Long-term neurological sequelae of SARS-CoV-2 infection

We show that patients who survive the first 30 days of acute SARS-CoV-2 infection have an increased risk of various post-acute neurological disorders after 1 year compared with uninfected contemporaries. The burden of these sequelae (aspects of ‘long COVID’) has serious implications for patients as well as society.

The question
SARS-CoV-2 infection can lead to post-acute sequelae in pulmonary and extrapulmonary organ systems — collectively referred to as long COVID. Experimental evidence in mice suggests that SARS-CoV-2 infection causes persistent neuroinflammation and neuronal damage. Neuroimaging studies in humans before and after SARS-CoV-2 infection show a reduction in brain size and grey matter thickness many months after the onset of SARS-CoV-2 infection. Against this background, we noted a major knowledge gap — the lack of a comprehensive evaluation of post-acute neurological sequelae after a long (1-year) follow-up — something that was also flagged by long COVID patient advocacy groups as a priority area for urgent investigation. We therefore resolved to address this by comprehensively characterizing post-acute neurological sequelae of SARS-CoV-2 infection to obtain estimates of the risks and burdens of these neurological outcomes at 1 year of follow-up.

The discovery
We used the healthcare databases of the US Department of Veterans Affairs, which operates the largest integrated healthcare system in the USA, to build a cohort of 154,068 patients with SARS-CoV-2 infection, and 5,638,795 uninfected contemporaries; to further validate the estimates, we built a pre-pandemic, historical control cohort (n = 5,859,621). Demographic and health characteristics were balanced at baseline using inverse probability weighting. The cohorts were followed for 1 year. In the COVID-19 group, follow-up started on the day of infection; in the uninfected control group, follow-up was randomly assigned but followed the same date distribution as the infected group.

In the post-acute phase, patients with COVID-19 had an increased risk of a wide range of incident neurological disorders, including cerebrovascular disorders, cognition and memory disorders (memory problems and Alzheimer’s disease), peripheral nervous system disorders, episodic disorders, extrapyramidal and movement disorders, musculoskeletal disorders, sensory disorders, other neurological or related disorders, and any neurological outcome (a composite outcome of any of the neurological outcomes we studied) (Fig. 1; see the associated paper for the full list of conditions assessed). Overall, we estimate that patients with COVID-19 have a 42% increased risk of developing a neurological sequela in the year after infection, translating to a burden of 7% of infected people. The risks were evident in subgroups based on age, race, sex, obesity, smoking, measures of socioeconomic deprivation, diabetes, chronic kidney disease, hyperlipidaemia, hypertension and immune dysfunction. The risks were evident even among patients who had mild acute COVID-19 that did not necessitate hospitalization, but were higher among people who were hospitalized and the highest risks were among patients who needed intensive care during the acute phase of COVID-19. The results were consistent in analyses involving the COVID-19 group versus either the contemporary or the historical control cohorts as the referent category.

The implications
Our report provides a comprehensive account of the neurological consequences of COVID-19 at 1 year after infection and shows the substantial risks and burdens of a wide range of incident neurological disorders. A limitation of our study is that despite the cohorts being large and including adults of various ethnicities and both sexes, on average they predominantly consisted of white males. Our findings suggest the need for attention to the long-term neurological consequences of SARS-CoV-2 infection. Although the absolute burden of any neurological sequela might seem small (7% at 1 year), given the large scale of the pandemic, this may translate into a large number of affected individuals. Furthermore, some of the neurological sequelae are chronic conditions that will require lifelong care and might impact patients’ lives and livelihood and, because of the magnitude of the pandemic, healthcare systems, the economy and societal wellbeing too.

Our report adds to the growing number of studies that show that SARS-CoV-2 infection can lead to post-acute sequelae in almost any organ system. Governments and health systems must respond to this challenge by developing robust research programs to better understand, prevent and treat long COVID. Health systems must also build care pathways to address the multi-system care needs of people with long COVID. The substantial and growing burden of long-term sequelae of SARS-CoV-2 infection must be considered when formulating policies for the ongoing management of the COVID-19 pandemic and exit strategies to a post-pandemic world.

Ziyad Al-Aly
Research and Development Service, Veterans Affairs St. Louis Healthcare System, St. Louis, MO, USA.
EXPERT OPINION

“This is a well-designed, large study with appropriate controls, which shows an increase in neurological complications in hospitalized and non-hospitalized patients with COVID-19 at 12 months after the onset of the infection. The long follow up, the large sample size and the syndromic approach as opposed to symptom-based characterization of the patients makes this a unique study.” Avindra Nath, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA.

FIGURE

Fig. 1 | Risks and 12-month burdens of incident post-acute neurological disorders in patients with COVID-19. Adjusted hazard ratios (HRs) and estimated excess burdens and their 95% confidence intervals (CIs) for the indicated composite neurological outcomes, based on a cohort of 154,068 patients infected with SARS-CoV-2 and a contemporary cohort of 5,638,795 uninfected people who served as the control group. Outcomes were ascertained 30 days after the COVID-19-positive test and until the end of 1 year of follow up. © 2022. Xu, E. et al., CC BY 4.0.

BEHIND THE PAPER

Our work on long COVID is inspired by the long COVID patient community. In the past 2 years, we heard from patients across the globe who were living with the long-term effects of COVID-19 (including devastating neurological or other consequences) but their health concerns were being dismissed by family members, friends and even healthcare providers. Patients felt that research empowered them, validated their personal experiences, and provided hope that long COVID might be better understood, treated and even prevented in the future. They urged us to expand our research on long COVID and investigate the post-acute neurological sequelae of SARS-CoV-2 infection. We hope that our findings will facilitate early recognition and treatment of these long-term neurological consequences and stimulate further research to deepen our understanding of these conditions. We are enormously grateful to the long COVID patient community for their inspiration and support — without which this work would not have been possible. Z.A.-A.

REFERENCES

1. Al-Aly, Z., Xie, Y. & Bowe, B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature 594, 259–264 (2021). This article provided the first systematic characterization of the post-acute sequelae of SARS-CoV-2 infection.

2. Fernández-Castañeda A. et al. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. Cell 185, 2452–2468. e16 (2022). This article describes neurobiological effects of COVID-19 in mice and humans.

3. Douaud, G. et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature 604, 697–707 (2022). This article describes structural brain abnormalities in patients with SARS-CoV-2 infection.

4. Xie, Y., Xu, E., Bowe, B. & Al-Aly, Z. Long-term cardiovascular outcomes of COVID-19. Nat. Med. 28, 583–590 (2022). This article describes the range of cardiovascular disorders in the post-acute phase of SARS-CoV-2 infection.

5. Yan Xie, Z. A.-A. Risks and burdens of incident diabetes in long COVID-19: a cohort study. Lancet Diabetes Endocrinol. 10, 311–321 (2022). This article describes the increased risk of diabetes in the post-acute phase of SARS-CoV-2 infection.

FROM THE EDITOR

“This study shows that individuals who had COVID-19 have an increased risk of developing a wide range of neurological complications after 12 months, even in those who were not hospitalized for infection. The findings from this study highlight the need for health systems and public policies to address the neurological consequences of COVID-19, which would have an effect on quality of life and productivity loss.” Editorial Team, Nature Medicine.