Chapter

The Pathophysiological Aspects of Cerebral Diseases

Henrique Coelho Silva, Rafael Costa Lima Maia, Paulo Roberto Leitao de Vasconcelos and Orleancio Gomes Ripardo de Azevedo

Abstract

Introduction. Cerebrovascular disorders are the main causes of heavy burden health worldwide, also, it is critical to understand the pathophysiological mechanism and then trying to prevent the neurological sequels. **Objective**. To discuss the inflammatory and oxidative stress aspects associated to the cerebrovascular diseases, focusing on biomarkers, also the role of omega oils, and the intracellular molecular network associated to the tissue burden on those conditions. **Results**. One of the most promising biomarkers it is Neuron-Specific Enolase (NSE). Serum NSE levels were elevated in stroke-patients compared to the non-stroke controls. Also, studies have demonstrated that in specific ratio omega oils 3, 6 and 9 can ameliorate the inflammatory and oxidative stress in nervous tissue and could be useful to the inflammatory and oxidative stress negative effects of cerebrovascular diseases. In addition, the study of the molecular mechanisms is essential to understand which molecules could be addressed in cascade of events preventing the permanent damage on the nervous tissue. **Final considerations**. The studies on cerebrovascular disorders must precisely identify the mechanisms and key molecules involved and improve the time of diagnostics and prognostics reducing the negative impacts of those conditions.

Keywords: Neuroinflammation, oxidative stress, omega oils, biomarkers, molecular Cascade, pathophysiology

1. Introduction

Cerebrovascular disease is an important cause of severe health impairment and/or death, being the stroke, the main event-related as a cause of this group of diseases. The American Association of Neurological Surgeons (AANS) define cerebrovascular disease as disorder, in which, an area of the brain is temporarily or permanently affected by ischemia or bleeding and one or more of the cerebral blood vessels are involved in the pathological process, which includes stroke, carotid stenosis, vertebral and intracranial stenosis, aneurysms, and vascular malformations [1].

Other conditions such as brain tumors, neurotrauma, intracerebral hematoma, and aneurysmal subarachnoid hemorrhage, could be potentially important depending on the incidence or prevalence in populations across the world [2]. Cerebrovascular diseases are frequently associated with the high financial cost to the public and private health system across developed and under-resourced countries.

2. Expenditures for cerebrovascular disease patients

Brazil has shown a high level of economic burden to manage and treat cerebrovascular diseases. In a Brazilian report, the authors have demonstrated the annual costs and use of health care compared, age and sex paired healthy individuals to patients with cerebrovascular disease [3].

Reis Neto and Busch evaluated the annual costs and the use of private health care systems comparing 71,094 individuals among healthy controls and patients with cerebrovascular conditions. The 12 months follow-up report, found that the annual individual expenditure was 65.6% higher compared to the control group without any cerebrovascular condition [3].

Several reports have demonstrated that the main cause of cerebrovascular disease is stroke, which leads to a huge impact on brain tissue due to restriction on blood flow compromising the nervous tissue and leading to negative effects.

3. Stroke

According to the World Health Organization (WHO), stroke is a condition that the blood flow is interrupted leading to a focal or global disturbance on brain functions showing symptoms during at least 24 hours or longer or even leading to the death of the patient [4].

3.1 Types of strokes

Since the stroke is related to the blood flow to the nervous tissue, the stroke could be divided into (1) ischemic stroke and (2) hemorrhagic stroke.

The ischemic stroke resulted in obstruction of a large vessel in the brain or cervical region leading to reduced levels of oxygen and glucose diffusion to the after-occlusion regions, particularly classified in two regions—*penumbra* and *ischemic core* (**Figure 1**) with some important characteristics. On the other hand, hemorrhagic stroke is produced due to a rupture of a vessel mainly due to hypertensive disease, coagulation disorders vascular malformation and could be potentialized by diet and other modifiable factors [4].

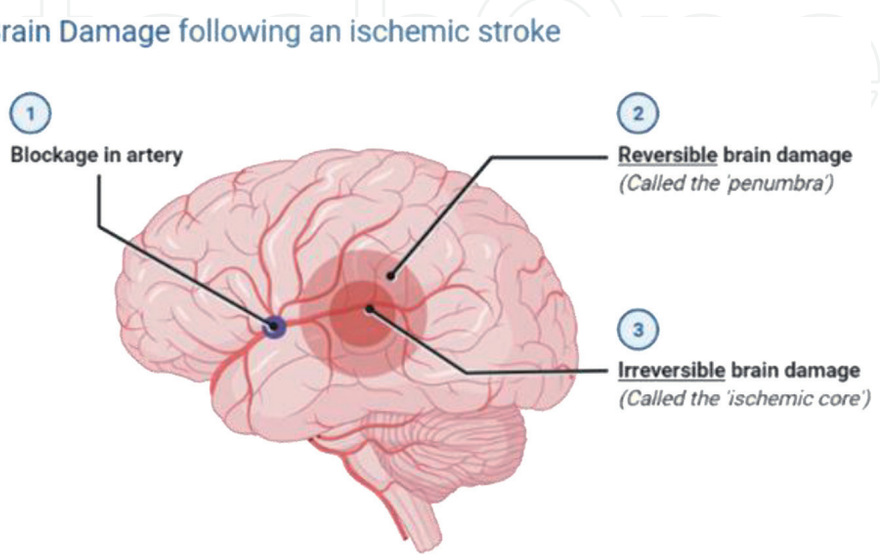

Figure 1.
A schematic illustration for brain damage provoked by an ischemic stroke (created with BioRender.com®).

Worldwide in 2016, there were 5.5 million deaths related to the consequences of stroke, in addition, 80.1 million prevalent cases, being 41.1 and 39.0 in female and male respectively, also 13.7 million new cases of stroke cases worldwide [5].

The last published 2021 guideline for the prevention of stroke summarizes the types and subtypes of stroke (**Figure 2**) according to the anatomy location and involvement [6–8]. Those phenotypes are key features to provide accurate information to the physician to take a correct decision and may deliver a proper assistance to the patients.

In the acute phase of cerebral arterial occlusion, the critical treatment consists of recovering cerebral reperfusion as soon as possible. Currently, two therapies are validated for this purpose—intravenous thrombolytic (rtPA) and/or mechanical thrombectomy [9].

Each of these modalities has advantages and disadvantages. However, less than 20% of all stroke patients are candidates for mechanical thrombectomy, making primary and secondary prevention still the major factors to reduce the number of cases in the world. The prevention of stroke is based on a healthy diet, regular exercise, and avoiding smoking and alcohol consumption.

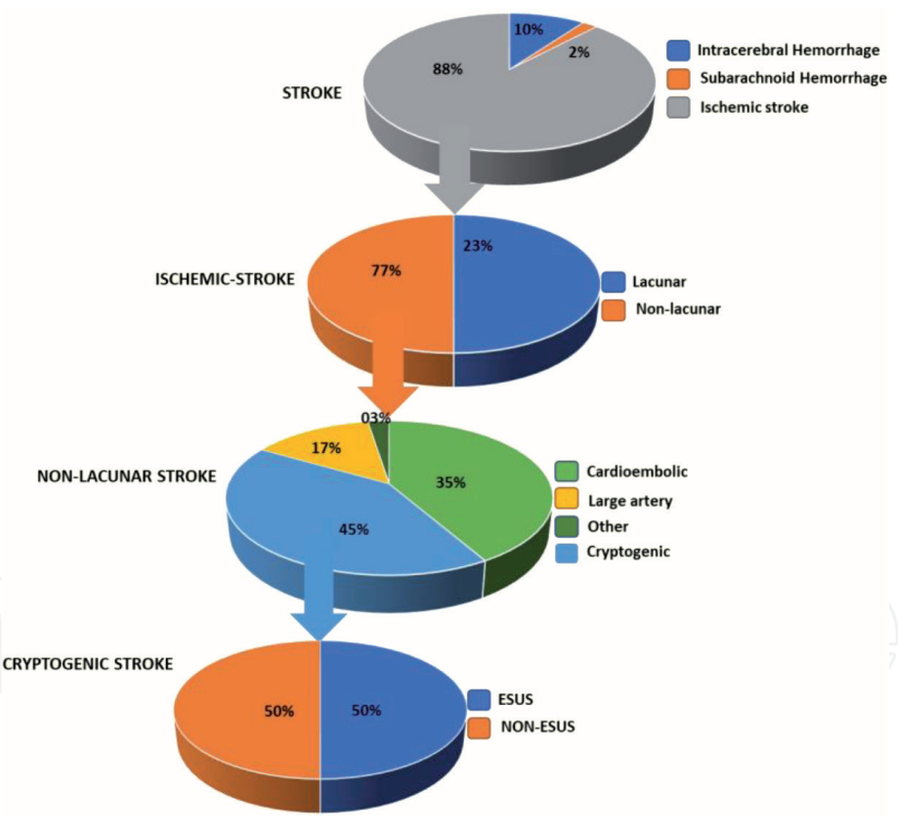

Figure 2.
The classification of stroke subtypes according to the definition and anatomical localization (created with BioRender.com®).

3.2 Pathophysiology of stroke

In ischemic stroke, an interruption in cellular oxidative metabolism decreases the oxidative metabolism, levels of calcium and sodium, these key factors lead to a reduction in oxygen-based neuronal mitochondrial function, energetic

debit, production, and releasing of inflammatory mediators (prostaglandin and leukotrienes), in addition, vasoconstriction, platelet aggregation, and vessel occlusion.

On the other hand, a hemorrhagic cerebrovascular event, an acute vessel rupture of encephalic structures; a secondary ischemic lesion around the hematoma may also occur [10–12].

The anti-inflammatory and antioxidative roles of omega oils 3, 6, and 9 have been largely investigated in cerebrovascular diseases [13–15].

The economical, epidemiological, and pathophysiology impacts of cerebrovascular diseases are huge and must be addressed to improve the comprehension of all the factors that are related to the genesis and the disease progression of these conditions. Thus, the animal models could be potentially positive helping to clarify all the key factors related to cerebrovascular diseases.

3.3 Inflammatory and oxidative state in stroke

Several studies have been conducted in the past to assess the benefit of cerebral arterial reperfusion, but only in 1995, the benefit was proven using intravenous thrombolysis with alteplase (tPA) to break the cerebral thrombus [16].

A recent report has suggested superiority in treatment with a new clot buster "tenecteplase" (TNK), a variant of tPA, but possesses greater fibrin specificity and a longer half-life, making it potentially safer and a more effective drug for stroke [17]. In addition to intravenous thrombolytic therapy, the treatment of patients with stroke is having profound modifications due to the endovascular treatment of cerebral reperfusion, increasing the therapeutic window for up to 24 hours from the onset of initial symptoms [18].

Early treatment is the most critical factor for successful reperfusion therapy of acute ischemic stroke. The researchers only discovered the correct way to treat stroke patients in the acute phase after understanding exactly how the alteration in cerebral blood flow modifies the cell function.

Acute occlusion of an arterial branch responsible for the irrigation of a brain area triggers an inflammatory cascade that clinically manifests as an acute neurological deficit. However, according to the degree of dependence of that cell on the vessel, different metabolic responses will occur. The brain requires a continuous supply of oxygen and glucose to maintain physiologic function.

The regular brain perfusion rate is approximately 50–60 mL/100 g tissue/min, if cerebral blood flow is interrupted, then neuronal metabolism can be affected after 30 seconds of interruption and will completely stop within 2 minutes of deprivation. Through the increase in the cellular capacity to extract oxygen under low supply conditions, no symptoms are observed until the brain blood flow reaches around 20–30 mL/100 g/min [19], and then the energy generation is shifted to the anaerobic glycolysis pathway.

This is the basis of the glutamate excitotoxicity theory and may explain why pyramidal neurons in the hippocampus and Purkinje cells in the cerebellum that rely on glutamate neurotransmission are particularly vulnerable to ischemia [20]. The center of the irrigated tissue area, when receiving less than 10 ml/100 g of brain tissue, after 4–5 minutes, cannot maintain the sodium and potassium transporter working, generating a cytotoxic edema that will evolve to cell apoptosis, a process mediated by calcium and the glutamate (**Figure 3**) [21].

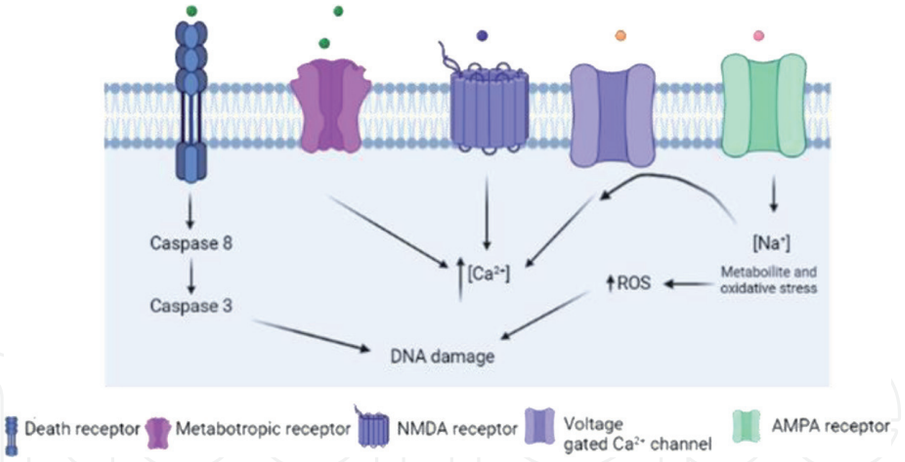

Figure 3.
Molecular pathways outlining the role of glutamate in excitotoxicity following stroke (created with BioRender.com®).

3.4 Stroke blood biomarkers

One of the major difficulties for the acute treatment of patients with cerebral ischemia is early diagnosis through a serum biomarker since stroke often occurs with atypical and nonspecific symptoms, known as *"stroke chameleons"* [22].

The biomarker must be reliable, rapidly measured, and readily available, to be considered a good biomarker for stroke. In addition, the biomarker must help in determining the mechanism of injury, differentiating in cardioembolic, atherothrombotic, or prothrombotic state [23].

However, the stroke biomarkers do not have sufficient data to support an ideal concept of sensitivity and specificity [24] to standard any biomarker by itself to characterize the progression of the disease. In addition, Lassen, and cols., first reported that acute occlusion of an arterial branch responsible for the irrigation of a brain area triggers an inflammatory cascade that clinically manifests as an acute neurological deficit. However, different metabolic responses will occur leading to difficulty to identify a biomarker that shows specificity and sensibility for a lab detection [19].

One of the most promising markers evaluated is neuron-specific enolase (NSE), an enzyme released after neuronal damage. Serum NSE levels were elevated in stroke patients compared to the nonstroke controls and are associated with infarct volume and high neurological deficit [25]. Nonetheless, the NSE major issue to be standardized as a biomarker is delayed-release into the blood flow after brain injury compromising, the key role of early diagnosis [26].

Furthermore, the brain natriuretic peptide (BNP) is the main cardiac biomarker studied for its relationship with stroke, including the presence of paroxysmal atrial fibrillation, although optimal cutoff values for individual profiles are undefined [27].

In addition, studies from a European consortium of the population-based cohort (approximately 58.000 stroke-free participants), evaluating brain natriuretic peptide (BNP) levels, demonstrated that increased levels of NT-proBNP were associated with the higher risk of ischemic and hemorrhagic stroke [28].

Another study assessing 381 patients diagnosed with the transient ischemic attack (TIA), has shown an NT-proBNP level > 800 pg./mL, which was independently associated with a higher risk of stroke over 37 months follow-up [29].

4. Animals models in cerebrovascular diseases

The pathophysiology of cerebrovascular diseases such as ischemia has been studied in several animal models. These models have shown many metabolic alterations leading to cellular lesions in specific brain regions, depending on the duration of the blood flow restriction [10–12].

The use of small animals (e.g., mice, rats, gerbils, or rabbits) have an important advantage; lower maintenance costs compared to larger animals. The rat is the most used in stoke studies, due to the physiology and anatomy similarity to the humans [30], however, the mouse could be potentially useful, since is the uses of transgenic technology that can assess the molecular pathophysiology of stroke [31, 32].

The middle cerebral artery permanent or transient occlusion (MCAo) is less invasive and does not require craniectomy and has been widely used in published reports. In the transient method, the duration of suture varies between 60 and 120 minutes inducing high levels of infarction (**Figure 4**) [33].

The photothrombosis model is based on intravascular oxidation through irradiation with a light beam in a specific wavelength, generating oxygen radicals that lead to inflammation-like damage [34]. The Endothelin-1, a potent vasoconstrictor, it is administered in the Middle of Cerebral Artery (MCA) leading to the animal develops stroke.

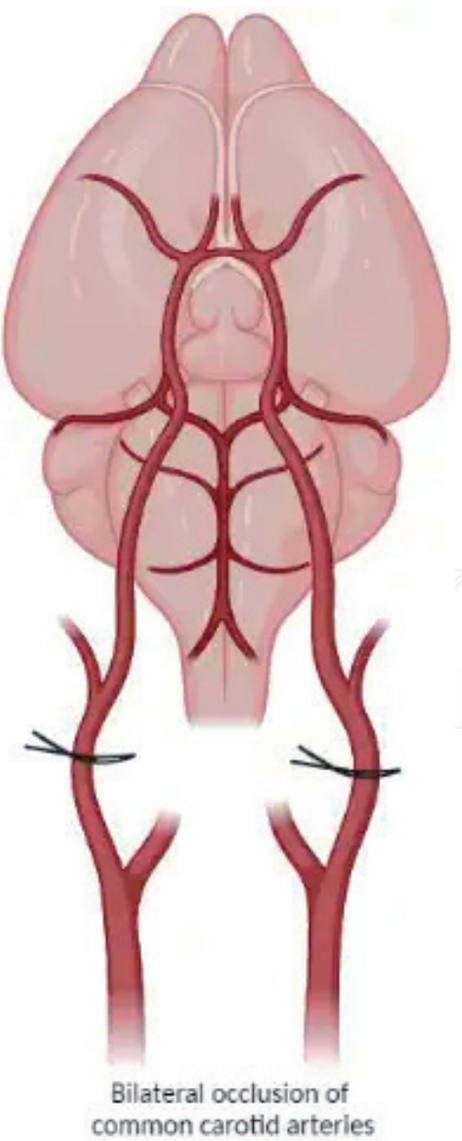

Figure 4.
The representation of bilateral occlusion of common carotid arteries. (created with BioRender.com®).

Another model is the embolic stroke that uses clots with spheres of dextran or other supraparamagnetic iron oxides, TiO_2, and ceramic that could develop occlusion and lead to stroke [35].

In the last years of animal models to understand the mechanisms involved in stroke, it is widely used to evaluate key targets and therapeutics molecules investigating the protectives and treatments tools. The administration of omega 3, 6, and 9 could be a useful tool to protect the nervous tissue against the inflammatory and oxidative damages produced by stroke [33–35].

4.1 Use of omega, 3, 6 and 9 in brain ischemia animal models

The brain ischemia leads to several metabolic alterations in carbohydrates metabolism in an experimental model of brain ischemia-induced only by the bilateral occlusion of common carotid arteries in rats [36].

However, some evidence suggests that ketone bodies are utilized to generate energy in some extreme situations such as ischemia [37]. In addition, in a report from Faria and cols in 2007, the authors have demonstrated, that using 48 male Wistar rats submitted to the occlusion of common carotid arteries, increased cerebral uptake of acetoacetate (ACT) and beta-hydroxybutyrate (BHB) following brain ischemia [38].

Pinheiro and cols in 2011, have shown that the preconditioning of 42 male rats with different omega oil mix preparations promoted protection against the deleterious effects of ischemia/reperfusion injury demonstrated by the reduction of red neurons in the group that received mix 2 (omega 6: omega 3 ratio— 1.4:1; omega 9: omega 6 ratio—3.4:1) source of omega 3 ALA (35%) + EPA (39%) + DHA (26%) [39].

In 2011 Campelo et al., using occlusion of the common bilateral carotid arteries ischemia model demonstrated that the pretreatment using nitrosyl-ruthenium (Rut-bpy) decreased the mean arterial pressure variations throughout the transition of brain ischemia to reperfusion, in addition, decreased the ischemic area, also Rut-bpy pretreatment reduced NF-kB hippocampal immunostaining and protein expression with improved histopathology scoring as compared to the untreated ischemic-group control [40].

Pires and colleagues in 2011, using the L-Ala-Gln preconditioned gerbils (*Meriones unguiculatus*) under the transient bilateral occlusion of the common carotid arteries, demonstrated a significant increased GSH levels [41]. Furthermore, Oliveira and cols. Demonstrated an important reduction on TNF-α, NF-κB, IL-6, and HO-1, inflammatory mediators in pretreated gerbils with L-Ala-Gln [42].

5. The pathophysiology of subarachnoid hemorrhage

In addition to stoke, the role of the oxidative state in the context of subarachnoid hemorrhage is another fascinating topic that deserves to be studied.

The incidence of delayed cerebral ischemia (DCI) is around 30%, with DCI remaining the major cause of morbidity and mortality among patients who survive the initial treatment of the ruptured aneurysm [43]. The DCI is frequently associated with the early arteriolar vasospasm with microthrombosis, perfusion difficulty and neurovascular uncoupling, spreading neurons depolarizations, and inflammatory responses that begin at the time of the aneurysmal subarachnoid hemorrhage (aSAH) and evolve over time, culminating in cortical infarction [44].

The aSAH (approximately the origin of 5% of all strokes) is a complex cerebrovascular disease with severe systemic complications. The worldwide incidence of aSAH is approximately 700,000 cases annually with a mortality rate of about 40% [45].

The initial global hypoperfusion after aSAH leads to inflammatory processes, which occur in blood vessels as well as in cerebrospinal fluid (CSF) and then macrophages and neutrophils enter the subarachnoid space releasing proinflammatory factors [46].

The initial aneurysmal rupture deposits blood within the subarachnoid space, the methemoglobin, heme, and hemin resulting from red blood cell breakdown and hemoglobin metabolism, which can lead to activation of TLR4, which stimulates a proinflammatory cascade damaging neurons and white matter. Hemin has been associated with the release of redox-active iron, which depletes antioxidant stores, such as, nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione while producing superoxide and hydroxyl radicals as well as increasing lipid peroxidation [47].

Some clinical studies have found that modulating inflammation following aSAH is beneficial, on the other hand, several studies have shown, no beneficial effect at all. It is likely that activation of inflammation at different time points post rupture, is associated with different protective or detrimental responses depending on the microenvironment and type of cells recruited to the inflammatory site [48].

One of the most commonly proinflammatory biomarkers used as a clinical indicator of its C-reactive protein (CRP), that plays an important role in disease diagnosis and treatment and management evaluation. Recent research has shown that CRP (C-reactive protein) is an independent predictor of outcome after aSAH [49].

In a study conducted from January 2012 to June 2017, developed in South Korea, the researchers evaluating 156 patients diagnosed with aSAH found, evidence that serial measurements of CRP may be used to predict neurological outcomes of SAH patients, in addition, maximal CRP levels within 4 days post-SAH are significantly correlated with poor neurological outcomes [50].

Injection of proinflammatory components induces cerebral vasospasm, even in the absence of blood breakdown products (**Figure 5**) [48].

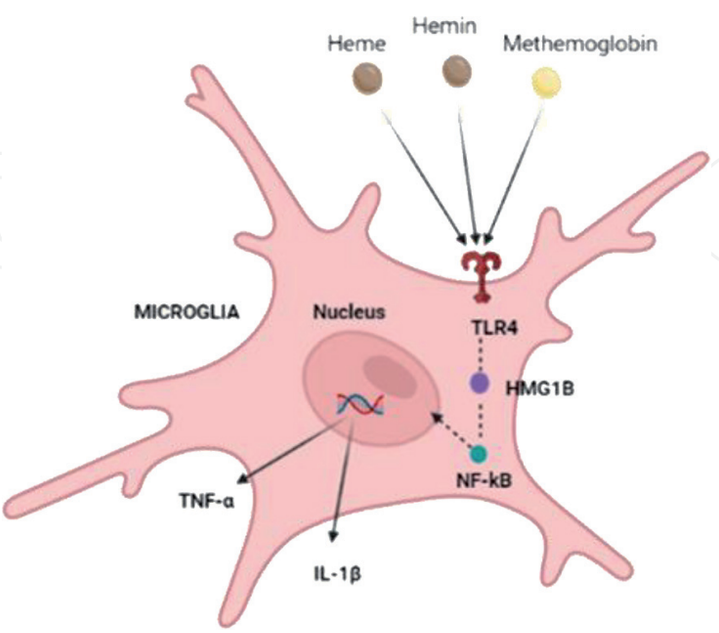

Figure 5.
The damage in red blood cells, led to the release of molecules such as heme, hemin, and methemoglobin, through the TLR4, activating the group box 1 genes and then leading to the production and releasing of proinflammatory molecules TNF-α and NF-κB [51] (created with BioRender.com®).

Clinically, the inflammatory response appears in close temporal relationship with the spasm and direct proportion to the magnitude of the inflammatory response [52]. These findings have been supported by evidence suggesting that the accumulation of inflammatory cells closely parallels neuronal cell death. Cell death near the vasculature has been substantially reduced by the depletion of inflammatory cells in preclinical studies [53].

One of the main lines of research related to aSAH is the identification of a specific biomarker related to the risk of a patient presenting late cerebral ischemia, allowing anticipation of specific therapy for the condition.

The difficulty in using biomarkers in clinical practice stems from the variability of inflammatory markers according to the phase of hemorrhage, which can protect the brain tissue in a certain phase and attack the brain tissue in another phase. In addition, the high financial, temporal, and human cost of measuring these markers makes them unfeasible, currently, for routine clinical use [54].

6. Inflammatory and oxidative state in brain tumors

Other types of brain lesions, in addition to primarily vascular ones, have inflammatory and oxidative aspects in pathogenesis. We will initially discuss brain tumors, and the next topic, brain trauma.

The importance of the inflammatory state in oncological diseases in the central nervous system (CNS) is already well established and valued. Even with damage to other systems, there are changes in the neuroinflammatory microenvironment induced by the underlying oncological disease that is reflected in the functioning of the CNS [55–57].

Primary tumors of the nervous system are strongly related to the production of reactive oxygen species (ROS), promoting abnormalities in DNA replication, activating of proinflammatory gene panel, and subsequent inflammation in the tumor microenvironment [58], which is reflected, for example, in the presence of tumor-associated macrophages (TAM's), which arise specifically from microglia in the context of gliomas [59, 60].

Presenting all proinflammatory-related genes, cytokines, and mediators involved in this state is beyond the scope of this chapter. However, this proinflammatory state has been present since the first stages of tumorigenesis [61] and can be fed back by the glioma cells themselves, as demonstrated by Lisi 2014 *et al*., who pointed out that brain tumor gene expression varies throughout the natural history of the disease, mainly alternating the expression of M1 and M2a/B, promoting the release of different growth factors according to the stages of advancement [62].

This "phenotypic shift" is also implicated in disrupting the natural cycle of microglial mitosis [63]. We should also discuss the key role of external elements, such as Benzo[a]pyrene, promoting oxidative stress, leading the DNA damage arising from DNA mutations. On the other hand, Patri 2019 *et al* suggest that noradrenaline may have a protective effect against this effect [64].

Feng 2020 demonstrated through enrichment levels of 28 immune cells in the tumor immune microenvironment in five datasets, demonstrating prognostic (and consequent therapeutic) implications through phenomena that diverge from those observed in other types of cancer. The phenotype involved, for example, allows the tumor to evade the immune response mechanism [65]. Among the ways to exercise this immune-resistant condition can be cited suppression of EZH2 [66] and T cell dysfunction promoting the sustained growth of the tumor [67, 68].

The understanding of neuroinflammatory implications extends beyond the formulation of specific therapies to combat the growth and perpetuation of

the neoplasm—oxidative stress has a strong influence on the outcome also in the postoperative state of tumor resection, and the correct conduct with this in mind can also influence the outcome [69].

7. Inflammatory and oxidative state in traumatic brain injury (TBI)

TBI is one of the main causes of brain damage, especially in the young population. The cumulation of inflammatory factors is associated with the increased tissue damage of the nervous system in both the brain and spinal cord [70], causing lesions through ischemic-like patterns mechanisms [71].

In the initial moments, proinflammatory cytokines IL-1α, IL-1β, IL-6, and TNF-α, are released in sustained-response patter reaching and activating the microglia, being predominant during the first 48 hours [70, 72, 73].

Even in cases of mild traumatic brain injury, which commonly do not present with more exuberant clinical conditions, there is evidence of neuroinflammation, and apoptosis related to oxidative stress [74].

Interestingly, there is evidence for similar patterns in psychiatric conditions where trauma itself is not (or at least is not sustained) the main factor involved, as in post-traumatic stress disorder [75, 76]. Hyperfibrinogenemia is another common factor in the proinflammatory state of TBI and other neurological conditions such as Alzheimer's disease [77].

Among the substances studied in this context is the release of nitric oxide (NO), produced by endothelial nitric oxide synthase [78]. Abdul-Muneer 2014 described the interactions involved between several inflammatory cytokines and growth factors involved in oxidative stress and neurovascular inflammation in the pathogenesis of TBI, highlighting blood–brain barrier dysfunction (BBB) in the onset and perpetuation of changes in the cellular microenvironment in this pathological condition [79].

Recognition of the role of the inflammatory microenvironment, both in the acute and later phases of TBI, offers a therapeutic opportunity by changing the phenotype from proinflammatory to anti-inflammatory, which represents the fertile area for research [74, 80]. Chemokines are emerging as powerful controlling inflammation-induced brain edema factors, especially regarding BBB dysfunction [81]. In another example, there is evidence that hypothermia can be used to curb the inflammatory cascade [70].

8. Closing remarks

Thus, the research of neurovascular diseases, as well as the understanding of other brain injuries initially nonvascular (such as neoplasms and traumas) should identify the critical molecules of the cascade of the disease mechanism that could be potentially used, such as, a biomarker and used to develops prognostics to understand how the disease progression is. On the other hand, as fast as, the inflammatory and oxidative mechanisms are revealed; more and more molecules can be used as therapeutical tools to address the negative clinical signs associated with disease.

Acknowledgements

The authors would like to be thankful to the surgery department of the Federal University of Ceara, for the entire support for the development of their studies and move forward on elucidating those very critical conditions that affect the population.

Conflict of interest

The authors declare no conflict of interest.

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