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AWAKE BRUXISM: FREQUENCY, PROGRESS AND CORRELATION WITH PHYSICAL, ENVIRONMENTAL, PSYCHO-SOCIAL PARAMETERS IN A SAMPLE OF HEALTHY ADULT SUBJECTS

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ABSTRACT

Bruxism is a multifactorial pathological behaviour that consists of a repetitive jaw-muscle activity characterised by clenching or grinding of the teeth and/or bracing or thrusting the mandible. Polysomnography is today considered the gold standard for diagnosis, but momentary ecological assessment (EMA) studies are also currently being used. In particular, a smartphone application named BruxApp® can provide real-time data on awake bruxism (AB) with great precision. The aim of the study is to analyse the correlation between the frequency of awake bruxism and physical, environmental and psycho-social parameters in a specific cohort, i.e. adult asymptomatic patients. Of a sample of 152 subjects with age ≥ 30, we obtained a 73,4% of responses during the 7-day long records. The mean percentage of AB recorded through BruxApp® was 35% (SD 25%), while patients' self-assessment questionnaire reported a 30% AB prevalence. No significant association was found between AB and age or gender. There is, however, a statistically significant association between AB and familiarity. The present study provided new data about the prevalence and correlation of AB in healthy adult patients. Further evidence has been produced about the absence of a relevant correlation between bruxism and age/gender, nor negative clinical consequences, linea alba aside. The psychological and neurological sphere and familiarity appeared to be much more positively associated with AB.

KEYWORDS: *bruxism, polysomnography, BruxApp®, masticatory muscles activity*

INTRODUCTION

Bruxism is defined as a repetitive jaw-muscle activity characterised by clenching or grinding of the teeth and/or bracing or thrusting of the mandible. This activity has two distinct circadian manifestations: it can occur during sleep (sleep bruxism-SB) or wakefulness (awake bruxism-AB) (1). SB is defined as a masticatory muscle activity during sleep characterised as rhythmic (short-term phasic activity) or non-rhythmic (long-term tonic activity); AB is characterised by repetitive or sustained tooth contact and/or bracing or thrusting of the mandible.

The aetiology is uncertain and multifactorial: while the occlusal discrepancies and the anatomy of the bony structures of the orofacial region play only a minor role, other factors, like smoking, alcohol, drugs, systemic diseases, stress, trauma,

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and heredity factors, appear to have an important role. This oral behaviour has been associated with tooth wear, masticatory muscle tenderness, headaches, and painful TMJ.

Polysomnography is the gold standard for diagnosing bruxism; however, a momentary ecological assessment (EMA) can be used to evaluate the muscles' prolonged isometric activity. EMA studies assess particular events in subjects' lives or assess subjects at periodic intervals, often by random time sampling, using technologies ranging from written diaries and telephones to electronic diaries and physiological sensors (2). Based on these EMA approaches, some recent research has been proposed for studying bruxism: a smartphone application named BruxApp®. This app collects real-time data on awake bruxism and has already been used in different studies in the literature (3-5).

The aim of the study is to investigate the frequency of awake bruxism in an asymptomatic adult patient because, until now, the samples were only students, and also to analyse the correlation between the frequency of awake bruxism and physical, environmental and psycho-social parameters.

MATERIALS AND METHODS

A dedicated smartphone application has been used (BruxApp®) on a sample of 152 subjects with age ≥ 30 until 100 questionnaires obtained a negative answer to item Q65 (Fig.1): in this way, 53 males and 47 females were selected with a mean age of 37.99 ± 8.98 years. This study is made to record real-time reports on five specific oral conditions (relaxed jaw muscles, tooth contact, teeth clenching, teeth grinding, mandible bracing) related to the spectrum of AB activities. Data were recorded over a 7-day period where the subject responded from 12 to 20 daily alerts within 5 min of the input. Seventeen subjects could not complete the data correction, so they were not considered for the final clinical test, narrowing the sample to 83 subjects. The distribution by gender comprises 41 males and 42 females. Mean age 38,7± 9,6 years while then stratification of the sample by age range discovers a significant majority between 30-39.9 (63 subjects) and a remaining distribution between 40-49.9 (11 subjects) and above 50 years (9 subjects).

Two questionnaires were utilised: the first one, DC for bruxism-anamnesis ITA (version 1.2), was anonymous about age, gender, and ID with different items; the other one was a self-assessment questionnaire. All data were collected in Excel and analysed with R 3.5 software.

First, an evaluation with a paired t-test was performed to compare the answers to the initial self-evaluation questionnaire with the results detected by BruxApp®. Subsequently, a descriptive statistical analysis of the data obtained was made: the correlation between the percentage of awake bruxism and ordinal categorical variables was evaluated with Spearman's Rank correlation coefficient. Finally, the association between the percentage of awake bruxism and binary variables was evaluated with Student's t-test. A p-value below 0.05 was considered significant.

Pain

56. Have you ever had pain in one or more highlighted areas in the figure below?

no□ yes□

Fig. 1. *Question 56 from anamnestic questionnaire DC for Bruxism - Anamnesis ITA (version 1.2).*

RESULTS

The mean compliance recorded with BruxApp® was 73.4% of the total alert. The average frequency of relaxed jaw muscles (RR) reports 64.4%; mandible bracing (SM)14.2%; teeth contact (CD) 17.9%; teeth clenching (SD) 3.1%; teeth grinding (DD) 0.2%. Overall, the mean percentage of AB was 35 (SD 25%). The numerical comparison with the data

obtained from the self-assessment questionnaire completed before starting to use BruxApp® is graphically shown below (Fig.2). From the data obtained from the questionnaire, it was possible to calculate the prevalence of AB in the sample equal to 30.1% (25 subjects with self-report AB ≥ 3 on the scale from 1 to 10). After that, the averages of the 6 percentage values of BruxApp® are calculated, and the results are the following: 71.7% alert; 50.2% RR; 27.4% SM; 17.5% CD; 4.8% SD; 0% DD. Therefore, the total value of AB for both AB+ (anamnestic self-assessment parameter on the presence of AB) and the total sample is 49.8% and 35.4%.

Fig. 2. *Numerical comparison with the data obtained from the self-assessment questionnaire completed before starting to use BruxApp®.*

Finally, from the available database, the average responses attributable to the frequency of AB were obtained for the first 3 and the last 3 days of the test: the results were 36.7% and 34.5%, with a differential of -2.2% (biofeedback).

DISCUSSION

Regarding the analysis of the average value, the examined sample responded on average to 73.4% of the alerts proposed by the app in the 7 days of registration which is indicative of a level of compliance slightly lower than that detected by Colonna et al. (5). As for the average of the values relating to the 5 conditions, the result (RR=64.6%, SM=14.2%, CD=17.9%, SD=3.1%, DD=0.2%) is correspondent with what was detected by Zani et al. (3) whose values (at the first week) were similar (RR=62%, SM=14%, CD=20%, SD=3%, DD=1%). Even the prevalence obtained from the initial anamnestic questionnaire equals 30.1% of the sample (6).

When analysing the reliability of the self-assessment questionnaire, the comparison of the data of the questionnaire and that obtained by BruxApp® showed that the average value of RR from the questionnaire was found to be 83.5%, while for MS, the average value was 2.8%; a clear difference is immediately evident for both conditions. On the other hand, analysing the BruxApp® data, only 45 subjects have an average of less than 10% responses. Therefore, SM would seem to be a condition hardly perceived by patients.

The subject predicts a minor discrepancy in the preliminary phase and the result obtained after 7 days of registration concerning the values of CD and DD, as the differences are + 5.4% and + 1.4%. However, even in this case, the Paired t-test resulted in a statistically significant difference for both conditions (Fig.3, $p < 0.05$).

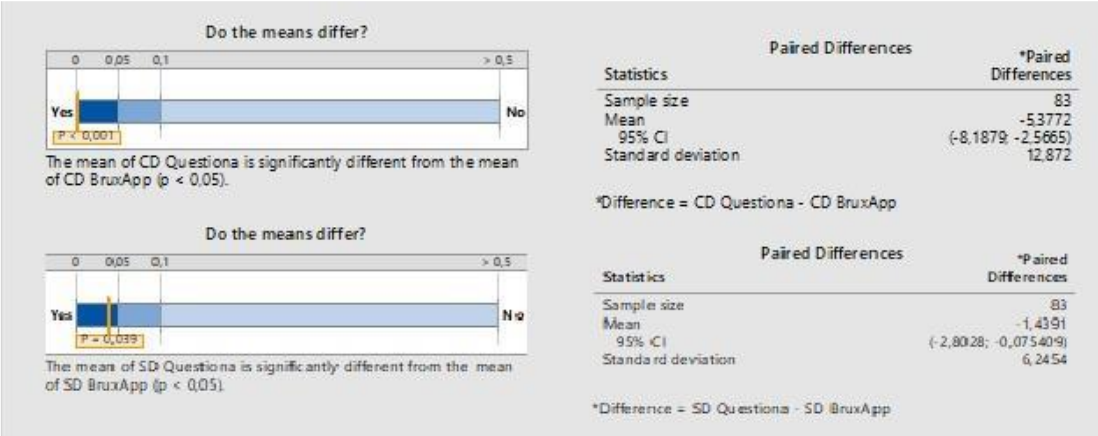

Fig. 3. *Paired t-test - comparison between CD and SD frequency expected by the subject and detected with BruxApp.*

The analysis of the associations between "AB" and the variables considered done in this study, just like in other works based on data collection through EMA devices (3, 4, 5), showed no significant association between male and female genders and AB values obtained (p = 0.39). Instead, a higher % of awake bruxism with a positive self-report for sleep bruxism, familiarity, non-functional oral habits and mostly the presence of linea alba was highlighted.

When discussing the frequency of AB and clinical correlates, it is impossible to completely detach the presence of AB with a relapse on a physical level; however, the findings align with what was recently stated in the consensus (7) regarding the clinical correlates of bruxism. Therefore, as proposed by the experts, we can identify situations in which bruxism is a harmless muscular behaviour just like others in which an increase in muscular activity is associated with one or more negative clinical consequences. Furthermore, although there are borderline cases, these subjects showed slight muscle pain but not high on clinical examination; this further confirms that bruxism should not be considered a pathology per se (7).

On the other hand, the analysis of the frequency of AB and statistically insignificant variables also suggests a possible correlation between the percentage of awake bruxism and the intake of alcohol, tobacco, and caffeine. However, the result was only near to the significance statistics (p = 0.08) and mainly, contrary to what is reported in the literature (8-11), the association turns out to be inverse; hence, as the score increases, the percentage of bruxism decreases.

On the sample studied, it is not possible to make any assertions concerning the correlation with dental information and the association with parafunctions, pain in the head, neck, shoulders and TMJ, noises and joint dysfunctions, presence of tinnitus, jaw trauma, whiplash and other habits (Table I). The frequency of AB was also analysed with the age of the subjects; however, the data showed no association (neither linear, quadratic, nor cubic) between them.

Table I. *Correlation with dental information and association with parafunctions.*

VARIABILITY	Average (SD)	p-value
Gender: Woman Man	 38 (23) 33 (27)	0.39
Report AB: No Yes	 34 (25) 50 (26)	0.21
Report SB: No Yes	 30 (23) 53 (23)	0.0003
Familiarity: No Yes	 32 (24) 48 (26)	0.02
Non-functional oral AB: No Yes	 31 (25) 43 (24)	0.04
Parafunction: No Yes	 36 (25) 34 (27)	0.84
Drugs and medicines use: No Yes	 35 (25) 52 (11)	0.25
Head/neck/shoulder/ATM pain: No Yes	 33 (24) 44 (27)	0.14
ATM click/dysfunction: No Yes	 35 (25) 42 (24)	0.40
Tinnitus: No Yes	 31 (23) 40 (27)	0.10
Mandibular trauma: No Yes	 35 (25) 34 (37)	0.96
Colpo di frusta: No Yes	 35 (25) 37 (26)	0.75
Other problems: No Yes	 34 (26) 39 (24)	0.43
Linea alba: No Yes	 19 (15) 50 (23)	<0.0001
Previous fixed orthodontic therapy: No Yes	 34 (26) 40 (20)	0.32
Previous removable orthodontic therapy: No Yes	 34 (24) 39 (29)	0.56

CONCLUSIONS

Thorough studies have been made to investigate the normality of awake bruxism; however, these were limited only to university students. The research has now been extended to asymptomatic adult patients, using the same variables used for the students. It also includes the correlation between awake bruxism and physical, environmental, and psycho-social parameters. The analysis of the collected data has shown that, regarding the frequency of awake bruxism in adult patients, the average values registered from the entire sample in the 7 days of registration through BruxApp® is equal to 35.4% of responses. As for the correlations between awake bruxism and the lifestyle, associated pathologies and clinical signs and symptoms from the study, the conclusive results differ. They reveal no significant association between AB and age or gender. There is, however, a statistically significant association between AB and familiarity. The causes related to the psychological and neurological sphere have also been implied. There has been further confirmation that awake bruxism

is considered a behaviour which can also not be correlated with negative clinical consequences. In addition, there is a correlation with clinics, which is not necessarily a source of spontaneous symptoms. Lastly, there is a strong association between high percentages of AB and the presence of mono- or -bilateral linea alba.

Conflict of interest

The authors declare that they have no conflict of interest.

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Letter to the Editor

PATHOPHYSIOLOGY AND NEUROINFLAMMATION IN COVID-19

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INTRODUCTION

COVID-19, the disease caused by the coronavirus-19 infection, has caused more than five million deaths worldwide. In addition, infection with SARS-CoV-2, a positive-sense, single-stranded RNA genome, has been associated with numerous symptoms (1) (Table I).

Table I. *Some of the numerous symptoms associated with SARS-CoV-2 infection.*

• Muscle pain	• dizziness	• impaired consciousness
• fever	• psychiatric symptoms	• neuromuscular disorders
• anosmia	• seizures	• myocarditis
• hyposmia	• stroke	• fatigue
• loss of taste	• chills	• delirium
• anxiety	• shortness of breath	• depression

In addition, a critical neurological symptom of COVID-19 is brain fog, a pathological state represented by cognitive dysfunction and fatigue. It has also been observed that in COVID-19, individuals experienced increased depressive phenomena and states of anxiety when compared to healthy subjects, symptoms that occurred, above all, after the clinical signs of COVID-19 were no longer evident (2). In COVID-19 survivors, psychological and neural dysfunction is seen during and after viral infection (2). These effects were more evident in women, even though they showed lower inflammatory parameters than men (3).

SARS-CoV-2 enters the nervous system through the nasal (olfactory bulb) and oral routes, binds to a converting enzyme called angiotensin-2 (ACE-2), and is mainly conveyed through neurons and blood circulation (4). The virus invades the central nervous system (CNS) and can cause long-term damage, a significant effect that should be considered. The spike protein S in the S1 and S2 sub-units allows the entry of the virus in the cytosol and binds to ACE-2 expressed in many body cells, including brain endothelial cells (4); this induces CNS inflammation and brain damage, which are mediated by pro-inflammatory cytokines produced by the immune system. The ACE-2 enzyme is also expressed in the

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brain in the cerebellum, thalamus, and inferior olivary nuclei (5). Therefore, COVID-19 is not only a lung disease but is also a brain disease, with long-term effects following the obvious symptoms of the disease. CNS disturbances in COVID-19 can range from quickly reversible mild symptoms to more complex and severe longer-lasting symptoms that devastate brain tissue (such as stroke) (6).

Induction of stroke by SARS-CoV-2 infection

Stroke is one of the most frequent symptoms of COVID-19 and often occurs in outpatients, demonstrating the severity of the disease. The activation of immune cells by the virus leads to the secretion of various cytokines and chemokines, which can cause cerebral hyperinflammation, detectable by electroencephalogram (7). In COVID-19, immune cells, including monocytes/macrophages and mast cells (MCs), are recruited and release inflammatory cytokines by activating the extrinsic coagulation pathway, resulting in a thrombotic state and ischemic stroke.

Women are more protected from SARS-CoV-2, as estrogen secretion stimulates immune cells, which inhibit coronavirus-19 replication (8). In fact, in women, 17β-estradiol inhibits adhesion molecules, such as ICAM-1, which are pro-inflammatory molecules (9). It also appears that females infected with the virus have fewer inflammatory cells in their lungs and, therefore, a lower level of inflammatory cytokines than males; this is why women are less vulnerable to COVID-19 than men. The release of pro-inflammatory cytokines causes the "cytokine storm" with thrombotic effects and brain damage.

Pro-inflammatory cytokines such as IL-1, TNF, and IL-6, as well as type I interferon (IFN), associated with some chemokines, cause endothelial cell dysfunction, provoking coagulopathy with increased prothrombin, which causes thrombosis, respiratory failure, and acute renal failure, mechanisms that are still under study (10). The neurologic impairments in COVID-19 can also be due to the passage of inflammatory cytokines from the bloodstream through the blood-brain barrier (BBB) (11). In addition, there is a poor oxygen supply since malfunctioning of the lung can occur. The virus can cause encephalopathy with changes in the brain's structure and/or functions, a condition that can be improved with pharmacological treatment (such as steroids) and ventilation (12); this demonstrates that SARS-CoV-2 affects mental health with neuropsychiatric complications due to inflammatory mediators activated by the virus through tissue colonization of immune cells in COVID-19 (13).

However, rare adverse events have occurred after vaccination, but most of these were resolved in the short term and with nonspecific therapy. The anti-COVID-19 vaccination is essential for immunity against coronavirus-19, although thrombosis with bilateral facial paralysis and encephalitis have occurred after vaccination and are considered side effects with a low incidence (14).

Myocarditis after anti-COVID-19 vaccination

Another rare side effect ff mRNA vaccination is myocarditis, mainly in young adult males between approximately 20 and 30 years of age and in adolescents (about 50 cases per million vaccinated) (15). Myocarditis is an inflammation of the myocardium that can cause cell and tissue death. It can be caused by many ailments, including viral infections, and can cause chest pain, shortness of breath, and sometimes death. Myopericarditis occurs if the inflammation involves the pericardium that surrounds the heart. However, future studies are needed to resolve these problems that may present after COVID-19 vaccination.

CONCLUSIONS

The above studies show that SARS-CoV-2 affects mental health with neuropsychiatric complications due to inflammatory mediators activated by the virus through tissue colonization of immune cells in COVID-19.

Conflict of interest

The authors declare that they have no conflict of interest.

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EFFECT OF THE COVID-19 PANDEMIC ON NEUROINFLAMMATORY DISEASES

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ABSTRACT

In December of 2019, SARS-CoV-2 surfaced and the global COVID-19 pandemic began. The pandemic has had far-reaching effects, socially, economically, and especially for healthcare, presenting challenges to patients with neuroinflammatory disorders. Apart from the well-known respiratory, pulmonary, and cardiovascular symptoms that COVID-19 is responsible for, studies continue to show its role in generating neuroinflammation and the different neurological effects that can arise. This review summarizes the relationship between the COVID-19 pandemic and neuroinflammatory diseases, with an emphasis on the effects on patients with neuroinflammatory disorders.

KEYWORDS: *neuroinflammation, pandemic, SARS-CoV-2, COVID-19, immunity*

INTRODUCTION

In December of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China in the city of Wuhan. The coronavirus disease (COVID-19) spread and quickly became a global pandemic (1). On January 30th, 2020, The World Health Organization proclaimed the COVID-19 outbreak as an International Public Health Emergency (2), and an official report stated that as of November 22, 2021, there have been approximately 250,000,000 confirmed cases and over 5,000,000 confirmed deaths (3).

SARS-CoV-2 can be asymptomatic or cause a range of symptoms, spanning from mild to severe, such as shortness of breath, dry cough, fatigue, fever, pneumonia, respiratory failure, and systemic inflammation (4). Older individuals and those with a weakened immune system and other comorbidities are more at risk for serious complications.

The pandemic has reshaped society and social habits, has had negative effects on the economy, and has presented great challenges in healthcare (5). COVID-19 can also be linked to neuroinflammation, and in this article, the effects of the pandemic are summarized with respect to neuroinflammatory diseases.

Neuroinflammatory diseases

The nervous system is comprised of two parts: the central nervous system (CNS) and the connective nerves of the peripheral nervous system. Neuroinflammation occurs in the CNS, affecting the brain, spinal cord, and optic nerves. When the CNS is damaged by an overly active immune response, neuroinflammatory diseases occur.

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The role of the immune system is to protect the body against injury and infection, which it performs by engaging in inflammatory challenges in response to harmful stimuli. But it may be over-reactive and attack healthy cells in response. Innate immune cells called microglia, which are central to immune surveillance, produce cytokines and chemokines and mediate the innate immune capacity of the CNS (6). In the situation of neuroinflammatory disorders, there is immune cell infiltration or glial cell activation, which can damage the CNS (7).

In many cases of neuroinflammatory diseases, inflammation may originate from another inflammatory response in the body. This chronic systemic inflammation may eventually pass through the blood-brain barrier (BBB) and enter the CNS, causing neuroinflammation by activating microglia and astrocytes. Neuroinflammatory disorders are variable, having different etiology and different pathogenic mechanisms, but they all result from this inflammation of the nervous system (8).

Multiple sclerosis (MS) is one of the better-known neuroinflammatory disorders. It is a demyelinating disease, meaning that the myelin sheath, which shelters nerve cells and axons, becomes damaged, and this results in neurological problems. Other CNS disorders that can be influenced by inflammation include neurodegenerative and even psychiatric disorders.

Some other neuroinflammatory disorders include:

- Alzheimer's disease
- Parkinson's disease
- amyotrophic Lateral Sclerosis
- acute disseminated encephalomyelitis (ADEM)
- Rasmussen's syndrome
- acute necrotizing encephalopathy
- opsoclonus-myoclonus ataxia syndrome (OMAS)
- autoimmune Encephalitis
- optic Neuritis
- transverse Myelitis
- neuromyelitis Optica (NMO)
- anti-myelin oligodendrocyte glycoprotein antibody disease (MOG)

Unfortunately, a cure for neuroinflammatory disorders is yet to be discovered. However, some treatment is available to reduce symptoms and disease severity.

Neuroinflammation and neurological diseases

Recent research continues to shed light on the role of neuroinflammation in neurodegenerative diseases that were not previously associated with inflammation, such as Alzheimer's disease or stroke. Due to this association, neuroinflammation needs to be focused on because it may be implicated in many pathologies and can enhance further research and treatment (9).

Upon immune system activation, inflammatory mediators are produced and can infiltrate the brain and create the CNS inflammatory response (10). Growing evidence continues to link the connections between immune cells and neurons, and the way in which neuroinflammation upsets the equilibrium of this homeostatic system (11).

Cytokine networks have been shown to vary between neuroinflammatory disorders and neurodegenerative diseases. Pro-inflammatory cytokine production may help distinguish neuroinflammatory disorders from neurodegenerative diseases; in the case of neuroinflammatory disorders, such as MS and encephalitis, leukocytes are usually responsible, whereas in neurodegenerative disease, CNS-resident cells are mainly responsible (12).

The effect of SARS-CoV-2 on neuroinflammation

Pulmonary and cardiovascular complications are well-recognized in COVID-19 patients, and now research is beginning to explore the neurological complications and effects, as patients continue to present neurological symptoms. It has been reported that neurological symptoms were present in 36.4% of patients with SARS-CoV-2 (13).

Neurologic symptoms can vary greatly and can include headache, anosmia, encephalopathy, encephalitis, stroke, hemorrhagic lesions, and neuronal impairment. A common symptom is impaired olfaction, the loss of smell, as the olfactory bulbs in the nasal cavity are affected (14). Neurological symptoms may also arise in response to microvascular injuries and thromboembolic events, which is supported by findings in autopsy tissue of cerebrospinal fluid and neuroimaging (15). Edema in the brain may result from SARS-CoV-2 neuroinflammation (16), and the acute autoimmune disorder, Guillain-Barré syndrome (GBS), has been linked to SARS-CoV-2 infection, especially amongst older patients (17).

Studies have shown that SARS-CoV-2 generates neuroinflammation. During infection with SARS-CoV-2 and lung invasion, there is an activated immunoinflammatory response with pro-inflammatory compounds being released and creating a "cytokine storm". These can cross the BBB, enter the CNS, and create neuroinflammation (18). With the activation of the immune system, cytokine, chemokine, and free radical levels are raised at the BBB, thus permitting the infiltration of inflammatory cells into CNS immune cells (19). The hyperinflammatory state induced by SARS-CoV-2 can also generate interleukins-2, 6, 7, and 10, TNF, and granulocyte colony-stimulating factor (20). COVID-19 can cause neuroinflammatory cascades and provoke the "cytokine storm", which can result in patient death (21).

Neuroinflammatory disorders and COVID-19 vaccination

SARS-CoV-2 vaccine hesitancy has surfaced amongst patients with neuroinflammatory diseases. This hesitancy arises from the exclusion of these patients in vaccine trials. Furthermore, such as in some cases of neurological diseases, hesitancy can also arise from the fear that immunotherapy may negatively affect the vaccine response. However, a study by Epstein et. al has shown that vaccine side effects do not differ between patients with neuroinflammatory disorders and the general public, and apart from a higher incidence of reported headaches, that their disorders did not degenerate after vaccination (22).

This supports the safety of SARS-CoV-2 vaccines for patients with neuroinflammatory diseases, although further research is still needed. The benefits of the protection provided by the vaccine are likely to outweigh the risks for persons with neuroinflammatory disorders.

Immunotherapies during COVID-19

Patients with neuroinflammatory disorders are often on immunosuppressive therapies, and this may, unfortunately, be a risk for infections, including SARS-CoV-2, and their resulting complications. Immunosuppressive treatment often includes the use of drugs such as methotrexate, mitoxantrone, azathioprine, cortisone, and cyclophosphamide, which may be linked with higher SARS-CoV-2 infection rates. At the same time, the benefits of this therapy in treating the neuroinflammatory disorder may take precedence (23).

The weight of the pandemic

The COVID-19 pandemic has presented significant challenges to the healthcare sector, putting hospitals and staff under immense stress, and anxiety and depression were shown to be higher among patients suffering from pre-existing conditions during the pandemic (24).

Many challenges were also presented for patients suffering from neuroinflammatory disorders. These patients need routine care with clinical visits and ongoing monitoring, and certain conditions such as MS have higher incidences of hospitalization. This care was severely affected by the pandemic and subsequent lockdowns, and the required hospitalizations during the COVID-19 pandemic also put patients at a higher risk of direct exposure to SARS-CoV-2 in the hospital setting.

Reduced access to physicians and medical services, loneliness, and the anxiety and uncertainty resulting from the COVID-19 pandemic are some factors of psychological stress that can lead to problems for patients with neuroinflammatory disorders, causing anxiety and depression, and exacerbating the disease condition (25). In their article, *Manifestations, and impact of the COVID-19 pandemic in neuroinflammatory diseases*, Levin et al. presents the results of a year-long study that explored the effects of the COVID-19 pandemic on patients with neuroinflammatory disorders. It was shown that the social distancing practices implemented during the pandemic can limit the access to healthcare resources and home care for patients with neuroinflammatory diseases and that patients perceived a lowered level of social support (26). Another example is a study revealing that during the COVID-19 pandemic, people with MS suffered from post-traumatic stress disorder, anxiety and stress, depression, and insomnia (27).

CONCLUSIONS

Since December 2019, SARS-CoV-2 continues to spread and remains a global pandemic and a public health emergency. It has been shown to cause neuroinflammation and cause neurological symptoms ranging from mild to severe. An overly active immune response can cause the "cytokine storm", changing the balance between neurons and immune cells in the CNS and causing damage and death.

Patients with neuroinflammatory diseases are at a higher risk of suffering more severe complications. Psychologically, the pandemic has been challenging for these individuals, as healthcare access has been limited and social restrictions have created anxiety and isolation. There was fear of the uncertainties concerning vaccinations and potential complications of their condition from SARS-CoV-2.

There is a need for more research focusing on the potential implications of COVID-19 for patients with neuroinflammatory diseases. Studies must continue in order to build a more concise pathological basis for the neuroinflammatory effect of SARS-CoV-2.

Conflict of interest

The authors declare that they have no conflict of interest.

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SARS-COV-2 INDUCES PRO-INFLAMMATORY CYTOKINES WITH AN IMPACT ON MENTAL HEALTH

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ABSTRACT

In December 2019, the novel coronavirus strain SARS-CoV-2 caused an outbreak that quickly spread worldwide and led to the COVID-19 pandemic. COVID-19, the severe infectious disease caused by SARS-CoV-2, often presents with symptoms including fever, cough, and mental confusion and can cause the acute respiratory inflammatory disorder. Additionally, viral infection with SARS-CoV-2 is associated with mental health, neuronal degeneration, and psychiatric complications. With infection by the virus, cytokines are released by immune cells, causing acute systemic inflammation affecting the lungs. Lung damage can occur, resulting in hypoxia, brain damage, and mental health dysfunction. In addition, a cascade of inflammatory cytokines, including IL-1, IL-6, and TNF, are released, a phenomenon termed the "cytokine storm" that causes serious pathological damage to tissues and organs and mental health. This exaggerated production of cytokines leads to lymphopenia and disrupts the balance of Treg and Th17 cells, weakening the immune system. The elderly population is particularly at risk for damage associated with the "cytokine storm", which can affect neurological functions or result in death.

KEYWORDS: *SARS-CoV-2, COVID-19, cytokine, mental health, neurodegenerative disease, inflammation, cytokine storm, immunity*

INTRODUCTION

Hundreds of millions worldwide suffer from chronic neurodegenerative diseases with memory impairment in various cognitive domains that can lead to death a few years following the disease. Neurodegenerative diseases are inflammatory disorders, often age-related such as Alzheimer's disease, which leads to memory impairment, but can frequently be unrelated to ageing. However, the pathogenic mechanisms underlying the inflammatory state remain unclear in many cases. Infections, such as viral infections due to SARS-CoV-2, a member of the coronavirus family, are often of great concern because they are associated with mental health, neuronal degeneration, and psychiatric complications (1).

Towards the end of 2019, an outbreak of a novel strain of coronavirus occurred in Wuhan, China, infecting the entire world within a short time. Soon after, this virus was seen to cause Coronavirus Disease 2019 (COVID-19), a severe infectious disease causing an acute respiratory inflammatory disorder that led to the deaths of millions of people

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worldwide, especially in individuals with previous illnesses and those who were in advanced age. Severe infection often presented with symptoms that included fever, cough, respiratory distress, and mental confusion ("brain fog"), frequently requiring hospitalization, including the intensive care unit. COVID-19 is provoked by virus entrance into the body or organs of infected individuals; however, in many cases, people have no symptoms after infection (2) due to an efficient immune response against SARS-CoV-2 (3).

The global spread of SARS-CoV-2 infections in 2020 created great concern and challenges for the healthcare system and the worldwide population, affecting mental health (4). Diverse neurodegenerative (5) and mental health conditions are associated with inflammation and elevated levels of pro-inflammatory cytokines, including depression (6), obsessive-compulsive disorder (7), generalized anxiety disorder (8), and post-traumatic stress disorder (9).

Inflammation in SARS-CoV-2

With SARS-CoV-2 infection, immune cells release cytokines and cause acute systemic inflammation, including the lungs. This process may also involve autophagic modulation, a "self-eating" effect due to digestion that occurs inside lysosomes, inducing lung inflammation (10). After digestion, the degradation products are translocated into the cytoplasm, allowing cellular homeostasis maintenance. Autophagy dysregulation can occur in many pathological processes, including infections and neurodegeneration (11). The virus often induces endothelial dysfunction, complement cascade hyperactivation, diffuse microvascular thrombi in multiple organs, and activation of pro-inflammatory cytokines causing the "cytokine storm" (12).

In the inflammatory process, the pathogenic virus activates the complement through the antibody-mediated pathway, which stimulates the complement component 1 (C1) complex, activating C4 and C1r (13). During a series of cascade reactions, C4b leads to the formation of C3a, which mediates chemotaxis and activates inflammatory cells with induction of cytokine production and degranulation of mast cells (MCs), resulting in enhanced vascular permeability and local blood flow (13). Elderly people with neurological disorders may present with an inflammatory state with a systemic emphasis on the disease, damage to the central nervous system (CNS), and psychiatric dysfunction (14).

SARS-CoV-2 can infect innate immune cells, making them less efficient, and can also affect endothelial cells of the blood-brain barrier (BBB) and other tissues and organs. By infecting the peripheral nerves, SARS-CoV-2 gains entry into the CNS and spreads into the olfactory bulb, cerebral cortex, and spinal cord, with subsequent encephalitis (15). One of the fundamental effects caused by the virus is lung damage resulting in hypoxia, which can lead to brain damage and mental health dysfunction (16). In addition, the inflammatory damage caused by cytokines, such as interleukin-1 (IL-1) (17), tumor necrosis factor (TNF) (18) and IL-6 (19), can also affect the nervous system (20).

The "cytokine storm" affects mental health

The "cytokine storm" is induced by a cascade of inflammatory cytokines that cause serious pathological damage to organs and tissues, compromising the health of the infected population, particularly the mental health of the elderly (14). The main pro-inflammatory cytokines released in COVID-19 are IL-1, IL-6, and TNF, and these trigger the activation of other cytokines, aggravating inflammation and affecting general health.

In the elderly, the "cytokine storm" causes severe pathological effects on organs and tissues and damages neurological functions (14). These effects can be lethal, but even the low-grade inflammatory state can harm this population and aggravate the mental state that is often already in suboptimal health conditions.

The pro-inflammatory cytokines induced by the virus, particularly IL-1, IL-18, TNF, and IL-6, can activate the microglia in an autocrine way and produce IL-2, interferon-gamma (IFN-γ), and other cytokines and chemokines (21) which damage the BBB. These pathological phenomena cause tissue neurodegeneration and induce symptoms of depression (22), effects that, in some instances, can become chronic. Under these circumstances, macrophages, perivascular mast cells (MCs) and endothelial cells are activated, and releasing cytokines affect the vagus nerve and hypothalamus (23).

Pro-inflammatory cytokines IL-1, IL-6, and TNF are often seen in elevated levels in individuals with depressive disorder (24). Cytokines can activate the mechanisms of depression by reducing the mammalian target of rapamycin (mTOR) (25). The mTOR signaling pathway regulates diverse cellular processes such as growth, homeostasis, and disease pathogenesis (26). Decreased mTOR facilitates infectious activity, even if, on the contrary, it seems that the mTOR activity can lead to the activation of some pro-inflammatory cytokines such as IL-6 and TNF (27). mTOR is also involved in reducing viral proliferation and, therefore, in decreasing the pathological phenomenon induced by SARS-CoV-2 (28). Virus-induced hypoxia in COVID-19 leads to the induction of a biochemical cascade that begins with the "regulated in development and DNA damage response-1" (REDD1), which is a stress-response gene and leads to the formation of mTOR (29,30).

Cellular activation in COVID-19

One of the characteristics, particularly of the elderly COVID-19 patient, is the pathological presence in the peripheral blood of lymphopenia and the increase in neutrophilic granulocytes (31), a pathological picture that in severe cases has resulted in the patient's death (32). In these cases, the number of lymphocytes is greatly reduced, such as CD8+ cells, which have α/β, γ/δ T cell receptor (TCR)+, CD3, and other receptors on their surface. These are intraepithelial lymphocytes that can develop intra- and extra-thymically. Most α/β TCRs are enriched through self-reactivity and require β2-microglobulin-dependent major histocompatibility complex (MHC) class I expression for their generation (33). In addition, these cells can have a regulatory function by producing the cytokines IL-10 and TGFβ (34). After activation by antigen-presenting cells (APCs), some CD8+ subpopulations differentiate into cytotoxic T lymphocytes (CTL) cells and memory lymphocytes. Because of this, their deficiency in COVID-19 is very important for the entire immune system, especially for forming antiviral antibodies.

SARS-CoV-2 carries out its pathogenic action using the spike protein S, a glycoprotein that binds to the host cell receptor called angiotensin-converting enzyme 2 (ACE2) receptor (35). Once the virus enters the cell by endocytosis, it releases its RNA, forming a pathogen-associated molecular pattern (PAMP) recognized by pathogen recognition receptors (PRR). The viral antigen is presented to T cells, including Th17 cells, which differentiate and release cytokines by amplifying the immune response (36). Th17 cells have a surface phenotype αβ TCR, CD3, CD4, IL-23R, CCR6, IL-1R and CD161 with functions of promoting protective immunity against microorganisms (37), including SARS-CoV-2, especially at the mucosal surface level. Th17 cells are generated in the presence of TGFβ, IL-6 and IL-21 and are sustained by IL-1 and IL-23. In addition to promoting inflammatory diseases, these important cells can mediate autoimmune diseases (38).

Virus-infected immune cells such as macrophages and lymphocytes produce cytokines such as IFN-γ and chemokines to promote virus clearance and aid the immune response. Excessive production of inflammatory cytokines leads to a decrease in both T and B lymphocytes. Lymphopenia is accompanied by the production of IL-6, decreasing Treg cells and altering the Treg/Th17 ratio. Th17 cells produce the IL-17 cytokine, which activates the generation of other cytokines such as IL-1, IL-6, TNF, and granulocyte G-CSF (39). Hence, Treg cells significantly decrease inCOVID-19, while Th17 cells increase, weakening the immune system (31).

Furthermore, in COVID-19, induced by SARS-CoV-2, various symptoms can occur, such as muscle fatigue with weakness and asthenia (40), cognitive impairment with deterioration (41), mental slowness, attention (42) and execution deficit (43), psychomotor dysfunction and "brain fog" (44,45). In addition, individuals with this disease have impaired social and occupational activity limits.

Conflict of interest

The author declares that they have no conflict of interest.

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NEUROPATHOLOGY AND BRAIN DISORDERS: MIGRAINE HEADACHE

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ABSTRACT

Migraine headache is a prevelant brain disorder and common form of pain with high rates of disability. Originally thought to be a vascular disorder, it is now believed have neurological involvement, leading to the modern neurogenic theory. Many preliminary migraine symptoms are neurological, as well as the aura phase that involves visual disturbances. In the promonitory phase before headache and during the actual headache phase, specific brain regions are activated, with distinct patterns of neuronal activation. Cortical spreading depression (CSD) is an electrophysiological phenomenon involving the spread of a depolarization wave across cerebral gray matter, which disrupts the ionic gradient of the brain and depresses signalling. It is likely that an altered state of brain excitability activates the trigeminovascular system (TVS), leading to vasodilation and plasma estravastion of meningeal vessels. However, migraine is a complex disorder with complicated symptomatolgy, and the pathophysiology is unknown. This paper discusses the combination of vascular and neurogenic components in the pathophysiology of migraine headache.

KEYWORDS: *migraine, headache, neurovascular, neurology, brain disorder, inflammation, CNS*

INTRODUCTION

Headaches are prevalent neurological disorders and common forms of pain which contribute greatly to worldwide levels of disability. Primary headaches cause episodic and chronic head pain that are not a symptom of another disease or medical condition and migraine headache is the most common form, characterized by pulsating head pain that is unilateral and diverse symptoms that are grouped into four phases.

The premonitory phase consists of “warning” symptoms of an impending migraine, which can include changes in mood and energy levels, food cravings, and excessive yawning (1). Following this is the aura phase involving visual disturbances that affects between 15-30% of migraine patients and occurs just before the migraine (2). The next phase is the actual headache, with throbbing head pain that can range in intensity, that lasts between 4-72 hours. During the headache, there may be nausea, vomiting, and sensitivity to light, sound, smell, and touch (allodynia) (3). Finally, the post-headache phase concludes the migraine with symptoms such as fatigue, mood changes, and cognitive impairments (4).

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Migraine can be triggered by endogenous or exogenous agents, including menstruation, stress, certain foods such as cheeses or processed meats, alcohol (particularly red wine), or changes in weather or sleep, amongst others (5). Females have a higher incidence of migraine, usually being affected two to three times more than males (6,7), implicating sex hormones in the pathogenesis of this disorder (8).

'Triptans' are widely used to treat migraine and can be effective in terminating an attack or decreasing the severity of symptoms (9). Triptans belong to a family of serotonin (5-HT)1b-receptor agonists and include sumatriptan, zolmitriptan, rizatriptan, eletriptan, and naratriptan (4). However, these medications are not effective for all patients (10), and there is a need for new treatment development.

Migraine is highly prevalent around the world and a major contributor to disability (11). In American migraine studies, about 12% of Americans reported experiencing migraine in the span of a year, with women three times more affected than men (12-14). Migraine negatively impacts work and school activities, family, and social relationships, and even the economic status of individual sufferers (15). Despite its high prevalence and intensive research efforts, the pathophysiological basis of migraine headaches is still unknown. This paper will discuss the combination of vascular and neurogenic components in the pathophysiology of migraine headaches.

The vascular theory

Until recently, the vascular system was believed to be the main mechanism inducing primary headaches such as migraine and cluster headaches. The fact that vasodilation could initiate headache (16), and that vasoconstrictors could arrest it (17), were convincing factors for the vascular basis of migraine.

In migraine, there is cerebral and meningeal arterial vasodilation and medications for vasoconstriction, such as triptans, are used to treat migraine. In line with this, vasodilators, substances that dilate blood vessels, can induce headaches such as cluster headaches and migraine (18).

The vasogenic theory is based on the correlation of migraine and variations in vascular caliber, but this does not indicate causation. Additionally, actual dilation of the vasculature is not correlated directly with pain, and so there must be other factors involved in this regard. There is bidirectional communication between the cells in blood vessels and neurons, with release and response of mediators including cytokines, adenosine triphosphate (ATP), nitric oxide (NO), norepinephrine, and calcitonin gene-related peptide (CGRP), and the two systems likely interact in the pathophysiology of headache (4). Integrating the vascular basis of migraine with nervous system interaction led to the neurovascular theory, a more appropriate approach to explain the pathogenesis of migraine.

The neurogenic theory

A more complete explanation of migraine pathophysiology is the neurogenic theory, which has gained evidence as the basis of migraine. It helps to explain many characteristics of migraine attacks that the vascular theory cannot.

For example, ergotamine-derived triptan medication used in treating migraine attacks functions on vasoconstriction and is not effective for all headache patients (19,20). The premonitory phase cannot be explained by changes in vasculature and triptans have no effect on symptoms during this stage. Chemical compounds and hormones play a role, as serotonin and estrogen can contract and constrict blood vessels. Neuronal genes have been implicated in migraine and evidence continues to support neuronal involvement during migraine aura and attack (21).

Triptans are not able to abort the premonitory symptoms of the first phase of a migraine attack, implicating that vasoconstriction does not create these symptoms (22). Many of these symptoms are neurological. The phase that follows, the aura phase, involves visual and sensory symptoms that are not vascular in nature (21).

Imaging studies have shown that migraine involves distinct patterns of neuronal activation. Studies using positron emission tomography (PET) identified specific brainstem regions that became activated during migraine attack, demonstrating periaqueductal gray (PAG), dorsal raphe (DR), and locus coeruleus (LC) activation (23,24). The premonitory symptoms could involve the hypothalamus, which has been seen to increase in activity in the time proceeding the migraine attack, along with elevated functional coupling to the trigeminal nucleus caudalis (TNC) (25). The hypothalamic nuclei is an important brain region for internal homeostatic regulation, where neurons function in diurnal, circadian, and circannual rhythms and hormonal regulation (26). Oscillations in these activities can alter functional connections in other areas of the brain, including subcortical and brainstem regions, with heightened reactions to sensory stimuli that could be involved in the provocation and termination of migraine attacks (27-29).

Cortical spreading depression (CSD) is believed to be the underlying cause of migraine with aura and could be a key player in overall migraine pathophysiology (30,31). It is an electrophysiological phenomenon in which a depolarization wave spreads across cerebral gray matter, disrupting ionic gradients and depressing electrocortical signals, which is then followed by a period of hyperpolarization (32).

CSD has also been hypothesized to initiate activation of the trigeminovascular system (TVS), that comprises neurons originating in the trigeminal ganglion that innervate cerebral vasculature, including the dura mater and large venous sinuses (33). Stimulation of dura mater in the vicinity of sinuses and blood vessels can produce migraine-like pain (34).

TVS activation is involved in the pathogenesis of migraine attack. The cervical nerve root projections come together in the TNC, which is connected by fibers to the thalamus and the sensory cortex, and subcortical regions (35).

The ganglion neurons produce neurotransmitters and vasoactive neuropeptides such as substance P, CGRP, and neurokinin A. Levels of CGRP were substantially elevated in patient jugular venous blood during migraine attacks (36) and intravenous administration of human alpha-CGRP can induce migraine headache (37).

Serotonin, estrogen, and stress

The monoamine transmitter 5-HT is believed to play a central role in migraine pathophysiology, although the exact role of serotonergic mechanisms is unclear. By injection, it has been found to induce migraine-like symptoms (17) and elevated levels of the 5-HT catabolite 5-hydroxyindoleacetic acid (5-HIAA) were found in patient urine during migraine attacks (38). Other studies showed lower plasma 5-HT levels in the intervals between attacks, with increasing levels during the actual migraine attacks (39). However, studies investigating brain levels of 5-HT have been inconclusive, having shown conflicting results of higher and lower levels (40). Triptans are a family of 5-HT1b receptor agonists and are the most effective treatment for migraine, however the exact modes of function are still unclear, and studies show complex mechanisms. It is believed cerebral 5-HT levels in migraine patients could be low in the periods between attacks, with elevated levels during the attack, although more conclusive evidence must be gathered from further studies (40).

Female hormones and the menstrual cycle are factors that can provoke headache. Estrogen levels vary during the lifetime of women, often in patterns correlating with symptom severity, development, and cessation of migraine. At the age of puberty, the rate of migraine in females increases significantly while the male rate remains relatively unchanged (41). During the fertile period and cyclic fluctuations of estrogen levels (42), the prevalence rate is much higher in females and remains so until post-menopause, when estrogen levels are low and female migraine improves (43).

Those who suffer from migraine often have sensitivity to various triggers, suggesting that maladaptive changes are involved in the nervous system of these individuals. Stress is a common trigger, with one study finding that 80% of patients indicate stress as a provoking factor (5). Stress can trigger a cascade of responses in the body, affecting hormone levels by activating the hypothalamic-pituitary-adrenocortical axis (HPA) and the sympathetic nervous system, with the release of stress hormones such as corticotrophin releasing hormone (CRH), cortisol, and epinephrine (44,45).

The stress response can cause biochemical changes and lead to the sensitization of afferent nociceptors (46). Migraine pain is referred to as dysfunctional pain of the nociceptive pain system because it is not caused by injury, but instead by sensitized peripheral nociceptors (47). Additionally, stress can affect migraine and pain sensitization by altering the immune system, as some proinflammatory mediators, including interleukin-1 (IL-1) and IL-6, are involved in pain transmission and sensitization (48). Elevated levels of intracranial inflammatory mediators, such as nerve growth factor (NGF), Substance P, and CGRP circulate during migraine and can sensitize primary afferent nociceptors (49-51). Mast cells and macrophages release proinflammatory mediators that can sensitize meningeal nociceptors, including 5-HT, histamine, and prostaglandins (52-54,46).

CONCLUSIONS

Migraine is a complex disorder, with a multifactorial origin and complicated symptomatology. Originally believed to be a vascular disorder due to meningeal vasodilation, modern studies have shown the neurological implications involved, with affected functioning of multiple cortical, subcortical, and brainstem regions (55).

The vasculature nature and neurogenic implications cannot be denied; however, the precise pathophysiology of migraine remains unknown. Most likely, a brain state of altered excitability leads to the activation of the TVS, resulting in vasodilation and plasma extravasation of meningeal vessels, likely affecting genetically susceptible individuals (3,56). Further research can hopefully discover the mechanisms involved in the activation of brain regions implicated in producing migraine.

Conflict of interest

The author declares that they have no conflict of interest.

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THE PSYCHOLOGICAL ASPECTS OF MUSCULOSKELETAL PAIN

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ABSTRACT

Musculoskeletal injuries occur when the skeletal or muscular system is damaged and are the leading worldwide cause of disability. Musculoskeletal pain can become chronic, leading to emotional distress for sufferers, and because pain is closely interlinked with emotion, this distress and subsequent maladaptive thinking patterns can intensify the pain and lead to further disability. Depression, anxiety, somatization, and catastrophizing may occur as a result of pain, and all have negative effects on pain levels, pain management, and mobility and contribute to a lower quality of life for the patient. A bidirectional relationship may also exist between the psychological disorder and the pain, with one worsening the other. Traditional therapy for musculoskeletal pain management has focused on pharmacological intervention and rehabilitation; however, because psychological factors are important to the therapy outcome, interventions such as stress reduction and cognitive-behavioral therapy, amongst others, may be highly beneficial.

KEYWORDS: *musculoskeletal, pain, psychology, depression, anxiety*

INTRODUCTION

Musculoskeletal injuries (MSIs) are incurred when there is damage to the skeletal or muscular system, which may affect joints, spinal discs, nerves, cartilage, tendons, or muscles. They can be a short-term problem that resolves after healing, as is the case for a sprain or fracture, or a chronic condition that severely affects a person's life, causing disability and limited mobility.

MSIs are very common, with a global prevalence of approximately 1.71 billion affected people, and are the greatest contributor to disability around the world. Low back pain, in particular, is responsible for the highest amount of global disability, affecting around 568 million people (1). Many people will have experienced musculoskeletal pain at least one time throughout their lives, as 47% of the general population is affected, and between 39 and 45% will suffer with chronic pain (2).

Some people are more at risk for developing musculoskeletal pain, as it is often influenced by personal habits, activity, and work. Apart from trauma and injury, some of the potential risk factors include medical conditions such as fibromyalgia, poor posture, advanced age, engaging in sustained repetitive movements, intensive physical activity, inflammation, a high-fat/high-protein diet, smoking, obesity, a sedentary lifestyle, work activity, and psychological conditions such as depression (with depression being a risk factor as well as a consequence of musculoskeletal pain) (3).

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Pain is the most common symptom of a MSI. The International Association for the Study of Pain (IASP) defines pain as an "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (4). Pain from MSIs can be short-lived or continue and develop into chronic pain, defined by musculoskeletal pain that lasts for more than three months. Chronic musculoskeletal pain has social and psychological consequences. It is usually managed by pharmacological treatment and rehabilitation. Chronic musculoskeletal pain severely affects a person's life with social and emotional repercussions, such as the loss of work, independence, and social interaction, depression, and anxiety (5). Daily pain can lead to disability, opioid dependency, and negative thought patterns that exacerbate the pain symptoms.

When dealing with MSIs, the physical symptoms are generally the focus of attention and have been well-identified. However, the pain can be debilitating, and focus needs to be given to the consequential emotional distress as well. Attention on the psychological aspects of musculoskeletal pain is useful for managing the acute and chronic pain that accompany MSIs and for improving patients' quality of life.

This paper will summarize some of the key psychological responses to musculoskeletal pain, focusing on depression, anxiety, somatisation, and catastrophizing.

The experience of pain

Chronic musculoskeletal pain is described by IASP as "chronic pain in the muscles, bones, joints, or tendons that is characterized by significant emotional distress (i.e., anxiety, anger, frustration, and depressed mood) or functional disability" and adds that pain is subjective and influenced by biological, psychological, and social factors (4). The pain is often intense and localized or may be felt throughout the entire body, as generalized aching, or as burning and nipping pain. Periods of inactivity may cause joint stiffness and aches, which may subside after movement. But the pain symptoms are variable, and the personal response to pain is unique and subjective (6). Levels of pain do not always correspond to the severity of an injury, and there is a wide variation of symptoms (2).

Because pain is subjective, self-reporting is used by clinicians to rate the intensity of a patient's pain symptoms. This information is an important tool to guide treatment and predict clinical outcomes (7). Pain is usually assessed using questionnaires, with the patient rating their level of pain and the extent to which it affects their daily life. Scales that are commonly used in pain measurement include the numeric pain rating scale, the visual analogue scale, and the verbal rating scale. On a scale of 0-10, pain levels in musculoskeletal disorders were reported at levels of 7 and greater by approximately 25% of patients (8).

Attention is the first response to pain, followed by cognitive processing, appraisal, and interpretation, which leads to acting on the pain. The initial noxious stimulus provokes our attention, and this serves as a warning signal to invoke a response and modify our behavior to avoid physical harm. However, in the case of chronic musculoskeletal pain, the pain persists and cannot be alleviated, and the attention response is continually activated, even though an action may be futile (9). This can provoke psychological interpretations for dealing with the pain which may be harmful or destructive to a patient's well-being. Pain is highly subjective, and each individual experiences pain in their own way, based on their previous experiences in the context of society and culture.

The perception of pain has a strong cognitive and emotional link. In fact, it was seen in imaging studies that independent of the actual pain stimulus, the emotional and attentional state does alter pain pathways in the brain, and that chronic pain sufferers show alterations in these brain regions. This could provide an explanation as to why those people with chronic musculoskeletal pain are at higher risk for anxiety and depression, and why psychological distress can even cause chronic pain to develop in the first place (10). Sex has also been shown to play a role in pain perception, with women being more susceptible to musculoskeletal pain due to biochemical and biological differences (11). Research has shown that women are generally more sensitive to pain and may experience higher levels of functional impairment, depression, and anxiety (12).

Environment and culture also play a role in the experience of pain, as behaviors can be influenced by societal expectations and cultural health beliefs. In fact, great differences have been shown between reported work-related musculoskeletal problems and disability between workers doing the same job in different cultural settings (13).

Health beliefs and distress intolerance

Pain is obviously uncomfortable and distressing for musculoskeletal pain sufferers. However, the cognitive response to pain can greatly influence the treatment outcome and the evolution of symptoms (9).

Distress intolerance is an important factor in the experience of pain. It is the perceived inability to cope with one's uncomfortable emotions. A person's life experiences and environment are factors for their ability to tolerate stress, and there may be a biological basis to it as well. With intolerance, the hopelessness and vulnerability of uncomfortable

emotions can lead to avoidance and escape behaviors, with intense negative emotions motivating reactions to provide relief as soon as possible. In the context of pain, this could lead to anxiety and opioid misuse (14). In a fear-avoidance model of pain, subjects with MSIs will actively avoid movements that can lead to pain, which can interfere with their recovery (15).

Psychological factors have been shown to affect the treatment outcome of people with musculoskeletal pain. Negative, maladaptive reactions can predict poor outcomes, while positive thinking patterns can improve them (16). A low mood can hinder recovery and lead to higher and more persistent levels of pain. A patient's preoccupation with their health places great attention on their symptoms and can exacerbate them (17).

It is important to discuss the Health Belief Model, which focuses on self-efficacy. It states that health-related behaviors are influenced by a person's personal beliefs concerning their health status, the risks related to their condition, and how their behavior can lead to a positive outcome (18). Positive and pessimistic beliefs can predict treatment outcomes and the duration of musculoskeletal pain (19). Health beliefs develop throughout a person's life and are based on experience. These attitudes shape the experience of pain and illness, and the subsequent patient behaviors during the course of their condition (17).

Finally, it is important to note the co-occurrence of negative thought patterns and their connection to the creation and continuation of musculoskeletal pain. Pain, emotion, and cognition are intertwined, and a destructive, cyclic pattern may arise between psychological conditions, such as depression, and musculoskeletal pain perception. Positive thinking patterns can improve pain symptoms, whereas chronic pain can create emotional distress and depression, anxiety, somatization, and catastrophizing, which in turn can increase the perception of pain (11). Psychological factors are decisive in the evolution of musculoskeletal pain, as depression and distress intolerance can cause acute pain to transition to chronic pain and lead to disability (20).

Depression

Musculoskeletal pain can be a predictor for depression, a mental health disorder characterized by a persistent low mood, loss of pleasure, and pessimistic thinking (21). It can be brought on by pain, and can also be the cause when depression exacerbates and even initiates pain, resulting in a destructive loop of pain causing depression and depression intensifying pain.

Depression can greatly affect a sufferer's quality of life and lead them into further destructive behavior, such as drug and substance abuse and suicide. A low mood generally aggravates the health condition and increases the rates of disability.

The link between chronic pain and depression is evident, with some studies showing that in between 30-60% of chronic pain sufferers there is depression as well (3). Depression ranks fourth as a cause of global disability and has additionally been linked with neck and low back pain (22). Research has shown that in musculoskeletal pain, depression is responsible for a worse prognosis, along with a higher degree of pain intensity, limited mobility, and disability. It has been demonstrated, in particular, to accompany knee pain, low back pain and neck pain (17). Musculoskeletal pain sufferers can have reduced physical activity and sleep problems, factors which have been linked to higher rates of depression (21).

The relationship between depression and musculoskeletal pain can be bidirectional, meaning that the pain may result in depressive symptoms that were not present before, as well as the reverse: depressive symptoms may actually bring about and worsen musculoskeletal pain in the first place.

Anxiety

As with depression, rates of anxiety are higher in individuals with musculoskeletal disorders when compared to the general public (23). Anxiety involves feelings of fear, worry, and unease to an extent that it becomes overwhelming and has a negative effect on a person's life. Concern and fear about their condition can lead to anxiety in sufferers of musculoskeletal pain. Anxiety is commonly seen in chronic pain sufferers, and like depression, it can be bidirectional, meaning that anxiety can cause pain and vice versa (24).

Results have shown a 38% general increase in trauma-related phobias, and a 20-35% increase in anxiety and depression 12 weeks after hospital discharge for orthopedic trauma patients (25). Post-traumatic stress disorder can result after orthopedic trauma, affecting 20-51% of people after acute orthopedic trauma, and after six months with a higher-rated pain scale score, those odds increased (25).

A fear-avoidance belief may develop with the conviction that rest is necessary for an injury and the physical stress and positions that cause pain should be avoided because they are damaging and can negatively affect recovery. Fear-avoidance behaviors can limit mobility because in order to avoid the sensation of pain, the patient may become sedentary

and avoid movement at the pain site, which can hinder improvement of the condition and interfere with rehabilitation. For example, management of knee osteoarthritis, a condition of chronic pain generally seen in older adults, calls for movement and physical activity despite the pain. However, anxiety over the sensations of pain and the potential damage can deter patients from following this recommendation (26).

Somatization

Somatisation occurs when stress or emotional distress leads to the experience and reporting of somatic, or bodily, symptoms. A somatic symptom burden can heighten the awareness of pain and may intensify it. People who suffer from musculoskeletal pain can become hypervigilant with their symptoms, with a heightened awareness and sensitivity to pain. This hypersensitivity can lead to distress over common somatic symptoms, the inclination to intensify them, and to seek medical help. A somatising tendency is generally assessed by using questionnaires where patients are asked to report their general symptoms on a numbered scale and indicate the level of distress the symptoms caused them.

Studies have examined the link between stomatisation and back pain, in particular, and it was found to predict a transition from acute to chronic pain, and the success of treatment (27). People who tend to somatise have a higher level of medical care seeking but a lower level of satisfaction from that care, and report lower levels of social and work-related functioning. In addition, people who tend to somatise are more likely to develop musculoskeletal pain and eventual disability from it. Finally, it has been linked with the transition from acute to chronic musculoskeletal pain (17).

Catastrophizing

Catastrophizing is another tendency that can occur in musculoskeletal pain sufferers. It is the tendency to view pain symptoms as overly severe, uncontrollable, and unmanageable, and leads to feelings of hopelessness in overcoming them. There is fear and difficulty in controlling pain-related thoughts before, during, or after they occur. Evidence has shown that people who catastrophize have heightened brain excitability, which can prepare them to be more sensitive to pain (28). It is an elevated emotional response that can influence the sufferer to retreat to escape or avoidance behaviors.

Studies have shown that the magnification of the negative effects of pain can have detrimental effects for those experiencing musculoskeletal pain (29). It can have negative effects for pain management and recovery, with increased mental stress, worsening and prolonging pain sensations, and leading to chronic pain. It can lead to pain intensity, a higher use of opioids, and disability (29). It has been shown that catastrophizing greatly increased the risk of the transition from acute back pain to chronic pain, and that it contributed to higher rates of nonrecovery in patients (29). Pain catastrophizing can lead to greater rates of pain reporting and seeking for medical care, with socioeconomic impacts (7).

Stress-reduction based treatments can be beneficial for patients who tend to catastrophize, though it is important to note that actual stress is not responsible for the outcomes of the condition, but the response to the stress. In fact, it was observed that catastrophizing is not dependent on the injury or impairment; it can occur throughout sufferers of chronic pain (30). In addition, cognitive-behavioral therapy can provide help and improvement.

CONCLUSIONS

There is a clear association between the psychological state and the degree of disability, pain severity, and quality of life for people suffering from musculoskeletal pain. Pessimistic health beliefs, depression, anxiety, somatisation, and catastrophizing can worsen musculoskeletal pain and cause disability. These cognitive factors may be intertwined, based on fear and helplessness that may result from maladaptive pain responses.

Maladaptive thinking patterns related to pain can exacerbate and lead to worsening of the condition, meanwhile positive thinking patterns, such as self-efficacy and resilience, combined with social support, can improve the long-term outcomes of chronic musculoskeletal pain. Based on this, if psychological distress can be lowered, improvements should be made in treating musculoskeletal pain, although further research is needed in this field.

Therapeutic avenues have traditionally included rehabilitation, the use of pharmaceuticals such as non-steroidal anti-inflammatory drugs, opioids, and surgery. However, due to the implications of psychological factors and their impact on recovery and pain management, other forms of treatment may be beneficial. These include exercise, yoga, meditation, acupuncture, cognitive behavioral therapy, stress reduction, and counseling. Yoga has been linked with improvement in back pain, while meditation has been shown to lower pain levels in many pain-related disorders (29). Cognitive behavioral therapy, which is based on the idea that “thoughts, feelings, physical sensations, and actions are interconnected,” aims to target the specific source of distress, and could be promising as a non-pharmacological intervention for the management of musculoskeletal pain (14,31).

Conflict of interest

The authors declare that they have no conflict of interest.

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