Post-Acute SARS-CoV-2 Antigenemia Is Associated With Some But Not All Long COVID Symptoms

947

Michael Peluso[1], Thomas Dalhuisen[1], Zoe Swank[2], Sarah Goldberg[1], Scott Lu[1], Samuel Han[2], Jessica Chen[1], Emily Fehrman[1], Khamal Anglin[1], Rebecca Hoh[1], Timothy Henrich[1], J. Daniel Kelly[1], Steven Deeks[1], David Walt[1], Jeffrey Martin[1], for the UCSF Long-term Impact of Infection with Novel Coronavirus (LIINC) Study

[1]University of California, San Francisco, San Francisco, CA, USA, [2]Harvard Medical School, Boston, MA, USA

Contact: Michael Peluso, MD
michael.peluso@ucsf.edu

BACKGROUND

- SARS-CoV-2 RNA and antigens can be found in blood and tissues many months after infection, but whether SARS-CoV-2 persistence causes Long COVID (LC) is unproven.
- The scant data in favor of causation has related persistent SARS-CoV-2 to non-specific LC definitions.
- It is unknown whether persistent SARS-CoV-2 is associated with all, or only some, of the different symptoms of this heterogenous condition.

OBJECTIVE

- Determine the causal influence of persistent SARS-CoV-2 antigen on the occurrence of post-acute neurologic, cardiopulmonary, gastrointestinal, musculoskeletal, and fatigue symptoms.

PARTICIPANTS

- Individuals up to 14 months following test-confirmed SARS-CoV-2 infection in UCSF's Long-term Impact of Infection with Novel Coronavirus (LIINC) Study.

MEASUREMENTS

Questionnaire-based

- We defined 5 LC case groups; each had ≥1 symptom in a given grouping that was rated "very bothersome" at ≥2 visits 3-14 months after the first confirmed SARS-CoV-2 infection:
  a) neurologic (headache, brain fog or dizziness);
  b) cardiopulmonary (cough, dyspnea, chest pain or palpitations);
  c) gastrointestinal (GI; nausea, vomiting, diarrhea, constipation, belly pain or appetite loss);
  d) musculoskeletal (back, joint or muscle pain);
  e) fatigue.
- The non-LC group included those whose acute symptoms resolved within 30 days of infection and who had no symptoms 3-14 months post-infection.

Laboratory-based

- SARS-CoV-2 spike, S1, and nucleocapsid (N) antigens were measured in plasma by single molecule array (Simoa).

ANALYSIS

- Odds ratios (OR) were used to relate antigenemia at any visit 3-14 months post-COVID to concurrent symptoms.

RESULTS

Table 1. Study participants.

Characteristic	Non-PASC N = 40[1]	PASC N = 76[1]
Age	40 (32, 53)	48 (38, 57)
Female sex	12 (30%)	45 (59%)
Race		
Hispanic/Latino	3 (7.9%)	18 (24%)
White	26 (68%)	43 (57%)
Black/African American	3 (7.9%)	2 (2.7%)
Asian	6 (16%)	8 (11%)
Pacific Islander/Native Hawaiian	0 (0%)	1 (1.3%)
American Indian/Alaska Native	0 (0%)	2 (2.7%)
Unknown/Unavailable	0 (0%)	1 (1.3%)
Comorbid conditions		
Diabetes	1 (2.5%)	8 (11%)
Obesity	8 (21%)	35 (46%)
Lung disease	7 (18%)	22 (29%)
HIV	9 (23%)	11 (14%)
Hospitalized for COVID-19	0 (0%)	16 (21%)
Number of vaccinations		
0	15 (38%)	38 (52%)
1	6 (15%)	3 (4.1%)
2	6 (15%)	9 (12%)
3	9 (23%)	15 (21%)
4	4 (10%)	8 (11%)

[1]Median (Q1, Q3); n (%)

Fig 1. Association between SARS-CoV-2 spike antigenemia and Long COVID symptoms.

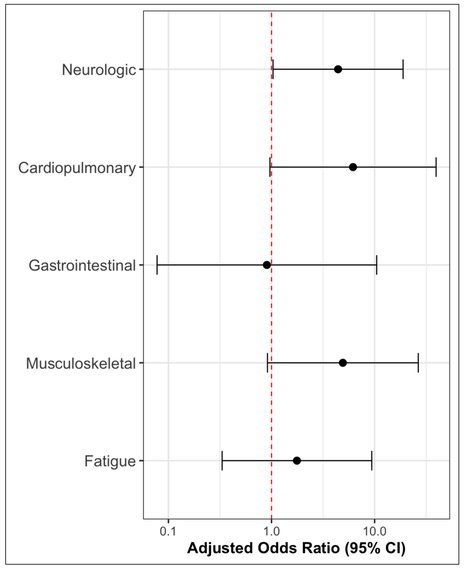


Table 2. Association between SARS-CoV-2 spike antigenemia and Long COVID symptoms.

Symptom Group	n	% with Spike Antigenemia	Unadjusted Odds Ratio* (95% CI)		Adjusted Odds Ratio* (95% CI)†	
Neurologic	56	23.2%	3.7 (0.99-14.1)	p=0.052	4.4 (1.04-18.9)	p=0.045
Cardiopulmonary	17	35.3%	6.7 (1.4-31.4)	p=0.015	6.2 (0.96-39.5)	p=0.055
Gastrointestinal	12	8.3%	1.1 (0.11-11.9)	p=0.924	0.9 (0.08-10.5)	p=0.934
Musculoskeletal	29	31.0%	5.6 (1.3-22.9)	p=0.018	4.9 (0.91-26.5)	p=0.064
Fatigue	33	12.1%	1.7 (0.35-8.2)	p=0.508	1.8 (0.33-9.38)	p=0.505

* Odds ratio refers to odds of experiencing one or more symptoms in the respective symptom group 3 to 14 months following SCV2 infection among persons who have one or more timepoints with SCV2 spike antigenemia compared to persons without spike antigenemia.
† Adjusted for hospitalization during acute SCV2 infection, number of antigen-assayed timepoints 3 to 14 months after first SCV2 infection, and time since first SCV2 infection.

Results Summary

- Spike antigenemia was found in 7.5% (3/40) of the non-LC group.
- In unadjusted analyses, spike antigenemia was associated with neurologic, cardiopulmonary, and musculoskeletal symptoms, but not GI symptoms or fatigue.
- After adjustment for confounding, associations endured for neurologic (OR 4.4, p=0.045), cardiopulmonary (OR 6.2, p=0.055), and musculoskeletal (OR 4.9, p=0.064) symptoms.
- After exclusion of timepoints within 1 month of known SARS-CoV-2 vaccination or reinfection, point estimates were similar but confidence intervals widened slightly.
- No significant associations were seen with S1 or N antigens.

CONCLUSION

- Among adults with prior SARS-CoV-2 infection, we found evidence for an association between spike antigenemia 3-14 months post-infection and some, but not all, LC symptoms.

IMPLICATIONS

- Deriving valid inferences via observational research about the role of persistent SARS-CoV-2 antigen in causing LC:
  - Will require well-characterized participants, both those with a variety of different LC symptoms and, to serve as the control group, those without symptoms. Identifying those who have stable clinical phenotypes over time offers the best chance at enhancing specificity of clinical status and finding associations (if they truly exist).
  - May require multiple measurements (assay insensitivity).
  - Will require overcoming several components of confounding. This will require making accurate measurements of these confounders.
- That some symptoms do not have strong evidence for a role of persistent SARS-CoV-2 suggests that different mechanisms might contribute to the variable presentation of LC. Lack of statistical power is another possible explanation.

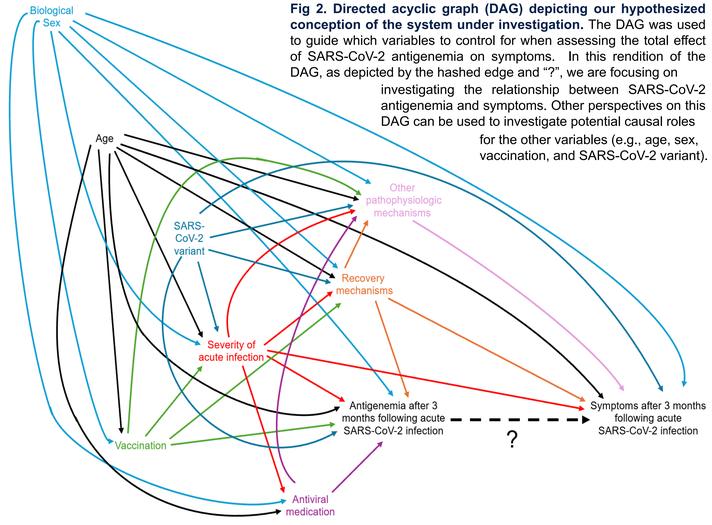


Fig 2. Directed acyclic graph (DAG) depicting our hypothesized conception of the system under investigation. The DAG was used to guide which variables to control for when assessing the total effect of SARS-CoV-2 antigenemia on symptoms. In this rendition of the DAG, as depicted by the hashed edge and "?", we are focusing on investigating the relationship between SARS-CoV-2 antigenemia and symptoms. Other perspectives on this DAG can be used to investigate potential causal roles for the other variables (e.g., age, sex, vaccination, and SARS-CoV-2 variant).

- Larger studies and complete measurement of confounders are needed to confirm our findings and mitigate the threat from confounding before causation is inferred. The complexity of the confounding structures suggests that interventional studies that target persistent SARS-CoV-2 will be needed to provide the most definitive proof for causation.

Acknowledgement: We are grateful to the study participants. LIINC is supported by the PolyBio Research Foundation and the National Institute of Neurologic Disorders and Stroke (NINDS).