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NEUROINFLAMMATION AND BRAIN FUNCTION: POSSIBLE IMPLICATIONS IN CHILDREN INFECTED WITH COVID-19

COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affects children differently than adults, with milder symptoms. However, several cases of neurological manifestations with neuroinflammatory syndromes, such as multisystem inflammatory syndrome (MIS-C), have been reported following infection. As with other viral infections such as rubella, influenza, and cytomegalovirus, SARS-CoV-2 causes a massive release of pro-inflammatory cytokines that affect microglial function, which can be critical for brain development. Along with viral induction of neuroinflammation, other non-infectious conditions may interact to cause additional inflammation, such as imbalances in fatty acid and polyunsaturated fatty acid diets and alcohol consumption during pregnancy. In addition, transient thyrotoxicosis caused by SARS-CoV-2 has been reported, with secondary autoimmune hypothyroidism that may go unnoticed during pregnancy. Together, these factors may represent an additional risk of infection by influencing neurodevelopmental mechanisms such as synaptic pruning and the formation of neuronal ensembles. In this review, we discuss these conditions to consider and the possible occurrence of neurodevelopmental disorders in children infected with COVID-19.

Keywords: neuroinflammation, children, COVID-19, synapse formation, brain development, nutrition.

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Introduction. COVID-19 is a systemic disease caused by severe acute respiratory syndrome coronavirus 2, which belongs to the betacoronavirus genus [3]. The most common neurological symptoms in response to SARS-CoV-2 infection include: headache, anosmia, impaired consciousness, infectious encephalopathies, and neuroinflammatory syndromes such as acute demyelinating encephalomyelitis [1]. A biomarker study (NfL, intraaxonal marker of neuronal injury; glial fibrillar acidic protein; GFAp, marker of astrocytic activation/damage) also provided evidence of neuronal damage and glial cell activation in patients with COVID-19 [39], strongly suggesting that SARS-CoV-2 has neurotropic activity. In addition, SARS-CoV-2 has been shown to be able to infect human neu-

ral progenitor cells [57]. Like SARS-CoV, SARS-CoV-2 uses the angiotensin-converting enzyme receptor (ACE2) for cell invasion by binding to it via the spike (S) protein [10]. In the central nervous system (CNS), glial cells and neurons express this receptor [19]. It is not yet known which pathway SARS-CoV-2 uses to reach the nervous system, but there are 2 theories. According to the first one, the virus enters the CNS by the hematogenous route, in which it can penetrate into leukocytes and cells of the blood-brain barrier (BBB), or, in the second case, the virus can migrate to the CNS via axonal transport [67].

SARS-CoV-2 infection in children. Children are less likely to develop severe COVID-19, but the main question that causes much controversy is related to the long-term consequences of mild or subclinical infection remains unresolved. In the child's brain, complex neural networks are subject to intensive modernization, which modulates the activity of neurons and immunological complexes of the CNS, such as microglia, cytokines, chemokines, the complement system, and peripheral immune cells [18], which further leads to synaptic pruning (pruning) and the formation functional neuronal ensembles [63]. In pathological conditions, some maternal cytokines and leukocytes cross the placenta and may impair fetal development [28]. In addition, ACE2 expression is intense in the placenta [5], suggesting a possible route for fetal infection with SARS-CoV-2 via vertical transmission [59]. There are now several case reports suggestive of intrauterine infection [49,66], and placental viremia has been confirmed by r-PCR and the presence of inflammatory cells in the cerebrospinal fluid along with neurological manifestations consistent with those described in adult patients [66]. In addition, during maternal infection, fetal microglia can be directly activated by viruses or cytokines and microchimeric maternal cells [28].

Since the beginning of the COVID-19 pandemic, it has been observed that in children, "subclinical infection" is either asymptomatic or mild [6]. Children with subclinical symptoms are potential carriers of the virus, but with a lower rate of infectivity than adult patients with a pronounced clinical picture, as was characteristic of the influenza virus [62]. In addition, children and adolescents with asymptomatic COVID-19 may develop a condition called multisystem inflammatory syndrome (MIS-C), with clinical and laboratory features that are not similar to those seen in Kawasaki disease and toxic shock syndrome [38]. Among the main symptoms associated with general systemic inflammation in blood vessels throughout the body, Kawasaki syndrome can cause a severe acute complication of encephalopathy [31]. The generalized vascular disorder caused by Kawasaki syndrome, as well as the complications that affect the body of a child infected with COVID-19, can also potentially alter the function of the neurovascular block, which plays an important role in brain development, and thereby contribute to an increased risk of late disorders. development of the nervous system. As with COVID-19, severe forms of H1N1 influenza are also characterized by a cytokine storm and multiple organ failure as a result of increased vascular permeability. Wang S. et al. it was theorized that BBB damage is the result of systemic exposure to pro-inflammatory cytokines produced in the lungs [30].

An additional possible complication in the mother's body during COVID-19 infection is associated with the expression of the ACE2 receptor in the thyroid gland, which has one of the highest expression levels of this receptor [20]. It has been described that SARS-CoV-2, like many other viral infections, may be associated with the development of subacute thyroiditis (SAT), which, although a self-limited and generally undiagnosed condition, can subsequently lead to autoimmune hypothyroidism [61]. The development of hypothyroidism in pregnant women deserves special attention, since congenital fetal hypothyroidism is the main cause of non-genetic treatable mental retardation in children [4]. The thyroid hormones thyroxine (T4) and triiodothyronine (T3) are essential for normal brain development [54], and their deficiency is associated with a delay in the development of sensory, motor and cognitive skills [33], reflecting the involvement of the latter in several processes such as neurogenesis, cell differentiation, migration, synaptogenesis and myelination, as well as the mechanisms of synaptic plasticity [13]. In addition, thyroid hormones may influence the development and function of microglia, as it has been demonstrated that hypothyroidism can change microglia morphology to a pro-inflammatory phenotype [52] and microglial function in general [16]. Thus, hypothyroidism secondary to viral invasion and the development of subacute thyroiditis may be a very strong endogenous correlate involved in fetal brain dysfunction.

Neuroinflammation and microglial dysfunction affect brain development and plasticity. Localization of the ACE2 receptor in microglia [62] increases the possibility of its direct activation by SARS-CoV-2, which may increase the risk of late neurodegenerative diseases, as shown for other viral infections [18]. Viruses such as Zika virus (ZIKV), cytomegalovirus, and rubella are able to cross the placental barrier and/or BBB and reach the CNS [37]. In ZIKV infection, along with damage to progenitor cells, an increase in neuroinflammation is observed, which disrupts the physiological role of microglia during brain development [69]. The same is true for other RNA viruses, such as cytomegalovirus [2]. It is possible that these data suggest that the inflammation caused by a viral infection will be more detrimental to the development of the nervous system than the direct cytopathic effect of the virus on neurons.

At the end of the gestational and early early postnatal periods, the homeostatic function of microglia plays an active physiological role in synaptic pruning and neural network formation [35], being highly reactive to its microenvironment. Abnormal microglial responses during synaptic remodeling during critical periods of development can lead to the emergence of inadequate neural networks that increase the risk of developing neurological and psychiatric disorders [46]. Thus, prenatal or perinatal infections can lead to impaired physiological functions of microglia, which is an important risk factor for the late onset of diseases such as schizophrenia, autism spectrum disorder (ASD), and attention deficit/hyperactivity disorder (ADHD) [18].

Viral infections affecting the brain induce the phagocytic activity of microglia, which is involved in the elimination of pathogens and cellular debris [14]. Microglia can also promote neurogenesis and induce neurotoxicity through the release of oxidants, which in turn can activate inflammation [40]. A triggering receptor expressed on myeloid cells 2 appears to be required for microglia-mediated synaptic pruning during brain development [63]. In a mouse model of coronavirus infection, it was shown that the microglia-associated triggering receptor expressed on myeloid cells 2 and DAP12 (12 kDa DNA activating protein) were among the most highly expressed genes [8]. Taken together, these studies suggest that microglial function is modulated by viral infections during development and may be associated with long-term complications in children infected with COVID-19.

The formation of microglia can also be influenced by T-lymphocytes involved in

its various functions at the early stages of development [36]. Indeed, the population of T cells that act as “catchers” in the CNS, localized both in the brain parenchyma and in the choroid plexus and meninges, are associated with the maintenance of functional neuroplasticity in a healthy brain. These T cells can also stimulate peripheral immune cells through a complex signaling pathway with the choroid plexus, releasing IFN-Y [27], and promoting plasticity through the release of IL-4 [51]. However, the “cytokine storm” mechanism in the pathogenesis of SARS-CoV-2 infection can disrupt the normal cytokine-mediated cross-pooling in the choroid plexus, when IFN-Y, together with IL-6, is one of the main active molecules of the pro-inflammatory profile. Also, a group of scientists found high levels of IL-6 and INF-Y in the CNS of K18-hACE2 transgenic mice infected with SARS-CoV [58].

Dietary modulation of neuroinflammation. Localization of the ACE2 receptor in microglia [62] increases the possibility of its direct activation by SARS-CoV-2, which may increase the risk of late neurodegenerative diseases, as shown for other viral infections [18]. Viruses such as Zika virus (ZIKV), cytomegalovirus, and rubella are able to cross the placental barrier and/or BBB and reach the CNS [37]. In ZIKV infection, along with damage to progenitor cells, an increase in neuroinflammation is observed, which disrupts the physiological role of microglia during brain development [69]. The same is true for other RNA viruses, such as cytomegalovirus [2]. It is possible that these data suggest that the inflammation caused by a viral infection will be more detrimental to the development of the nervous system than the direct cytopathic effect of the virus on neurons.

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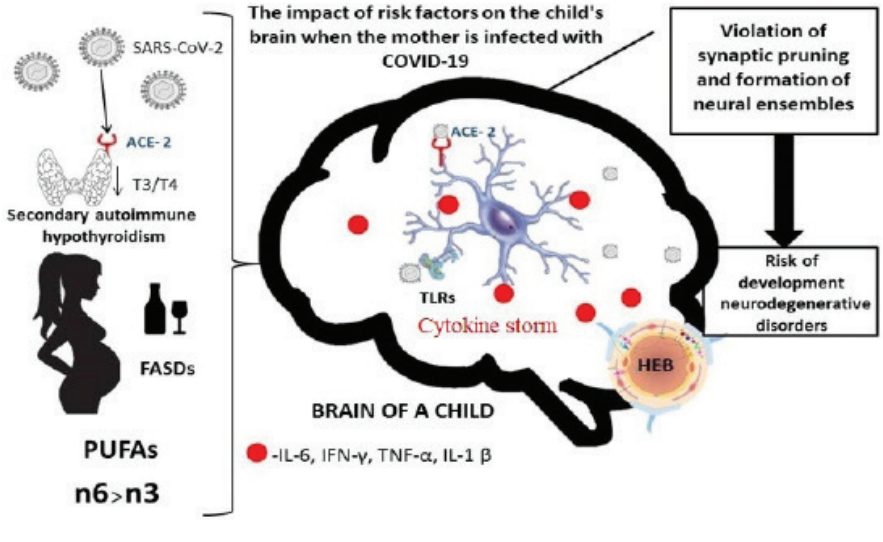
Relationship between maternal alcohol use during pregnancy and neuroinflammation in COVID-19. Fetal alcohol spectrum disorders include several pathologies and side effects associated with alcohol use by pregnant women [11]. Some of the neurocognitive impairments seen in alcohol spectrum disorders include: memory or visuospatial decline, low behavioral self-control, rapid mood changes, impulsive behavior, loss of adaptive functions such as speech and communication, poor social interaction, and movement disorders [68]. Alcohol can interfere with the development of the fetal nervous system through changes in a number of events such as neurogenesis, gliogenesis, myelination, and impaired development of functional neural networks [34]. Thus, the teratogenic effects of ethanol during pregnancy are considered as a risk factor for the development of brain anomalies [25], and there is a strong correlation between alcohol use during pregnancy and ADHD and ASD [45, 44].

Ethanol-induced brain malformations are often associated with microglial activation via toll-like type 4 receptor (TLR4) [65] and release of pro-inflammatory cytokines and chemokines [29]. TLR4 activation can induce inflammation through a MyD88-dependent signaling pathway



Infectious and noninfectious factors alter the microglial function and contribute to developmental brain disorders. SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2; FASDs- fetal alcohol spectrum disorder; HEB - hematoencephalic barrier; PUFAs - polyunsaturated fatty acids; ACE2 - angiotensin-converting enzyme 2; IL-6 - interleukin 6; IFNY - interferon gamma; TNFa - tumor necrosis factor alpha; IL1ß - interleukin 1 beta.

that interacts with nuclear factor kappa-bi (NF-kB) [17]. In addition, maternal alcohol consumption during pregnancy contributes to the development of newborn infections [32], reducing the immune response to the fight against viral and bacterial infections [7] with impaired adaptive immunity and altered B-cell responses, leading to an increase in the severity of viral infections [23]. It has recently been reported that SARS-CoV-2 also interacts with TLR receptors that induce pro-inflammatory cytokines [55]. Thus, SARS in COVID-19 and alcohol use during pregnancy may interact in converging inflammatory pathways. A generalized scheme of the impact of risk factors on the brain of a child when a mother becomes infected with COVID-19 is shown in Figure.

Clinical presentation in children with MIS-C temporally associated with SARS-CoV-2. In a retrospective study, which took place in the UK at the Great Ormond Street Hospital [48], scientists selected 58 case histories of children (mean age, 9 years [interquartile interval {IQR}, 5.7-14]; 33 girls [57%]) that met MIS-C criteria. PCR tests for SARS-CoV-2 were positive in 15 of 58 patients (26%), and IgG test results were positive in 40 of 46 (87%). A total of 45 of 58 patients (78%) had evidence of current or previous SARS-CoV-2 infection. All children had fever and nonspecific symptoms, including vomiting (26/58 [45%]), abdominal pain (31/58 [53%]), and diarrhea (30/58 [52%]). Rash was present in 30 of 58 (52%) cases and conjunctival injection was present in 26 of 58 (45%) cases. Laboratory evaluation indicated a marked inflammatory response, such as C-reactive protein (229 mg/L [IQR, 156-338] estimated in 58 of 58) and ferritin (610 μg/L [IQR, 359-1280] estimated in 53 out of 58). Of the 58 children, 29 developed shock (with biochemical signs of myocardial dysfunction) and required inotropic support and hospitalization in the intensive care unit. Of those admitted to the ICU, 23 of 29 [79%] received mechanical ventilation. Eight patients (14%) developed dilatation or aneurysm of the coronary arteries. Comparison of PIMS-TS with Kawasaki syndrome and toxic shock syndrome showed differences in clinical and laboratory characteristics, including older age (mean age, 9 years [IQR, 5.7–14] vs. 2.7 years [IQR, 1.4– 4.7] and 3.8 years [IQR, 0.2-18] respectively) and greater elevations in inflammatory markers such as C-reactive protein (median, 229 mg/L [IQR 156-338] vs 67 mg/L [IQR, 40-150 mg/L] and 193 mg/L [IQR, 83-237], respectively).

Conclusion. Since the onset of the COVID-19 outbreak, children have remained less susceptible to infection in most cases with subclinical manifestations and a mild course. Despite reports of MIS-C syndrome, parents and pediatricians are not fully aware of the possible long-term effects of inflammation on brain development and possible interactions between viral infections and non-infectious conditions such as nutritional imbalances of FAs and PUFAs and alcohol consumption during pregnancy. Transient thyroiditis caused by SARS-CoV-2 has also been reported, which can lead to autoimmune hypothyroidism. In the present review, we hypothesize that these conditions may interact to cause an increase in neuroinflammation, which may alter the physiological role of microglia by influencing the mechanisms of synaptic pruning and neural circuit formation that occur from 2 years of age through adolescence. Thus, it should be noted that autoimmune hypothyroidism, malnutrition, and maternal alcohol consumption during pregnancy may be considered risk factors in children infected with COVID-19, who may be more susceptible to neurodevelopmental disorders such as schizophrenia, autism, ADHD and cognitive impairment. Therefore, attention should be paid to possible interactions between risk factors that can lead to long-term brain developmental abnormalities and occur in the next few years. Therefore, careful monitoring of children exposed to SARS-CoV-2 or born to infected mothers is strongly recommended, and future studies that could identify additional risk factors are highly recommended.

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THE ROLE OF MELATONIN IN DISORDERS OF THE PSYCHO-EMOTIONAL SPHERE

An analysis of the works of domestic and foreign literature devoted to the study of the effect of melatonin on the psycho-emotional state of the organism was carried out. According to most researchers, the trend towards an increase in the prevalence of depressive disorders continues. Currently, there is a search for new approaches in the treatment of depression. The relationship between melatonin and the occurrence of depressive disorders requires further study.

Keywords: melatonin, depression, circadian rhythm, neuroinflammation, nervous system, chronotype.

Introduction. According to the World Health Organization (WHO), the June 2022 World Mental Health Report noted that 1 billion people in the world suffer from mental disorders, including 15% of working age. During the coronavirus pandemic, the prevalence of depression increased by 25%. Depression remains a major problem in the modern world. Despite research on depressive disorders and their treatment with antidepressants, about 80% of inpatients with depression and 70% of outpatients complain of sleep disturbances. Currently, there are several available hypotheses for the occurrence of depressive disorders. Among them are neurotransmitter dysfunction hypotheses and chronobiological concepts, i.e. altered circadian rhythms mediated by melatonin. Melatonin is a universal biological regulator of vital rhythms for all living organisms, as evidenced by its secretion in all animals, starting with unicellular [1,2].

The history of the discovery of melatonin (MT) is associated with the name of Aaron Lerner, a professor of dermatology at Yale University, who studied the nature of vitiligo. Having reviewed the publication of C. McCord and F. Allen (1917), who found that the use of an extract of the pineal glands of cows led to a lightening of the cover of tadpoles by compressing the dark epidermal melanophores. Professor A. Lerner came to the conclusion that a substance responsible for pigmentation and destruction of pigments is formed in the pineal gland, and thought that this substance would help in the treatment of skin diseases. In the early 1950s a group of scientists led by Lerner succeeded in isolating an extract from cow pineal glands that brightens the skin of frogs. The experiment was delayed, so it was decided to complete work on it, but shortly before the end of the term, scientists managed to isolate and determine the structure of the main substance - it turned out to be N-acetyl-5-methoxytryptamine, which was named melatonin. The resulting discovery was described by Lerner in an article published in 1958 in the Journal of the American Chemical Society [17].

Melatonin performs important antioxidant and chronobiotic functions for the body, but also affects carbohydrate metabolism, secretion of insulin, leptin, adiponectin, adipocyte proliferation, and eating behavior. The mechanism of action of melatonin lies in its amphiphilicity, which allows it to penetrate through cell and nuclear membranes and directly interact with intracellular organelles. The antioxidant function of MT can be distinguished, and it consists in the inhibition of the formation of hydroxyl radicals, the protection of lipids, proteins and DNA, and cellular apoptosis. Melatonin also has the ability to limit oxidative stress and regulate energy metabolism. Including body weight, insulin sensitivity and glucose tolerance. The effects of MT are realized at the stages of energy consumption (nutrition), redistribution of energy reserves and energy consumption. Synchronization of human eating behavior with metabolic processes also occurs with the participation of melatonin.

It has been found that melatonin is synthesized in the human body in the cells of the bone marrow, intestines, on the skin and in the retina of the eye. According to the first assumptions, melatonin was considered a hormone involved in the regulation of circadian rhythm mechanisms in living beings, but later it was found that, in addition to this hormonal function, MT is involved in the regulation of seasonal and lunar cycles in animals and humans. The level of melatonin in human blood fluctuates during the day: during daylight hours

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