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Commentary

Long COVID: A growing problem in need of intervention

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The number of people who have survived COVID-19 is overwhelming—official figures approach half a billion. Thus, any long-term consequences in COVID-19 survivors could have a huge impact on public health and on healthcare services in the coming months and years, with potentially 100 million individuals affected.

Clinical features of long COVID

Long COVID is still an emerging clinical concept that is not fully characterized. Studies have identified numerous symptoms potentially related to long COVID. A consensus process led by the World Health Organization has gathered support for a case definition consisting of a clinical picture dominated by a combination of dyspnea, fatigue, and cognitive symptoms, such as impaired memory and concentration, that impacts daily functioning and lasts beyond three months after the onset of acute COVID-19. Other common accompanying symptoms include disturbed taste and/or smell, gastrointestinal discomfort, chest pain, paresthesia, headache, and depression.[1]

Epidemiology of long COVID

Early in the pandemic, clinicians observed that COVID-19 survivors had a substantial burden of persisting symptoms. Initial studies focused on hospitalized patients, and long-term symptoms were thought to be related to the severity of disease.[2] This was not surprising because intensive care and ventilator support are strongly associated with long-lasting sequela, with half of patients experiencing reduced function a year after discharge from hospital.[3] An early report documenting high prevalence of long COVID also in home-isolated patients with milder COVID-19 showed that even adolescents and young adults were affected.[1] Other research on both hospitalized patients and those with milder disease followed and confirmed long COVID as an emerging entity. The long-term perspective and prognosis for individual patients remain unclear, and there are still no definitive treatments.

Relationship between long COVID and other post-infectious syndromes

Long COVID appears reminiscent of syndromes that follow several other infections. As far back as 150 years ago, concepts such as neurasthenia and encephalitis lethargica gained hold as syndromes of fatigue, anxiety, depression, and neuralgia that frequently occurred after infections such as influenza, although causal association remains unproven. Subsequently, chronic fatigue syndromes or post-infectious fatigue syndromes have been associated with several infectious diseases, notably brucellosis, Q-fever, giardiasis, mononucleosis, and flavivirus infections such as dengue fever. In all these syndromes, excessive fatigue is a key symptom, and several other accompanying symptoms seem to align with key symptoms reported with long COVID. Research has found similar clinical presentations in post-infectious syndromes caused by different microbes and has proposed that the host response may be a more important determinant than the etiological agent. As the pathogenesis of post-infectious fatigue syndromes remains to be elucidated, long-COVID pathogenesis is equally unclear. Interestingly, certain symptoms appear characteristic of long COVID, such as disturbed taste/smell and dyspnea, indicating that long COVID might be conceptually different from other post-infectious syndromes.

Biology and pathogenesis

Currently, the biological underpinning of long COVID is not well understood. There is considerable interest, however, in understanding the biology underlying symptoms such as disturbed taste and/or smell because these appear distinctive of long COVID and could provide clues to any unique pathogenetic features. The combination of cranial nerve symptoms of dysgeusia and anosmia and central nervous system symptoms such as memory and concentration problems and so-called "brain-fog" alludes to pathological processes involving the central nervous system. Autopsy studies have not found evidence of widespread viral dissemination in the brain.[4] While overt signs of meningeal inflammation with lymphocytic pleocytosis are not typical, other inflammatory markers (neopterin, beta-2-microglobulin) have been identified in the spinal fluid of COVID patients with neurological symptoms,[5] and autoimmunity has been implicated in cranial nervous involvement.[6]

As much as the pathogenesis of long-term neuro-cognitive debility is unclear, we do not fully understand the independent psychological effect of lockdown measures, social isolation, and impact on work and school. Importantly, prospective data show higher prevalence of long-COVID symptoms in COVID-19 convalescents than in non-infected household members recruited during the same period.[1] This argues for an independent biological effect, in addition to any psychological effects of the pandemic life.

Dyspnea is also of particular interest, as it is a more prominent symptom in long COVID than in other post-infectious syndromes. There is evidence that a high SARS-CoV-2 spike antibody response to acute infection is independently related to dyspnea on long-term follow-up.[1] A recent study showed a correlation between long COVID and T cell responses eight months after acute infection.[7] It is not entirely clear whether there is a causal link between immune activation (humoral and cellular responses) and long COVID or to what extent severity of initial infection could confound this association. However, the finding that peak SARS-CoV-2 spike-specific antibody responses 6–8 weeks after acute infection are independently associated with fatigue and symptoms of long COVID at 6 months follow-up suggests there may be a biological link between the immune response and long COVID.[1]

There is emerging evidence that different features of long COVID, particularly dyspnea, dysgeusia, and dysosmia, have different pathological mechanisms.[8] Therefore, it may be an oversimplification to describe long COVID as one syndrome, and further research should attempt to uncover whether there are sub-constellations of symptoms that have specific pathophysiology.

Long COVID and vaccines

Currently, most of the populations in affluent, Western countries have been vaccinated against COVID-19, while low and middle income countries, particularly on the African continent, are lagging far behind.

The most obvious way in which vaccines impact long COVID is by protecting individuals from getting COVID-19 infection in the first place. Vaccines are highly efficacious and have, together with social distancing and general infection control measures in society, prevented a large burden of illness and death from acute COVID-19, thereby undoubtedly also averting a large burden of long COVID. Vaccines, including boosters, will thus continue to be a major intervention against long COVID as vaccination expands.

Vaccines have a greater effect on severity and survival than preventing infection. Therefore, there is great interest in whether vaccination influences the risk of long COVID in those who get breakthrough infection despite being vaccinated. Methodological issues complicate such comparisons, in terms of defining appropriate control groups and assessing differential effects of type, number, and timing of vaccines. A major challenge in studying this is that a large, unknown number of COVID-19 infections in vaccinated people will be missed because patients with mild symptoms are less likely to get tested and diagnosed.

Studies investigating the role of reinfection after vaccination and its impact on long COVID have so far produced conflicting results. In a study of vaccinated Israeli healthcare workers, three percent (39/1,497) had breakthrough infections. Among those, most had mild symptoms, but 19% had symptoms lasting more than 6 weeks.[9] A recent British study by Michaela Antonelli and colleagues[10] found that vaccinated patients with breakthrough infections had a significantly lower risk of persisting symptoms and a higher probability of being completely asymptomatic two months after infection compared to unvaccinated individuals. As the study population was recruited from users of the COVID Symptom Study app, there is, however, a risk of selection bias. The UK Office for National Statistics published self-reported data from patients indicating that the first dose of vaccination reduced the risk of long COVID by 13% and the second dose by an additional 9%.[11] A study of US veterans found that prolonged symptoms (>28 days) were significantly less frequent in vaccinated (5%) than unvaccinated persons (11%).[12] Another study, currently only available as preprint,[13] comparing 9,479 vaccinated COVID-19 patients to unvaccinated matched controls, found a protective effect of vaccines on severity and clinical outcome of the acute illne ss but no difference in the risk of long COVID.

Whether the protective effect of vaccination on long COVID remains in people infected by Delta and the now-dominant Omicron, as well as by potential future variants, remains unresolved.

There is interest in determining whether vaccines could have a potential therapeutic effect against already-existing long COVID. However, because one of the proposed mechanisms underpinning long COVID includes immune-mediated pathogenesis, there is also a theoretical risk that vaccination could cause, or exacerbate, long-COVID-like symptoms. Data on this question are so far are inconclusive, as illustrated by a French study of 380 patients with long COVID who were vaccinated approximately one year after initial infection, finding improvement of symptoms in 22%, worsening symptoms in 31%, and no effect in 47%.[14]

There is, however, cause for optimism, mainly in that vaccination averts countless acute COVID-19 cases, some of which might otherwise develop into long COVID. There is some evidence that vaccination protects against long COVID in cases of breakthrough infections.

Impact of treatment for acute COVID-19 on long-term symptoms

Considering the massive public health impact of long COVID, the need for specific medical therapy is pressing. Of equal interest as vaccine effects is whether early treatment aimed at preventing severe disease and hospitalization can also prevent long COVID. An Italian study provides some evidence that treatment with remdesivir during hospitalization for acute COVID-19 prevents up to one-third of long-COVID cases.[15] Remdesivir must be given as an injection and is, therefore, unlikely to be useful on a large scale for non-hospitalized patients. Two oral and less expensive antiviral drugs have recently been licensed, the protease inhibitor nirmatrelvir/ritonavir and molnupiravir, a drug that introduces mutations in the viral genome, but there are so far no data to support any protective effect on long COVID. Whether treatment-as-prevention could be applied as a strategy to combat long COVID in general, or for select risk populations, should be investigated further.

The more urgent question of whether any antiviral drugs could be helpful directly as treatment for long COVID is unclear. As viral persistence is probably not important for the pathogenesis of long COVID, any direct effect of antivirals on long COVID would be surprising.

Corticosteroids, such as dexamethasone and prednisolone, are widely used

for hospitalized COVID-19 patients because of their proven efficacy against severe disease, but they are not effective in mild COVID-19. There is no evidence that corticosteroid treatment in acute COVID-19 can prevent long COVID.[15] However, a small study suggests some beneficial effect on dysgeusia from a short-course treatment with oral corticosteroids in combination with olfactory training.[8] Available data, so far, do not support the widespread use of corticosteroids in otherwise healthy individuals, as the risks of side effects would outweigh the marginal benefits.

Management of long COVID lacks proven medical therapies. However, physical rehabilitation is considered helpful. Cognitive therapy has been promising in the management of other post-infectious syndromes, but any benefit in long COVID remains to be determined.

Future perspectives

Two years into the pandemic, the case definition and epidemiology of long COVID are still not well established, and the pathogenesis and potential interventions are largely unknown.

There is urgent need for research into the biology of long COVID to understand how to best prevent and manage this public health problem. For society, it is essential to know whether interventions before or during acute illness will affect the duration and long-term prognosis of COVID. This will impact vaccination strategies, particularly in younger age groups where severe disease is rare, but long-lasting cognitive difficulties are a particular concern.

At present, the Omicron variant is overwhelming societies across the world. While apparently causing milder disease and less hospitalization, it is too early to say whether the risk of long COVID is also lower. If not, the prospects of millions of infected individuals suffering from long COVID could have a severe public health impact. As governments now debate whether the wave of the highly contagious, but less virulent, Omicron variant warrants continued lockdowns and strong infection control measures, it is vital to gain more information on persisting symptoms after infection with Omicron and other variants.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and writing of the paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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