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Editorial
Investigating the Immune Dysregulation in Long COVID-19

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The long COVID-19 syndrome is a complex clinical state that lasts for several months and extends beyond the initial acute infectious phase. More than 200 known symptoms impact two or more organ systems. The most common symptoms include arthralgia, weakness, exhaustion, low effort tolerance, cognitive impairment, poor focus, palpitations, and chest pain [1]. Approximately 65 million people globally are affected by long coronavirus disease (COVID-19), calculated from a conservative estimate of 10% of infected individuals and over 651 million officially recorded COVID-19 cases globally. The actual number is likely much greater because of numerous unregistered cases. The estimated incidence is 10% to 30% for non-hospitalized cases, 50% to 70% for hospitalized cases, and 10% to 12% for vaccinated cases. The occurrence of long COVID-19 is observed across all age groups and levels of acute-phase disease severity. The age group with the highest diagnoses is between 36 and 50 years. The majority of long COVID-19 cases are found in non-hospitalized patients with a mild acute illness, as this group constitutes the bulk of all COVID-19 cases. Long COVID-19 is linked to several new-onset disorders, such as type 2 diabetes, myalgia encephalomyelitis/chronic fatigue syndrome, postural orthostatic tachycardia syndrome, and cardiovascular, thrombotic, and cerebrovascular diseases. Many years can pass before symptoms disappear, and in cases of newly formed dysautonomia and myalgia encephalomyelitis/chronic fatigue syndrome in particular, they may never eliminate [2].

Analysis of electronic healthcare records reveals a notable rise in the documentation of several new-onset autoimmune disorders in subjects who have been infected with SARS-CoV-2, as compared to individuals who have not been infected. Extracted hazard ratios for rheumatoid arthritis, lupus, vasculitis, and inflammatory bowel disease following COVID-19 were 2.98, 2.99, 1.96, and 1.78, respectively, among records including almost six million persons. A preliminary analysis of healthcare data in Germany, encompassing 642000 individuals diagnosed with COVID-19, revealed a 43% higher probability of developing new-onset autoimmunity [3].

Even with these great advances, we still do not have a complete framework that links the widely reported range of persistent symptoms to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. End-organ damage, a persistent reservoir of SARS-CoV-2, an atypical immune response to acute COVID-19, the reactivation of other viruses, such as Epstein-Barr virus, altered systemic immunity, auto-immunity (including

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effects on the autonomic nervous system), coagulopathy, and microbiome dysbiosis are among the mechanisms that have been proposed [3]. Some evidence related to the hypothesized mechanisms are mentioned below.

An analysis examining the initial anti-nucleocapsid antibody response during acute infection revealed an inverse correlation between antibody levels and the probability of experiencing symptoms at 3 months or later. This finding supports the idea that an insufficient early response may increase the risk of long COVID-19 [4]. The analysis of a cohort of hospitalized patients, in which 20% would develop chronic COVID-19 symptoms one year after infection, revealed that the long COVID group had notably reduced antibody levels to spike, whereas T cell responses were not affected [5]. The only significant difference was a lower percentage of anti-nucleocapsid-specific IFNγ/CD107a+memory CD8+T cells in those with persistent symptoms following SARS-CoV-2 infection [6].

A cohort with ongoing pulmonary long COVID-19 showed substantially increased CD4+ and CD8+ T cell responses to peptide pools from spikes, anti-nucleocapsid, and membrane proteins [7], In contrast, a comparable study revealed minimal disparity in peptide response between individuals with long COVID-19 and those who had fully recovered [8]. Analysis of serum biomarkers revealed that both IFNβ and IFNγ levels remained high eight months after infection in the long COVID-19 group in the ADAPT research. The authors presented an extensive COVID-19 prognostic model utilizing the analytes IFNβ, IFNγ, PTX3, and IL-6. Moreover, they identified 24 subsets within PBMCs, with 3 clusters absent at eight months in individuals with long COVID-19, highlighting effects on CD127lowCD8+ cells, CD4+ cells, and B cells. However, CD38+HLA-DR+ activated myeloid cells were raised in patients with long COVID-19. A subset of CD8+T cells had increased expression of the exhaustion markers PD1, and TIM3 [9]. On the other hand, a study that searched for a diagnostic biomarker for serum cytokines two years after infection proposed that elevated levels of TNF, IL-6, and IL-1β be combined. Another study used a multi-parameter flow assay to examine a long-term COVID-19 population and found a profile consistent with T-cell fatigue. This and other observations have led to the theory that protracted COVID-19 could be caused by SARS-CoV-2 infection-induced T-cell fatigue. The PD1 ligand PDL1 is expressed less on antigen-presenting cells six months after infection, which is significant information to know for determining if changes in PD1 expression correlate to variations in functional responses [10]. In a different study, the immunological phenotyping of forty healthy convalescent adults and 99 non-hospitalized individuals with prolonged COVID-19 showed elevated levels of CCL4 and IL-8. Consistent with prior research, a subset of activated B cells (CD86hiHLA-DRhi) was seen, along with elevated T cell PD1 and TIM3 expression and a diminished subset of CD4+ central memory T cells. Their results showed no particular relationship between autoantibody profiles and protracted COVID-19 symptoms [11]. Subsequent research indicated elevated CCL11 levels in the plasma of long-term COVID-19 patients experiencing cognitive impairment, particularly in male patients. Interestingly, CCL11 has gained widespread recognition as a mediator linked to the decline in neurocognitive performance associated with aging [12].

Evidently, within the few years required to identify and characterize long COVID-19, a substantial amount of rigorous research has been carried out and several elements of the pathophysiology puzzle have been established. Among these associations, the pivotal role of dysregulation of the immune system could be speculated. The question raised here is whether the immune-dysregulation is the cause of these disorders and abnormalities observed in long-COVID-19 or whether the long-COVID-19 causes this dysregulation. The existence of cyclical and feedback relationships between post-COIVD-19 and immune system dysregulation worsens these conditions. Given that several clinical characteristics of long COVID-19 can be seen in common autoimmune conditions, such as vasculitis, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, antiphospholipid syndrome, and myositis, it is reasonable to suggest that there may be shared contributing factors in terms of autoimmune repertoires. Thus, the increase in the occurrence rate of autoimmune diseases, which are the result of immune system deregulation, draws more attention to the relationship between immune system dysregulation and long-COVID-19.

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