CHIEF SCIENTIST OFFICE

CODE: COV/LTE/20/26

RESEARCH PROJECT BRIEFING

Clinical phenotyping to enable targeted treatment of persistent cognitive symptoms after COVID-19

AIMS

The primary aim of this project is to positively identify distinct clinical phenotypes of cognitive impairment in patients with persistent cognitive symptoms after acute COVID-19. Clinical phenotype refers to the observable presentation of a disorder or disease in a patient.

KEY FINDINGS

In a study of detailed clinical phenotyping of 81 patients complaining of persistent cognitive symptoms one year after COVID 19 we found that:

- On average patients' cognitive function was in the mild cognitive impairment range
- In almost all patients there was a recognised clinical explanation for the cognitive symptoms.
- Depression, anxiety, post-traumatic stress disorder (PTSD), and functional cognitive disorders were the commonest reasons.

- Obstructive sleep apnoea, migraine, poorly controlled asthma and coeliac disease were among the other recognised conditions.
- These disorders all have recognised, evidence-based treatments.
- However, the disorders had often gone unidentified with symptoms being subsumed as 'long covid'.
- There were abnormalities in biomarkers of low abundance brain proteins but it was not clear how they corresponded to clinical phenotypes or imaging findings; more complex analyses are planned.
- 'Long covid' is a heterogenous collection of disorders and both research and clinical care requires detailed phenotyping.

WHAT DID THE STUDY INVOLVE?

This was a cross-sectional prospective cohort study of adult patients with persistent cognitive symptoms after COVID-19. We planned to recruit 100 patients who had both clinical and laboratory confirmed SARS-COV-2 infection with persistent cognitive symptoms at 3 months post COVID 19. We assessed them clinically, supplemented with structured neurological and psychiatric examinations, psychometrically with Montreal Cognitive Assessment Battery (MOCA) and COGNITRON (a digital battery of psychometric tests), imaging with 3T structural MRI, and blood biomarkers for low abundance brain proteins. The assessments were conducted by two consultant neuropsychiatrists and all clinical diagnoses were independently reviewed and verified by two independent consultant neurologists.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

81 patients completed the full assessment. The average age was 44, 28 male & 53 female, at a mean of 12.8 months post COVID 19. The average MOCA 25/30 (mild cognitive impairment). 43 had BMI>30 with 10 BMI>40. 16 had been hospitalised acutely. 9 patients had encephalopathy at time of acute infection; including 3 of the non-hospitalised patients.

Main explanation for cognitive symptoms	n
Anxiety (phobic or general) and Functional Cognitive Disorder	7
Autistic Spectrum Disorder + Functional Cognitive Disorder	2
Poorly controlled asthma, depression and migraine	1
Chronic Fatigue Syndrome and Functional Cognitive Disorder	9
Coeliac disease	1
Depressive disorder	16
Dysfunctional breathing	1
Fibromyalgia, Functional Cognitive Disorder, Obstructive Sleep Apnoea	1
Functional Cognitive Disorder	11
Functional Neurological Disorder (including Persistent Postural Perceptual Dizziness= 4)	6
Inflammatory bowel disease (new onset)	1
Migraine	3
No diagnosis	3
Obstructive sleep apnea (OSA)	11
PTSD (covid experiences= 2, non covid experiences= 2)	4
Resolving encephalopathy	2
Resolved between referral and review	2

WHAT IMPACT COULD THE FINDINGS HAVE?

- The findings highlight that skilled diagnostic assessment is the foundation stone of management of patients presenting with cognitive symptoms post covid. Generic treatment of 'long covid' will likely fail.
- This needs to be reflected in service planning and structure.
- Phenotyping is likely central to biological research in the condition

HOW WILL THE OUTCOMES BE DISSEMINATED?

The work will be disseminated via conference presentation, scientific publication and social media. The work was the centre of Panorama- Season 33 episode 24- Long Covid: will I ever get better?'. The authors have presented data from this study to RCPsych, ABN, FNDS and at a range of national and regional meetings. Scientific reports to date are:

- McWhirter, L. (2025). Brain fog. Practical neurology, 25(2), 137-142.
- McWhirter, L., Smyth, H., Hoeritzauer, I., Couturier, A., Stone, J., & Carson, A. J. (2023). What is brain fog?. Journal of Neurology, Neurosurgery & Psychiatry, 94(4), 321-325.
- Kearns, P. K., Dixon, C., Badonyi, M., Lee, K., Czapiewski, R., Fleming, O., ... & Gilbert, N. (2024). Structural epitope profiling identifies antibodies associated with critical COVID-19 and long COVID. eLife, 13.

The next steps are the development of new clinical tools to aid diagnosis of functional cognitive disorders and novel treatments for such conditions:

- Cabreira, V., Alty, J., Antic, S., Araujo, R., Aybek, S., Ball, H. A., ... & Carson, A. (2025). Development of a diagnostic checklist to identify functional cognitive disorder versus other neurocognitive disorders. BMJ neurology open, 7(1), e000918.

- Cabreira, V., Frostholm, L., Stone, J., & Carson, A. (2025). Feasibility trial of a self-help digital intervention for functional cognitive disorder. Brain Communications, 7(4), fcaf248.

CONCLUSION

Cognitive symptoms post COVID 19 were clinically heterogeneous (ie composed of different disorders). Most cognitive symptoms could be explained by recognised disorders that already have evidence-based treatments. The search for biological understanding is likely to be limited by a failure of accurate clinical phenotyping. 'Lumping' everything together as 'Long Covid' is likely unhelpful.

RESEARCH TEAM & CONTACT

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Additional Information
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