Endometriosis and Migraine

Endometriozis ve Migren

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ABSTRACT

Endometriosis and migraine are two of the most disabling pain disorders in the world, effecting millions of people and causing a big socioeconomical burden. Endometriosis is defined as the presence of endometrium-like tissue outside of uterus. It is a chronic, hormone dependent, neuroinflammatory disorder, presented with pain and infertility as its two main symptoms. Migraine is characterized by episodic headaches accompanied by nausea, vomiting and photo-phonophobia. Even though both disorders have been studied extensively, our understanding of their pathophysiology and treatment are limited. There are population based and genetic studies showing their co-morbidity. Early menarche and late menopause are well known risk factors for both diseases. Migraine is seen three fold more in women than men. The main strategy for the medical treatment of endometriosis related pain is estrogen suppression. In this review, we approached endometriosis and migraine co-morbidity by discussing the hormone-inflamation relationship, neurovascular structures and the modifications in the central and peripheral nervous system.

Keywords: Migraine, endometriosis, pain, cgrp, hormone, central sensitization

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ÖZET

Endometriozis ve migren, dünyada milyonları etkileyerek büyük sosyoekonomik engellere neden olan iki ağrı bozukluğudur. Endometriozis, endometrium benzeri dokunun uterus dışında bulunması olarak tanımlanan, en önemli iki semptomu ağrı ve kısırlık olan kronik, hormon bağımlı, nöroinflamatuar bir hastalıktır. Migren ise bulantı, kusma, ses ve ışık hassasiyeti gibi bulgularla görülen epizodik baş ağrıları olarak tanımlanır. İki hastalık üzerine pek çok çalışma yapılmış olmasına rağmen patofizyolojileri ve tedavileri hakkında bildiklerimiz hala kısıtlıdır. Komorbid hastalıklar olduklarını gösteren popülasyon bazlı ve genetik çalışmalar mevcuttur. Erken menarş, geç menapoz iki hastalık için de ortak iyi bilinen risk faktörleridir. Migren kadınlarda erkeklere göre üç kat daha sık gözükmektedir. Endometriozis ilişkili ağrının temel tedavi stratejisi östrojeni baskılamak üzerinedir. Bu derlemede hormon-inflamasyon ilişkisi, sinir ve damar oluşumları ve sinir sistemi değişiklikleri tartışılarak ağrı patofizyolojisi endometriozis migren komorbiditesi açısından ele alınmıştır.

Anahtar Sözcükler: Migren, endometriozis, ağrı, cgrp, hormon, santral sensitizasyon

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INTRODUCTION

The presence of endometrium-like tissue outside of the uterus is the traditional and lately much-disputed definition of endometriosis. However, the diagnosis is still valid only after seeing lesions through surgery. There is no consensus on the etiology nor the treatment, however both are often delayed, and public awareness is low. All of these make the two major symptoms of endometriosis, pain and infertility, worse for individuals and more costly to governments (1). Migraine, as the third most prevalent medical condition and the second most disabling neurological disorder, is also a costly disease to society, with 20 billion USD per year. It is characterized by episodic headaches, nausea, vomiting, and phono-photophobia. It is seen three-fold more in women than men (2). There is cumulating data on the co-morbidity of these pain disorders. Mutual genetic susceptibility was established (3). The relationship with estrogen in both diseases is evident, which mediates neuroinflammation . Neural and vascular compositions establish the pain pathway with the help of essential neurotransmitters such as Calcitonin Gene-Related Peptide (CGRP) (4). Both head and pelvic pain cause alterations in the peripheral and central nervous system that make these pain conditions more complex and harder to treat (5). In this review, we aim to learn from each disease's pathophysiology and treatment to understand the other one better.

Endometriosis

Endometriosis Pathogenesis

The pathogenesis of endometriosis still has not been understood entirely. One of the widely accepted mechanisms is retrograde menstruation. Menstrual fluid passages through fallopian tubes and leaks into the pelvic cavity. The fact that only menstruating mammals have endometriosis supports retrograde menstruation theory. However, almost 90% of women experience retrograde menstruation, but only 10% have the disease. And also, this theory of mechanism is only good at explaining pelvic lesions. Even though endometriosis is presented mainly with its three subtypes, peritoneal, ovarian, and deep infiltrative, some unusual locations, such as the brain and lungs, have been reported. Venous or lymphatic transportation of the menstrual tissues and bone marrow differentiation are other hypotheses on extra pelvic endometriosis. Mesothelial cell differentiation is the source of peritoneal lesions according to the coelomic metaplasia theory (1).

With its rich content of growth factors, cytokines, and altered genetic and immune structure, menstrual fluid makes the suitable environment for pelvic organs and peritoneum (6). Genetics' role is 26% in the risk of developing endometriosis, and 19 independent single nucleotide polymorphisms (SNPs) were found (1).

Gonadotropin-releasing hormone (GnRH) secreted from the hypothalamus makes the hypophysis gland secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These two hormones enhance the expression of ovarian steroidogenic genes, including aromatase which makes fat and skin produce estradiol as a second source other than ovaries. Endometriosis lesions show increased estrogen-receptor β (ER-β), aromatase, and steroidogenic acute regulatory protein (StAR) and decreased 17β-hydroxysteroid dehydrogenase expression. ER-β promotes cell adhesion, proliferation, and transformation by increasing interleukin-1β (IL-1β). Plasma IL-1β was shown to be increased years before the diagnosis of endometriosis (1, 7). IL-1β, TNF-alfa, and IL-6 are pro-inflammatory cytokines, and they are increased in the macrophages of endometriosis patients' peritoneal fluid, as well as vascular endothelial growth factor (VEGF) and nerve growth factor (NGF). All these contributors create an appropriate environment for endometriosis lesions to grow new vessels to survive and new nerve fibers to generate pain (6).

Endometriosis Associated Pain

Pain is one of the two major features of endometriosis besides infertility. Different pain presentations are found to be related to endometriosis, but dysmenorrhea, dyspareunia, dysuria, dyschezia, and non-cyclic pelvic pain are more distinctive and common (1). Studies have revealed that endometriosis-associated pain (EAP) is far more complex than it was thought to be. It is both nociceptive and neuropathic, and also it causes alterations in both peripheral and central nervous systems (8). It is not possible to point out only one factor as the main determinant of pain as it is not possible to talk about pain without talking about the pathogenesis and lesion formation.

Neuroangiogenesis is the most plausible explanation for pain-generating lesion formation (6). Peritoneal fluid and endometriosis lesions are rich in pro-inflammatory cytokines and pro-angiogenic growth factors (7). Blood supply is a must for every transplanted tissue to survive and grow. Vessels and nerves are shown to be branching together (9). Many animal and human studies show newly grown nerve cells within endometriosis lesions (10). Endometriosis-associated pain is found to be correlated with nerve density (11). Women with deep-endometriosis lesions have been shown to have higher pain scores and increased hyperalgesia. Hyperalgesia points to the presence of a lower pain threshold and the involvement of central mechanisms in endometriosis (12). And deep-endometriosis lesions contain a higher density of nerve fibers compared to peritoneal lesions (13). Deep-endometriosis lesions comprise significantly more mast cells which are also closer to the nerve cells than they are with ovarian and peritoneal lesions (12). Proinflammatory cytokines contribute to hyperalgesia by provoking inflammatory pain (8). A case-control study in French population found that migraine is seen significantly more in women with deep-endometriosis, and then with ovarian disease, with greater non-cyclic chronic pelvic pain scores (14).

Estrogen-mediated inflammation results in a cytokine and growth factor-rich environment. New vessels and nerve fibers grow. Nociceptive A and C nerve fibers are present in endometriosis lesions and they get sensitized. Nerve fibers carry the noxious stimuli to the dorsal root ganglia where nerves from other pain disorders such as irritable bowel syndrome and interstitial cystitis also make a stop. This is interpreted as cross-organ sensitization (8). In the end brain structure changes and make this complex disorder harder to treat (5).

Treatment of Endometriosis-Associated Pain

Although there is no certain cure for endometriosis, pain relief is provided by two main strategies, hormonal suppression and surgery, which are offered with their own disadvantages.

Medical therapy is focused extensively on hormonal suppression. Combined oral contraceptives (COCP) are the first-line treatment, followed by progestogens (5). There is an increased risk of thromboembolism with estrogen treatment in patients with concomitant factors like smoking, age, and/or history of thromboembolism. GnRH agonists are widely used and very effective in reducing pain by providing a hypoestrogenic environment. In order to prevent bone loss a low dose of estrogen-progesterone, add-back therapy should be prescribed with GnRH analogs. With and without add-back therapy, GnRH was reported to provide successful treatment for migraine patients. Even though these treatments have all been shown to reduce pain, one of the biggest problems with these hormonal therapies is fertility. Many reagents have been studied for the medical treatment of endometriosis-related pain without hormonal suppression. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used and found effective in peripheral mechanisms and inflammatory pain. Although the evidence is poor to recommend their generous use (1). Neuromodulators were used to be recommended to target the central part of the endometriosis-related paid. Gabapentin was approved for migraine prophylaxis, but currently it is not preferred in migraine prophylaxis. No pain relief and more side effects were reported for Gabapentin against placebo in endometriosis-related pain (15). There isn't enough evidence for antidepressants on endometriosis-related pain.

Surgical removal or ablation of lesions is an invasive, expensive, and risky option which doesn't guarantee that pain will be gone or not be coming back. The possibility of pain coming back in 5 years is up to 50%. And 30% of the patients don't experience pain relief from surgery at all, most probably due to the central sensitization mechanisms. As new mechanisms of pain are highlighted, it is understood that treating pain requires a much more complex. Therefore the importance of a multidisciplinary approach providing physiotherapy, psychotherapy, and diet modifications is bigger than before (16).

Migraine

Migraine Pathogenesis

Migraine is characterized by episodic headaches often accompanied by nausea, vomiting, and discomfort from sounds, lights, and odors. "People ever having had at least two attacks of migraine with aura or at least five attacks of migraine without aura" is the diagnostic criteria that was set by the International Classification of Headache Disorders (ICHD). Most migraine patients have episodic attacks. If the attacks are more than 15 per month and 8 of those attacks meet the criteria then it is diagnosed as chronic migraine. Patients often feel symptoms before (prodromal) and after (postdromal) the attacks. Attacks may occur with focal transient neurological symptoms called aura in one-third of the patients (2).

Migraine prevalence differs between 8-15% depending on age, sex, and subtype. While it is 18% in men, it is as high as 33% in women. These prevalences are similar before puberty and around 4% only. It is an estrogen-dependent disorder like endometriosis. Attacks don't usually start before puberty and they tend to disappear after menopause (17). Genetics plays a role in up to 60% of the cases and so far 38 susceptibility loci were found in genome-wide association studies (GWAS) (18). Although studies on functional imaging, pharmacology, and neurophysiology improved our understanding of the pathophysiology of migraine, there are still missing pieces.

Spreading depolarization is shown to be the reason behind aura. It is characterized by a short, complete membrane depolarization followed by a long hypoperfusion. In animal studies, spreading depolarization was shown to cause inflammation and some structural changes, that can activate the trigeminovascular system (2).

Migraine is considered a neurovascular disorder and the biggest role is played by the trigeminovascular system. The trigeminal ganglion has nerve projections reaching the dura mater and cranial vasculature. Neurons originating from trigeminal ganglion are of utmost importance in migraine pathophysiology. They provide the communication between meninges, periorbital skin, pericardial muscles, brainstem, thalamus, and hypothalamus. Trigeminocervical Complex activity allowed us to explain the mechanism of many migraine symptoms. TCC enhances Calcitonin Gene Receptor Peptide (CGRP) to be released when stimulated and is rich with CGRP receptors. CGRP causes vasodilation of the cranial vascular structures. It was shown that the level of CGRP decreases with triptan treatment during migraine attacks and infusion of CGRP can induce migraine. CGRP is a pivotal neurotransmitter in migraine pathophysiology and emerging treatments. CGRP levels are higher in women than men, especially if they are using COCP (19).

Migraine Treatments

Patients often use paracetamol, acetylsalicylic acid, or non-steroid anti-inflammatory drugs (NSAIDs) which are effective in mild and moderate migraine attacks and they seek migraine-specific drugs when these fail to give pain relief. In migraine-specific acute treatment, triptans have been the first-line treatment for over 30 years. They act as selective serotonin (5HT1B, 5HT1D, 5HT1F) receptor agonists and bind to receptors that take place in the trigeminal cervical complex, rostral brainstem, and thalamus. They can cause vasoconstriction through binding to 5HT1B receptors hence it is advised to be cautious against vascular adverse effects (19). Although it is now known that triptans are safe with a low rate of adverse effects even in patients with serious cardiovascular co-morbidities. On the other hand, medication-overuse headaches due to triptans and simple analgesics, are a bigger concern than their vascular adverse effects. Ergot derivatives were once the primary treatment of acute migraine but now are not preferred due to the poor oral bioavailability and serious adverse effects due to vasoconstriction. Self-administered use of nasal, subcutaneous, or intramuscular dihydroergotamine is used in patients who don't respond to triptans. They can reverse central sensitization and do not cause medication-induced headaches (2).

Small molecule CGRP receptor antagonists (gepants) and selective 5- HT1F receptor agonists (ditans) were shown to reduce migraine headaches without causing vasoconstriction. It was understood that vasoconstriction was not essential in migraine treatment. This was seen as an advantage over triptans in terms of adverse vascular effects but then it was shown that they caused more serious side effects than triptans do. Newer gepants are shown not to cause liver toxicity, adverse cardiovascular effects, and medication overuse headaches (20). A study using Telcagepant in perimenstrual headaches was able to show its CGRP-blocking effect on hormone-related migraine (21).

Opioids and barbiturates are effective but are not recommended due to the possibility of addiction. Even though acute treatment is perceived as drug treatment, education and behavioral therapy are important parts of acute control of migraine attacks (19). Beta Blockers, tricyclics, and anticonvulsants have been used as preventive treatments for migraine attacks but they were associated with poor effectiveness and tolerability (19).

Monoclonal antibodies against CGRP and CGRP receptors were developed to reduce the number of attacks experienced in a month. Four injectable monoclonal antibodies were developed and they were successful in reducing the number of migraine attacks with better patient adherence and tolerability. The only study which used a CGRP monoclonal antibody (Galcanezumab) other than migraine was for knee pain, and no reduction in symptoms was observed (22). Monoclonal antibodies haven't been reported to have differences between genders. Erenumab was shown to reduce the number of migraine attacks in throughout the cycle in women with menstrual migraine (23).

Endometriosis & Migraine

Comorbid Diseases

Both migraine and endometriosis are chronic pain conditions dating back to Hippocratic times. It was revealed that in a Spanish language paper in 1951 dysmenorrhea and migraine were linked. The relationship between headaches and pelvic pain was first reported in 1975 by asking pelvic pain patients before their surgeries if they were having regular headaches. Endometriosis patients had headaches more often than those without (24).

However, the relationship between migraine patients diagnosed with International Headache Society (IHS) criteria and surgically proven endometriosis patients, was reported in 2004. It showed a significantly higher prevalence of migraine in the endometriosis patients compared to the control group, 33.8% to 15.1% ($p<0.001$) respectively. 13.5% of these patients with migraine and endometriosis, had aura symptoms before the headache (25). Endometriosis was reported to be present in 22% of the migraine population compared to the control group with 9.6% ($p<0.01$) (26). Diagnosis is a problem for both disorders. One-third of patients in a chronic pelvic pain population didn't know their situation would be diagnosed as migraine according to the IHS criteria, and one-third of patients who stated that they had migraine actually had non-migraine headaches (27). Also, migraineurs were found to be 4.6 times more likely to have severe endometriosis (OR=4.6; 95% CI 2.7-8.1), although the severity in this paper used the revised American Society for Reproductive Medicine (rASRM) score (1997) which is not correlated with pain scores nor infertility. The same study evaluated the Visual Analog Scale (VAS) scores and stated that migraineurs with endometriosis had higher VAS scores than those without endometriosis (7.3 ±1.4 vs. 5.6 ±2.2; $p<0.002$) (28). The chances of having migraine were 69.3% in adolescents with endometriosis compared to the ones without endometriosis 30.7%. Between adolescent endometriosis patients, the ones with severe pelvic pain had almost twice the odds of having migraine compared to the ones with mild pain. Migraine pain severity and the odds of endometriosis were also found correlated (29).A population-based cohort study gathered 20.220 Endometriosis and 263.767 control patients' information from

The National Health Insurance Research Database in Taiwan, has shown that migraine was more prevalent amongst endometriosis patients compared to the control patients (odds ratio [OR], 1.70; 95% confidence interval [CI] [1.59, 1.82]; p<0.001) even after the data was controlled for age and hormone therapies. (OR, 1.37; 95% CI, [1.27, 1.47]; p<0.001) (30).

Nyholt et al. collected the data from the Australian cohort of 931 families with at least two sisters who were surgically diagnosed with endometriosis and from an independent cohort of 457 dizygotic and 815 monozygotic twins. Migraine risk was found to be increased in endometriosis patients in endometriosis families compared to the ones without endometriosis [OR] 1.57, 95% confidence interval [CI]: 1.12–2.21, P<0.009). With further bivariate heritability analysis, a significant additive genetic correlation (RG 5 0.27, 95% CI: 0.06–0.47) and bivariate heritability (h250.17, 95% CI: 0.08–0.27) were shown but no evidence for common environmental factors. Also, the twins, when compared between groups showed both individual and shared meaningful genetic results for migraine and endometriosis.

This extensive epidemiological study confirmed that the comorbidity of these disorders was not a result of coincidence, selection bias, shared environmental factors, or one disorder being the cause of the other one (31).

After many studies pointed out the comorbidity in epidemiological, genetic, and pathophysiological levels, three overlapping genes (ARL14EP, TRIM32, and SLC35G6) were found significant between endometriosis and migraine using GWAS data. These genes were also understood to be important in explaining the hormonal, inflammatory, immune, and adhesive features of endometriosis and migraine pathophysiology (3).

Health-related quality of life score was lower in endometriosis and migraine patients. Patients often suffer from co-morbid conditions such as irritable bowel syndrome (IBS), fibromyalgia (FM), interstitial cystitis (IC), chronic fatigue syndrome (CFS), and heavy menstrual bleeding. Mood disorders such as depression and anxiety are significantly higher in patients with these disorders (26). All of these co-morbidities together drift patients into lower socioeconomic and educational levels. Absenteeism and presenteeism are shown to be higher in endometriosis patients which contribute to the socioeconomic burden caused by the disease. Headache frequency is a factor for higher disability scores and lower quality of life (32).

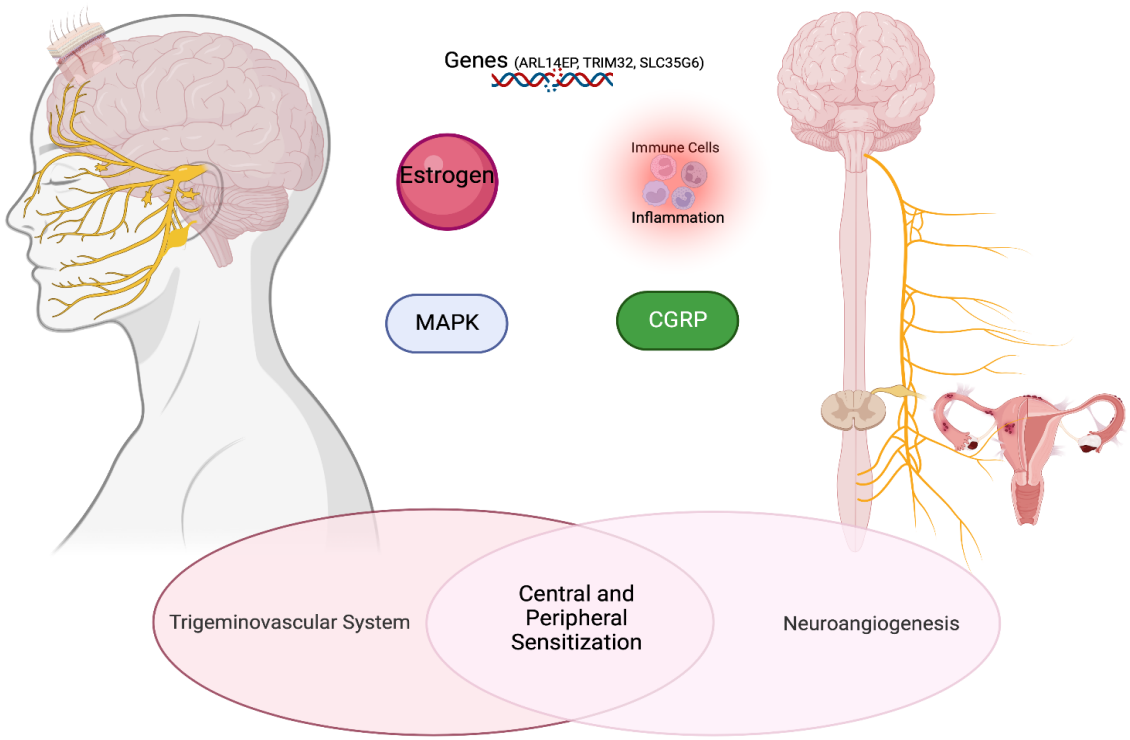

Figure 1: Pathophysiology of pain in endometriosis and migraine.

Relationship with Hormones

The estrogen-dependent natures of both diseases are well established. Early menarche, late menopause, and shorter menstrual cycles are risk factors for endometriosis and migraine. Both disorders are related to nervous and vascular structures (14). Estrogen and inflammation help one another with cytokines, growth hormones, and receptor modifications to make a suitable environment for lesions/disorders to be formed. Even though these disorders have been called as ''estrogen-dependent'' this label was challenged in a recent review and the ''steroid-dependent'' term was proposed (33). In both disorders, it is well known that estrogen is needed. In migraine studies, estrogen presence is not the reason for pain, but estrogen fluctuation is. ''Estrogen fluctuation '' as a term, is not as popular in endometriosis-associated pain as it is in migraine. It is known that estrogen is needed for lesions to exist and survive, but there is no information on estrogen administration provoking endometriosis-associated pain. Therewithal, Estrogen was shown to have anti-inflammatory effects. We think it is not the estrogen presence but the estrogen fluctuations could be the reason behind endometriosis-associated pain. As estrogen drop causes attacks. COCP is the first line of treatment in endometriosis-associated pain. CGRP levels fall with estrogen. And patients receiving regular COCP have less frequent migraine attacks (34).

Increased ER-β expression and progesterone resistance are the two distinctive features of endometriosis' relationship with hormones. The prevalence of migraine is similar between boys and girls before puberty. After puberty, migraine becomes three times more common in women than men (18% vs 6%) and the attacks don't usually occur until puberty. Transgender women who take estrogen treatment end up having a similar prevalence of migraine to cisgender women with 26% (35).

Estrogen is strongly linked to migraine with many strong observational and experimental studies. Early menarche and late menopause are risk factors. Migraine attacks tend to disappear with surgical, drug-induced, or natural menopause. COCP and hormone replacement therapies exacerbate migraine attacks. Even in postmenopausal migraineurs when they start hormone replacement therapy (36). It has been recommended to screen patients for migraine before prescribing hormone treatments. Although the quality of the studies relating hormonal treatment and migraine is poor and new generation COCPs haven't extensively been studied (5).

The risk of experiencing attacks during menstruation is higher. It's the fluctuations in estrogen levels that trigger migraine. However, a drop in estrogen can trigger the attacks and high estrogen levels can be protective against migraine (34). CGRP is raised in ovariectomized rodents and the levels fall after estrogen treatment (17). Trigeminal ganglion and trigeminocervical complex comprise the three receptor subtypes of estrogen, which makes them targets for hormonal changes and proposes a possible relationship with CGRP (34). Outside of the estrous cycle, female rats were shown to express CGRP more in the medulla, while male rats had the three components of the CGRP receptor, CLR, RAMP1, and RCP, expressed more in the medulla and the trigeminal ganglion (37). Antecubital vein CGRP plasma levels of the patients with both endometriosis and migraine were found lower than the healthy controls'. The comorbid patients' CGRP levels were higher at the time of menstruation compared to the periovulatory time. Unlike the healthy controls whose levels were lower during menstruation than ovulation. Women with only migraine and only endometriosis showed no difference. No correlation was seen between CGRP levels and migraine and/or endometriosis pain frequency (4). Another study applied capsaicin on the forearm to stimulate the transient receptor potential vanilloid type 1 (TRPV1) receptor and release CGRP and measured it with dermal blood flow (DBF). No difference was observed with time and also between healthy male controls and male migraineurs. Women with migraine showed higher DBF responses than the healthy female controls throughout the cycle. However, the CGRP-mediated DBF responses of women with migraine weren't affected by the menstrual cycle, unlike healthy controls who showed a higher DBF response during menstruation (38).

Even though progestin-only pills (POP) were shown to reduce the frequency of migraine attacks, progesterone withdrawal didn't trigger the attacks, and progesterone administration didn't have protective effects on migraine (34). A study found that POP decreased pain and was tolerated better compared to COCP in patients with migraine and endometriosis (5).

However, progesterone decreased the CGRP levels in rats unlike testosterone had no effect (39). Pregnancy is characterized by high Progesterone and Estrogen which have been shown to reduce CGRP levels. Interestingly during pregnancy CGRP peaks, especially towards term, and yet the attacks are decreased. Oxytocin was hypothesized to have a role in preventing migraine but more studies are needed (34).

Relationship with Ion Channels

Ion channels, such as cystic fibrosis transmembrane conductance regulator (CFTR), aquaporins. (AQPs) and chloride channel (CIC-3) have been shown to be regulated by estrogen, fluctuate through the menstrual cycle, and play part in endometriosis pathophysiology. CFTR promotes endometriosis migration and invasion by increasing the expression of nuclear factor kappa-light-chain-enhancer of activated B cells-urokinase plasminogen activator receptor (NF B-uPAR). AQP2, AQP5, AQP8, and AQP9 have been shown to be present in endometriosis lesions and fluctuate throughout the menstrual cycle, showing a dose-dependent manner to estrogen. AQP5 is over-expressed and activates the phosphatidylinositol-3-kinase and protein kinase B (PI3K/AKT) pathway and also could be affected by progesterone. AQP9 was shown to be present but decreased in the ectopic endometrium compared to healthy controls. However, when human endometrial cells were transfected with AQP9, it caused a significant increase in metalloproteinases (MMPs) 2 and 9. MMP-9 was found to be an important factor in lesion formation and survival.

Another ion channel that contributes to migration and invasion through MMP-9 is ClC-3. It also increases inflammation through tumor necrosis factor (TNF)-alfa (40). Calcium-binding proteins, calbindin, parvalbumin, and calretinin, have been shown to have a role in peripheral and central sensitization of peritoneal endometriosis lesions(8). Voltage gated calcium channels regulate the release of glutamate which plays a critical role in cortical spreading depolarization (2).During CSD, increased potassium (K), intracellular calcium (Ca) and *N*-methyl-d-aspartate (NMDA) receptor activation cause an important megachannel Pannexin-1 to stimulate inflammation and vasodilation that result in headache (41). A similar ATP permeable P2X3 receptor plays a role in nerve sensitization and was found to correlate with endometriosis pain. A selective P2X3 receptor antagonist (Eliapixant) was reported to alleviate endometriosis-related hyperalgesia in an animal model (42). TRPM8, KCNK5, GJA1 are three out of thirty-eight genes in the biggest migraine GWAS, that were found related to ion channels (18).

Central Sensitization

Women with endometriosis were shown to have an earlier onset of migraine with similar severity compared to the other migraineurs (25). In another study migraine attacks were found to be more frequent and disabling in the endometriosis group compared to migraineurs with no endometriosis (26). In adolescent endometriosis patients, those who described severe pelvic pain had a nearly two folds higher possibility to have migraine. Adolescents with endometriosis and migraine had more pain during periods than those without migraine (29).

It's been shown that women with endometriosis and migraine have more non-cyclical chronic pelvic pain than dysmenorrhea, dyspareunia, or digestive symptoms compared to endometriosis patients without migraine (14). Lower pain threshold levels were observed in dysmenorrhea patients independent of endometriosis (43). Karp et al. studied migraine in chronic pelvic patients with and without migraine. Unlike other studies with patients who were operated on for pelvic pain which showed increased migraine prevalence with endometriosis, this study found a similar prevalence in chronic pelvic pain patients with or without endometriosis (26, 27). Adolescents with severe migraine headaches had a two-fold increased chance of having endometriosis, even after the results were adjusted for chronic pelvic pain. However, in this study, all adolescents were operated due to pelvic pain, so groups were separated into mild-moderate pain and severe pain when adjusting the data to study chronic pelvic pain independent from endometriosis. There were only 15 adolescents with chronic pelvic pain without endometriosis and only 10 adolescents describing mild-moderate pain with endometriosis. So Endometriosis is related with chronic pelvic pain, these two concepts together are correlated with migraine and this result is supporting the central sensitization hypothesis (29).

A voxel-based morphometry study compared pain-processing brain regions of chronic pelvic pain patients with and without endometriosis. CPP patients with endometriosis showed decreased gray matter volume in the left thalamus, left cingulate gyrus, right putamen and right insula. CPP patients without endometriosis also showed decreased gray matter volume in the left thalamus. And no decrease was observed in patients with endometriosis but without CPP. This study showed that central modifications take place with CPP independent of endometriosis (44). Voxel-based morphometry in migraine also showed decreased gray matter volume in pain-related areas in the right superior temporal gyrus, right inferior frontal gyrus, and left precentral gyrus. Chronic migraine patient's gray matter was decreased in the bilateral anterior cingulate cortex, left amygdala, left parietal operculum, left middle and inferior frontal gyrus, right inferior frontal gyrus, and bilateral Insula, compared to episodic migraine patients (45). In the fMRI studies, higher activity in the pain-facilitating regions and lower activity in the pain-inhibiting regions have been observed when painful heat was applied (46). It was also showed in another study that the patients with CPP showed lower pain thresholds whereas no difference was observed between healthy controls and endometriosis patients with no pain (47). Increased response to subthreshold triggers was shown with the fMRI images of increased functional networks in the matrix as a result of the pain memory (46). Medication-overuse headache is also the result of similar neural plasticity characterized by increased CGRP, neuronal nitric oxide synthase, and lower pain thresholds (48). There is no study on medication overuse in endometriosis or CPP patients.

78.8% of women were shown to experience migraine attacks after the diagnosis of endometriosis, unlike 21.2% who experience them before. The mean duration for migraine attacks to occur was 1,477±953.6 days after and 490±410.5 days before the diagnosis of endometriosis (30). The risks of developing migraine headaches and endometriosis-associated pain are higher with early adverse childhood events (49).

These could be related to similar genetic susceptibilities. But also peripheral sensitization might be lowering the pain threshold and last but not least, central modifications could make one feel head pain easier, faster, and stronger than the ones with no other pain conditions.

CONCLUSION

These two pain disorders are more prevalent in each other's populations. This co-morbidity is important in exploring the nature of each disease and pain in general. In both diseases there's an impaired genetics and immune system. Estrogen and macrophages promotes each other's role in establishing neural and vascular structures that generate the pain. CGRP is important in migraine pathophysiology and the emerging therapies are targeting it. Also it is affected by the hormones. CGRP's role in endometriosis related pain should be studied more extensively to see if the newer drugs could be repurposed. Central sensitization mechanisms revealed that these pain disorders are more complicated and harder to treat with traditional treatment options such as surgery or medical treatment. Therefore, education, behavioural therapy, dietary changes, psychotherapy and physiotherapy should be considered with a team when approaching these patients.

Conflict of interest

No conflict of interest was declared by the authors.

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