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Review

CENTRAL SENSITIZATION IN PATIENTS WITH CHRONIC MUSCULOSKELETAL PAIN

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SUMMARY – Central sensitization is the mechanism of nociplastic pain and leads to an overemphasized response to a painful stimulus (hyperalgesia) or pain to stimuli that do not otherwise cause pain (allodynia). Persistent nociceptive pain is a risk factor for nociplastic pain, which can often occur in isolation or combination with other types of pain, most often in patients with chronic musculoskeletal pain (osteoarthritis, lumbar and cervical syndrome, fibromyalgia, rheumatoid arthritis, complex regional pain syndrome, tendinopathy, etc.). Diagnosis of central sensitization is established through clinical examination, questionnaires and quantitative sensory testing (QST), which serves to assess and quantify sensory functions, i.e., determine the threshold for detection of sensory stimuli (heat-cold, pressure, vibration). Conditioned Pain Modulation (CPM) testing is important for clarifying pain modulation profiles, which can be pro-nociceptive (less effective CPM facilitation) and anti-nociceptive (effective, inhibitory CPM effect). In the pronociceptive modulation profile that is common in patients with musculoskeletal disorders, there is a higher risk of developing chronic pain, a higher prevalence of pain conditions and higher pain associated with injury. CPM testing is also important in the individualization of drug therapy for pain, based on predicting the effectiveness of drugs in the treatment.

Key words: *central sensitization; conditional pain modulation; musculoskeletal pain*

Introduction

Central sensitization (CS) is physiological phenomenon that relates to how the central nervous system processes sensory input. According to the International Association for the Study of Pain (IASP) the definition of central sensitization is: "Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"[1]. It can contribute to the transition from acute to chronic pain, as well as the amplification of pain in existing conditions[2,3]. CS can explain the absence of a clear source of nociceptive input and the resulting disability and severity. The World Health Organization recognizes pain as main cause of disability globally[4,5]. Features of central sensitization have been documented in numerous pain conditions including fibromyalgia, osteoarthritis, rheumatoid arthritis, upper extremity tendinopathies, headache and spinal pain[6–9]. There are often discrepancies between the degree of inflammation and structural damage in patients suffering from musculoskeletal diseases[9]. Understanding the mechanisms by which central sensitization can be triggered by these conditions could lead to a better treatment strategy. In addition to this, numerous studies in neuroscience have revealed that the development of chronic pain can be influenced

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by the presence of CR[10-14]. This knowledge can help improve the diagnosis and treatment[15]. Although it is possible to predict poor treatment outcomes of certain patients due to central sensitization, there are still various non-pharmacological and pharmacological treatments that can effectively treat this condition[16].

Prevalence of CS in patients with chronic pain cannot be conclusively determined due to overlapping disorders, but it is established based on the individual characteristics of the patient, clinical examination and use of diagnostic and clinical tools[17].

Fibromyalgia syndrome (FM) is the most common syndrome linked to central sensitization, with its prevalence of 5% in the general population[18,19]. It is characterized by widespread pain and other symptoms that can lead to functional impairment. While FM is typically considered a syndrome of middle-aged women, it affects both sexes at any age[18]. The characteristics of central sensitization are usually present in a majority of patients, while they are only found in a subset (osteoarthritis) in other conditions[8]. Signs of central sensitization in patients with FM are usually abdominal pain, anxiety, depression, sleep disorders and poor cognitive functioning. Evidence for both structural and functional brain changes exists, but the results are currently somewhat inconclusive[20].

The second most common musculoskeletal pain condition with central sensitization is osteoarthritis (OA). There are indications that central sensitization in OA causes disabling symptoms, such as physical and psychological dysfunction[17,21].

Rheumatoid arthritis (RA) is the third most common musculoskeletal disorder with musculoskeletal pain with regard to CS. The prevalence of central sensitization in people with rheumatoid arthritis is known to be associated with the disease's symmetrical manifestation and poor relationship between symptoms and activity. It is widely believed that peripheral sensitization is responsible for the pain and tenderness that patients experience when they have damaged or inflamed joints. However, patients with RA have a generalized increase in pain sensitivity, even when there is a lack of joint inflammation[17].

Clinical symptoms

Central sensitization can also explain various symptoms in patients with chronic musculoskeletal pain. The dysfunctions within the central nervous system in CS are responsible for increasing the responsiveness to various stimuli, such as mechanical pressure, chemical substances, light, sound, cold, heat, stress and electricity[16,22].

Some of the symptoms of sensitization that can be triggered by chronic pain are muscle pain and increased muscle sensitivity[23]. In addition to these, other pain manifestations such as tenderness and pain that is accompanied by increased muscle volume can also be caused by central and peripheral sensitization. Increased muscle sensitivity manifests as pain evoked by a normally non-nociceptive stimulus (allodynia), increased pain intensity evoked by nociceptive stimuli (hyperalgesia) or increased referred pain areas with associated somatosensory changes[2].

These changes in functioning of the central nervous system lead to other symptoms in patients, such as fatigue, sleep difficulties, a swollen feeling in various tissue areas, paresthesia, cognitive dysfunction, dizziness and symptoms of overlapping conditions such as irritable bowel syndrome, headache and restless legs syndrome[24].

Diagnostic tools

Clinical examinations remain the first mandatory step for diagnosis of central sensitization. As the second step, a reliable and useful screening tool for CS is the central sensitization inventory (CSI) that was developed in 2012[25]. The self-reporting CSI questionary consists of two parts. Part A is comprises a collection of 25 items, Likert-type questions with 0 to 100 ranging that can be used to measure the symptoms of central sensitization. Part B helps diagnose central sensitization syndrome disorders, such as anxiety and depression. Only part A is scored, with results over 40 confirming the presence of CS. The nine-item short form of the CSI is suitable for use in assessing the central sensitization of patients with musculoskeletal pain[26]. CSI has been shown to have good clinic and metric properties[27-30]. The high sensitivity (81%) and specificity (79%) values of the test were demonstrated[28].

In recent years, the development of quantitative sensory testing (QST) has allowed researchers to identify the various mechanisms by which people experience pain. This type of testing can be performed on a variety of subjects and can be used to assess sensitization to pain[31]. Quantitative sensory testing can be used for assessing hypersensitivity to pressure, heat and cold. Although there are many useful and

reliable protocols, there is no golden standard[32]. QST is mostly followed by a set of phycological tests, mostly self-reported, that facilitate evaluation of anxiety, depression, sleep quality and quality of life[33].

Patients with chronic conditions show imbalanced pain facilitation and pain inhibition, which are usually assessed, respectively, by temporal summation (TS), controlling for increasing evoked pain by fixed repetitive stimuli, and CPM, controlling for the ability to reduce evoked pain by a second stimulus. Examining Conditioned Pain Modulation (CPM) is significant in elucidating the profile of pain modulation, which can be pro-nociceptive (less effective CPM-facilitation) and anti-nociceptive (effective, inhibitory CPM effect)[34,35]. With the pronociceptive modulation profile common in patients with musculoskeletal disorders, there is a higher risk for developing chronic pain, a higher prevalence of pain conditions and higher injury-related pain.

A significant number of studies has clarified the involvement of central sensitization in osteoarthritis. Thermal and mechanical pain thresholds study in patients with OA of the hands demonstrated that central mechanisms contribute to hyperalgesia related to movement pain. In OA, lower CPM was associated with constant intermittent pain, while higher conditioned pain modulation was linked with a higher likelihood of experiencing unpredictable pain[36,37]. Bilateral involvement and primary hyperalgesia in patients with RA are also strongly suggested as possible reasons for the impaired processing of pain in the central nervous system[38].

Clinical significance

The multimodal approach in clinical practice should be tailored to specific pain conditions and may include pharmacology and a non-pharmacology approach, such as exercise therapy, stress management, sleep management, etc. Exercise therapy, manual therapy and pharmacological therapy have been demonstrate to desensitize the central nervous system in patients with chronic pain[8,39,40].

The effects of exercise on central sensitization are known to be robust in people with mild to moderate pain. However, their effects are not consistent in those with more complex conditions. In addition to decreasing the effects of exercise on central sensitization, emotional functioning can also help prevent it from occuring in the first place[41-43].

The results of randomized trials suggest that psychological treatments can help reduce the pain levels in people with chronic conditions. However, there is also evidence that these effects can be mediated by other mechanisms. For instance, by improving one's self-efficacy, these interventions can also help decrease one's catastrophizing. A meta-analysis of the literature suggests that dietary patterns and nutrient intake can help improve the analgesic properties of certain types of pain. However, there is insufficient evidence supporting the positive effects of these interventions on central sensitization[39-43].

The clinical characteristics of central sensitization can help identify individuals with knee osteoarthritis who are more likely to respond to duloxetine, a selective serotonin reuptake inhibitor. For instance, duloxetine was able to reduce pain levels in patients with multiple painful sites. However, it was not able to do so in those with fewer than three painful sites.

Conclusions

Pain phenotyping in patients with chronic musculoskeletal pain remains a hot topic. An assessment protocol for central sensitization could be of added value for clinicians to improve the prescription of precision pain medicine. CPM testing is also important in the individualization of drug therapy for pain, based on predicting the effectiveness of drugs in the treatment.

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Sažetak

CENTRALNA SENZITIZACIJA U BOLESNIKA SA KRONIČNOM MIŠIĆNO-KOŠTANOM BOLI

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Centralna senzitizacija predstavlja mehanizam nastanka nocicepcijske boli, a dovodi do prenaglašenog odgovora na bolni podražaj (hiperalgezija) ili do boli na podražaj koji inače ne izazivaja bol (alodinija). Trajna nociceptivna bol je rizični faktor za nastanak nociplastične boli, koji se često može javljati pojedinačno ili udruženo sa drugim tipovima boli najčešće kod bolesnika s kroničnom mišićno koštanom boli (osteoartritis, lumbalni i cervikalni sindrom, fibromijalgija, reumatoidni artritis, kompleksni regionalni bolni sindrom, tendinopatije i slično). Dijagnoza centralne senzitizacije se postiže putem kliničkog pregleda, upitnika i kvantitativnog senzornog ispitivanja (QST) koje služi za procjenu i kvantificiranje senzornih funkcija, tj određivanja praga detekcije na senzorne stimuluse (toplo-hladno, pritisak, vibracije). Ispitivanje uvjetne modulacije bola (engl. *Conditioned Pain Modulation*-CPM) je značajno u pojašnjenju profila modulacije bola, koji mogu biti pro-nociceptivni (slabije efikasan CPM-facilitacija) i anti-nociceptivni (efikasan, inhibitorni CPM efekat). Kod pronociceptivnog profila modulacije koji je čest kod pacijenata sa mišićno koštanim oboljenjima postoji veći rizik za razvoj kronične boli, veća prevalencija bolnih stanja i jača bol povezan sa ozljedom. Ispitivanje CPM ima značaja i u individualizaciji medikamentoznog liječenja boli, na osnovu predviđanja djelotvornosti lijekova u liječenju.

Ključne riječi: *centralna senzitizacija, uvjetovana modulacija bola, mišićno koštana bol*