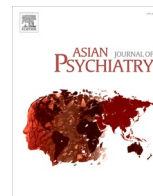




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Letter to the Editor

A physiological link for psychiatric symptoms in COVID-19: Role of amino acid deficiency

Dear Editor,

A variety of signs and symptoms are associated with SARS-CoV-2 infection. Clinical manifestations of COVID-19 include, but not limited to, acute respiratory distress syndrome, pneumonia, hyperthermia, intravascular disseminated coagulation, multi-organ damage, and gastrointestinal (GI) disturbance (Soni et al., 2020a). Psychiatric illnesses are also being invariably reported among COVID-19 patients (Tandon, 2020). Fear of adverse treatment outcome and mental trauma are linked with such psychosis. However, several other factors are also conjectured to prompt distress in SARS-CoV-2-infected patients, including socioeconomic state, nutritional practice, and immunity (Tandon, 2020). Cellular and physiological damage to body organs including lung, heart, vasculature, and intestine remains as collateral damage to physical health in recovered patients (Rozga et al., 2020). The abnormal physiological state is often correlated with psychotic manifestations. A significant fraction of recovered COVID-19 patients also experience post-traumatic stress disorder (PTSD). Moreover, major depression disorders (MDD) are also prevalent in patients and are predicted to have long-lasting consequences on mental as well as physical health (Tandon, 2020). Distorted physical well-being in COVID-19 patients, as well as recovered individuals, can be hypothesized to affect mental well-being. Therefore, it becomes imperative to explore the association of physiological disturbance and psychiatric compromise to identify targets and treatment of the later (Tandon, 2020).

One of the common clinical manifestations of SARS-CoV-2 infection is a disturbance in GI function. Abdominal pain, vomiting, and diarrhea are common GI symptoms in COVID-19 patients (Rozga et al., 2020; Ayres, 2020). Such GI symptoms lead to loss of appetite; and physiological damage caused by viral infection poses a hindrance in nutrient uptake culminating in malabsorption of nutrients. Rao et al. (2008) have reviewed the role of nutrients including omega fatty acids and other amino acids in maintenance of mental health; and a deficiency may lead to depression. A significant decline in uptake of nutrients was reported in COVID-19 patients (Ayres, 2020). Nutrient deficiency can invite physiological stress and provoke psychiatric symptoms (Ayres, 2020; Nisoli et al., 2020; Rao et al., 2008). Qualitative and quantitative set-up of amino acids has been shown to regulate various dimensions of psychiatric presentations including depression and schizophrenia (Rao et al., 2008). In Amine theory, reduced levels of neurotransmitters (dopamine, norepinephrine, and serotonin) act as foremost factors associated with depression. Besides being structural components of proteins, amino acids serve as precursors for neurotransmitters; and its malabsorption and nutritional deficiency can provoke mood change and depressive disorders. Dysfunction of angiotensin-converting enzyme-2 (ACE2), cellular anchor of SARS-CoV-2, can cause GI disturbance; and its cellular internalization during infection has been postulated to dwindle the expression sodium-dependent neutral amino acid

transporter (B⁺AT1) in cells of the intestine (Nisoli et al., 2020). Hartnup disorder, an inherited condition with defective B⁺AT1 amino acid transporter encoded by mutated SLC6A19 gene, shares several psychiatric symptoms with COVID-19 (Nisoli et al., 2020). A reduced level of cofactors (vitamin C and zinc) may also cause a deficient conversion of amino acids into neurotransmitters; and thus corollary affects mental well-being.

Glutamine, glutamate, tryptophan, and tyrosine are among major amino acids that serve as the precursor for neurotransmitters like gamma-aminobutyric acid (GABA), norepinephrine, epinephrine, dopamine, serotonin, and melatonin (Rao et al., 2008). Adequate conversion of amino acids to these neurotransmitters can have regulatory consequences on brain function as well as the prevention of psychiatric illness. In COVID-19, a disrupted uptake of amino acid consequently drops off the level of neurotransmitters and may invite psychiatric symptoms (Nisoli et al., 2020). Moreover, a reduced level of brain interstitial amino acid correlates with the onset of depression (Kofler et al., 2019). Hasler et al. (2019) also demonstrated an association of prefrontal glutamine level, glutamine-glutamate ratio, and glutamatergic abnormality with the manifestation of anxiety, depression, and neuroticism. Tryptophan catabolites (TRYCATs) have pleiotropic effects in physiological and psychiatric health. TRYCATs also regulate the manifestation of depressive disorders (Rao et al., 2008); and have been postulated as a link for psychoneuroimmunomodulation in COVID-19 (Soni et al., 2020b)

Precursor amino acid therapy has shown significant success in pain management as well as in clinical management of psychosomatic disorders (Rao et al., 2008). Attempts for management of COVID-19 are not limited to physiological well-being; but also encompass the mental well-being (Tandon, 2020). An evidence-based analysis of medical nutrition therapy (MNT) for efficacy in COVID-19 was carried out. A supervised MNT, including micronutrients and conditional amino acid supplementation, was speculated to reduce the adverse effects of COVID-19 (Rozga et al., 2020). Considering the importance of amino acids as nutrients and regulators of mental well-being as well, a controlled and randomized clinical trial is underway for evaluation of amino acid supplementation in severely ill COVID-19 patients (clinicaltrials.gov, NCT04443673).

Collectively, it can be concluded that psychiatric symptoms in COVID-19 patients have a significant contribution from physiological injuries triggered by SARS-CoV-2-infection. Nutritional deficiency, especially those in level and ratio of amino acids may alter the balance of neurotransmitters in provoking a state of anxiety, depression, and mood change in COVID-19 patients. A supplementation of conditional amino acids may not only assist the mental well-being but also improves the immunity and treatment outcome of COVID-19.

<https://doi.org/10.1016/j.ajp.2020.102426>

Received 29 August 2020

Available online 25 September 2020

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Author agreement statement

Authors declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

Authors confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

Ethical statement

Authors confirm that any aspect of the work covered in this manuscript does not involve human patients or animal subjects.

Authors' contribution

KS, DS, SK and NKV conceived the idea; VKS, KS and AM compiled the literature; VKS, KS, AM, YKR, DS and NKV wrote the manuscript; KS, DS, SK and NKV reviewed the manuscript; all authors have approved the final version of manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

A financial support to VKS [UGC-SRF] and AM [GGU-VRET-Fellowship] as fellowships is acknowledged. The authors also acknowledge the UGC-Special Assistance Program [UGC-SAP] at Department of Biotechnology, Guru Ghasidas Vishwavidyalaya for necessary facilities in preparation of the manuscript.

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