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Letter to the Editor

# Potentials to alleviate coagulopathy and enhance microglial function of beta (β)- glucans, making them worth a clinical study for COVID-19's neurological sequalae

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*Dear Editor,*

Widespread neurological and psychiatric sequalae of COVID-19 have been reported affecting all age groups [1] with presence of low-grade chronic inflammation and down-regulated ACE-2 levels making the individual more vulnerable for severe neurological effects of COVID-19 [2] as there will be greater disruption of the blood-brain barrier and hyper inflammation. Systemic immune inflammation index (SII) including neutrophil, platelet and lymphocyte counts serve as potential biomarkers to find an individual's risk of neurological effects of COVID-19 [2]. SARS-CoV2 has been shown to affect the immune pathways associated with the central nervous system (CNS) and the peripheral nervous system (PNS) leading to long-term neurological sequelae [3]. Intracranial hemorrhage, ischemic stroke, parkinsonism, dementia, anxiety disorders and psychotic disorders have been reported as sequalae of COVID-19 [4]. A recently published retrospective cohort study on the neurological and psychiatric sequalae of COVID-19 in 236,379 patients [5] has shown that the incidence of ischemic stroke in about 10% of patients, majority with COVID-19 associated encephalopathy which is alarming and necessitates steps to prevent or manage in those already affected. Werner et al. [6] have reported yet another neurological sequala, incidence of transient global amnesia during the COVID-19 hypothesizing the mechanism to be an encephalitic autoimmune pathology by the SARS CoV2 virus. Neurological manifestations of COVID-19 are thus postulated to be due to the binding of SARS-CoV-2 to ACE-2 activating intracellular pattern recognition receptors (PRRs) which sense the pathogen associated molecular patterns (PAMPs) setting off maladapted immune responses leading to inflammatory and immune activities disrupting the coagulation-embolism pathways in the CNS and PNS [7]. The different types of cells in the CNS and PNS including the glial cells, neurons, endothelial and arterial smooth muscle cells are all affected leading to the neurological manifestations of COVID-19 [8]. However, the effects of SARS-CoV2 on human astrocytes, especially the microglia being the key-players in neural inflammation [6] makes us specifically focus on microglia in the context of conditions that involve neural- inflammation such as stroke, Parkinson's disease, Alzheimer's etc. For recovery, optimal functioning of the neuroglia is essential for synaptic organization, neurotrophic support, phagocytosis of apoptotic cells, debris removal, myelin turnover, control of neuronal excitability besides brain protection and repair. Microglia during COVID-19 are postulated to be in a primed state due to a previous encounter of inflammatory stimuli, when challenged with SARS-CoV-2 infection, in those with co-morbidities including psychological stress, gut dysbiosis, metabolic disorders, obesity and ageing lead to severe neurological sequalae [7]. Therefore, strategies towards beneficial reprogramming of microglia, apart from management of co-morbidities gain critical importance to prevent and manage COVID-19 associated neurological sequalae. Some of the vaccines themselves associated with possible coagulation risk apart from not widely available and lack of definitive therapies for COVID-19, divert our attention to supportive strategies such as biological response modifying beta glucans which are safe food supplements, yet with potentials for a long-term prophylaxis. Especially, an AFO-202 beta (β)- glucan possessing potentials as a vaccine adjuvant COVID-19, exerting beneficial influence on all arms of immunity, on blood glucose and lipid levels while modulating immune-dysfunction associated coagulopathy [9] is worth considering for clinical trials. Beta (β)- glucan -mediated microglial activation elicits a unique immune response that doesn't result in significant production of cytokines or chemokines via its major receptor, the Dectin-1 mediated signaling pathway [10]. Reports have documented that β-Glucans have the potential to prevent or treat excessive microglial activation during chronic inflammatory conditions [11] and their triggering of neuro-inflammation has been shown to actually enable CNS axon regeneration [12]. Above all, β-Glucans have been shown to have neuroprotective effects after transient retinal ischemia and reperfusion [13] beside having been proven to exert antioxidant effects on the brain [14] in a diabetic neuropathy model. Their direct antiplatelet, antioxidative, anticoagulant and antithrombotic actions on the systemic hematological components support the beneficial effects to prevent COVID-19-associated coagulopathy [9]. These positive effects of β-Glucans along with capabilities to improve elements of cognition and brain function via the gut-brain axis in an obese mouse model [15] adds to their merit as a prophylactic agent in the fight against COVID-19 and its neurological sequalae.

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NI, and SA contributed to conception and design. SA drafted the manuscript. KR, RK and MI performed critical revision of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

## Declaration of Competing Interest

Author Samuel Abraham is a shareholder in GN Corporation, Japan which in turn is a shareholder in the manufacturing company of the AFO 202 Beta Glucan.

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