RESEARCH ARTICLE

COVID-19 brain inflammation and autism spectrum disorder

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ABSTRACT

The recent Coronovirus [severe acute respiratory syndrome (SARS)-CoV-2] is associated with high morbidity and mortality, known as COVID-19, primarily due to the release of pro-inflammatory cytokines, especially IL-6, in the lungs. There is increasing evidence that COVID-19 also results in mental and neurologic symtpoms. Recent publications have also reported the presence of Multisystem Inflammatory Syndrome in children (MIS-C). SARS)-CoV-2 and/or the associated cytokines could enter the brain from the upper respiratory system, especially via the nose that communicates directly with the brain, resulting in Pediatric Acute Neuropsychiatric Syndrome (PANS) or Autism Spectrum Disorder (ASD), which involve activated microglia. These disorders also involve activation of mast cells, which can be triggered by viruses and secrete multiple cytokines including IL-1 and IL-6, thus potentially contributing to the pulmonary and neurologic symptoms of COVID-19. It will be important to design longitudinal studies to investigate the prevalence of ASD in children who were positive for COVID-19, and consider reducing inflammation of the brain as a prophylactic intervention.

Key Words: *Autism spectrum disorder; Brain; Corona virus; Children; Cytokines; Inflammation; Mast cells; Microglia*

INTRODUCTION

The recent Coronovirus [severe acute respiratory syndrome (SARS)-CoV-2] is associated with high morbidity and mortality in adults [1] known as COVID-19 [2]. COVID-19 has also been reported to contribute to neurological [3-5] and mental [6-9] disorders, including anxiety, depression, and obsessive-compulsive behaviors [10-13]. Moreover, the health and economy-related stress associated with COVID-19 [14] has also contributed significantly to the emotional burden of patients, [15-20] with social isolation, loneliness and anxiety being key components [21].

Interestingly, children have been reported to either not get infected or have milder symptoms than adults, [22-27] possibly due to differences in their immune responses [28,29]. Nevertheless, a number of papers recently reported the presence of Multisystem Inflammatory Syndrome in children (MIS-C) with symptoms resembling toxic shock or Kawasaki syndrome [30-32]. These findings indicate that COVID-19 in children may present with inflammation in other organs, as evidenced by flares of allergies and asthma, [33,34] including the brain [35].

COVID-19 patients who recover have been reported to have increased levels of specific antibodies and activated T cells [36,37]. Instead, the pulmonary pathology appears to result from release of multiple pro-inflammatory chemokines, especially IL-6, [36,38-40] that damage the lungs [39,41]. A key source of such cytokines in COVID-19 [42] is the mast cells, [43-45] which express the renin-angiotensin system, [46] the metalo-ectoenzyme Angiotensin Converting Enzyme 2 (ACE2) required for SARS-CoV-2 binding to the target cells, and [47,48] serine proteases, [49] including TMPRSS2 required for priming of the corona spike protein [50]. Mast cells can be triggered by viruses [51] and secrete multiple pro-inflammatory mediators [52-54] including IL-1 [55] TNF [56] and IL-6, [57] thus potentially contributing to COVID-19.

Vulnerable populations especially those diagnosed with different "brain biotypes," [58] such as neuropsychiatric diseases including ASD, [59,60] may be particularly vulnerable [61]. Some reports indicate that ASD may be a risk factor for COVID-19 [62,63].

In this paper, we review the available evidence in Pubmed and propose that SARS-CoV-2 itself and/or SARS-CoV-2-generated cytokines may trigger or worsen ASD. We further propose that SARS-CoV-2-could enter the brain from the upper respiratory system, especially the nose that communicates directly with the brain through the olfactory nerve tract via the cribriform plexus leading to focal inflammation in the amygdala (Figure 1) [64]. As a result, COVID-19 could contribute to Pediatric Acute Neuropsychiatric Syndrome (PANS) and/or Autism Spectrum Disorder (ASD), which involve focal inflammation of the brain [65,66].

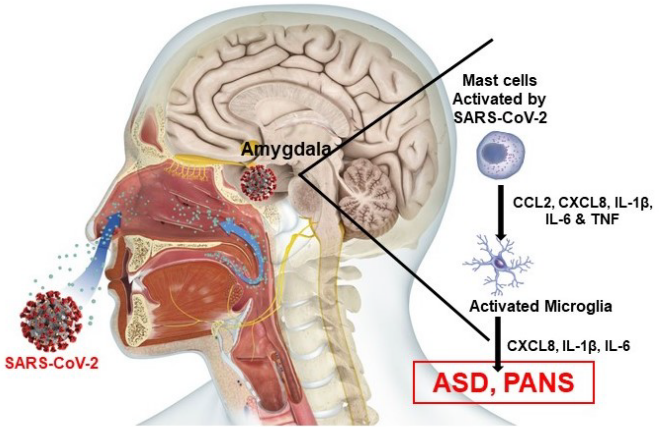

Figure 1) *The nose that communicates directly with the brain through the olfactory nerve tract via the cribriform plexus leading to focal inflammation in the amygdala.*

COVID-19, Stress and Neuropsychiatric Symptoms

Psychological stress can contribute to pathological processes in various diseases, [67] including allergies, [68] anaphylaxis, [69] asthma, [70,71] atopic dermatitis (AD) [72] and mastocytosis, [73] conditions which are characterized by increased number and/or degree of activation of mast cells. Psychological stress associated with COVID-19 could also worsen auto-immune and inflammatory responses [14] and adversely affect brain development and function [74]. Moreover, allergic diseases in preschoolers had more behavioral problems [75]. Epidemiological studies have shown that atopic diseases, [76-79] such as allergies [77,78,80] and asthma, [81] are significantly associated with ASD [82,83].

Maternal psychological problems during pregnancy increased the risk of childhood AD [84,85]. In fact, stress during gestation increased cord blood levels of IgE [86]. In this context, a recent paper reported the important observation that fetal mast cells in utero can respond to the mother's circulating IgE and results in vetical transmission of postnatal skin and airway inflammation [87]. This finding implies that fetal mast cells could also respond to other alarmins, such as IL-33, [88,89] with detrimental effects in

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brain development especially in premature babies [90].

Prenatal stress was associated with higher risk of newborns developing ASD [91-94]. A meta-analysis showed a significant association between anxiety disorders and ASD [95]. Moreover, children with ASD are more vulnerable to stress [96,97] with an exaggerated fear response [98,99]. Moreover, anxiety disorders are highly prevalent in individuals with ASD [100]. We recently discussed the combined detrimental effects of stress, inflammation and auto-immunity. Hence, there is now discussion of potential points of intervention to potentially reduce parental stress and it effect on maternal immune dysregulation [101].

COVID-19 can affect the neuroendocrine-stress axis [102]. Stress stimulates secretion of corticotropin-releasing hormone (CRH) from the hypothalamus leading to activation of the hypothalamic-pituitary-adrenal (HPA) axis [103]. Even though HPA activation leads to anti-inflammatory actions, stress can also have pro-inflammatory effects [103,104] via stimulation of mast cells by CRH [105,106].

Inflammation of the brain and ASD

Autism Spectrum Disorder is characterized by impaired social interactions and communication, as well as stereotypic behaviors [107-111], affecting [in children in the US [110,112]. Most autistics have a number of comorbidities [113]. The pathogenesis of ASD is still unknown and hence no pharmacologic treatment is available for the core symptoms of ASD [114,115].

We had proposed that focal inflammation in the amygdala may lead to inflammation of the brain, [116] a process that has since been supported by differet investigators [117-119]. As a result, we propose that the fear threshold in lowered in children with ASD [120]. Inflammation of the brain may involve activation of microglia, [121-124] which were recently also implicated in COVID-19 [125]. Microglia express receptors for the peptide neurotensin (NT) [126] and Toll-like receptors (TLRs) [127] activated by damage associated molecular patterns (DAMPs), such as SARS-CoV-2. We reported that NT is increased in the serum of patients with ASD [128,129] and can activate human microglia to secrete pro-inflammatory molecules [130]. We also reported increased gene expression of the pro-inflammatory microRNA-155 (miR-155) in the amygdala of children with ASD, [131] as well as reduced expression of the anti-inflammatory cytokine, IL-38 [132].

With respect to cytokines implicated in COVID-19, a longitudinal study of mother's serum measurements during gestation linked IL-6 to decreased executive function in their offspring [133]. Another study showed that prenatal and early postnatal stress were associated with elevated serum levels of IL-6 [134]. Interestingly, pre-existing differences in mouse bone marrow-derived leukocyte release of IL-6 predicted subsequent social behavior so that the highest the IL-6, the more likely the mice were to develop a phenotype susceptible to chronic stress [135]. Another study reported that prenatal stress or exposure to IL-6 resulted in increased microglia ramification in mice, and it was prevented by IL-6 blockade [136]. We had shown that acute restraint stress significantly increased serum IL-6 in mice that was entirely dependent on mast cells [137].

Inflammation of the brain involves interactions between mast cells and microglia [138-140]. Stimulation of mast cells can lead to activation of microglia [141-143] an effect also absents in mast cell-deficient mice [144]. We had reported that ASD is much more common in children born to mothers with systemic mastocytosis, [145] characterized by a greater number of hyperactive mast cells than the general population [44] and may lead to focal inflammation in the brain. The involvement of mast cells is supported by large epidemiological studies showing a strong association between ASD and atopic diseases, such as asthma and AD, Theoharides TC., 2016 24603 /id;Xu, 2018 27065 /id} conditions that involve activation of mast cells, and occur more frequently in mothers who experienced stress during pregnancy [146-148].

Mast cells are ubiquitous in the body, especially the lungs and are critical for allergic and pulmonary diseases, including mastocytosis by secreting histamine and multiple pro-inflammatory cytokines and chemokines, [149] especially IL-6, which has been involved in COVID-19. Mast cells are also abundant in the brain, especially the meninges [150,151] and they are stimulated by stress. 71 Specifically, we showed that stress increases dura vascular permeability, an effect that was absent in mast cell-deficient mice [152]. Mast cells are also plentiful in the median eminence, juxtaposed to nerve endings positive for CRH [150]. Moreover, mast cells have been implicated in the regulation of the HPA axis [153-155]. In particular, histamine, [156] IL-6 [157] and CRH [158] released from mast cells can activate the HPA axis.

Mast cell-derived mediators, especially cytokines, [159,160] can also increase the permeability of the blood-brain barrier (BBB) in rodents [161-164]. We showed that restraint stress increased BBB permeability via CRH stimulating mast cells [162,165-169]. Hence, SARS-CoV-2 could affect brain cells directly, via activation of mast cells or by permitting cytokines to enter through a disrupted BBB [170-173].

CONCLUSION

This is the first time to our knowledge that COVID-19 is discussed in the context of contributing to ASD. In particular, the evidence reviewed indicates that SARS-CoV-2 could enter the brain via the upper respiratory system following the olfactory nerve tract and reach the amygdala where it could stimulate release of pro-inflammatory cytokines from mast cells and/or microglia thus contributing to the pathogenesis of ASD and PANS. Autism symptoms may not be immediately apparent in children infected with SARS-CoV-2 and it will be important to initiate longitudinal observational studies. In the meantime, one may address psychoneuroimmunity by using the natural flavonoid luteolin, reported to inhibit both microglia, and mast cells, which have been implicated in COVID-19, especially when luteolin is formulated in a liposomal form to increase oral absorption.

ABBREVIATIONS

ACE2: Angiotensin Converting Enzyme 2; ASD: Autism Spectrum Disorder; BBB: Blood-brain Barrier; CMSIS: Childhood Multisystem; Inflammatory Syndrome; HPA: Hypothalamic-Pituitary-Adrenal axis; NT: Neurotensin; PANS: Pediatric Acute Neuropsychiatric Syndrome

DECLARATION

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Consent for publication: N/A

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Competing interests: N/A

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