

Letter to the Editor

Metabolomics by magnetic resonance spectroscopy may not sufficiently explain “brain fog” in neuro-COVID

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Dear Editor,

We eagerly read the article by Sklinda *et al.* about a prospective study of 11 patients with post-COVID-19 “brain fog” by means of magnetic resonance spectroscopy (MRS) and the following neuropsychological batteries: Addenbrooke’s cognitive examination III (ACE-III), the Rey complex figure test (RCFT), the California verbal learning test (CVLT), the Trail Making Test (TMT), the Wechsler adult intelligence scale (WAIS), and the hospital and anxiety depression scale (HADS), after an undetermined time after onset of the infection [1]. It was found that the Lac/Cr ratio was decreased and that the Glx/Cr ratio was increased on MRS in COVID patients with “brain fog” [1]. The study is very interesting but raises concerns that require discussion.

The main limitation of the study is that the term “brain fog” is not well defined and is generally a vague description that includes various different conditions, such as impaired consciousness, cognitive dysfunction, memory decline, concentration difficulty, disorientation, trouble finding words, decreased fluency of speech, dizziness, confusion, delirium, deficits in executive functions, impaired episodic and visuo-spatial memory, dysfunctional memory processing, non-convulsive epileptic state, depression, anxiety, hallucinations, multitasking problem, reduced ability of meeting activities of daily living (ADLs), and even sleep disorders. Accordingly, it is quite likely that the 11 included patients experienced variable deficits, constituting an inhomogeneous cohort.

A further limitation is that the various causes of “brain fog” were not entirely encountered in the 11 patients. Par-

ticularly, we should know the results of cerebral MRI, with regard to the statement that the study also aimed at investigating the macroscopic status of the brain in patients with “brain fog” [1]. Knowing the results of the MRI investigation is crucial because many of the cerebral manifestations of neuro-COVID can clinically manifest with “brain fog”. These include stroke, bleeding, immune encephalitis, meningitis, acute, disseminated encephalomyelitis (ADEM), posterior reversible encephalopathy syndrome (PRES), venous sinus thrombosis (VST), multiple sclerosis (MS), neuromyelitis optica (NMO), cerebral vasculitis, and reversible cerebral vasoconstriction syndrome (RCVS).

Some key characteristics of the study population are missing. We should know the current medication the 11 patients were taking at the time when the MRS was carried out. Knowing the medication is crucial because antidepressants, sedatives, or even analgesics may cause “brain fog” as a side effect. We also should know the latency between onset of COVID-19 respectively the positivity of the PCR test and the MRS investigation. Knowing this latency is essential because “brain fog” may continuously disappear with increasing latency to the investigation. Results of the electroencephalography (EEG) and the information about how many patients required mechanical ventilation or extra-corporal membrane oxygenation (ECMO) are also missing. Knowing the results of these investigations is crucial because “brain fog” can result from seizure activity or from hypoxia in patients requiring mechanical ventilation or ECMO. Investigations to study the test-retest variability, reproducibility, and reliability, are also lacking, as well as follow-up investigations. The sensitivity of the method seems to be low because

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not every patient had abnormal results. How were motion artefacts, suppression of the water signal, and magnetic field heterogeneity addressed?

We do not agree with the notion that “brain fog” is only a long-term complication of COVID-19. “Brain fog” can also occur in acute SARS-CoV-2 infections, as has been reported in several patients [2,3].

Overall, this interesting study has several limitations, which challenge the results and their interpretation.

The missing information should be provided and differentials affecting Lac/Cr and Glx/Cr ratios excluded. As long as “brain fog” does not follow a clear-cut definition, any biomarker applied to quantify “brain fog” will remain non-specific.

Conflict of interests

The author declares no conflict of interest.

References

1. Sklinda K, Górecki A, Dorobek M, et al. Ischaemic background of brain fog in long-haul COVID-19 – a nuclear magnetic resonance spectroscopy-based metabolomic analysis. Preliminary results. *Pol J Radiol* 2021; 86: e654-e660. doi: 10.5114/pjr.2021.111100.
2. Matias-Guiu JA, Delgado-Alonso C, Yus M, et al. “Brain Fog” by COVID-19 or Alzheimer’s disease? A case report. *Front Psychol* 2021; 12: 724022. doi: 10.3389/fpsyg.2021.724022.
3. Al-Jassas HK, Al-Hakeim HK, Maes M. Intersections between pneumonia, lowered oxygen saturation percentage and immune activation mediate depression, anxiety, and chronic fatigue syndrome-like symptoms due to COVID-19: A nomothetic network approach. *J Affect Disord* 2022; 297: 233-245.