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NEUROIMMUNOLOGICAL MECHANISMS LINKING PRIMARY DYSMENORRHEA AND MIGRAINE: A SYSTEMATIC REVIEW OF THE LITERATURE

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ABSTRACT

Introduction and Purpose: Primary dysmenorrhea and migraine are among the most prevalent pain disorders in women of reproductive age, often coexisting and exhibiting overlapping pathophysiological mechanisms. This systematic review aims to identify and summarize the shared neuroimmunological pathways that may underlie both conditions, with particular emphasis on inflammatory mediators, neuropeptides, hormonal modulation, and glial activation.
Results: The analysis of studies published between 2000 and 2025 reveals consistent evidence of increased levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α) and prostaglandins (especially PGE_2) in both disorders. These mediators contribute to peripheral and central sensitization, amplifying nociceptive signaling. Pain-related neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P are involved in neurogenic inflammation, vascular dysregulation, and microglial activation within central pain pathways. Moreover, estrogen fluctuations appear to modulate both immune and neuronal responses, influencing microglial phenotype and cytokine release, thereby explaining the cyclic nature and female predominance of these conditions.
Conclusion: Dysmenorrhea and migraine share a common neuroimmune-endocrine framework, in which inflammatory mediators, neuropeptides, and hormonal fluctuations interact to enhance pain sensitivity. Recognition of these shared mechanisms provides a foundation for developing integrated therapeutic approaches targeting COX-2, CGRP, and microglial activation. Future translational research combining animal models with clinical data is essential to refine and personalize treatment strategies for both disorders.

KEYWORDS

Primary Dysmenorrhea, Migraine, Neuroimmunology, Cytokines, Prostaglandins, CGRP, Microglia, Estrogen, Inflammation

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1. Introduction

Migraine and primary dysmenorrhea are among the most common pain disorders affecting women of reproductive age, and their coexistence represents a significant clinical and social problem. It is estimated that migraine affects approximately 18–25% of women, whereas primary dysmenorrhea occurs in as many as 45–90%, depending on the population and diagnostic criteria used (Itani et al., 2022); (Barcikowska et al., 2020) Both disorders share a similar pattern of symptom occurrence, typically intensifying during the luteal or menstrual phase of the cycle, suggesting a substantial contribution of sex hormones—particularly estrogens—to their pathophysiology. The high prevalence of comorbidity between these conditions, along with overlapping nociceptive and inflammatory profiles, indicates that they may share common underlying mechanisms.

The aim of this review is to identify and describe the shared neuroimmunological mechanisms linking migraine and primary dysmenorrhea, with particular emphasis on the role of inflammatory mediators, neuropeptides, and hormonal factors.

A growing body of evidence highlights the crucial role of dysregulation within the neuroimmune axis, which integrates the nervous and immune systems, in the development of both migraine and dysmenorrhea. In migraine, activation of the trigeminovascular pathway leads to the release of proinflammatory neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P, which trigger neurogenic inflammation, dilation of meningeal blood vessels, and glial cell activation (Russo, 2015). In primary dysmenorrhea, a key element is the upregulation of cyclooxygenase-2 (COX-2) expression and excessive production of prostaglandins (PGE_2, $PGF_2\alpha$) within the endometrium, initiating local inflammation and nociceptor activation (Itani et al., 2022). Both disorders are also characterized by elevated levels of proinflammatory cytokines—including IL-1β, IL-6, and TNF-α—which can modulate nociceptive transmission and sustain peripheral and central sensitization processes (Thuraiaiyah et al., 2022).

2. Methodology

This systematic review was conducted in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search was performed across four major electronic databases: PubMed/MEDLINE, Scopus, Web of Science, and Embase. Publications from 2000 to 2025 were included, encompassing original research articles, review papers, and experimental studies involving both human subjects and animal models. The search strategy combined free-text keywords and controlled MeSH terms, including”Migraine Disorders”, ”Primary Dysmenorrhea”, ”Neuroimmunology”, ”Neuroinflammation”, ”Cytokines”, ”Prostaglandins”, ”Microglia”, ”Neuropeptides”, ”Estrogens”, and”Pain Modulation”. Only articles published in English or Polish were considered.

Studies were included if they met the following criteria: (1) involved women of reproductive age or animal models reflecting menstrual or migraine-related pain mechanisms; (2) provided data on neuroimmunological biomarkers, glial cell activity, proinflammatory cytokines, or hormonal interactions; (3) presented original results or high-quality systematic reviews.

Studies were excluded if they focused on secondary dysmenorrhea (e.g., due to endometriosis or uterine fibroids) or secondary migraine (e.g., post-traumatic or vascular in origin), as well as those lacking full-text access or exhibiting low methodological quality.

The methodological quality of included studies was assessed using validated tools appropriate for study design: the Newcastle–Ottawa Scale (NOS) for observational studies, the SYRCLE’s Risk of Bias Tool for animal research, and AMSTAR 2 for systematic reviews and meta-analyses. Two independent reviewers performed the quality assessment, and discrepancies were resolved through discussion and consensus.

From each eligible article, key information was extracted, including population characteristics, experimental models, evaluated neuroimmunological markers (e.g., IL-1β, IL-6, TNF-α, prostaglandins, CGRP, substance P), described neuroimmune interaction mechanisms, and relationships with hormonal fluctuations. Due to substantial heterogeneity in study design and measurement approaches, a qualitative (narrative) synthesis was conducted instead of a quantitative meta-analysis. The findings were organized to enable comparison of the main pathophysiological pathways shared between primary dysmenorrhea and migraine.

3. Results

Shared Neuroimmunological Mechanisms

3.1 Inflammation and Proinflammatory Cytokines in Both Conditions

In the pathogenesis of primary dysmenorrhea, activation of inflammatory processes within the endometrial mucosa plays a pivotal role, with proinflammatory cytokines—IL-1β, IL-6, and TNF-α—acting as the principal mediators of pain and uterine muscle contraction. During the luteal and early menstrual phases, production of IL-1β increases, stimulating cyclooxygenase-2 (COX-2) activity and enhancing prostaglandin synthesis (particularly $PGF_2\alpha$). This leads to increased uterine contractility and ischemia of the myometrium, which clinically manifests as pain. TNF-α acts synergistically by promoting further release of prostaglandins and leukotrienes and amplifying the local inflammatory response in the endometrium. This cytokine may also contribute to heightened sensitivity of nociceptive receptors in the pelvic region. IL-6 serves as an intermediary between the inflammatory process and activation of the nervous system—its elevated concentrations in menstrual fluid and serum correlate with pain intensity. IL-6 also participates in neutrophil and monocyte recruitment and stimulates acute-phase protein synthesis, thereby potentiating local inflammation. Collectively, IL-1β, IL-6, and TNF-α form a network of mutually reinforcing proinflammatory mediators that sustain endometrial inflammation. Their excessive activity contributes to increased prostaglandin production, tissue edema, and nociceptive hypersensitivity—mechanisms regarded as the main source of pain in primary dysmenorrhea (Barcikowska et al., 2020).

In a study by Crona Guterstam et al., 2021 cytokine profiles in menstrual blood were analyzed to identify local inflammatory mechanisms associated with menstruation and menstrual pain. The results showed that concentrations of IL-1β, IL-6, and TNF-α were significantly higher in menstrual blood than in peripheral serum. This finding indicates that the endometrium is a local source of intense inflammatory activity during menstruation. Moreover, increased levels of IL-1β and TNF-α were correlated with greater pain intensity, suggesting their direct involvement in nociceptor activation and prostaglandin synthesis stimulation. Elevated IL-6 levels pointed to activation of acute-phase responses and recruitment of immune cells into the endometrium. The authors emphasized that the distinct cytokine profile of menstrual blood reflects a localized, rather than systemic, inflammatory response, which may play a crucial role in the pathogenesis of primary dysmenorrhea.

In another study by Yu et al., 2021, the impact of acupuncture on proinflammatory cytokine levels in women with primary dysmenorrhea was evaluated, focusing on the roles of IL-1β, IL-6, and TNF-α in pain mechanisms. The authors demonstrated that a series of acupuncture sessions led to a significant reduction in the levels of all three cytokines, both in serum and in local endometrial tissues. The decrease in IL-1β was associated with inhibition of COX-2 activity and reduced prostaglandin production, resulting in diminished uterine contractions and pain intensity. Lower IL-6 levels indicated an attenuation of the inflammatory response and decreased immune cell activation, whereas reduced TNF-α concentrations correlated with improved uterine perfusion and alleviation of pain symptoms. These findings suggest that the analgesic effect of acupuncture in dysmenorrhea may be mediated through modulation of the neuroimmune axis and suppression of excessive proinflammatory cytokine production.

In a systematic review by Thuraiaiyah et al., 2022 available evidence regarding the role of pro-inflammatory cytokines in the pathogenesis of migraine was analyzed, with particular emphasis on IL-1β, IL-6, and TNF-α. The authors demonstrated that migraine patients exhibit significant alterations in cytokine profiles both during attacks and in interictal periods. During the ictal phase, IL-1β levels markedly increase, activating glial cells and amplifying the neuroinflammatory response within the central nervous system. This process contributes to a lowered pain threshold and the persistence of nociceptive hypersensitivity. In contrast, IL-6 and TNF-α remain elevated even during interictal phases, suggesting a state of chronic low-grade inflammation. These cytokines interact with endothelial and sensory neuronal cells within the trigeminovascular system, promoting the release of neuropeptides such as CGRP and contributing to vascular dysregulation. The review confirmed that an imbalance in pro-inflammatory cytokines represents a key component of migraine pathophysiology and may serve as a potential target for emerging anti-inflammatory and immunomodulatory therapies.

In a subsequent systematic review Musubire et al., 2023 expanded upon these findings by examining the role of pro-inflammatory cytokines not only in migraine but also in other primary headache disorders, such as tension-type headache and cluster headache. The authors noted that while IL-1β, IL-6, and TNF-α are consistently elevated in most migraine studies, their dynamics and expression profiles vary depending on

headache type and disease phase. In chronic migraine, persistently elevated moderate levels of IL-6 and TNF-α indicate sustained low-grade immune activation. In contrast, in cluster headaches, TNF-α and IL-1β exhibit rapid fluctuations corresponding to attack phases, suggesting a distinct neuroinflammatory mechanism. The authors emphasized that elevated cytokine levels may not only reflect inflammatory activity but also modulate neuronal excitability within pain-processing structures such as the trigeminal nucleus and thalamus. This review thus provides a broader perspective, positioning immune dysregulation as a shared yet differentially modulated pathophysiological mechanism across primary headache disorders.

Recent evidence increasingly supports the view that migraine is not solely a neurovascular disorder but also a disease with a prominent immune component. It was reported that women with primary dysmenorrhea exhibit significantly elevated serum and menstrual blood concentrations of IL-1β, IL-6, and TNF-α. These findings suggest that local inflammatory activation within the endometrium is a crucial mechanism underlying menstrual pain. The study describes that increased IL-1β stimulates cyclooxygenase-2 (COX-2) expression and prostaglandin (particularly $PGF_2α$) synthesis, leading to uterine muscle contractions, ischemia, and pain. Similarly, TNF-α enhances the inflammatory response by promoting the production of additional inflammatory mediators and increasing nociceptor sensitivity. IL-6, on the other hand, functions as a link between inflammation and the immune system, facilitating leukocyte recruitment into the endometrium and augmenting systemic inflammatory effects. The authors emphasize that targeted modulation of these cytokines may represent a promising therapeutic strategy for managing primary dysmenorrhea (Barcikowska et al., 2020).

Table. 1. Comparing recent studies on inflammatory mechanisms in migraine and dysmenorrhea, including proinflammatory cytokines and their concentrations.

Year	Study Type	Population	Cytokines	Concentration Levels	Findings
2023	Review	Women with primary dysmenorrhea	IL-1β, IL-6, TNF-α	Elevated in serum and menstrual blood	Indicates local inflammatory activation within the endometrial mucosa
2024	Clinical study	Women with migraine	IL-1β, IL-6, TNF-α	Increased during the attack phase	Confirms the role of cytokines in migraine pathophysiology
2025	Experimental study	Animal models	IL-1β, IL-6, TNF-α	Increased in response to inflammatory stimuli	Demonstrates inflammatory mechanisms involved in migraine

3.2 Pain-related neuropeptides: Substance P and CGRP (Calcitonin Gene-Related Peptide) — shared neuroinflammatory components

In the context of primary dysmenorrhea, neuropeptides such as Substance P and CGRP play a significant role in menstrual pain mechanisms. Studies have demonstrated that their serum levels are elevated in women with dysmenorrhea, suggesting their involvement in the pathophysiology of the disorder. Similar to migraine, these neuropeptides may influence microglial activation and the release of proinflammatory cytokines, leading to the amplification of menstrual pain. CGRP inhibitors, including monoclonal antibodies, have shown efficacy in alleviating menstrual pain; however, their application in this context requires further investigation (Xu et al., 2021).

In migraine, Substance P and CGRP are key neuroinflammatory mediators. CGRP is released from peripheral and central nerve endings during migraine attacks, contributing to cerebral vasodilation and the activation of nociceptive neurons within the trigeminovascular system. Likewise, Substance P is involved in the transmission of pain signals and may enhance inflammatory responses within the dura mater. Research on CGRP receptor antagonists, including monoclonal antibodies, has demonstrated their effectiveness in preventing and treating migraine attacks, underscoring the critical role of these neuropeptides in migraine pathophysiology (Pellesi & Edvinsson, 2025).

3.3 Microglial involvement in the modulation of menstrual and migraine pain

Microglia play a crucial role in the central modulation of pain in both migraine and dysmenorrhea. Understanding the mechanisms underlying microglial activation and its interactions with other glial cells and neurons may lead to the development of new therapeutic strategies for these disorders. Microglia are key contributors to central sensitization in migraine-related pain. Activation of microglia in regions such as the trigeminovascular nucleus (TNC) and the anterior cingulate cortex (ACC) results in the release of proinflammatory cytokines and neuropeptides, enhancing pain transmission and contributing to migraine chronification. Evidence supports the involvement of microglia in neuroinflammatory processes associated with migraine, suggesting that microglia may represent a potential therapeutic target for chronic headache management (Sudershan et al., 2023). Although research on the role of microglia in menstrual pain remains limited, existing data suggest that microglial cells may participate in the processing of menstrual pain stimuli. Activation of microglia within the spinal cord may influence nociceptive responses during menstruation; however, further studies are required to fully elucidate this mechanism (Martin, 2008).

3.4 Shared pain pathways associated with prostaglandins

Prostaglandins—particularly prostaglandin E_2 (PGE_2)—and the enzyme cyclooxygenase-2 (COX-2) play pivotal roles in both dysmenorrhea and migraine. Elevated levels of these inflammatory mediators lead to microglial activation, the release of proinflammatory cytokines, and increased pain sensitivity. COX-2 inhibitors, such as celecoxib, have demonstrated efficacy in alleviating pain in both conditions while offering improved gastrointestinal safety compared with traditional nonsteroidal anti-inflammatory drugs (NSAIDs).

In studies of primary dysmenorrhea, elevated levels of prostaglandins, especially PGE_2, have been detected in both serum and endometrial tissue. These prostaglandins are synthesized via COX-2 and are central to the mechanism of menstrual pain. Clinical trials have confirmed the efficacy of COX-2 inhibitors—such as celecoxib—in reducing menstrual pain. As a selective COX-2 inhibitor, celecoxib offers superior gastrointestinal tolerability compared to conventional NSAIDs and is widely used in the management of primary dysmenorrhea (Zyryanov & Baybulatova, 2024).

Prostaglandins, including PGE_2, are also implicated in the pathophysiology of migraine. COX-2 inhibitors, such as celecoxib, have shown effectiveness in the treatment of acute migraine attacks, again providing gastrointestinal safety advantages over traditional NSAIDs. Celecoxib thus represents a promising therapeutic option for both menstrual and migraine-related pain management (Zyryanov & Baybulatova, 2024).

3.5 Modulation of immune and neuronal responses by estrogen fluctuations

Estrogens, particularly 17β-estradiol, influence microglial activity within the central nervous system. Studies have demonstrated that estrogens can modulate microglial responses by affecting their activation state and the secretion of proinflammatory cytokines (Habib & Beyer, 2015). It has also been shown that estrogens promote the shift of microglia from a proinflammatory (M1) phenotype to a neuroprotective (M2) phenotype, which may be significant in the context of neurodegenerative disorders. Furthermore, estrogens may affect neurosteroid metabolism within microglia, thereby modulating neuronal responsiveness (Jellinck et al., 2007).

Estrogens also influence the activity of both innate and adaptive immune cells. Estrogen receptors (ERα, ERβ, and GPER) regulate the development and function of immune cells such as macrophages and T and B lymphocytes. Estrogens can modulate intracellular signaling pathways, including NF-κB activity, thereby influencing the production of proinflammatory cytokines. Dysregulation of estrogen signaling may contribute to the pathogenesis of autoimmune and neoplastic diseases (Chakraborty et al., 2023).

Research has identified the presence of estrogen receptors on various immune-responsive cells, including thymocytes, macrophages, and endothelial cells. Estrogens modulate cytokine production by these target cells through interference with their transcriptional activity (Cutolo et al., 1995).

4. Discussion

This review demonstrates that dysmenorrhea and migraine share key neuroimmunological pathways: increased prostaglandin production mediated by COX-2 induction and elevated levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α) create an environment conducive to both local and central pain sensitization. In dysmenorrhea, the overproduction of $PGF_2α$/PGE_2 in the endometrium and menstrual blood mediates uterine contractions, ischemia, and nociceptor activation—mechanisms consistently described in the literature on pathophysiology and NSAID/COX-2-based treatment (Barcikowska et al., 2020). Meanwhile, provocation and

clinical studies indicate that PGE_2 may induce migraine-like pain and that patients with migraine exhibit increased COX-2 expression and elevated PGE_2 concentrations, linking the prostaglandin pathway to migraine attack pathophysiology (Antonova et al., 2012).

Despite these shared mechanisms, there are significant differences in inflammatory marker expression between the two conditions: in dysmenorrhea, the inflammatory response is predominantly local within the endometrium, with high prostaglandin concentrations and localized leukocyte recruitment; in migraine, however, both episodic (ictal) cytokine surges in IL-1β and persistently mild interictal elevations in IL-6/TNF-α are observed, reflecting a more diffuse (central and peripheral) neuroinflammatory profile (Barcikowska et al., 2020).

The role of sex hormones—particularly estrogen fluctuations—serves as a modulating factor for these mechanisms. Declines in estrogen levels around menstruation or during perimenstrual phases promote dysregulation of local inflammatory pathways in the uterus (enhanced COX-2/prostaglandin activation) and may lower the excitability threshold of central pain pathways, increasing susceptibility to microglial activation and cytokine release in the CNS. This mechanism links hormonal fluctuations with the exacerbation of both menstrual pain and migraine attacks (Itani et al., 2022).

The clinical significance of these findings is multifaceted. First, they validate the rationale for employing targeted therapies aimed at distinct pathological nodes: COX-2 inhibitors and NSAIDs in dysmenorrhea (blocking prostaglandin synthesis), and anti-CGRP or neuroinflammatory modulatory therapies in migraine (reducing neurogenic vasodilation and proinflammatory neuropeptide release) (Marjoribanks et al., 2015). Second, observations regarding the role of microglia and immune signaling suggest that modulation of microglial activity—such as targeting the TREM1/NLRP3 pathways or metabolic receptors like GLP-1R—may represent a promising direction for future therapies in chronic pain sensitization seen in both migraine and, potentially, persistent forms of menstrual pain (Sun et al., 2024).

However, this review has certain limitations. Many studies differ in methodology (serum versus tissue sampling, ictal versus interictal measurements), complicating direct comparisons; there is a scarcity of large prospective studies tracking dynamic changes in biomarkers throughout the menstrual cycle and migraine course. Additionally, publication and language restrictions may introduce bias in the synthesis of available evidence.

Given these limitations, we recommend further translational studies that integrate precise animal models (enabling manipulation of COX-2/prostaglandin pathways, CGRP receptors, and microglial activation) with prospective clinical trials in women. Such studies should concurrently monitor local (menstrual blood, endometrium) and systemic (serum, CNS biomarkers) markers and evaluate their relationship to hormonal fluctuations. This approach would enable the identification of the most promising, individualized therapeutic targets.

5. Conclusions

The collected scientific evidence provides strong support for the existence of shared neuroimmunological mechanisms in the pathophysiology of primary dysmenorrhea and migraine. Both conditions are characterized by activation of the neuro–immune–endocrine axis, in which key roles are played by inflammatory mediators such as IL-1β, IL-6, and TNF-α, as well as prostaglandins that enhance nociceptor sensitivity and contribute to central pain generation. A significant common feature also involves pain-related neuropeptides—primarily calcitonin gene-related peptide (CGRP) and substance P—whose increased release is observed both during migraine attacks and throughout menstruation. Additionally, estrogen fluctuations modulate inflammatory responses and microglial activity, which may explain the cyclic nature and higher prevalence of these disorders among women.

Understanding these interconnections has important clinical implications—it opens the possibility of developing integrated targeted therapies, including COX-2 inhibitors, CGRP antagonists, and potential microglial modulators. Future translational studies combining animal models with clinical observations are needed to confirm causal relationships and to support the development of more precise therapeutic strategies addressing the shared pathophysiological pathways of dysmenorrhea and migraine.

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