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Zika and SARS-CoV-2: neuroinflammation and neurodegenerative outcomes

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ABSTRACT: Through the emergence of new viral infectious diseases, epidemics and pandemics have brought great impacts on public health in recent decades. In this review, we sought to understand the association between the neurological outcomes of two relevant infectious diseases, Zika and COVID-19. Zika can trigger neurological and ophthalmic damage in children born from infected mothers, as well as, Guillain-Barré syndrome, encephalitis, and myelitis in adults. On the other hand, the SARS-CoV-2 virus has great potential to trigger an inflammatory process in the optic nerve, with optic neuritis as the most reported pathology. Although Zika and SARS-CoV-2 infections are associated with different clinical manifestations, both may trigger similar pathogenic processes, through the induction of pro-inflammatory chemokines and cytokines release, triggering neurological and ophthalmological damage in infected patients. Elements in common have been found in both infections, such as antibodies against myelin oligodendrocyte glycoprotein, and the production of CXCL10, a chemokine responsible for the activation of several cellular types (T cells, eosinophils, monocytes and NK cells) in which are responsible to the induction of a cytokine cascade in the body. Based on these last findings, we suggest that both infections have similar activation characteristics as well as common pathogenic mechanisms associated with central nervous system involvement.

Keywords: COVID-19; Infection; Inflammation; Neurodegeneration; SARS-CoV-2; Zika virus.

Abbreviations: Zika virus (ZIKV), SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), severe acute respiratory syndrome (SARS), pattern recognition receptors (PPRs), central nervous system (CNS), Congenital Zika Virus Syndrome (CZS), World Health Organization (WHO), tumor necrosis factor (TNF), interleukin-1β (IL-1β), N-methyl-D-aspartate receptor (NMDAR), Guillain-Barré syndrome (GBS), antibodies against myelin oligodendrocyte glycoprotein (anti-MOG), interferons (IFNs), COVID-19 (Corona Virus Disease 2019), peripheral nervous system (PNS), human angiotensin-converting enzyme 2 (hACE2), production of angiotensin-2 (AT2), interferon-inducible protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1), tumor necrosis factor alpha (TNF-α), optic neuritis (OIN), multiple sclerosis (MS), blood-brain barrier (BBB), ACE-2 (angiotensin-converting enzyme 2), protein S (Spike), granulocyte colony stimulating factor (G- CSF), macrophage inflammatory proteins-1 alpha (MIP-1α).

1. INTRODUCTION

In the last decades, infectious diseases have been more frequent largely due to ecologic (animal niche alterations), environmental (climate changes) and demographic factors (globalization and increasing of the people traffic around the world) [1]. Viral infections, classically known by their local geographic distribution and dissemination, had these patterns changed in the last decade, spreading over other regions, mostly by epidemic outbreaks, as happened with Dengue, and Zika, which were responsible for great impact at population health and, more recently, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) by the new Coronavirus pandemic [2].

Viral infectious diseases are caused by virus adsorption and replication in host cells, generating immunopathological responses characterized by the activation of the first and second defenses line, which are responsible to trigger the local and systemic inflammatory processes associated with these physiopathologic conditions. As viruses are easily transmitted, different tissue injury and functional commitment of some organs appear, aggravating host health and, therefore, the population in general, becoming a serious health public problem [3].

Arboviruses such as the Zika virus (ZIKV), a member of the *Flaviviridae* family, are indirectly transmitted by *Aedes aegypti* and *Aedes albopictus* mosquito bite, being mainly associated with microcephaly in neonates due to infection in pregnant women [4]. SARS-CoV-2, a member of the *Coronaviridae* family, has direct transmission through nasal and mouth secretions, having severe acute respiratory syndrome (SARS), the main and more severe disease-associated symptom [5]. Despite the distinct transmission routes, both infections share similar immunopathological responses, based on the virus entry into the host cells and viral replication using cellular synthetic-secretory machinery for viral dissemination into the host organism [6]. Upon adsorption, viral RNA from either both viruses are recognized by pattern recognition receptors (PPRs) in cells of the immune system. Once in the intracellular space, viral proteins and nucleic acids are synthesized from genetic strands between cell DNA, which leads the cell to produce viral components and, in turn, releasing many virions capable to infect other cells. [7].

Based on this information, this work aims to review the pathogenic characteristics associated with ZIKV and SARS-CoV-2 infections, focusing on neurodegenerative and ophthalmologic lesions. More broadly, we sought to understand the similarity between the pathogenesis of these microorganisms to target and install the central nervous system (CNS), as well as understand the molecular mechanisms that both viruses use to infect nerve cells, capable to cause low and high complexity neurological damage.

2. ZIKA VIRUS

The first findings about ZIKV infection date from 1952 in Uganda, when ZIKV spread to most parts of the African and Asian continents. However, the attention of health organizations turned to the epidemic outbreak of Congenital Zika Virus Syndrome (CZS) in the Americas in 2015, where newborns and fetuses with microcephaly were recorded in large numbers in Brazil, after the infection of pregnant women with the virus [8]. The importance and increase in the number of cases with this congenital defect made the World Health Organization (WHO) declare International Public Health Emergency in February 2016 [9]. Even with efforts to combat the disease, there is no vaccine to prevent ZIKV infection, and the most recommended way to prevent the disease is to control the transmitting mosquitoes [10]. Even after the outbreak of CZS and efforts to control it throughout the national territory, suspected and confirmed cases of the disease are still reported annually in several states, as recently published in the epidemiological bulletin in Brazil, between 2015 and 2020. In these

years, the number of confirmed cases of CZS was 3,536, where 78.0% (2,778) were newborns with an average of 28 days of life, 15.5% (551) represented children between 7 and 8 months, and 6, 6% (234) were from stillbirths, fetuses, and miscarriages [11]. Even though acute and severe cases occur in a smaller proportion of neonates, who had contact with ZIKV during pregnancy, the bulletin reports a significant number of children who were born alive and who later died, corresponding to 13.8% of them (mean age of 11.4 months).

It is known that ZIKV can present high neurotropism and trigger neuroinflammation with neural cell death as induce apoptosis in a non-cellular autonomous way, triggering cell death of uninfected neurons by the release of cytotoxic and pro-apoptotic factors [12]. ZIKV-infected cells can release high levels of tumor necrosis factor (TNF), interleukin-1β (IL-1β) and glutamate, been associated with N-methyl-D-aspartate receptor (NMDAR) sensitivity, leading to an increased influx of Ca^{2+} (calcium) into the cells, thus promoting greater excitotoxicity, and causing the release of neurotoxins by already infected cells, which may contribute to the death of nearby uninfected neurons [13].

Although ZIKV infection is often associated with microcephaly in neonates, it is believed that the virus has the capacity to cause other serious neurological consequences, such as Guillain-Barré syndrome (GBS), encephalitis and myelitis in adults [14]. Children without microcephaly, born to infected pregnant women, may present dysphagia, motor, auditive and visual impairments. Thus, congenital infection is directly related to ophthalmological complications including macular, bilateral perimacular lesions and, mainly, optic nerve abnormalities. A study with 112 babies born to ZIKV-infected mothers, reported that 24 (21.4%) of them had mild to severe eye/visual abnormalities. Among the 24 babies mentioned, 41.7% (10) did not develop microcephaly, 33.3% (8) had no CNS alterations and 8.3% (2) had ocular alterations despite the maternal infection have already occurred in the third trimester of pregnancy [15].

Studies with experimental models have demonstrated important data corroborating the neurodegenerative damage of ZIKV. In this study, mice were congenitally infected by ZIKV, demonstrating later in their puberty, motor incoordination and visual dysfunctions, with retinal and cerebellar cortex abnormalities as the responsible factor. As a result, it was possible to note that the infected mice retina was thinner and lamination of the cerebellum molecular layer was interrupted, being this histopathologic anomaly indicative of ophthalmological lesions noticed in people regardless of age, such as in those with macular atrophy [16].

In adult humans, ZIKV infection is asymptomatic in 80% of cases and, when symptoms are apparent, they have similar symptoms with other arboviruses, such as fever, myalgia, arthralgia, conjunctival hyperemia, rash, itching and nausea, and, even in the rarest form of the disease, it is possible to find reports of ocular manifestations of the acute phase [17]. From the manuscripts analyzed, the information collected suggests that infection by the Zika virus can trigger neurological damage, including mild to high degree of ophthalmic damage. The most common signs are GBS, encephalitis and myelitis in adults. In a case report of the disease, it was demonstrated in a 38-year-old patient positive for ZIKV, the presence of antibodies against myelin oligodendrocyte glycoprotein (anti-MOG), causing myelitis in the patient, a syndrome responsible for inflammation in the spinal cord [18]. The presence of antibodies anti-MOG after infection by the virus still needs to be widely studied, due to its ability to progressively destroy the myelin sheath of neurons, present in demyelinating diseases of the CNS. It is also known the importance of Müller cells in pathological conditions of neurodegenerative diseases, where they are activated and produce inflammatory cytokines and growth factors that lead to retinal inflammation, vascular leakage, and neuronal degeneration in retinopathies [19].

3. MECHANISM OF INFECTION BY ZIKA VIRUS

ZIKV infection normally has an incubation period between 3-14 days, leading to a high viremia that affects several organs, infecting different cell types. However, cases of patients with GBS point to a prolonged viremia, up to 21 days after infection [20]. ZIKV mainly infects the placenta, testes, and brain. In a study with mice, human and non-human primates, the presence of ZIKV was identified in glial cells, such as microglia and astrocytes, and in ocular tissues, such as the cornea, sensorineural retina, optic nerve, and aqueous humor of the eye anterior chamber, in addition to the presence of macrophages in the retina [21]. During viral transmission, the site receives virions that replicate in tissue macrophages and dendritic cells, which carry the virus to the draining lymph nodes and other lymphoid tissues [22]. After the viremia interval, the virus eventually spreads to monocytes, macrophages or dendritic cells in various tissues, and the assembled virions spread out to infect other tissues [23] (Figure 1).

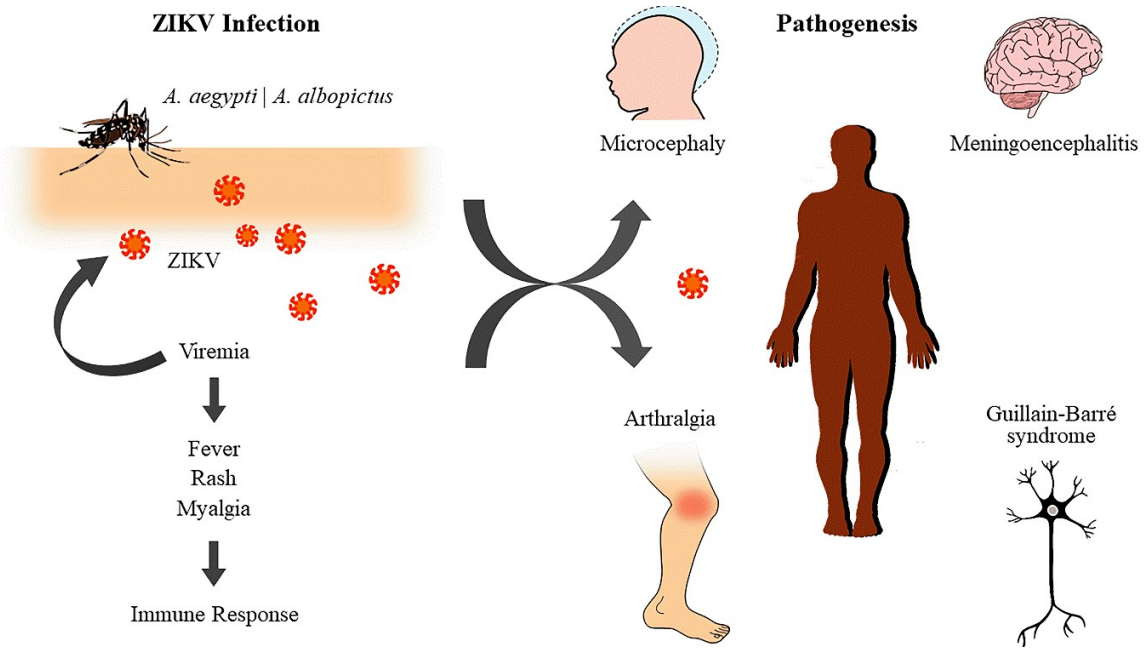

Figure 1. Zika virus (ZIKV) infection and possible damage to the central nervous system (CNS). After a ZIKV vector mosquito bite (female *Aedes aegypti* or *Aedes albopictus*), dermis target cells such as dendritic, endothelial and Langerhans cells are infected, leading to a fast viral replication, in a few days. Viral particles (virions) produced at the virus entry site are transported through the circulatory system to secondary lymphoid organs to then, reach different body organs. During the acute phase of infection, there is an increase in the levels of type I interferons (IFNs), which lead to immunomodulation of pro- and anti-inflammatory cytokines as chemokines, associated with the progress of specific cellular immune responses. This scenario can trigger many pathologic conditions as self-limited meningoencephalitis to congenital disorders such as microcephaly or Guillain-Barré syndrome (GBS).

Zika virus has a positive-sense and single-stranded RNA genome, and its translation generates only one viral polypeptide, which is cleaved by viral proteases, generating three structural proteins (capsid, pre-membrane and envelope) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5), according to their coding sequences. This type of genome allows its proteins to be translated directly by the host cell from the viral RNA, facilitating the multiplication of new viruses in the organism [24].

Through the antigen presentation to the immune system, viral RNA is detected by RIG (RIG-I and MDA5) and Toll (TLR3) type cell receptors, driving the secretion of type I interferons (IFN I-α and β) responsible for inhibiting viral replication and pro-inflammatory cytokines, being efficient in the immune response [25]. The acute phase of ZIKV infection is related to the high release of IFN-I, followed by the release of many other cytokines and chemokines, in addition to the development of specific cellular immune responses, where certain cytokines can be considered fundamental for the pathogenesis of ZIKV. In this context, the production of CXCL10 and IL-10 is directly related to the damage to neurogenesis associated with ZIKV, such as in GBS, causing the recruitment of leukocytes to the inflammatory sites associated with the neurodegeneration process [26].

4. SARS-COV-2

In December 2019, cases of respiratory pneumonia, with symptoms characteristic of severe acute respiratory syndrome, were reported in the city of Wuhan, China. Although similar to other types of SARS, COVID-19 (Corona Virus Disease 2019), as popularly known, arrived as a new viral, infectious disease of easy and rapid transmission, with clinical manifestations such as shortness of breath, tiredness and fever, besides other symptoms still unknown at that time [27].

SARS-CoV-2 was spreading rapidly in most countries around the world, like a pandemic, leading the WHO to declare an international public health emergency, which to date, has done millions of victims due to the main and most serious clinical manifestations of the disease, such as the consequent inability to breathe, due to progressive and sometimes irreversible lung injury [28]. Although these most common symptoms, patient reports and recent clinical case studies have demonstrated an imminent ability of the new coronavirus (SARS-CoV-2) to cause damage to the central and peripheral nervous system (PNS), including those associated to ophthalmological complications [29].

It is known that the disease severely affects, in most cases, people of older age and with comorbidities, such as hypertension, diabetes, obesity, heart/lung diseases and those in immunosuppressive therapies, due to the immunological changes that occur during these events. However, the latest findings indicate that the presence of the virus and its possible damage and sequelae to the human body are not restricted to this group [30, 31].

Since the first months of the pandemic, many labs and research institutes have worked hardly trying to unravel the viral characteristics and viral spread [32]. Recent findings show that SARS-CoV-2 is a virus composed by one positive RNA segment, allowing it to be translated directly by intracellular structures. Its genome has less than 30,000 nucleotides that encode around 29 identified viral proteins. The main proteins are a) Spike (S) glycoproteins, which allow the entry of the virus into the host cells through binding to the specific cell receptor and fusion with the plasma membrane [33]; b) the nucleocapsid (N) protein, which regulates viral replication and is largely linked to viral pathogenesis, being the most numerous proteins in the coronavirus and quite immunogenic [34].

In the target organs, the virus has the ability to infect cells related to respiration and the transport of oxygen throughout the body. At these sites, an acute inflammatory response is triggered and develops due to the action of resident cells of the immune system and those that migrate to the inflammatory site. Spike proteins bind to the human angiotensin-converting enzyme 2 (hACE2) receptor, largely found in type II pneumocytes, triggering a negative regulation of this receptor, leading to greater production of angiotensin-2 (AT2) and increasing potentiates vascular permeability in the lungs, causing serious pulmonary injury. SARS-CoV-2 can bind to host dendritic cells activating macrophages, which leads to a severe immune response, represented by a

high release of pro-inflammatory cytokines and chemokines. Such inflammatory mediators most potentially damage the cellular membrane of epithelial cells, falling into the blood circulation, and causing damage to other organs [35].

SARS-CoV-2 is also responsible for raising the levels of inflammatory cytokines and chemokines, such as interleukins IL-2, IL-6, IL-7, IL-10, interferon-inducible protein 10 (IP-10), IFN-I, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1) and tumor necrosis factor alpha (TNF-α), thus contributing to the worsening of the lesion and disease commitment [36]. Despite most cases are linked to cardiac and pulmonary complications, extra-pulmonary cases, such as those linked to ophthalmic lesions, have been reported in patients infected with SARS-CoV-2, even in those who did not develop serious complications from the disease [37].

Optic neuritis (OIN) is an autoimmune inflammatory disease that affects the optic nerve, usually associated with acute pain in the eye or periorbital pain, affecting rapid vision loss and related to multiple sclerosis (MS), being responsible for causing chronic neuroinflammation and neurodegeneration of CNS myelin [38], while other studies demonstrate that COVID-19 may even be associated with MS exacerbations [39]. OIN has been mentioned in clinical studies of patients after SARS-CoV-2 infection, causing progressive demyelination and swelling of the nerve fibers of the optic nerve due to the systemic activation of T cells, which leads to a local antigen-antibody immune reaction [40]. A case study was reported in which the virus infection generated viral encephalitis causing the death of the patient, thus suggesting that the new coronavirus may have the ability to develop neurological complications [41]. SARS-CoV-2 can also contribute to the aggravation of neurodegenerative outcomes, such as in Parkinson's [42] and Alzheimer's disease [43].

One of the ophthalmological complications recently observed is the ability of the virus to cause conjunctivitis in cases of infection and the potential to develop other significant eye diseases. In one of these studies, a 50-year-old patient positive for SARS-Cov-2 reported pain for 8 days when moving the eyeball, blurred vision, and redness in the right eye. When analyzing his eye clinically, a relative afferent pupillary deformity, central scotoma (dark spot located in the center of the vision field), and impaired vision in terms of color and contrast were found. Additional examinations found mild anterior chamber inflammation and papillary edema, with minor inflammation of the vitreous humor and retina [44].

Another important case report relates to a 44-year-old patient with a positive diagnosis of the SARS-CoV-2 virus, no medical history of pre-existing diseases, and a good evolution in recovery, without need for hospitalization and the absence of drug use as treatment. The study described the condition of the patient, who after two weeks reported eye pain, blurred vision, and vision loss, and from the brain magnetic resonance, it was possible to observe differences between the right optic nerve in relation to the left, such as deformity and increased caliber [45]. These symptoms are characteristic of optic neuritis, considered an inflammatory neuropathy that may be related, even if still poorly studied, to anti-MOG antibodies. This glycoprotein is implicated in the production of myelin, and the presence of this antibody is associated with demyelinating optic neuritis. Anti-MOG is found exclusively in the CNS, and its presence is responsible for demyelinating diseases, both inflammatory and autoimmune [46].

Therefore, it is suggested that the new coronavirus SARS-CoV-2 has great potential to trigger an inflammation process in the optic nerve, being the most cited pathological condition in the literature related to optic neuritis, leading to demyelination of the myelin sheath of the nerve optic, which in turn is immunomodulated [47]. It is known that soon after the first symptoms of SARS-CoV-2 infection, resulting from the presentation of antigens by cells of the immune system, the systemic activation of T cells occurs, thus

triggering the release of cytokines and inflammatory mediators. However, the exact mechanisms of antigenic activation that orchestrate the neurological inflammatory process are still unknown, requiring in-depth studies in order to understand the molecular and cellular processes triggered by the infection [48, 49].

5. MECHANISM OF INFECTION BY SARS-COV-2

The main characteristic of the SARS-CoV-2 infection is the presence of the virus in the airways and lungs in the first days of infection, and the symptoms appear after 5 to 6 days of incubation, commonly evolving with flu-like to other mild symptoms. This incubation time may change depending on the variants found throughout the pandemic – 4 days for the SARS-CoV-2 variant B.1.617.2 (Delta) and approximately 3 days for the SARS-CoV-2 variant B.1.1. 529 (Omicron) [50]. In contrast to mild cases, infection by the virus, which is highly pathogenic, can lead to severe respiratory failure due to the death of epithelial pneumocytes, endothelial cells and resident macrophages. Overall, SARS-CoV infections depend on entry into the host via the respiratory tract, and once this access occurs, airway and alveolar epithelial cells, vascular endothelial cells, and alveolar macrophages become prime targets for viral entry [51].

In addition to the classic pulmonary manifestations of the disease, neurological manifestations have been described in those infected with SARS-CoV-2, indicating the potential ability of the virus to reach and infiltrate the brain, as in the entire CNS, after crossing the blood-brain barrier (BBB) and cause vascular and neuronal damage, also aided by circulating leukocytes recruited through the bloodstream towards the BBB (Figure 2), considering this way the most probable route to SARS-CoV-2 enters in the brain [52].

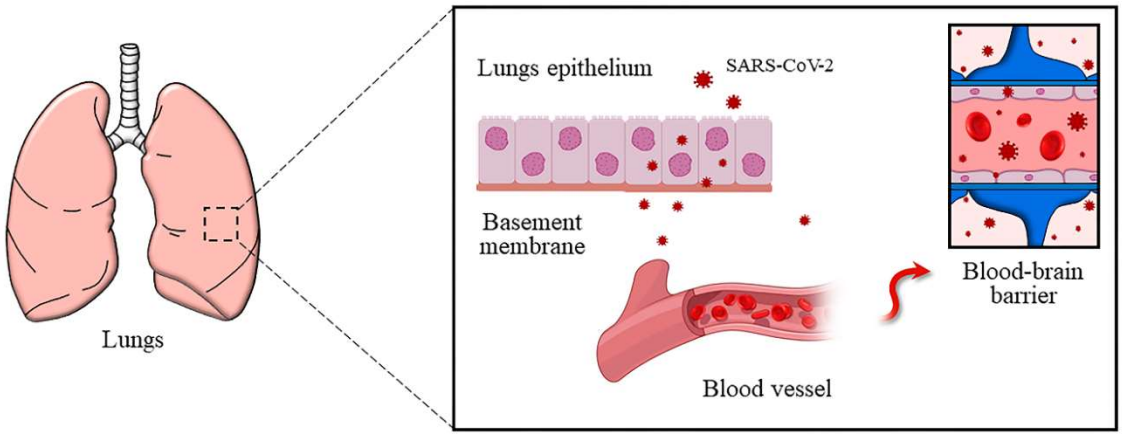

Figure 2. Probable olfactory-hematogenous route for the SARS-CoV-2 neuro-transmission. As the SARS-CoV-2 virus enters into the body through the olfactory tract or pulmonary epithelium, it can gain access to the brain. In the lungs, viruses are normally located on the apical surface of epithelial cells, and sometimes infect the basolateral regions. After crossing the lung epithelium cells wall crosses and the basement membrane, they reach the blood vessel to be transported to the brain through the blood-brain barrier (BBB).

This mechanism facilitates the virus to reach the CNS, since the permeability of the BBB varies according to the degree of inflammation caused by the infection [53]. Also, based on knowledge about the infection of humans with the already known SARS-CoV, studies suggest that the entry of SARS-CoV-2 into the CNS can occur through other routes, such as: a) olfactory-hematogenous, where the virus has access to the brain through the olfactory tract or through the pulmonary epithelium on the apical surface of the epithelial cells, and from these areas, it crosses the basement membrane to reach the blood vessel where it is transported to the brain by crossing the BBB (Figure 2); b) trans-neuronal retrograde dissemination machinery, identified as a possible

route, which the virus infects peripheral nerve terminals to invade the CNS through axonal retrograde transport and synapses [54, 55] (Figure 3).

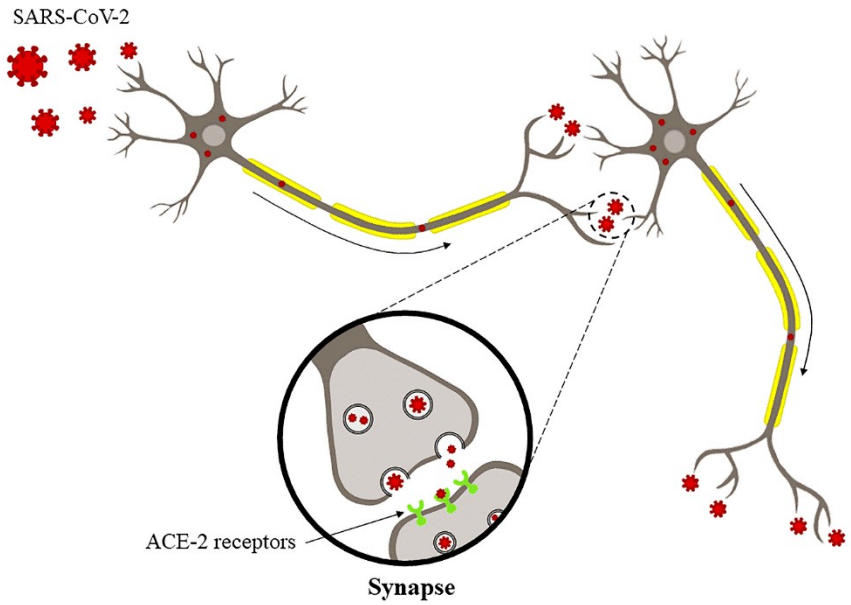

Figure 3. The probable mechanism mediating SARS-CoV-2 neuro-transmission. After the virus infects a peripheral neuron in the trans-neuronal route, it infects other neurons by retrograde transport through axons and consequent synapse with another neuron. The virus targets the presynaptic terminal through the process of exocytosis. Viruses bind to ACE-2 (angiotensin-converting enzyme 2) receptors on the postsynaptic neuron and then, is taken by specific endocytosis mediated by the ACE-2 receptor.

Independently of the access ways, during the SARS-CoV-2 infection, the S virus protein binds directly to the angiotensin-converting enzyme 2 (ACE2) receptor on the host's target cells, a receptor that is most expressed in the lungs, kidneys and intestines, the main target organs of SARS-CoV-2 (Figure 3). The mediator protein S (Spike) has two subdivisions that play a fundamental role in mediating the binding of the virus to the host cell membrane: S1 (N-terminal), responsible for binding the virus to the host cell through the recognition of a specific receptor in its membrane; S2 (C-terminal), which favors the fusion of the viral envelope with the host cell membrane [56]. The recognition of viral antigens leads to a signaling cascade and deregulation of cytokine balance in a systemic way, overloading the body due to this immune response, determined by low levels of type I and III interferons together with high levels of chemokines and IL-6 expression [57]. Due to the increase in pro-inflammatory cytokines and chemokines during the course of infection, COVID-19 may include a broad spectrum of cytokines such as TNF-α, IL-1β, IL-6, granulocyte colony stimulating factor (G- CSF), IP-10, MCP-1 and macrophage inflammatory proteins - 1 alpha (MIP-1α) [58]. Significant production of CXCL10 was also observed in SARS-CoV-2 infection, and it can be considered the chemokine responsible for triggering the cytokine cascade in the body [59].

Supporting this strong evidence, an experimental study carried out prior to the COVID-19 pandemic showed that C57BL/6 mice infected with SARS-CoV showed neural death after infection, confirming the virus is capable to reach the brain, especially through the olfactory bulb, and resulting in rapid trans-neuronal dissemination to all connected areas of the brain, putting the target neurons as cells with high susceptibility to SARS-CoV [60], mechanism evidenced today in studies related to infection by the new coronavirus [61].

6. DISCUSSION

It is known that both infectious diseases, Zika and COVID-19, brought with them major impacts on population health and on public and private healthcare systems. Through the occurrence of many cases in a short period of time, the two infections have risks of aggravation and complications, which lead or not to death, put the infected people to face different situations of health risk, or by the appearance of new symptoms during infection or by long-term permanence of these symptoms, in chronic manifestations of the disease [62, 63] (see Table 1).

Table 1. Reported symptoms of ZIKV and SARS-CoV-2 [40, 64, 65].

Virus	Slight/Moderate	Severe/Critical
ZIKV	Conjunctivitis	Encephalitis
	Fever	Guillain-Barre Syndrome
	Headache	Hematosperm
	Muscle and joint pains	Myelitis
	Rash	Thrombocytopenia
SARS-CoV-2	Anosmia	Acute kidney injury
	Coryza	Breathing difficulty
	Diarrhea	Cardiac failure
	Dry cough	Encephalopathy
	Fever	Optic neuritis
	Sore throat	Pneumonia

Although the symptoms of infection by ZIKV and SARS-CoV-2 have different manifestations, both are responsible for the emergence of pro-inflammatory chemokines and cytokines, overloading the body, and leading to tissue damage and injuries, which develop similar pathologies at the neurological and ophthalmological level in infected patients, such as encephalitis, conjunctivitis, and optic neuritis [66, 67]. The emergence of this hypothesis is due to the recent observation of anti-MOG antibody in ZIKV and SARS-CoV-2 infection, an antibody that is present only in the CNS, and triggers demyelination diseases, both inflammatory and autoimmune, as well as the synthesis of CXCL10, an important chemokine and main candidate to trigger the cytokine cascade in the body.

Both ZIKV and SARS-CoV-2 infections occur when the individual is exposed to the environment, whether by vector insect bite, present in the unsustainable urban environment, or through close contact with people and infected surfaces. Even though most cases of infected people do not evolve to severe cases and deaths (COVID-19 lethality of 2.0% in September 2022 in Brazil) [68] (Zika lethality of less than 0.05% by the year 2019 in Brazil) [69], a data compendium of the two diseases reveal the presence of neurological damage in varying degrees, including ophthalmologic disorders.

7. CONCLUSIONS

Despite each infection be mediated by different ways, recent findings reveal an apparent association between pathogenesis and clinical manifestations, which leads us to propose a conserved cellular and molecular mechanism, responsible for orchestrating the development of neurological and ophthalmic lesions in both infections. Drawing attention is necessary for new research and a greater understanding of these diseases as the relevant socioeconomic impacts that these permanent sequels can bring to patients and to public health.

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