

Neuroinflammation and Brain Development: Possible Risk Factors in COVID-19-Infected Children

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Keywords

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Abstract

COVID-19, a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) betacoronavirus, affects children in a different way than it does in adults, with milder symptoms. However, several cases of neurological symptoms with neuroinflammatory syndromes, such as the multisystem inflammatory syndrome (MIS-C), following mild cases, have been reported. As with other viral infections, such as rubella, influenza, and cytomegalovirus, SARS-CoV-2 induces a surge of proinflammatory cytokines that affect microglial function, which can be harmful to brain development. Along with the viral induction of neuroinflammation, other noninfectious conditions may interact to produce additional inflammation, such as the nutritional imbalance of

fatty acids and polyunsaturated fatty acids and alcohol consumption during pregnancy. Additionally, transient thyrotoxicosis induced by SARS-CoV-2 with secondary autoimmune hypothyroidism has been reported, which could go undetected during pregnancy. Together, those factors may pose additional risk factors for SARS-CoV-2 infection impacting mechanisms of neural development such as synaptic pruning and neural circuitry formation. The present review discusses those conditions in the perspective of the understanding of risk factors that should be considered and the possible emergence of neurodevelopmental disorders in COVID-19-infected children.

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Introduction

COVID-19 is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that belongs to the same betacoronavirus strain of SARS-

CoV and MERS-CoV viruses, and their similarities may be helpful for a better understanding of this new disease and the implications on brain inflammation [1]. In addition to the most common symptoms, neurological manifestations in response to SARS-CoV-2 infection include headache, anosmia, disturbances of consciousness, infectious encephalopathies, and neuroinflammatory syndromes, such as the acute demyelinating encephalomyelitis [2]. A study with biomarkers also provided evidence of neuronal injury and glial activation in patients with COVID-19 [3], strongly suggesting that SARS-CoV-2 has a neurotropic activity. Furthermore, it has been shown that SARS-CoV-2 is able to infect human neural progenitor cells [4]. Like SARS-CoV, SARS-CoV-2 uses the ACE2 receptor, human angiotensin converter 2, for cellular invasion, binding to it through its spike (S) protein [5]. In the central nervous system (CNS), glial cells and neurons express this receptor [6]. It is not yet known for sure which pathway SARS-CoV-2 uses to reach the nervous system, but two pathways already known as routes of entry for other viruses are considered: the hematogenic pathway, in which the virus could infect leukocytes and blood-brain barrier (BBB) cells, or alternatively, the virus could infect peripheral neurons reaching the brain through axonal transport [7].

SARS-CoV-2 Infections in Children

Although children are less susceptible to severe COVID-19, a remaining question that is under debate is related to the long-term impact of mild or subclinical SARS-CoV-2 infection in the developing brain, where complex neural networks are undergoing an intense remodeling process modulated by neural activity and immunological components of the CNS, such as microglia, cytokines, chemokines, the complement system, and peripheral immune cells (reviewed in [8]), that results in synaptic pruning and formation of functional neural circuitry [9]. Indeed, in pathological conditions, several cytokines and maternal leukocytes cross the placenta and can be harmful to fetal development [10]. In addition, ACE2 is also well distributed in the placenta [11], which suggests a possible SARS-CoV-2 route of fetal infection by means of vertical transmission [12]. Currently, there are a few case reports that demonstrate in utero infection [13, 14], and placental viremia was demonstrated by RT-PCR and the presence of inflammatory cells in cerebrospinal fluid, together with neurological manifestations, consistent with those described in adult patients [14]. Furthermore, during maternal infection, fetal microglia can be directly activated by viruses or can

be indirectly activated by cytokines and microchimeric maternal cells [10].

Since the beginning of the COVID-19 outbreak, it has been noticed that children present the “subclinical infection” either asymptomatic or paucisymptomatic [15]. Children with subclinical symptoms are still potential viral transmitters, probably at lower rates than fully symptomatic individuals, as it has been shown for the influenza virus [16]. Furthermore, children and adolescents with COVID-19, usually asymptomatic, can develop a condition called multisystem inflammatory syndrome (MIS-C) with clinical and laboratory features that overlap those observed in Kawasaki disease and toxic shock syndrome [17]. Among the main symptoms related to the general inflammation in blood vessels throughout the body, Kawasaki syndrome can cause a severe acute encephalopathy complication [18]. The generalized vascular impairment induced by the Kawasaki syndrome, like the complications that affect COVID-19-positive children, can also potentially change the neurovascular unit function, compromising its role in brain development and contributing to the increased risk for late-onset neurodevelopmental disorders. As observed in SARS-CoV-2 infection, the severe forms of influenza H1N1 are also characterized by a cytokine storm and multiorgan failure due to vascular hyperpermeability. It has been suggested that damage to the BBB results from systemic effects of proinflammatory cytokines produced in the lungs [19].

An additional possible complication of maternal SARS-CoV-2 infection is related to the expression of ACE2 receptor in the thyroid, which has one of the highest levels of this receptor [20]. It has been described that SARS-CoV-2, like many other viral infections, may be linked to subacute thyroiditis (SAT) that, although self-limited and usually an underdiagnosed condition, may result in autoimmune hypothyroidism later on [21]. The induction of hypothyroidism in pregnant women deserves special attention since congenital hypothyroidism is the main cause of nongenetic treatable mental retardation in children [22]. Thyroid hormones (TH) thyroxine (T4) and 3,5,30-tri-iodo-L-thyronine (T3) are essential for normal brain development [23] and their deficiency is associated with a delay in the development of sensory, motor, and cognitive skills [24], reflecting the involvement of TH in several processes, such as neurogenesis, cell differentiation, migration, synaptogenesis, and myelination, and brain mechanisms of synaptic plasticity [25]. Furthermore, TH can influence microglial development and function since it has been demonstrated that hypothyroidism may change microglial morphology to a

proinflammatory phenotype [26] and microglial function [27]. Thus, hypothyroidism secondary to a viral induction of SAT might be highly harmful to brain development.

Neuroinflammation and Microglial Dysfunction Affect Brain Development and Plasticity

The presence of ACE2 receptor in microglia [28] raises the possibility of direct microglia activation by SARS-CoV-2, which could increase the risk for late-onset neurodevelopmental diseases as demonstrated for other viral infections [8]. Viruses such as ZIKV, cytomegalovirus, and rubella are classically described as a great risk for brain development due to their potential to cross the placental barrier and/or BBB and reach the CNS [29]. In the ZIKV infection, along with lesions to progenitor cells, the induction of neuroinflammation was observed, disrupting the physiological role of microglia during brain development [30]. The same was observed with other RNA viruses, such as cytomegalovirus [31], suggesting that inflammation induced by viral infection would be more harmful to neurodevelopment than the direct cytopathic effect of the virus on infected cells.

At the end of the gestational period and during early postnatal development, homeostatic microglia has an active physiological role in synaptic pruning and neural network formation [32], being very reactive to the microenvironmental context. An abnormal microglial performance on synaptic remodeling and stabilization during critical periods of development may result in the emergence of inappropriate neural networks, which increase the risk for neurodevelopmental and psychiatric disorders [33]. Therefore, prenatal or perinatal infections can cause a detour upon microglial physiological functions representing an important environmental risk factor for the late onset of diseases such as schizophrenia, autistic spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) (reviewed in [8]).

Viral infections that affect the brain induce phagocytic microglia that act in pathogens and cellular debris elimination [34]. Microglia can also promote neurogenesis and induce neurotoxicity through the release of oxidants, which in turn can activate an inflammasome [35]. The triggering receptor expressed on myeloid cells 2 seems to be essential for microglia-mediated synaptic pruning during brain development [9]. In a model of murine coronavirus, it has been shown that microglia-related triggering receptor expressed on myeloid cells 2 and DAP12 were among the most highly expressed genes [36]. Together, those studies suggest that microglial func-

tion is modulated by viral infections during development and can be implicated in long-term complications in COVID-19-infected children.

Microglial maturation can also be influenced by T lymphocytes, involved in different microglial functions in the early stages of development (Pascuito et al. [37], 2020). Indeed, a population of T cells that act as “gatekeepers” of the CNS located both in the cerebral parenchyma and in a specific niche such as the choroid plexus and meninges has already been associated with the maintenance of functional neuroplasticity in the healthy brain. These cells can also recruit peripheral immune cells through the composite interface with the choroid plexus, by the release of IFN- γ [38], and promote plasticity through IL-4 release [39]. However, the “cytokine storm” mechanism of SARS-CoV-2 pathogeny can unbalance the normal cytokine-mediated cross-talk in the choroid plexus, once IFN- γ , together with IL-6, is one of the main actors of COVID-19 proinflammatory response. Accordingly, high levels of IL-6 and INF- γ were also found in the CNS of K18-hACE2-transgenic mice infected by SARS-CoV [40].

Dietary Modulation of Neuroinflammation

The role of nutrition as an environmental factor in the control of immune system development, homeostasis, and host resistance to infections is well documented [41]. Excessive consumption of processed foods, high in sugar and saturated fats, is one of the main triggers to the burden of noncommunicable chronic diseases, such as obesity and type 2 diabetes, which are highly increasing in the infant population. These lifestyle-related diseases characterized by chronic low-grade inflammation due to the recruitment and infiltration of macrophages in adipose tissue, activation of inflammatory pathways, and dysregulation of glucose signaling, generate an impaired redox signaling with increased production of proinflammatory cytokines [42]. The state of low-grade chronic inflammation that is characteristic of noncommunicable chronic diseases generates a greater risk for the development of hyperinflammation and worsening of SARS-CoV-2, and there is a growing body of evidence that highlight the impact of immunonutrition in the prevention and/or management of inflammatory status, with a special focus on coronavirus cytokine storm [43, 44].

Furthermore, it has been shown that a dietary imbalance between *n*-3 and *n*-6 polyunsaturated fatty acids (PUFAs) and an overall reduction in DHA content are frequently observed in modern western diets, which may result in abnormal development of brain neural circuits

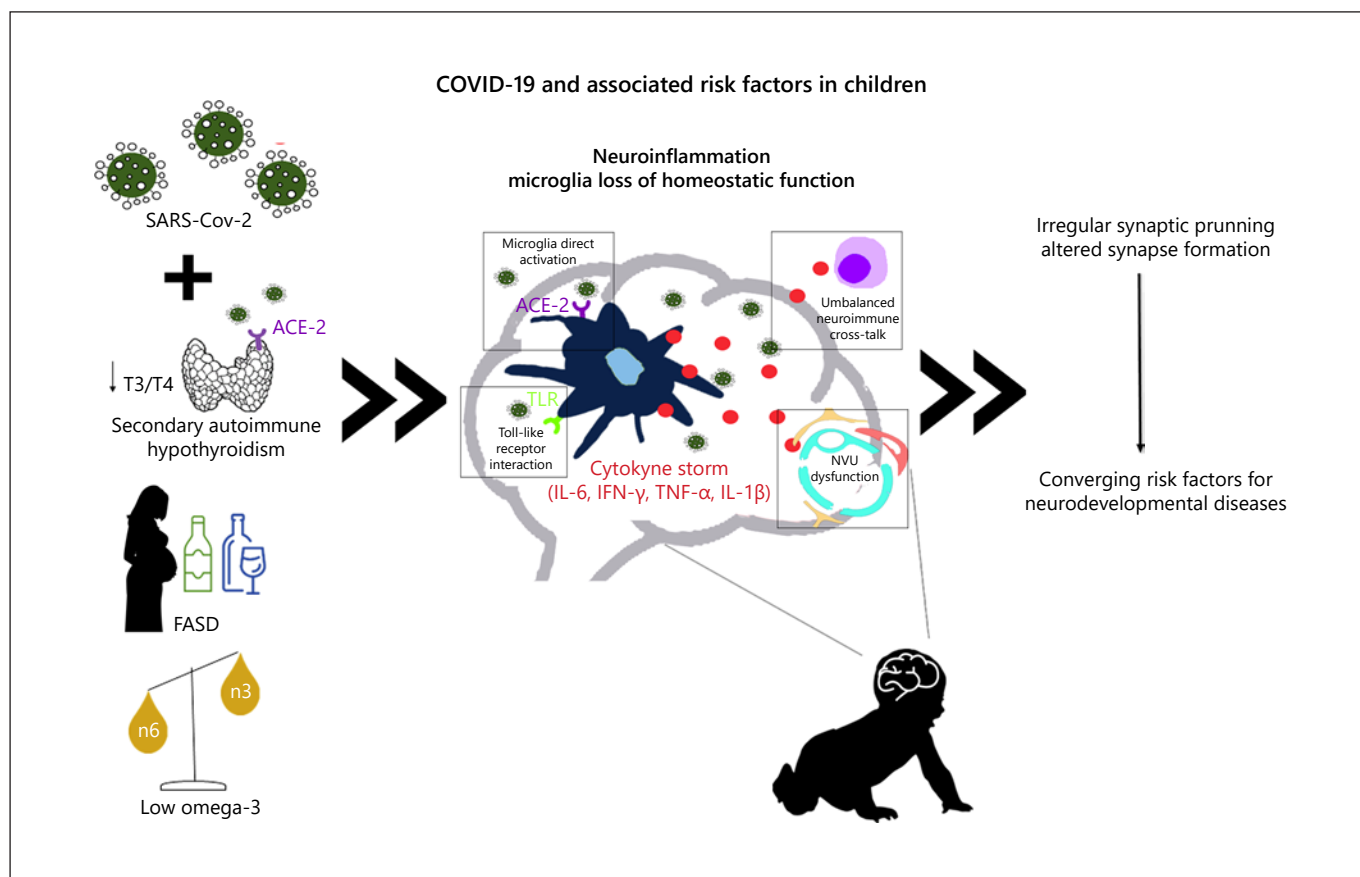


Fig. 1. Infectious and noninfectious factors alter the microglial function and contribute to developmental brain disorders. In children, SARS-CoV-2 produces either a cytokine storm and MIS-C or mild inflammation. Other environmental factors such as a low omega-3 intake may deplete DHA levels and contribute to a neuroinflammatory outcome. Also, maternal alcohol consumption may be associated with neuroinflammation and deficits in brain

development. Together, those risk factors may pose a threat to brain development, which is sensible to microglial dysfunction. SARS-CoV-2 may also induce secondary hypothyroidism that may compromise brain development. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MIS-C, multisystem inflammatory syndrome; NVU, neurovascular unit; FASD, fetal alcohol spectrum disorder.

(reviewed in [45]). A n -3/ n -6 imbalance results in reduced conversion of n -3 fatty acids (FAs) to DHA, and it has been shown that deficits in DHA concentration during early brain development may be associated with an increased risk of developing psychiatric disorders, such as schizophrenia, ASD, and ADHD [46, 47], which may be related to the influence of PUFAs on microglial activity [48]. Indeed, DHA is able to change microglial polarization for the M2, anti-inflammatory phenotype [49] and DHA deficiency during pregnancy and lactation changes the microglial phenotype and motility in the brain, leading to a more reactive microglial profile [50]. Such events define the microglial activation, leading to the release of proinflammatory cytokines [51]. Therefore, PUFA-derived proinflammatory signals may lead

to severe disturbances in the microglial activity, specifically during critical periods of brain development, interfering with synapse formation and maturation with resulting deleterious effects on the development of fully functional neural networks [8]. Indeed, a proinflammatory microglial profile was observed in omega-3/DHA nutritional restriction protocols during brain development and has been associated with delayed synaptic elimination and abnormal plasticity in the rat visual system [45, 52].

Specialized pro-resolution mediators (SPMs) derived from PUFAs could drive inflammatory resolution pathways and omega-3-derived SPMs, such as neuroprotectins and maresins that protect the brain and retina from oxidative stress and viral infections during early brain de-

velopment [53, 54]. Therefore, in the context of the SARS-CoV-2 outbreak, it has been proposed that the supplementation of n-3 PUFAs may be beneficial in reducing proinflammatory mediators such as TNF- α and IL-6, in addition to mediating membrane lipid rafts, where ACE2 receptors are anchored, suggesting the role of omega-3 PUFAs as possible therapeutic adjuvants during COVID-19 infections [55]. Thus, it should be noted that the nutritional status of essential FAs should be carefully evaluated during the critical period of brain development in children up to the age of 7 years old in order to reduce the risk of multiple factors converging to a surge of proinflammatory cytokines under pandemic conditions such as SARS-CoV-2.

Alcohol, Immune Response, Inflammation, and Brain Development

Fetal alcohol spectrum disorders comprise several pathologies and adverse effects associated with alcohol intake by pregnant women [56]. Some of the neurocognitive impairments observed in alcohol spectrum disorder are reduced memory or visuospatial capacity, low behavioral self-control, rapid mood changes, impulsive behavior, loss of adaptive functions such as language and communication, poor social interaction, and difficulty in motor skills [57]. Alcohol can disrupt neural development through alterations in a series of events, such as neurogenesis, gliogenesis, myelination, and impairment in functional neural circuitry development by use-dependent synaptic plasticity [58]. Thus, the teratogenic effects of ethanol during pregnancy are considered as a risk factor for developmental brain abnormalities [59], and there is a close correlation between alcohol use during pregnancy and ADHD and ASD [60, 61].

Ethanol-induced brain malformations are often associated with the activation of microglia through TLR4 [62] and the release of proinflammatory cytokines and chemokines [63]. TLR4 activation can induce inflammation by the MyD88-dependent signal pathway that interacts with NF κ B [64]. Furthermore, maternal alcohol consumption during pregnancy favors newborn infections [65], reducing the immune response to fight viral and bacterial infections [66] with impaired adaptive immunity and altered B-cell responses resulting in increased severity of viral infections [67]. Curiously, it has been recently reported that SARS-CoV-2 also interacts with TLR receptors inducing proinflammatory cytokines [68]. Thus, SARS-CoV-2 and alcohol consumption during pregnancy may interact in converging inflammatory pathways.

Conclusion

Since the beginning of the COVID-19 outbreak, children have been considered less susceptible to complications, presenting, in most cases, subclinical manifestations and mild symptoms. Despite the reports of MIS-C syndrome, parents and pediatricians are not fully aware of possible long-term effects of inflammation on brain development and possible interactions between viral infections and noninfectious conditions such as the nutritional imbalance of FAs and PUFAs and alcohol consumption during pregnancy. A SARS-CoV-2-induced transient thyroiditis which can lead to autoimmune hypothyroidism has also been reported. All those conditions have already been associated with pathological brain development. In the present review, we suggest that those conditions may interact to produce increased neuroinflammation, which may change the physiological role of microglia, impacting mechanisms of synaptic pruning and neural circuitry formation that takes place from the age of 2 until adolescence (Fig. 1). Thus, it should be noted that autoimmune hypothyroidism, malnutrition, and maternal alcohol intake during pregnancy may be considered as risk factors in COVID-19-infected children, which could be more susceptible to neurodevelopmental disorders such as schizophrenia, autism, ADHD, and cognitive impairment. In this way, attention should be paid to possible interactions between risk factors, which may result in long-term abnormal brain development that may arise in the next few years. Thus, a close monitoring and early intervention of children exposed to SARS-CoV-2, or born to infected mothers and future studies that could detect additional risk factors would be highly recommended.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

L.S.C. and C.A.S. conceived and designed the study idea. L.S.C., P.C.S., P.C.V., N.C.A.R.R., H.M., A.L.B., L.B.A.M., J.H.F., and

C.A.S. managed literature search, wrote the manuscript, and critically reviewed the manuscript. L.S.C., P.C.S., L.B.A.M., and C.A.S. designed the figure. All authors contributed to and have approved the final manuscript.

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