CSF markers of viral persistence are absent in neurological long COVID

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Background

The causes of NeuroPASC (new or worsened neurologic and or/psychiatric symptoms present 3 months after a COVID-19 illness and lasting for more than 2 months) remain unknown.

Persistence of SARS-CoV-2 in the central nervous system (CNS) has been hypothesized as a cause of NeuroPASC.

We assessed cerebrospinal fluid (CSF) for markers of SARS-CoV-2 viral persistence in the CNS of people with Neuro-PASC as compared to Acute COVID, Post-COVID Asymptomatic, and Pre-pandemic never-COVID controls.

Methods

- Participants with **laboratory-confirmed** prior (> 3 months) COVID-19 enrolled in the **COVID Mind Study at Yale** underwent lumbar puncture and phlebotomy.
- Frozen plasma and CSF supernatant were assayed using:

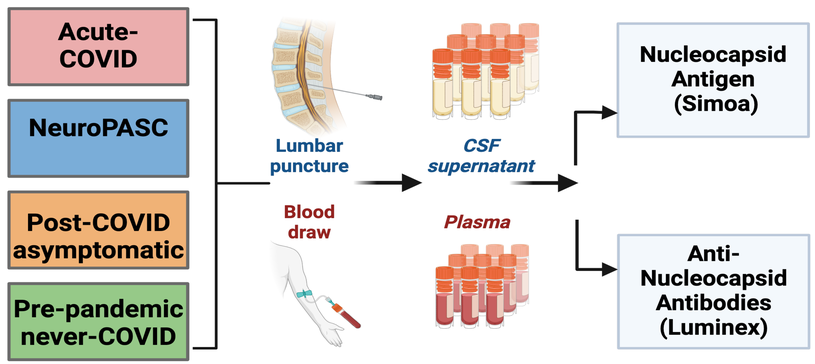
1) A Simoa (Single Molecular Array) micro-bead-based sandwich ELISA to detect **SARS-CoV-2 nucleocapsid antigen.** The Simoa assay was validated using N-antigen spiked CSF and buffer.

2) A Luminex bead-based immunoassay to detect **antiviral antibodies in CSF and plasma.**Nucleocapsid MFI Antibody Index was calculated via:
(CSF N-MFI/Plasma N-MFI) /
(CSF total IgG/Plasma total IgG)

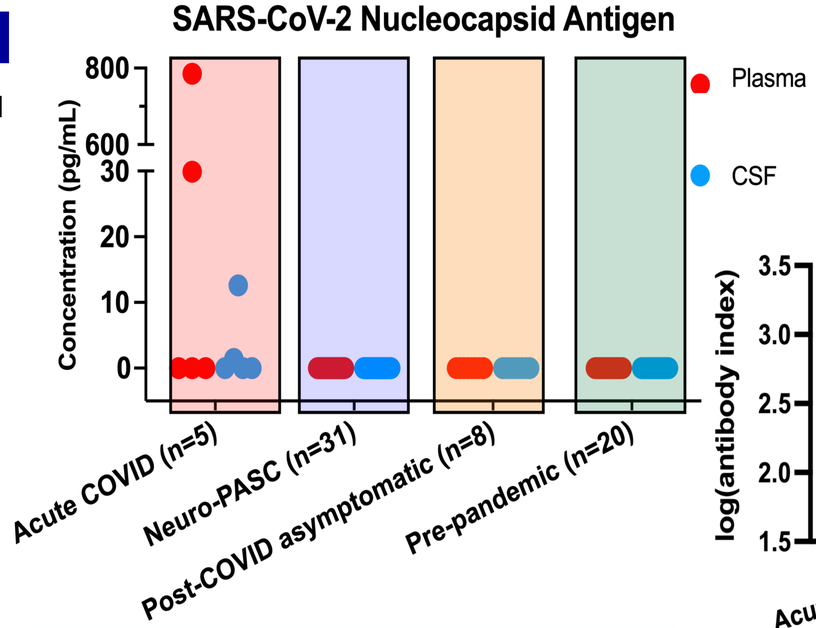
MFI = mean fluorescence index

- R Studio was utilized to perform Mann Whitney U and Chi-squared tests.

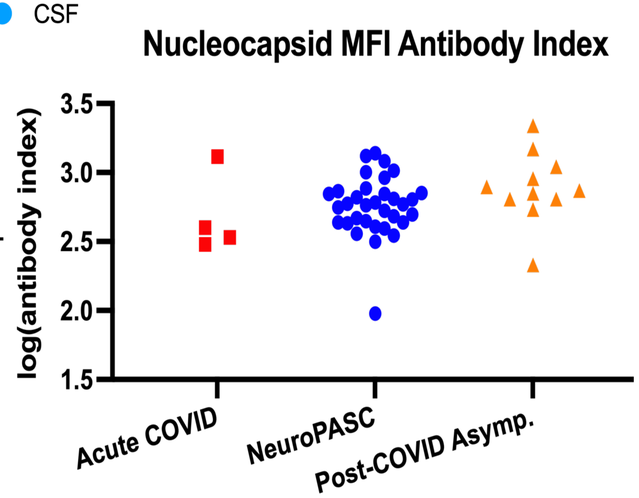
Study Design



Results



Post-COVID symptoms (Neuro-PASC group)	No. (%)
Cognitive Impairment	30 (83.3)
Fatigue	30 (83.3)
Anxiety/Depression	28 (77.8)
Off Balance/Falls	21 (58.3)
Headache	20 (55.6)
Neuropathy	19 (52.8)
Rapid Heart Rate	19 (52.8)



	Cohort, No. (%)			*P value* (NeuroPASC vs post-COVID asymptomatic)
	Acute COVID-19 (n=5)	NeuroPASC (n=36)	Post-COVID asymptomatic (n=13)	
Median age (IQR)	60 (48.5-74)	51.5 (40-61)	37 (30.5-43.5)	*0.009*
Gender				
Female	2 (40)	24 (66.7)	9 (69.2)	*0.90*
Male	3 (60)	12 (33.3)	4 (30.7)	
BMI, median (IQR)	25.5 (22.27-35.47)	27.28 (24.60-30.11)	26.56 (26.56-36.85)	*0.99*
Days from acute COVID-19 to post-COVID visit, median (IQR)	10 (2-27.5)	366.5 (282.5-569.5)	510.5 (298.5-812.5)	*0.46*
Acute COVID-19 infection severity				
Home	0 (0)	26 (72.22)	10 (76.92)	*0.20*
Hospital Floor	2 (40)	6 (16.67)	1 (7.69)	*0.54*
ICU	3 (60)	4 (11.11)	0 (0)	*0.27*
Vaccination status at time of infection				
Fully vaccinated	0 (0)	5 (13.89)	6 (46.15)	*0.00098*
Unvaccinated	5 (100)	31 (86.11)	2 (15.38)	*0.00011*
Acute COVID-19 symptoms				
Headache	2 (40)	29 (80.56)	8 (61.54)	*0.56*
Shortness of breath/cough	4 (80)	24 (66.67)	7 (53.85)	*0.52*
Nausea/vomiting/diarrhea	3 (60)	20 (55.56)	2 (15.38)	*0.074*
Fever	2 (40)	22 (61.11)	6 (46.15)	*0.76*
Congestion/Sore throat	1 (20)	19 (52.78)	8 (61.54)	*0.048*
Anosmia/Aguesia	0 (0)	18 (50)	3 (23.08)	*0.37*

We found no SARS-CoV-2 antigen in CSF in neurologic long COVID (NeuroPASC) and no difference in CSF to plasma SARS-CoV-2 antibody index in NeuroPASC versus post-COVID controls. These findings suggests that neurological long COVID symptoms are not due to viral persistence in the CSF.

Acknowledgements:
Funding: This research was supported by the RECOVER Pathobiology Program (R01MH125737-02S1), NIMH, and the Merck Investigator Studies Program.
Thanks to Yale COVID Mind Study Team and to all of our research participants

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