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Viewpoint

Bidirectional associations and common inflammatory biomarkers in COVID-19 and mental health disorders: A window of opportunity for future research?

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The new coronavirus disease (COVID-19) has drawn the interest of mental health and neuroscience research, with emerging literature illustrating potential psychiatric and neurological manifestations following the COVID-19 infection (Varatharaj et al., 2020; Rogers et al., 2020; Pierce et al., 2020; Taquet et al., 2020). Recently, it was published a large retrospective cohort study conducted in US with a sample of 62 354 patients suggesting a bidirectional association between COVID-19 and psychiatric disorders, particularly anxiety and mood disorders (Taquet et al., 2020). In this study, the diagnosis of COVID-19 was independently associated with greater risk for psychiatric disorders, in the following 14–90 days, when compared with other acute conditions (e.g. influenza, respiratory infection, skin infection, fracture). Additionally, a psychiatric diagnosis confirmed in the previous year (prior to the infection) was associated with 65% increased risk for subsequent COVID-19 infection. Findings were robust after sensitivity analysis accounting for other potential confounders such as race and other comorbidities.

The novelty here is the reciprocal association found between psychiatric disorders and an acute infection such as COVID-19. Prior to the pandemic era, a bidirectional relationship had been mainly hypothesized and found between depression and chronic inflammatory conditions (Wium-Andersen et al., 2020; Golden et al., 2008; Poole and Steptoe, 2018). The mechanisms underpinning a bidirectional relationship between depression and physical illness are still unclear. However, evidence from studies on the neurobiology of psychiatric disorders, and recent evidence from studies on the neuroimmunology of COVID-19, are providing important cues on the nature of such reciprocal relationship.

The neurobiological literature has robustly suggested the occurrence of immunologic dysregulations entailing inflammatory processes in several psychiatric disorders (Wohleb et al., 2016). There is growing evidence that an increased expression of pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), occurs in psychiatric disorders (Wohleb et al., 2016; Costello et al., 2019; Dowlati et al., 2010; Passos et al., 2015), including generalized anxiety disorder (Costello et al., 2019), major depressive disorder (Dowlati et al., 2010), and post-traumatic stress disorder (Passos et al., 2015). A recent large cohort study using network analysis suggested that IL-6 might be a key inflammatory marker in depression (Fried et al., 2020). IL-6 is a cytokine known to play a mediating role in the regulation of inflammatory and immunological responses, and in hematopoiesis (Tanaka et al., 2014). The underlying mechanisms of pro-inflammatory responses in depression remain unclear, although recent research has proposed that inflammation might be triggered by prolonged exposures to psychological stress via dysregulation of peripheral myeloid cells and brain-resident microglia (Wohleb et al., 2016; Rudzki and Maes, 2020).

The occurrence of pathogenic inflammatory processes in COVID-19 patients has been well-documented (Coomes and Haghbayan, 2020; Mehta et al., 2020). These inflammatory manifestations are known to result from virus-induced cytopathic effects triggering an immune response (Qin et al., 2020). In severe cases of COVID-19 infection, a

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dysregulated immune response involving an excessive cytokine release, frequently called "cytokine storm", has been described (Mehta et al., 2020). A retrospective study conducted in China with 452 COVID-19 patients (Qin et al., 2020), analyzed biomarkers of immunological dysregulation in patients with severe (N = 286) and non-severe infection. IL-6 and TNF-α were the only cytokines found elevated in patients with severe and non-severe infection. In severe COVID-19, levels of TNF-α, IL2R, IL-6, IL-8, and IL-10 were significantly higher compared with non-severe cases. Another study examined the predictive biomarkers of pathogenic inflammation in 1484 hospitalized COVID-19 patients in US (Del Valle et al., 2020). High serum levels of IL-6, IL-8 and TNF-α were found at the time of hospitalization, and IL-6 and TNF-α independently predicted disease severity and patient survival. Finally, a meta-analysis reviewing eight studies (N = 1798) highlighted the prevalence of elevated concentrations of IL-6 among COVID-19 patients, being this cytokine 2.9-fold higher (95% CI, 1.17–7.19) in patients with severe infection, compared with non-severe cases (Coomes and Haghbayan, 2020).

Remarkably, evidence from studies on psychiatric disorders, particularly depression, and evidence from studies on COVID-19, are driving us to similar key biomarkers of pathogenic inflammation, especially IL-6, and TNF-α. The prospect of both conditions sharing a similar inflammatory outcome is intriguing, as the mechanisms leading to inflammatory manifestations in psychiatric disorders and in COVID-19 are known to be dissimilar, and to include distinct molecular pathways (Wohleb et al., 2016; Qin et al., 2020). Very few studies have explored potential common inflammatory processes between COVID-19 and mental health disorders, and to the best of our knowledge no study has yet examined why COVID-19 and mental health disorders were reciprocally associated. A recent study examining psychiatric symptoms in 402 adult COVID-19 survivors at one month follow-up after hospital treatment found depression and anxiety at follow-up positively associated with baseline systemic inflammation, based on peripheral lymphocyte, neutrophil, and platelet counts (Mazza et al., 2020). These findings highlight the potential importance of the interplay between psychiatric symptoms and immunological and inflammatory processes for the comorbidity of both conditions. There is current evidence that increased serum levels of some inflammatory biomarkers such as IL-6 and C-reactive protein are a risk factor for subsequent depression, shown by longitudinal research (Lee and Giuliani, 2019). Finally, as previously mentioned, elevated levels of IL-6 have been associated with poor outcomes among COVID-19 patients (Qin et al., 2020; Del Valle et al., 2020).

In light of recent findings presented, the hypothesis of a synergistic relationship between depression and COVID-19 can be raised, where inflammatory manifestations in depression would boost, and be boosted by the inflammatory response triggered by COVID-19. This hypothesis takes us to the question of whether such common inflammatory manifestations would also be present between depression and some chronic inflammatory illnesses. Previous research has robustly suggested that depression is highly comorbid with chronic illnesses (Wium-Andersen et al., 2020; Golden et al., 2008; Poole and Steptoe, 2018; Nouwen et al., 2019), being depression itself a potential risk factor for subsequent incidence of chronic illnesses (Poole and Steptoe, 2018). In 2018, a large longitudinal study had highlighted that depression can have a predictive effect on the incidence of chronic illness up to 10 years later, including coronary heart disease, lung disease, arthritis, and osteoporosis (Poole and Steptoe, 2018). Other longitudinal studies have robustly showed a reciprocal association between depression and some chronic inflammatory diseases, particularly stroke, diabetes, and cardiovascular disease (Wium-Andersen et al., 2020; Golden et al., 2008; Poole and Steptoe, 2018; Nouwen et al., 2019; Senra and McPherson, 2021). Diabetes is one of the main conditions where bidirectional associations with depression have been found (Nouwen et al., 2019; Senra and McPherson, 2021). Interestingly, in recent studies on COVID-19, a complex bidirectional relationship between diabetes and COVID-19 has been suggested (le Roux, 2021; Muniangi-Muhitu et al., 2020). The main causes of such relationship remain unclear but the hypothesis of this being an indirect effect of an immune response involving a "cytokine storm" was suggested (le Roux, 2021).

Evidence in this topic is still limited, but current research on COVID-19 is drawing attention to plausible hypotheses to be considered in future studies. Topics that might benefit from this input include the neuropathogenesis of comorbidity of depression and physical illness, and the neuro-immunology of mental health disorders. COVID-19 research has eminently targeted new treatment solutions, but incidentally it might be opening a new window of opportunity for future research initiatives in the fields of psychiatry, psychosomatics, and neurosciences.

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