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Brain Biomarkers in Patients with COVID-19 and Neurological Manifestations: A Narrative Review

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Abstract

Acute hyperinflammatory response (cytokine storm) and immunosuppression are responsible for critical illness in patients infected with coronavirus disease 2019 (COVID-19). It is a serious public health crisis that has affected millions of people worldwide. The main clinical manifestations are mostly by respiratory tract involvement and have been extensively researched. Increasing numbers of evidence from emerging studies point out the possibility of neurological involvement by COVID-19 highlighting the need for developing technology to diagnose, manage, and treat brain injury in such patients. Here, we aimed to discuss the rationale for the use of an emerging spectrum of blood biomarkers to guide future diagnostic strategies to mitigate brain injury-associated morbidity and mortality risks in COVID-19 patients, their use in clinical practice, and prediction of neurological outcomes.

Keywords
- brain
- biomarkers
- COVID-19
- neurologic injury

Introduction

Infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have the potential to affect multiple organs (including the brain and respiratory system), resulting in a significant fatality and long-term disability.[1] As of August 24, 2021, almost 212 million cases and 4.43 million deaths have been reported worldwide due to the SARS-CoV-2.[2] There is increasing evidence worldwide of several neurological and neuropsychiatric manifestations in coronavirus disease 2019 (COVID-19) patients; however, underlying mechanisms, the clinical manifestations, and the associated sequelae produced by SARS-CoV-2 infection are poorly understood.[3–7] Neurological manifestations in COVID-19 patients include impaired consciousness,[8] headache,[9] long-term cognitive defects, altered mental status,[10] anosmia/dysgeusia,[8] neuropsychiatric disturbances,[11] cerebrovascular injury,[12,13] encephalopathy, seizures,[9] meningoencephalitis, encephalomyelitis, demyelination,[13] acute disseminated encephalomyelitis (ADEM),[14] hypoxic injury,[13,15] hydrocephalus,[16] and Guillain–Barré syndrome.[17] A blood biomarker (BB) is a biological measure that provides information about the state of a pathogenic or biological process, assists in diagnosis, monitoring disease progression, response to therapy, and the patient's overall clinical course. These neurologic biomarkers are glial fibrillary acidic protein (GFAP) (astrocyte marker); neurofilament-light chain (NfL; axonal markers), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1; neuronal marker), tau protein, S100 calcium-binding protein B (S100B), neuron-specific enolase (NSE), and inflammatory markers (interleukin [IL]-6, tumor necrosis

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Table 1 Showing biomarker abnormalities in COVID-19 patients[18,19]

	CSF	Blood
Glial-specific and neuronal-specific biomarkers	GFAP, UCH-L1, S100B, NSE, NfL, tau protein, Beta2-microglobulin	GFAP, UCH-L1, S100B, NSE, NfL, Beta2-microglobulin
Inflammatory biomarkers	IL-6, IL-8, TNF-α	↑ (ESR, CRP, IL-2, 6, 8,10, Serum ferritin, PCT, TNF-α, IL-1β)
Biochemical biomarkers		↑ (AST, ALT, BUN, LDH, CK, Creatinine) ↓ Albumin
Hematologic biomarkers		↑ (Neutrophil count, WBC count) ↓ (B cell count, T cell count, Eosinophil count, Platelet count, Lymphocyte count, NK cell count)
Coagulation biomarkers		↑ (D-dimer, PT)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; GFAP, glial fibrillary acidic protein; IL, interleukin; LDH, lactate dehydrogenase; NSE, neuron-specific enolase; NfL, neurofilament light chain; NK, natural killer; PCT, procalcitonin; PT, prothrombin time; S100B, S100 calcium-binding protein B; TNF-α, tumor necrosis factor α; UCH-L1, ubiquitin C-terminal hydrolase-L1 protein; WBC, white blood cell.

factor [TNF]-α, C-reactive protein [CRP]) as summarized in ►**Table 1**.[18,19] The use of BBs in COVID-19 patients help in understanding the risk factors associated with neuro-axonal injury and detection of neurologic morbidity (neurological deficits and neuropsychiatric problems). These biomarkers may be particularly useful for critically ill patients in whom transportation to imaging suites and clinical evaluation of neurological functions are difficult. This article explains the current status of biomarker research in COVID-19 patients for early diagnosis of brain injury and characterization of central nervous system (CNS) response to infection by either direct invasion by pathogen or by inflammatory response.

Pathophysiology

SARS-CoV-2 is a positive sense single-strand ribonucleic acid with spike proteins (S1 and S2) on its envelope. The spike proteins play an important role in binding to angiotensin-converting enzyme 2 (ACE2) receptors to enter the host alveolar epithelial type 2 (AT2) cells by endocytosis.[17,20] SARS-CoV-2 can be transmitted through coughing and sneezing. The virus enters the lungs through the respiratory tract and attacks AT2 cells, which produce surfactants to decrease the surface tension within alveoli. ACE2 receptors are also found in the kidneys, heart, pancreas, and endothelial cells.[20,21] This result in releases of specific inflammatory mediators to stimulate macrophages,[22,23] which releases cytokines (IL-1, IL-6, and TNFα) and chemokines (CXCL10 and CCL2) into the bloodstream resulting in abnormal inflammatory responses (vasodilation, increased capillary permeability, increase in body temperature, and decrease in surfactant levels in AT2 cells leading to alveolar collapse and impaired gaseous exchange).[14,24–26] ACE2 receptors and transmembrane serine protease 2 are also expressed in the CNS (neurons, glia, and the cerebrovascular endothelium).[19,27] Vasculopathy and breach in the blood-brain barrier (BBB) provide a route to SARs-CoV-2 invasion in the human brain through the bloodstream.[28] CNS invasion with infection of the hypothalamus and brainstem (containing medullary respiratory center) leads to an increase in body temperature and respiratory distress in COVID-19 patients.[29–31] This may later attribute to neurological deficits and/or increased risk for neurodegenerative diseases.

Methodology

The details of the search strategy for this narrative review have been described in detail in an illustrative table (►**Table 2**). The search was limited to English language reviews and original research articles, and the titles and abstracts were read to obtain relevant studies. Pertinent historical papers were also included.

Neurofilament-Light Chain Protein

NfL is a subunit of neurofilaments, which are exclusively located in the neuronal cytoplasm and are thought to be critical for structural stability and radial growth of axons.[20,32] It is an intra-axonal structural protein and a biomarker of neuronal injury.[33,34] Over the last two decades, neurofilaments are gaining increasing attention as highly

Table 2 Details of search strategy

Database searched	Time duration	Mesh terms used for search
PubMed Central, EMBASE, Google Scholar	From November 1, 2019 to January 31, 2021	"Brain, biomarkers," "COVID-19," "inflammatory cytokines," and "neurological manifestations"

specific indicators of axonal injury (as they are abundantly expressed in neurons). It could have a prognostic value when its measurement reaches pathological levels as a result of neuroaxonal damage in a variety of neurological diseases (neurodegenerative, inflammatory, vascular, and traumatic), not only in the cerebrospinal fluid (CSF) but also in blood levels offering a key advantage over other possible biomarkers. The role of NfL as a biomarker has been largely reported in multiple sclerosis (MS), Alzheimer's disease (AD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), atypical parkinsonian disorders, stroke, and traumatic brain injury (TBI).[35,36] Plasma NfL level elevates later during acute brain injury (whereas GFAP levels appear rapidly) and remains elevated for more than 10 days.[37] Since it is feasible to measure NfL concentration in the blood, it may be a promising biomarker for monitoring the disease progression, and for assessing the efficacy and/or toxicity of treatment in CNS disorders. Its levels in the blood can be measured in many different diseases with enzyme-linked immunosorbent assay (ELISA), single-molecule array assays, and electrochemiluminescence assay.[35,36] Recent studies have shown increased concentrations of serum NfL in COVID-19 patients and may be a predictor of a severe disease course and increased mortality.[19] A prospective, cohort study (100 health care workers) conducted by Ameres et al revealed a significantly increased level of serum NfL in 28% of mild-to-moderate COVID-19 patients (with neurological symptoms, like headache and anosmia) when controlling for age and sex.[38]

Beta2-Microglobulin

Beta2-microglobulin (β_2-m) is a low molecular weight, light-chain class I major histocompatibility complex proteins present on the surface of all nucleated cells. It is present in the CSF, blood, urine, synovial, and other body fluids.[39,40] Serum and CSF β_2-m is a reliable marker for activation of the cellular immune system in different inflammatory, neoplastic, or autoimmune CNS disorders. It is dissociated and released to all biological fluids during metabolism and degradation, and increased values reflect a rate of cell membrane renovation, immune activation, and cellular turnover. Pilotto et al highlighted raised level of CSF inflammatory proteins (IL-6, IL-8, TNF-α, and β_2-m) in a COVID-19 patient suffering from encephalitis. They demonstrated normalization of CSF cytokines along with progressive clinical improvement after high-dose steroid treatment.[41]

Substantial elevation of β_2-m CSF concentration should lead to a suspicion of bacterial or viral meningitis/encephalitis, malignant infiltration, and disease progression caused by an inflammatory response (immune activation or tissue destruction); this has been documented in multiple studies. It is a useful marker for differential diagnosis, early therapy, and monitoring of the therapeutic effect of CNS diseases.[40,42] Besides this, further studies are required to find out the significance of this potential marker in COVID-19 patients in relation to CNS damage and prognostication.

Glial Fibrillary Acidic Protein

GFAP is a type III intermediate filament of the cytoskeleton of astrocytes and other glial cells but is not found outside the CNS.[43] It is a cell-specific marker engaged in processes like cell communication and functioning of BBB, regulating astrocyte mechanical strength, morphology, and stability. It is highly expressed in astrocytes and serves as a marker of astrocytic activation/injury.[33]

GFAP is released into the bloodstream during brain injury, which causes the increased functional activity of astrocytes or the development of reactive astrocytosis, which aids in determining the severity of the injury. This upregulation of GFAP concentration relates to damage to the nerve tissue, development of neurodegenerative states, and metabolic abnormalities during brain injury. This makes GFAP an attractive biomarker for brain injury screening. Recent studies have documented elevated CSF and serum GFAP levels after mild, moderate, or severe TBI in adult patients, which correlate with TBI magnitude and outcomes in children as well.[43–46] Mao et al[47] in a retrospective, observational case series (214 COVID-19 patients) demonstrated increased neurological manifestations (36.4%) such as acute cerebrovascular diseases (5.7%) in COVID-19 patients. Similar findings were observed by Avula et al[48] in a retrospective study on four patients who had radiographic evidence of stroke in COVID-19 infection.

Recent studies document increased levels of brain injury biomarkers (GFAP and UCH-L1, S100B, NSE, and neurofilament light chain protein) in COVID-19 patients with different brain injuries like stroke,[49] seizures,[50] delirium, and TBI.[19,33,51] They can be used to assist in the prognosis of poor neurological outcomes, close monitoring for neurological complications, and making prompt decisions and management. Reichard et al[52] revealed a range of neuropathological lesions (resembling both demyelinating and vascular etiologies) which were also confirmed by GFAP immunostains in the postmortem analysis of the brain of a SARS-CoV-2 patient. Such findings raise the possibility of association of microthromboembolic events and related complications in COVID-19 patients which may provide insight into their clinical management.[52]

Ubiquitin C-terminal Hydrolase L1

UCH-L1 is an extremely abundant multifunctional globular protein in the brain (1–5% of total neuronal protein) with a complicated three-dimensional knotted structure. It is involved in ubiquitination, deubiquitination, and ubiquitin homeostasis. It is primarily expressed in neuroendocrine cells, and neuronal cells and its high levels correlate with multiple malignancies (pancreatic cancer, colorectal cancer, and invasive breast cancer) and various diseases. It plays an essential role in the maintenance of axonal integrity and stability, and the dysfunction of this enzyme has been associated with neurodegenerative disease (Parkinson's disease and AD) due to axonal degeneration and neuronal death.

Cooper et al in a prospective, observational study (27 COVID-19 patients) demonstrated a positive correlation of

significantly increased levels of UCH-L1, GFAP, and NfL and delirium (Intensive Care Delirium Screening Checklist score) during the first week of intensive care unit (ICU) stay in the COVID-19 group compared with the ICU control group.[46] A similar association has been described in multiple studies of acute brain injury like stroke,[49] seizures,[50] and TBI.[19]

S100B

S100B is a calcium-binding peptide of the S-100 protein family, widely expressed in astroglial cells. It plays a significant role in normal CNS development (cytoskeletal structure and cell proliferation) and recovery after injury.[53] It is predominantly found in astroglial and Schwann cells, and is a marker of astroglial cellular integrity/activation and can be measured by several methods, like ELISA, Western blot, quantitative polymerase chain reaction, immunoradiometric assay, immunoluminometric assay, and mass spectroscopy.[54] S100B can be measured in peripheral blood, urine, and CSF.

Elevated levels of extracellular S100B has been detected in patients with acute brain injury, circulatory arrest, stroke,[55] neurodegenerative (ALS, Parkinson's disease, and MS),[54] and inflammatory diseases,[56] which stimulates expression of proinflammatory cytokines. S100B helps in predicting the efficiency of treatment and prognosis and is a reliable neurobiomarker for the evaluation of severity in patients with severe head trauma (along with an early prediction of the development of raised intracranial pressure),[54,57] subarachnoid hemorrhage, and stroke.[54,58,59] Aceti et al collected serum samples from 74 hospitalized COVID-19 positive patients and found a significant correlation between S100B and other key parameters of COVID-19 severity (ferritin concentrations, procalcitonin, D-dimer, CRP and, alanine aminotransferase [ALT]). S100B levels were found to be higher in high-intensity care ward patients (8.80 ± 10.24 vs. 0.62 ± 2.10 ng/mL) in comparison to low-intensity care ward patients. They concluded that raised serum levels of S100B correlate with the severity of COVID-19 disease and inflammatory processes, which would be beneficial in monitoring the disease course and prognosis.[60]

Tau Protein

Tau is a microtubule-associated protein, required for stabilizing neuronal microtubules and maintaining the structural integrity of axons under normal physiological conditions. The other important cellular function involves neuronal development, axonal sprouting, cellular proliferation, signal transduction, and synaptic transmission. However, in certain pathological situations, hyperphosphorylation of tau protein in neurons is associated with neurofibrillary degeneration. This process results in the pathogenesis of several neurological disorders (FTD, AD, and other tauopathies).[61,62]

Espíndola et al[63] analyzed the CSF profile of 58 patients with SARS-CoV-2 infection and demonstrated elevated tau and NfL concentrations in patients with encephalopathy and ADEM. They implicated that SARS-CoV-2 infection contributes to the stimulation of host inflammatory responses triggering the infiltration of immune cells into the brain with a subsequent neuronal injury. Ramani et al[64] by imaging cortical neurons of organoids demonstrated that patients with SARS-CoV-2 infection are associated with an enhanced level of phosphorylation of tau at position T231 and missorting of tau from axons to soma, implying neuronal stress reactions and early neurodegeneration-like effects upon virus entry.

COVID-19 is significantly associated with cerebrovascular injury, encephalopathy, seizures, meningoencephalitis, and delirium which might affect the clinical presentation, disease severity, and may result in fatal outcome with worsening of respiratory situation. Inflammation may be a potential mechanism for CNS dysfunction. According to recent studies, there is a significant correlation between S100B, ferritin concentrations, D-dimer, CRP, tau protein, and ALT with the severity of COVID-19 disease and inflammatory processes.[19,60,63] Elevations in these nonspecific markers of inflammation have prognostic value and may support clinical judgment regarding involvement of the CNS.

Inflammatory Markers

Besides brain biomarkers, the level of acute response cytokines was found to be raised in COVID-19 patients with CNS involvement. This overlapping of immune system cytokine and CNS cytokine network was seen especially in patients with a breach of BBB integrity. Increased production of reactive oxygen species, phagocytosis, apoptosis, and cytokine occurs within the brain due to IL-1 and microglia activation, which may lead to neural tissue damage.[65] Multiple studies have shown an elevated level of IL-6, CRP, ferritin, D-dimer, and procoagulant factors in critically ill COVID-19 patients.[19,66]

Ruan et al conducted a retrospective multicenter study in 150 patients and suggested that mortality in COVID-19 might be due to the virus-activated cytokine storm. They concluded that the presence of underlying diseases, secondary infection, age, and raised inflammatory markers (IL-6, CRP) in the blood are the predictors of a fatal outcome in COVID- 19 patients.[67] Similarly, Bodro et al observed raised CSF levels of IL-6, IL-8, and monocyte chemotactic protein-1 in SARS-CoV-2 children suffering from acute encephalitis. They concluded that such a systemic hyperinflammatory response to the virus may result in CNS dysfunction.[68]

There is a lack of literature on clinical manifestations and disease severity in pregnant women and newborn with COVID-19. Large studies examining the effectiveness of treatments specific for the neurological injury are needed to reduce the disease burden.

Conclusion

The BBs measurement in COVID-19 patients could provide timely and effective approach to address this medical crisis and also alert clinicians to take precautionary measures to prevent secondary complications. The available studies on BBs in COVID-19 patients are of poor quality methodology

and carries low evidence. Future studies and follow-up of COVID-19 patients will be required to better understand the specific pathological mechanism of cytokine storm and biomarkers to target strategies for critically ill COVID-19 patients and deliver improved outcomes.

Conflict of Interest
None declared.

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