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Impact of SARS-CoV-2 infection during pregnancy on postnatal brain development: The potential role of glial cells

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Abstract: Glial cells are crucial for maintaining central nervous system (CNS) homeostasis. They actively participate in immune responses, as well as form functional barriers, such as blood-brain barrier (BBB), which restrict the entry of pathogens and inflammatory mediators into the CNS. In general, viral infections during the gestational period can alter the embryonic and fetal environment, and the related inflammatory response may affect neurodevelopment and lead to behavioral dysfunction during later stage of life, as highlighted by our group for Zika virus infection. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induces a cytokine storm and, during pregnancy, may be related to a more severe form of the coronavirus disease-19 (COVID-19) and also to higher preterm birth rates. SARS-CoV-2 can also affect the CNS by inducing neurochemical remodeling in neural cells, which can compromise neuronal plasticity and synaptic function. However, the impact of SARS-CoV-2 infection during pregnancy on postnatal CNS, including brain development during childhood and adulthood, remains undetermined. Our group has recently highlighted the impact of COVID-19 on the expression of molecular markers associated with neuropsychiatric disorders, which are strongly related to the inflammatory response. Thus, based on these relationships, we discussed the impact of SARS-CoV-2 infection either during pregnancy or in critical periods of neurodevelopment as a risk factor for neurological consequences in the offspring later in life, focusing on the potential role of glial cells. Thus, it is important to consider future and long-term public health concerns associated with SARS-CoV-2 infection during pregnancy.

Introduction

New public health concerns have been raised by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in pregnant women, which may be related to the development of a more severe form of the coronavirus disease-19 (COVID-19), gestational complications, and higher preterm birth rates (Beys-da-Silva *et al.*, 2020; Celewicz *et al.*, 2021; Karasek *et al.*, 2021). However, the impact of COVID-19 during pregnancy on postnatal development, particularly development of the central nervous system (CNS), including during childhood and adulthood, remains undetermined. In general, viral infections during the gestational period can alter the embryonic and fetal environment, and the related inflammatory response may affect neurodevelopment and lead to subsequent behavioral dysfunctions (Zimmer *et al.*, 2021). While relevant evidence has suggested vertical transmission of SARS-CoV-2 infection, pro-inflammatory mediators involved in the maternal cytokine storm may also pass through the placenta, resulting in an indirect inflammatory response in the fetus (Joma *et al.*, 2021; Vivanti *et al.*, 2020).

Neurological complications have also been increasingly reported in individuals with COVID-19, which may be due to either direct viral entry into the CNS or a systemic cytokine storm (Doyle, 2021; Solomon, 2021). Angiotensin-converting

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enzyme 2 (ACE-2) is expressed in glial cells and neurons, which supports the potential neurotropism of SARS-CoV-2 (Hernández *et al.*, 2021). Moreover, glial cells, particularly microglia and astrocytes, perform immune and inflammatory functions that allow them to respond to both viral infection and systemic inflammation (Liddelow *et al.*, 2020; Tremblay *et al.*, 2020). Importantly, glial cells also play crucial roles in neurodevelopment. In this context, the dysfunction of these cells during the fetal and postnatal periods may be related to neuropsychiatric disorders such as autism spectrum disorder (ASD) and schizophrenia, later in life (Dietz *et al.*, 2020; Scuderi and Verkhratsky, 2020). In addition, TORCH (an acronym used to refer to toxoplasmosis, rubella, cytomegalovirus, herpes simplex) congenital syndromes have been associated with several neurological complications (Megli and Coyne, 2021). In this article, we highlight the potential consequences of SARS-CoV-2 infection during pregnancy on brain development.

Immune, homeostatic, and neurodevelopmental roles of glial cells

Glial cells can be subdivided into macroglia (astrocytes and oligodendrocytes) and microglia, which are essential for brain development and homeostasis (Zuchero and Barres, 2015). Although microglial cells are resident immune cells in the CNS, astrocytes actively participate in innate immunity and inflammatory responses (Colombo and Farina, 2016). Both microglia and astrocytes synthesize and release several cytokines and chemokines that can propagate inflammation within the CNS (Liddelow *et al.*, 2020). Astrocytes possess a specific cytoarchitecture that allows intimate contact with blood vessels, synapses, and other glial cells, which enables them to sense their surroundings and dynamically respond to changes in their microenvironment. They form functional barriers, such as the blood-brain barrier (BBB), which restricts the entry of pathogens and inflammatory mediators into the CNS (Greenhalgh *et al.*, 2020). It is noteworthy that peripheral immune cells can affect the CNS when BBB permeability is compromised, and that astrocytes can guide inflammatory processes under healthy as well as diseased and injured conditions. Moreover, astrocytes regulate neurotransmitter systems, metabolic activity, and synthesis and release neurotrophic factors (Quincozes-Santos *et al.*, 2021b).

Macroglia are derived from radial glial cells that have a neuroepithelial origin and are pluripotent neural cell precursors (Zuchero and Barres, 2015). Microglial cells have a distinct (mesodermal) origin from the embryonic yolk sac and infiltrate the developing neural tube (Ginhoux and Prinz, 2015). The proliferation of glial and neuronal cells peaks during fetal development, between the 9th and 16th week post-conception. This means that glial cells are present during most brain development processes, including neurogenesis, neuronal circuit building during prenatal periods, and synaptic pruning in postnatal stages (Ziats *et al.*, 2015). While glial cells develop, proliferate, differentiate, and acquire functional properties, they establish important crosstalk with other glial cell types and neurons, which is continuously required not only during development but also in the mature brain. This communication occurs mainly via secreted molecules, including trophic and growth factors, cytokines, chemokines, neurotransmitters, and hormones (Han *et al.*, 2021; Tay *et al.*, 2017).

During development, astrocytes are essential for synaptogenesis, production and delivery of glutamate to neurons, extracellular potassium buffering, and metabolic support, and can respond to neuronal activity. Thus, they display a wide range of homeostatic functions that are necessary for synapse formation and maintenance (Zuchero and Barres, 2015). Microglia are necessary for neurogenesis and neuronal migration, orchestrating the assembly of prenatal neuronal circuits (Colonna and Butovsky, 2017). During postnatal development, both microglia and astrocytes are responsible for tagging and eliminating redundant neurons that do not form functional neuronal circuits, a process known as synaptic pruning (Colonna and Butovsky, 2017).

Glial cells are at the center of CNS homeostasis and respond to damage. Disturbances in glial morphology, gene expression, and functions have been reported in a growing number of neurodevelopmental and neuropsychiatric disorders, such as ASD and schizophrenia (Bristot Silvestrin *et al.*, 2013; Dietz *et al.*, 2020; Gottfried *et al.*, 2015). While the precise time of onset and cellular neurobiology of these disorders remain poorly understood, the role of glial cells in these disorders has gained evidence. Different mechanisms have been proposed to link aberrant glial development/activity during gestational and postnatal periods to ASD and schizophrenia. Neuroinflammation is guided by morphological and functional changes in microglia and astrocytes. In this context, in utero exposure to pathogens and other neurotoxic environmental factors that cause neuroinflammation in the developing brain has emerged as an etiological factor for these disorders (Gottfried *et al.*, 2015; Scuderi and Verkhratsky, 2020). Moreover, non-inflammatory mechanisms may involve defects in synaptogenesis or synaptic pruning, disruption of glutamate metabolism, potassium homeostasis, secretion of neurotrophic factors, and abnormal glial coverage and synaptic support (Ballas *et al.*, 2009; Dietz *et al.*, 2020; Maezawa and Jin, 2010). All of these glial cell-associated failures may result in dysregulated synaptic transmission and/or a lack of functional neurons.

Maternal infections and later neurological consequences in the offspring: potential roles of glial cells

An important connection between maternal infections during pregnancy and congenital syndromes and/or later neuropsychiatric disorders has been established using epidemiological and experimental animal models (Estes and McAllister, 2016; Knuesel *et al.*, 2014). Gestational transmission can occur during the prenatal period through the transplacental hematogenous route, during the perinatal period through contact with blood and vaginal secretions from the mother, and during the postnatal period through breast milk (Neu *et al.*, 2015). Importantly, although evidence of infection can be observed at birth and/or in childhood, it is possible that certain symptoms might manifest only in adulthood.

TORCH refers to congenital syndromes with clinical similarities, namely infections caused by Toxoplasma gondii,

rubella, cytomegalovirus (CMV), and herpes simplex (HSV) (Megli and Coyne, 2021). The common clinical manifestations of TORCH congenital syndromes include microcephaly, cerebral calcifications, hydrocephalus, motor and brain dysfunction, sensorineural hearing loss, and intellectual disability (Megli and Coyne, 2021). CMV infection has been shown to alter the proliferation, migration, and differentiation of neural precursor cells, including astrocytes, which may explain the abnormalities in brain development observed in congenital infections (Odeberg *et al.*, 2007). Amendments in the term TORCH, such as TORCHES or STORCH, have been proposed to include syphilis, which is caused by *Treponema pallidum* (Kinney and Kumar, 1988). More recently, due to the severity of congenital infection, Zika virus (ZIKV) infection has also been proposed to be included as a new member, as TORCHZ or STORCHZ (Coyne and Lazear, 2016).

Although ZIKV infection during pregnancy is mainly associated with microcephaly, it has recently been correlated with ASD diagnosis in childhood (Santi *et al.*, 2021; Vianna *et al.*, 2018). These neurodevelopmental abnormalities may be associated with neuroimmune changes caused by the release of inflammatory mediators by ZIKV-infected neural cells (Bobermin *et al.*, 2020). Moreover, fetal human astrocytes can be used as a viral reservoir, contributing to chronic brain infections (Limonta *et al.*, 2018). Other viruses, such as rubella virus and influenza, can also target glial cells and interfere with neuron-glia communication, resulting in aberrant neuronal migration, synaptogenesis, and synaptic pruning associated with ASD-like behaviors and an increased risk for schizophrenia (Fatemi *et al.*, 2008; Scuderi and Verkhratsky, 2020). It is important to note that several neuropsychiatric disorders, other than STORCHZ, have also been reported to be associated with morphofunctional changes.

Of note, both direct infection by viruses in the fetal CNS and maternal immune responses may be critical for these neurodevelopmental and/or neuropsychiatric sequelae. Activation of Toll-like receptor (TLR) pathways (including TLR3) in host immune cells, which may include glial cells, induces the expression of inflammatory cytokines and interferons through nuclear factor κB (NFκB) signaling (Alexopoulou *et al.*, 2001; Greenhalgh *et al.*, 2020). In this context, pro-inflammatory cytokines such as interleukins (IL-6, IL-1β, IL-17) and tumor necrosis factor a (TNF-α) have been described in animal models as key signaling molecules that predispose the individual to neurodevelopmental and neuropsychiatric disorders (Favrais *et al.*, 2011; Gilmore *et al.*, 2005).

Current evidence on SARS-CoV-2 vertical transmission

Relevant evidence has raised the possibility of SARS-CoV-2 vertical transmission, either during the antepartum, intrapartum, or postpartum periods. ACE-2 expression in the placenta and detection of SARS-CoV-2 in the placenta and amniotic fluid suggest that transplacental transmission can occur (Hosier *et al.*, 2020; Li *et al.*, 2020; Vivanti *et al.*, 2020). Pathological findings have also shown increased inflammatory infiltration in the placentas of SARS-CoV-2-infected pregnant women (Schoenmakers *et al.*, 2021). Notably, the placenta may become more susceptible to SARS-CoV-2 infection when it is inflamed (Lye *et al.*, 2020). Moreover, SARS-CoV-2 has been detected in the umbilical cord, vaginal mucosa, and milk (Fenizia *et al.*, 2020).

In neonates born from SARS-CoV-2-infected women, severe respiratory symptoms are not common, although there are some cases of respiratory diseases, abnormal Apgar indexes, and pneumonia (Nayak *et al.*, 2020; Wu *et al.*, 2020). However, a case report documented viremia and neurological symptoms in a newborn, which, in addition to supporting the transplacental transmission of SARS-CoV-2, suggested the effects of SARS-CoV-2 infection in the immature brain with evidence of gliosis (Vivanti *et al.*, 2020).

Neurological symptoms associated with SARS-CoV-2 infection: Potential role of glial cells and possible implications in neurodevelopment

Neurological manifestations are increasingly common in COVID-19 adult patients in addition to some degree of encephalitis, which could indicate substantial damage to the CNS (Doyle, 2021; Moriguchi *et al.*, 2020). Moreover, the development of neurological symptoms in children with COVID-19 has been described (Abdel-Mannan *et al.*, 2020). Although neurotropism and the mechanisms associated with SARS-CoV-2 entry into the CNS are still under investigation, it is important to note that other coronaviruses can compromise the nervous system by directly targeting neural cells and inducing a significant inflammatory condition that can lead to neuronal death (Li *et al.*, 2016).

In line with this, it has been demonstrated that the main cells of the CNS, such as neurons, astrocytes, and microglia, may be direct targets of SARS-CoV-2 owing to the expression of ACE-2 (Cama *et al.*, 2021; Crunfli *et al.*, 2020; Song *et al.*, 2021). In particular, astrocytes have been shown to be permissive to SARS-CoV-2, serving as a potential site for replication of the virus in the CNS. Moreover, astrocytes undergo several functional alterations after infection, including metabolic remodeling, which can compromise neuronal plasticity and synaptic functions (Crunfli *et al.*, 2020). Therefore, astrocyte dysfunction may be a mechanism underlying the short-and long-term neurological consequences of SARS-CoV-2 infection.

Reactive astrogliosis has also been observed in post-mortem brains of COVID-19 patients, along with microglial activation and infiltration of T lymphocytes, reinforcing the presence of an inflammatory process (Matschke *et al.*, 2020). Notably, both astrocytes and microglia are sensitive to peripheral cytokine storms, which can disrupt the BBB and facilitate viral entry into the CNS (Greenhalgh *et al.*, 2020; Huang *et al.*, 2021). Importantly, glial inflammatory phenotypes may contribute to various brain dysfunctions, including neurodegenerative diseases, neuropsychiatric symptoms, and neurodevelopmental disorders (Garden and Campbell, 2016; Pantelis *et al.*, 2020).

The cytokine storm caused by SARS-CoV-2 may be an aggravating factor in pregnant women, since maternal pro-inflammatory mediators can be transferred across the placenta and subsequently reach the developing CNS (Joma *et al.*, 2021; Reyes-Lagos *et al.*, 2021). In this regard, high levels of important inflammatory markers, including IL-6, IL-17, and TNF-α, have been reported in the blood of pregnant women with COVID-19 and the umbilical cord, as

well as in the serum of neonates born to infected mothers (Joma *et al.*, 2021; Xiao *et al.*, 2020; Zhu *et al.*, 2020). Among them, the role of IL-6 in maternal systemic inflammation during fetal brain development has been particularly studied. In an animal model, maternal treatment with IL-6 alone was sufficient to predispose the offspring to neuropsychiatric disorders such as schizophrenia and autism (Smith *et al.*, 2007). Interestingly, inhibition of IL-6 signaling through its placental receptors prevented increased IL-6 expression in the fetal brain and neurodevelopmental abnormalities (Wu *et al.*, 2017). Moreover, studies in humans have shown architectural and functional brain alterations in children exposed to increased levels of IL-6 during pregnancy (Rasmussen *et al.*, 2019; Rudolph *et al.*, 2018). Therefore, since IL-6 is an important component of the cytokine storm in COVID-19, it might act as a crucial molecular mediator in the potential link between SARS-CoV-2 infection during pregnancy and neurodevelopmental and neuropsychiatric disorders in the offspring.

It is also important to consider that TNF-α and IL-17, in addition to other inflammatory mediators whose levels are commonly increased in COVID-19 patients (C-reactive protein, IL-1β, IL-2, IL-8, and interferons), may contribute to neurodevelopmental and neuropsychiatric diseases related to maternal immune activation (Jiang *et al.*, 2018). Although the mechanisms by which cytokines affect brain development remain poorly understood, they seem to involve changes in functional brain connectivity, white matter damage, and abnormalities in neurotransmission (Jiang *et al.*, 2018; Mirabella *et al.*, 2021; Saunders *et al.*, 2020). Cytokines from the periphery can also induce CNS responses in several ways, including diffusion across the disrupted BBB and induction of synthesis and release of cytokines by glial cells (Gu *et al.*, 2021; Jiang *et al.*, 2018). Therefore, even in the absence of vertical transmission or direct neuroinvasion by SARS-CoV-2, changes in the fetal and neonatal brain functions may occur due to immune activation.

In addition to environmental factors, susceptibility to neurodevelopmental and neuropsychiatric disorders may also involve molecular factors. Defects in glial genes related to synaptogenesis, synaptic transmission, and neuroinflammation have been reported in patients diagnosed with ASD (Scuderi and Verkhratsky, 2020). Supporting the role of altered glial-neuronal relationships during fetal CNS development in ASD, some genes that are essential for brain development and highly expressed in different glial cell types were also found to confer susceptibility to ASD (Scuderi and Verkhratsky, 2020). Notably, an analysis of differential gene expression datasets for clinical samples of COVID-19 patients identified a high number of genes that are associated with the pathophysiology of several neuropsychiatric disorders, including ASD, schizophrenia, bipolar disorder, depression, and Alzheimer's disease (Quincozes-Santos *et al.*, 2021a; Quincozes-Santos *et al.*, 2021).

Concluding Remarks

Glial cells are important players in neurodevelopment and maintenance of brain homeostasis, and disruption of their functions has been strongly associated with a wide range of neuropsychiatric disorders. The relationship between maternal infections and possible neurodevelopmental disorders and/or later neuropsychiatric consequences in the offspring has been established, in which the available evidence supports glial-related pathogenesis. Based on these relationships, SARS-CoV-2 infection either during pregnancy or during critical neurodevelopmental periods could be related to an increased risk of neurological consequences in offsprings later in life (Fig. 1); thus, efforts to unravel this hypothesis are currently needed. It is also possible to conceive expansion of the current TORCH/STORCHZ family, generating a new acronym to incorporate other emerging pathogens. Moreover, it is also important to consider the future and long-term public health concerns associated with SARS-CoV-2 infection during pregnancy, as well as a careful follow-up of infants born to COVID-19 positive mothers.

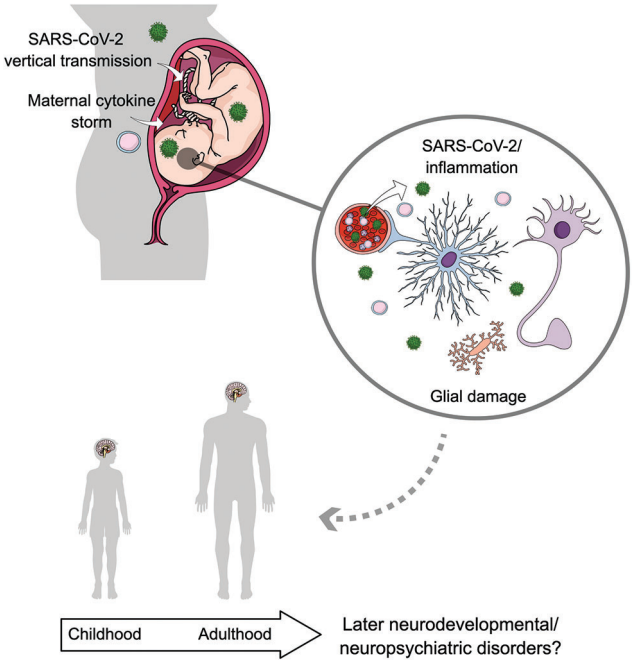

FIGURE 1. Putative role of glial cells in the possible neurodevelopmental and/or neuropsychiatric consequences related to SARS-CoV-2 infection during pregnancy. Recent evidence has raised the possibility of vertical transmission of SARS-CoV-2 as well as a direct brain infection. Additionally, maternal cytokine storm related to COVID-19 may cause fetal neuroinflammation. Both a direct infection and an inflammatory response triggered by SARS-CoV-2 might impact brain development by affecting critical functions of glial cells, as it has been demonstrated for other viral infections. These altered glial functions may increase the risk of later neurodevelopmental/neuropsychiatric disorders. The cells in the circle represent functional glial cells and neurons. Astrocytes are represented in blue; microglia are represented in yellow; SARS-CoV-2 is represented in green and cytokines/immune cells in pink.

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