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Review article

Update of recent studies of adenomyosis-associated dysmenorrhea



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ABSTRACT

Adenomyosis is characterized by invasion of endometrial glands and stromal cells into the myometrium. It is a common gynecological disorder that usually occurs in women during their reproductive years. The primary clinical manifestations of adenomyosis are menorrhagia and progressive dysmenorrhea. The pathogenesis of adenomyosis-associated dysmenorrhea is complicated. However, it is predicted that oxytocin, inflammatory factors, and prostaglandin F_{2α} are responsible for adenomyosis-associated dysmenorrhea via the induction of uterine smooth muscle contractions. Additionally, the pain conductivity of the pelvic viscera (internal organs) involves both the sympathetic (T10–L1) and parasympathetic (S2–4) nervous systems located in the abdominal region. This article provides a review of the pathophysiology of dysmenorrhea in adenomyosis and the nociceptive afferent pathway of the pelvic splanchnic nerves.

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Introduction

Adenomyosis is characterized by the presence of heterotopic endometrial glands and stroma within the myometrium, accompanied by a variable degree of adjacent myometrial hyperplasia and infiltration of inflammatory cells.^{1,2} Menorrhagia and dysmenorrhea are the two major adenomyosis-associated symptoms, and > 30% of patients with these symptoms have typical secondary, progressive dysmenorrhea.³ Dysmenorrhea is also the main reason that women seek medical attention for uterine adenomyosis. The pathogenesis of adenomyosis and adenomyosis-associated dysmenorrhea is complicated. To provide an effective treatment, it is important to understand and clarify the pathophysiology of dysmenorrhea in adenomyosis and the nociceptive afferent pathway of the pelvic splanchnic nerves.

Types of dysmenorrhea in adenomyosis and pathophysiological factors

According to different pathological changes, clinically, there are two types of dysmenorrhea in adenomyosis, lateral and midline.⁴

Lateral dysmenorrhea is related to the pathological changes of the adjacent pelvic organs, such as inflammatory adhesion of the accessory or peritoneum. This refers to the complicated nociceptive afferent pathway of the pelvic organs and peritoneum, which is reported as referred pain in most cases, with no significant efficacy for nonsteroidal anti-inflammatory drugs and presacral neurectomy. Midline dysmenorrhea is a typical form of dysmenorrhea in adenomyosis and can be triggered either by nerve secretory factors, which directly stimulate the spasmodic contractions of the uterine smooth muscle, or by inflammatory cytokines and chemical neurotransmitters, which indirectly stimulate nerve endings. Nonsteroidal anti-inflammatory drugs and presacral neurectomy show some efficacy towards this form of dysmenorrhea.

Nerve secretory factors

Within the nerve secretory pathway, pituitrin and its derivatives, such as vasopressin and oxytocin, stimulate vascular and uterine smooth muscle cells to contract. Ischemic hypoxia and acid products accumulate as pain factors outside cells to cause sodium channel phosphorylation, enhance receptor excitation, activate several silent nociceptors, or damage low threshold mechanoreceptors, resulting in the sensitization of primary afferent nerves. This leads to the abnormal expression of ion channels in primary afferent nerve fibers, and peripheral sensitization causes hyperalgesia and dysmenorrhea. Vasopressin and oxytocin are the most important factors regulating uterine contractions. Vasopressin-1a

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receptor (VP1aR) expression is associated with dysmenorrhea in adenomyosis, and the oxytocin receptor (OTR) in uterine smooth muscle cells is positively correlated with the amplitude of uterine contraction.⁵ Mechsner et al⁵ used an immunohistochemical examination for both OTR and VP1aR expression in the endometrium, myometrium and adenomyotic lesions in 40 patients with histologically proven adenomyosis and 40 patients without adenomyosis who underwent hysterectomy for dysmenorrhea, bleeding disorders, and fibroids. The results showed that VP1aR was only expressed in myometrial cells and blood vessels, and no immunoreactive staining of VP1aR in the epithelial and stromal cells of an adenomyotic lesion or endometrial cells was detected. The VP pathway related to the development of dysmenorrhea may be related to myometrial hyperactivity with reduced uterine blood flow due to increased VP plasma levels. It also shows that there are no differences in the endometrial OTR expression pattern between the uteri of patients with and without adenomyosis. In adenomyotic lesions, OTR expression was detectable in epithelial cells, demonstrating moderate to strong cytosolic immunoreactive staining. There is an overexpression of OTR in myometrial cells surrounding the stromal cells during adenomyosis. However, these myometrial cells are highly compact, and it is possible that OTR overexpression is due to this compact morphology. Guo et al⁶ found that the contractile amplitude and OTR expression levels were significantly higher in adenomyosis cases than controls. Dysmenorrhea visual analog scale scores correlated positively with the contractile amplitude and OTR expression level. Both trichostatin A (TSA) and andrographolide dose-dependently inhibit OTR expression in myometrial smooth muscle cells (MSMCs). In conclusion, OTR overexpression in MSMCs may be responsible for increased uterine contractility and adenomyosis-associated dysmenorrhea. Zhang et al⁷ performed an experimental prospective clinical study and provided information on the spatial and temporal characteristics of OTR expression in the uterus in both normal women and women with adenomyosis. Changes in OTR expression may lead to abnormal uterine contractions and cause the reproductive failure and dysmenorrhea associated with this condition.

Inflammatory factors

Proinflammatory/inflammatory cytokines acting as chemical neurotransmitters can stimulate uterine contraction and cause dysmenorrhea. Immune cells produce pain factors, such as tumor necrosis factor and chemokine factors. Peripheral nerve sensitization of the primary afferent nerve with L-glutamic acid, substance P, and calcitonin gene-related peptide as its neurotransmitter cause the abnormal expression of ion channels on primary afferent nerve fibers, thereby increasing the sensitivity of nociceptive sensory neurons when stimulated. This eventually causes hyperalgesia and dysmenorrhea. Nuclear factor (NF)- κ B is a pivotal proinflammatory transcription factor and can be activated by various proinflammatory agents, growth factors, and oxidative stress; nearly all of which are involved in adenomyosis and endometriosis. NF- κ B proteins themselves and the proteins regulated by NF- κ B are linked to proliferation, apoptosis, angiogenesis, and invasion. NF- κ B inhibitors are promising for the treatment of endometriosis and adenomyosis in animal models. Li et al⁸ designed a study with 29 patients (cases) with histologically confirmed adenomyosis and 14 (controls) without adenomyosis or endometriosis to detect the protein levels of the NF- κ B subunits p50 and p65 in both cases and controls. The constitutive NF- κ B DNA-binding activity and protein expression levels of p50 and p65 in cases were significantly higher than in the controls. The binding activity level correlated positively with dysmenorrhea severity in cases, and compared to the control endometrium, adenomyotic lesions had significantly higher

cyclooxygenase (COX)-2, vascular endothelial growth factor, and tissue factor (TF) protein ($p < 0.0017$) and mRNA levels ($p < 0.018$), as expected. We also found that the NF- κ B binding activity correlated positively with the severity of dysmenorrhea in adenomyosis. Because of the feed-forward relationship between pro-inflammatory factors, such as cytokines/chemokines, and NF- κ B activation and the cross-talk between chemokines and neuronal receptors, it is likely that the activated NF- κ B may result in the increased production of proinflammatory chemokines, which subsequently activate neuronal receptors and cause hyperalgesia and dysmenorrhea.

Prostaglandins

Prostaglandin (PG) 2α can cause dysmenorrhea via direct or indirect pathways. The ectopic endometrium can produce PG 2α , similar to the normal endometrium. On the one hand, uterine hyperstimulation via PG 2α irritation and blood vessel contracture can cause uterine ischemia, as characterized by a lack of oxygen and dysmenorrhea. On the other hand, COX in the inflammatory tissue is activated, promoting an increase in the local PG 2α and improving the sensitivity of the nociceptors, leading to hyperalgesia. PG 2α can also cause dysmenorrhea by stimulating afferent nerve fibers directly. PG synthetase inhibitors inhibit local COX, blocking the production of PGs and preventing uterine contractions and spasms, to reduce or eliminate dysmenorrhea. Nie et al⁹ assessed the ectopic and homologous eutopic endometrium from 50 women with adenomyosis, and endometria from 18 women without adenomyosis were used for immunohistochemical analysis of OTR and TRPV1 (transient receptor potential vanilloid type 1). Compared to the normal endometrium, the immunoreactivity of OTR and TRPV1 was significantly increased in the ectopic endometrium. The immunoreactivity of OTR and TRPV1 was positively correlated with the severity of dysmenorrhea and represented significant predictors for dysmenorrhea severity. TRPV1 is expressed by sensory neurons and integrates multiple noxious stimuli on peripheral terminals or primary sensory neurons, such as heat ($> 43^\circ\text{C}$), acid ($\text{pH} < 5.9$), and inflammatory mediators. The authors proposed that because the activation of TRPV1 in epidermal keratinocytes results directly in the release of COX-2, increased TRPV1 expression in adenomyosis could also induce the release of COX-2, contributing to dysmenorrhea and its severity. In addition, both PGE2 and PGI2 can facilitate the activation of TRPV1, contributing to inflammatory pain and/or dysmenorrhea in women with adenomyosis. As a molecular integrator of noxious stimuli and inflammatory mediators, many of these factors, such as PGs, are abundant in the adenomyosis foci in the peripheral terminals of primary sensory neurons, and TRPV1 activation may trigger the release of neuropeptides, such as substance P and calcitonin gene-related peptide, causing increased blood flow and hyperalgesia and possibly dysmenorrhea.⁹

Other factors

The pathophysiological mechanism of dysmenorrhea in adenomyosis is complex. In addition to the above factors, there are other factors related to dysmenorrhea. For example, there is increased immunoreactivity to SLIT/roundabout (ROBO)1, and it is correlated with the severity of dysmenorrhea in adenomyosis. SLIT is a secretory glycoprotein consisting of three members, SLIT1–3. The receptor for SLIT is the transmembrane protein ROBO, which currently consists of four members, ROBO1–4. Compared to the normal endometrium, SLIT expression is significantly higher in the ectopic endometrium from women with adenomyosis, while ROBO1 immunoreactivity and microvessel density were significantly higher in both eutopic and ectopic endometria than the normal endometrium. SLIT/ROBO1-mediated crosstalk in adenomyosis may facilitate angiogenesis,

ensuring the blood supply to the growing ectopic endometrium, facilitating myometrial infiltration, and thus exacerbating dysmenorrhea.¹⁰ Liu et al¹¹ used immunostaining and microscopic evaluation to assess the presence and localization of TF in both eutopic and ectopic endometria and normal endometrium. They found that the TF staining levels in both eutopic and ectopic endometria were significantly correlated with the severity of dysmenorrhea (Spearman's $r = 0.51, p = 0.0001$ and $r = 0.31, p = 0.029$, respectively). TF is a cell-membrane-bound glycoprotein and a member of the cytokine receptor superfamily. Conversely, thrombin, which is downstream to TF in physiological conditions, can increase uterine contractility. Therefore, a feed-forward loop could be established, with elevated TF expression and increased contractility. The increased uterine contractility may be easily perceived as pain or cramps due to innervations and/or elevated TRPV1 signaling because women with symptomatic adenomyosis are likely to experience central sensitization, similar to endometriosis.

Dysmenorrhea and pain nerve conduction

Pelvic splanchnic nerve anatomy

The pelvic viscera (internal organs) receive nerve impulses from both sympathetic (thoracolumbar) and parasympathetic (craniosacral) nervous systems. Visceral nociceptive fibers mainly transmit through the sympathetic nerve and parasympathetic nerve along the side of the spinal cord side. The parasympathetic and sympathetic pelvic nerves that dominate the pelvic organs (uterus, rectum, and bladder) come from the second to fourth sacral segments (S2–4) and the 10th thoracic (T10) to the first lumbar segment (L1), respectively. T10 to L1 merge into the superior hypogastric plexus (presacral nerve), situated in front of the sacrum and lying within the boundaries of the interiliac triangle and the dendritic or reticular triangle, also called the Cotte triangle.

The presacral nerves travel to the pelvis, together with the second to fourth sacral segments (parasympathetic), eventually merging into the inferior hypogastric plexus; also called the pelvic splanchnic nerve, and this plexus divides into the vesical, middle rectal and uterovaginal (Frankenhauser's) plexuses at the paracervix. Uterovaginal plexuses lie on both sides of the cervix and vagina as part of the uterosacral ligaments (USLs) that arrive in at the paracervix. The vesical plexus lies on both sides of the bladder, dominating the bladder detrusor and internal sphincter to control urination. The rectal plexuses dominate the rectum and anal canal and rectum anus sphincter, as well as the control of bowel movements. In clinical practice, presacral nerve resection is a type of treatment for dysmenorrheal in adenomyosis that blocks the pain pathways of the uterus. However, the nerve branches of the bladder or rectum can be damaged by surgery, leading to rectal and bladder dysfunction, with complications, such as constipation and urinary retention.^{12,13} A recent 2012 retrospective analysis over 6 years demonstrated improvement in the midline pain in 73% (22 of 30) of patients.¹⁴ To analyze the distribution of autonomic nerves in the USL, Chen et al¹⁵ assessed their insertion into the uterine body and cervix, and the USLs were cut into cervical, intermediate, and sacral sections. They also marked the superficial portion, the deep portion, medial surface (the side of the USL close to the rectum), and lateral surface (the side of the USL near the ureter) of the samples at the same time. After hematoxylin–eosin and immunohistochemistry staining, they found that the sympathetic nerves are the major conduits of nerve fibers in the USL. The content of the sympathetic nerve is concentrated on the deep portion and the distant section. Fujii et al¹⁶ found that the greatest number of nerve fiber bundles was at a distance of 16.5–33 mm and a depth of 3–15 mm distal to the site of attachment of the USL to the uterine

cervix. Furthermore, there were many more sympathetic and parasympathetic nerve fiber bundles than sensory nerve fiber bundles in the USL and its surrounding tissue.

Ramanah et al¹⁷ evaluated the precise anatomy of pelvic splanchnic nerve and found that they represented the lateral boundaries of the posterior cul-de-sac and were positioned lateral to the rectum and medial to the ureters. They attached distally to the posterolateral aspect of the cervix at the level of the internal cervical os and at the lateral vaginal fornix and proximally to the presacral fascia and the S2–S4 vertebrae. The ligament had a fan shape, with mean widths of 5.2 ± 0.9 cm, 2.7 ± 1.0 cm, and 2.0 ± 0.5 cm at the sacral, intermediate and cervical portions, respectively. The USL is a multifaceted, mesentery-like structure containing loose connective tissue, smooth muscle, vessels, and autonomic nerve fibers from the inferior hypogastric plexus, with contributions from sacral nerves. The USL has more nerve content than the cardinal ligament (CL). The superficial part consists mainly of smooth muscle peritoneal connective tissue. The deep part consists primarily of nerve fibers. The pelvic plexus, splanchnic nerve plexus, bladder plexus, uterovaginal plexuses, and connective tissue form a pelvic nerve plane behind the uterine wall. The plane near the side of the uterus is the uterovaginal plexuses, with the travel of the uterus deep vein dominating the feel of the uterus. The pelvic splanchnic nerve and bladder branch of the inferior hypogastric plexus form the T-shaped nerve plane.¹⁸ At present, presacral neurectomy is used to treat the dysmenorrhea of adenomyosis. The careful separation and block of the uterovaginal plexuses is the key to reducing postoperative complications and effectively relieving dysmenorrhea. The insufficient resection depth of the sacral ligament during the operation can increase the risk of the postoperative recurrence of dysmenorrhea. A more recent randomized controlled trial of 141 patients followed over 24 months demonstrated improvement in dysmenorrhea, dyspareunia, and quality of life in patients with endometriosis who underwent a concurrent presacral neurectomy at the time of conservative laparoscopic surgery over those who did not.¹⁴

Pain receptors and nerve terminals

Pain sensation begins with stimulation of a nociceptor, or nerve ending, and the resultant activation of a sensory nerve. Nerve fibers are divided into A, B, and C categories, of which, A is divided into α , β , γ , and δ subtypes. A signal passes through the lightly myelinated A δ fibers, which are responsible for the response to cold and mechanical stimuli that produce stinging and sharp, fast pain. The C fibers are also stimulated and are associated with mechanical and thermal stimuli to transmit warm pain. Specialized bodies are responsible for the response to texture (Meissner's corpuscles), vibration, tickle, and deep pressure (pacinian corpuscles) and proprioception (Ruffini's corpuscles). The release of chemicals, such as potassium, bradykinin, and arachidonic acid, from inflammatory processes is an endogenous source of pain sensation.¹⁹ In inflammatory processes, the damaged cells release chemicals, including K, bradykinin, and arachidonic acid; also called pain factors. When the concentration of pain factors in the intercellular space exceeds a certain threshold, nerve endings undergo a transmembrane inward current, membrane depolarization, and action potential on the nerve terminal of A δ fibers and C fibers to the cerebral cortex causing pain. The pelvic viscera receive nerve impulses from both sympathetic and parasympathetic nervous systems. Adenomyosis ectopic endometrium directly stimulates the peripheral nerve fibers of the myometrium and signals through the pelvic visceral nerves and afferent spinal cord and brain to cause nerve pain. In addition, in the early 21st century, to study the relationship between dysmenorrhea in endometriosis and nerve distribution, histological sections of endometrial tissue were stained

immunohistochemically with the highly specific polyclonal rabbit anti-protein gene product 9.5 and monoclonal mouse anti-neurofilament protein to identify nerve fibers. The small nerve fibers were identified throughout the basal and functional layers of the endometrium in all endometriosis patients, but were not seen in the functional layer of the endometrium in any of the women without endometriosis ($p < 0.001$). Additionally, the small nerve fibers detected in the functional layer in all women with endometriosis may have important implications for understanding the generation of pain in these patients.^{20,21} Zhang et al²² used a retrospective immunohistochemical study with the same method to assess 37 women with uterine fibroids and 29 with adenomyosis, and they reached the same conclusion. Adenomyosis and endometriosis are caused by an ectopic endometrium with growth functions. However, the mechanism by which these nerve fibers cause dysmenorrhea requires further study.

Conclusion

Adenomyosis is a common benign disorder that usually occurs in women during their reproductive years, and dysmenorrhea is one of the common clinical manifestations. It is also the main reason that women seek medical attention for uterine adenomyosis. The pathogenesis of dysmenorrhea in adenomyosis is complicated. The pathophysiology of dysmenorrhea in adenomyosis occurs via nerve secretory factors, inflammatory factors, PGF2 α , and other factors. The precise anatomy and nociceptive afferent pathway of the pelvic splanchnic nerves should be studied to clarify their roles, thereby providing more effective treatment options for dysmenorrhea in adenomyosis.

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