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MAYO CLINIC

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Findings From Mayo Clinic's Post-COVID Clinic: PASC Phenotypes Vary by Sex and Degree of IL-6 Elevation

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A significant proportion of individuals suffer from persistent symptoms after acute infection with SARS-CoV-2. This syndrome, called long COVID by patient advocates, has been named post-acute sequelae of COVID-19 (PASC) by the National Institutes of Health. The World Health Organization developed a clinical case definition that includes (1) history of probable or confirmed SARS-CoV-2 infection with onset at least 3 months earlier and (2) symptoms that last for at least 2 months that cannot be explained by an alternative diagnosis.[1]

Basic, translational, clinical, and public health researchers have just started to understand the epidemiology and pathobiology of PASC,[2] which continues to evolve along with changes in the pandemic, vaccines, and treatments. At the same time, post-COVID clinics have been developed around the world to provide care for individuals suffering from PASC. It is readily apparent that there are different clinical presentations of PASC (eg, neurologic, cardiopulmonary), but these remain poorly defined entities.[3] Therefore, more research is needed to establish clinical phenotypes, to understand underlying mechanisms, and to identify potential therapeutic targets for the millions of individuals who are suffering or at risk for development of PASC.

In this issue of *Mayo Clinic Proceedings*, Ganesh et al[4] describe the first 108 patients in the Mayo Clinic's post–COVID-19 care clinic (PCOCC) who were evaluated at a median 149 days after acute infection. They report demographic characteristics, symptoms, laboratory findings, and 6-minute walk test results of adults referred for symptoms attributed to PASC. A notable strength of the study is inclusion of a large proportion of individuals who were not hospitalized during acute infection (84%).

Women made up the majority of those seeking care at the PCOCC, which is similar to other studies that have reported a female predominance of PASC,[5-7] especially those that included nonhospitalized individuals. Among the study sample, they found notable differences in predominant phenotypes by sex; fatigue-, orthostasis-, and chest pain–predominant phenotypes were more common among women and dyspnea among men. Based on expert consensus, the authors grouped fatigue-, myalgia-, and orthostasis-predominant phenotypes as central sensitization (CS) phenotypes and compared them with the dyspnea/chest pain phenotype (cardiopulmonary phenotype). There was a higher proportion of women with CS phenotypes. These findings are consistent with reports that female sex is associated with specific PASC subtypes (fatigue/muscle weakness, anxiety/depression, diffusion impairment).[8]

Why are more women presenting for care for PASC? Possible explanations include differences in risk factors for SARS-CoV-2 infection or PASC; differences in severity, organ involvement, or immune response of acute illness; differences in PASC phenotypes (more women with multisystem symptoms and no evident organ dysfunction); differences in the trajectory of post-COVID inflammation or symptoms; and differences in care-seeking behavior. Men have a higher risk of mortality in acute COVID-19 accounting for comorbidities,[9,10] possibly because of sex-related differences in the innate immune system. The gene encoding toll-like receptor 7 (TLR7), which activates the initial interferon response to SARS-CoV-2, is on the X chromosome and escapes X chromosome inactivation, resulting in higher expression in women.[11] Loss-of-function mutations in TLR7 resulting in down-regulated interferon signaling have been found in young

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men with severe COVID-19.[12] Similarly, TLR7 expression and downstream interferon signaling may explain greater control of acute HIV infection but higher risk of progression to AIDS among women compared with men.[13]

Female predominance is well established in autoimmunity and other postinfectious conditions that may be related to CS, such as myalgic encephalomyelitis/chronic fatigue syndrome, fibromyalgia, and postural orthostatic tachycardia syndrome. Central sensitization may be closely related to autonomic dysfunction. SARS-CoV-2 can infect the central nervous system,[14] including the regions of the brain responsible for autonomic regulation. Microvascular thrombosis, autoimmunity, chronic immune activation and systemic inflammation, or localized inflammation of the peripheral autonomic nervous system (ie, in the heart) may also be implicated in PASC-associated autonomic dysfunction. Whether PASC is a distinct entity or whether COVID-19 is a risk factor for development of these other CS-associated syndromes is not yet known.

The second major finding was that the inflammatory cytokine interleukin 6 (IL-6) is elevated among most of those with PASC, with higher levels in women and those with the CS phenotype compared with the cardiopulmonary phenotype. It is interesting that the degree of IL-6 elevation varied by phenotype, especially in considering cardiopulmonary phenotype as the reference. Given the risk of confounding in this observational study, these analyses would have been strengthened by adjusting for likely confounders for the relationship between IL-6 and PASC including age, sex, time since acute infection, body mass index, and pertinent comorbidities as well as by inclusion of a control group. In a study of individuals with PASC in San Francisco, our group found that high-sensitivity C-reactive protein and possibly IL-6 were elevated in those with the cardiopulmonary phenotype.[15] In our cohort, IL-6 level was 44% higher among those with PASC compared with those without PASC, with no change after adjustment for age, sex, hospitalization status, history of autoimmune disease, and body mass index.[16] Others have found similar elevations in inflammatory markers, including IL-6, among those with PASC.[17-19] In comparison with other non-PASC CS conditions, IL-6 is elevated in women with postural orthostatic tachycardia syndrome[20] and individuals with fibromyalgia[21,22] but not myalgic encephalomyelitis/chronic fatigue syndrome.[23]

The consistent association of systemic inflammation and specifically elevated IL-6 with PASC across multiple studies raises the possibility of IL-6 inhibition as a potential PASC treatment. In acute COVID-19, IL-6 inhibition reduced all-cause mortality at 28 days on the basis of meta-analysis of 10 randomized controlled trials that collectively randomized 6428 patients.[24] Yet IL-6 inhibition has not yet been studied as a potential intervention for PASC. Given the high burden of morbidity and uncertain long-term risks of PASC, studies of therapeutic strategies including IL-6 inhibition are urgently needed.

Because of the risk of selection bias, the findings that clinical phenotypes vary by sex will require confirmation with rigorous epidemiologic population-based sampling. As a clinic-based study, individuals thought to have PASC, either self-referred or physician referred, were included in the study of Ganesh et al. Whether a positive SARS-CoV-2 test result was required is not described; if confirmatory testing was not required, individuals not infected with SARS-CoV-2 may bias the findings. The referral process excluded those with symptoms attributed to a single organ system, and importantly, those with already identified end-organ damage (such as pulmonary fibrosis) were also excluded. The authors did not report severity of acute infection by sex. Men who survived COVID-19 acute respiratory distress syndrome may have been more likely to be referred to PCOCC, hence more men with a dyspnea-predominant phenotype, whereas women with milder acute COVID-19 may be referred with CS phenotypes. Collectively these issues could lead to selection bias, which could be differential by sex. As noted by the authors, lack of racial and ethnic diversity is a limitation of the study. The COVID-19 pandemic has disproportionately affected non-White populations within the United States, and whether phenotypes of PASC vary

by race/ethnicity is not clear. Presumably many if not all of these patients were evaluated before vaccination, but this is not reported, and effects of vaccination on the natural history of PASC are not yet known. Nonetheless, the study provides valuable insights into the phenotypes of PASC seen in clinical practice at post-COVID clinics and strengthens the evidence that IL-6 is elevated among those with PASC.

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