Adenomyosis and Pain

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Adenomyosis affects about 20% of women of reproductive age and is responsible for menorrhagia, dysmenorrhea, menstrual pelvic pain, dyspareunia, and infertility [1]. The causes of adenomyosis-related pain are unclear. When combined with endometriosis, especially deep infiltrating endometriosis (DIE), dysmenorrhea is more severe in patients with adenomyosis, and the chance of progressive dysmenorrhea will increase. Other pain mechanisms related to adenomyosis include abnormal uterine contractility and abnormal expression of the oxytocin receptor (OTR), abnormal expression of prostaglandin (PG) and cyclooxygenase 2 (COX-2), abnormal growth and distribution of local nerve fibers, neuropeptides, macrophages, abnormal secretion of cells and inflammatory factors, and so on. There may still be some unknown mechanisms that need further study and research.

5.1 Clinical Characteristics

The most common clinical manifestation of adenomyosis is pain, which mainly exists in the form of dysmenorrhea. Ultrasound examination for young women between 18 and 30 years of age suffering from dysmenorrhea showed a 34% incidence of adenomyosis and is associated with dysmenorrhea [2]. Adenomyosis-induced pain often occurs during the menstrual period, moreover at the uterine area, more than other endometriosis sites; its pain is severe. It is the first main reason for patients to seek medical treatment [3].

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." The complaint of dysmenorrhea in

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women with adenomyosis is more often than any other gynecological diseases [4, 5]. It is the leading cause of gynecological morbidity in young Asian women, regardless of age, race, and economic status [6]. They are so-called secondary dysmenorrhea, which is mainly due to endometriosis and adenomyosis. In young women, this complaint is often unresponsive or partially responsive to non-steroidal anti-inflammatory drugs or to oral contraceptives. Some women with adenomyosis have very severe pain, severe enough to render them requiring absence from school or work. They suffered severely painful cramps occurring over several days every month, persisting for decades. Moreover, previous reports showed that adenomyosis negatively impacts daily activities and the quality of life of the affected women, with a subsequent increase in the risk of anxiety, depression, and other psychological disorders [7–9]. Then, it ends up reducing individual women to work and socialize in society, resulting annually in an important loss of productivity [6]. Therefore, the World Health Organization concluded that dysmenorrhea is probably the most important cause of chronic pelvic pain [10].

Clinical presentation of adenomyosis can vary, with mild adenomyosis that can be highly symptomatic, whereas others with very enlarged uteri due to adenomyosis may present only with mild symptoms. One-third of women with adenomyosis are asymptomatic [11]. Although the association of adenomyosis with dysmenorrhea is still debatable, the reported incidence of dysmenorrhea in adenomyosis was reported to be between 50 and 93.4% [12, 13]. A linear correlation had also been described between the extent of the adenomyosis and the severity of dysmenorrhea [14].

5.2 Pain Mechanisms of Adenomyosis

5.2.1 Related to Endometriosis

Adenomyosis often associates with concomitant diseases that have similar symptomatology, and it thus masks the causal relationship between the disease and its symptoms. For patients with adenomyosis, the most frequent coexisting morbidities are endometriosis and fibroids [15].

About 24.6–80.6% of adenomyosis patients are associated with endometriosis [16, 17], and both conditions share the same pathogenesis and symptoms, such as dysmenorrhea, heavy menstrual bleeding, infertility, dyspareunia, and chronic pelvic pain [18–20]. It is also well-defined that there is an overlap in the pathogenesis of DIE and adenomyosis [21, 22]. These patients with both conditions had a higher rate of a moderate-to-severe degree of dysmenorrhea (60.0% vs. 39.3%, $P = 0.001$) and a higher percentage of progressively worsening dysmenorrhea (47.8% vs. 32.0%, $P = 0.007$). [23]. If associated with DIE, the severity of dysmenorrhea is more apparently related to the extent of infiltrating endometriosis. In patients with DIE, the prevalence of adenomyosis is 48.7–66.3% [24, 25]. There is a statistically significant correlation between pelvic pain and the presence of adenomyosis, in agreement with the previously reported results [26]. When patients had both DIE and adenomyosis, 95.5% described the pain

intensity of dysmenorrhea as severe while that of dyspareunia and dysuria moderate to severe [27–29].

Focal adenomyosis of the outer myometrium was more frequently found in endometriosis-affected women, especially those with deep endometriosis [25], and it supports the hypothesis of different pathogenesis between the inner and outer myometrium forms of adenomyosis [30].

In some studies, women with adenomyosis were found to have a higher incidence of dysmenorrhea than those with fibroids, only with an odds ratio of 3.4 (95% CI 1.8–6.4) [13, 15]. A retrospective study showed that women with adenomyosis had 4.5 folds more of having endometriosis compared with women with fibroids [31]. Therefore patients with symptomatic uterine fibroids should be wary of having associated adenomyosis at the same time.

5.2.2 Related to Anatomical Factors

The uterine myometrium has two layers of structures, (1) the outer myometrium and (2) the inner myometrium. The latter is also known as the sub-endometrial layer or endometrial–myometrial junctional zone (JZ). The JZ is just next to the endometrium and also undergoes cycle-dependent changes. It is from the Mullerian origin, while the outer myometrium is from the mesenchymal origin [32]. The dysperistaltic uterine contraction of the JZ in patients with endometriosis and adenomyosis can result in a more retrograde menstruation and a disturbed tubal sperm transport [33].

First, in terms of the depth of infiltration of adenomyosis, some authors suggested that the severity of symptoms and the clinical features correlated with the extent and depth of the infiltration [19, 34]. Bird et al. 1972 [35] reported that dysmenorrhea was present in 4.3% of women whose uterus had histologically defined grade I penetration and in 42.4% and 83.3% of women with grade II and grade III penetration, respectively. Second, the number of adenomyosis lesions was closely related to the patient's symptoms. Levgur et al. 2000 [36] reported a positive correlation between the number of ultrasound features of adenomyosis and the severity of dysmenorrhea. The relationship between the number of histopathology features and clinical manifestations had been clarified in previous studies on specimens obtained from hysterectomies. These studies confirmed the direct correlation of adenomyotic foci number with severe dysmenorrhea [36–38]. Based on these findings, the hypothesis of a causal relationship was established between the number and depth of infiltration of the adenomyotic and specific symptoms.

5.3 Related to Molecular Mechanisms

5.3.1 Prostaglandins and Cyclooxygenase 2

The molecular mechanisms of dysmenorrhea and pelvic pain in women with adenomyosis are not well-understood, but PG may play an important role [39].

Although PG could excite nociceptors and cause pain, it is believed that PG indirectly cause cramping pain by stimulating uterine contractility [40], thus causing abnormal contraction of the uterus and increased contraction. Some previous studies had reported that PGF2α administration increased uterine contractility and elicited visceral pain. Drugs that inhibit PG syntheses, such as ibuprofen and naproxen, reduce uterine contractility in dysmenorrheic women [41]. It has been suggested that PG produced cramping pain via temporary elevations in uterine pressure. However, not all women with dysmenorrhea have alterations in uterine pressure; other mechanisms might have contributed to the menstrual pain, for example, reduced uterine blood flow, myometrial ischemia, and hypoxia [42].

Preclinical research studies suggested that PG-dependent mechanisms cause dysmenorrhea in majority of women [43]. The breakdown of endometrial tissues frees phospholipids from the cellular membrane. Uterine phospholipases convert the available phospholipids into arachidonic acid, which is then synthesized into PG via cyclooxygenase (COX)-1 and -2. COX-2 is a key enzyme in the process of synthesis of various endogenous PG. COX-2 has certain associations with inflammation, cell mitosis, and specific signaling transduction pathways. The level of PG in the peritoneal fluid of patients with endometriosis or adenomyosis is significantly increased compared with those without these diseases. It is positively associated with the severity of dysmenorrhea. Therefore non-steroidal anti-inflammatory drugs can effectively relieve pain [44, 45]. Notably, COX-2 expression is highest during menses, and the end products prostaglandin E2 (PGE2) and PGF2α are elevated in the menstrual effluent in dysmenorrheic women with adenomyosis when compared with healthy controls [46, 47].

5.3.2 Abnormality of Uterine Contraction and Oxytocin/Vasopressin Receptors

It is well-known that oxytocin can cause painful contraction of the uterine smooth muscle. The expression of OTR in the ectopic endometrial glands and interstitial tissues was significantly increased and was positively correlated with the degree of dysmenorrhea [55]. Uterine hyperperistalsis and the increased expression levels of OTR in patients with adenomyosis may contribute to the severity of dysmenorrhea. Mechsner et al. 2010 [48] in their immunohistochemical study of both OTR and vasopressin receptor (VP1αR) expression in the endometrium, myometrium, and adenomyotic lesions demonstrated that overexpression of OTR was in the adenomyosis-surrounding myometrium, while overexpression of VP1αR was in the myometrial cells and blood vessels. These specific receptor expressions in the myometrial tissues suggested that the induced dysperistalsis played an essential role in the development of dysmenorrhea in patients with adenomyosis.

5.3.3 Other Inflammatory Factors

The local immune response in patients with adenomyosis can lead to the production of cytokines and the release of inflammatory factors from the ectopic endometrial lesions that influence the severity of pain. Hyperestrogenism is common in patients with adenomyosis and can stimulate the production of cytokines [49]. Local inflammation is involved in the pathogenesis of dysmenorrhea in adenomyosis because of the high expression of interleukin 1β, corticotropin-releasing hormone (CRH) and urocortin (UCN), and nerve growth factors (NGFs) in adenomyotic lesions [50]. Local production of interleukin-1 (IL-1) is due to tissue traumatization and healing, and it also induces the COX-2 enzyme, causing PGE2 production. The high levels of CRH and UCN in adenomyosis are also involved in increased PG synthesis [50].

5.3.4 Nerve Fibers

It has been reported that patients with endometriosis and dysmenorrhea have a greater tendency to stimulate the release of NGFs, and patients with endometriosis can release these growth factors to lead nerve fiber growth into ectopic lesions [51]. The myometrium is innervated by a subserosal nerve plexus and a plexus at the endometrial–myometrial junction [52]. Sensory unmyelinated C nerve fibers innervate the endometrium, and inflammatory mediators released from the endometrium may activate or sensitize these nerve fibers, resulting in neurogenic inflammation. As a result, PGE2, prostacyclin, and norepinephrine will be released from adrenergic fiber endings, which then affect sensory C [53] pain fibers. Post-hysterectomy specimens showed the focal proliferation of small-diameter nerve fibers at the margins of adenomyosis in some uteri [54]. Zhang et al. 2010 [55] studied nerve fiber density in women with painful adenomyosis by using protein gene product (PGP) 9.5 immunostaining; they found that nerve fiber density was significantly increased in the basal layer of the endometrium and myometrium. They believed that these nerve fibers might play a role in pain generation in adenomyosis. Lertvikool et al. 2014 [56] also studied the nerve fiber density in adenomyosis tissue with both PGP 9.5 and neurofilament (NF) immunostainings; they found that nerve fiber density was significantly increased in women with adenomyosis experiencing moderate and severe pain as compared with those experiencing mild pain. Therefore it showed a good correlation between the severity of dysmenorrhea and the concentration of nerve fibers in adenomyosis specimens. Choi et al. 2015 [57] found a higher NF expression in the endometrium and the lesions of adenomyosis. They assumed that NF-positive cells might play a role in the pathogenesis of adenomyosis.

5.3.5 Neurogenic Factors

Nerve growth factor is reported to be involved in pain, neural plasticity, immune cell aggregation, and release of inflammatory factors. The increase of NGF-β and its

receptor levels when the adenomyosis worsens suggests a role of NGF-β in adenomyosis pathogenesis [58].

CD56, a neural cell adhesion molecule (NCAM) is expressed in neural tissues, neuroendocrine tissues, and tumors; it is involved with the growth and aggregation of nerve fibers and neuroendocrine tumor metastases [59]. In endometriosis, increased CD56 was found in the interstitial tissue of endometriotic foci, suggesting that endometriosis-related pain may be due to increased nerve fiber density, which leads to hyperalgesia in the interstitium [60]. Wang et al. 2015 [61] found that CD56 was mainly expressed in the endometrial glandular epithelium. Its CD56 immunostaining intensity in the ectopic endometrium of patients with adenomyosis was found positively correlated with the severity of dysmenorrhea. Because CD56 increases the sensitivity and density of local nerve fibers, patients who have high CD56 expression in the adenomyotic tissue are more likely to suffer from dysmenorrhea than those who have low expression.

Additionally, estrogen and progesterone receptors have been detected in adenomyotic tissues, and estradiol is known to increase the expression of CD56, whereas progesterone treatment suppresses estradiol-induced gene expression of CD56 [62]. This evidence may partly explain the cyclic variation of CD56 expression in the eutopic endometrium of adenomyosis.

As in previous studies of adenomyosis, macrophages were detected not only in adenomyosis but also in large enough numbers in the myometrium, around the major blood vessels and in the stroma between bundles of the smooth muscle cells. These nerve fibers in the myometrium and the eutopic endometrium can be stimulated by inflammatory humoral factors, including histamine, serotonin, bradykinin, PG, leukotriene, etc., that cause increased pain. Macrophages themselves secrete many of the above substances. Therefore increasing macrophages and their secreted algogenic (pain-inducing) factors are possible causes of pain in women with adenomyosis and endometriosis [63]. There is also strong evidence that macrophages are important in the regeneration process of nerve fibers in the peripheral nervous system and involve the inflammation of nerve terminals in the myometrium. In adenomyosis, local inflammation is also accompanied by the release of various algogenic factors and changes of nociceptors and causes an increase in their excitability [64]. When the functions of macrophages are disrupted, the regeneration of sensory nerve fibers is reduced. Therefore, the viability and repair of the nerve fibers depend on many factors whose products are regulated by activated macrophages [65]. Adenomyosis is known as a chronic inflammatory disease, which is accompanied by an abnormal immune reactivity in the myometrium. An increase in the number of activated macrophages in the perivascular compartments and areas of the myometrium leads to a vicious cycle of increased neurogenic inflammation and hypersensitivity of nociceptors, activation of peripheral nerve fibers. It serves as the main pathogenetic mechanism of the formation of chronic pelvic pain in women with adenomyosis [66].

To summarize, there is no commonly accepted mechanism to account for adenomyosis-induced menstrual pain and chronic pelvic pain. There are still many uncertainties about the cause and mechanism of adenomyosis pain. For example,

why the presence of an irregular endometrial–myometrial junction should be associated with painful periods and so on? As pain can seriously affect the quality of life of patients with adenomyosis, these findings do suggest some directions of future research to investigate the mechanisms of pain in adenomyosis. When the characteristics of adenomyosis pain are sufficiently understood, diagnosis and differential diagnosis may be made when there are early symptoms. Then early intervention can be achieved, and the medication and treatment of pain in adenomyosis may be more accurate.

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