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Pain in gynecology and neuroinflammation: the evil twin

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Background

Chronic pelvic pain (CPP) is a not uncommon occurrence in gynecological disorders such as endometriosis and vaginal/vulvar syndromes. The uterus, cervix, and adnexa share the same visceral innervation as the lower ileum, sigmoid colon, and rectum, and it is often difficult to distinguish pain of gynecologic from gastrointestinal origin. Shared neuronal pathways, together with mast cell infiltration, may cause sensitization of adjacent pelvic organs, resulting in frequent overlap and/or co-occurrence in pelvic disorders (1-3). Women suffering from CPP have a mean prevalence of around 48% in co-existing bladder pain syndrome/interstitial cystitis (BPS/IC) and endometriosis (4). In pelvic diseases associated to CPP such as endometriosis, vulvar vestibulitis/provoked vestibulodynia (VV/PV), BPS/IC and irritable bowel syndrome (IBS), chronic pain and underlying inflammation frequently co-occur with mood disorders such as anxiety and depression (5-9).

Chronic pain such as CPP is associated with changes in the central nervous system (CNS) that may maintain the perception of pain in the absence of acute injury. Such CNS changes may occur throughout the entire neuroaxis. Abnormal efferent activity may underlie functional changes such as IBS and structural alterations (e.g. neurogenic oedema) in BPS/IC (10). Central changes could account also for psychological changes which modify pain mechanisms *per se*.

Changes capable of altering pain perception and regulation are related not only to somatosensory neuronal system damage but also to dysregulation of peripheral and central immune and other non-neuronal cells such as mast cells (MCs), microglia and astrocytes. In particular, MCs are viewed as coordinators of peripheral inflammatory processes (11,12) and as important players in the development and maintenance of neuroinflammation, given their capacity to directly or indirectly interact with glial cells (13-15). MCs might pilot the persistent low-grade inflammation which characterizes CPP, and sensitize peripheral somatosensory afferents thereby facilitating central sensitization and neuroinflammation by activating microglia in spinal and supra-spinal areas.

Peripheral organ inflammation and neuroinflammation can alter neuronal activity both within and outside the brain, thereby contributing to the shift from acute to chronic and neuropathic pain as well as the onset of co-morbid conditions such as depression and anxiety.

The present report aims to summarize current progress in research on the role of inflammation and neuroinflammation in pelvic diseases associated with CPP, focusing on endometriosis, VV/PV, BPS/IC, and IBS, the four major contributors to CPP.

Endometriosis, inflammation and pain

Endometriosis is defined as the presence of endometrium in ectopic sites. It may be localized in the myometrium ("adenomyosis"), a major contributor of severe dysmenorrhea, and/or in different pelvic and extrapelvic organs. Deep endometriosis is the major contributor to severe pelvic pain, in > 95% of cases it is associated with very severe pain. Its prevalence is estimated to be 1-2% and is the leading etiology of CPP in women (16).

Elevated numbers and activation of MCs has been consistently reported in endometriotic tissue as compared to normal or eutoptic endometrial tissues (17,18). Stem cell factor, the major growth, differentiation and chemoattractant factor for MCs, is found in higher concentrations in the peritoneal fluid of patients affected by endometriosis (19). This augmentation in MCs is more evident in deep infiltrating lesions and in close proximity to nerve fibers. A concomitant alteration of somatosensory fibers, namely an augmentation of nerve fiber density, parallels the alteration of MCs in the affected tissues (20). Importantly, pain intensity in endometriosis patients having increased endometrial tissue MC numbers was higher as compared with endometriosis patients without MC increase and activation (21). MCs reportedly express estrogen receptors and respond to estrogens by releasing mediators (22), while high levels of locally produced estrogens may induce and/or facilitate MC activation and MC-driven inflammation.

A recent study reported that women with endometriosis-associated CPP had decreased gray matter volume in brain regions involved in pain perception, including the left thalamus, left cingulated gyrus, right putamen, and right insula (23). Women with CPP but without endometriosis also showed decreases in gray matter volume in the left thalamus. Such alterations were absent in patients with endometriosis but no CPP. Brain MCs are localized mainly in the thalamic area, where they can be regulated by environmental and hormonal factors, stress, or neurogenic inflammation (24). These data suggest that brain MCs may behave similarly to endometriotic MCs in inducing somatosensory neuron alterations and contribute, together with other non-neuronal cells, to brain thalamic alteration observed in patients with endometriosis associated to CPP.

VV/PV, inflammation and pain

VV/PV is increasingly recognized as the most frequent etiology of coital pain located at the entrance of the vagina ("introital dyspareunia") during the fertile age (25). Tissues from women with localized vulvodynia displayed a significant increase in vestibular MC number, paralleled by subepithelial heparanase activity (26). Additionally, dysregulation of MC activity and nerve terminal density has been reported in VV (27-29). Subepithelial hyperinnervation and MC degranulation are consistently found in localized vulvodynia, as well as in primary and secondary vestibulodynia. The associated hyperinnervation is thought to cause vestibular hyperesthesia distinct from vulvodynia. A concomitant augmentation of somatosensory nerve fiber density parallels the increased number of MCs and degranulating MC in the affected VV tissue (27-29).

Central pain regulatory mechanisms have been reported to be disrupted in VV/PV. In particular, morphological alterations observed in supra-spinal pain modulatory circuitry might contribute to the clinical symptoms of these patients (30).

BPS/IC, inflammation and pain

The current definition of BPS/IC approved by the American Urology Association is "an unpleasant sensation (pain, pressure, and discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of six weeks duration, in the absence of infection or other identifiable causes" (31). BPS/IC mainly occurs in females and its weighted prevalence, based on the high sensitivity and specificity definitions, was 4.2% and 1.9%, respectively (32).

Involvement of MCs in the pathogenesis of BPS/IC was initially put forward based on the beneficial role of anti-histaminic agents in its management. Different studies have shown the accumulation and activation of MCs in bladder, especially in the detrusor, lamina propria, and submucosa, of patients with IC (33,34). Clinical studies have confirmed increased urine levels of MC mediators (35-37). Activation of urinary bladder-associated circuits in the CNS may initiate substance P release from peripheral nerves in the bladder, thereby promoting substance P-mediated MC activation. The latter may, in turn, induce bladder inflammation by acting on the urothelium. While histamine has been postulated to modulate pelvic pain, tumor necrosis factor-α seems to be involved in pathophysiological changes in the urinary bladder, including inflammatory changes (34,38). The pronounced activation of spinal cord astrocytes in an animal model of BPS has been suggested to play an important role in the pain syndrome (39).

IBS, inflammation and pain

IBS is a common disorder characterized by abdominal pain or discomfort and altered bowel habit (chronic or recurrent diarrhea, constipation, or both) that occurs more frequently in women than in men. Severe IBS may be under-recognized and inadequately managed in clinical practice (40). Current pathophysiologic understanding, based on solid histological data, supports the shift from a "psychologically-driven symptomatology" to a progressive inflammation of the bowel wall. Inflammation can be triggered by food, immuno-allergic factors, infections, antibiotics, disruption of colonic ecosystems and/or systemic pathologies. Stress can further contribute through the corticotropin-releasing pathway by provoking MC degranulation. IBS patients have increased serum concentrations of interleukin-8, a cytokine primarily responsible for attraction of MCs and granulocytes (41). While reports on absolute MC numbers in the intestine vary considerably, they are qualitatively consistent in documenting an increase (42-44). Increased numbers of MCs associated with elevated numbers of serotoninergic cells have been described in colonic biopsies from IBS patients, suggesting that release of serotonin directly or indirectly from intestinal MCs may be responsible for sensory neuron activation and abdominal pain in this pathology (45). MC tryptase and histamine may also activate enteric nerves, resulting in neuronal hyperexcitability (46). In humans, degranulation of MCs in close proximity to nerves innervating the colonic mucosa correlates with abdominal pain in IBS patients. The density of colonic tissue MCs in IBS shows a linear relationship with pain intensity, as reported by women patients interviewed with pain questionnaires (42). MC-induced sensitization of peripheral nociceptive afferents has been proposed as one of the principle mechanisms in the development of visceral pain and hypersensitivity. On the other hand, central mechanisms also play an important role, since IBS in female patients is associated with alterations in structural brain networks (47).

Concluding remarks

There is increasing evidence that gynecological disorders associated to CPP and co-morbid diseases are characterized by a neuroimmune dysregulation, involving mainly MC distribution/function and nerve terminal fibers. MCs dysregulation might also promote spinal and supraspinal alterations associated with CPP. Collectively, these observations propose that a pharmacological strategy targeting MCs might represent an innovative strategy for the effective management of these disorders.

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