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Cognitive, behavioral, neuroimaging and inflammatory biomarkers after hospitalization for COVID-19 in Brazil

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Abstract

Post-COVID-19 Condition (PCC) refers to a multisystemic syndrome that persists for months after SARS-CoV-2 infection. Cognitive deficits, fatigue, depression, and anxiety are common manifestations of the condition, but the underlying mechanisms driving these long-lasting neuropsychiatric features are still unclear. We conducted a prospective multi-method investigation of post-

hospitalization COVID-19 patients in Rio de Janeiro, Brazil. Months after hospital admission (mean=168.45±90.31 days; range=75.00–365.00 days), COVID-19 survivors (n=72) presented significant difficulties in tests tapping global cognition, episodic memory, working memory and inhibitory control relative to controls and to validated normative scores. A considerable proportion of participants suffered from fatigue (36.1%), anxiety (27.8%), and depressive symptoms (43.1%). Elevated blood levels of TNF-α, during hospitalization, and TNF-α and IL-1β, at follow-up, correlated with changes in brain microstructural diffusion indices (β=0.144, p=0.005). These neuroimaging markers were associated with decreased episodic memory (β=-0.221, p=0.027), working memory (β=-0.209, p=0.034) and inhibitory control (β=-0.183, p=0.010) at follow-up. Severity of depressive symptoms correlated with deficits in global cognition in post-COVID-19 cases (β=-0.366, p=0.038). Our study provides preliminary evidence that long-term cognitive dysfunction following COVID-19 may be mediated by brain microstructural damage, triggered by persistent neuroinflammation. In addition, depressive symptoms may contribute to prolongated global cognitive impairments in those cases.

Introduction

After consecutive COVID-19 waves have ravaged the global population, concerns have shifted from the acute to the enduring effects of the disease on bodily systems. “Post-COVID-19 Condition” (PCC), defined as a multisystemic syndrome that persists for months after probable or confirmed SARS-CoV-2 infection (World Health Organization, 2021), has been reported to affect 43% of positively tested individuals and nearly half of the patients after hospitalization (Chen et al., 2022). While early reports have expanded this concept to cover every new, returning, or ongoing health problem following the acute disease, a recent consensus defined the core set of outcomes to be measured in future studies into the condition (Munblit et al., 2022). Fatigue, pain, neurological conditions, cognitive decline, and mental health disorders were listed as the prevailing signs and symptoms related to the nervous system among long-haulers (Munblit et al., 2022).

As for cognitive complications, colloquially known as “brain fog” (Davis et al., 2021), impairments in global cognition, attention, memory, and executive functions have been acknowledged (Crivelli et al., 2022, García-Sánchez et al., 2022, Velichkovsky et al., 2023). However, discrepancies across studies - from variable assessments of critical epidemiological factors to methodological heterogeneity, including excessive reliance on brief screening tests and lack of comparison groups - may limit the generalization of these results (Crivelli et al., 2022, Frontera and Simon, 2022, Lynch et al., 2022). Likewise, studies assessing the relationships between

neuropsychological and neuroimaging variables in PCC have yielded inconsistent or inconclusive results (Douaud et al., 2022, Shan et al., 2022). For instance, data on the links between memory impairments and structural and functional brain changes ranged from a lack of significant association to widespread unspecific cortical and subcortical abnormalities (Douaud et al., 2022, Heine et al., 2023, Shan et al., 2022). In addition, while the UK Biobank imaging group reported significant correlations between longitudinal volume changes in the crus II of the cerebellum and performances in an executive function task (Douaud et al., 2022), such findings were not replicated in other studies (Díez-Cirarda et al., 2022, Heine et al., 2023).

Unraveling the pathological pathways driving these long-lasting symptoms is crucial for future therapeutic development. One plausible and overarching framework integrating lingering cognitive problems and diffuse brain changes could be related to a sustained inflammatory activation after the acute disease (Schultheiß et al., 2022, Shafqat et al., 2022). Although exuberant inflammatory activity has become a widely recognized mechanism to explain a range of target-organ damages in the condition, encompassing acute respiratory distress syndrome (Kalinina et al., 2022), cardiac disease (Wang et al., 2020) and acute kidney injury (Joseph et al., 2020), there is no accepted definition of the term cytokine storm (Sinha et al., 2020). In individuals with COVID-19, synergistic and pleiotropic effects of these abundant circulating cytokines may elicit protracted cell proliferation and differentiation reactions, prompting chronic inflammation (Kalinina et al., 2022). Whether as a response to direct SARS-CoV-2 neuroinvasion (Purja et al., 2022) or to severe systemic hypercytokinemia (Sun et al., 2022), durable neuroinflammation could interfere with cerebral signaling and functioning, leading to neuropsychiatric features, such as depression (Milaneschi et al., 2021, Osimo et al., 2020), anxiety (Milaneschi et al., 2021), fatigue (Milaneschi et al., 2021), cognitive disorders (Su et al., 2019), and neurodegeneration (De Felice and Lourenco, 2015).

Besides infection and inflammatory-related factors, mental health conditions, including depressive symptoms, anxiety, and post-traumatic stress disorder (PTSD), might prompt or worsen cognitive deficits after hospital discharge in COVID-19 survivors (Pihlaja et al., 2023). Hence, characterizing the relationships among multiple converging elements affecting cognition in these patients could shed light on the underpinning pathophysiology of PCC. For this purpose, we conducted a prospective multi-method investigation of post-hospitalization COVID-19 patients in Rio de Janeiro, Brazil.

Section snippets

Sample

Participants were admitted to Rede D'Or São Luiz Hospital Network in Rio de Janeiro, Brazil, between May 2020 and March 2021. Inclusion criteria were: (i) age≥18 years old and (ii) confirmed COVID-19. Subjects with a confirmed infection by other agents and those with dementia or other severe psychiatric disorder (for example, schizophrenia, intellectual disability, and history of severe mood disorders) (American Psychiatric Association, 2013) were excluded. Eligibility criteria was confirmed…

Severity of acute COVID-19 is not associated with prevalence of neurological symptoms at hospital admission

Seventy-two patients from four hospitals of the Rede D'Or São Luiz Hospital Network were included in this study after participating in the follow-up assessment (mean=168.45±90.31 days; range=75.00–365.00 days). Participants' recruitment schema is summarized in Fig. 1. SARS-CoV2 infection was determined by a positive reverse-transcriptase-polymerase-chain-reaction (RT-PCR) from nasopharyngeal or nasal sampling (n=69, 95.8%) or by blood detection of anti-SARS-CoV-2 IgM antibodies (n=1, …

Discussion

Months after hospital discharge, COVID-19 survivors presented subtle, yet significant cognitive abnormalities relatively to controls. These clinical features might result from multiple mechanisms of brain insult, both directly and indirectly associated with SARS-CoV-2 infection, including increased protracted inflammatory activity and depressive symptoms. Our findings suggested that higher levels of circulating TNF-α at the acute phase and sustained elevated blood TNF-α and IL1-β in…

Conclusions

Our study provides preliminary evidence that long-term cognitive dysfunction following COVID-19 may be inflicted by brain microstructural damage, triggered by persistent neuroinflammation. In addition, depressive symptoms may contribute to prolongated

global cognitive impairments in those cases. Given the major detrimental effects of PCC on people, the economy, and public health (Malik et al., 2022, Tene et al., 2023, Van Wambeke et al., 2023), and the prospect of continuing worldwide…

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

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