

Editorial

Treatment of Brain Fog of Long COVID Syndrome: A Hypothesis

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The emergence of the SARS-CoV-2 (COVID-19) virus has exacted a significant toll on the global population in terms of fatalities, health consequences, and economics. As of February 2023, there have been almost 800 million confirmed cases of the disorder reported to the WHO [1], although the actual case-positive rate is estimated to be much higher. While many cases recover, the mortality rate associated with the illness is about 1% (based on the WHO data). Most patients experience the illness as a mild to moderate disorder and recover without significant sequelae. However, as the COVID-19 pandemic has continued, there has emerged a significant group of COVID-19 survivors who experience persistent symptoms beyond the acute course of the illness. As many as one in eight patients report persistent symptoms 90 to 150 days after the initial infection [2]. These so-called Long COVID or post-COVID syndrome patients are mostly drawn from those who were hospitalised for the disorder, but both non-hospitalised and vaccinated subjects may also experience the syndrome [3]. While an agreed definition of Long COVID is yet to be settled, a multiplicity of symptoms affecting most major organ systems has been reported in patients. Common Long COVID symptoms include fatigue, dyspnoea, headaches, myalgia, anosmia, dysgeusia, cognitive symptoms, and mental disorders such as depression and anxiety [4]. It is estimated that approximately a third of patients with Long COVID exhibit either fatigue, cognitive impairment, or both up to 12 weeks after a confirmed diagnosis of COVID-19 [5].

1. Tryptophan Metabolism and Long COVID

Although various aetiologies have been proposed for Long COVID, immune system dysfunction is well recognised in the disease [6]. In particular, activation of proinflammatory cytokines has been reported in Long COVID patients [3]. Inflammatory disorders are associated with the tryptophan–kynurenine pathway, in which many of the metabolites play specific immunoregulatory roles [7]. Although tryptophan is well recognised as a precursor to the production of serotonin (and melatonin), this pathway accounts for only a small proportion of the metabolism of this amino acid. The main route of metabolism is the conversion of tryptophan to kynurenine and further catabolism into compounds such as nicotinamide adenine dinucleotide (NAD⁺). A key inducible and rate-limiting enzyme in the pathway is indoleamine 2, 3-dioxygenase-1 (IDO-1); however, an isoform IDO-2 is also recognised as a contributor to metabolism, but is of subordinate importance to IDO-1 [7]. In inflammatory conditions, the tryptophan pathway is shunted to increase kynurenine production by activation of IDO principally via the action of interferons but also by other interferon-independent mediators [8]. Post-mortem studies have identified that IDO-2 is selectively activated in the central nervous system of COVID-infected patients [9]. Increased IDO-2 activity was associated with an increased presence of the kynurenine metabolites 3-hydroxy-anthranilic acid (3-OH-AA) and quinolinic acid (QA). A study examining plasma concentrations of cytokines, chemokines, and amino acids in patients positive for COVID-19 described alterations in the tryptophan–kynurenine pathway among changes in other analytes examined [10]. Although the study was relatively small and did not specifically identify Long COVID subjects, significantly increased concentrations of the metabolites QA and 3-OH-AA were reported. On the other hand, serotonin concentrations were decreased, although not statistically significantly, while kynurenine was increased, in line



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with increased conversion from tryptophan. A meta-analysis of fourteen studies examining the pathway in COVID patients supported the findings for the kynurenine/tryptophan ratio [11]. A more recent study points to the elevation of QA and 3-OH-AA concentrations in plasma and a decrease in the tryptophan/kynurenine ratio [12].

2. The Kynurenine Pathway and Neurotoxicity

Compounds along the tryptophan kynurenine pathway have been demonstrated to have both neuroprotective and neurotoxic effects [13]. Thus, kynurenic acid acts as a N-Methyl D-Aspartate (NMDA) antagonist and has been demonstrated to prevent neuronal loss following excitotoxicity [14]. On the other hand, QA, 3-OH-AA, anthranilic acid, and 3-hydroxy-kynurenine are neurotoxic, the latter two compounds due to their ability to generate free radicals and increase oxidative stress [13]. Of particular interest in the context of Long COVID is the potential role that QA may play in generating, at least in part, the cognitive symptoms experienced by patients. QA is an NMDA receptor agonist associated with excitotoxicity [15]. The compound demonstrates regional differences in neurotoxicity, with, significantly, the hippocampus, striatum, and neocortex being more sensitive to the effects of quinolinic acid than other neuroanatomical areas see [15] for review. All three areas are involved in memory formation, while dysfunctional memory is among the many symptoms complained of by patients with Long COVID. For example, in a study of 128 participants with confirmed COVID, cognitive function, blood cytokine levels, and kynurenine metabolites were assessed 2, 4, and 12 months after the diagnosis [16]. Across the 12-month observation period, overall cognitive performance declined significantly with a small to medium effect size. Moreover, the increase in kynurenine and the metabolites QA and 3-OH-AA were the only biological markers significantly associated with the decline in cognitive performance, reinforcing the importance of the pathway in generating cognitive changes.

Alongside its direct NMDA agonist actions, QA has a multiplicity of effects that increase glutamate concentrations in the immediate environment of neurons by release from the neurons, inhibiting uptake by astrocytes, and inhibition of glutamate catabolism by inhibiting glutamine synthetase [15]. Other actions, such as the production of hydroxyl-free radical species through a ferrous ion-dependent mechanism, may also contribute to neurotoxicity [17]. Thus, it is posited that blocking the effects of QA (and/or other neurotoxic metabolites of the kynurenine pathway) may offer benefits in overcoming aspects of the 'brain fog'/cognitive dysfunction complained of by many patients with Long COVID.

3. Counteracting the Effects of Quinolinic Acid

Agents which might be effective in blocking the effects of quinolinic acid within the central nervous system have been suggested from pre-clinical investigations, including cell culture and whole animal studies. Inhibition of the synthesis of QA from its precursors has been demonstrated to provide protection from its neurotoxic effects [18]. Furthermore, the metabolic pathway producing QA also produces other metabolites which oppose the neurotoxic effects of QA. Kynureinase inhibitors increase levels of endogenous kynurenic acid, a metabolite of the pathway with demonstrable NMDA receptor antagonism. These inhibitors are unsuitable for human use or at least have not been evaluated for use in humans.

In recombinant CHO cell lines stably expressing various heterodimeric subtypes of the NMDA receptor, esmethadone protected cells from excessive calcium ion influx induced by QA [19]. As is well recognised, an excessive calcium influx is associated with increased neurotoxicity. Recent studies as an adjunct to the treatment of major depressive disorder show that esmethadone has an acceptable safety profile, in particular with respect to potential dependence-producing properties [20].

Similarly, the Alzheimer's medication, memantine, was protective against the cytotoxic effects induced by quinolinic acid in rat embryonic hippocampal cells [21]. An earlier study showed that pre-treatment with memantine prevented hippocampal damage

induced by intracerebroventricular injection of quinolinic acid [22]. Memantine acts as an uncompetitive antagonist at the NMDA receptor, which leads to the potential clinical benefit of relatively sparing normal neurotransmission while blocking excessive calcium channel activation. Based on this reasoning, the hypothesis proposes that repeated administration of memantine might ameliorate the cognitive symptoms of Long COVID. As the medication is currently registered in many jurisdictions and the safety and side effect profile well established, it represents a readily available agent to test the hypothesis of quinolinic acid-induced activation of microglial cells leading to the phenomenon of ‘brain fog’.

While the diagnosis of Long COVID is syndromal and, as such, lacks a clear set of agreed diagnostic criteria, treatment is likely to remain symptomatic. Each identified case will present a unique set of symptoms most problematic for that individual. From a neurobiological point of view, at least some of these symptoms may be explicable by alterations in the tryptophan metabolic pathway to produce the NMDA receptor agonist QA. ‘Brain fog’, a troublesome symptom for a substantial group of Long COVID sufferers, may arise as a direct consequence of the accumulation of QA in specific brain regions. The use of NMDA receptor antagonists, which oppose the actions of QA, may offer symptomatic relief. As proposed here, memantine might prove uniquely useful because of its non-competitive antagonism at the NMDA receptor, as it dampens activity at the NMDA receptor without completely blocking such actions. The use of double-blind placebo-controlled evaluations in sufficiently large numbers of patients will be required to test the hypothesis presented here.

Conflicts of Interest: The author declares no conflict of interest.

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