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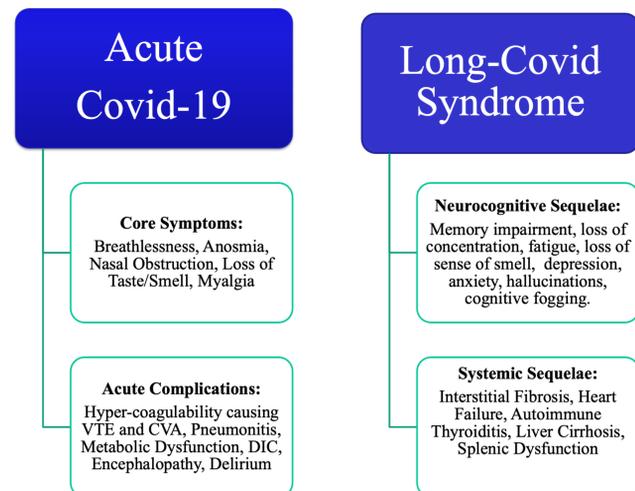
Introduction

The neurotrophic effects of Covid-19 are becoming increasingly recognized, with altered mental state recognised as the second most common presenting complaint¹. A key question is whether this has long term consequences?

Many patients worry that it does and have described long term symptoms, even after seemingly trivial initial illness; the so-called 'long covid' syndrome. NICE defines the "Long-Covid" Syndrome as symptoms of Covid that persist beyond 3 months¹. Cognitive symptoms are commonly reported as part of Long Covid but their nature and cause is poorly understood.

The neurocognitive symptoms described by patients include memory and concentration impairment, cognitive fogging, language disruption including aphasias, seizures, loss of smell/taste, fatigue and hallucinations, among a multitude of symptoms. What is less clear is the nature of underlying syndromes- do patients really suffer true aphasia or is it the 'normal' phenomena of word finding difficulties and mixing up words in speech? Similarly, are 'hallucinations' true auditory or visual hallucinations or benign hallucinatory experiences like pareidolia or vivid imagery in context of depersonalisation? Systematically describing the nature of the phenomenology is critical to interpreting what is actually happening at a clinical level, and consequently how to interpret laboratory finding of, for example, high inflammatory markers. All symptoms, including functional and anxiety disorders, must have biological correlates but what does that biology actually mean?

Symptoms of Covid-19 Vs. Long-Covid Syndrome



Rationale

- There is currently no framework for UK clinicians to systematically evaluate and investigate cognitive sequelae of Covid-19
- We describe our structured approach, based on general neuropsychiatric principles and our reading of the emergent literature.

Background

- An examination of the neurological and psychiatric outcomes of 236,379 Covid-19 survivors at six months found 33.6% of them to have significant sequelae³
- In comparison to other respiratory infections, Covid-19 was found to have a far greater chance of causing neurocognitive dysfunction.³ This increase in risk however only seems to be apply to those patients who had had encephalopathy at initial presentation.

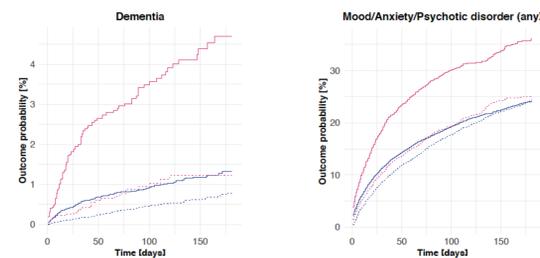


Figure 2: Kaplan-Meier estimates for the incidence of major outcomes after COVID-19 comparing patients requiring hospitalization (solid blue line) with matched patients not requiring hospitalization (dashed blue line), and comparing those who had encephalopathy (solid red line) with matched patients who did not have encephalopathy (dashed red line). For

Areas Well Established :

The two most common identified CNS complications of Covid-19 are ischaemic stroke and encephalitis⁵.

Other CNS complications that would be anticipated to cause neurocognitive dysfunction include haemorrhagic stroke, acute disseminated encephalomyelitis, meningitis, venous sinus thrombosis, and endothelialitis⁵.

Relatively benign neurological complications such as migraine and myalgia have also been identified as extremely common but are less likely to be associated with cognitive impairment⁵.

Areas Underexplored by the Literature:

There are suggestions that COVID 19 may precipitate Parkinson's Disease, CIDP, and MS⁴

Isolated delirium, including in younger adults without an ICU admission, is increasingly described; 18.1% of patients, according to one study⁶. The impact of delirium on neurodegeneration remains to be considered in non- covid scenarios it is known to lead to stepwise deterioration in Alzheimer's disease presumed secondary to inflammatory mechanisms.

The nature and extent of autoimmune encephalitis and related conditions

"Cognitive Fogging" has been reported by many patients, but the significance of this is unclear. In other disorders such as CFS/ME it has been found to be a functional cognitive disorder.

Suggested Plan

Part 1 Likelihood patient had COVID 19- core symptoms at time of infection should be confirmed, and extent of exposure to confirmed Covid-19 positive patients.

Any prior positive test by means of PCR or LAMP that perform core RNA analysis can be interpreted as confirmatory and are the advocated methods of testing⁷. These tests detect active infection, rather than prior infection. Utility of recently introduced tests for acute infection is summarised below (BMJ evidence)

Covid-19 Antibody tests can be used to detect previous infection with 81% sensitivity and 93% specificity. Their use in new variants is unknown.



Part 2 of the assessment should focus on the background neuropsychiatric risk:

- Symptoms at onset including disruptions to consciousness and altered mental state- was the patient encephalopathic?
- Was there an ITU admission? Was ARDS likely?
- Were there acute neurological complications, eg stroke, encephalitis, etc.?
- What was pre covid neurocognitive function? Was there underlying dementia, gradual cognitive deterioration or significant psychiatric disorder?
- Did memory or other cognitive disorders develop during acute phase?

Part 3 of the assessment focusses on the current cognitive or mental state.

- Note mental state abnormalities, pay particular attention to obsessional thinking impacting on cognitive performance and expectation of failure biases. Look specifically for agoraphobia-framing questions around being overwhelmed by symptoms on going outside and subsequent avoidance.
- Assess anhedonia relative to activities patient can participate in.
- Anterograde memory impairment should be assessed determining its development over time from acute episode. Retrograde memory and the nature of any temporal gradient should be considered.
- Note evidence of internal inconsistency in cognitive symptoms- such detailed history of episodes of forgetting and look for attentional dysregulation. Ask about recent TV programmes watched, books read, and ask about recent news events.
- Explore areas of cognition that are believed more robust to the impact of anxiety and expectation such as motor sequencing and praxis
- Consider ecological evidence in comparison to clinic performance. Did someone attend alone and yet fails basic memory tests?
- Explore meta-cognitive abilities

Standard Measures

- Time duration of answer to first open ended question in seconds
- Check can answer a compound question
- Check comprehension to complex grammar
- Current Symptom Burden (PHQ-15 and SNSS extended version including 15 commonest neurological symptoms)
- Current Functional Status (Liverpool Outcome Scale and the SF-12)
- Current Emotional State (Hospital Anxiety and Depression Scale)
- Fatigue (Chalder Fatigue Scale with added items on post exertional malaise)
- Pittsburgh Sleep Quality Inventory (PSQI)
- Loneliness- (Chalder 2 item scale)
- Occupational status (Work and Social Adjustment Scale)
- Likert scales of illness beliefs.
- COVID-CNS Digital Cognitive Screening Battery developed by Adam Hampshire for COVID-CNS and related projects (<https://covidcns.cognitron.co.uk>) (15 minutes), including:

Test Domains

- Immediate verbal recall STM (verbal memory)
- Spatial Span Visuo-spatial WM
- 2D Manipulations Visuo-spatial WM, exec fx – Performance IQ (Gf)
- Verbal Analogies Verbal-Semantic reasoning – Verbal IQ (Gc)
- Delayed verbal recall LTM (verbal memory)
- Motor Control Motor coordination/RT
- Target Detection Spatial Attention
- Tower of London Executive Function
- Perspectives Spatial navigation/reasoning

- Height, weight, pulse and blood pressure (erect and supine), peripheral oxygen saturation
- Standardised Neurological examination recorded using the NIH Stroke Scale
- Standardised record of internal inconsistency in neurological or cognitive symptoms - Functional Disorder Examination Recording Scale
- The Montreal Cognitive Assessment, Luria 3-step test, Interlocking Fingers test, and an abbreviated version of the Faux Pas Test of social cognition

Investigations

CT imaging can exclude acute neurological complications and also provide detail regarding brain health (ex: small vessel disease).⁷

MRI is modality of choice. Changes consistent with Covid-19 include signal changes in the medial temporal lobe, nonconfluent multifocal white matter hyperintense lesions, and isolated white matter microhaemorrhages⁸. Remember routine MRI indications such as lobar atrophy.

There is contradictory evidence at present for the use of biomarkers that signal neurocognitive dysfunction, however novel biomarkers on the horizon include IL-6, MCP-1, SLP-1, GFAP, and IP-10⁹

Acknowledgements

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¹ NICE. COVID-19: Clinical Management of COVID-19 in Primary Care. London: NICE; 2020. <https://www.nice.org.uk/guidance/ng191>

² NICE. COVID-19: Clinical Management of COVID-19 in Hospital. London: NICE; 2020. <https://www.nice.org.uk/guidance/ng191>

³ Carson AJ, Mathur J, et al. Neurocognitive sequelae of COVID-19: A systematic review. *Journal of Clinical Pharmacy and Therapeutics*. 2021;46(1):1-11. <https://doi.org/10.1111/jcpt.12500>

⁴ Carson AJ, Mathur J, et al. Neurocognitive sequelae of COVID-19: A systematic review. *Journal of Clinical Pharmacy and Therapeutics*. 2021;46(1):1-11. <https://doi.org/10.1111/jcpt.12500>

⁵ Carson AJ, Mathur J, et al. Neurocognitive sequelae of COVID-19: A systematic review. *Journal of Clinical Pharmacy and Therapeutics*. 2021;46(1):1-11. <https://doi.org/10.1111/jcpt.12500>

⁶ Carson AJ, Mathur J, et al. Neurocognitive sequelae of COVID-19: A systematic review. *Journal of Clinical Pharmacy and Therapeutics*. 2021;46(1):1-11. <https://doi.org/10.1111/jcpt.12500>

⁷ Carson AJ, Mathur J, et al. Neurocognitive sequelae of COVID-19: A systematic review. *Journal of Clinical Pharmacy and Therapeutics*. 2021;46(1):1-11. <https://doi.org/10.1111/jcpt.12500>

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