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Author/s:

Debnath, M;Berk, M;Maes, M

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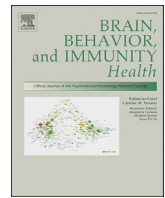
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Changing dynamics of psychoneuroimmunology during the COVID-19 pandemic



Monojit Debnath^{a,*}, Michael Berk^{b,c}, Michael Maes^{b,d,e}

^a Department of Human Genetics, National Institute of Mental Health and Neurosciences, Bangalore, India

^b Deakin University, IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Australia

^c Orygen, Centre of Excellence in Youth Mental Health, Department of Psychiatry and Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Australia

^d Department of Psychiatry, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

^e Department of Psychiatry, Medical University of Plovdiv, Plovdiv, Bulgaria

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ABSTRACT

The Coronavirus Disease-2019 (COVID-19) pandemic has led to a global health care crisis. Emerging research suggest an unanticipated impact of COVID-19 on mental and/or psychological health of both the general community and affected individuals. The fear of the COVID-19 epidemic and the consequent lockdown and economic crisis has led to globally increased psychological distress. The biological bases of immediate and new onset of psychiatric symptoms in individuals with COVID-19 are not yet known. COVID-19 infection may lead to activated immune-inflammatory pathways and a cytokine storm. Activated immune-inflammatory pathways, especially chronic low-grade inflammation, are associated with major psychiatric disorders in at least a subset of individuals. We propose that both the (sub)chronic inflammatory response and cytokine storm might crucially be involved in the immediate manifestation of neuropsychiatric symptoms in individuals with COVID-19 infection as well as heightened expression of psychiatric symptoms in COVID-19 infected individuals with prior psychiatric conditions. These events might expand concepts in psychoneuroimmunology, with the importance of chronic-low grade inflammation augmented by the cytokine storm hypothesis. Additionally, this might augment and refine diagnosis and prognostic management as well as treatment.

1. Introduction

There is a growing recognition that Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) possesses neurotropic properties and can lead to neurological manifestations similar to SARS and Middle East Respiratory Syndrome (MERS). COVID-19 is envisaged to have enduring cognitive, psychological and psychiatric consequences, however, data pertaining to this are limited. There is a growing anticipation that COVID-19 might cause delirium, depression, anxiety, fatigue, and post-traumatic stress disorder (PTSD) (Rogers et al., 2020). A recent report suggests immediate psychological distress, especially higher levels of depression, anxiety and PTSD symptoms in quarantined patients with COVID-19 (Guo et al., 2020). As observed in SARS survivors, COVID-19 survivors may also have long-term psychiatric morbidities (Mak et al., 2009).

Various mechanisms are being proposed to contribute to the neurobiological sequelae of COVID-19. SARS-CoV-2 can transmigrate to brain by disrupting blood brain barrier (BBB) and interact with the angiotensin-converting enzyme 2 (ACE2) receptor, expressed by brain tissue. The ACE2 receptor has pleiotropic roles in the stress response system and mood regulation (Vian et al., 2017). SARS-CoV-2 could affect the brain and behavior of people by causing i) direct neuronal damage, ii) immune injury, and iii) hypoxia and biogenesis. Contextually, these mechanisms have been implicated in the pathogenetic pathways of many psychiatric disorders by multiple studies. However, one pertinent question arises “how COVID-19 associated immune changes will influence the risk, progression and outcomes of psychiatric conditions?”

* Corresponding author. Department of Human Genetics, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore, 560029, India.
E-mail address: monojit-d@nimhans.ac.in (M. Debnath).

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2. COVID-19 and the cytokine storm in the central nervous system (CNS)

The genesis of a cytokine storm is evident in both infectious and non-infectious disease states occurring throughout the body, including brain. It was used to describe the underlying mechanisms of multiple infectious diseases such as variola virus, severe influenza (H1N1, H5N1), and SARS. The CNS is particularly vulnerable to cytokine storms as most of the cytokines involved in cytokine storm are either produced within the brain or reach brain from periphery, especially in the context of disrupted BBB permeability (Morris et al., 2018). Notably, the cytokine storm appears to drive chronic neurotoxic and neurodegenerative processes in conditions like post-traumatic brain injury, post-stroke and Alzheimer's disease. Multiple sclerosis, a classical example of neuroinflammatory disorder of the CNS is suggested to be associated with a cytokine storm (Link, 1998). The acute spike in circulating inflammatory moieties has also been associated with post-operative cognitive decline (Skvarc et al., 2018).

Evidences of the CNS impact of a cytokine storm in infectious diseases are relatively sparse. Acute necrotizing encephalopathy (ANE) is the most severe type of influenza-associated encephalopathy and a rare complication of influenza; this has been associated with intracranial cytokine storms. There is a significant lack of information whether cytokine storm leads to neuroinflammation in individuals with COVID-19 infection. Interestingly, a study based on CT and MRI features for the first time reports the presence of COVID-19 associated acute necrotizing encephalopathy, indicating a potential consequence of a CNS cytokine storm in patients with COVID-19 infection (Poyiadji et al., 2020).

3. Changing paradigm in psychoneuroimmunology: chronic low-grade inflammation to cytokine storm

Immunopathogenesis is one of the predominant etiological models of major psychiatric disorders. Activation of immune-inflammatory pathways, both peripherally and in the brain has been linked with the genesis and progression of neuropsychiatric disorders. It is noteworthy that most of the neuropsychiatric conditions have consistently been linked to chronic low-grade inflammation. This implies a sustained low-level inflammation throughout the body. Systemic inflammation causing neuroinflammation is a well-documented fact.

The notion that cytokine storm can lead to neuropsychiatric disorders has not been comprehensively tested so far. Most of the cytokines involved in a cytokine storm are associated with neuropsychiatric disorders like schizophrenia, and bipolar disorder. Indirect evidence indicates that a cytokine storm could be involved in driving the manifestation of psychiatric symptoms. Influenza infections have been shown to result into cytokine storm. Besides this, SARS and MERS were also reported to induce cytokine storm. Contextually, influenza infections, SARS and MERS were shown to be associated with neuropsychiatric symptoms. Based on this understanding, a neurobiological consequences of cytokine storm seems highly likely in individuals with COVID-19 infection.

There is a concern whether patients with psychiatric conditions will experience more psychiatric symptoms during COVID-19 pandemic. A recent study reports that COVID-19 has severe negative psychological impact in patients with pre-existing psychiatric conditions and these patients displayed higher risk of developing symptoms of PTSD, depression, anxiety, stress and insomnia (Hao et al., 2020). The patients with SARS-CoV-2 infection mostly exhibit a cytokine storm. Does this mean that patients with pre-existing psychiatric disorders experience a higher risk of psychiatric episodes due to dramatic increase of inflammatory response elicited by cytokine storm? Through there is a considerable lack of data towards this notion, this seems to be a possibility. Support towards this was derived from studies showing coronavirus immunoreactivity based on the measures of antibody levels and

seroprevalence of certain coronavirus strains in patients with recent onset psychotic symptoms (Severance et al., 2011). A study examining correlation between psychological distress and peripheral inflammation demonstrated positive correlation between the levels of depression and levels of C-reactive protein (CRP) among COVID-19 quarantined patients with depression symptoms (Guo et al., 2020). SARS-CoV-2 triggering new neuropsychiatric conditions were shown to be accompanied by elevated CRP levels.

We propose that SARS-CoV-2 associated immediate or new-onset neuropsychiatric manifestations are likely immune-mediated. The presence of a cytokine storm that determine the severity and mortality of patients with COVID-19 appears to escalate psychiatric manifestations. This also seems to exert deleterious effects on multiple organs and systems and lead to long-lasting changes in brain and behavior. The long-standing theory that chronic low-grade inflammation lead to psychiatric diseases may not constitute the full picture of the underlying pathway of immediate psychological distress. It is therefore assumed that the classical concept of chronic low-grade inflammation as an etiological model of psychosis may require a revision and may well be augmented by the cytokine storm model.

Most people suffering from COVID-19 recover without experiencing severe neuropsychiatric conditions, with short-term delirium as the most common neuropsychiatric symptom. People with pre-existing neuropsychiatric conditions might have a reduced incidence of SARS-CoV-2 or might be protected from COVID-19. This could be explained in the light of chronic-low grade inflammation which is already present in individuals with pre-existing neuropsychiatric conditions. The on-going chronic low-grade inflammation could potentially make an individual with pre-existing neuropsychiatric condition less vulnerable to COVID-19 or if the person with pre-existing mental illness develops COVID-19, the on-going chronic low-grade inflammation might be involved in moderating the COVID-19 associated cytokine storm. The other alternative underlying mechanism might be a disrupted Inflammatory Response System (IRS) and compensatory immune-regulatory system (CIRS). Recently, functional implications of IRS-CIRS axis have been highlighted in various neuropsychiatric disorders (Noto et al., 2019). Infections are known to activate the IRS, and the activated IRS induces the CIRS, which exerts negative feedback through production of anti-inflammatory cytokines. Those individuals with pre-existing mental illnesses and an activated IRS could be more prone to COVID-19. However, an over-active CIRS pathway as proposed in patients with major depressive disorder and bipolar disorder (Maes and Carvalho, 2018) might provide protection against the consequences of COVID-19 infection including cytokine storm and increased oxidative stress, although in some cases an overzealous CIRS response could induce immunoparalysis thereby increasing morbidity or mortality. Though these are hypothetical assumptions, such possibilities cannot be ruled out. These factors will remain as challenge to the clinicians in diagnosing and treating patients with psychiatric conditions with a history of COVID-19. Post COVID-19, immunopsychiatry may increasingly take centre stage in psychiatry.

Declaration of competing interest

None.

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