Studying severe long COVID to understand post-infectious disorders beyond COVID-19

To the Editor — As the COVID Human Genetic Effort consortium (https://www.covidhge.com/), we have studied genetic and immunological determinants of life-threatening COVID-19 pneumonia[1], multisystem inflammatory syndrome (MIS-C)[2], resistance to SARS-CoV-2 infection[3] and 'COVID toes'[4], and here we present our efforts to investigate post-acute COVID-19 syndrome, or 'long COVID'.

Most people infected with SARS-CoV-2 experience a mild to moderate acute infection, while ~10% develop hypoxemic pneumonia and 3% develop critical illness, which are outcomes associated with older age and male sex. Inborn errors of type I interferon immunity involving the viral sensors TLR7 or TLR3 can explain critical disease in 1–5% of people less than 60 years of age, whereas neutralizing autoantibodies to the type I interferons IFN-α, IFN-β and IFN-ω are seen in 15–20% of people over 70 years of age[1], which highlights the importance of type I interferon immunity for protective immunity against acute SARS-CoV-2 infection in the respiratory tract.

Although hypoxemic pneumonia typically occurs 2 weeks after infection, a small fraction of children and young adults develop MIS-C at about 4 weeks after infection. This disorder overlaps Kawasaki disease and superantigen-mediated toxic shock syndrome. Immunological analyses have revealed hyperinflammatory immune responses, distinct from those of acute COVID-19 and Kawasaki disease[5], and activation of T cells, possibly by a SARS-CoV-2 superantigen[6]. There is massive expansion of T cells expressing the T cell receptor (TCR) β-chain variable region TRBV11-2 in combination with variable TCR α-chains and broadly reactive autoantibodies[2]. Intriguingly, the delayed presentation of MIS-C after infection is at odds with other superantigen-mediated disorders, which might be explained by viral persistence specifically in the intestine and repeated superantigen-mediated activation through a leaky gut. Viral persistence has been proposed to be associated with the degree of activation of the immune system during acute infection with SARS-CoV-2[7].

Signs and symptoms after SARS-CoV-2 infection have been reported to also persist even longer in some children and adults. The World Health Organization defines the 'post COVID' condition as one that "occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis" (https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1). Long COVID spans from very mild to severely debilitating disease with objective organ damage, but sometimes the distinction between recovery from post–intensive care unit syndrome and ongoing pathology is not clearly defined or reported in studies.

Interestingly, an acute multi-organ phenotype encompassing multiple neurological, neuropsychological–neurocognitive, cardiopulmonary, gastrointestinal and dermatological complaints during acute COVID-19 correlates with longer persistence of signs and symptoms[8].

The World Health Organization's definition of long COVID is vague, which leads to concerns that a variety of conditions, including psychosomatic complaints, become intermixed with more severe, post-infectious organ dysfunction. To maximize our chances of identifying the human genetic immunological determinants of disease, we will focus our efforts on the most severe cases of long COVID available through our international network of collaborators and clinics. We will include patients with over 3 months of persistent signs and symptoms after PCR-verified SARS-CoV-2 infection. We will also limit our studies to patients with severe organ damage or dysfunction that can be objectively verified by imaging and physiological or biochemical–molecular

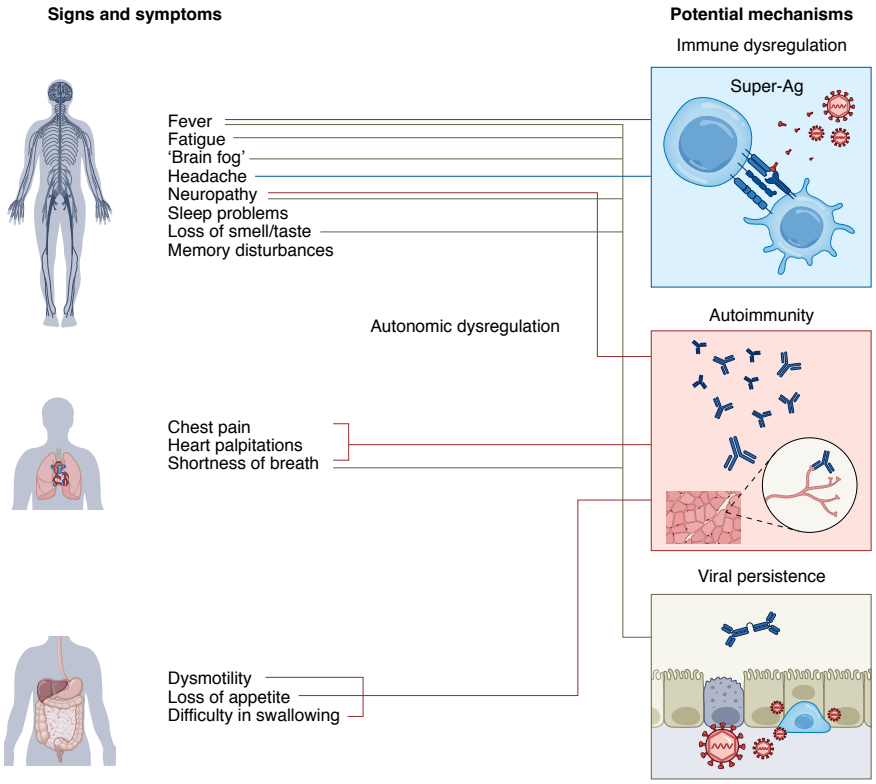

Fig. 1 | Common signs and symptoms and possible causes of long COVID. a, Signs and symptoms frequently present or reported in patients with long COVID. **b**, Hypothetical mechanisms that could explain key signs and symptoms targeted for further investigation. Super-Ag, superantigen. Figure by P.B.

tests (Fig. 1a). Finally, to distinguish these patients with severe long COVID from patients with post–critical illness syndromes, we will include only patients whose persistent organ dysfunction cannot be explained by the severity of the preceding SARS-CoV-2 infection or by the treatments or medical interventions experienced.

Long COVID could occur by various mechanisms, including viral persistence, SARS-CoV-2 superantigen–mediated activation of the immune system, and autoimmunity.

The signs and symptoms of long COVID are variable among people and follow a relapsing–remitting pattern, with recurrent spikes of fever as a common component. These findings have led us and others to hypothesize that persistent viral reservoirs may be one cause of long COVID (Fig. 1b). Such viral reservoirs could be present even if a person is negative by SARS-CoV-2 PCR tests of nasopharyngeal swabs or stool samples. One study of B cell responses to SARS-CoV-2 infection showed continuous evolution and somatic hypermutation of SARS-CoV-2 as late as 6 months after infection, and that the SARS-CoV-2 nucleocapsid protein was detectable in intestinal biopsies 4 months after mild COVID-19[9]. Moreover, persistent viral proteins have been identified 3 months before death in the lungs of a transplant donor who recovered from COVID-19, as well as in skin biopsies obtained from 'COVID-toes' (i.e., chilblain lesions) after SARS-CoV-2 infection[4].

In our cohort of patients with severe long COVID, we will investigate B cell and T cell responses to SARS-CoV-2 and will assess somatic hypermutation and clonal evolution relative to the patterns seen in people who recovered from COVID-19 without persistent signs and symptoms. This will serve as an indirect test of ongoing antigen exposure in patients with severe long COVID. Also, by assessing functional states of SARS-CoV-2-specific T cells, we will determine if patients with long COVID exhibit evidence of functional impairment that could explain viral persistence.

One study used structural modeling to identify a possible superantigen motif within the SARS-CoV-2 spike protein near the S1–S2 cleavage site[6]. As indirect support for the possibility of superantigen-mediated stimulation, expansion of TRVB21-3$^+$ cells has been observed in patients with MIS-C[2] (Fig. 1b). Many pathogens contain superantigens able to activate T cells in a nonspecific manner, such as staphylococci that cause staphylococcal toxic shock syndrome. Interestingly, this syndrome has been reported to induce persistent symptoms that bear similarity to those seen in severe long COVID[10]. This overlap of symptoms suggests either a direct effect of the superantigen on tissues or immune dysregulation that gives rise to persistent symptoms after infection.

As for the neurological symptoms common in long COVID and other post-infectious disorders, it is worth considering possible neurotoxin motifs. Such motifs have been described for the SARS-CoV-2 coronavirus[6], and these neurotoxins could in theory exert direct effects on both the central nervous system and peripheral nervous system. We plan to perform TCR sequencing in patients with severe long COVID in search of expansion of TRVB21-3$^+$ cells, as in MIS-C, and we will also perform in vitro stimulation assays using soluble S1 protein to assess T cell reactivity and possible functional dysregulation as an element of disease.

Superantigen-mediated T cell activation can trigger broad B cell activation, and production of autoantibodies against a range of tissues has been shown in MIS-C[2,5] and in patients with acute COVID-19. Also, chronic activation of the immune system by viral persistence can induce autoimmune responses, and molecular mimicry between components of a pathogen and host tissue can lead to specific post-infectious autoimmunity. Structural similarity between human neuronal antigens and SARS-CoV-2 proteins has been suggested. A particular form of autoimmunity described in long COVID is postural orthostatic tachycardia syndrome, a form of autonomic dysregulation that is possibly induced by functional autoantibodies that target G protein–coupled receptors on neurons (Fig. 1b).

Another type of autoimmunity relevant to SARS-CoV-2 infection is the production of neutralizing autoantibodies to type I interferons, which explains a sizeable fraction of cases of hypoxemic COVID-19 pneumonia[1]. If such neutralizing autoantibodies are present before SARS-CoV-2 infection, due to prior infections or vaccinations, then a patient is clearly at risk of developing severe acute COVID-19. However, such neutralizing autoantibodies might also appear after SARS-CoV-2 infection, in which case they might instead enable viral persistence, the formation of a viral reservoir and long COVID. To test this hypothesis, we will look for the presence of neutralizing autoantibodies to type I interferons in patients with long COVID.

Collectively, we believe that our genetic and immunological studies of patients with severe long COVID hold potential for better understanding of this complex condition, and by focusing on severe cases that develop after mild COVID-19, we maximize our chances of success. Our results would probably be applicable beyond COVID-19 and will hopefully provide important insights of relevance into other post-infectious disorders such as myalgic encephalomyelitis. ❐

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Competing interests

The authors declare no competing interests.

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A comparison of Sars-Cov-2 vaccine platforms: the CoviCompare project

To the Editor — Since December 2019, the COVID-19 pandemic has spread from China across the world. As the pandemic continues, 19 vaccines using different technologies have been authorized and are now being used for large vaccination programs worldwide. These vaccines are based on different vaccine platforms (mRNA, recombinant viruses, adjuvanted recombinant proteins and inactivated viruses) that have never been compared in terms of immunogenicity using the same standardized immunological readouts.

There are important questions that remain unanswered regarding the durability of the immune response, the need for and timing of booster injections, and the relative efficacies of the different vaccines against different variants. Several countries have a limited choice of authorized and available vaccines, and so a given vaccine may be used in a given demographic situation with a subset of a given variant. Local immunological data will help advise on the best protection for a given population, as will an analysis of different age groups.

To this end, we have implemented a collaborative research program involving