Autoimmunity

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# High risk of autoimmune diseases after COVID-19

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The full picture of post-COVID-19 autoimmune diseases and their prevalence is lacking despite numerous case reports and small series. Two studies that use large cohorts now highlight that SARS-CoV-2 infection is linked to a substantially increased risk of developing a diverse spectrum of new-onset autoimmune diseases.

REFERS TO: Chang, R. et al. Risk of autoimmune diseases in patients with COVID-19: a retrospective cohort study. *eClinicalMedicine* 56, 101783 (2023).

The triggering of autoimmune conditions by viral infections has been of interest to the scientific community for decades. The COVID-19 pandemic provides a unique opportunity to understand this link and the underlying pathogenesis. SARS-CoV-2 infection leads to a spectrum of symptoms in the host, with respiratory symptoms dominating the clinical picture. SARS-CoV-2 was originally thought to mostly cause respiratory illness, with comparisons being made to common influenza. However, in a steep learning curve, the spectrum of SARS-CoV-2 infection was observed to range from self-limiting mild infection to critical respiratory distress, with symptoms including fever, cough, myalgia, fatigue and dyspnea[1]. Severe COVID-19 cases have demonstrated a substantial inflammatory response with pro-inflammatory cytokines and chemokines that stimulate pulmonary inflammation[1]. As the burden of COVID-19 cases increases worldwide, so does our understanding of the condition. Owing to worldwide vaccination efforts, mortality due to COVID-19 has been decreasing, but we continue to witness considerable morbidity and increased rates of post-COVID-19 conditions and in particular, new-onset autoimmune and inflammatory diseases in individuals who have had COVID-19. The range and incidence of these post-COVID-19 disorders have now been highlighted in two large retrospective cohort studies[2,3].

Some of the earliest evidence that SARS-CoV-2 infection leads to dysregulated immune responses came from paediatric patients who presented with multisystem inflammatory syndrome in children (MIS-C), which, as the name indicates, involves diffuse organ system involvement and a clinical spectrum that overlaps with other hyperinflammatory syndromes, such as Kawasaki disease, toxic-shock syndrome, and macrophage activation syndrome[4]. Since the start of the pandemic, many researchers have also reported isolated cases of adults with various post-COVID-19 autoimmune conditions[5]. But like the tip of an iceberg, the true spectrum of autoimmune conditions, their prevalence, and the risk of their development in individuals with COVID-19 as compared with those without remain unknown. Lack of data from a large cohort of individuals was the main stumbling block to precisely understanding these facts. Using electronic health record data from large cohorts of individuals, Chang et al.[2] and Tesch et al.[3] attempted to fill this important gap.

Chang et al.[2] used the TriNetX network, which maintains the largest global COVID-19 dataset, and identified a study population of over 5.9 million adults from 48 global health care organizations. Propensity score matching was used to generate two cohorts (COVID-19 and non-COVID-19) of 887,455 individuals each to identify the incidence of autoimmune conditions during the study period (1 January 2020 to 31 December 2021). As SARS-CoV-2 vaccination could be a potential confounding factor, only unvaccinated individuals were included in the analyses. The incidence of autoimmune conditions at 6 months follow-up was significantly higher in the COVID-19 cohort than in the non-COVID-19 group. The unique aspect of the autoimmune diseases after exposure to SARS-CoV-2, as compared with other previously known viral pathogens (such as coxsackie type 1, coronaviruses and Epstein–Barr virus), is the spectrum of conditions seen. In this COVID-19 cohort, an entire range of autoimmune conditions was noted, including rheumatoid arthritis (adjusted hazard ratio (aHR) 2.98; 95% confidence interval (CI) 2.78–3.20), systemic lupus erythematosus (aHR 2.99; 95% CI 2.68–3.34) and vasculitis (aHR 1.96; 95% CI 1.74–2.20) as well as inflammatory bowel disease (aHR 1.78; 95% CI 1.72–1.84) and type 1 diabetes mellitus (aHR 2.68; 95% CI 2.51–2.85)[2]. The risk of autoimmune conditions was generally consistent across all age groups.

A similar study by Tesch et. al.[3], which has not yet been peer-reviewed, evaluated a cohort of 640,701 vaccination-naive individuals with PCR-confirmed COVID-19 during 2020 for the risk of autoimmune conditions. The researchers identified a 42.6% higher likelihood of acquiring an autoimmune condition 3–15 months after infection compared with a non-COVID-19 cohort of 1,560,357 individuals matched for age, sex and whether they had a preexisting autoimmune disease[3]. The highest incidence rate ratios were found for vasculitis conditions, which are relatively rare autoimmune diseases. The results also emphasize that among individuals with preexisting autoimmune conditions, COVID-19 increased the risk of developing another autoimmune disease by 23%. Owing to the inherent nature of their design (retrospective cohort), these two studies do not prove a causal link between SARS-CoV-2 and the development of autoimmune diseases; however, based on the temporal association with a history of COVID-19, they provide compelling and reliable evidence that SARS-CoV-2 infection is linked to a substantially increased risk of developing diverse new-onset autoimmune diseases after the acute phase of SARS-CoV-2 infection.

In general, autoimmune and inflammatory pathologies have been linked to various infectious diseases, including COVID-19. Therefore, most of the autoimmune conditions listed in these articles are not specific for COVID-19. But an important aspect of COVID-19 is a notable increase in the overall incidence and range

of autoimmune conditions in individuals after infection. Various theories have been proposed to explain the molecular basis of COVID-19-related immune dysregulation, which include molecular mimicry by viral proteins, systemic manifestation and multiorgan involvement of COVID-19 due to widespread expression of the SARS-CoV-2 receptor ACE2, bystander activation of immune cells, release of autoantigens from tissue damaged by the virus, superantigen-mediated activation of lymphocytes and epitope spreading[6,7]. In addition, a variety of host factors such as age, comorbidities and genetic factors may also contribute. Liu et al.[8] compared similarities in the immune response in COVID-19 and autoimmune disease and concluded that organ damage in COVID-19 is largely immune-mediated, similar to autoimmune diseases. They also highlighted the detection of various autoantibodies in individuals with COVID-19 (such as antinuclear antibodies, lupus anticoagulant cold agglutinins and anti-Ro/SSA antibodies) that are also seen in autoimmune conditions.

The reports by Chang et al.[2] and Tesch et al.[3] provide a comprehensive overview of diverse new-onset autoimmune conditions after COVID-19. In addition, an earlier preprint of a retrospective matched cohort analysis using data from the Clinical Practice Research Datalink Aurum database of 458,147 SARS-CoV-2-infected and 1,818,929 uninfected adults across England between 31 January 2020 and 30 June 2021 reported that the incidence of type 1 diabetes mellitus, inflammatory bowel disease and psoriasis are significantly associated with SARS-CoV-2 infection[9]. All these studies should prompt various national health authorities to conduct similar studies to obtain nationwide data. Although the definitive molecular mechanisms such as genetic and epigenetic predisposition and pathophysiology are still unknown, the many potential theories suggest future investigations using specific gene-deficient experimental animal models, bioinformatics and systems biology approaches. For example, by analyses of more than 45,000 transcriptomic datasets of viral pandemics, Ghosh et al.[10] extracted a 166-gene signature panel to evaluate the host immune response to viral triggers. Importantly, with the exception of MIS-C, the new-onset autoimmune diseases reported to follow COVID-19 are known entities and effective treatments are already available for many of them. Even for MIS-C, owing to overlapping symptoms with Kawasaki disease, patients with MIS-C receive many of the treatments that were established for Kawasaki disease[4]. Therefore, understanding how COVID-19 affects the risk of post-COVID-19 complications such as autoimmune disease will help to implement preventive measures and early treatment in individuals who have had COVID-19 to prevent morbidity and mortality. This knowledge will also be highly pertinent for future pandemics and for analysing the long-term effects of SARS-CoV-2 vaccines, particularly those that obtained emergency use authorization without undergoing vigorous clinical trials.

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## Competing interests

The authors declare no competing interests.