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Original

Central sensitization in episodic and chronic migraine

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Abstract

Introduction
In chronic migraine, central sensitization (CS) may play a significant pathophysiological role, since it amplifies pain signals, causing increased pain and disability. However, there are no studies confirming CS in other migraine subtypes, such as episodic migraine. The authors studied the relationship between central sensitization syndrome (CSS) in episodic and chronic migraine and its severity levels.

Objectives
To evaluate the occurrence and severity of CS in patients with episodic and chronic migraine, comparing with a control group.

Methods
Central Sensitization Inventory was investigated in adult patients with one of three categories: 1) episodic migraine, 2) chronic migraine and 3) control group. Group 1 included 35 patients while groups 2 and 3 comprised 30 subjects.

Results
The study included 63 women (66%) and 32 men (34%). Average age was 34.7 years. Mean score in the CS Inventory was significantly different according to groups (episodic migraine 37.3, chronic migraine 47.0 and control group 20.2). Chronic migraine presented the higher score of severity, followed by episodic and control group.

Conclusions
Central sensitization is found in episodic migraine patients, although the severity is not as high as in chronic migraine patients. This evidence may save effort and costs in unnecessary complementary exams, allowing earlier treatment and better patient satisfaction.

Keywords:
Migraine
Central sensitization syndrome
Central sensitization inventory
Episodic migraine
Chronic migraine

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Introduction

Pain is an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[1] This experience would prevent increase in tissue damage through a sensitive alert for own protection. Peripheral and central sensitization (CS) may occur after prolonged, repeated or intense nociceptive stimuli.[2] This mechanism works by amplifying the nociceptive response, as well as decreasing its suppressive signals, resulting in an activation of pain pathways after decreased threshold stimuli.[2,3] It is assumed that probably the function of sensitization is to avoid further injury of the affected area and adjacent tissue.[3]

Pathophysiological mechanisms of CS involve changes in ascending and descending pain pathways, including various neuromodulators, such as bradykinin and substance P. In addition, there is presynaptic overproduction of other factors associated with nociceptive C fibers, like: aspartate, glutamate and nerve growth factor (NGF), which contribute to neuronal hyperexcitability stimulating second-order postsynaptic receptors that extends and favors the transmission of nociceptive stimuli. Some receptors, such as neurokinin (NK) and N-methyl-D-aspartate (NMDA), when activated, may cause significant functional changes, further amplifying neuronal hyperexcitability and stimulation increase. These impulses reach other areas, such as the trigeminal-autonomic tracts, limbic system, thalamus and hypothalamus, supporting neuronal hyperecitability.[2] In CS there is also a decrease in activity of descending pain suppression pathways, evidenced by the reduction of neurotransmitters such as serotonin, enkephalins and gamma-aminobutyric acid (GABA) in the cortico-reticular system, *locus coeruleus* and hypothalamus.[2,4]

Central sensitization syndrome (CSS) is a well-described and recognized phenomenon described in the literature that can be related to several disorders. Such syndrome may occur either in pathophysiological processes that holds nociceptive stimulation for prolonged periods (such as osteoarthritis), as well as in diseases where tissue damage is not well recognized (such as fibromyalgia).[3,4] Other examples include migraine, temporomandibular disorder, chronic fatigue syndrome, restless legs syndrome, primary dysmenorrhea and irritable bowel syndrome.[2]

In clinical practice, there are few validated tools to help health professionals to identify signs and symptoms that may be linked to CSS. The Central Sensitization Inventory (CSI) is a patient self-report questionnaire which aims to identify the presence of the main clinical and emotional symptoms and comorbidities associated with CS and CSS, as well as numerically quantifying the degree of such symptoms.[5] The purpose of collecting these data is to assist health professionals in the recognition of sensitization and its severity, for a better planning treatment, avoiding unnecessary interventions and procedures.[5,6,7]

Migraine is a primary headache that can be related to severe disability and is the third most common cause of economic burden worldwide. It is an inherited disorder of the brain that involves dysfunction of subcortical structures that modulate sensory input.[8] Great progress has been made in understanding the pathophysiology of migraine. However, some questions still remain about the origin of pain attacks and its chronification. Despite that the presence of CS is well-described in chronic migraine, there are no major studies showing the occurrence of CS in episodic migraine, which would lead to different forms of treatment. This study analyzes the prevalence of CS in patients with episodic and chronic migraine, comparing with a control group.

Methods

The study included patients of both sexes, older than 15 years old. Group 1 included patients with an established diagnosis of episodic migraine (with or without aura). Group 2 included patients with chronic migraine. Group 3 (control group) enclosed patients with no previous history of migraine or other headaches, as well as any diagnosis of diseases illustrated in Brazilian Population-CSI (BP-CSI; figure 1.1 and 1.2) Part B. The diagnosis of episodic and chronic migraine was based on the 3rd edition of the International Classification of Headache Disorders (2018). Patients with a documented diagnosis of any disease listed in BP-CSI Part B were excluded from the control group. Additionally, pregnant and patients with major psychiatric disorders were also excluded.

Patient data were obtained through the application of the BP-CSI in individuals filling one of three categories: control group, episodic migraine and chronic migraine. This questionnaire consists of 25 general questions scoring 0 to 100 in order to identify the presence of CSS symptoms. Higher scores were related to increased CS phenomena. Each question was related to one symptom and should be answered as: 0 - Never; 1 - Rarely; 2 - Sometimes; 3 - Often; 4 - Always. The second part contains ten CSS comorbid diagnoses where patient should answer Yes or No for each diagnosis as well as providing for how long it's been known.

Questionário de Sensibilização Central
Brazilian Portuguese Central Sensitization Inventory – BP-CSI

PARTE A

PARTE B

Figure 1.1. Central sensitization inventory (CSI) - page 1

Figure 1.2. Central sensitization inventory (CSI) - page 2

All individuals were recruited in a neurological center basis from November 2019 to February 2020 and all participants signed a consent inform. The project was sent and approved by the Ethics and Research Committee in October 2019.

This was an exploratory, quantitative, observational and cross-sectional study, based on data from the BP-CSI. Statistical analysis was performed using SPSS software and ANOVA one way test. When testing differences by contrasting between the groups, Games-Howell post hoc analysis was done. It was considered a p value <0.05 to achieve statistical significance.

Results

Ninety-five patients took part in this study, from October 2019 to February 2020. The Table 1 summarize the results. 66% were female (n = 63) and 34% male (n = 32). There was a higher prevalence of men in the control group (33.3% woman; 66.7% men) versus those with migraine: episodic migraine (77.1% women; 22.9% men) and chronic migraine (86.7% women; 13.3% men).

Table 1. Summarized data of patients with episodic (EM) and chronic migraine (CM) and control group (CG). Results are presented as percentage, and absolute values are found in the text.

Variables		Parameters (n=95)
Sex	**Female**	66%
	EM	77.1%
	CM	86.1%
	CG	33..3%
	Male	34%
	EM	22.9%
	CM	13.3%
	CG	66.7%
Age group (years)	15-30	46%
	30-50	41%
	50-70	12%
	>70	1%
Schooling	**High school**	15%
	EM	22.9%
	CM	16.7%
	CG	3.3%
	University education	85%
	EM	77.1%
	CM	83.3%
	CG	96.7%

The mean age was 34.7 years (standard deviation: 12.9 years), minimum age of 15 years and maximum of 73. In subgroups, the average age was 37.8 in episodic migraine, 35.5 in chronic migraine and 36.7 in control group.
Our group had a higher level of education in all subgroups, where in overall, 15% of them (n = 14) finished only high school and 85% had university education. In subgroups, this rate was: control (3.3% high school; 96.7% university education), episodic migraine (22.9% high school; 77.1% university education) and chronic migraine (16.7% high school; 83.3% university education).

Our study found that the control group had the lowest index in BP-CSI Part A questionnaire: 20.2 (standard deviation: 8.0). Episodic migraine had an average of 37.3 (standard deviation: 12.41), and the highest score was found in the chronic migraine group, with an average of 47.0 (standard deviation: 14.02) The difference in scores between the three groups was statistically significant in all comparisons (F=39.783; p <0.05). The distribution is shown in Figure 2.

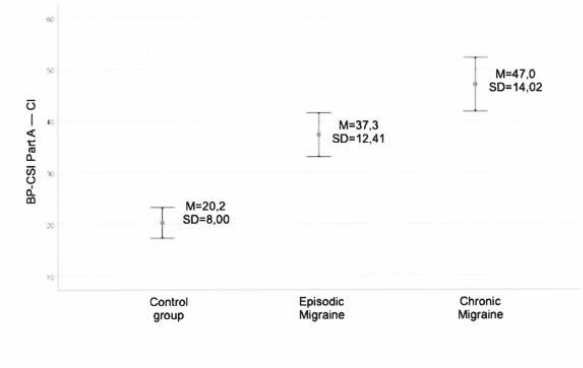

Figure 2. BP-CSI (Part A) mean scores in each subgroup.

The analysis of BP-CSI Part A in each subgroup showed that the chronic migraine group had a higher index when compared with the episodic migraine and control group (p <0.05), as shown in Table 2.

Table 2. BP-CSI (Part A) averages compared between each subgroup.

Groups	Means Differences	Significance
EM vs. CG	17.0	p < 0.001
CM vs. CG	26.8	p < 0.001
CM vs. EM	9.8	p < 0.05

The evaluation of BP-CSI Parts A and B depicted that the chronic migraine group had the higher number of patients with severe or extreme levels of CS, followed by the episodic migraine and control group, respectively (Table 3).

Table 3. Central sensitization levels between each subgroup.

Groups	Subclinical	Mild	Moderate	Severe	Extreme	Total
CG	29	1	-	-	-	30
EM	10	12	9	2	2	35
CM	3	5	11	5	6	30

Discussion

The purpose of this study was to evaluate the CS levels in patients with episodic and chronic migraine, comparing them with a control group using the BP-CSI. This questionnaire is useful as a screening tool for CS diagnosis with a cut-off greater than 40 (total of 100 points; sensitivity of 81% and specificity of 75%).[13] Also, this inventory divides patients into 5 categories according to the score obtained: subclinical (0-29), mild (30-39), moderate (40-49), severe (50-59) and extreme (60-100), aiding the pain physician as an objective measurement for future chronic pain studies, control of response to treatment, avoiding misdiagnosis and unnecessary procedures.[14]

The sample of our patients with migraine was similar to those described in literature, with two thirds of the patients with migraine being female (66%).[15] In our group, 87% of patients started migraine symptoms in young adulthood.

In the present study, the vast majority of migraine patients had already completed university education (80%), mostly explained by the fact that patients were evaluated in a private hospital, with a sample of a high socioeconomic level. North American studies found an inverse relationship between prevalence of migraine and socioeconomic status, measured by financial income or educational level.[16] Factors such as stressful lifestyle and poor diet can contribute to a higher incidence in the poorer population. Despite the fact that socioeconomically deprived individuals have a higher incidence of migraine and chronification, our evaluation with individuals with higher education level allowed us to have a more reliable result in the BP-CSI.

The pathophysiology of chronic migraine suggests the occurrence of structural and functional brain changes, including central sensitization.[25]

In a brain MRI study comparing 11 patients with chronic migraine and 16 with episodic migraine, structural changes were identified with a significant volume decrease in several areas of the gray matter such as: anterior cingulate gyrus, amygdala, parietal operculum, inferior frontal gyrus and insular lobe. In addition, there was a reduction in the anterior cingular cortex and the frequency of migraine attacks.[25]

Increased brain iron deposits have also been detected in migraine patients. Through high-resolution MRI, Welch et al. compared patients with episodic migraine (n = 17), chronic daily headache (CDH; n = 17) and a control group (n = 17). Increased iron deposition was shown in patients with episodic migraine and CDH when compared to the control group and this iron accumulation was positively correlated with disease duration and migraine chronification.[27]

Functional changes, such as cortical excitability in certain brain areas, are associated with chronic migraine. Aurora et al. compared 25 patients with chronic migraine and episodic migraine patients with a control group. The individuals underwent PET-CT and there was an increase in metabolism in the pons and right temporal cortex, suggesting greater cortical excitability. The researchers concluded that the high cortical excitability can make patients with chronic migraine more susceptible to the triggers of the disease, explaining the high frequency of attacks.[28]

CS is a well-established clinical phenomenon and its concepts have been recognized for more than 10 years. The first article that correlated sensitization and headache was published by Nature in 1996, which hypothesized - and later validated - chemosensory similarity and sensitization of meningeal sensory neurons with nociceptive neurons found throughout the body.[29]

While nociceptive pain is a physiological response to a stimulus, severe enough to generate pain (as trauma, extreme temperatures, inflammation and infections), neuropathic pain is a pathological status with abnormalities in the transmission and processing (as in post-traumatic, post-infectious or post-ischemic painful neuropathy). Migraine, in the other hand, is under the group of nociplastic pain, characterized by pain mechanism dysfunction, since there is no anatomical lesion that could explain the symptoms.[30]

During the final stages of a migraine attack as well as in chronification period, the sensory neurons that innervate the meninges synapse with second-order neurons of the trigeminal caudate nucleus (TCN) in the brain stem. This leads to two nociceptive properties: chemosensitivity and sensitization. Chemosensitivity is characterized by a process in which a neuron previously insensitive to a specific stimulus in its resting state becomes sensitive to that stimulus in the presence of an altered chemical environment. Sensitization is the process in which the stimulus needed to generate a response decreases over time, while the amplitude of the response increases ("peripheral" sensitization refers to the process that occurs in neurons in the peripheral system and "central" sensitization, the analogous process in the central nervous system).[25,31] The result of these changes is expressed by hyperalgesia (exaggerated and intensified pain in response to a stimulus that is supposed to cause lower intensity of pain) or allodynia (painful response to a non-painful stimulus).[32]

In migraine, sensitized nociceptors send stimuli of increasing intensity (peripheral sensitization) to the spinal cord and brainstem, which, if repeated, may lead to CS and additional pain amplification. Peripheral sensitization in migraine is due to dural neuroinflammation and meningeal trigeminal nociceptors activation. The beginning of this process may include widespread cortical depression or autonomic dysfunction with excessive parasympathetic activity.[30]

CS is associated with abnormal neuronal excitability in the TCN. Increasing stimuli expressed by the trigeminal nerve, as a consequence of peripheral sensitization, triggers this neuronal hyperexcitability. Other chemical disorders, such as decreased magnesium and increased calcium and glutamate are mediated by NMDA receptors and are also associated with this change in TCN. Recent evidences suggest that CS is maintained by glial cells activation surrounding the TCN, generating multiple changes including the production of prostaglandins.[30]

In the present study, when evaluating BP-CSI Part A of each subgroup, a higher average score is shown in patients with chronic migraine in relation to episodic and control group (mean: 47.0, 37.3 and 20.2, respectively). There are no known studies comparing directly migraine with CS levels through BP-CSI, but it can be assumed that there is a higher level of CS in patients with chronic migraine, in relation to the episodic group, and both in relation to the control group.[33] Furthermore, we can conclude that patients with episodic migraine have lower levels of CS. This data is useful in the management and treatment, because earlier identification of CSS may reduce time, efforts and financial resources in high-cost diagnostic tests, invasive procedures and even surgeries. Through low cost and time savings, the use of BP-CSI allows us to increase diagnostic sensitivity and start treatment in advance, reducing hospital costs and improving rates of response to treatment and patient satisfaction.

However, our study had some weaknesses that need further discussion. First of all, the samples were not paired by sex, since the episodic and chronic migraine subgroups had twice more women than the control group. One additional concern was that the control group did not include any other sensitization syndrome diagnosis other than migraine (like fibromyalgia, irritable bowel syndrome, depression etc) which, in turn, is listed in the BP-CSI Part B. Finally, some patients with episodic or chronic migraine had previous treatment modalities such as antidepressants and anticonvulsants, which could modify the final BP-CSI score.

We suggest that in the future, studies should include a higher number of patients, selecting a better sample profile in each

subgroup, in order to standardize the research and provide unified results. Additionally, these studies should consider other comorbidities not related to migraine and CS (which could distort the perception of clinical manifestations) and select migraine patients before pharmacological interventions for a better analysis of the results.

Conclusion

CS in chronic migraine is a well-established phenomenon and described in the literature. However, the present study also shows evidences of mild CS in patients with episodic migraine, evaluated in a private hospital specialized in neurological disorders through the application of BP-CSI. Despite the limitations of our study, scientific evidence in the previous current literature did not show incontestable occurrence of CS in patients with episodic migraine. The identification of this disturbance is important for better management and early control of treatment, reducing time, efforts and financial resources in high-cost diagnostic tests and invasive procedures.

Author's Contribution: MAN - Data Collection, Conceptualization, Methodology, Writing - Preparation of the original, Writing - Review and Editing; PSFS - Writing - Proofreading and Editing, Supervision; DBA – Writing, Proofreading and Editing, Supervision

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