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The impact of COVID-19 on diagnostic biomarkers in neuropsychiatric and neuroimmunological diseases: a review

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Abstract: Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Evidence-based emerging reports of neurological manifestations show that SARS-CoV-2 can attack the nervous system. However, little is known about the biomarkers in disease in neuropsychiatric and neuroimmunological disorders. One of the important keys in the management of COVID-19 is an accurate diagnosis. Biomarkers could provide valuable information in the early detection of disease etiology, diagnosis, further treatment, and prognosis. Moreover, ongoing investigations on hematologic, biochemical, and immunologic biomarkers in nonsevere, severe, or fatal forms of COVID-19 patients provide an urgent need for the identification of clinical and laboratory predictors. In addition, several cytokines acting through mechanisms to emerge immune response against SARS-CoV-2 infection are known to play a major role in neuroinflammation. Considering the neuroinvasive potential of SARS-CoV-2, which can be capable of triggering a cytokine storm, the current evidence on inflammation in psychiatry and neurodegenerative by emerging neuroinflammation is discussed in this review. We also highlighted the hematologic, biochemical, and immunologic biomarkers in COVID-19 diagnosis. COVID-19 prognostic biomarkers in patients with neuropsychiatric and neuroimmunological diseases are also explained.

Keywords: biomarkers; COVID-19; neuroimmunological diseases; neuropsychiatric; SARS-CoV-2.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by a new coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was detected in Wuhan, China, in December 2019. It became a public health issue, with high fatality rate, particularly among older patients who have underlying health issues (Hanaei and Rezaei 2020; Wei and Shah 2020). The viral agent enters the target cells, using the angiotensin-converting enzyme 2 (ACE2), as a receptor on the host-cell surface (Gralinski and Menachery 2020). The wide distribution of ACE2 receptors in different organs and cell types such as intestinal mucosa cells, renal tubular cells, lymphatic cells, reticuloendothelial cells, and nervous system cells makes them as a potent target for SARS-COV-2 infection (Zou et al. 2020).

The existence of close interactions between SARS-CoV-2 infection and possible impairment in the immune, nervous, and endocrine systems, results in alterations in psycho-neuroendocrine-immune (PNI) circuits (Raony et al. 2020). It is well documented that COVID-19 patients can develop neuropsychiatric symptoms (Kong et al. 2020), while increased levels of pro-inflammatory cytokines (Mehta et al. 2020; Rokni et al. 2020; Saghazadeh and Rezaei 2020) have been observed in several psychiatric disorders in association with SARS-CoV-2 infection. Furthermore, some reports demonstrated that high levels of cytokines/chemokines have been associated to the pathogenesis of neuroimmunological disorders and neurodegenerative diseases (Frank-Cannon et al. 2009). Although some patients with COVID-19, in particular those...
with underlying health issues, are at risk of severe disease or high fatality rate of the disease, early prediction of severe cases, using relevant biomarkers, could play a critical role in management of patients (Zhang and Guo 2020). Considering the ability of the SARS-CoV-2 to infect the nervous system and increased levels of cytokines, the neuroinflammatory consequences of SARS-CoV-2 infection in neuroimmunological and neuropsychiatric disorders is discussed in this review. The impact of COVID-19 on prognostic biomarkers in neuropsychiatric and neuroimmunological diseases is also reviewed.

Search strategy

We performed a literature search, using EMBASE, MEDLINE, and Google Scholar, for studies reporting the use of diagnostic biomarkers in neuropsychiatric and neuroimmunological diseases and COVID-19, published until November 2020, using the medical subject headings (MESH) terms: “laboratory biomarkers”, “Immune biomarkers,” “COVID-19,” “neuropsychiatric diseases”, “neuroimmunological diseases”, and “SARS-CoV-2.”

Importance of biomarkers for COVID-19 prognosis

Several immunologic and laboratory biomarkers have been introduced in association with disease severity and patient prognosis since the beginning of COVID-19 outbreak.

Laboratory biomarkers

Lymphopenia and increased neutrophil/lymphocyte ratio are the most reliable prognostic hemocytometric markers in COVID-19 patients (Khartabil et al. 2020). Platelet-to-lymphocyte ratio (PLR) along with neutrophil-to-lymphocyte ratio (NLR) are considered as valuable prognostic markers. Their high values are associated with poor prognosis in COVID-19 patients (Chan and Rout 2020). Imbalance in inflammatory cytokine production, increased low-density neutrophil, and increased in lymphocyte death all could lead to increased NLR in COVID-19 (Yan et al. 2020). NLR is considered as a valuable inflammation indicator, which was previously described as an Alzheimer disease (AD) predictor, suggesting that neutrophils and lymphocytes play important roles in AD pathophysiology illuminated via NLR (Kuyumcu et al. 2012). Similar results were found in patients with multiple sclerosis (MS), defining NLR as an independent predictor of MS prognosis and also a useful marker for disease diagnosis and activity (Demirci et al. 2016).

Thrombocytopenia is also a useful prognostic laboratory finding. Based on a recent meta-analysis of nine studies, thrombocytopenia is associated with severe disease and also poor prognosis with high mortality rates both in early admission and later in disease course (Lippi et al. 2020). Microthrombi, resulting from endothelial injuries in lung or other organs, may account for the thrombocytopenia, especially in severe cases. Meanwhile there are some controversies among studies whether thrombocytosis or thrombocytopenia is associated with severe disease (Ponti et al. 2020; H. Xu et al. 2020; P. Xu et al. 2020).

A meta-analysis of several studies on the Asian populations revealed that an increase in liver function markers (aspartate transaminase [AST], alanine transaminase [ALT], Bilirubin), kidney function markers (blood urea nitrogen [BUN], Cr), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, prothrombin time (PT), D-dimer, procalcitonin (PCT), lactate dehydrogenase (LDH), glucose level, neutrophil, and NLR are associated with severe disease. Conversely, decreased lymphocyte, monocyte, and eosinophil, platelet, lymphocyte to C-reactive protein ratio (LCR), leukocyte to C-reactive protein ratio (LeCR), leukocyte to IL-6 ratio (LeIR), albumin and serum sodium are associated with severe disease and poor prognosis. The levels of cardiac and muscle injury biomarkers (Creatine Kinase [CK], troponin I, myoglobin), IL-6, and potassium showed no significant differences between severe and nonsevere disease (Gahramani et al. 2020). Liver damage may result from either direct hepatocyte or cholangiocyte infection or from systemic inflammatory response and multiorgan failure (Chai et al. 2020). Acute kidney injury may be due to endothelial and tubular...
damage from direct endothelial damage and subsequent microthrombi formation and necrosis (Batlle et al. 2020). PPCT increased levels may result from increased inflammatory cytokines in severe COVID-19 cases, even in the absence of bacterial infection (Ponti et al. 2020). Elevated glucose levels are believed to maintain viral replication and monocyte responses through HIF-1α/glycolysis-dependent axis and are associated with severe disease and poor prognosis (Codo et al. 2020; Wu et al. 2020). Interestingly, CRP acts as an early predictive value in COVID-19 patients, even before detection of computed tomography (CT) abnormalities. Compared to other biomarkers, CRP increases at early stages of disease, especially in cases becoming severe later in disease course (Chew et al. 2020). Another study showed that CRP levels are independently associated with disease severity prediction as other comorbidities such as hypertension (P. Zhou et al. 2020; Y. Zhou et al. 2020).

**Immune biomarkers**

Identification of effective biomarkers in COVID-19 disease progression partly relies on the “cytokine storm” (Chen et al. 2020, 2021). The cytokine storm in COVID-19 patients is responsible for acute respiratory distress syndrome (ARDS), resulting from the surge of inflammatory cytokines, including Interleukins (IL)-6, -8, -10, -18, tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma, and GM-CSF in the blood circulation (Mehta et al. 2020). In the central nervous system (CNS), IL-6, in particular, has been expressed initially by astrocytes and microglia documented and have a potent role in immune dysregulation during COVID-19 infection and subsequent neuroinflammation (Erta et al. 2012; Mandel et al. 2020). In a recent retrospective studies, an elevated level of IL-6 was observed in COVID-19 infection, indicating the case fatality of SARS-CoV-2 infection (Chen et al. 2020a, 2021). A recent finding showed that circulating IL-6 levels are closely linked to the severity of COVID-19 infection. An increased IL-6 level has previously been observed in patients with respiratory dysfunction (Wang et al. 2020). Additionally, highly pathogenic SARS-CoV-2 infection seems to be related with rapid virus replication and high affinity to attack the lower respiratory tract, resulting in severe respiratory distress induced by an elevated response of IL-6 (Ulhaq and Soraya 2020). In another report by Meduri el. elevated immunologic biomarkers, especially IL-6 and serum ferritin, were observed in patients who did not survived (Meduri et al. 1995). Overall, these observations demonstrated underlying mechanisms of elevation of interleukins in COVID-19 patients, which is responsible for blood–brain barrier (BBB) dysfunction and consequences neurological symptoms. In COVID-19 patients, a pathological state in critically severe stage, named CRS, is developed. CRS is characterized by fast and prolonged systemic elevation in both inflammatory cytokines and chemokines (Huang et al. 2020). Furthermore, significantly high IL-10 concentrations were observed in COVID-19 patients who are admitted in the ICU (Diao et al. 2020; Huang et al. 2020). Additionally, IL-10 concentrations are strongly associated with IL-6 and CRP levels as well as other inflammatory markers. However, IL-10 has been reported as a putative immune biomarker in investigation of COVID-19 disease severity. Meanwhile, both increased IL-6 and IL-10 expression can predict poor similar outcomes in COVID-19 patients (Han et al. 2020). Furthermore, neuroinflammation is a significant etiological factor in many neuropsychiatric and neurocognitive diseases, including neurodegenerative disorders, depression, psychosis, autism, drug abuse, sleep disorders, and epilepsy (Steardo and Verkhratsky 2020). Two of the important candidate biomarkers in either COVID-19 or neurodegenerative disorders are IL-6 and its receptor (IL6R) (Garbers et al. 2018). In a recent cohort of 271 DNA samples from the Italian general population, it has been reported that IL6-IL6R-related biomarkers could be useful for evaluating the susceptibility and progression of neuroinflammatory disorders, which could be the most suitable strategies for treatment and improve patients’ prognosis (Strafella et al. 2020) (see Table 1).

**Neuroinvasive potential of SARS-CoV-2 on the nervous system**

Previous studies on other coronaviruses revealed that neuronal retrograde, transcriptrial, as well as hematogenous dissemination are some possible pathways for entering SARS-CoV-2 into the CNS. In a study by Dodding and Way, it has been shown that motor proteins, including dynein and kinesins moving along microtubules associated with retrograde or anterograde transportation of viruses (e.g., adenovirus and α-herpes viruses) in the both sensory and motor nerve endings (Dodding and Way 2011).

**Direct pathway**

It should be mentioned that SARS-CoV-2 could be considered as a neuroinvasive virus. The underlying mechanisms
of SARS-CoV-2 invasion are linked to membrane-bound ACE2 receptors, similarly to infectivity mechanisms of SARS-CoV and MERS-CoV (Wong et al. 2020; H. Xu et al. 2020; P. Xu et al. 2020). Within the brain, ACE2 receptors are particularly present in the brainstem and medulla as part of reticular activating system function involved in regulation of cardiovascular system (Xia and Lazartigues 2010). Viral antigens were detected in respiratory brain stem centers like nucleus of the solitary tract and nucleus ambiguous. Damage to these centers could be a contributing factor for cardiac or respiratory arrest (Steardo et al. 2020; Xia and Lazartigues 2008).

Table 1: Biomarker abnormalities in COVID-19 patients.

<table>
<thead>
<tr>
<th>Laboratory biomarkers</th>
<th>Covid-19 UNDERLING mechanism</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>Direct lymphocyte infection by SARS-COV-2 virus and cell lysis, apoptosis caused by the cytokine storm, and finally simultaneous lactic acidosis</td>
<td>(Fathi and Rezaei 2020; Khartabil et al. 2020; Terpos et al. 2020; Wagner et al. 2020; P. Zhou et al. 2020; Y. Zhou et al. 2020)</td>
</tr>
<tr>
<td>Neutrophil/lymphocyte ratio</td>
<td>Imbalance in inflammatory cytokine production, increase in anomalous low-density neutrophil increase in lymphocyte death</td>
<td>(Chan and Rout 2020; Khartabil et al. 2020; Yan et al. 2020)</td>
</tr>
<tr>
<td>Platelet-to-lymphocyte ratio (PLR)</td>
<td>High values associated poor prognosis</td>
<td>(Chan and Rout 2020)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet consumption for thrombi production in endothelial injury sites</td>
<td>(Terpos et al. 2020; Xia and Lazartigues 2008)</td>
</tr>
<tr>
<td>Liver function markers (AST, ALT, Bilirubin)</td>
<td>Direct viral infection of hepatocytes or cholangiocytes Multiorgan failure of systemic inflammatory response origin</td>
<td>(Chai et al. 2020; Ghahramani et al. 2020)</td>
</tr>
<tr>
<td>Kidney function markers (BUN, Cr)</td>
<td>Direct endothelial and tubular damage and subsequent microthrombi formation</td>
<td>(Chai et al. 2020; Ghahramani et al. 2020)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR)</td>
<td>Higher levels associated with severe disease</td>
<td>(Chan and Rout 2020)</td>
</tr>
<tr>
<td>Prothrombin time (PT)</td>
<td>Increased levels associated with severe disease and poor prognosis</td>
<td>(Ghahramani et al. 2020)</td>
</tr>
<tr>
<td>Fibrinogen, D-dimer, prothrombin time</td>
<td>Increase as an inflammation indicator in severe viral infections</td>
<td>(Ghahramani et al. 2020; Ponti et al. 2020)</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>Higher levels indicate severe disease</td>
<td>(Ghahramani et al. 2020)</td>
</tr>
<tr>
<td>Glucose level</td>
<td>Elevated levels maintain viral replication and increased monocyte response via HIF-1α/Glycolysis-Dependent Axis</td>
<td>(Codo et al. 2020; Ghahramani et al. 2020; Wu et al. 2020)</td>
</tr>
<tr>
<td>IL-6</td>
<td>Circulating IL-6 levels are closely linked to the severity of COVID-19 infection Activates T cell growth and CD8+ T cell proliferation</td>
<td>(Benenameur et al. 2020; Chen et al. 2020a, 2021; Erta et al. 2012; Garbers et al. 2018; Han et al. 2020; Mandel et al. 2020; Meduri et al. 1995; Mehta et al. 2020; Naka et al. 2002; Strafella et al. 2020; Ulhaq and Soraya 2020; Wang et al. 2020)</td>
</tr>
<tr>
<td>IL-8</td>
<td>Elevated levels of IL-8 in the cerebrospinal fluid of COVID-19-associated with neurological symptoms</td>
<td>(Diao et al. 2020; Han et al. 2020; Huang et al. 2020; Mehta et al. 2020)</td>
</tr>
<tr>
<td>IL-10</td>
<td>Putative immune biomarker in investigation of COVID-19 disease severity Reported</td>
<td>(Huang et al. 2020; Mehta et al. 2020; Qin et al. 2020)</td>
</tr>
<tr>
<td>Tumor necrosis factor (TNF)-alpha</td>
<td>Higher levels in COVID-19 patients have been reported</td>
<td>(Huang et al. 2020; Mehta et al. 2020)</td>
</tr>
<tr>
<td>Interferon (IFN)-gamma and GM-CSF</td>
<td>A key cytokine for antiviral immune response</td>
<td>(Mehta et al. 2020)</td>
</tr>
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Considering the widely distribution of ACE2 receptors through the CNS, there is a robust relationship between SARS-CoV-2 and direct neuron loss, induced by viral infection (Desforges et al. 2020). The possible neural pathways, including olfactory pathway, cranial nerves, and hematogenous pathway are known to provide a directly accessible gate for SARS-CoV-2 to enter the CNS (Keyhanian et al. 2020). The nasal epithelium connects to CNS regions, including cortex, basal ganglia, and midbrain as a virus affected targets, through bipolar neuronal structure of olfactory nerves (Netland et al. 2008). In a recent study on mild to moderate COVID-19 (417 European cases), olfactory dysfunction has been observed in 85.6% of the patients; among them, it was appeared in 11.8% before the onset of other symptoms (Lechien et al. 2020). Recently, it has been indicated that either partial loss of the sense of smell or total anosmia are early markers of SARS-CoV-2 infection. This phenomenon may be caused through different factors, including “cytokine storm” initiated in some patients or directly via the olfactory receptor neurons (ORNs) damage, which located in the olfactory epithelium (Olender et al. 2016; Saraiva et al. 2015). The mechanisms underlying COVID-19-associated anosmia is linked to expression of SARS-CoV-2 entry genes non-neuronal cells in olfactory bulb, which represent a potential entry way for SARS-CoV-2 (Brann et al. 2020).

The onset of hyposmia besides the other neurological symptoms in COVID-19 patients makes the olfactory system as a potent target to SARS-CoV-2 infection. Another study also demonstrated that SARS-CoV-2-induced olfactory impairment is linked to olfactory bulbs (Coolsen et al. 2020). Accessory cells in olfactory system may also be a region to trigger cytokine storm and consequence immunological response. Cytokine release might be contributed in olfactory sensory neurons damage (Jakhmola et al. 2020). Olfactory nerves are activated by pathogen-associated molecular patterns (PAMPs) and inflammatory cytokines. The viral transmission in the olfactory bulb leads a neuroinflammatory response through an excessive release of cytokines to protect the CNS. Therefore, anosmia, an initial symptom of COVID-19, might be a result of such neuroinflammatory response (Balcıoğlu et al. 2020).

The other cranial nerves, including trigeminal nerve and vagal nerve, might be a way for SARS-CoV-2 retrograde neuronal transmission since neuroinvasion through the transport within vagal nerve afferents has been assumed (Toljan 2020). As noted before, one of the possible ways for virus entry into the CNS is via the hematogenous route. Due to the slow flow of blood through the cerebral microcirculation, and given the detection of virus in the general circulation, the virus may interact with ACE2 receptors, expressed in the capillary endothelium. Additionally, increased the BBB permeability following disrupting the BBB (Hamming et al. 2004) ultimately exacerbates penetration into the CNS and causes neurological symptoms. This proposed mechanism can also contribute to the endothelial damage, which results in subsequent cerebral bleeding in patients with acute COVID-19 (Serrano-Castro et al. 2020).

**Indirect pathway**

SARS-CoV-2 may affect the CNS indirectly at least in part through underlying neurodegenerative diseases. Recently, a strong relationship between neuroinflammation and CNS diseases have been reported. It has been proposed that SARS-CoV-2, potentially by acting on alterations in the gut microbiota may contribute to neuroinflammation, which may result in neurodegeneration (Lin et al. 2018).

**Psycho-neuroendocrine-immune contribution in COVID-19**

Neuroinflammation basically exerts its devastating effects through several pathways, including alterations in hypothalamic-pituitary-adrenal (HPA) axis, neurotransmitter metabolism, neural framework, and neuroplasticity changes (Morris et al. 2018; Rhie et al. 2020). SARS-CoV-2 virus is believed to promote a cascade of inflammatory immune factors capable of initiating or intensifying neuroinflammatory pathways associated with psychiatric or neuroimmune disorders either indirectly through cytokine storms or by direct infection of neural cells including nerves and glial cells. Also, it has been hypothesized that COVID-19 virus persistence in CNS as a latent asymptomatic infection may result in neurodegeneration (Lin et al. 2018).
associations between previous neurological disorders and developing severe diseases or exacerbations of previous neurological disorders in severe cases (Kubota and Kuroda 2021; Romagnolo et al. 2020). Previous chronic neurological disorders (dementia, movement disorders, prior stroke with long-term sequelae, neuromuscular disorders, etc.) in COVID-19 patients acted as independent mortality predictors in a cohort study on more than 500 hospitalized patients. However, these neurological conditions were not significantly associated with disease severity (García-Azorín et al. 2020).

**SARS-CoV-2 and the neuroendocrine stress axis**

CNS infection activates first line defense barriers of innate immunity through either hematogenic or neural routes. Innate immunity in turn releases IL-1, IL-6, and TNFs through which activates local responses to eradicate infecting pathogen. As a feedback control mechanism, HPA axis is activated by neuronal responses and the end product corticosteroids suppress the immune responses activated in infected regions (Bellavance and Rivest 2014; Sternberg 2006). Along with this, chronic stressful conditions like COVID-19 pandemic itself may cause an over-activation of body stress coping mechanisms, including sympathetic-adrenal axis, renin-angiotensin-aldosterone axis, and HPA axis. This chronic recurrent over-activation is believed to disrupt the normal structure and function of coping systems, leading to initiation or exacerbation of a variety of psychiatric disorders, including depression and anxiety (Oyola and Handa 2017; Steenblock et al. 2020). Acute and chronic stress is believed to elicit adrenal medulla responses through activation of sympathetic nerves transferring the messages to the adrenal medulla, causing catecholamine release either in acute or chronic patterns. Dysregulations in this feedback system has been suggested to be responsible at least partially for developing depressive anxiety conditions or worsening pre-existing ones (Brindley et al. 2017; Ströhle and Holsboer 2003). Moreover, it has been suggested that SARS-CoV-2 virus might directly infect hypothalamus and pituitary glands and result in hypocortisolism during the acute infection period or several months later as confirmed for SARS infection previously (Leow et al. 2005). Recently, a post mortem COVID-19 patient brain investigation revealed direct olfactory bulb and hypothalamic infection and replication of the virus. Further analysis of the gene expression hypothalamic regions revealed that neural cell in this region express ACE2 and transmembrane proteinase, serine 2 allowing direct virus entry and initiating replication pathways (Nampoothiri et al. 2020). Magnetic resonance imaging (MRI) findings also were reported in positive COVID-19 cases, as involvement of pituitary gland and its stalk along with hypothalamic regions among other regions, which showed improvement in control MRIs after one week and one month periods, concomitant with subsidence of clinical neurological symptoms (Pascual-Goñi et al. 2020). Interestingly, in 2004, it was mentioned that SARS virus may express peptide sequences resembling ACTH sequencing as an escape mechanism to deceive immune responses and thereby neutralizing ACTH in blood circulation with specific antibodies resulting in adrenal deactivation (Wheatland 2004). All these together suggest possible detrimental effects of COVID-19 on the brain; the pathophysiology associated with neuroendocrine stress processes implicates in promoting a wide spectrum of psychiatric conditions.

**SARS-CoV-2 and neuroendocrine-immune axes**

The CNS-endocrine-immune axis is known to be implicated in the stress-mediated dysregulation of the immune response. Following CNS stimulation, stressors provoke the release of several hormones, including catecholamines, adrenocorticotropic, cortisol, growth hormone, and prolactin. Excess secretion of these stress hormones results in over-activation of immune cells and dysregulation of an immune response. Moreover, this interaction between the CNS and the immune system is bidirectional. Enhancing immune response, as indicated by levels of CD4⁺, CD8⁺, CD4⁺/CD8⁺ ratio, and free cortisol in serum, is involved in the psychological intervention. Furthermore, an increase in natural killer (NK) cells after psychological treatments indicates an increase in immune responses (Hannan et al. 2020). Activation of the HPA axis has been observed in pathogenesis of immune/inflammatory processes, including viral infections (Silverman et al. 2005).

The activation of this neuroendocrine axis by pro-inflammatory cytokines causes increased glucocorticoid production, a physiological response that contributes to avoid the deleterious effects of excessive production of inflammatory mediators and a nonspecific recruitment of cells with no or low affinity for triggering antigens (del Rey and Besedovsky 2017). ACE2 overexpression in corticotropin-releasing-hormone (CRH)-producing neurons in the hypothalamic paraventricular nucleus alters the processing of psychogenic stress in mice, decreasing the CRH content in the hypothalamus and corticosterone
plasma levels, as well as anxiety-like behaviors (Wang et al. 2018). While genomic sequences of SARS-CoV have been found in the human hypothalamus, it remains to be determined if the virus also decreases ACE2 content in this region of the brain. A down-regulation of hypothalamic ACE2 levels may be considered as another potential mechanism by which SARS-CoV/SARS-CoV-2 induces hyperactivity of the HPA axis with consequent psychiatric disturbances that are observed in these patients, such as the anxiety for example. However, the role of ACE2 in the SARS-CoV-2 pathogenesis is still unknown and more studies are needed to test this mechanism (Raony et al. 2020). By contrast, in a study that prospectively assessed the presence of hormonal changes in 61 SARS survivors (without pre-existing endocrine disorders) three months following recovery, 24 patients (39.3%) displayed late HPA axis hypoactivity, with hypocortisolism. This alteration appeared to be a pathological effect of SARS-CoV, since nearly two-third of the patients did not use steroids and the majority were young (mean age: 36.5 years) and previously healthy. Retrospective data from SARS survivors do not support changes in HPA axis activity during the acute phase, suggesting that SARS-associated hypocortisolism is a late onset phenomenon (Leow et al. 2005). Since the “cytokine storm” is observed in the acute phase of SARS, it is unlikely that the rise in cytokine levels is secondary to the hypofunction of the HPA axis. Although pro-inflammatory cytokines classically increase the activity of the HPA axis (i.e., a down-regulation mechanism of the inflammatory response), under some conditions, TNF-α and transforming growth factor beta (TGF-β) may induce HPA axis hypoactivity (Morris et al. 2017).

As a result, it is possible that certain cytokines that are increased in SARS patients play a causal role in SARS-associated hypocortisolism. Because HPA hyperactivity and hypoactivity are associated with depression (Maripuu et al. 2014), hypocortisolism may also be associated with depressive symptoms that may develop in survivors of SARS. Furthermore, because of the similarities between SARS-CoV-2 and SARS-CoV, it is possible that this mechanism involved in HPA axis hypoactivity could also be observed in COVID-19 (Hauer et al. 2009). Therefore, studies that simultaneously assess HPA axis activity, cytokine levels and psychiatric disorders in COVID-19 patients and survivors will surely improve current knowledge (Chiappelli et al. 2016). Interestingly, elevated levels of circulating IL-6 have been found in early episode psychosis patients (Stojanovic et al. 2014).

Several studies reported symptoms of psychosis during the acute or long-term phase in SARS patients. Therefore, it is possible that SARS-CoV-2 infection and stressors related to hospitalization may increase the risk of psychosis by increasing levels of cytokines and/or by disrupting the glucocorticoid-immune circuits. Since infections are associated with increased risk of developing schizophrenia (Benros et al. 2011), it could be suggested that future studies further assess the potential association between SARS or COVID-19 and the development of schizophrenia. Indeed the importance of measures that prevent or reduce the impact of COVID-19 on mental health should also be assessed. Therefore, it is possible that increased pro-inflammatory cytokine levels in COVID-19 lead to hypoactivity or hyperactivity of the HPA axis. This neuroendocrine axis is not able to reduce the production of inflammatory mediators, due to a dysfunction in the negative feedback between the HPA axis and the immune system. Therefore, we hypothesize that such a dysfunction in the negative feedback between the HPA axis and production of pro-inflammatory cytokines may also be associated with mental health outcomes of the SARS-CoV-2 infection; thus it could conceptually correspond to a PNI dysfunction.

Cytokine storm and possible pathogenic mechanisms of COVID-19 in neuropsychiatric and neuroimmunological diseases

Cytokine storm denotes a hyperactive immune response, characterized by the release of IFNs, interleukins, tumor necrosis factors, chemokines, and several other mediators (Sinha et al. 2020). Recently, increasing studies indicated that the cytokine storm may contribute to the mortality of SARS-CoV-2 infected patients (Tang et al. 2020), which appears to play an important role in the pathogenesis of several severe manifestations of COVID-19 (Bhaskar et al. 2020). The immune mechanisms triggering the cytokine storm in SARS infection are frequently contributed to the pathogenesis and even a wide range of neurodegenerative diseases progression (Serrano-Castro et al. 2020). For example, in AD, high levels of pro-inflammatory cytokines (especially IL-1 and IL-6) are involved in beta amyloid (Aβ) phagocytosis inhibition by microglial cells, which induced by pro-inflammatory cytokines results in pathogenic Aβ deposition (Koenigsknecht-Talboo and Landreth 2005).

COVID-19 causes a hyperinflammatory response associated with cytokine storm by the activation of monocytes/macrophages, dendritic cells, mast cells, T-cells, and endothelial cells. SARS-CoV-2-activated mast cells can cause either protection by fighting infection or
deleterious effects by inducing inflammation. COVID-19 can aggravate neuroinflammation through psychological and other stressful conditions, activation of mast cells, neurons, astrocytes, microglia, and increase inflammatory cytokine and chemokine levels in the CNS. COVID-19 is a risk factor for stroke pathogenesis and it can exacerbate neuroinflammatory disorders such as neurotrauma, including traumatic brain injury (TBI) pathogenesis. In addition to monocytes/macrophages, dendritic cells, epithelial and endothelial cells, mast cell activation-mediated inflammatory mediators could contribute to the cytokine storm and neuroinflammatory response in COVID-19 (Baig et al. 2020; Kempuraj et al. 2020; Saleki et al. 2020). It is proposed that the immune system cytokine network may also communicate with the CNS cytokine network, especially when the BBB is compromised. Microglia and IL-1 activation can cause increased reactive oxygen species (ROS) production, phagocytosis, apoptosis, and increased cytokine expression within the CNS (Kennedy and Silver 2016), leading to neural tissue damage through neuroinflammation, increased oxidative stress and excitotoxicity, and dysfunction in synaptic pruning (Achar and Ghosh 2020). The systemic immune system cytokine network and the CNS cytokine network may also communicate with the CNS cytokine network, especially when the BBB is compromised. Microglia and IL-1 activation can cause increased reactive oxygen species (ROS) production, phagocytosis, apoptosis, and increased cytokine expression within the CNS (Kennedy and Silver 2016), leading to neural tissue damage through neuroinflammation, increased oxidative stress and excitotoxicity, and dysfunction in synaptic pruning (Achar and Ghosh 2020). The systemic immune system cytokine network and the CNS cytokine network influence each other through the nepotopidelic pathway, involving neurokinin C and B, neuroendocrine peptides (NPY)/gastrin-releasing peptide (GRP), SPA-GRP: (D-Arg, D-Trp, Leu) Substance P), and vasoactive intestinal polypeptide (VIP). Activation of macrophages and phagocytosis, chemotaxis with neutrophils and degranulation of mast cells, and activation and proliferation of T-cells activate this pathway. Inflammatory cytokines are also be transported through the blood, which could further amplify the cytokine storm (Vaninov 2020). TNF-α, IL-1, and IL-6 are primary cytokines of the acute immune response and the IFNs are key cytokines for antiviral immune response, but the excessive response of these pro-inflammatory mediators have been considered major triggers of multiorgan failure (Unal et al. 2020). On the other hand, the CNS might be the first affected organ due to a compromised BBB, which is closely associated with increased circulating levels of cytokines. These cytokines induce the production of ROS through stimulation of astrocytes and glial cells. ROS and peripheral cytokines activate two different types of microglia; microglia-1 (M1) and microglia-2 (M2). While M1 involves in inflammatory processes in the CNS, M2 are responsible for the anti-inflammatory processes. Thus, M1 activation results in an increase of pro-inflammatory cytokines and M2 initiates the astrogliosis in order to protect CNS. All of these opposite reactions, induced by SARS-CoV-2, may cause a CNS dysfunction that becomes apparent as encephalopathy (Serrano-Castro et al. 2020).

Impact of SARS-CoV-2 infection on neuroimmunological diseases

The cytokine storm, caused by SARS-CoV-2 virus infection, apart from its highly destructive effects on respiratory, renal, digestive, and cardiovascular systems, may cause either BBB disruption directly or by contributing to direct vascular endothelial cell damage through direct viral infection (Achar and Ghosh 2020). Sine COVID-19 pandemic, there has been abundant evidence, suggesting CNS involvement of the COVID-19 virus infection, either with acute symptoms like encephalopathy-meningitis or seizure-epilepsy scenarios or with subacute and chronic syndromes like depressive-anxiety and psychotic syndromes. Neuroinflammation is believed to be one of the cornerstone pathophysiology underpinning neuroimmunological and neurodegenerative disorders, including AD, MS, Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS), etc. (Chew et al. 2020).

A group of evidence suggested that SARS-CoV-2 infection might be capable of promoting acute and chronic neuroinflammatory processes, contributing to neuroimmunological pathways, leading to age related or nonrelated neurological and psychiatric diseases (Bossù et al. 2020). SARS-CoV-2 virus is capable of activating mast cells, neuroglial cells, dendritic cells, macrophages, neutrophils, and lymphocytes, creating and promoting a cascade of inflammatory responses, causing cytokine storms even extra-cranially in circulation and intracranially in the neural environment, augmenting a variety of degenerative neurological disease mechanisms (Kempuraj et al. 2020).

COVID-19 and multiple sclerosis

MS is considered as a neuroimmunological and neurodegenerative disease of auto-immune demyelinating nature, encompassing a variety of immune pathways as its main pathophysiology (Salvetti et al. 2015). Some viral infections predominantly respiratory ones along with other respiratory infections are believed to be associated with MS underlying pathophysiology or its recurrent exacerbations. Epstein-Barr virus, adenovirus, varicella-zoster, and influenza viruses have been previously studied to have interactions with MS-related mechanisms (Djelilovic-Vranic and Alajbegovic 2012). A group of
studies have suggested that COVID-19 infection might exacerbate MS-related clinical manifestations through some proposed mechanisms. TLR immune modification, infection induced alterations in immune cell population, neuroinflammation following BBB disruption, direct neural cell infection and virus induced demyelination are mentioned in these studies (Sadeghmousavi and Rezaei 2020). There is a report of a-29-year old woman living with his COVID-19 positive father, presenting with MS symptoms (right sided optic neuritis with asthenia and proximal limb myalgia) and anosmia from 2 to 3 weeks earlier with dysgeusia, with positive CSF IgM and IgG antibodies but negative PCR and positive MRI demyelinating findings with no enhancement (so inactive), implied a possible association between a past COVID-19 infection and MS like lesions (Palao et al. 2020).

Some of medications used or investigated for MS treatment are considered forbidden in case of concomitant infectious diseases, including COVID-19, because of their immunosuppressive properties. However, in these situations risk assessment should be done with special precise precautions to avoid MS flares. Furthermore, it should be considered that immune compromised state may not be totally against COVID-19 prognosis since some detrimental complications associated with COVID-19 infection, including severe pneumonia which is believed to result from immune over-activation and cytokine storm. Therefore, it is necessary to predict the exact consequences of MS treatment in simultaneous COVID-19 infection to achieve a reasonable prognosis for the patient (Boziki et al. 2020). For example, comparing two cases of MS patients first one being on fingolimod treatment and the second one being on teriflunomide, presented with COVID-19 symptoms and confirmed positive through swab test, showed that previously fingolimod treated patient (the treatment was discontinued during admission course) never develop pneumonia during disease course, but developed an incomplete seroconversion for virus-related antibodies. On the other hand, previously teriflunomide treated patients (which was also discontinued) was admitted with diffuse interstitial pneumonia and a dropped O2 saturation, but later developing an acceptable seroconversion and anti-COVID-19 IgG production similar to normal immune responses (Bollo et al. 2020). Tocilizumab, maybe for its inhibitory effects on IL-6 tissue entry from circulation, showed special therapeutically effects in an MS patient (previously being on fingolimod) presenting with severe COVID-19 complications (including sever pneumonia), not exacerbating patient MS-related conditions (Valencia-Sanchez and Wingerchuk 2020).

Other neuroimmunological disorders

COVID-19 is capable of worsening both motor and non-motor symptoms of PD and also mental health conditions of these patients (Ferini-Strambi and Salsone 2020). These negative effects partially might result from the direct consequences of viral infection or mental and behavioral conditions resulted from disease itself or COVID-19 pandemic (Ferini-Strambi and Salsone 2020). Another study revealed that PD patients especially those on intense therapies, are more notably vulnerable to COVID-19 disease with high mortality and morbidity rates recorded (Antonini et al. 2020). Apart from these indirect effects, it was suggested that SARS-CoV-2 virus might play a role in promoting chronic neurodegenerative processes by dysregulation of proteostatic mechanisms in the affected brain regions, resulting in deposition of unwanted toxic protein components like α-synuclein. Thereby, SARS-CoV-2 might be able to trigger a cascade of neuroimmune processes leading to apoptosis of cells in substantia nigra (SN) and related regions, as confirmed for H1N1 infection of dopaminergic cells (Marreiros et al. 2020). Another group of evidence also showed that SARS-CoV-2 intestinal infection may cause a type of gut dysbiosis, along with other inflammatory states from SARS-CoV-2 infection, causing increased intestinal wall permeability allowing excess lipopolysaccharides (LPS) passing to the circulation. This excess LPS in the circulation promotes increased neuroinflammation in the brain SN regions, contributing to PD pathophysiology. Another pathway for damaging SN dopaminergic cells that was mentioned in this study is via α-synuclein deposition both in SN or intestine which may be transferred to the brain via vagal nerve (Follmer 2020). Previously, it was mentioned that AD symptoms or neuropsychiatric symptoms may be intensified with concomitant COVID-19 or pandemic associated conditions. COVID-19 resulted hypoxia also may have an important role in promoting AD cognitive and neuropsychiatric deterioration (Ferini-Strambi and Salsone 2020). Vice versa, a group of studies showed higher mortality rates of COVID-19 patients with dementia, compared to non-dementia patients in similar settings (Bianchetti et al. 2020).

The ability of SARS-CoV-2 virus in infecting microglial cells and astrocytes is proposed to be effective in promoting neuroinflammatory state in the brain both acutely and chronically, causing AD neurodegenerative processes. Some discussions have been made about possible roles of APOEɛ3 gene in AD appearance and its association with increased possibility of COVID-19 infection, but there has
not been a clear evidence of direct association between this gene and SARS-CoV-2 synergistic activities resulting in AD-related dementia syndromes so far (Abate et al. 2020). Other studies concluded that olfactory bulb infection by SARS-CoV-2 virus may activate M1 phenotype of microglial cells triggered by cholinergic neurons damage. M1 microglial phenotype is responsible for promoting neuroinflammation. Furthermore, viral proteins produced through viral infection of neural cells are thought to activate the NF-κB pathway to trigger inflammatory cytokine production, finally resulting in AD-related amyloid fibrils deposition in olfactory bulb or other brain regions including brain cortex (Lennon 2020; Mahalaxmi et al. 2020). All these together suggest that COVID-19 infection may be associated with different neuroimmunological and neurodegenerative conditions via different possible mechanisms that warrant more researches to be fully and clearly elucidated.

Conclusion

COVID-19 pandemic causes a public health emergency of global concern. The high spreadability, lethality, and specifically because of its strong effect on health consequences in the medium and long-term makes this pandemic as a global threaten. There is evidence that the nervous system could become a potential target of infection. Cytokine storm in COVID-19 is involved in triggering of auto-immune response. Neuroinflammation as a result of high levels of cytokines/chemokines play a critical role in pathogenesis of a wide range of neurodegenerative diseases. Furthermore, SARS-CoV-2 invades the CNS and causes the immune dysregulation, which is involved in the pathogenesis and development of numerous neurodegenerative diseases. Similarly, activation of HAP axis in viral infections stimulates the progression of immune/inflammatory processes. One of the vital keys to management of COVID-19 is accurate diagnosis for effective treatment, and subsequent prevention. Traditionally, biomarkers provided valuable information in the early detection of disease etiology, diagnosis, further treatment and prognosis. Due to the neuroinvasive potential of SARS-CoV-2 infection, immune and HPA axis dysregulation are involved in developing of such related disorders.

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