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LETTER TO THE EDITOR

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Ketamine in COVID-19 patients: Thinking out of the box

Coronavirus disease 2019 (COVID-19), identified as the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was recognized as a public health emergency by World Health Organization, and declared a pandemic on March 11, 2020. Symptoms of respiratory tract infection along with signs of the systemic inflammatory response, represent its dominant manifestation, however, extra-respiratory symptoms including abdominal pain, diarrhea, symptoms of pericarditis, or severe myalgias have been recorded. Even though not common, neurological and neuropsychiatric complications, as a predominant symptom in COVID-19 patients have become increasingly apparent.[1,2] Recent analysis including 40,469 COVID-19 patients, utilizing ICD-10 codes for neurological and psychiatric systems, identified neuropsychiatric manifestations related to COVID-19 in 22% of patients, including anxiety, depression, mood disorders, and psychosis.[1]

Whether the psychiatric manifestations in these patients, are attributed to excessive systemic inflammatory response, in the form of viral sepsis, immune-mediated response or SARS-CoV-2 direct virus-induced damage to brain vasculature, warrants further study. Either way, recent work has unveiled a unique pattern of immune dysregulation in SARS-CoV-2 patients, that could explain their presentation and outcomes, including defective antigen presentation driven by interleukin 6 (IL-6), or a haemophagocytosis like syndrome mediated by IL-1β.[3,4] These findings have paved the way for current therapeutic efforts utilizing immunomodulatory regimens, including IL-1 receptor antagonist (anakinra) and IL-6 blockade (tocilizumab), to blunt hyperinflammatory response noted late in the course of COVID-19 disease and ensure better outcomes.[3] However, even though promising, in the absence of specific antiviral therapy, immune-modulatory interventions, such as tocilizumab, do not go without critical thought or caution. The latter remains costly and bears the risk of secondary complications including bacterial superinfections or viral reactivation, hence; actually compromising outcomes, following severe iatrogenic immunosuppression.

Ketamine, on the other hand, has been long used in the management of treatment-resistant-depression, as a nonselective NMDA receptor antagonist, utilising both its intranasal and intravenous form, even though the latter showing better efficacy.[5–7] Recent data have come to show that, it effectively treats both typical/melancholic and atypical depressive symptoms, even though, the exact mechanism underlying its efficacy remains unclear.[5] Previous animal studies have unveiled that, ketamine generates an anti-inflammatory effect that could contribute to its antidepressant action.[8] After all, low-grade inflammation, characterized by an increase in serum proinflammatory cytokines, including IL-6, IL-1β, CRP, and so forth, may play a role in depression pathogenesis and represents a good predictor of clinical response.[8,9] Apparently, patients with an activated inflammatory state, need a step up to dopaminergic or glutaminergic drug like ketamine, to avoid aggravated alteration in neurotransmitter metabolism,[9] that blunts response to first-line drugs. In clinical models, ketamine downregulates the level of several inflammatory cytokines, including IL-6, while changes at their level significantly correlate with symptom improvement on day 13.[8] What the exact path and timing from micro-molecular changes to symptom improvement remains under investigation.[8] Further evidence shows that, it may actually exert both its beneficial anti-depressant and toxic effects via the same IL-6 blockade in a dose-dependent manner; even though, exact timing remains elusive.

Even though, the need for more extensive prospective studies for the establishment of causality relationships and safer conclusions to be drawn is pivotal, the role of antidepressants and especially ketamine is worth to explore in COVID-19 with presenting or the previous history of mental disease and/or depressive symptoms. Given its suggested role in the treatment of certain mental health disorders and its anti-inflammatory effect, the role of ketamine in SARS-Cov-2 patients presenting with specific neuropsychiatric symptoms including depression should be put into trial. It would be interesting to explore whether, presenting symptoms and concurrent administration of neuropsychiatric regimens, including ketamine could have an impact on outcome in this cohort of patients having a history of or presenting with the neuropsychiatric disease, potentially offering an alternative to high-cost tocilizumab in the future immunomodulatory interventions. Of note, as one might expect from previous experience, its cardiovascular and neurological side effects, could limit its utility. Nonetheless, even though, the intravenous form is better used in hospital environment, its intranasal counterpart (esketamine), avoiding systemic toxicity and allowing for administration of lower dosages, could represent a safe regimen for controlled community use.[6] Amid results from clinical trials and drug repurposing, we should consider the possibility that COVID-19 patients with increased levels of IL-6 and/or history or presentation of depressive symptoms could represent candidates of a new "Special K" population.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Karolina Akinosoglou, Athanasios Gogos, Elias Angelopoulos, Charalambos Papageorgiou, and Charalambos Gogos conceived the

idea and performed literature searches. Karolina Akinosoglou wrote the manuscript. Charalambos Gogos critically corrected the manuscript. All authors contributed to the study's perception, design, have seen and approved the manuscript. This manuscript has not been published or is considered for publication elsewhere.

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