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THE BIDIRECTIONAL RELATIONSHIP BETWEEN KIDNEY DISEASES AND BRAIN DISORDERS

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ABSTRACT

The correlations between neurological and renal diseases have been increasingly described and studied, and both often involve vascular deterioration. The brain and kidney are connected by efferent sympathetic and afferent sensory nerves. Kidney damage that can lead to chronic renal failure is often related to vascular and neurological disorders, and impaired renal function can lead to vascular deterioration with cerebral microbleeding. Risk factors such as hypertension, ageing, diabetes, dyslipidemia, and obesity can all lead to vascular impairment, and neurological diseases can also be present in dialysis patients. In uremic encephalopathy, motor and mental dysfunctions can occur, with emotional changes and cognitive deficits. Uremia leads to elevated concentrations of inflammatory molecules and metabolic dysfunction, resulting in the degradation of muscle proteins. Protein catabolism generates toxic compounds which may be present in brain tissue, serum, and cerebral spinal fluid (CSF). Therapies are lacking in this field of research, although a slight positive effect has been observed with the use of antioxidants and anti-inflammatories. Here, we describe the bidirectional interrelationship between kidney diseases and neurovascular disorders. Further studies are needed to clarify several points regarding this interesting issue.

KEYWORDS: *kidney, brain, hemorrhage, neurology, vascular, metabolism, inflammation*

INTRODUCTION

Chronic kidney disease (CKD) is a major global health problem, affecting approximately one in ten adults (1). It is defined as decreased kidney function lasting at least three months and associated with a range of health problems from mild kidney damage to end-stage disease. Many patients with acute kidney injury frequently develop neurologic dysfunction that increases with chronic renal failure (2). Renal insufficiency causes central and peripheral nervous system disturbances in multiple ways, such as cognitive decline and cerebrovascular events; crosstalk vectors are thought to include hormones, baroreceptors, osmoreceptors, and direct organ innervation (3).

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There is strong evidence that CKD is related to intracerebral hemorrhage (4,5), suggesting a close relationship between stroke and CKD. Patients with vascular impairment, such as that occurring in strokes, have a higher incidence of CKD (6,7). One study showed that about 30% of patients undergoing hemodialysis showed mental impairment, of which 8% showed severe symptoms (8). For example, in uremic encephalopathy, there may be motor and mental dysfunctions such as emotional changes, depression, and cognitive and memory deficits, but also more serious problems, including suicidal thoughts, confusion, tremors, delirium, psychosis, loss of muscular tone, seizures, coma, and death.

It is well known that the brain nerves control the kidney in physiological and pathophysiological conditions, but it is not clear how this mechanism occurs. Renal innervation plays an important role in regulating the hemostasis of body fluids. The brain and kidney are connected by efferent sympathetic and afferent sensory nerves. The efferent nerves are involved in regulating renal function, such as sodium reabsorption and glomerular function, while the afferent nerves modulate cerebral sympathetic blood flow (9) (Fig.1).

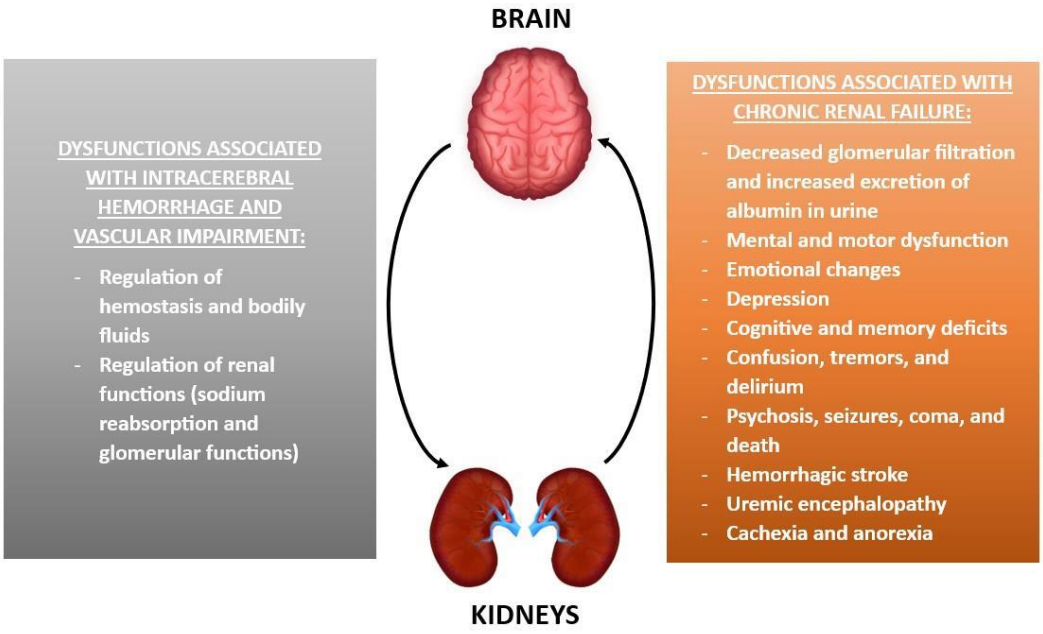

Fig. 1. *Correlation between the kidneys and brain. Chronic renal failure may lead to several mental dysfunctions. On the other hand, brain dysfunctions such as intracerebral hemorrhage and vascular impairment may cause dysregulation of renal function, hemostasis, and body fluids.*

DISCUSSION

Several metabolic diseases, such as hypertension, are due to chronic activation of the sympathetic efferent nerves of the kidney (10). In fact, via the renal sympathetic nerves, the autonomic nervous system allows kidney function to be adjusted dynamically in response to changes from all the visceral organs (11). Neurological and renal diseases are increasingly described and studied and often share vascular deterioration (12,13). For example, cerebral microbleeds may be associated with impaired renal function (14,15). Analysis of published research demonstrates a bidirectional relationship between brain disease and renal pathophysiology (16-19). Considering kidney diseases, a relationship between these and brain dysfunctions is highlighted, even if the studies can be very heterogeneous and, therefore, have a certain variability (19). Therefore, there seems to be an association between the physiological state of the kidney and brain diseases related to small vessel dysfunction and cerebral hemorrhage. This disease has a high pathogenicity due to a lack of effective therapy, so prevention, such as blood pressure control, is very important. Angiotensin II is central in this mechanism, acting as a neuromodulator or neurotransmitter. Its effects are hemodynamic, regulating blood pressure, and non-hemodynamic, maintaining the water-electrolyte balance.

In addition to sharing the same cerebral pathophysiological mechanisms as cardiovascular disease, it has been reported that cardiovascular risks may be higher in individuals with kidney disease (20). Kidney and neurovascular diseases, including stroke, are common risk factors (21). The traditional risk factors such as hypertension, ageing, diabetes, dyslipidemia, and obesity can lead to vascular impairment and endothelial dysfunction, as occurs in cerebrovascular

diseases such as stroke, white matter lesions, silent brain infarction, and microbleeds. In addition, risk factors such as stress, sympathetic nerve overactivity, chronic inflammation, and impaired coagulation, amongst others, contribute to vascular disease and endothelial dysfunction in the brain in patients with CKD. There is a higher risk of CKD after hemorrhagic stroke (22), although this needs to be confirmed by additional studies. However, the data on renal dysfunction linked to a higher incidence of cognitive impairment is often conflicting. Moreover, there seems to be a correlation between some kidney diseases and brain responses (23), but conversely, also between brain diseases (especially involving small vessel rupture) and kidney dysfunction (17).

In CKD, there is a decreased glomerular filtration rate and increased excretion of albumin in the urine, contributing to cerebrovascular risk (24). The presence of albuminuria has been reported as an independent factor of greater stroke risk, but it has not yet been well established if there is a greater risk of stroke with progressively higher levels of albuminuria (25). In fact, CKD is a risk factor for stroke (24) and other brain pathologies with impaired cognitive function (26). In kidney disease, uremia is related to sodium and water retention, uremic toxins, anemia, calcium and phosphate metabolism dysfunction (hyperparathyroidism), and other anomalies. Hypoalbuminemia may occur in uremia, leading to cardiovascular risk in dialysis patients (27). Impaired albumin levels are associated with the release of acute phase proteins such as fibrinogen, C-reactive protein, serum amyloid A and P (28,29), ferritin, ceruloplasmin, and others, all markers of inflammation. All these pathophysiological alterations can lead to cerebrovascular disease. Moreover, reduced albumin synthesis can cause anorexia with loss of body weight and muscle mass (30).

Uremic encephalopathy, an organic brain disease that can develop in patients with acute and chronic renal failure, can lead to pathologies ranging from mental disorders to death (31). Among patients with end-stage renal disease, nervous system dysfunction is a major cause of disability; those patients may develop sensorial clouding, delirium, tremor, asterixis, multifocal myoclonus, and coma. These patients can also develop peripheral neuropathy and progressive intellectual dysfunction (32). Elevated concentrations of inflammatory cytokines associated with cachexia, anorexia, and other dialysis-related disorders may occur in uremia (33,34). In uremia, various metabolic dysfunctions occur, such as acidosis and resistance to insulin with consequent degradation of muscle proteins, an effect mediated by caspase activation (35). The inhibition of this molecule could represent a therapeutic target.

Neurological complications can occur in uremia and include concentration disturbances, mood alterations, headache, sleep disturbances, movement alterations, epileptic seizures, and coma (2,36). This brain pathology is mediated by guanidine compounds such as guanidine-succinic acid, guanidine, methyl guanidine, and creatine (37). These compounds are waste products of protein catabolism, which are elevated in brain tissue, serum, and cerebral spinal fluid (CSF) after a uremic state (37). The alteration of calcium and phosphorus homeostasis, regulated by the parathyroid hormone (PTH), can mediate encephalopathy caused by uremia (38). These effects damage neurons and increase levels of neuropeptides that stimulate immune cells and increase inflammation (39,40). These metabolic dysfunctions involving monoamines cause norepinephrine reduction and dopamine inhibition with motor activity dysfunction (41).

Uremia and the consequent malfunctioning of neurons can be increased by the metabolites of some drugs (such as cimetidine), which inhibit organic anion transporters (OATs), causing neurotoxic crises (42). OATs are normally localized in epithelial barriers and are involved in the uptake and intracellular movement of metabolites, drugs, and toxins (43). In uremic encephalopathy, increased calcium due to hyperparathyroidism promotes renal failure by altering calcium transporters in neurons which may become hyperexcited. In such cases, blood-brain barrier (BBB) dysfunction can occur with excessive tryptophan input and increased serotonin (44) leading to decreased appetite, acidosis, cachexia, and inflammation. Inflammatory cytokines such as IL-1, tumor necrosis factor (TNF), and leptin can mediate the release of neuropeptides involved in anorexia (45,46). Leptin acts on the brain system and the hypothalamus, and one of the most important functions of this molecule is to regulate food intake and to modulate energy processes (47). Patients with renal insufficiency who are malnourished may have thiamine deficiency encephalopathy (48), an effect reversible with supplemental thiamine.

Dialysis dementia may occur in patients undergoing chronic hemodialysis, but in kidney transplantation patients, this dementia does not often occur, and cognitive functioning has been seen to improve following transplantation (49-51). In the case of severe encephalopathy with convulsions and seizures, symptoms can be relieved using anticonvulsant drugs such as anti-epileptics. Even after adequate dialysis therapy, patients may continue to be afflicted with nervous system dysfunction, such as weakness, peripheral neuropathy, and mental disturbances. The dialytic treatment of end-stage renal disease has been associated with two separate disorders of the central nervous system (CNS): dialysis disequilibrium and dialysis dementia (52), which is progressive, fatal encephalopathy; this can occur in some cases and is linked to aluminum phosphate which is transported in the CNS via transferrin, causing brain alterations; this can be avoided with the preparation of dialysate water by reverse osmosis. Chronic renal disorder can also lead to convulsions due to uremia and toxic substances causing encephalopathy.

Therapy

CKD often predicts bidirectional neurological alterations that may even be lethal due to a lack of specific therapy, an issue requiring more investigation. Special attention has been paid to antioxidants in the therapy of neurological, microbial, and tumor diseases due to their anti-inflammatory properties. For example, it has been reported that curcumin, a versatile ingredient used particularly in Asian food recipes, can prevent or delay the onset of neurological diseases afflicting the CNS (53). Curcumin effectively prevents negative ageing processes, depression, Parkinson's disease, Alzheimer's disease, autism, amyotrophic lateral sclerosis, and other brain diseases (53,54).

CONCLUSIONS

There is a bidirectional relationship between kidney disease and brain diseases. Some pathological states of the brain can influence the kidneys and *vice versa*. These findings are very important for discovering new therapeutical approaches for treating CKD and intracerebral hemorrhage.

Conflict of interest

The authors declare that they have no conflict of interest.

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FIBROMYALGIA: AN INFLAMMATORY DISEASE CHARACTERIZED BY WIDESPREAD PAIN, SLEEP DISTURBANCES, FATIGUE, AND MEMORY PROBLEMS

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ABSTRACT

Fibromyalgia affects 2–7% of the population and 12 million people in the United States and has a higher incidence in females. The disease is likely caused by interactions between the sympathetic nervous system, neurotransmitters, external stressors, and hormones. Increased levels of immunologic signaling molecules have been documented in fibromyalgia, implicating immune dysfunction in this disorder. The most common symptoms that occur are skin sensitivity, abdominal pain (the most common), chronic fatigue, headache, disrupted sleep, cough, upper airway obstruction, hypoxia, breathing dysfunction, depression, epidemic neuro-myasthenia, diffuse idiopathic multifocal pain syndrome, cognitive dysfunction, and lowered quality of life. In addition, fibromyalgia may occur together with other diseases such as autoimmune disorders and cerebral diseases. In this article, we discuss the roles of the immune system and inflammation in the widespread pain, sleep disturbances, fatigue, and memory problems that occur in fibromyalgia.

KEYWORDS: *fibromyalgia, inflammation, immune system, cytokine, chemokine*

INTRODUCTION

Fibromyalgia is an inflammatory disease present in 2-7% of the population that is characterized by chronic and widespread musculoskeletal pain and neurological problems such as fatigue, sleep disturbances, memory problems, and depression (1). The first published paper on fibromyalgia appeared in 1990 with the American College of Rheumatology classification criteria (2). The disease mostly affects women (3), can occur at any age, and is characterized by trigger points where multifocal pain can be activated. The symptoms of this complex and heterogeneous disorder can be debilitating for the patient. However, not all fibromyalgia patients are depressed and not all depressed people suffer from chronic bodily pain.

The exact causes of fibromyalgia are not known, although it is thought that multiple genetic and environmental factors may contribute to the development of the disease (4,5). It seems that subjects with a healthy lifestyle, practicing regular physical activity, healthy sleep habits, and correct nutrition, can counteract the onset of the disease. The most accredited hypothesis for the onset of fibromyalgia is chronic pain correlated with an impairment in the processing of the pain stimulus. It is classified as a central sensitivity syndrome, with amplified pain mediation in the central nervous system (CNS) (6,7). The guidelines dictated by the International Association for the Study of Pain (IASP) and the Canadian Pain

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Society help to formulate adequate diagnosis and therapy indications for this complex and heterogeneous inflammation-based disorder (8,9).

In recent decades, there has been much progress in understanding the epidemiology, diagnosis, and therapy of fibromyalgia, although many points remain controversial. Given that the incidence of the disease is rising, fibromyalgia should no longer be a mysterious disease that is unknown to the population. Moreover, it is now known that it is an inflammatory pathology with a therapeutic strategy aimed at reducing symptoms and restoring the physiological state. Symptoms of the disease can persist for years, often debilitating the patient and reducing their quality of life. The diagnosis can remain difficult, but today, guidelines are in place to distinguish fibromyalgia from other pathologies which present with similar symptoms.

DISCUSSION

Psychiatric comorbidities have a high level of prevalence in fibromyalgia and are linked to a poorer clinical profile, with psychosocial distress and negative emotional states aggravating the disease (10). Additionally, population-based studies have shown an association between trauma, abuse, or the loss of a parent sustained in early life, with the development of chronic pain and fibromyalgia in later life (11,12). Fibromyalgia can be triggered by psychological stress factors, chronic fatigue, or even viral infections. Symptoms of the disease may be similar or overlap with other chronic pain disorders, such as systemic lupus erythematosus, osteoarthritis, and rheumatoid arthritis (13) (Table I). Dysregulated neurotransmitter levels with the involvement of the hypothalamic-pituitary axis may be responsible for chronic pain with fatigue, memory problems, and mood and sleep disturbances (14). Therefore, psychological and/or psychiatric disorders may aggravate the disease, causing chronic pain. The pain can improve with physical exercise while avoiding taking drugs. Aerobic and muscle strengthening exercises have been seen to lower pain levels and increase well-being in fibromyalgia patients, with stretching also providing beneficial results to overall quality of life (15). Together, these forms of physical activity are beneficial for reducing symptoms of depression as well (16,17).

Table I. *Fibromyalgia symptoms.*

Central nervous system (CNS):	anxiety, depression, headache, insomnia, dizziness, cognitive deterioration, memory impairment.
Muscles:	muscle pain, fatigue, contractions
Joints:	stiffness, mandibular joint dysfunction
Kidneys:	urinary problems and/or interstitial cystitis
Eyes:	tiredness, vision problems
Skin:	tingling, hypersensitivity
Chest:	pain
Stomach:	nausea
Female reproductive system:	accentuated menstrual pain, dysmenorrhea

It seems that fibromyalgia involves the expansion of nociceptors and the hyperexcitability of central neurons, leading to chronic pain and inflammation (18). Pain can occur throughout the body, but there are nine pairs of common trigger points for pain which are hypersensitive to the touch and can be determined by a thorough medical examination (19) (Table II). Patients may present with diffuse or multifocal neuropathic pain accompanied by widespread pain, sleep disturbances, fatigue, and memory problems that characterize fibromyalgia. In addition, the disease presents inflammation, hyperalgesia, cognitive dysfunction, allodynia, and pain at specific points accompanied by stiffness, and fatigue.

Table II. *Some classic trigger points that are present in fibromyalgia.*

- Occiput: lower point of the skull where the trapezius muscle inserts.
- Lower cervical: anterior part of the cervical vertebrae (C5-C7).
- Trapezoid muscle: midpoint of the upper border.
- Supraspinatus: above the medial border of the spine of the scapula.
- Lateral epicondyle: two centimeters below the lateral part of the elbows.
- Gluteus: extreme upper part of the muscle.
- Knees: fat body anterior to the joint.
- Greater trochanter: below and behind the union of the femur with the hip.

Cytokines are modulators of the immunological response that can also mediate the inflammatory state, pain, and tissue dysfunction. In fibromyalgia, both cytokines and chemokines, cellular chemoattraction proteins, appear to be involved in the inflammatory process of the disease (20) (Fig.1). It has been reported that patients with renal cell carcinoma treated with T cell growth factor (IL-2) immunotherapy presented classic signs of fibromyalgia with pain, cognitive dysfunction, and sleep disturbances which were also caused by increased IL-1 induced by IL-2 (21).

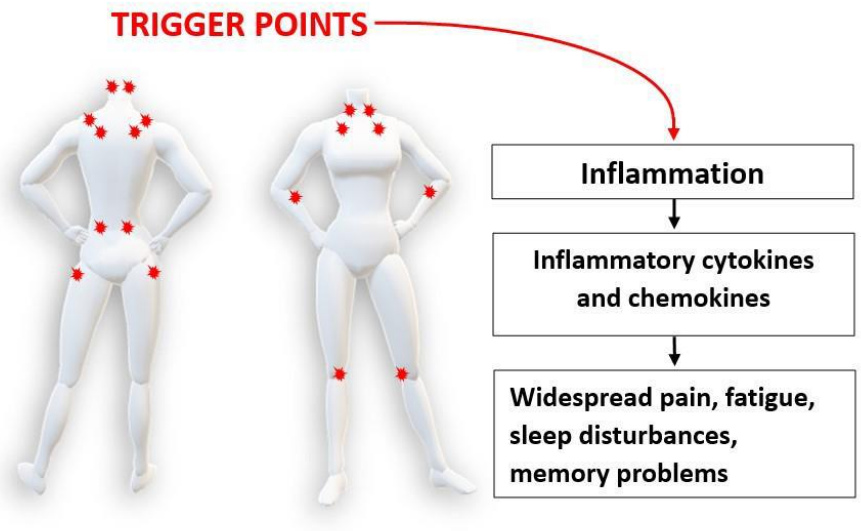

Fig. 1. *Trigger points in fibromyalgia cause hyperexcitability of the central nervous system (CNS), leading to chronic pain and inflammation, which are mediated by inflammatory cytokines and chemokines. Widespread pain, sleep disturbances, fatigue, and memory problems are symptoms that characterize fibromyalgia.*

Chemokines can attract inflammatory cells, and these chemotactic proteins can participate in synaptic transmission and the pain-inflammatory process. Pro-inflammatory cytokines such as IL-1, TNF, IL-2, IL-6, IL-8, IL-12, and IFN, could play an important role in the pathogenesis of fibromyalgia, as in neuropathic pain, where there is a dysregulation of these proteins and a disrupted balance between pro-inflammatory and anti-inflammatory cytokines such as IL-10, IL-4, IL-13, and TGF-β (22). IL-1 is an inducer of other pro-inflammatory cytokines such as TNF and stimulates the arachidonic acid cascade in the brain with an increase in prostaglandin E2 (PGE2), a prostaglandin involved in inflammation and pain (23).

Therapy for fibromyalgia may include neurotransmitter depressants, such as serotonin and norepinephrine reuptake inhibitors, anti-inflammatory drugs, the use of cannabinoid compounds, or a combination of these drugs. In our experience, cannabinoid therapy has proved to be effective in alleviating diverse symptoms in many cases of fibromyalgia (unpublished data). Therapy can be either pharmacological or non-pharmacological, or a combination of both, and can be executed by a rheumatologist, neurologist, immunologist, or by a team that includes all three specialists (Table III).

Table III. *Treatments to improve fibromyalgia.*

- Stress management: reduce stress, a potential cause of pain
- Patient education to improve coping skills
- Use of medications to improve sleep
- Use of medications to relieve pain
- Meditation and deep breathing exercises
- Ensure a regular, sufficient sleep cycle
- Aerobic exercises
- Routine physical exercise
- Improve physical fitness
- Cognitive therapy
- Thermotherapy and massage therapy

Fibromyalgia has numerous comorbidities, but inflammation, pain, and fatigue play a predominant role in this pathology. Recent studies report that the disease is also mediated by immune factors such as cytokines, chemokines, lipid mediators, and oxidative stress (24,25). However, further research is necessary to establish the precise immunological, pain, and inflammatory mechanisms that mediate the pathological state of the patient with fibromyalgia.

CONCLUSIONS

Fibromyalgia, a disease with various symptoms such as widespread musculoskeletal pain, sleep disturbances, fatigue, and memory problems, is an immune disorder mediated by inflammatory molecules released by cells of the innate and acquired immune systems. The disease is characterized by chronic inflammation, where the immune system is disrupted by elevated levels of pro-inflammatory proteins. In conclusion, inflammatory cytokines and chemokines may play an important role in the pathophysiology of fibromyalgia, and further research is needed to focus on the specific inhibitors of these mediators.

Conflict of interest

The author declares that they have no conflict of interest.

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Letter to the Editor

THE ROLE OF DIET IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

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KEYWORDS: *attention-deficit hyperactivity disorder, diet, therapy, inflammation, antioxidant*

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that presents with symptoms of hyperactivity, impulsivity, and inattention, that interfere with functioning or development. It is one of the most common mental disorders diagnosed in childhood, affecting approximately 7% of children and adolescents (1). Children with this deficit may show alterations in the size of the frontal lobes and caudate nucleus and present differently in the performance of psychological tests, even if these tests are nonspecific (2). The diagnosis is based on behavioral symptoms since there are no specific laboratory tests, and therefore, pharmacological treatment needs to be used with attention. Several articles have reported that ADHD may depend on a lack of dietary factors (3-5). Therapeutic nutritional treatments have been carried out, such as the use of food supplements, additional vitamin D, vitamin D plus magnesium, and anti-inflammatory omega-3 fatty acid (6).

DISCUSSION

The topic of nutrition in the treatment of ADHD in children is addressed with great interest today, even if at the moment, there is not enough published data to truly clarify the effect of food supplements. The topic is important because if nutrition were to have a positive effect on ADHD, pharmacological treatment, which is currently on the rise, could be avoided. The effect of diet on this brain disorder is not easy to evaluate; however, there are several interesting publications that may justify an in-depth study on this topic. The difficulty in evaluating the therapeutic effects of the diet lies in analyzing which foods are effective and which are not.

It has been observed that some dietary elements such as additives, sugars, and carbohydrates in general, can be harmful to ADHD, while others such as vitamins, omega-3 fatty acids, and vegetables can be helpful. However, to date, there are no specific and effective treatments for ADHD symptoms. Drug therapy has proven to be unsatisfactory and increasingly indicates that the nutritional route may be the right one.

In children, diet is very important for brain development and correct nutrition and a healthy environment can deter the development of neurological disorders and impaired cognition. In order to avoid behavioral changes, it is important to find out which foods aggravate or cause illness and contribute to mental disorders. Eliminating some foods, for example,

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those that could cause allergic phenomena, and being careful not to cause food deficiencies, could help the disease (Table I). Treatment with some vitamins is also recommended to avoid deficiencies.

Table I. *List of some allergenic and hypoallergenic foods correlated with ADHD. Allergenic foods could potentially generate or trigger ADHD and should be eliminated from the diet. Hypoallergenic foods should be consumed in the diet.*

Allergenic foods:	• dairy products	• preservatives
	• wheat, barley, oats, rye	• artificial sweeteners
	• artificial flavors and coloring	
Hypoallergenic foods:	• poultry	• pears
	• cod fish	• apples
	• lettuce	• rice

Some studies attribute the disease to an inflammatory state, since there is often a difference in the expression of anti-inflammatory omega-3 fatty acids in the plasma and cellular membranes of the erythrocytes in patients with ADHD, when compared to normal individuals, with consequent alteration of levels of dopamine and serotonin (7,8). However, therapy with Omega-3 fatty acid supplementation has given unsatisfactory results (9). Some scientific evidence reported in the literature demonstrates that oxidative stress and chronic inflammation can develop in ADHD (10,11) and could be counteracted with an antioxidant dietary treatment. On the other hand, chronic inflammation and/or oxidative stress can lead to the onset of ADHD (12-14). The chronic neuroinflammation that develops in ADHD can be activated by immune cells such as T cells with neuronal damage and brain dysfunction. But microglial cells can also be activated by oxidative brain damage with the release of inflammatory mediators such as cytokines and chemokines. These effects demonstrate that the immune status in ADHD patients can be very important both in tissue protection and in brain damage due to inflammation, where immune cells are hyperactivated.

Therefore, the use of antioxidants could be of help in this disease and in others involving neurodegeneration. In addition, micronutrient and probiotic supplementations have been seen to have mild positive effects on ADHD (15,16), but dietary treatments require more scientific evidence to be used as therapeutics.

Several studies suggest the use of polyphenols as antioxidants and immunoregulators with beneficial functions in ADHD (17,18). Polyphenols are a vast group of plant organic substances widespread in nature such as flavonoids, tannins, and others. Polyphenols are also produced by bacteria, fungi, and animals and have beneficial properties with antioxidant and anti-inflammatory capabilities in all tissues, including the brain system. The dietary intake of polyphenols is well tolerated by the body and their use is considered safe, even if there is no data on high-dose intake of these beneficial substances.

Reactive oxygen species (ROS) are involved in brain oxidative damage which can be prevented by efficient tissue oxygen gradients, inhibiting intracellular free radicals. Nutritional foods containing vitamin C, a water-soluble molecule, and fat-soluble vitamin E, are antioxidant substances capable of crossing the blood-brain barrier (BBB) with a protective function for the entire organism, including the brain. In ADHD, these antioxidant substances protect cells from oxidative stress and have the property of controlling cholesterol levels in the peripheral blood. Antioxidants have an antibacterial, antiparasitic, and antitoxic action and are protective for neurons. Oxidative stress may be involved in ADHD by causing damage to neurotransmitter receptors, dopamine damage and subsequent neuronal deterioration. Damaged dopamine can be cytotoxic to the cortex and ganglia involved in activity and attention, two important functions in ADHD. In ADHD, chronic inflammation could lead to an increase in STAT6, a molecule involved in the transduction and transcription of proinflammatory cytokines. It has been reported that rodents deficient in STAT6 may exhibit increased physical activity comparable to that seen in ADHD (19).

CONCLUSIONS

In conclusion, it can be deduced that oxidative stress and inflammation produced by the hyperstimulation of the immune system in ADHD could contribute to neuronal damage with brain alterations. Beneficial effects, although mild, can be produced using antioxidant and anti-inflammatory substances, such as polyphenols, which reduce oxidative stress.

Conflict of interest

The author declares that they have no conflict of interest.

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STRESS, DEPRESSION, AND DEMENTIA CONTRIBUTE TO NEURODEGENERATION

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ABSTRACT

Stress, depression, and dementia are disorders that affect one another and can lead to neurodegeneration. Chronic stress is often linked to chronic inflammatory diseases (sterile inflammation) such as cardiovascular disease, autoimmune diseases, and diabetes. Neurodegenerative diseases, caused by a dysregulation of the immune system, are mediated by inflammatory proteins, including cytokines and chemokines. Mast cells (MCs) are immune cells involved in inflammation and the mediation of stress through the secretion of chemical mediators and pro-inflammatory cytokines. Depression often occurs in adulthood and accompanies stress, leads to mood disorders, and involves the affective and cognitive spheres. Deficiency of brain-derived neurotrophic factor (BDNF), which affects neurons, is often responsible for depression. Depression and decline in cognitive function in the elderly lead to memory loss and dementia. In these brain diseases of advanced age, an inflammatory state often arises due to the activation of microglia and other innate immune cells, which release pro-inflammatory cytokines. The use of antidepressants could have a therapeutic effect by inhibiting inflammatory proteins. Further studies on these important topics related to the brain system will help clarify many aspects that are still obscure today.

KEYWORDS: *neurodegeneration, dementia, depression, stress, brain*

INTRODUCTION

Stress, depression, and dementia are contributing factors for neurodegeneration. In many clinical studies, it has been observed that stress is often implicated in neurodegenerative diseases, with the involvement of some hormone receptors showing an increase in the phosphorylation of abnormal proteins such as amyloid beta (Aβ) in Alzheimer's disease (AD), and activation of the kinase, resulting in inflammation (1, 2). With increasing age, 90 years or more, about 30% of people present senile dementia (3), and each year there are almost 10 million new cases worldwide (4). In the elderly, AD is the most common cause of dementia and has been estimated to account for roughly half the cases of dementia (3). Various risk factors such as social aspects, illnesses, genetic predisposition, malnutrition, and psychiatric factors can be involved in neurodegeneration (Table I). In this article, we will discuss the influences of stress, depression, and dementia on one another, and their contribution to the process of neurodegeneration.

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Table 1. *Important neurodegenerative disease risk factors.*

• Poor social class	• Hypertension
• Low level of education	• High blood cholesterol
• Low birth weight	• Sedentary lifestyle
• Brain damage and/or trauma	• Diet lacking in essential vitamins and minerals
• Cerebral vascular disorders	• Continuous contact with a polluted environment
• Hormonal dysfunction	• Depression
• Stress	• Dementia

Stress

Stress is the psychophysical response to excessive emotional, physical, and mental factors. The body responds to stress with psychological and physiological responses, which affect the body in different ways and levels of severity and can alter homeostasis (5). Chronic stress is a debilitating pathological state, and often manifests after trauma, leading to hyperexcitation, cognitive disorders, and mood and memory alterations. It can affect memory and has been correlated with reduced executive functioning (6), and in the elderly, chronic stress is often linked to senile dementia, a debilitating pathological state accompanied by hyperexcitation, cognitive disorders, and alterations of humor.

Long-term stress negatively affects the innate and adaptive immune systems and can result in chronic low-grade inflammation. Chronic stress is a risk factor for disorders such as metabolic dysfunction, chronic hepatitis, cardiovascular disease, autoimmune disease, diabetes, and obesity (7), diseases which impact the immune system, causing dysregulation and "sterile inflammation" (not induced by microorganisms) in which neuroinflammation contributes to neurodegenerative pathology (8). A better understanding of the immune and inflammatory pathogenetic mechanisms linked to stress should be of help in the search for new therapeutic strategies.

Often individuals with chronic stress have high levels of inflammatory markers, such as C-reactive protein (CRP), IL-6, TNFα, IL-1β, and the transcription factor nuclear factor kappa B (NF-κB) (9), and possibly, acute phase Aβ. In addition, pro-inflammatory cytokines such as TNF, IL-1β, and IL-6 can also be elevated in both peripheral blood and cerebrospinal fluid, leading to depression and other mental disorders (10-12). The cytokine IL-6 appears to be the one most involved in chronic stress, with a higher incidence in the serum of women with this pathology compared to men (11). IL-4, an anti-inflammatory cytokine produced by T lymphocytes that helps B cells to produce antibodies, appears to be decreased in chronic stress (13,14), and therefore unable to counteract the effect of pro-inflammatory cytokines.

Therefore, considering these observations above, we can deduce that inflammation constitutes a predisposing factor for chronic stress, and above all, involves innate immunity. The activation of inflammation occurs through danger-associated molecular patterns (DAMPs). These endogenous non-microbial molecules increase in chronic stress and mediate inflammation (15), whether it involves inflammasome or not (Fig.1). Acute and chronic inflammation can mediate neurodegenerative processes and therefore should be treated.

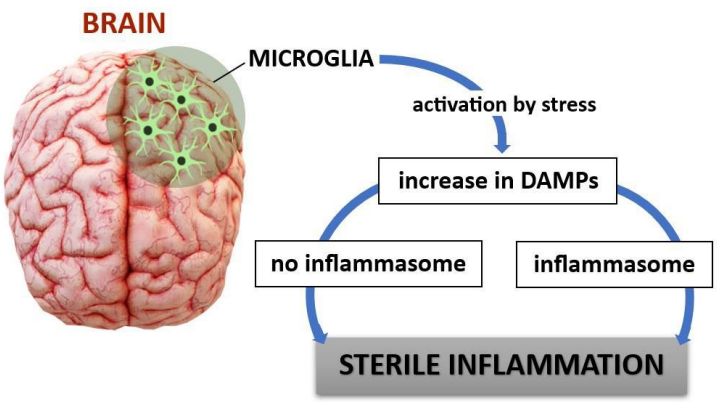

Fig. 1. *When activated by stress, microglia increase danger-associated molecular patterns (DAMPs), which can act with or without inflammasome to generate "sterile inflammation" in the brain.*

Several immune cells are involved in mediating stress, including mast cells (MCs). Allergic diseases, asthma, and dermatitis worsen with stress (Table II), so it is pertinent to think that MCs involved in these pathologies can mediate inflammation.

Table II. *Some symptoms which can aggravate stress.*

• Allergy	• Fatigue	• Itching	• Palpitations
• Anxiety	• Headache	• Myalgia	• Weakness
• Asthma	• Hypotension	• Pain	• Wheezing

In stress, neuropeptides are released and activate MCs to secrete both chemical mediators and pro-inflammatory cytokines. Neuropeptides such as substance P, neurotensin, and corticotropin, together with IL-33 released by MCs and macrophages, generate a stronger inflammatory state than these compounds alone (16,17). The inflammatory effects can be inhibited by non-steroidal anti-inflammatory drugs (NSAIDs) which act by blocking the enzyme cyclooxygenase 2 (COX-2) induced by IL-β and/or TNF (18). Glucocorticoids are powerful anti-inflammatory and immunosuppressive agents that work by blocking inflammatory cytokines and can have a therapeutic effect in stress where cortisol levels have been shown to be below the physiological concentration (19).

Depression

Depression is defined as a sustained state of low mood accompanied by sadness and irritability, with altered brain physiology that can lead to bipolar disorder. Depression is a psychiatric illness that occurs in 10-15% of the population worldwide (29). It can be very serious and is associated with a higher number of suicides. The highest incidence of depression is seen between the ages of 18 and 25 and women appear to be the most vulnerable (21,22). There is no satisfactory cure for this disease and anti-depressant drugs are non-specific and come with unwanted side effects. There are various degrees of clinical depression, including endogenous, unipolar, and recurrent depression, which leads to mood disorders involving the affective and cognitive spheres.

Neurotransmitters such as serotonin (5-HT), norepinephrine, and dopamine are often used as therapeutic drugs with poor results. 5-HT is a neurotransmitter that derives from L-tryptophan and acts on synapses, and its deficiency can lead to depression (23). Psychosocial stress, such as social isolation, has also been linked to defective 5-HT functioning and can contribute to depression and anxiety disorders (24,25). Brain-derived neurotrophic factor (BDNF) is known to have effects on the nervous system and belongs to the neurotrophin family. BDNF affects memory by acting on synaptic connectivity, growth, and repair of neurons. Its deficiency at the hippocampal level causes effects of depression, which can be restored by raising BDNF levels through therapeutic interventions (26). BDNF injected into the rat brain increases 5-HT, dopamine, and norepinephrine levels by acting biologically on tyrosine kinase receptors (27).

Low-grade inflammatory processes, as well as immune system dysfunction, are involved in the pathogenesis of depression. The primary brain immune response induces microglia to produce inflammatory cytokines, such as IL-1, which raises body temperature and stimulates liver cells to produce CRP and other inflammatory mediators (9).

Dementia

Dementia is characterized by a decline in many cognitive functions such as memory loss, inability to carry out daily activities, inability to judge and criticize, decline in language, loss of autonomy, and behavioral disorders. It can be caused by brain disorders, such as AD and Huntington's Disease, and it increases exponentially with age. The activation of microglia leads to an increase in inflammatory cytokines that participate in this pathology. Both innate immune cells such as microglia and macrophages, and adaptive immune cells such as T and B lymphocytes, participate in chronic brain inflammation that may lead to dementia (28). The inflammatory state leads to deterioration of cerebral white matter and neuronal and glial damage, resulting in memory loss (29). Anti-inflammatory therapies can be used if the pathological state is not severe and may improve the state of dementia (30).

Depression is a risk factor for dementia and cognitive impairment (31). In fact, one study highlighted that after a diagnosis of depression, the risk of developing dementia within six months is 15 times greater (32). Experiments on rodent models have highlighted that therapeutic treatment with antidepressants can improve both anxiety and cognitive status (33,34). The improvement in depression after taking antidepressants could be attributed to an inhibition of the glia and/or a high neurotrophic function (35,36). The exact mechanisms of action of antidepressants are not yet clear, and some

authors have reported that these drugs, which target monoamines, are associated with increased rates of dementia (37,38). These contradictions probably occur because states of dementia can have different origins. Considering what is reported above in this paper, the number of researchers who recommend the use of antidepressants is greater than those who advise against it. Therefore, the use of antidepressants can reduce depression and related dementia.

CONCLUSIONS

In conclusion, depression, stress, and dementia are frequent in the global population and contribute to cognitive impairment and neurodegeneration. Psychological distress can occur in depression, anxiety, and chronic stress, and its symptoms can lead to dementia and predict neurodegeneration. The pharmacological therapies adopted today have unwanted side effects and are unsatisfactory. It is therefore necessary to increase clinical research to more effectively combat mental disorders that affect both social relationships and productivity, and lead to lower quality of life for sufferers.

Conflict of interest

The author declares that they have no conflict of interest.

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Letter to the Editor

COVID-19: THE OMICRON B.1.1.529 VARIANT

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INTRODUCTION

Since the first outbreak of severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2) in China in 2019, variants such as Alpha, Beta, Gamma, and Delta have appeared with mutations in the genome of the virus. Omicron B.1.1.529 is a recent addition to such variants; It was first identified and registered with the World Health Organization (WHO) in November 2021 (1) and has raised concern worldwide due to its high level of transmissibility.

The Omicron B.1.1.529 variant is very contagious, and infects people who have already been immunized, including those who have recovered and have already developed antibodies. Fortunately, for now, vaccination is also effective for this variant. The Omicron variant of SARS-CoV-2 has an increased ability to evade immunity and cause widespread infections, which can be quite serious.

DISCUSSION

Since November 2021, the Omicron variant has spread rapidly in many countries. It features a spike protein that is very different from previously known variants (Delta) and raised concerns that it could escape antibody responses.

There was a spike in Coronavirus disease (COVID-19) mortality due to Omicron following the November outbreak (2). However, these deaths were commonly due to complications in patients with previous illnesses and those with a compromised clinical history. By 2022, the Omicron variant had spread to 135 different countries.

The high number of Omicron mutations lead to diversified BA.1, BA.2, BA.3, BA.4, and BA.5 subvariants with elevated immune escape capacity (3). The Omicron variant generates a highly mutated virus defined by the WHO as "worrying". It was also declared that the Omicron variant of SARS-CoV-2 presents a very high risk of infection. This statement reignited past anxiety concerning the recovery of the economy and social life.

The Omicron variant of the SARS-CoV-2 genome constitutes almost 20,000 mutations (4), and more than thirty amino acid mutations have been found within the spike proteins located primarily in the receptor binding domain that binds to the target cell (5). Globally, over 270 million SARS-CoV-2 infections have been reported and the virus has been seen to evolve over 1,500 times (6).

Numerous factors can influence the high transmissibility of the Omicron variant. The genome sequenced data has demonstrated more than 30 mutations in the spike protein which, as we know, is the gene part that recognizes the host cell. Data analysis of these mutations indicates the possibility of increased viral transmission and the potential to evade

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the immune response. Mutations can increase the binding affinity to the ACE2 receptor, which is one of the main factors influencing increased transmission. This creates a stronger binding affinity and greater ease of entry of the virus into the host cell and has occurred with the Omicron BA.5 variant.

Furthermore, the risk of reinfection with the Omicron variant in patients previously infected with COVID-19 is very high, indicating greater transmissibility and making the virus more contagious. The new Omicron BA.5 subvariant can render a false negative result in molecular polymerase chain reaction tests, complicating the situation and allowing the infection to spread at a faster rate around the world. The Omicron variant has also been identified in patients vaccinated against COVID-19, suggesting viral immune invasion, and resulting in a demand and urgency for updated vaccines (7).

The mRNA booster vaccine doses were moderately effective in preventing Omicron variant infection (8). Although, it has been reported that the estimated effectiveness of the Moderna vaccine is greater than the Pfizer vaccine in both the first vaccination and the booster (9). The validity of vaccines and antivirals against the Omicron BA.4 and BA.5 subvariants needs to be urgently evaluated. Anti-viral drugs such as molnupiravir and nirmatrelvir-ritonavir have yet to demonstrate their effectiveness and safety in the real world and healthcare systems must be adequately adapted for their correct use (10).

The first three doses of the Delta vaccine did not completely cover the infections induced by the Omicron BA.4 and BA.5 subvariants in some cases. The US pharmaceutical company Moderna, which already produces the mRNA vaccine which has, to date, immunized millions of people globally, announced a new version of the vaccine which would cover the Omicron subvariants BA.4 and BA.5.

In March of 2022, new Omicron subvariants were identified. These included XF and XD, recombinant subvariants of the Delta variant and the BA.1 sub-lineage, and XE, a recombinant form of BA.1 and BA.2 Omicron sub-lineages. In particular, the XE subvariant was seen to be highly transmissible due to numerous mutations in the spike protein of this virus (11).

As of today, Omicron sub-lineages have expanded to include the following variants in circulation: BA.4, BA.4.6, BA.5, BA.2.75.2, BQ.1, BQ.1.1, XBB, and XBB.1 (12). These variants have not been seen to cause severe Covid-19 disease, although they can tend to evade vaccines and antibody neutralization, and are therefore, still of concern, especially for people with other illnesses or who are immunocompromised. In August 2022, the Federal Drug Administration permitted the emergency use of updated COVID-19 boosters, which were bivalent forms of the Moderna and Pfizer-BioNTech vaccines (13). This vaccine contains the mRNA components of the original SARS-CoV-2, as well as the Omicron subvariants BA.4 and BA.5.

COVID-19 produces diverse systemic symptoms, including neurological sequelae that affect the CNS such as dizziness, motor delay, depression, anxiety, headaches, myalgia, impaired cognitive function, and more severely, stroke. Neurological symptoms can occur not only in acute infection, but also in the post-infection period, which has been termed long COVID. Structural and functional brain changes have also been demonstrated after infection. Some evidence suggests that incomplete clearance of SARS-CoV-2 infection could contribute to the persistence of symptoms after COVID-19 (14).

Studies have demonstrated that infection with the Omicron variant, like the original and Delta strains, can involve neurological symptoms. One recent imaging study by Y. Du et al. showed altered gray matter thickness and subcortical nuclear volume post-infection in men (15). Another study, using a K18-hACE2 mouse model, found that the Omicron virus can cause brain infection with lymphoid depletion (16).

CONCLUSIONS

The SARS-CoV-2 infection is responsible for a pandemic that has caused millions of deaths across the globe. Over time, the virus has changed its genetic composition, creating new variants that can partly escape vaccination, and therefore has created the need to generate new vaccines. Today, highly transmissible variants such as BA.4, BA.4.6, BA.5, BA.2.75.2, BQ.1, BQ.1.1, XBB, and XBB.1 are spreading quickly and can also infect immunized individuals. It should be underlined, however, that the new sub-lineages are less aggressive and pathogenic than the previous Delta variant. Since the number of variants is numerous, there is a need for close monitoring, and we must always be ready to create updated vaccines that can defend against new viruses that threaten human health.

Conflict of interest

The author declares that they have no conflict of interest.

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T LYMPHOCYTE INTERACTION IN THE CENTRAL NERVOUS SYSTEM

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ABSTRACT

Physical and mental health are inextricably intertwined. Neuroimmunology seeks to define and characterize the physiological relevance, the pathological significance, and the cytological and biochemical mechanisms of the communication between the nervous and the immune systems. The migration of lymphocytes to and from lymphoid organs is essential to the physiological regulation of the immune response, and the efficiency of cellular immune processes depends largely upon the distribution and trafficking of T lymphocytes in the CNS, a mechanism that is fundamental for the pathogenesis of various neurological disorders, including autoimmune diseases. Immune cells, including lymphocytes, are activated and mediate brain disease, such as multiple sclerosis (MS), in which myelin-reactive T cells attack the central nervous system (CNS) and cause demyelination. T lymphocytes infiltrate the brain and the interaction of CD4+ and CD8+ cells with adhesion molecules mediates neuroinflammation, contributing to CNS pathology. T regulatory cells (Tregs) are found both in lymphoid tissues and non-lymphoid tissue and differentiate after activation with antigen and specific cytokines, generating anti-inflammatory cytokines that are involved in immune regulation, cellular homeostasis, and the immune response. In tumors of the CNS, the infiltration of lymphocytes has important effects on tumor progression and immunosuppression.

KEYWORDS: *lymphocyte, T cell, CNS, inflammation, autoimmunity, cancer, lymphocyte migration*

INTRODUCTION

Both T and B lymphocytes are generated by bone marrow and are responsible for cellular and humoral responses respectively (1). B (bursal) lymphocytes are immune cells responsible for producing antibodies against specific antigens. T (thymus) lymphocytes participate in the immune response by producing cytokines and other molecules. The immune system plays an important role in the pathophysiological processes of the brain. Immune cells, including lymphocytes, are activated and mediate brain disease. Lymphocytes are developed in the primary lymphoid organs, the thymus and bone marrow, and include B Cells, T cells, and natural killer (NK) cells. When immune cells are activated, they cause inflammation that may result in neuronal necrosis, disruption of the blood-brain barrier (BBB), microglia activation, and the release of inflammatory molecules. T regulatory cells (Tregs) are lymphocyte cells that play an immunosuppressive and anti-inflammatory role in various diseases (Table I). For example, in the autoimmune disease multiple sclerosis (MS),

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myelin-reactive T cells, in addition to other immune cells, attack the central nervous system (CNS), causing progressive demyelination. The infiltration of lymphocytes into tumors of the CNS has important effects on tumor progression and immunosuppression. Tregs, which are naïve CD4+ T cells, differentiate after activation with antigen and some specific cytokines, such as IL-2 and transforming growth factor-β (TGF-β) (2). Tregs generate anti-inflammatory cytokines such as IL-10 and TGF-β that are involved in immune regulation, cellular homeostasis, and the immune response (3). These cells are found both in lymphoid tissues and in non-lymphoid tissues such as lung, adipose and muscle tissue, skin, and brain tissues.

Table I. *Different functions of lymphocytes activated by antigen in the immune system. In addition, T cells also participate in cellular immunity by killing bacteria.*

Activation of lymphocytes			
Lymphocytes + antigen	→ Effector cells + phagocytes + complement	→ Elimination of antigen	
	→ Memory cells		
	→ Cell death		
Cellular immunity			
Bacteria →	Phagocytes and killing →	T lymphocyte activation →	Macrophage activation and bacteria killing

Lymphocytes in the central nervous system

It is known that lymphocytes participate in neuroinflammation. Furthermore, in neurological diseases, there is a dramatic influx of T cells and other inflammatory cells including macrophages and mast cells (MCs). The chemoattraction of lymphocytes in the CNS is mediated by some cytokines and chemokines. When T lymphocytes are activated by antigen in the CNS, they release several cytokines including T cell growth factor (IL-2) which activates IL-1 and tumor necrosis factor (TNF), inducing inflammation (4) (Fig.1). The knowledge of these latter molecules has made it possible to better understand neuropathological phenomena and cerebral inflammation.

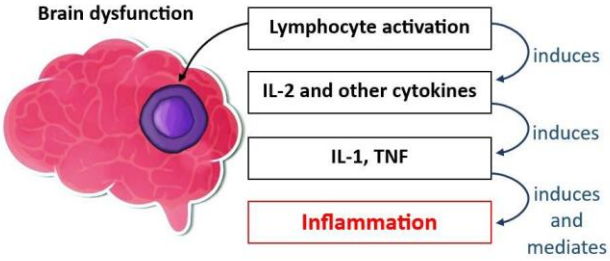

Fig. 1. *Lymphocytes infiltrate the brain, where they are activated by damage to the central nervous system (CNS) and secrete T-cell growth factor (IL-2) and other cytokines, which induce the secretion of IL-1 and TNF that mediate inflammation.*

CD4+ cells infiltrating the CNS mediate the immune response and inflammation. Th1, Th17 cells, and various cytokines and chemokines participate in these pathophysiological processes, mediating the inflammatory reaction. Conversely, Th2 and Treg cells act as immune mediators and are found to be anti-inflammatory. Lymphocyte entry into the CNS is limited by the BBB and glial cells which are abundant and control various biological aspects through communication with macrophages, T cells, NK cells, and other cells.

The meninges are formed by the pia mater, arachnoid mater, and dura mater which surround the CNS. The meninges also contain various immune cells including lymphocytes that participate in brain immunity and immune surveillance of the CNS. Meninges are made up of meningeal lymphatic vessels which drain the brain and are important in health and diseases. In the CNS, B lymphocytes represent a small cellular population that participates in the pathogenesis of some neurological diseases through the production of antibodies, antigen presentation, and secretion of inflammatory and anti-inflammatory molecules (5).

MS is an autoimmune disease that affects the CNS, in which lymphocytes play a crucial role. MS is characterized by chronic inflammation, demyelination, the loss of neurons, and gliosis, and although the exact etiology is unknown, T and B lymphocytes appear to be involved in the processes of demyelination and axonal damage that occur in the CNS. The most well-known hypothesis is that certain CD4+ T cells, with activation by environmental factors, differentiate into Th cell subsets, such as Th1 and Th17 cells, responsible for the activation of other inflammatory immune cells and the generation of cytokines (6). In the animal MS model, experimental allergic encephalomyelitis (EAE), B cells were seen to produce IL-10 that modulates the immune response and IL-10 and Foxp3 expression was enhanced in non-encephalitogenic T cells of the CNS (7).

Lymphocytes in tumors of the central nervous system

Over the last twenty years, the subject of tumor immunity has been increasingly investigated with many scientific publications, particularly regarding the functions of lymphocytes (8-12). This has allowed for improved diagnosis, treatment, and care for cancer patients, although there is much more that remains to be discovered (13). Tumor tissue is made up of different types of cells, such as fibroblasts, pericytes, endothelial cells, and immune cells. Neurons, microglia, astrocytes, and other cells play an important role in neurodegenerative disorders and in brain tumors (14).

T lymphocytes are responsible for cell-mediated immunity and are generally classified into T helper lymphocytes (or CD4+ lymphocytes) and cytotoxic T lymphocytes (also called killer lymphocytes) or CTLs (also called CD8+ lymphocytes). T lymphocytes, such as NK cells, can directly kill tumor cells, while CD4+ T helper cells produce IL-4 that helps to release antibodies by B cells. Treg cells, which are regulatory lymphocytes, generate cytokines and participate in the immunological network. Treg lymphocytes exert tolerance to the antigen and suppress effector T lymphocytes.

It has been observed that in tumor tissue, there are immune cells, such as tumor infiltrating lymphocytes (TILs), that probably have not undergone the immunosuppression that usually occurs in cancer and can respond to tumor antigens (15). This phenomenon occurs in all types of cancer, including brain tumors. These immune cells infiltrate the tumor tissue and should act as effector cells, but the tumor microenvironment inhibits their defensive action. The immunotherapy adopted in brain tumors is increasingly assuming a fundamental importance and the use of TIL lymphocytes has aroused great expectations in both *in vitro* and *in vivo* experiments (16-19).

The immune system is very important in brain diseases, including CNS tumors. In some tumors, such as gliomas, for example, the infiltration of TILs (albeit in low concentrations), has aroused much interest in the scientific community (20). In gliomas, some TILs colonize the perivascular tissue and invade the external parts of the tumor. Various types of lymphocytes have been identified in these tumors including CD45R0+, CD8+, CD4+, and FOXP3+ (21). The presence of these lymphocytes in gliomas serve as biomarkers that indicate both the pathological state of the patient and the therapy to be adopted, although further research in this field is still needed. Lymphocytic infiltration is also found in meningiomas where the rare intratumoral T lymphocytes, also present in the perivascular area, can indicate the severity of the disease (22). These lymphocytes are often represented by NK, CD4+, CD8+, CD45+, and CD20+ cells (23). Although the significance of the presence of these lymphocytes is not clear, it could be argued that their infiltration may represent a weak attempt at an immune response against the tumor.

T lymphocytes expressing CD3+ and CD8+ receptors with anti-tumor activity can infiltrate brain tumors (24,25). Treg lymphocytes expressing CD25, CD4+, and FOXP3 receptors, also present in the tumor microenvironment, inhibit anti-tumor lymphocytes (26). Th cells with CD3+, CD4+, CTLA4, and PD-1 receptors help B cells produce anti-tumor antibodies (27). Often, these reactions are rather mild and do not help to completely defeat the tumor.

Recent knowledge of tumor immunology has led to new immunotherapies including cytotoxic therapies with T lymphocytes and vaccines (28). Today, tumor immunotherapy researchers are studying a type of anti-tumor lymphocyte called chimeric antigen receptor T-cells (CAR-T), which are cells engineered to express chimeric antigen receptors (29). CAR-T cells are assembled by the fusion of a recognition domain, a single-chain antibody, and a T-cell stimulation domain. So far, this therapy has shown promising results in the treatment of hematologic cancers (30), but it is hoped that in the near future, it will find application for other tumors as well, including brain tumors.

CONCLUSIONS

The immune system defends the body against infections from microorganisms, protecting the individual and ensuring health. Innate and adaptive, or cell-mediated immunity, is the first classification of the immune system. Innate immunity acts non-specifically on all foreign microorganisms with the activation of phagocytic cells, including microglia in the brain. Humoral immunity is mediated by circulating antibodies responsible for specific antigen recognition, while cellular immunity is mediated by lymphocytes. Activation of the immune system leads to the production of cytokines, inducing

cell death and generating antibodies. Microbial agents coming from outside the body can break down the BBB, enter the CNS, and cause cerebral dysregulation with activation of myelomonocytic cells. T lymphocytes infiltrate the brain and the interaction of CD4+ and CD8+ cells with adhesion molecules mediates neuroinflammation, causing CNS pathology. Therefore, it is important to underline that the trafficking of T lymphocytes in the CNS is fundamental to the pathogenesis of various autoimmune diseases of the brain. Here, we summarized the aberrant function of T lymphocytes in the CNS, an effect that mediates neuroinflammation rather than protecting the brain from external stimulus.

Conflict of interest

The authors declare that they have no conflict of interest.

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IL-4, IL-1 RECEPTOR ANTAGONIST, IL-37, AND IL-38 INHIBIT IL-1 AND TNF GENERATED BY MICROGLIA

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ABSTRACT

Microglia are innate immune cells resident in the brain with phagocytic activity similar to macrophages. Microglia are protagonists in inflammatory brain diseases and are large producers of interleukin (IL)-1. IL-4 is a growth factor for hematopoietic cells, helps B cells to produce immunoglobulins, and has the ability to down-regulate and inhibit the production of IL-1 generated by both macrophages and microglia. Here, we report that the anti-inflammatory cytokines, IL-1 receptor antagonist (IL1-Ra), IL-4, IL-37, and IL-38 can inhibit the generation of IL-1 produced by microglia in inflammatory brain diseases.

KEYWORDS: *IL-4, IL-1, IL-1-Ra, microglia, inflammation*

INTRODUCTION

Interleukin (IL)-4 is a 20-KDa cytokine glycoprotein product produced by T helper cells that has interesting biological effects. It is involved in the generation of the immunoglobulins IgG1 and IgE in mice, it has growth factor activity for T cells, mast cells (MCs), and thymocytes, and can activate T and B cells (1). IL-4 is also a growth factor for hemopoietic cells as well as an activation factor for macrophages (2,3). However, we believe the most interesting biological effect discovered so far for IL-4 is its capacity to down-regulate and inhibit IL-1 and tumor necrosis factor (TNF) produced by macrophages (4). In relation to the clinical sphere, it appears that IL-4 may suppress the generation of fever *in vivo*, and more surprisingly, in cancer patients, there seems to be a return of appetite and of weight gain after treatment with IL-4, thus reversing undesired symptoms generally mediated by IL-1 and TNF (5). Cytokine therapies for cancer patients have been shown to produce unwanted side-effects due to potent inflammation. Hypotension, thrombocytopenia, capillary leak syndrome, leukopenia, fever, and arachidonic acid product formation, are all involved in the toxic shock-like syndrome and are among the many undesired effects produced by IL-2, IL-1, TNF, IL-6, GM-CSF, and other cytokines. This cytokine release syndrome may even lead to death by inducing toxic shock syndrome (6).

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DISCUSSION

The interleukin-1 receptor antagonist (IL-1Ra), IL-37, and IL-38 have been seen to inhibit IL-1 (7), the master of inflammation which induces other inflammatory cytokines. These anti-inflammatory proteins are monokines secreted by human monocytes and are structurally similar to IL-1β, but with no IL-1-like activity. They dump IL-1 by binding to its cell surface receptor and exert their biological effects.

It has been found that IL-1Ra is not only an IL-1 inhibitor, but that this protein can also potentiate IL-2 to activate natural killer (NK) cells and down-regulate DNA synthesis in mitogen stimulated lymphocytes (8); this latter phenomenon is most probably due to the IL-1 inhibition. However, the reason for these biological effects is not yet totally understood.

The inhibitory effects of IL-4 and IL-1Ra on IL-1 and TNF production plays an extremely important role in controlling the delicate immunoregulatory balance during immunity and inflammation following cytokine immunotherapy.

Microglia are macrophage-like cells that are part of the innate immune system of the central nervous system (CNS). Microglia can exhibit pro- or anti-inflammatory behavior in response to Th1 cytokines and Th2 cytokines, respectively (9). In fact, when these cells are activated, they can produce both pro-inflammatory IL-1, TNF, and IL-6 (M1 polarization) and anti-inflammatory IL-4 and IL-13 (M2 polarized phenotype) which reduce inflammation (10). The activation of microglia occurs with the consumption of mitochondrial energy which allows for cell survival, which is important for the intervention of microglia in neurodegenerative processes. Therefore, polarization of M1 microglia leads to the release of pro-inflammatory cytokines; while M2 polarization leads to the secretion of anti-inflammatory cytokines, including IL-4 (10) (Fig.1).

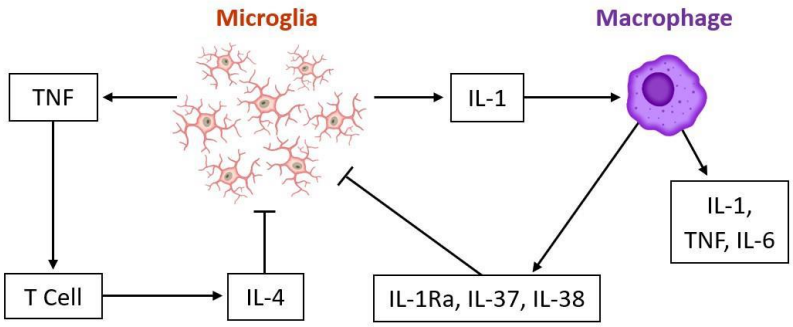

Fig. 1. *Activated microglia secrete IL-1 and TNF which stimulate macrophages and T cells, respectively. Upon activation, macrophages release autocrine IL-1, pro-inflammatory TNF, and IL-6; while TNF secreted by microglia activates T cells to release IL-4. Activated macrophages can also secrete anti-inflammatory cytokines that inhibit microglia; while T cells release anti-inflammatory IL-4 which inhibits microglia.*

IL-4 has its gene located on the Th2 cytokine locus and is an epigenetic regulatory cytokine that is produced by various cells, including CD4+ cells, MCs, NK cells, basophils, eosinophils, and ILC2 cells. In the CNS, IL-4 is released by both microglia and neurons (11). IL-4 has many similarities with IL-13, of which it shares approximately 30% of the amino acid sequence, and the two cytokines also share the same receptor (12). The receptor for IL-13 is located on the Th2 cytokine locus.

The anti-inflammatory process can also be regulated by IL-37 which suppresses the activation of IL-1□ and stimulates the generation of IL-10, another anti-inflammatory cytokine, and T regulatory (Treg) cells (13). IL-37 is generated by activated macrophages. Five isoforms (a, b, c, d, e) of this cytokine have been discovered, of which the most active and studied form appears to be "b" (14). IL-37 may inhibit IL-1 released by microglia and may relieve inflammation in neurological diseases (15).

IL-38 is also a macrophage product that can inhibit IL-1 produced by microglia and dump inflammation (16). IL-38 is one of the most recently discovered cytokines and is part of the IL-1 family. Since IL-38 is related to IL-36, its function is to block the IL-36 receptor, an effect reminiscent of that of IL-1Ra (17). IL-38 is expressed by various cells such as those located in the tonsils, heart, placenta, and brain. This cytokine has anti-inflammatory properties and has been implicated in several autoimmune and CNS diseases including autism spectrum disorder (16), Alzheimer's disease (18),

ischemic stroke (19), systemic lupus erythematosus (20), and psoriasis (21). In addition, IL-38 is produced by B cells. Since IL-1-producing microglial cells play a fundamental role in inflammatory brain diseases, inhibition of IL-1 with IL-38 may have a significant therapeutic effect.

CONCLUSIONS

In addition to the previously discovered anti-inflammatory cytokines such as IL-4, IL-13, and IL-10, new anti-inflammatory compounds such as IL-Ra, IL-37, and IL-38 have now appeared on the scene (7,22). These cytokines may inhibit cerebral inflammation and could be an additional tool to utilize in therapies for inflammatory diseases that are mediated by IL-1.

Conflict of interest

The authors declare that they have no conflict of interest.

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