Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Mental health among COVID-19 survivors: Are we overlooking the biological links?

Sir,

The ongoing COVID-19 pandemic shows little signs of easing up soon. As it forces nations into lockdown, people into quarantine and existing systems into duress, the direct and indirect effects of the pandemic on mental health in the population is, deservedly, gaining clinical and research attention (Tandon, 2020). A wide spectrum of psychological issues has been documented among the general population, health care workers and certain high-risk sub-groups like the elderly, homeless and marginalized sections as well as children and adolescents. Most commonly demonstrated disorders in these groups include depression, anxiety and general psychological distress (Pfefferbaum and North, 2020; Rajkumar, 2020).

In contrast, few reports are available on mental health sequelae among COVID-19 survivors. Two reports from China (Yao et al., 2020a; Zhu et al., 2020) and a recent correspondence in the Lancet (Yao et al., 2020b) draws attention to the increased vulnerability for infection among those with pre-existing mental illness. Reasons pointed out include cognitive impairment, poor adherence to hygienic practices and social discrimination against mentally ill people which may prevent them from accessing services in a timely manner. Similarly, among the general population, documented factors responsible for mental health issues amidst the pandemic are mostly psychosocial in nature and include social isolation, loneliness, feelings of fear, helplessness as well as legitimate anxiety related to essential supplies, job security and concerns about contracting the virus (Armitage and Nellums, 2020; Brooks et al., 2020).

As we await data on short term and long-term mental health issues among COVID-19 survivors, we also need to focus on possible mechanistic pathways that may underlie these mental health sequelae and, crucially, why some people may be more predisposed than others. In this regard, the immune activation hypothesis which has been postulated for a wide range of psychiatric disorders may be a relevant candidate pathway for post COVID-19 mental health issues (Troyer et al., 2020). Pre-natal influenza has been linked to schizophrenia in later life (Brown et al., 2004). Likewise, a robust body of evidence points to elevated levels of systemic inflammation in depression and psychoses (Menon and Ameen, 2017). Stress induced alterations in the psychoneuroimmunoendocrine axis, the components of which include the hypothalamopituitary adrenal axis, the hypothalamopituitary thyroid axis and gut-brain axis, is now being increasingly viewed as central to the genesis of severe mental illness (Loftis et al., 2010; Mörkl et al., 2020; Smyth and Lawrie, 2013).

Pertinent to these considerations, emerging evidence suggests that the SARS-CoV-2 virus infection can herald a cytokine storm as part of the innate immune response to a highly inflammatory variety of programmed cell death referred to as pyroptosis, commonly observed in cytopathic virus infections (Shi et al., 2020). In most people, this is an adaptive response and serves to recruit immune cells such as monocytes, macrophages and T-cells, necessary to quell the infection. However, in certain individuals, this process can extend into an unfettered inflammatory response that may then mediate multiple organ failure through an outpouring of catalysing enzymes such as proteases and toxic free radicals (Tay et al., 2020). These processes can leave potentially damaging immune residue in brain neural circuits among COVID-19 survivors.

Currently, the mechanisms that drive these aberrant immune responses in some COVID-19 patients or how long their effects may linger in the body remain unclear. Nevertheless, it is understandable that these immune-inflammatory sequelae may also leave the individual biologically vulnerable to develop mental health disorders. Elevated levels of cytokines, following the cytokine response storm, can affect neuroendocrine axis and activate the hypothalamo-pituitary-adrenal axis either through direct effects on the brain exerted through cytokine receptors as well as by inducing gluco-corticoid resistance (Zunszain et al., 2011). These aberrant processes may worsen the severity of infection by impairing the immune system and compound the vulnerability of COVID-19 survivors to mental health sequelae (Dinakaran et al., 2020).

As much as these processes seem relevant to the pathobiology of psychiatric disorders following COVID-19 infection, they also open up new avenues for treatment of those afflicted. Indeed, trials of several immunosuppressive therapies for COVID-19, aimed at limiting the cytokine response storm and consequent inflammation-mediated damage, are currently underway. These include agents as diverse as corticosteroids, IL-6 antagonists such as tocilizumab, granulocyte-macrophage colony stimulating factors such as gimsilumab and lenzilumab among others (Shi et al., 2020; Tufan et al., 2020). Some of these trials are also evaluating the preventive effects of these agents. Convalescent plasma or immunoglobulin therapy, aimed at enhancing antibody titres to reduce viraemia, have been found to be beneficial in reducing morbidity and mortality related to COVID-19 (Chen et al., 2020).

At this point in time, the role of these agents in treating depression or anxiety following COVID-19 is unknown but certainly worth exploring based on available general evidence for various immunomodulatory treatments for mood disorders and emerging evidence for immune sequelae in COVID-19 (Tay et al., 2020; Wittenberg et al., 2019). Likewise, non-pharmacologic interventions with proven immunomodulatory effects may be researched for their relevance to post COVID-19 mental health sequelae (Phillips and Fahimi, 2018).

To summarize, in addition to the ongoing focus on psychosocial aspects of COVID, the biological links between COVID-19 and mental health must certainly not be overlooked. Long term promotion of mental health following COVID-19 will be better facilitated using the biopsychosocial model that incorporates psychoneuroimmune and psychoneuroendocrine elements. Immune-inflammatory activation during COVID-19, and their residue following recovery, may contribute to the pathogenesis of mental illness through many known, and as yet

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unknown, mechanisms. This could have key implications for treatment and prevention of mental health disorders as well.

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