0.01$), even after correcting for use of oral contraceptives (OCs), hormone-replacement therapy (HRT), and NSAIDs. It seems likely that menorrhagia and a slight bleeding diathesis could result in an increased risk of retrograde menstruation, which, according to Sampson's theory, could induce endometriosis. However, a weakness of the study is that many patients in the migraine group had endometriosis, making it likely that the menorrhagia can be caused by the endometriosis, at least in some cases.

Also, the comorbidity may be explained by common causal factors. One such factor could be the use of estroprogestins because both headache and endometriosis show a similar, although not identical, relation to use of these medicines. For endometriosis, it is well established that OCs, for instance, represent a valuable treatment option for the disease by relieving pain and possibly preventing the disorder [31•, 32•]. On the other hand, a recent meta-analysis of 18 studies showed that there is an increased risk of endometriosis in present and former users of OCs [33•]. It also has been demonstrated that the use of OCs and HRT are associated with headache [34, 35]. Therefore, one could hypothesize that the comorbidity may be due to widespread use of these substances. However, in spite of the positive epidemiological association between OC use and endometriosis, there may not be a direct causal link. In one study,

women with and without endometriosis were asked about the reason they started with OCs. Women with endometriosis more often started it due to dysmenorrhoea, which was taken as an indication that early symptoms of endometriosis were the cause of the OC use, rather than the opposite [31•]. Similarly for headache, it has been discussed whether the positive association between headache and OC use or HRT is explained by the fact that many women use estrogen supplements to relieve headache. Therefore, OC use as cause of the comorbidity may be less plausible.

Genetics

An Australian study was performed in a cohort of 931 families with at least two sisters with endometriosis, using 815 independent monozygotic and 457 dizygotic female twin pairs as control patients [36••]. A significant additive genetic correlation was found, indicating common genetic influences to explain their co-occurrence within individuals. Analyses to explore the direction of the causation indicated an underlying genetic disposition common to both disorders. There was no evidence that neuroticism could explain the association. Further research is needed to detect the exact genetic risk loci.

Some genetic studies support a role of the estrogen receptor 1 gene in migraine susceptibility, although the exact variant is not identified [37, 38]. This receptor also has been reported to be associated with endometriosis [39, 40].

Conclusions

It seems likely that headache and endometriosis are comorbid disorders. The mechanism for the comorbidity is not known. It could be a common pathogenetic factor, such as common susceptibility genes, or it could be related to the fact that early menarche is associated with both disorders. Also, increased pain sensitivity induced by one of the disorders could make a diagnosis of the other more likely. Some observations indicate that increased sensitivity can be related to similarities in NO or prostaglandin production. Because both are very prevalent disorders, it may be important for the clinician dealing with one of the disorders to take the other into consideration to give the optimal treatment.

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