Viewpoint

COVID-19 and hyperammonemia: Potential interplay between liver and brain dysfunctions

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Abstract

Although COVID-19 affects the respiratory system, extrapulmonary manifestations frequently occur, including encephalopathy and liver damage. Here, we want to call attention to a possible connection between liver and brain dysfunctions, in which ammonia can play a role targeting astrocytes. Importantly, astrocyte dysfunction can produce future and/or long-term neurological consequences.

1. Pathological events in sepsis-associated and hepatic encephalopathies

Encephalopathy is a neurological manifestation that can occur in both bacterial and viral infections. During sepsis, severe systemic inflammation produces a cytokine storm, which consists of a marked increase in pro-inflammatory mediators, such as tumor necrosis factor α (TNF-α), interleukins (IL-1β, IL-6, IL-12) and chemokines (Tranah et al., 2013). IL-6 is an important inducer of the acute phase response in the liver, inducing the production of C-reactive protein among other effects, in addition to potentially causing acute liver injury. In COVID-19, both hyperinflammatory scenarios and hepatic overactivation have been described and are marked by an increase in another acute phase protein particularly associated with viral infections, ferritin (Fara et al., 2020). It is important to note that liver failure, which frequently complicates...
sepsis, causes hyperammonemia in addition to potentiating systemic inflammation. As a consequence, both accumulated pro-inflammatory mediators and ammonia can synergically damage the blood-brain barrier (BBB), triggering a wide range of effects on neural cells and brain dysfunction.

2. Effects of systemic inflammation and hyperammonemia on astrocytes

Astrocytes participate in the formation and maintenance of the BBB, thus constituting a physical barrier to protect CNS. It is important to note that, during systemic inflammation and/or hyperammonemia, astrocytes undergo an activation process, which leads to morphological and functional changes that significantly and similarly participate in the pathogenesis of sepsis-associated encephalopathy (SAE) and HE (Bellaver et al., 2018; Bobermin et al., 2020; Tranah et al., 2013). Morphological remodeling during astrocyte reactivity can facilitate the disruption of BBB, resulting in infiltration of peripheral cytokines and immune cells. Importantly, in response to inflammation, astrocytes can acquire an activated state, leading to nuclear factor kappa B (NFkB)-dependent up regulation and the production and release of pro-inflammatory cytokines and chemokines (including TNF-α, IL-1β, IL-6 and monocyte chemotactic protein-1, MCP-1), as well as the expression of genes associated with inflammatory responses, such as cyclooxygenase-2 (COX-2) and inducible nitric oxide (iNOS). Therefore, astrocytes perpetuate and self-amplify the inflammatory response within the CNS, acting as a bridge between systemic inflammation and neuroinflammation.

Importantly, the expression of the cyclin-dependent kinase inhibitor p21 gene in astrocytes is also modulated by systemic inflammation and hyperammonemia (Bobermin et al., 2020). p21 is potentially involved in NFkB activation and is an important cell cycle regulator that has been used as a marker of cellular senescence. Although senescence occurs biologically with aging, it may be prematurely induced by several stressors, especially during inflammatory conditions and hyperammonemia (Bellaver et al., 2018; Bobermin et al., 2020). Senescent cells, in turn, also acquire a pro-inflammatory secretory phenotype that characterize the phenomenon of inflammaging. It is important to note that the senescence of astrocytes, or "glial inflammaging", has emerged as a potential mechanism associated with the cognitive dysfunctions observed in SAE and HE. Additionally, oxidative imbalance, down-regulation in cytoprotective pathways and alterations in neurotransmission involving astrocytes can also contribute to the pathophysiology of encephalopathies.

Considering the multisystemic aspect of COVID-19 and the well-known cytokine storm produced during infection, it is reasonable to assume that similar events can occur in the CNS of COVID-19 patients. With particular regard to glial cells, autopsy data from COVID-19 patients have shown astroglial and microglial activation throughout the brain, accompanied by cytotoxic T cells infiltration, without current evidence of SARS-CoV-2 infection (Matschke et al., 2020). Moreover, increased plasma levels of glial fibrillary acidic protein and neurofilament light chain reinforce astroglial and neuronal commitment in COVID-19 (Kanberg et al., 2020). In addition to encephalopathy, an increasing number of studies have reported neuropsychiatric manifestations in COVID-19 patients. Alterations in the expressions of molecular markers associated with several neuropsychiatric disorders (such as depression, bipolar disorder, schizophrenia, alcohol dependence, among others) have also been identified in COVID-19 clinical samples and, interestingly, many of them are related to inflammatory signaling (Quincozes-Santos et al., 2021). Taken together, these data support roles for peripheral immune cells and inflammatory molecules and metabolites, produced by systemic inflammation and potentially by liver dysfunction, in the brain abnormalities observed in COVID-19 patients.

3. Concluding remarks

The need to assess the abnormalities associated with COVID-19 in different organs/systems in an integrative manner is becoming increasingly clear. Here, we call attention to the association between liver and brain dysfunctions, in which ammonia may play a crucial role, along with the production of cytokines and other inflammatory mediators (Fig. 1). Considering the versatility of astrocyte functions, it may be hypothesized that these cells are primary central targets of this relationship, receiving and integrating the peripheral signals to produce CNS responses. It is also important to point out that the occurrence of pre-existing liver diseases may aggravate and/or increase the risk of neurological manifestations in COVID-19, and that there may be a necessity for follow-up to observe hepatic function after infection. Finally, and just as importantly, while the encephalopathy associated with SARS-CoV-2 infection can be transient, cognitive deficits, neurodegenerative and psychiatric disorders might be long-term consequences of COVID-19.

Funding

The authors of this study are supported by Universidade Federal do Rio Grande do Sul (UFRGS), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Fundação de Amparo à Pesquisa L.D. Bobermin, A. Quincozes-Santos.
of the Rio Grande do Sul (FAPERGS).

**Ethics approval**

Not applicable.

**Consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and material**

Not applicable.

**Code availability**

Not applicable.

**Author’s contributions**

LDB and AQS conceived, wrote and revised the manuscript. LDB and AQS designed and created the figure.

**Declaration of competing interest**

The authors declare that they have no conflict of interest.

**Acknowledgements**

The authors are supported by the Universidade Federal do Rio Grande do Sul (UFRGS), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

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