LETTER TO THE EDITOR

"Brain fog" and COVID-19

Dear Editor:

Coronavirus disease (COVID-19) is an infectious condition caused by the SARS-CoV-2 virus. As of August 2022, more than 500 million people have been infected with COVID-19 infections, with more than 6 million deaths (https://ourworldindata.org). Any long term post-COVID-19 sequela for the millions who have recovered can be a major concern. The term "brain fog" has been frequently attributed to COVID-19 infections and widely publicized in mass media as a long term neurological consequence of COVID-19, in addition to other symptoms of long COVID syndrome such as fatigue and cognitive problems.[1-3] Frequently, patients describe their "brain fog" symptoms as "slow and sluggish thinking", "fuzziness" and "blur" feelings, and "not their usual self". While "brain fog" is not a scientific diagnosis, the collections of patients' perceived symptoms (which may also include memory, inattention and language deficits) have attracted considerable attention in the scientific community even though there is no quantifiable definition of "brain fog". Here, we review current available scientific evidence in published literature that studied patients with "brain fog" symptoms, highlight the biological evidence that might explain this phenomenon, and draw attention to limitations of current studies and challenges for future investigations.

We searched the key words "brain fog", "COVID-19", in PubMed and Embase from 1st May 2020 to 30th June 2022 and identified 3 clinical studies (with sample size of >50 subjects and with age >18 years old)[1-3] and 2 biological studies[4,5] that examined the association of post COVID-19 infections and "brain fog".

The key findings of the 3 clinical studies are summarized in Table 1. In general, the studies suggest that COVID-19 infection is associated with inattention, worsened memory, and slower processing speed with improvement in neurological deficits a few months from initial infection. There appears to be a correlation between symptom severity and the degree of neurological deficits. One study found that chronic post-COVID "brain fog" was significantly associated with the severity of respiratory symptoms at onset and with intensive care unit admission,[1] and another identified fatigue and dermatological symptoms during the initial 3 weeks of illness to be linked with memory performances and slower reaction times on the executive function performance.[3]

Charnley et al.[4] postulated that neurotoxic amyloidogenic peptides in the proteome of SARS-COV2 might promote neurodegeneration. In their study, they found that the COVID-19 proteasome contains Open Reading Frames that can give rise to amyloid protein assemblies, ILLIIM and RNYIAQVD, which are cytotoxic even at low concentrations. These amyloid proteins are similar to those found in neurodegenerative diseases like Alzheimer's disease and may contribute to long term cognitive dysfunction. Separately, Fernández-Castañeda et al.[5] found that even mild COVID can cause prominent inflammation in the brain with elevated cytokine CCL11 which can promote further inflammatory responses resulting in increased reactivity of microglia (particularly high in the hippocampus which is responsible for learning and memory), and impairment of hippocampal functions can lead to cognitive dysfunction.

As "brain fog" comprises a constellation of symptoms and signs, it is difficult to conduct a pooled analyses since there is no standardized definition and the methodologies and outcome measures differ. As such, some authors may have examined similar domains without using "brain fog" as an inclusion criterion, while others considered "brain fog" symptoms separately from cognitive symptoms. In addition, the 3 studies that included "brain fog" patients have limited sample size which may cause a bias result due to inadequate representation of the population. In addition, most studies required participants to fill up a questionnaire where they had to recall their cognitive symptoms post COVID-19, as well as the severity of other symptoms. This has an inherent recall bias which may affect the severity of the cognitive symptoms experienced. Two of the studies had no control group, which makes it difficult to establish a baseline of comparison (Table 1).

Based on current literature and evidence, we do not suggest using "brain fog" as a disease entity for clinical studies as this may add to confusion in the inclusion and exclusion criteria making comparisons difficult. In a recent meta-analysis, Ceban and colleagues specifically included studies that reported on fatigue, cognitive impairment and inflammatory parameters. They found a significant proportion of them having persistent fatigue and/or cognitive symptoms 12 weeks or more after COVID-19 infection.[6] These findings corroborate to some extent the observations in our included studies identified using "brain fog" as a search term.

It is currently unclear if "brain fog" is a separate entity or subset of long COVID syndrome or if there is an overlap in the pathogenesis with cognitive impairment and other non-specific systemic complaints. To address neurological sequalae post COVID-19 regardless of "brain fog" symptoms, there is a need for long-term large multicenter prospective studies to evaluate quantitatively the different "brain fog" symptoms, and also to assess a spectrum of neuropsychological domains (such as attention, processing speed, learning and memory, executive functions, visuospatial skills, mood and personality). In addition, comprehensive and standardized validated assessments tools are required, and the results should

Table 1. Summary of the studies on "brain fog".

Study	Asadi-Pooya et al, 2021	Callan et al, 2022	Guo et al, 2022
Sample size	194	50	366
Age (years)	18 - 55	29 - 74	18 and over
Race/Countries	Fars Province	Mainly Caucasians	United Kingdom, Ireland, United States, Canada, Australia, New Zealand, South Africa
Methods	At least 3 months after their discharge from hospital, phone call with a set questionnaire	Phone Call Interview to follow up on their neurocognitive symptoms. Followed up by email 4-6 months (10-12 months after their acute illness) regarding neuro-cognitive symptoms	One time online survey and cognitive test, where subjects were asked to recall the symptoms (clustered into 5 groups cardiopulmonary, neurological, GIT, fatigue/mixed, dermatological) in the initial 3 weeks, time since then and the past 1-2 days. Cognitive tests were administered for Executive Functions (Performance), Executive Functions (Reaction Time), Memory, and Category Fluency. (A) Wisconsin Card Sorting Test; (B) Pictorial Associative Memory Test; (C) Category Fluency Test; (D) Word List Recognition Memory Test; (E) 2D Mental Rotation Test; (F) Number Counting Test.
Outcome measures	Severity of COVID "brain fog"	Neurological symptoms post COVID infection	Cognitive function
Follow up period after illness	3 months	4-6 months	Unclear
Findings	"brain fog" has significant association with sex (female), respiratory symptoms at onset and the severity of illness (ICU admission).	Most of the participants' descriptions are often related to specific domains of cognitive function - particularly executive function, attention, memory and language. Most reported emergence of neurocognitive symptoms 1-4 months after their initial illness and 13/20 felt that they had improving brain fog at the time of follow up.	Worsened memory after post COVID infection when controlling for age, sex, country and education level. The severity of COVID correlated with memory issues (Word recognition). Those reporting brain fog had lower performance on Word List Recognition and produced more repetition on Category Fluency than those not reporting the symptoms.

be compared with appropriate age and gender matched healthy controls. Advanced structural and functional imaging (such as diffusion tensor magnetic resonance imaging, positron emission tomography, etc.) and biochemical measurements of amyloid and tau proteins in the blood and cerebrospinal fluid should be performed and the data correlated with the cognitive tests and clinical parameters. This will provide more robust evidence on the cause and effect association between COVID-19 and brain functions. In the laboratory, using mouse models to investigate the neuroinflammatory nature of the COVID infection may not be ideal as mice lack the ACE receptor that COVID virus use to invade human cells. In this context, certain non-human primate models which share similar ACE-2 receptor at positions critical for the interaction with SARS-CoV-2 spike may be better suited to study the long term neurological effects of COVID.

DECLARATION OF COMPETING INTEREST

The authors have no conflict of interest to declare.

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