

Review Article

Exploring the Role of Central Sensitization in Young Women with Chronic Pelvic Pain and Endometriosis

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Abstract

Chronic pelvic pain (CPP) can result from endometriosis, which can be or over time can become unresponsive to standardized surgical treatment and hormonal therapy- possibly due to excessive pain and sensitivity known as central sensitization. These patients continue to experience significant pain and disability, such as missed school and activities, decreased feelings of accomplishment, and decreased general well being, often leading to symptoms of depression and anxiety. This brief review discusses the role that central sensitization may assume in the etiology of CPP-particularly in adolescent women, because the neural development can be altered during this critical window of development. Detection of central sensitization can identify young women who may potentially benefit from centrally mediated pharmacotherapies that can be coupled with cognitive behavioral approaches to pain management.

INTRODUCTION

Endometriosis is a clinical disorder affecting approximately 10% of women of reproductive age, in which abnormal growths of distinguished endometrial tissue are found outside the uterus, usually in the abdominal and/or pelvic cavity [1-3]. The presence of extra uterine endometrial glands and stroma, and the subsequent inflammation and fibrosis, can lead to persistent inflammatory pain, infertility, and significant disruption of quality of life [4,5]. While research efforts are focused on noninvasive diagnostic modalities [6], currently the only way to confirm a diagnosis is through laparoscopic surgery, which also serves as treatment for the removal of the ectopic tissue. Adolescents are uniquely impacted by endometriosis. Endometriosis occurs in girls as young as 8 years old and there have been documented cases of endometriosis occurring prior to the onset of menarche [7]. The disease in adolescents often presents as cyclic and non-cyclic persistent pelvic pain, resulting in the diagnosis being more difficult to suspect, and as such there is a high rate of misdiagnosis and delayed treatment [8,9]. However, it is crucial that an adequate diagnosis is made, as adolescent endometriosis

can be a debilitating chronic disease that negatively impacts participation in school and daily activities and emotional well being, often leading to additional symptoms such as anxiety and depression [8,10-12].

Following laparoscopic surgery, patients are commonly managed with a hormonal regimen during the childbearing years [6]. While most patients respond well to these treatments and have decreased pain, there is a subset of patients who present with ongoing pain despite surgical intervention and continued use of hormonal therapies [7]. Among adolescents seen at pediatric pain management clinics, endometriosis is a frequent culprit, affecting 45% to 70% of adolescents with chronic pelvic pain (CPP) [7]. Even among those whose pain is initially well controlled, over time CPP can become unresponsive to the standardized treatment methods. It is hypothesized that this is driven by central sensitization caused by prolonged increase in the excitability and efficiency of neurons in response to nociceptive input (for a detailed review see Woolf, 2011) [13]. While animal models have provided insight into the potential role of central sensitization in CPP associated with endometriosis,

there has been virtually no research conducted among humans. Further, no research at all has been conducted in adolescents with endometriosis and CPP [9]. This lack of knowledge is problematic given that neural development can be altered in young people, thus missing a potentially critical window for beneficial intervention and resulting in long-term morbidity well into adulthood.

Previous Studies – What we know

Previous studies support that central sensitization could play a significant role in the development of CPP. Local trauma or infection leads to increased sensitivity of peripheral pain receptors that generally resolves with time after the initial cause is resolved [11]. However, in endometriosis-associated CPP this hypersensitivity is sustained and amplified by an extensive central neural network that receives input from numerous visceral afferents within the peritoneal cavity and results in neuropathic pain [5,11,14]. Endometriosis lesions can be found on various organs and surfaces within the peritoneal cavity [3], many of which share at least part of their central sensory projection with the organ that they are associated with [15]. This may trigger the phenomena of cross-sensitization and central sensitization and result in referred pain [15].

Animal models support the hypothesis that a process of central sensitization likely results in CPP in this population via a viscera-visceral referred hyperalgesia. This refers to a process in which increased input to the nervous system from one visceral domain cause changes in the central network and leads to heightened sensitivity in neurons that receive convergent input from a different visceral domain [16]. Because almost all spinal neurons that receive visceral input also receive somato sensory input from the muscle and skin through a process known as viscera somatic convergence, precise localization and discrimination of sensory information is hindered [17]. Specifically, in the rat, it is confirmed that input from the uterus to the spinal cord is mainly by way of the hypogastric nerve, whose fibers enter the spinal cord via the T12, T13, L1, and L2 dorsal roots, and from the vagino cervix by way of both the pelvic and hypogastric nerves; suggesting possible routes of convergence and referred pain [18]. It has been demonstrated that neurons within both sets of segments respond convergent to stimulation of the uterus, colon, and vagina, and significant interactions exist between these two separated sets of caudal spinal segments [18, 19]. These studies support the hypothesis that sensitized afferents directly innervate regions surrounding the endometrial growths resulting in a central sensitization within the caudal spinal cord that is then referred to other visceral domains, including the vaginal canal [16].

While these animal models are interesting and provide insight into the potential role of central sensitization in CPP associated with endometriosis, there has been virtually no research conducted among humans. One study found that peripheral pressure-pain thresholds were lower in women with endometriosis and CPP and in women with CPP without endometriosis, when compared to both women with endometriosis but no CPP and to pain-free women [20]. The sensory testing methodology used by this study has been validated as a surrogate measure of central pain amplification, suggesting that the CPP population has a generalized up regulation of nociceptive processing. This also appears to be independent of the presence of endometriosis;

supporting the notion that central sensitization may contribute to the development of CPP. Another study proposed modulating central nervous system activity in chronic pain states by non-invasive brain stimulation in the form of transcranial direct current stimulation (tDCS). This study, performed by Simis et al., (2015), found that patients with CPP had significant increases in pain thresholds after active tDCS, suggesting further presence of neuromodulatory involvement in CPP [11]. Despite these findings, no research of this type has been conducted with the specific aim of understanding these relationships in young women with endometriosis and CPP.

Future directions – what we need

Systematic evaluation of pain sensitivity of painful (referred pain to lower abdominal wall cutaneous and muscles) and of non-painful (remote non-abdominal) sites and how they interact with psychosocial functioning could be important for monitoring clinical progress of CPP and response to treatment. With central sensitization believed to play a significant role in the development of CPP [5,11,14,15], exploring the psychophysical substrates of sensitization is imperative. Central sensitization can lead to changes in the spinal segments that innervate the endometriosis-affected visceral organs. These altered neural pathways can lead to increased nociceptive signals directed to the spinal cord and result in continuous increased pain sensations and larger areas of referred pain [21]. The resulting peripheral nociceptive stimulus has been shown to be related to the release of various cytokines (glutamate, prostaglandins, bradykinin) that are known activators of nociceptors, leading to a vicious cycle of increased pain sensation [21,22,23].

Particular to endometriosis as an inflammatory process, positive associations between catastrophizing and inflammatory cytokines have been found in other similar disease processes such as arthritis and rheumatic disease, and could be relevant to the study of pain in endometriosis [5,24,25]. Exposure to painful stimuli leads to an up regulation of inflammatory cytokines. Higher levels of catastrophizing have been found to be related to greater pain-related increases in levels of inflammatory cytokines, suggesting that catastrophizing leads to increased responsiveness to painful stimuli and might represent an important mechanism in shaping long-term pain outcomes secondary to endometriosis [16]. In particular, Interleukin-6 (an inflammatory cytokine) is directly known to induce muscle and joint heightened sensitivity to pain.

Measurements of cytokines levels in blood samples from patients with endometriosis should be carried out to assess their possible impact on nociceptors and their ability to cause increased pain [21,22,23]. This is of particular interest for advancing our understanding of endometriosis as both a visceral and inflammatory process. Visceral pain, catastrophizing, and inflammation have all been linked to the up regulation of cytokines that are known to activate nociceptive receptors and potentiate pain [22,23,26]. Further, in order to understand the mechanisms underlying central sensitization and CPP in an adolescent population, we need to obtain a full somato sensory phenotype for healthy adolescent controls at the pelvic and abdominal sites, which is currently missing from the literature.

CONCLUSION

It is extremely important to explore and assess these

relationships in adolescents as they are still within the progressing stages of neural development and possess neuroplasticity, suggesting potential for intervention. Unchecked, alterations in central and peripheral sensory networks during this time could result in long-term pain experience consequences well into adulthood. A better understanding of how central sensitization results from endometriosis and its mechanisms of pain potentiating might allow for earlier diagnosis or prediction of potential development of CPP in the adolescent population. In other chronic pain disorders, such as fibromyalgia, cognitive-behavioral therapy (CBT) has been shown to decrease hyperalgesia and pain catastrophizing, leading to improvements in pain outcomes [27] and could be promising for this population as well. Elucidating the psychophysical factors that contribute to central sensitization and the role it plays in the development of CPP could allow us to more efficiently and effectively identify adolescents who are at heightened risk for developing CPP and could allow for early and perhaps personalized intervention in hopes to help avoid the development of debilitating chronic pain.

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