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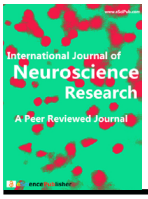

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NEUROINFLAMMATION

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ABSTRACT

Inflammation is a complex process, mediated by cellular and molecular mechanisms caused by a response to a tissue damage from an aggressive agent, whether if biological, chemical or physical origin. This process occurs, ultimately, with the purpose of promoting defense, repair and tissue regeneration. The inflammatory process leads to changes in blood vessels that have their diameter and flow altered, with the objective of leading to increased vascular permeability and consequent leakage of fluids and cells into the extracellular space of the affected tissue. This sequence of events generates the cardinal signs of inflammation, which are: pain, heat, redness, edema, with loss or alteration of function. The process occurs through mechanisms induced by cytokines and that despite having local manifestation, it can lead to systemic responses involving the whole organism with fever, chills, tremors, tachycardia, leukocytosis, sweating, diuresis and blood dyscrasias.

In the cascade of events related to inflammation, there is initially a local stimulus that promotes morphological and functional changes in the attacked tissue that trigger the release of signaling molecules, the defensins that have a chemotactic effect on monocytes, neutrophils and lymphocytes, and pro-inflammatory mediators. that are directly involved in the next inflammatory phases. There is, then, the recognition of aggression and the aggressor agent by the receptors of cells of the immune system and release of inflammatory mediators, of the cyclooxygenase pathway that will release prostaglandin, prostacyclins and thromboxanes and by the lipooxygenase pathway that will produce leukotrienes (Figure 1). Then, there is a modification of the local microcirculation promoting vasodilation, initially arteriolar and subsequently of the venules by the action of histamine release by mast cells, and associated with an increase in local blood flow, generate the cardinal flushing and heat signals.

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As a consequence of this vasodilation, there is an increase in vascular permeability, triggering extravasation of plasma and its proteins (albumin, globulins and fibrinogen), altering the concentration gradients favoring the passage of water and electrolytes to the extracellular medium, generating local edema. As a result of this leakage of fluids, hemoconcentration occurs in small vessels that reflects in stasis, both causing a reduction in the speed of blood flow, and it is at this same moment that the leukocytes are also marginalized in the endothelium, mainly neutrophils, where they adhere to vessel wall and migrate between endothelial cells, through diapedesis, to the extracellular environment. Subsequently, these cells in the battered tissue differentiate and act to eliminate the offending agent and repair the local aggression.

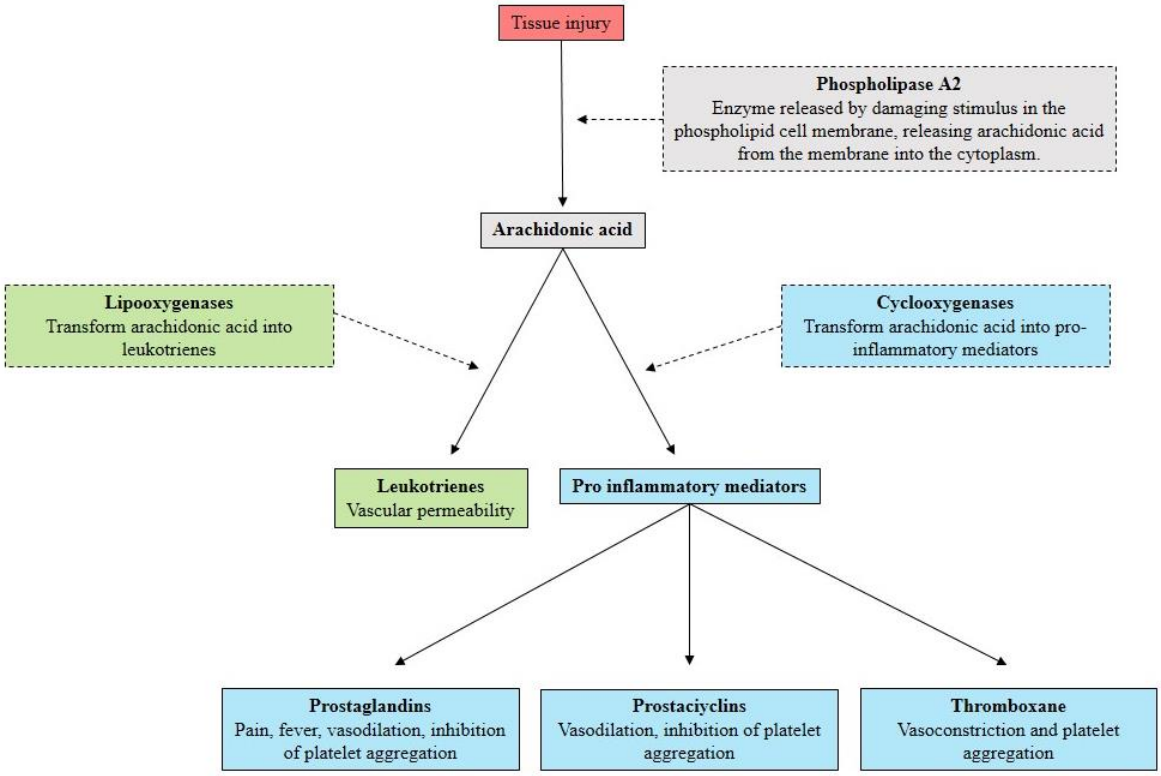

Figure 1 – Cascade of arachidonic acid pathway

In the acute phase, inflammatory signs are present, for a short and self-limited time, with the presence of neutrophils and macrophages in the exudate. In the chronic phase, there is persistence of the inflammatory agent with prolonged exposure, and the inflammatory signs may not be present or evident, with the presence of macrophages and lymphocytes in the exudate, and granuloma formation may occur.

All of these mechanisms aim at the defense of the organism either by diapedesis followed by phagocytosis of the aggressor agent, or by its isolation and the action of antibodies and, finally, the repair / healing / regeneration process. However, this response does not always occur in a compensated manner, so when there is a persistent and excessive response, there may be an impairment and organic dysfunction resulting from a disproportionate response and associated sequelae.

NEUROINFLAMMATION AND PAIN

The presence of inflammatory mediators in neural tissues is also present in the same neurophysiological mechanisms as acute and chronic pain. Acute pain differs from chronic pain precisely because of the maintenance of the

painful sensation despite the resolution of the peripheral inflammatory process that gave rise to the pain.

When we talk about neuroinflammation in pain, we must identify the main actors in this process. They are: pro and anti-inflammatory mediators and glial cells. Components of glial cells are: Schwann cells and satellite glial cells in the Peripheral Nervous System (PNS) and, in the Central Nervous System (CNS), microglia, astrocytes and oligodendrogliocytes. Formerly regarded as quiescent cells, with an exclusively structural and supportive function, glial cells play an important role in neuroinflammation and chronicity of pain[15,37]

Acute pain

Acute pain is configured as a crucial mechanism for the survival of living beings. After the stimulus is generated by any aggressive factor, it causes the unpleasant sensation of pain, the body is forced to move away from the harmful stimulus, allowing the gradual recovery of the injured tissue. It is intrinsically related to the peripheral nociception process, in which the nerves detect thermal, mechanical or chemical changes, transduce these changes in an electrical signal and transmit it to the cortex, where there is a conscious interpretation of what pain is.

The acute injury promotes tissue destruction with the consequent release of arachidonic acid degradation products, neutrophil infiltration, complement activation, mast cell degranulation, pro-inflammatory chemokines and cytokines (TNF, IL-1β, IL-6, IL- 15, IL-17) and anti-inflammatory drugs (IL10, IL4, TGF-β), adenosine triphosphate (ATP), reactive oxygen species and hydrogen ions. These mediators bind to receptors on the membrane of nerve terminations, depolarizing the first neuron (AUSTIN, 2010) [7].

Then, there is the conduction of the signal by the first neuron to the first synapse in the dorsal horn of the spinal cord or in the trigeminal nucleus. The first-order neuron then releases excitatory neurotransmitters in the synaptic cleft, as substance P, a peptide related to the calcitonin gene (CGRP), glutamate and brain-derived neutrophic factor (BDNF). Such neurotransmitters bind to their respective receptors in the second order neuron, to then transmit the stimulus to the upper centers (thalamus, somatosensory cortex, frontal cortex, insula, among others (RU-RONG, 2013) [15].

In the acute pain phase, there is activation of the glial satellite cells in the dorsal root ganglion and astrocytes and microglia in the CNS. This early activation leads us to believe that the central sensitization process already takes place in the first hours after contact with the harmful stimulus (CHEN, 2018) [15].

When the nociceptive stimulus is interrupted, the action of anti-inflammatory mediators released in the area of injury tends to resolve the inflammation. Among these mediators, the most important are resolvins, protectins and maresines. If the pain persists even after the stimulus has ceased and the inflammation is resolved, we are faced with a chronic pain condition (CAYLOR, 2019; DUNLIN, 2007; CARACI, 2019) [13,14,18].

Chronic Pain Syndromes and the role of neuroinflammation

Fibromyalgia

Fibromyalgia is characterized by generalized muscle pain associated with sleep disorders, cognitive disorders and fatigue. Its pathophysiology is not yet well established, however, as well as in other pains whose nociplastic mechanism is the predominant one, it is believed that there is an imbalance in the nociceptive pathways, with special impairment of the descending analgesic pathway. There is evidence of increased serum TNF, IL-8, IL-17, substance P and corticotrophin releasing hormone (CHR) in patients with fibromyalgia. Substance P and IL-8 are also increased in the cerebrospinal fluid (CSF) of these patients.

It is assumed that mast cells found in the hypothalamus and thalamus, secrete inflammatory mediators (such as histamine and

CHR) and activate microglia, leading to the release of pro-inflammatory cytokines such as TNF, IL-6 and IL-1β. However, further studies are needed to understand the full pathogenesis of fibromyalgia and the implication of neuroinflammation (THEOHARIDES, 2019; SOMMER, 2018) [42,45].

Regional Complex Pain Syndrome (CRS)

In patients with CRS, it is possible to differentiate between an initial “hot” phase, with striking inflammatory signs in the affected limb, and a second chronic, “cold” phase, with atrophy and loss of limb function. Although clinically there seems to be local inflammation and an increase in TNF has already been reported in the skin of the affected limb, conflicting results are still found when researching inflammatory mediators in the CSF and blood of these patients.

Such discrepancy can be explained by the heterogeneity of groups of patients affected by the syndrome and the stages of the disease. In addition, not only the inflammatory mechanism must be taken into account when looking for the genesis of CRPS, but sympathetic dysregulation is also of great importance (SOMMER, 2018; SCHINKEL, 2008) [38,42].

Chronic migraine

The explanation of a pathophysiological mechanism for chronic migraine is still a challenge. In addition to the traditional trigeminovascular theory, the role of neurogenic inflammation has gained strength in recent years. Despite little evidence of the participation of acute inflammation as a trigger for migraine attacks, especially with regard to the prodromal phase and hypothalamic neuroinflammation, the role of neuroinflammation in chronification is better established. And the main site would be the trigeminal ganglion. In the same way that the chronicity of acute pain is due in large part to neurogenic inflammation in the dorsal root ganglion and the posterior horn of the spinal cord, the satellite cells of the trigeminal ganglion play an important role in the migraine chronification.

It has been shown in animal studies that the Calcitonin Gene-Related Peptide (CGRP), as well as substance P and neurokinin A, induces characteristic hyperalgesia and peripheral sensitization through the activation of inflammatory cells in the posterior horn of the spinal cord.

During a migraine crisis, there was an increase in the concentration of CGRP in the jugular vein. The continuous action of CGRP in the trigeminal ganglion, promotes persistent stimulation of C fibers and activation of A delta fibers. Such fibers stimulate the glial satellite cells and increase the sensitivity to painful stimuli of the trigeminal ganglion. Clinically, hyperactivation of the trigeminal ganglion leads to hyperalgesia and promotes the chronicity of migraine [22].

The use of monoclonal antibodies that bind to CGPR or that inhibit its binding to its CGRP receptor is a reality in medical practice and has had satisfactory results in the control of chronic migraine (ALASAD, 2020) [4].

New targets for research

The attempt to block the neuroinflammation that leads to chronic pain has led to the discovery of possible new therapeutic targets. Resolvins and Protectins are endogenous substances derived from polyunsaturated fatty acids called pro-resolving lipid mediators (PRLM) whose function is to accelerate the anti-inflammatory process. They modulate peripheral vanillode receptors (mainly TPRV1) and inhibit TNF, IL-1β and IL-6. Further studies with substances that act in the context of PRLM are still needed, but their inhibitory action on acute inflammation and on sensitization in chronic pain is promising.

Naltrexone, an opioid receptor antagonist, when used in low doses (0.5-4.5mg) acts on the modulation of microglia through antagonism of the Toll-like 4 receptor (TLR-4), decreasing the release of inflammatory mediators. Its use has been studied in case series of patients with complex regional pain, chronic pain due to osteoarthritis, fibromyalgia, multiple sclerosis and inflammatory bowel disease, showing itself

as an option for the treatment of central sensitization with few side effects (ALASAD, 2020; KIM , 2020) [4,26].

INFLAMMATION AND INFECTIONS IN THE NERVOUS SYSTEM

If, on the one hand, inflammatory processes are present in several neurological diseases, on the other hand there are diseases in which inflammation is the central agent of pathophysiology.

Living organisms are continually invaded. This is called infection. Evolution led to the development of the immune system, in order to protect organisms from infections. Inflammation is a set of cellular and biochemical processes that occurs during the immune response and is responsible for a large part of the symptoms that are observed.

Virtually any system can fall victim to infection. Systems with greater contact with the external environment, such as the respiratory and genitourinary systems, are the most frequent victims. Others are better protected. This is the case of the Central Nervous System, which has an extra layer of protection, called the blood-brain barrier, which isolates it from the rest of the body and makes it less susceptible to external aggressors.

Viral Infections

Viruses are single-celled microorganisms without a nucleus that need to infect other beings to multiply. Several species of viruses infect humans and an important part of them have a preference for cells of the nervous system (also called neurotropism). They can cause acute damage to the nervous system or become latent in your cells after infecting them, reactivating in future opportunities (usually when there is an imbalance in the body with reduced immune response).

Viral meningitis and meningoencephalitis

Three meninges line the entire CNS (including brain and spinal cord). The most superficial is also the most resistant and thickest, called dura-mater. The intermediate is called arachnoid and, the deeper and thinner, pia mater. The two joints comprise of leptomeninges and are the preferred place for infectious agents (ROPPER, 2019) [36].

Among the causes of meningitis, those of viral etiology are the most common. Enteroviruses are the most common cause of viral meningitis (about 80% of cases). They are a genus with a wide range of species that can cause meningitis and, in general, their symptoms are mild.

The most common form of manifestation is a variable mix of the 4 main symptoms of meningitis (headache, fever, stiff neck and altered mental status). Most of the time the symptoms are tenuous and can be confused with a common viral infection of other systems. In general, these cases are treated only with symptomatic drugs. Any type of virus can cause more serious symptoms. However, there are some species that are more likely to cause severe conditions.

Other types of viruses cause meningitis less frequently than enteroviruses. Arboviruses, which are viruses transmitted by a host, usually a mosquito or a tick, also cause meningitis. Examples present in tropical countries are the dengue virus, chikungunya and zika. It has been documented that the latter has a pathological effect on the formation of the Nervous System of fetuses when infecting pregnant women, causing microcephaly and implying a delay in the development of these children.

The herpes virus family is another very common cause of diseases of the nervous system. The most commonly implicated viruses are Herpes Simplex types 1 and 2 and varicella zoster. Herpes simplex type 1 is the cause of one of the most serious viral meningoencephalitis. Changes in the level of consciousness, epileptic seizures and behavioral changes are some of the symptoms commonly observed. In the evolution, the patient can evolve with a state of convulsive illness and coma. If not treated in time, the mortality rate exceeds 70%.

Many other types of viruses can affect the central nervous system. Some examples are

measles, mumps, rabies, rubella viruses (BECKHAM, 2016; LYONS, 2018) [8,27].

Bacterial Infections

Although viral meningitis is the most common cause of meningoencephalitis, the ones that lead to the most typical clinical picture are bacterial.

Bacteria reach the central nervous system in two ways. Most often, it happens through dissemination through the bloodstream (hematogenic), in which the pathogen is already present in other systems of the body (usually in the respiratory tract or in the bloodstream) and ends up breaking the blood-brain barrier. It can also occur by contiguity, when the bacterium is housed in a structure close to the infected structure, after surgery on the skull. (ROPPER, 2019; ANDERSON, 2016) [5,36]

Many different species of bacteria can cause meningitis, but two are the most common. The most common is Streptococcus pneumoniae (or pneumococcus), which is the same agent as most pneumonias, sinusitis and otitis. When it causes meningitis, the symptoms can be quite aggressive and, if not treated in time, there can be serious complications, such as epileptic seizures, stroke and even death. It is a bacterium that is most often sensitive to standard antibiotics, such as third generation cephalosporins, but there are already cases of antibiotic resistance. Therefore, in severe cases or in places with a high frequency of resistant bacteria, it is recommended to associate a second antibiotic to the empirical treatment (before the agent is identified) (HASBUN, 2020) [23].

The second most common agent to cause bacterial meningitis is Nesseria meningitidis (also called meningococcus), a bacterium with low resistance to antibiotics, which causes a typical picture of acute meningitis. The severity of meningitis caused by meningococcus tends to be less than that of pneumococcus and treatment is usually easier. However, one should be aware of the possibility of a potentially fatal condition, called meningococcemia. In these cases, the bacterium spreads throughout the body, causing a severe sepsis that leads to death if not treated in time.

Other agents deserve attention, such as *Listeria* sp, *Staphilococcus Aureus*, *Enterococcus* sp and *Haemophilus influenza*, the latter that used to be the main cause of bacterial meningitis, until the emergence of specific vaccination (HASBUN, 2020) [23].

Chronic infections

Other infectious agents behave differently when they reach the central nervous system. They reproduce more slowly and cause a more tenuous infectious process, with evolution over weeks to months. For this reason, the classic symptoms of acute meningitis are less present. For example, the patient may have a mild isolated headache, which develops slowly over many weeks, only then to show an increase in temperature or stiff neck. Or you may be asymptomatic for months before you start to become disoriented. Symptoms that are atypical in acute meningitis are more common in chronic ones, such as changes in cranial nerves, inflammation in the vessels (vasculitis) and behavioral changes.

Some bacteria and almost all fungi and protozoa that reach the central nervous system cause the chronic pattern of infection. In Brazil, the relevant agents are Mycobacterium tuberculosis (which causes tuberculosis) and *Treponema pallidum* (which causes syphilis), both bacteria with slow multiplication and that remain in the body for years before causing the first symptoms. Fungi, such as cryptococcus and protozoa, such as *Toxoplasma gondii* and *Taenia solium* (which causes neurocysticercosis) also cause chronic inflammation in the CNS.

Because these agents have low infectivity and slow multiplication, immunocompetent organisms are able to suppress them and prevent the disease from manifesting clinically in most cases. In immunosuppressed people, whether by drugs, hematological neoplasms or

acquired immunodeficiency syndrome (caused by HIV), the risk of disease in the CNS is significantly higher (SEXTON, 2020) [40].

Syphilis

Syphilis is caused by a spiral-shaped bacterium (order of spirochetes) called *Treponema pallidum*. It comes into contact with the infected organism mainly through sexual transmission (but it can occur transplacentally or by blood transfusion) and causes a clinical picture that varies according to the stage of the disease and that can affect almost any system.

Syphilis is classified, according to the time of infection, into early and late. The interval of one year after the onset of infection is considered early and the period after the first year is late. A second way to classify the evolution of the disease is according to the clinical manifestation: primary, secondary, latent and tertiary syphilis. The primary and secondary stages occur in the early stage of syphilis. The latent can happen in both the early and late phases and the tertiary one usually occurs in the late phase (HICKS & CLEMENTS, 2020) [25]

Primary syphilis occurs shortly after the inoculation of the spirochete, where a crusted, non-painful and non-exudative lesion may develop. It is more common for the lesion to appear on the genital organ, but it can appear on other mucous membranes or even not manifest. Secondary syphilis appears from weeks to a few months after the cancer has disappeared in about a quarter of untreated patients. It is manifested by constitutional symptoms (fever, headache, malaise, weight loss, etc.), lymphadenopathy and changes in practically all systems, including characteristic skin rashes, gastrointestinal, joint and renal changes (HICKS & CLEMENTS, 2020) [25]. The central and peripheral nervous system can also be affected at this stage of the disease. Headache often develops over weeks to months. Another common finding is subacute or chronic meningitis (syphilitic meningitis), which can be associated with dysfunction of cranial nerves and inflammation of intracranial vessels (meningovascular syphilis), which can cause ischemic stroke. The eyes are also frequently affected (ocular syphilis) and practically any form of ocular involvement can occur (ROPPER, 2019; BORGES, 2019) [10,36].

Individuals with syphilis, even if untreated, often progress to the latent phase, where the treponema remains inactive. When this occurs, they may remain asymptomatic for many years or never develop tertiary disease. We call late syphilis the period that exceeds 1 year after inoculation of the spirochete. Some untreated patients may develop tertiary syphilis in this period. There are three main forms of tertiary syphilis: cardiovascular, gumatous and central nervous system involvement.

Syphilitic meningitis, the meningovascular form and the ophthalmic form can also happen at any time in the late phase. However, in this phase, usually after many years and decades of initial infection, classic manifestations can occur: general syphilitic paresis and Tabes Dorsalis. Fortunately, after the advent of antibiotics, these clinical forms of syphilis have become rare. General syphilitic paresis usually occurs 10 to 25 years after the initial infection. There is a slowly progressive dementia that can manifest with symptoms of mood, mania and psychotic symptoms (ROPPER, 2019) [36].

Tuberculosis

Tuberculosis is caused by a bacterium called Mycobacterium tuberculosis. It comes into contact with the organism through aerosols, reaching the pulmonary alveoli. It is a bacillus that reproduces slowly, but that generates a strong inflammatory response in the carrier. A minority of individuals can get rid of the bacteria immediately, through the innate immune response, without developing the disease, and others end up developing the primary form of the disease. These people react to the pathogen through a cell-mediated immune response. When the bacilli reach the alveoli, macrophages encompass them, forming granulomas. Some bacteria end up escaping into the bloodstream, but are contained in regional lymph nodes,

where there is a new inflammatory response. These lymph nodes become enlarged and inflamed at the time. This immune response is favorable in the vast majority of individuals (90%), inactivating mycobacteria. When latent, the bacillus remains disease-free in most individuals (RILEY, 2019) [35]. However, especially in situations of immunodeficiency, such as HIV infection, immunosuppressive treatments and weakened general conditions, the bacteria can reactivate.

In about one tenth of the cases, the host's cellular immune response is not favorable, allowing the mycobacterium to spread through the lungs, causing tissue destruction and consequent functional impairment. Progressive coughing and shortness of breath are common symptoms. If the active disease is not treated, the mortality rate is about 80% of cases (RILEY, 2019) [35]. Unlike the spread of other bacteria, which cause meningitis by hematogenous mechanism or by contiguity, the tuberculosis bacillus gradually implanted in the meninges and in the subpial regions (which are below the pia mater), forming tubers (granulomatous masses). When one or more tubers rupture, the mycobacterium spreads through the subarachnoid spaces causing tuberculous meningitis (ROPPER, 2019) [36].

Tuberculous meningitis is more likely to affect the meninges of the posterior fossa than cerebral convexity. Clinically it evolves more slowly than a viral or bacterial meningitis, with evolution times longer than a week, which can reach months. The initial manifestations are low fever, headache, neck stiffness and progressive malaise, but also confusion, lethargy and coma. Active tuberculosis is found in other systems in about two-thirds of patients with tuberculous meningitis. Most of the time the other focus is pulmonary, but you can also find foci in other organs, such as intestines, bones and kidneys. The presence of immunosuppression, in addition to increasing the chance of reactivation of the disease, can accelerate the clinical evolution. (ROPPER, 2019) [36]

If the patient is not treated, neurotuberculosis progressively evolved from signs of intracranial hypertension, dysfunction of cranial nerves and other focal neurological symptoms and with a decrease in the level of consciousness and coma. On average, the patient dies in 4 to 8 weeks after the onset of neurological symptoms. Treatment should be prolonged compared to other forms of meningitis, but it can radically change the natural course of the disease if done in time.

NEUROINFLAMMATION IN NEURODEGENERATIVE DISEASES

Neurodegeneration is one of the main causes of motor and cognitive dysfunction, especially in the elderly, with diseases such as Parkinson's and Alzheimer's, being in prevalence behind only cerebrovascular diseases. In the coming decades, however, with the aging of the population and the reduction of morbidity and mortality related to cerebrovascular diseases, there is an increase in the prevalence of neurodegenerative diseases (WHO, 2018). Chronic activation of innate and adaptive immune responses can trigger neurotoxic stages that culminate in neurodegeneration. The processes of repair, regeneration and control of inflammation are involved in this process (AMOR, 2014) [2]. The importance of knowledge related to these pathways lies in the possibility of developing and investigating therapeutic strategies that modify the natural evolution of the disease, both prophylactically in individuals at risk of neurodegenerative diseases, and modulating in individuals with these, especially in the early stages (CHITNIS & WEINER, 2017) [16].

In the central nervous system (CNS), the mechanisms of repair and regeneration and immunological activity are very peculiar and different from those of other regions of the human body. Several responses related to inflammatory processes can be observed in the course of neurodegenerative diseases, as well as in other CNS diseases, such as stroke, epilepsy and infections. Such responses are

important in the pathogenic process not only in favor of the process, but also in limiting and controlling it (SCHAIN & KREISL, 2017) [41].

Immunological therapies have been investigated and are likely to be the treatment for neurodegenerative diseases in the future. These strategies can prevent neuronal loss or contribute to neuronal growth (CHITNIS & WEINER, 2017) [16]. Although it is characteristically the trigger of the pathophysiological process, the immune system presents a sustained response, related to the progression of neurodegenerative diseases (GLASS, 2010) [21]. Neurodegeneration mechanisms include: cell apoptosis, necroapoptosis, neuronal autophagy, retrograde degeneration and Wallerian degeneration, demyelination and astrogliopathy. These mechanisms involve the CNS endogenous immune system cells: mononuclear astrocytes and phagocytes (perivascular and meningeal microglia and macrophages) (CHITNIS & WEINER, 2017; GLASS, 2010) [16,21].

Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease in the world. The pathophysiology of this disease involves the formation of β-amyloid peptide and neurofibrillary aggregates with hyperphosphorylated tau. There is evidence of pro-inflammatory conditions in specific regions of the CNS of patients with Alzheimer's disease, however, the question that has not yet been adequately clarified is whether the inflammation is more implicated as a cause or appears as a consequence of the β-amyloid peptide and aggregates. neurofibrillary (HEPPNER, 2015) [24].

Few cases of AD have any associated genetic alteration. Several risk factors increase the chances of developing the disease, such as diabetes mellitus, hypertension, metabolic syndrome, head trauma and aging. What seems to unite these factors with the disease is the immune mechanism associated with them, and chronic inflammation seems to be the key to this understanding (NEWCOMBE et al., 2018). In addition to these, several genes have been described with an increased risk of developing the disease, the main one being APOEε4, but others described are: TREM2, CLU, CR1, EPHA1, ABCA7, MS4A4A / MS4A6E, CD33, CD2AP (OZBEN & OZBEN, 2019) [28].

Some anti-inflammatory therapies, such as non-steroidal (NSAIDs), steroidal (corticosteroids) and others (Gingko biloba, propentophylline, vitamin E), have been studied as therapies that can slow the evolution of Alzheimer's disease (AKIYAMA, 2000) [3]. Also, the treatment of AD by monoclonal antibodies is quite recent and appears to be promising. As the disease is chronic and progressive, it is important that studies related to the intervention in these inflammatory mechanisms are carried out, since they may influence the natural evolution of the disease. In addition, the disease has both cognitive and non-cognitive symptoms, studies should clarify which symptom (s) may or may not be affected with the treatments. The pathophysiological changes in advanced stages of the disease are irreversible, recently it has turned to investigated strategies that prevent the development of the disease (OZBEN & OZBEN, 2019) [28].

Parkinson's disease

Idiopathic Parkinson's disease is the second most common neurodegenerative disease, and it is also the second most common movement disorder. It is a disease that has classic motor symptoms: bradykinesia associated with plastic stiffness or tremor at rest. But other symptoms can occur: postural instability, falls (motor symptoms), dysphagia, dysphonia, cognitive changes, hallucinations, REM sleep behavior disorder (non-motor symptoms). Even some non-motor symptoms can precede the diagnosis by up to 20 years: constipation, REM sleep behavior disorder, anxiety, depression and hyposmia. Pathophysiology is associated with the presence of α-synuclein and Lewy bodies, affecting several neurotransmitter systems in specific regions, according to the stage of the

disease (BRAAK, 2003) [11]. Etiopathogenesis is multifactorial, probably related to genetic, environmental and immunological conditions. Immunological changes of both innate and adaptive responses have already been well described, and it is not known whether the effects are promoters or protectors of neurodegeneration (DE VIRGILIO, 2016) [17].

There is scientific evidence of the presence of infiltration of CD4 + T cells in the substance nigra and that these cells are directly related to the oxidation process of α-synuclein in Lewy bodies (ACUÑA, 2018) [1].

Other neurodegenerative diseases

The influence of neuroinflammation has been studied in other neurodegenerative diseases, such as frontotemporal dementia; multiple system atrophy; amyotrophic lateral sclerosis; ataxia-telangiectasia, Huntington's disease among others (BRIGHT, 2019; ILLARIOSHKIN, 2018; STEPHENSON, 2018) [12,28,44]

CONCLUSION

The CNS immune system has specific characteristics that distinguish it from other human organs and the understanding of its participation in the pathophysiology of neurodegenerative diseases has been growing exponentially. The future points to therapeutic strategies that aim to change the natural evolution of the disease, through strategies that act on immunological targets. The role of neuroinflammation in the context of pain applies not only to the initial nociceptive stimulus to control acute pain. But also, it is known of its essential role in the chronicity of pain, especially in the neuronal modulation carried out by glial cells. The chronicity of specific painful syndromes, such as fibromyalgia and chronic migraine, needs unequivocal pathophysiological explanations. In this context, new therapeutic approaches aimed at neuroinflammatory involvement are very promising and give us hope for a long-term control of these conditions.

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