‘Brain Fog’ and cognitive impairment: pathogenesis and clinical presentations

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Brain fog is a colloquial term for a common complaint among patients with Post-acute Covid-19.

It is an umbrella term used to describe the constellation of cognitive function impairment such as confusion, short-term memory loss, dizziness, and inability to concentrate.

Krishnan et al., *J Health Serv Psychol*, 2022
Garg et al., *Int J Gen Med*, 2021
Lived experience of ‘brain fog’

- 50 participants’ own descriptions of their symptoms
- Five focus groups of 60–90-minute duration were held via Zoom
- An accessible and well-known shorthand to disclose their wide-ranging cognitive difficulties to others

Callan et al, *BMJ Open*, 2022
Brain fog symptoms

Difficulty with the ability to:

- think and reason
- concentrate,
- remember things,
- process information,
- learn, speak, and understand
- often related to specific domains of cognitive function— particularly, executive function, attention, memory and language, with most describing difficulties across all of these domains
Prevalence of Brain Fog

- Cohort study from Fars, Southern Iran
- Telephonic follow-up post 3 months
- 194 of 2696 (7.2%) developed Brain Fog

<table>
<thead>
<tr>
<th></th>
<th>Brain fog, N = 194</th>
<th>No brain fog, N = 2502</th>
<th>p, df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female: male)</td>
<td>102: 92 (ratio: 1.11)</td>
<td>1120: 1382 (ratio: 0.81)</td>
<td>0.036, 1</td>
</tr>
<tr>
<td>Age (mean ± SD), years</td>
<td>42 ± 8</td>
<td>41 ± 9</td>
<td>0.109</td>
</tr>
<tr>
<td>Length of hospital stay (mean ± SD), days</td>
<td>6.9 ± 4.9</td>
<td>6.4 ± 6.1</td>
<td>0.221</td>
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<tr>
<td>Respiratory problems at the onset</td>
<td>180 (93%)</td>
<td>2195 (88%)</td>
<td>0.038, 1</td>
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<tr>
<td>Neurological problems at the onset</td>
<td>40 (21%)</td>
<td>486 (19%)</td>
<td>0.707, 1</td>
</tr>
<tr>
<td>Gastrointestinal problems at the onset</td>
<td>27 (14%)</td>
<td>405 (16%)</td>
<td>0.417, 1</td>
</tr>
<tr>
<td>Pre-existing chronic medical problems</td>
<td>56 (29%)</td>
<td>652 (26%)</td>
<td>0.398, 1</td>
</tr>
<tr>
<td>ICU admission*</td>
<td>28 (14%)</td>
<td>200 (8%)</td>
<td>0.004, 1</td>
</tr>
</tbody>
</table>

Abbreviations: df, degree of freedom; ICU, intensive care unit; SD, standard deviation.

*Nine missing values.
Prevalence of Brain Fog

Duration of key persistent symptoms or signs after acute COVID-19 infection
Online survey from South Korea of 241 participants

Kim et al., *BMC Infect Dis*, 2022
Great British Intelligence Test:
Cognitive deficits post recovery
<table>
<thead>
<tr>
<th>Possible mechanisms</th>
</tr>
</thead>
</table>
| Neuronal degeneration, Neuro-genesis impaired  
| Coagulopathy, Cellular apoptosis  
Ramakrishnan, *Front Immunol*, 2021 |
| Oxygen deprivation (hypoxic-ischaemic), Oxidative stress  
| Vasculopathy, Viral invasion?  
Zubair, *JAMA Neurol*, 2020 |
| Inflammation, Immune dysregulation  
| Dysautonomia, Disturbed metabolism  
Tsivgoulis et al., *Eur J Neurol*, 2021; Tsivgoulis et al., *J Neurol Neurosurg Psychiatry*, 2021; Stefano et al., *Ther Adv Chronic Dis*, 2022 |
PET-CT studies

Hypometabolism in ACE2-rich brain areas:

• Orbital gyrus
• Amygdala
• Hippocampus
• Hypothalamus-thalamus
• Brain stem

?autoimmunity
Gut and brain

- Prolonged SARS-COV2 shedding in GIT post-infection

- 7/14 (50%) intestinal biopsies: SARS-COV2 nucleic acids and protein persisting at 4 months

- More studies required to elucidate link

Are neurological manifestation a result of direct invasion of CNS by the virus?

Direct invasion of CNS by COVID-19 virus are rare

SARS-CoV-2 RNA absent in all 76 patients, where tested
Schweitzer et al., *Ann Neurol*, 2022

RESEARCH

Cerebrospinal fluid findings in COVID-19: a multicenter study of 150 lumbar punctures in 127 patients


SARS-CoV-2 RNA absent in all 76 patients, where tested
Jarius et al., *J Neuroinflammation*, 2022
Neuro-inflammation

Damage to small vessels of the brain

Neuronal injury via Amyloid Fibrils & Microglial activation

Serena Spudich & Avindra Nath, Science, 2022

Hardan et al., Medicina, 2021
Large Genetic studies implicate same gene for COVID-19 severity and Alzheimer’s Disease (AD)

- GWAS of 2,244 critically ill (208 ICUs form UK) vs 5 times population controls → OAS1 locus: Pairo-Castineira et al., *Nature*, 2021
- Has a protective haplotype of ~75 kilobases derived from Neanderthals: Zeberg & Pääbo, *Proc Natl Acad Sci USA*, 2021
- OAS1 variant, rs1131454 associated with AD, 1313 sporadic AD vs 1234 controls: Magusali et al., *Brain*, 2021
- Human induced pluripotent stem cell-derived microglia with lowered OAS1 expression, shows exaggerated production of TNF-α with IFN-γ stimulation: Magusali et al., *Brain*, 2021
Thank you