Gynecology and Minimally Invasive Therapy 5 (2016) 137–140

Contents lists available at ScienceDirect

Gynecology and Minimally Invasive Therapy

journal homepage: www.e-gmit.com

Review article

Update of recent studies of adenomyosis-associated dysmenorrhea

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ARTICLE INFO

Article history:
Received 15 January 2016
Received in revised form
14 May 2016
Accepted 6 June 2016
Available online 1 August 2016

Keywords:
adenomyosis
dysmenorrhea
inflammatory factors
neuroendocrine
pelvic splanchnic nerves

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 F2α 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.

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

Conflict of interest: The authors have no conflicts of interest relevant to this article.

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http://dx.doi.org/10.1016/j.gmit.2016.06.002

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 al[5] 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 al[6] 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 al[7] 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)-κB 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-κB proteins themselves and the proteins regulated by NF-κB are linked to proliferation, apoptosis, angiogenesis, and invasion. NF-κB inhibitors are promising for the treatment of endometriosis and adenomyosis in animal models. Li et al[8] 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-κB subunits p50 and p65 in both cases and controls. The constitutive NF-κB 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-κB 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-κB activation and the cross-talk between chemokines and neuronal receptors, it is likely that the activated NF-κB 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 PG2α, similar to the normal endometrium. On the one hand, uterine hyperstimulation via PG2α 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 PG2α and improving the sensitivity of the nociceptors, leading to hyperalgesia. PG2α 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 al[9] 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 predicators for dysmenorrhea severity. TRPV1 is expressed by sensory neurons and integrates multiple noxious stimuli on peripheral terminals or primary sensory neurons, such as heat ($> 43^{\circ}C$), acid ($pH < 5.9$), 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,