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BRIEF COMMUNICATION

Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19

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Abstract

Cognitive post-acute sequelae of SARS-CoV-2 (PASC) can occur after mild COVID-19. Detailed clinical characterizations may inform pathogenesis. We evaluated 22 adults reporting cognitive PASC and 10 not reporting cognitive symptoms after mild SARS-CoV-2 infection through structured interviews, neuropsychological testing, and optional cerebrospinal fluid (CSF) evaluations (53%). Delayed onset of cognitive PASC occurred in 43% and associated with younger age. Cognitive PASC participants had a higher number of pre-existing cognitive risk factors (2.5 vs. 0; $p = 0.03$) and higher proportion with abnormal CSF findings (77% vs. 0%; $p = 0.01$) versus controls. Cognitive risk factors and immunologic mechanisms may contribute to cognitive PASC pathogenesis.

New and persistent cognitive symptoms are a common post-acute sequelae of SARS-CoV-2 infection (PASC) and can follow severe disease or mild illness.[1–9] A history of COVID-19 managed in an outpatient setting eliminates the comorbidities of prolonged hospitalization that can confound investigations into the pathogenesis of cognitive PASC. Research has been limited in this non-hospitalized PASC population, but objective weaknesses in attention and working memory have been described.[1–4,7–10] These impacted cognitive domains suggest involvement of frontostriatal and/or frontoparietal brain networks with theorized mechanisms including direct viral damage, microvascular injury, persistent immune activation, and/or misguided host immunologic responses.[11–12] However, it is unclear why some adults develop cognitive PASC after SARS-COV-2 infection while others do not. Clinical features associated with cognitive PASC may inform groups at greater risk and highlight possible underlying mechanisms.

To identify salient clinical factors associated with cognitive PASC after mild COVID-19 that may inform pathogenesis, we enrolled adults with confirmed SARS-CoV-2 infection not requiring hospitalization who either reported new, persistent cognitive symptoms or were without cognitive symptoms (cognitive controls) and

performed structured neurocognitive interviews, neuropsychological testing, and optional lumbar puncture (LP) for cerebrospinal fluid (CSF) collection.

All participants were enrolled in the Long-term Impact of Infection with Novel Coronavirus (LIINC) study (NCT04362150) that evaluates recovery from COVID-19 in adults prospectively enrolled 14 days or more from symptom onset with confirmed SARS-CoV-2 infection by nucleic acid amplification test.[13] LIINC enrolls individuals referred by clinicians and those self-referred to the study, and has several focused sub-studies, including the Coronavirus Neurocognitive Study. LIINC participants who consented to be contacted by the Coronavirus Neurocognitive Study were screened for additional exclusion criteria, including inability to complete evaluations in English; a history of serious or untreated medical or psychiatric condition(s) that may confound cognitive issues (e.g., liver failure, bipolar disorder); active substance use disorder; or daily recreational substance use. For the focus of this work, we analyzed data from individuals who had not been hospitalized with COVID-19 and without significant medical complications (e.g., thrombotic events). We received study approval from the institutional review board at UCSF and all participants provided written, informed consent for participation in research. All participants underwent a structured interview with a cognitive neurologist covering COVID-19 illness, past medical history, pre-existing cognitive risk factors, medications, and the presence of 23 different cognitive symptoms following onset of COVID-19. Participants were designated as having cognitive PASC based on reports in the structured interview of one or more new, persistent cognitive symptom(s) after acute illness with COVID-19, per World Health Organization definition.[14] Cognitive controls reported no new cognitive symptoms after acute SARS-CoV-2 infection. Participants underwent a 1.5-h, in-person cognitive testing battery with a neuropsychologist evaluating the domains of memory, executive functioning, processing speed, attention and working memory, visuospatial abilities, and language (Appendix S1). Raw scores were demographically adjusted per published manuals. As there are currently no published neuropsychological testing criteria for cognitive PASC, we applied the equivalent criteria for HIV-associated neurocognitive disorder (HAND), a similar, well-established, virally associated cognitive disorder that requires z score performance ≤ -1 on one or more test in two or more cognitive domains without evidence of a pre-existing cause.[15] Individuals who consented to LP had CSF collected with a corresponding serum sample for clinical testing ($n = 13$ cognitive PASC and $n = 4$ cognitive controls; Quest Diagnostics) using published upper reference limits for calculated CSF-serum albumin ratio, a measure of blood–brain barrier (BBB) permeability.[16] Univariate analyses were reported as proportions, or medians with interquartile ranges (IQR). Group comparisons utilized Fisher's exact tests for comparing proportions and Mann–Whitney *U*-tests for continuous data due to the small sample size. All analyses were performed using Prism 9.

We evaluated 22 participants with cognitive PASC and 10 cognitive controls with a median age of 41 years old (IQR: 34–52; range: 19–69), a median of 16 years of education, assessed a median of 10.1 months from first COVID-19 symptom (IQR: 7.1–14.2; range: 2.3–19.0) (Table 1). There were no group differences in terms of age, gender, years of education, or distribution of race/ethnicity (all $p > 0.05$). Cognitive PASC participants were evaluated closer to the onset of first COVID-19 symptom than cognitive controls (9.3 vs. 15.2 months, $p = 0.01$); this did not differ for the participants who underwent LP (Table 1).

Among participants with cognitive PASC, 43% (9/21) reported a delayed onset of cognitive symptoms starting one or more month after first COVID-19 symptom (range: 1–6 months). Twenty-nine percent (6/21) reported that cognitive PASC symptoms began two or more months after the first COVID-19 symptom. One participant could not date symptom onset. Participants with delayed onset of cognitive PASC were younger than those with acute onset of cognitive PASC (median of 39 vs. 50 years, $p = 0.04$). Compared to cognitive controls, participants with cognitive PASC had a greater median number of pre-existing cognitive risk factors (2.5 vs. 0; $p = 0.03$) with no differences in the presence of specific cognitive risk factors (Table 2). Neuropsychological testing revealed that 59% (13/22) with cognitive PASC met equivalent HAND criteria for objective cognitive impairment, compared to 70% (7/10) of cognitive controls.

CSF was analyzed in 53% of participants (17/32), reflecting 59% (13/22) with cognitive PASC and 40% (4/10) of cognitive controls. Among those who underwent LP, cognitive PASC participants were older than cognitive controls (median of 47 vs. 28 years, $p = 0.03$) with no other groups differences (Table 1). LPs were performed a median of 9.7 months (IQR: 6.9–13.9) after first COVID-19 symptom (Table 1). Overall, 77% (10/13) of participants with cognitive PASC had a CSF abnormality compared with 0% (0/4) of cognitive controls ($p = 0.01$). Two participants with cognitive PASC displayed elevated CSF protein without other explainable cause (59 and 76 mg/dL; reference range 15–45 mg/dL) and the only reported cognitive risk factor was a remote history of corrected B12 deficiency in one participant. All participants had normal values for CSF white blood cells, glucose, calculated CSF/serum albumin ratio, IgG index, CSF IgG level, and serum IgG level and did not differ between participant groups (all $p > 0.05$). Abnormal oligoclonal

Table 1. Demographics and characteristics of participants following non-hospitalized SARS-CoV-2 infection.

	Cognitive PASC	Cognitive controls	*p* value
Total cohort			
Number	22	10	–
Female[1]	59% (13)	50% (5)	0.71
Age, years (IQR; range)	47.5 (38–53; 21–69)	39 (30–43; 19–53)	0.06
White/non-white race/ethnicitys[2]	73% (16)/27% (6)	60% (6)/40% (4)	0.68
Education, years (IQR; range)	16 (16–18; 11–25)	18 (16–22; 12–27)	0.29
Months to evaluation (IQR; range)	9.3 (6.6–11.5; 2.3–14.5)	15.2 (8.8–17.6; 5.5–19.0)	0.01*
% Equivalent HAND criteria[3]	59% (13)	70% (7)	0.70
LP participants			
Number	13	4	–
Female	62% (8)	75% (3)	>0.99
Age, years (IQR; range)	47 (37–55; 21–69)	28 (21–37; 19–39)	0.03*
White/non-white race/ethnicity[4]	77% (10)/23% (3)	50% (2)/50% (2)	0.54
Education, years (IQR; range)	16 (16–19; 11–25)	16 (13–25; 12–27)	0.88
Months to evaluation (IQR; range)	9.0 (4.9–10.7; 2.3–14.5)	12.3 (6.5–17.5; 5.5–18.3)	0.25
Months to LP (IQR; range)	9.0 (6.3–12.0; 2.5–15.3)	12.6 (7.3–18.0; 6.5–18.9)	0.30
Vaccination status at LP[5]	69% (9)/15% (2)/15% (2)	100% (4)/0%/0%	>0.99
% Equivalent HAND criteria[3]	62% (8)	100% (4)	0.26

Proportions are represented with participant number in parenthesis. Median values are presented for age, education, and months to evaluation/LP. Months to evaluation/LP reflect time from first reported COVID-19 symptom. PASC, post-acute sequelae of SARS-CoV-2; IQR, interquartile range; HAND, HIV-associated neurocognitive disorder; LP, lumbar puncture.

[1] Male gender included one transgender male on gender-affirming hormone therapy.

[2] Cognitive PASC, non-white race/ethnicity reflected 4 participants identifying as Hispanic/Latino (18%), 1 Asian (5%), and 1 American Indian or Alaskan Native (5%); cognitive controls, non-white race/ethnicity reflected 4 participants identifying as Asian.

[3] Equivalent HAND criteria indicates the proportion of participants with neuropsychological testing performance of at least one standardized z score of ≤ -1 in 2 or more domains.

[4] Cognitive PASC, non-White race/ethnicity reflected 2 participants identifying as Asian (8%),1 participant identifying as Hispanic/Latino (8%) and 1 participant identifying as American Indin or Alaskan Native (8%); cognitive controls, non-White race/ethnicity reflected 2 participants identifying as Asian (50%).

[5] Vaccination status at LP represents the proportion (number) of individuals fully/partially/or not vaccinated after COVID-19. p value reflects comparison of fully or partially vaccinated versus not vaccinated participants. No participants were vaccinated prior to developing COVID-19.

banding (OCB) patterns were identified in 69% (9/13) of participants with cognitive PASC compared to 0% of cognitive controls ($p = 0.03$). The abnormal OCB patterns reflected matched bands in CSF and serum for 8/9 participants. One participant had two well-defined gamma restriction bands in CSF that were not present in serum. The presence of abnormal OCB patterns was independent of participant vaccination status at time of LP ($p > 0.99$). One of the two unvaccinated participants displayed matched OCB and the other had no detected bands in CSF. One cognitive PASC participant with elevated CSF protein (59 mg/dL) had matched OCBs in CSF and serum; the other did not. When CSF analyses were restricted to only the cognitive PASC participants with objective cognitive performance issues per equivalent HAND criteria ($n = 8/13$), only 62.5% had CSF abnormalities ($p = 0.49$). This group did not include the participant with unique OCB in CSF or the individuals with high CSF protein levels. It is notable that the five cognitive PASC participants excluded for not meeting equivalent HAND criteria had estimated premorbid IQ levels above 100 (with four participants 115 or above), suggesting HAND criteria for z scores ≤ -1 may not have had the sensitivity to detect changes with a high pre-morbid cognitive baseline.

In this small study, we identified that adults reporting new, persistent cognitive symptoms after mild SARS-CoV-2 infection had delayed symptom onset in 43% of cases, a higher median number of pre-existing cognitive risk factors and a higher proportion with CSF abnormalities compared to cognitive controls who also recovered from SARS-CoV-2 infection. The large proportion of participants reporting a delayed onset of cognitive PASC implies that events occurring after the acute period of SARS-CoV-2 infection may contribute to pathogenesis and respond to early intervention. Mechanisms that may have a delayed onset include microvascular injury, persistent immune activation, and a post-infectious autoimmune response. This delayed symptom onset could reflect a response bias in some participants. Cognitive PASC participants had a greater number of pre-existing cognitive

Table 2. Pre-existing cognitive risk factors by participant group.

	Cognitive PASC $n = 22$	Cognitive controls $n = 10$	p value
Hypertension	14% (3)	0% (0)	0.53
Diabetes	5% (1)	0% (0)	>0.99
Sleep apnea	9% (2)	0% (0)	>0.99
Living with HIV	5% (1)	0% (0)	>0.99
Depression	23% (5)	30% (3)	0.68
Anxiety	32% (7)	20% (2)	0.68
ADHD	18% (4)	10% (1)	>0.99
Learning disability	23% (5)	0% (0)	0.16
Daily psychoactive medication	18% (4)	0% (0)	0.28
History of mild TBI	18% (4)	10% (1)	>0.99
History of hypothyroidism	23% (5)	0% (0)	0.16
History of vitamin B12 deficiency	14% (3)	0% (0)	0.31
History of recurrent stimulant use	14% (3)	0% (0)	0.53
History of heavy alcohol use	14% (3)	0% (0)	0.53
At least one cognitive risk factor	73% (16)	40% (4)	0.12
Median # of cognitive risk factors[1]	2.5 (0–3.3; 0–9)	0 (0–1.3; 0–3)	0.03*

Proportions of individuals with pre-existing cognitive risk factors are displayed with participant number in parentheses. Other cognitive risk factors assessed and not endorsed by participants in either group are a history of stroke, transient ischemic attack, intracranial hemorrhage, seizure disorder, meningitis, encephalitis, multiple sclerosis, mild cognitive impairment diagnosis, and dementia diagnosis. PASC, post-acute sequelae of SARS-CoV-2; ADHD, attention deficit hyperactivity disorder; mild TBI, mild traumatic brain injury.

[1]Median values are followed by interquartile range and range.

risk factors, suggesting some individuals may be selectively vulnerable, possibly in frontostriatal and/or frontoparietal brain networks. It is notable that some cognitive risk factors may not be mentioned when taking a standard medical history. This study was underpowered to detect differences in specific cognitive risk factors.

More than 75% of cognitive PASC participants who underwent LP had CSF abnormalities, although they were older than the small group of cognitive controls ($n = 4$) who displayed no abnormalities. It is also unclear whether the higher rate of baseline cognitive risk factors in the cognitive PASC group may have contributed to CSF abnormalities. One cognitive PASC participant displayed intrathecal IgG antibody production, indicating central nervous system (CNS) adaptive immune activation. The target antigens of these antibodies are unknown but may reflect anti-SARS-CoV-2 antibodies compartmentalized in CNS, intrathecal autoimmunity, or another process. There are reports of COVID-19-associated autoantibodies to neural tissue, immunomodulatory proteins, and prothrombotic autoantibodies.[17–19] The matched OCB in cognitive PASC participants does not exclude intrathecal antibody production from plasma cells crossing the BBB, but this most likely reflects systemically produced antibodies with passive transfer across the BBB, despite normal BBB permeability measurements. These matched antibodies were independent of vaccination status and may be autoantibodies. The high frequency of matched OCB suggests systemic activation of the adaptive immune system may be common in cognitive PASC, and has been reported during acute SARS-CoV-2 infection in hospitalized, neurologically ill patients.[20] Further investigations in larger studies will be important to understand these findings in the context of broader systemic and CNS immunologic responses.

Only 59% of those with cognitive PASC had objective cognitive impairment per equivalent HAND criteria, highlighting the challenges and incongruities of using subjective versus objective cognitive assessments for diagnosis. However, comparing cognitive performance to normative references may not identify true change within an individual, particularly in those with a high pre-morbid cognitive baseline. In contrast, most cognitive controls met the equivalent HAND criteria despite denying an extensive list of cognitive symptoms. This may have reflected pre-morbid cognitive differences or subtle COVID-associated changes of which the participants were unaware. Future efforts will need to develop objective criteria for cognitive PASC to facilitate patient care and clinical research. Our study limitations include a small participant sample size which may hinder validity of the results, particularly for LP. Additionally, the study demographics may not reflect the broader population of those impacted by PASC. The age difference between cognitive PASC and cognitive control participants, although not significant, could have altered the presence of pre-existing cognitive risk factors, although the most prevalent cognitive risk factors were not age-associated. Further research on cognitive PASC is needed in larger, epidemiologically derived cohorts.

We found that individuals who were not hospitalized for SARS-CoV-2 infection can have variable onset of cognitive PASC symptoms associated with a greater number of pre-existing cognitive risk factors and abnormal CSF findings.

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Author Contributions

J. H. is the principal investigator and author of the project protocol. J. H., B. M. A., and M. L. S. conceived the study design. M. J. P. referred participants from the LIINC study, which is overseen by M. J. P., T. J. H., J. D. K., S. G. D., and J. N. M., J. H. and A. O. enrolled the patients in this study and collected study data. M. L. S., A. C. A., B. M. A., and A. O. conducted neuropsychological evaluations. A. A., J. H., I. E. A., and A. O. designed and performed statistical data analyses. A. A. and A. O. conducted a literature review and A. A. and J. H. developed the manuscript. All authors contributed intellectual content to the manuscript and approved the final version for submission.

Conflicts of Interest

Dr. Apple, Ms. Oddi, and Dr. Peluso have no disclosures. Dr. Asken received speaker honorarium from the American College of Sports Medicine outside of the submitted work. Dr. Henrich is the received research funds from the National Institutes of Health and holds grants/contracts with Merck and Co. and Gilead Biosciences outside of the submitted work. Dr. Kelly hs no disclosures. Dr. Pleasure received the National Institutes of Health/NINDS grant R01NS118995-14S supporting this work. Dr. Deeks, Dr. Allen, and Dr. Martin have no disclosures. Dr. Ndhlovu received consulting fees from work as a scientific advisor for Abbvie, ViiV, and Cytodyn outside of the submitted work. Dr. Miller is the recipient of grants/contracts P30AG062422, P01AG019724, R01AG057234 from the National Institute of Health/NIA outside of the submitted work; has received royalties/licenses from Cambridge University Press, Guilford Publications, Inc., Johns Hopkins Press, Oxford University Press, Taylor & Francis Group, Elsevier, Inc. and Up-to-Date outside of the submitted work; has participated on advisory boards for The John Douglas French Foundation (Medical Advisor), The Larry L. Hillblom Foundation (scientific advisor), Association for Frontotemporal Degeneration (scientific advisor), National Institute for Health Research Cambridge Biomedical Research Centre and its subunit, the Biomedical Research Unit in Dementia (scientific advisor), University of Washington ADRC (external advisor), Stanford University ADRC (external advisor), Arizona Alzheimer's Disease Center (external advisor), Massachusetts Alzheimer Disease Research Center (external advisor), The Buck Institute for Research on Aging (scientific advisor), University of Southern California P01 Urban Air Pollution and Alzheimer's Disease: Risk, Heterogeneity and Mechanisms (external advisory committee) outside of the submitted work. Dr. Hellmuth received grant support from the National Institutes of Health/NIMH K23MH114724 supporting this work and personal fees for medical-legal consultation outside of the submitted work.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Neuropsychological battery.

