



CLINICAL OPINION

Decoding the unknowns in long covid

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Relatively few peer reviewed papers have documented the disease features of “long covid,” but patient groups report several months of sequelae. These can be varying, relapsing, and remitting, and may include respiratory, cardiovascular, urological, neurological, and/or gastrointestinal symptoms in unpredictable combinations. We do not know whether long covid will come to be seen as a condition that typically lasts months, years, or is life long.

Many of the risk factors for severity of acute covid-19, such as age, male sex, obesity, and ethnicity do not appear explicitly to enhance the chance of long covid. Also, there seems no clear correlation between severity of the acute disease and long term sequelae. Indeed, many patients come from that large, hidden group who self-isolated when they were unwell at home, did not access a polymerase chain reaction test, and so have no formal health record of covid-19. These points highlight an uncharted pathophysiology, and demand a better answer than “post-viral syndrome” or the notion that people are bound to “feel a bit rough” coming out of hospital.

Starting points

At least 10% of people with acute covid-19 are estimated to have symptoms that do not resolve over the subsequent months.^{1,2} Extrapolated to the current global burden of covid-19, this suggests potentially more than five million current “long haulers.” Biomedical research is needed to tackle the many challenges imposed by these estimates: formal assessment of the epidemiology, risk factors, symptoms, and pathology. We need recognised criteria for a working diagnosis, not least to facilitate access to appropriate services and allow healthcare provision planning. But we must also move beyond the observational to the interventional. Achieving this will need some hard thinking to decode aetiological mechanisms in a confounding condition that seems to move around the body and between systems and, thus, in healthcare management, between distinct clinical specialties and treatment pathways. What should our starting points be in decoding the unknowns?

Infection with covid-19 can leave a lingering trail of changes on computed tomography scans of the lungs.³ ACE-2 positive cells within the lung, heart, kidney, and elsewhere are susceptible to direct infection with SARS-CoV-2, which can lead to fibrosis. Initial reporting of the COVERSCAN magnetic resonance imaging study of more than 200

individuals with long covid at around four months after infection shows multi-organ involvement, especially the heart and lungs.⁴

Conceptual models

The notion of long term virus persistence has not previously been considered for coronaviruses, yet gastrointestinal biopsies taken four months after acute covid-19 show persistent live virus in about a third of individuals.⁵ Nonetheless, presence of the virus would not be a prerequisite to account for persistent disease. Several acute viral infections are known to induce immune and inflammatory responses and lead to long term sequelae. Autoimmune/inflammatory conditions can persist for years after Ebola virus or Chikungunya virus, and profound immune subset perturbations can be provoked by Epstein-Barr virus (EBV) in infectious mononucleosis. Furthermore, the status of EBV in aetiological risk of multiple sclerosis exemplifies the potential roles of viral infection in triggering autoimmunity.

The mechanisms underlying autoimmune diseases may offer some conceptual models relevant to symptom patterns in long covid. Cyclical relapsing and remitting disease is a key feature of multiple sclerosis. This is often taken to reflect fluxes of immune effector and regulatory cellular subsets, though consensus is lacking. Lupus, which is the result of an autoantibody driven disease process, can variably affect many organs, so that a patient may need to see a rheumatologist, nephrologist, neurologist, or immunologist in different care pathways. It is a disease of a single system—the immune system—yet it affects diverse organs at different times. Chikungunya virus—a mosquito-borne virus causing acute fever, headache, and myalgia, sometimes with neurological involvement—can cause a substantial minority of patients to later develop severe arthralgia, which can persist for years.

In Brazil, which has a high Chikungunya case burden, it is this aftermath of disease which has been the most devastating with respect to individuals’ employment, quality of life, mental health, and long term unforeseen demand on national health provision. In the UK, the Royal College of General Practitioners is already predicting a significantly increased workload owing to long covid.

Long covid patients need insights into the nature of their condition, how long it’s likely to go on for, what

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can be done about it, and through which clinical specialties.

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